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ET DE PHARMACIE - MARRAKECH
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Biomarkers in the emergency department: state of knowledge and future perspectives.

THESIS

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BY

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Born on 16/03/1995 in Marrakech

TO OBTAIN THE DEGREE OF DOCTOR OF MEDICINE

KEYWORDS

Biomarkers, emergency department, point of care testing, physician knowledge, medical biostatistics, Troponin, D-dimer, B-type natriuretic peptide, N-terminal pro-B-type natriuretic peptide, C-reactive protein, procalcitonin, S100B protein.

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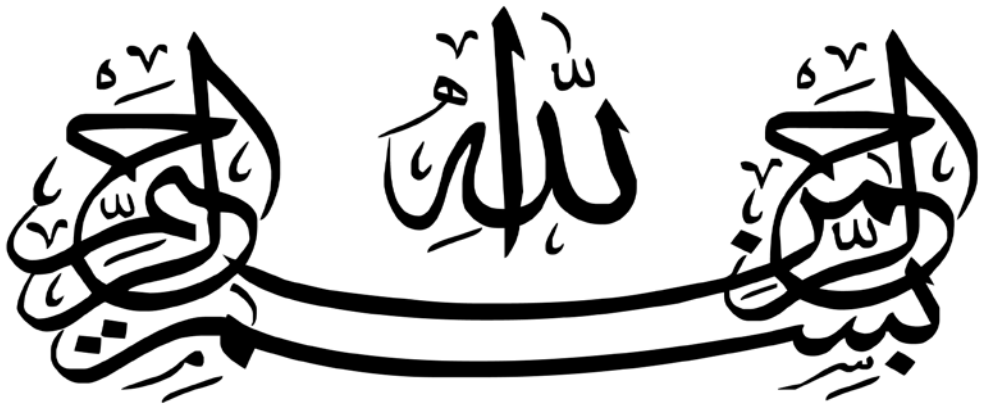

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أنعمت عليَ وعلى والديَ وأن أعمل
صالحا ترضاه وأصلح لي في ذريتي إني
تبت إليك وإني من المسلمين"

HIPPOCRATIC OATH

At the time of being admitted as a member of the medical profession:I solemnly pledge to dedicate my life to the service of humanity; the health and well-being of my patient will be my first consideration;I will respect the autonomy and dignity of my patient; I will maintain the utmost respect for human life; I will not permit considerations of age, disease or disability, greed, ethnic origin, gender, nationality, political affiliation, race, sexual orientation, social standing or any other factor to intervene between myduty and my patient;

I will respect the secrets that are confided in me, even after the patienthas died; I will practice my profession with conscience and dignity and inaccordance with good medical practices; I will foster the honor and noble traditions of the medical profession;I will give to my teachers, colleagues, and students the respect and gratitude that is their due I will share my medical knowledge for the benefit of the patient andthe advancement of healthcare; I will attend to my health, well-being, and abilities in order toprovide care of the highest standard; I will not use my medical knowledge to violate human rights and civilliberties, even under threat; I make these promises solemnly,

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DEDICATIONS

To my dearest parents,

This thesis is not only a culmination of my academic journey but a testament to your unwavering love, support, and sacrifices. Your encouragement, belief in my abilities, and the countless years you dedicated to nurturing my dreams have been my guiding light. Your love has provided me with the strength and determination to pursue this path. This accomplishment is as much yours as it is mine. Thank you for being my pillars of strength and for shaping me into the person I am today.
With all my love and gratitude,

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With heartfelt thanks,

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To Professor NEJMI Hicham
Thesis Chairperson
Head of the Emergency Department

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To my esteemed supervisor, Professor ABOU EL HASSAN Taoufik
Professor of Intensive Care Medicine and Anesthesiology

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To Professor EL ADIB Ahmed Ghassan
Thesis Jury Member
Professor of Intensive Care Medicine and Anesthesiology

Professor EL ADIB Ahmed Rhassan served as a big inspiration throughout my academic journey. He taught me about the value of the scientific method, the art of dissecting medical articles, and the significance of evidence-based medicine. I vividly recall the first time I had direct contact with him in my second year when he imparted his knowledge on CPR. It was a dream come true for a fresh medical student, and I am indebted to him for this invaluable experience.

To Professor HACHIMI Abdelhamid
Thesis Jury Member
Professor of Anesthesiology and Intensive Care Medicine

Professor HACHIMI Abdelhamid is not just an amazing professor but a true beacon of kindness. His willingness to give students time and his numerous human qualities have been a source of inspiration and support. I extend my sincerest appreciation for his unwavering guidance and support throughout this journey.

ABBREVIATIONS

Liste des abbreviations:

AA	Amino acid
ABG	Arterial Blood Gas
ABMS	American Board of Medical Specialties
ACC	American College of Cardiology
ACE	Angiotensin-converting-enzyme
ACS	Acute coronary syndrome
ACT	Activated clotting time
ADP-ribose	Adenosine diphosphate ribose
AF	Atrial fibrillation
AHF	Acute heart failure
AIDS	Acquired Immunodeficiency Syndrome
AIS	Acute ischemic stroke
AMI	Acute myocardial infarction
ANCA	Anti-Neutrophil Cytoplasmic Antibody
ANP	Atrial natriuretic peptide
ANSM	Agence nationale de sécurité du médicament et des produits de santé
APACHE	Acute Physiology and Chronic Health Evaluation
APE	Acute pulmonary embolism
ARBs	Angiotensin receptor blockers
ARDS	Acute Respiratory Distress Syndrome
ASAT	Aspartate aminotransferase
ASP	Antimicrobial stewardship program
ATP	Adenosine triphosphatase
AUROC	Area under the ROC curve
BC	Before Christ
BMI	Body Mass Index
BNP	B-type natriuretic peptide
BRCA	Breast Cancer gene
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CAGE	Cut down, Annoyed, Guilty, Eye-opener
CALC-1	Calcitonin gene-related peptide
CAP	Community-acquired pneumonia
CBC	Complete Blood Count
CCHR	Canadian CT Head Rule
CCT	Cranial computed tomography
CD3	Cluster of Differentiation 3
cGMP	Cyclic Guanosine Monophosphate
CGRP	Calcitonin Gene-Related Peptide

CHADS2-VASC	A tool used to assess the risk of stroke in patients with atrial fibrillation
CHF	Congestive heart failure
CHIP	CT in Head Injury Patients
CHU	Centre Hospitalier Universitaire
CI	Confidence interval
CK-MB	Creatine Kinase-MB
CLIA	Clinical Laboratory Improvement Amendments
CMAJ	Canadian Medical Association Journal
CME	Continuing medical education
CNP	C natriuretic peptide
CoaguCheck	Portable Coagulation Monitor
COPD	Chronic obstructive airway disease
COVID-19	Coronavirus Disease 2019
CPK	Creatine phosphokinase
CPK-MB	Creatine phosphokinase-MB
CPKMB-mass	Mass of creatine phosphokinase-MB
CPR	Clinical prediction rules
CRF	Chronic Renal Failure
CRM	Certified reference material
CRP	C-reactive protein
CRP-us	Ultrasensitive C-reactive protein
CSF	Cerebrospinal fluid
CSP	Code de la santé publique
CT	Computed tomography
cTnC	Cardiac Troponin C
cTnI	Cardiac Troponin I
cTnT	Cardiac Troponin T
CTPA	Computed Tomography Pulmonary Angiogram
CURB65	A tool used to assess the severity of community-acquired pneumonia
CV	Coefficient of variation
CXR	Chest X-ray
DDU	D Dimer unit
DDx	Differential Diagnosis
DIC	Disseminated intravascular coagulation
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
DRESS	Drug reaction with eosinophilia and systemic symptoms
DVT	Deep vein thrombosis
DXplain	An online decision support system that differential diagnostic guidance

ECG	Electrocardiogram
ED	Emergency department
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
ELFA	Enzyme-linked immunofiltration assay
ELISA	Enzyme-linked immunosorbent assay
EMS	Emergency Medical Services
EPSS	E-point septal separation
EQA	External quality assessment
ESC	European Society of Cardiology
ESR	Erythrocyte sedimentation rate
ESRD	End-stage renal disease
FDA	U.S. Food and Drug Administration
FDPs	Fibrinogen degradation products
FEU	Fibrinogen equivalent unit
FF	Filtration fraction
FN	False negatives
FNR	False negative rate
FP	False positives
FPR	False positive rate
FXIIIa	Fibrin stabilizing factor
GCS	Glasgow Coma Scale
GFAP	Glial fibrillary acidic protein
GFR	Glomerular filtration rate
GP	General practitioner
GRACE	Global Registry of Acute Coronary Events
HAS-BLED	a tool to assess the risk of bleeding in patients with AF under anticoagulant therapy
HbA1c	Hemoglobin A1c
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HEART	A tool used to assess the risk of major adverse cardiac events
HemoCue	Hemoglobin analyzer
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen antigen
HPV	Human papillomavirus
HsTn	High-sensitivity troponin
ICU	Intensive care unit
IFN-gamma	Interferon-gamma
IgG	Immunoglobulin G
IL	Interleukin

INR	International normalized ratio
ISO	International Organization for Standardization
IT	Information Technology department
IV	Intravenous
JCI	Joint Commission International
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LFTs	Liver function tests
LMS	Learning management system
LOC	Loss of consciousness
LOS	Length of stay
LPS	Lipopolysaccharide
LR	Likelihood ratios
LRTI	Lower respiratory tract infections
LV	Left ventricule
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiovascular events
MAS	Macrophage activation syndrome
MCQ	Multiple-choice question
MELD	Model for End-Stage Liver Disease
MI	Myocardial infarction
mRNA	Messenger RNA
mTBI	Mild traumatic brain injury
NACB	National Academy of Clinical Biochemistry
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NMDA	N-methyl-D-aspartate
NOC	New Orleans Criteria
NP	Natriuretic peptide
NPR	Natriuretic peptide receptor
NPR-A	Natriuretic peptide receptor A
NPR-B	Natriuretic peptide receptor B
NPR-C	Natriuretic peptide receptor C
NPV	Negative predictive value
NSTE-ACS	Non-ST-elevation acute coronary syndrome
NSTEMI	Non-ST-segment elevation MI
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OKT3	Orthoclone OKT3
PARP	Poly ADP-ribose polymerase
PCI	Percutaneous coronary intervention
pCO2	Partial pressure of carbon dioxide
PCR	Polymerase chain reaction

PCT	Procalcitonin
PE	Pulmonary embolism
PERC	Pulmonary embolism rule-out criteria
PESI	Pulmonary embolism severity index
PID	Pelvic Inflammatory Disease
POC	Point of Care
POCT	Point of care testing
PORT	Pneumonia Patient Outcomes Research Team
PPV	Positive predictive value
PSA	Prostate-specific antigen
PSI	Pneumonia Severity Index
PT	Prothrombin time
PTT	Partial thromboplastin time
QTc	Corrected QT interval
RA	Rheumatoid arthritis
RAAS	Renin-angiotensin-aldosterone axis
RAGE	Receptor for advanced glycation end products
ROC	Receiver operating characteristic
ROTEM	Rotational thromboelastometry
RSV	Respiratory syncytial virus
RTI	Respiratory tract infections
S100B	Serum biomarker S100 astroglial calcium-binding protein B
SAMU	Service d'aide médicale urgente
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCQ	Single-choice question
SFBC	Société Française de Biologie Clinique (French Society of Clinical Biology)
SIRS	Systemic Inflammatory Response Syndrome
SLE	Systemic lupus erythematosus
SMUR	Service Mobile d'Urgence et de Réanimation
SOFA	Sequential Organ Failure Assessment
SPILF	Société de Pathologie Infectieuse de Langue Française (French Society of Infectious Diseases)
STEMI	ST-segment elevation MI
TAT	Turnaround time
TBI	Traumatic brain injury
TEG	Thromboelastography
TIMI	Thrombolysis In Myocardial Infarction
TN	True negatives
TNF-alpha	Tumor necrosis factor alpha
TnIc	Cardiac Troponin I
TnTc	Cardiac Troponin T
TP	True positives

TROD	Rapid diagnostic orientation test or “Test rapide d'orientation diagnostique”
TTE	Transthoracic echocardiogram
UA	Unstable angina
UK	United Kingdom
USA	United States of America
UTIs	Urinary tract infections
VQ	Ventilation-perfusion
VTE	Venous thromboembolic disease

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INTRODUCTION

The healthcare system has undergone significant transformation in recent years due to advances in science and the incorporation of new technologies. Emergency medicine, in particular, faces the challenge of improving the value and cost-effectiveness of healthcare services while dealing with an increasingly complex field.

In the field of medicine, biomarkers are valuable tools that can offer valuable insights into specific organ function or physiological mechanisms within the body. These markers are useful for identifying and characterizing diseases, simplifying clinical algorithms, and improving clinical problem-solving in routine care. Furthermore, they can help reduce the length of hospital stays, lower overall healthcare costs, and enhance outcomes in terms of mortality and re-hospitalization, thereby increasing patient satisfaction. The widespread use of biomarkers, particularly in emergency departments, has become essential in modern healthcare. After all, it is difficult to imagine an emergency department operating without troponin testing. However, it is crucial to recognize the limitations of biomarkers and use them appropriately to avoid confusion in diagnosis and potentially harmful treatments. It is important to note that none of the current or likely future biomarkers are ideal, as each one has its own set of limitations.

The increasing complexity of medical care has made it necessary for physicians to possess a high level of expertise to provide high-quality care (1). To meet this requirement, clinicians must continually update their knowledge, skills, and clinical reasoning abilities, including the use of biostatistics and epidemiology to evaluate hypotheses and the appropriate selection of biomarkers for testing. The responsible use of biomarkers is essential in maximizing their diagnostic value in the medical process.

The Covid-19 pandemic highlighted long-standing issues within the healthcare system, including overcrowding and stress in emergency departments. This crisis accelerated the adoption of technologies such as point of care testing (POCT), which demonstrated benefits in terms of faster turnaround times and more rapid medical decision-making. However, it's important to consider the opinions and perspectives of clinicians before implementing POCT in a clinical setting, as their buy-in and support are crucial to the success of the program. Therefore,

it's necessary to address their concerns and provide evidence-based information about the benefits and limitations of POCT, as well as appropriate training and education on its use.

As we move towards a post-pandemic world, it's necessary to consider the integration of technologies such as biomarkers and POCT into the healthcare system. However, before we can effectively implement these technologies, it's essential to assess our current knowledge and understanding of them. The maintenance and improvement of medical skills are based on ongoing evaluation of knowledge, practice, and care. In this light, it is relevant to question the knowledge of hospital practitioners regarding biomarkers and their use and explore the opinions and perspectives of clinicians on POCT. Therefore, this study aims to determine whether physicians at the Marrakesh Teaching Hospital possess the fundamental knowledge required for the prescription and interpretation of biomarkers, assess the need for POCT, and investigate the opinions of physicians on the implementation of this technology.

RESEARCH QUESTION AND HYPOTHESIS

Research question: To what extent do hospital practitioners at the Marrakesh Teaching Hospital possess knowledge of biomarkers used in the emergency department, and how do they perceive POCT?

Hypothesis: Hospital practitioners at the Marrakesh Teaching Hospital are hypothesized to have limited knowledge regarding biomarkers used in the emergency department. However, they are expected to exhibit positive opinions and perspectives regarding POCT.

METHODS

A cross-sectional study was conducted to evaluate the knowledge of biomarkers among physicians working in the emergency department at the Mohammed VI teaching hospital in Marrakech, Morocco.

To carry out the study, an electronic survey was administered through Google Forms and distributed through social media groups and individual emails. Data collection took place between April 2nd and May 10th, 2022.

The survey included two parts; one for demographic questions and the other for questions related to biomarkers and POCT. The data were collected anonymously, ethical approval was not necessary since participation served as consent, with the study's scientific purpose clearly explained in the preamble. The questionnaire is available in the appendix.

To analyze the survey responses, descriptive and inferential statistical analyses were performed using both parametric and non-parametric tests. The aim was to examine the demographics, knowledge of biomarkers and POCT among hospital practitioners, as well as to assess the relationships between these variables.

I. Bibliographic research:

We conducted a literature review in both French and English languages to identify studies related to the use of biomarkers in the emergency department. The review used relevant keywords such as biomarker, prognosis, diagnosis, predictive values, sensitivity, specificity, likelihood ratio, Fagan nomogram, clinical reasoning, procalcitonin, troponin, CRP, BNP, S100B, POCT, inflammation, sepsis, community-acquired pneumonia (CAP), Myocardial infarction, heart failure, deep vein thrombosis (DVT), pulmonary embolism (PE), head trauma, and overcrowding.

Questions were developed based on this research. The questions aimed to test the necessary knowledge for the use of biomarkers, such as pathophysiology, kinetics, thresholds, target population, and guidelines.

The search identified 54 articles that met the inclusion criteria of being published in peer-reviewed journals, related to the use of biomarkers in the emergency department, and written in either French or English. To provide a more comprehensive overview of the field, additional articles were included in the review. These articles were selected based on their ability to provide important or influential studies, present alternative viewpoints or perspectives, or address related or tangential topics.

The aim of this literature review was to provide a thorough and nuanced understanding of the topic by analyzing and synthesizing the relevant literature on the use of biomarkers and POCT in the emergency department.

II. Development of the questionnaire:

In this study, a questionnaire was administered to gather data on physicians' knowledge of biostatistics, biomarkers, and POCT. The questionnaire included a mix of multiple-choice questions (MCQs), single-choice questions (SCQs), and open-ended questions, for a total of 22 questions on demographics, 17 questions on biostatistics, 58 questions on biomarkers, and 9 questions on POCT. To validate the questionnaire, it was necessary for all questions to be answered, except for those in free-text format, which were only completed by individuals who chose to do so voluntarily.

To enhance the response rate and minimize potential biases, the questionnaire was designed to be completed within approximately 15 minutes. A pre-questionnaire was developed and reviewed by the supervisor to ensure the relevance and validity of the questions. One question was removed, and several were modified based on the review, and the questionnaire was pilot tested with a sample of 5 physicians to evaluate its clarity and comprehensibility. To enhance the reliability of the data and reduce the possibility of random responses, the option to answer "Don't know" was provided for a number of items.

III. Objectives and Implications of the study:

Objectives:

The study aims to achieve the following objectives:

- Evaluate the current level of understanding of biomarkers among emergency department physicians.
- Assess the knowledge and perspective of emergency department physicians on POCT.

Implications:

Achieving our study's objectives will set the stage for the following potential outcomes or implications:

- Identifying areas that require additional education and training on the use of biomarkers and POCT in the emergency department.
- Improving patient management in the emergency department through the use of biomarkers and POCT by implementing the results of the educational program.
- Continuously monitoring and evaluating the effectiveness of the educational program to ensure that the healthcare providers have updated knowledge on the use of biomarkers in emergency medicine.

IV. Scoring and grouping for analysis:

The demographic data and data on the type of practice were analyzed using descriptive statistics, including frequencies and percentages, mean and standard deviation.

To increase the statistical power of the analysis, the data were grouped together in certain cases, while in other cases, insufficient sample sizes prevented analysis. The responses to the questionnaire were scored using the following system:

In this study, descriptive statistics such as frequencies, percentages, mean, and standard deviation were used to analyze demographic data.

To enhance the statistical power of the analysis, some data were grouped, while in other cases, the sample size was insufficient for analysis.

The responses to the questionnaire were scored based on a point system:

- 1 point was awarded for each correctly answered single-choice question (SCQ).
- 1 point was awarded for each correctly answered multiple-choice question (MCQ).
- Open-ended questions were not scored.

In order to assess physicians' knowledge of biomarkers, their responses were compiled into various scores, including an overall score and scores for each subcategory. The overall score, which totaled 75 points, was comprised of individual scores for each of the following categories:

- Biostatistics: a score out of 17 points, based on 2 MCQs and 15 SCQs.
- Troponin: a score out of 19 points, based on 12 MCQs and 7 SCQs.
- D-dimer: a score out of 5 points, based on 3 MCQs and 2 SCQs.
- BNP/NT-pro BNP: a score out of 11 points, based on 9 MCQs and 2 SCQs.
- Procalcitonin: a score out of 12 points, based on 4 MCQs and 8 SCQs.
- CRP: a score out of 6 points, based on 3 MCQs and 3 SCQs.
- S100B: a score out of 5 points, based on 3 MCQs and 2 SCQs.

V.Study population and period of data collection:

The study was conducted among intern and resident physicians at CHU Mohammed VI de Marrakesh teaching hospital in Marrakesh, Morocco.

These physicians were selected because of their role as primary caregivers in the emergency department, and the study aimed to evaluate their knowledge and skills, identify gaps, and assess the effectiveness of their training.

All participants were eligible for inclusion if they were intern or resident physicians practicing at the CHU de Marrakesh during the study period and provided informed consent by completing the survey. Exclusion criteria included interns and residents who declined to participate in the study.

VI. Statistical tools:

As part of the research study for this PhD in medicine, an electronic questionnaire was distributed via Google Forms to collect survey data. The data was then transcribed into Excel for analysis.

To summarize the collected data, descriptive statistics were calculated, including frequencies, percentages, means, and standard deviations.

Normality of the data was assessed through visual inspection of histograms and the Shapiro-Wilk test. For normally distributed data, parametric tests, such as the Student's t-test and analysis of variance, were applied, while nonparametric tests, such as the Mann-Whitney test, were used for non-normal data.

Correlations were also examined between scores and ordinal variables, such as gender, age, years of practice, perceived knowledge, and prescription frequency.

These statistical analyses were performed using SPSS software, and a p-value of less than 0.05 was considered statistically significant.

RESULTS

I. General characteristics of the studied population:

1. Gender:

The sample size of this study consisted of 108 emergency department physicians, 66 of whom were female and 42 of whom were male. The sex ratio was 0.63, with 61% of the participants being female and 39% being male (Figure 1).

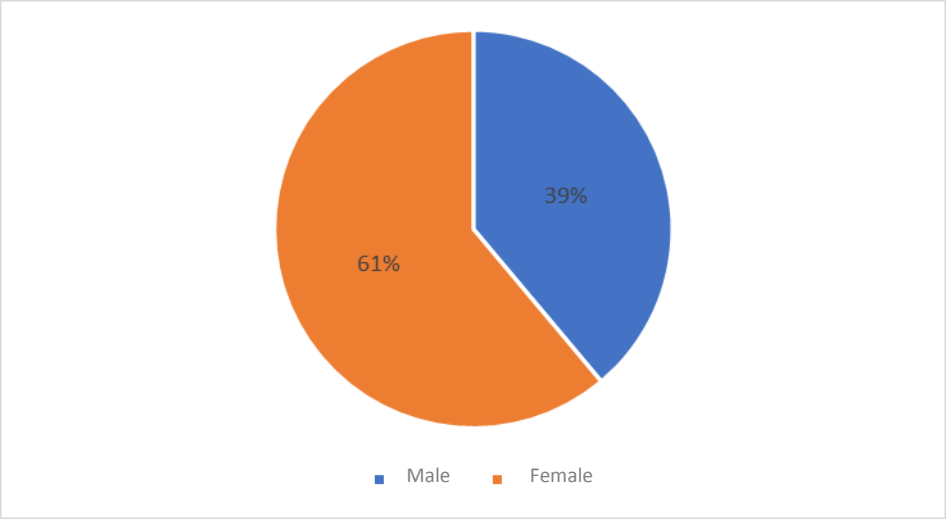


Figure 1: Distribution by gender.

2. Age:

The age of the participants was divided into two groups, with 56 (51.85%) being younger than 27 years old and 52 (48.15%) being older than 27 years old (Figure 2).

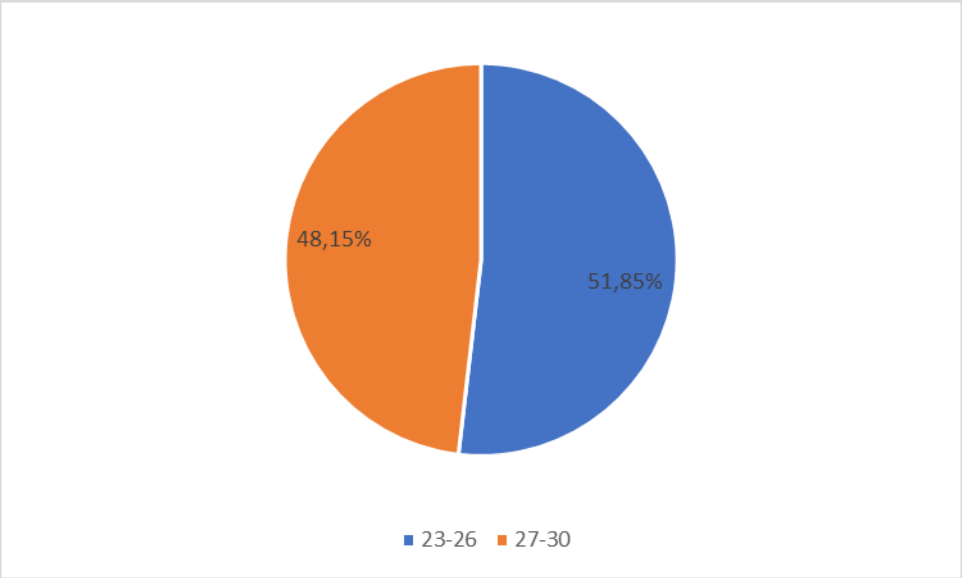


Figure 2: Distribution by age.

3. Professional status:

The majority of the sample was made up of resident physicians, accounting for 72 (67%) of the participants, followed by intern physicians, accounting for 36 (33%) of the participants (Figure 3).

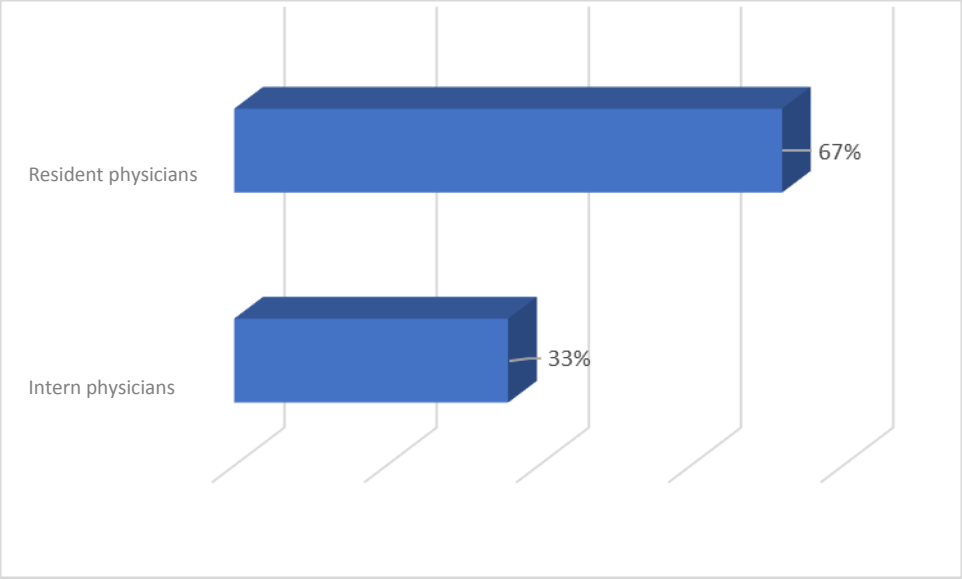


Figure 3: Distribution by professional status.

4. Seniority

4.1. Resident physicians: (years of practice as a resident)

Among the resident physicians, 42% were in their first year of training, 32% were in their second year of training, 15% were in their third year of training, 7% were in their fourth year of training, and 4% were in their fifth year of training (Figure 4).

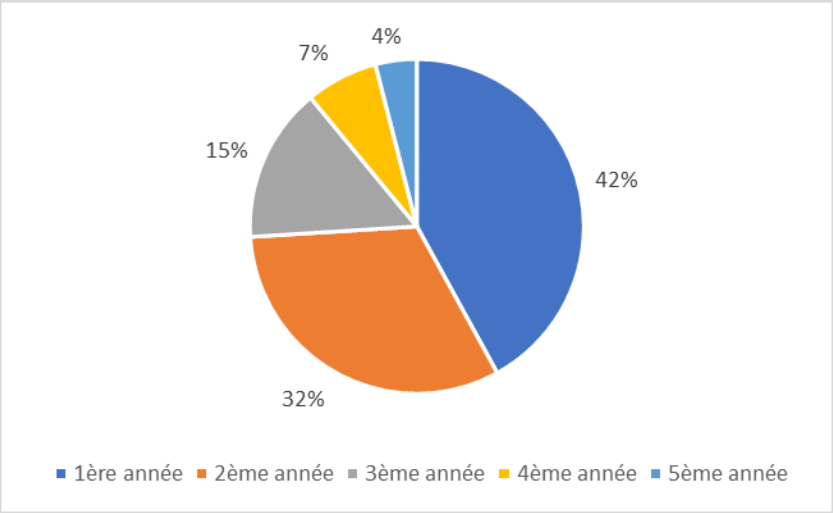


Figure 4: Distribution of resident physicians by years of training.

4.2. Intern physicians: (years of practice as an interne)

The intern physicians were divided into two groups, with 64% being first year interns and 36% being second year interns (Figure 5)

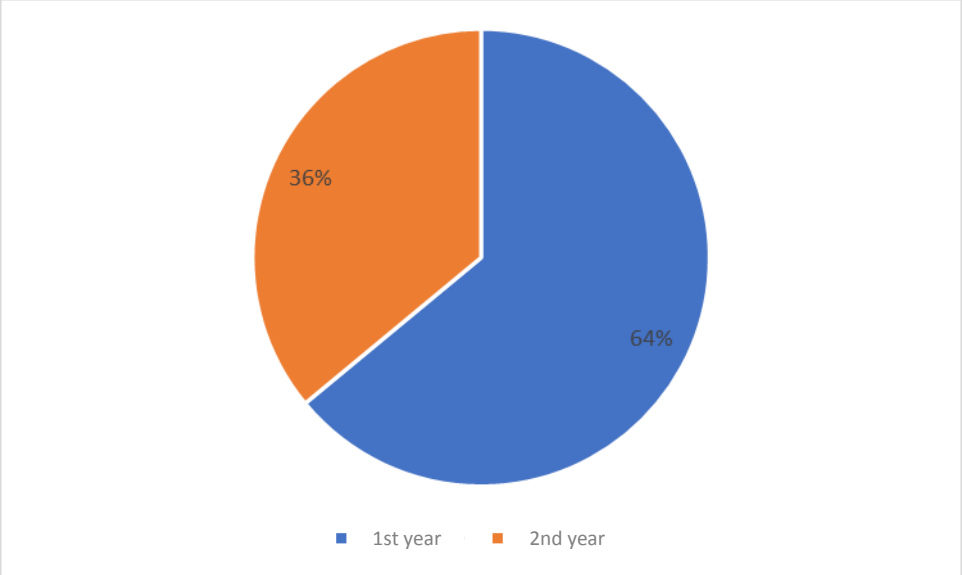


Figure 5: Distribution of intern physicians by years of training.

5. Type of specialty:

The 108 physicians who completed the questionnaire were also divided into five specialty groups: medical specialties (53, or 49%), surgical specialties (30, or 28%), biology (9, or 8%), anesthesiology (16, or 15%), and critical care and emergency medicine (Figure 6).

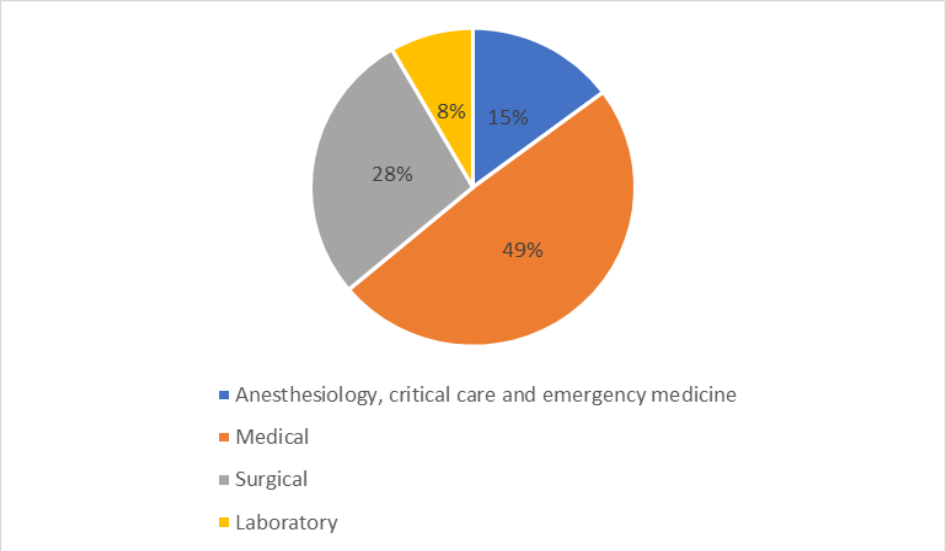


Figure 6: Distribution by type of specialty.

II. Opinions and perceptions:

1. Point of care testing

1.1. Knowledge of POCT:

A large proportion (89%) of the surveyed emergency department physicians reported that they had not heard of POCT, while a smaller proportion (11%) had heard of POCT. Only a small fraction (6 practitioners) were able to provide a definition for POCT (Figure 7).

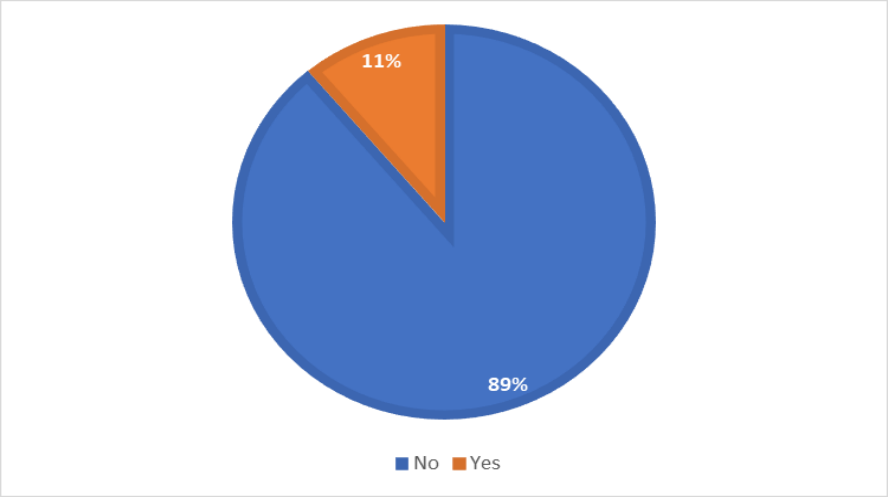


Figure 7: Knowledge of POCT.

1.2. Availability of POCT devices:

The survey revealed that the most commonly available POCT devices in the practices of the surveyed emergency department physicians were urine dipsticks and blood glucose/ketone analyzers, each being present in 97.22% of the practices. Urine pregnancy test kits and blood gas analyzers were each present in 50% of the practices, while Hemoglobin analyzer (HemoCue) and RSV test kit were present in 19.44% and 11.11% of the practices, respectively. The least commonly available devices were INR coagulation analyzers (Coagucheck), complete blood count

analyzers (Sysmex), and blood coagulation analyzers (TEG or ROTEM), which were present in 3.7%, 0.93%, and 0.93% of the practices, respectively (Figure 8).

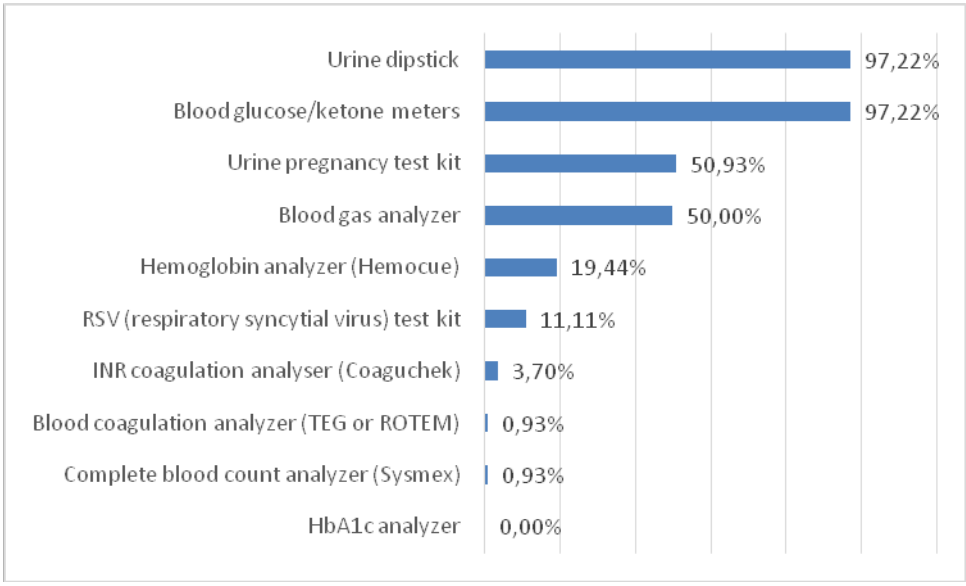


Figure 8: Availability of POCT devices.

1.3. Training on POCT use:

The survey results showed that a majority (86 participants, 79.63%) of the surveyed emergency department physicians had not received training on the use of POCT devices, while a minority (22 participants, 20.37%) had received such training (Figure 9).

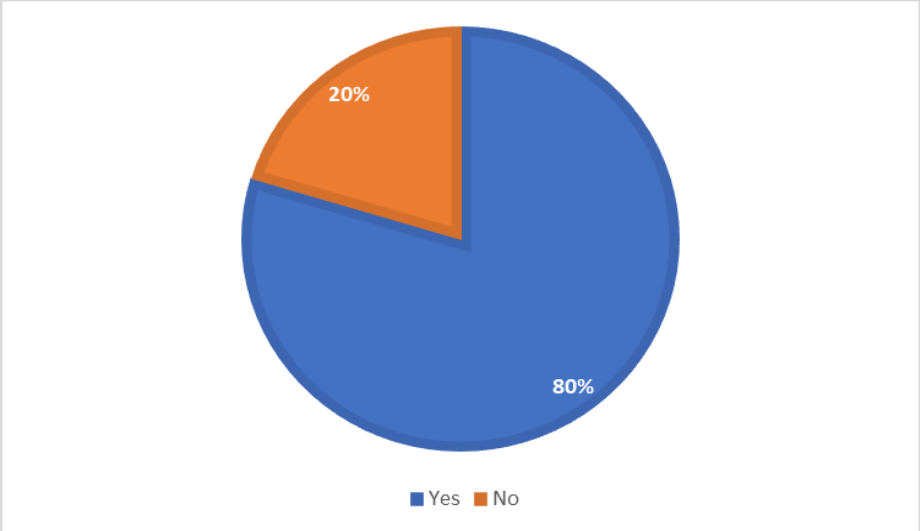


Figure 9: Training prior to the use of POCT devices.

1.4. Causes of errors in POCT accuracy:

The surveyed emergency department physicians identified several potential causes of errors in the accuracy of POCT devices. These included sampling errors (78.70%), operator error (73.15%), reagent issues (62.04%), calibration errors (58.33%), and environmental factors (50.93%) (Figure 10).

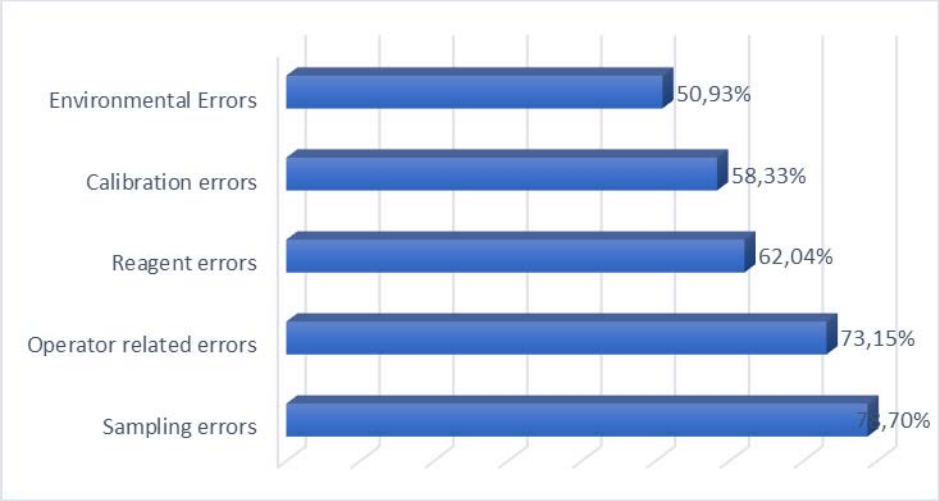


Figure 10: Perceptions over the causes of POCT related errors.

1.5. Benefits of POCT devices:

The surveyed emergency department physicians identified several potential benefits of POCT devices. The most commonly cited benefit was the ability to obtain faster results and make earlier medical decisions (95 practitioners, or 92.59%). Other benefits included the ability to employ less manpower in settings where patients required frequent testing (77 practitioners, or 71.30%), and the potential to lower the cost of care (49 practitioners, or 45.37%). A small proportion (5 practitioners, or 4.36%) did not see any added benefit to POCT devices (Figure 11).

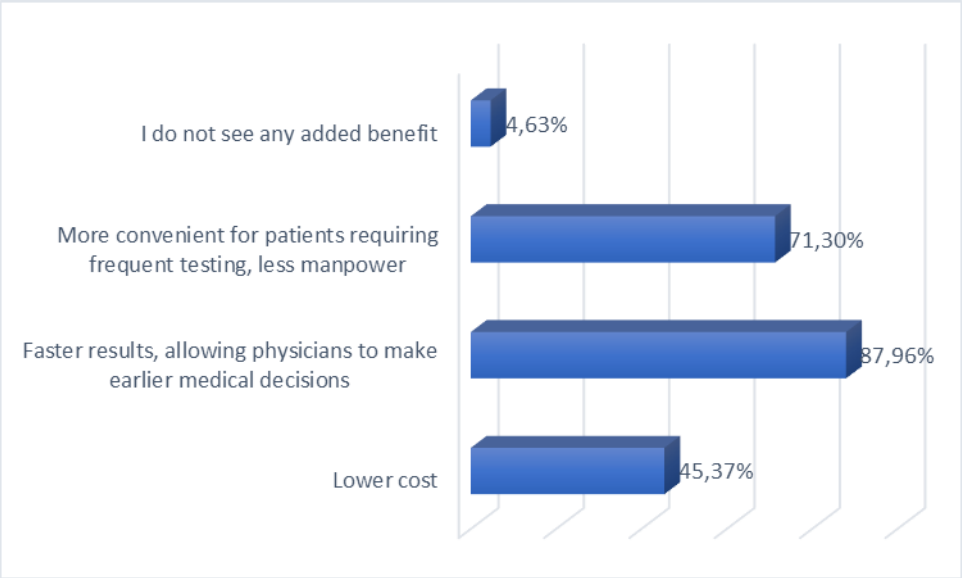


Figure 11: Perceptions over the benefits of POCT.

1.6. Perceived severity of ED overcrowding:

The surveyed emergency department physicians were asked to assess the severity of overcrowding in the emergency department. A large proportion (69 practitioners, or 64.81%) considered overcrowding to be a very serious problem, while a smaller proportion (33 practitioners, or 30.56%) considered it to be a fairly serious problem. A small fraction (1 practitioner, or 0.93%) considered overcrowding to be a small problem (Figure 12).

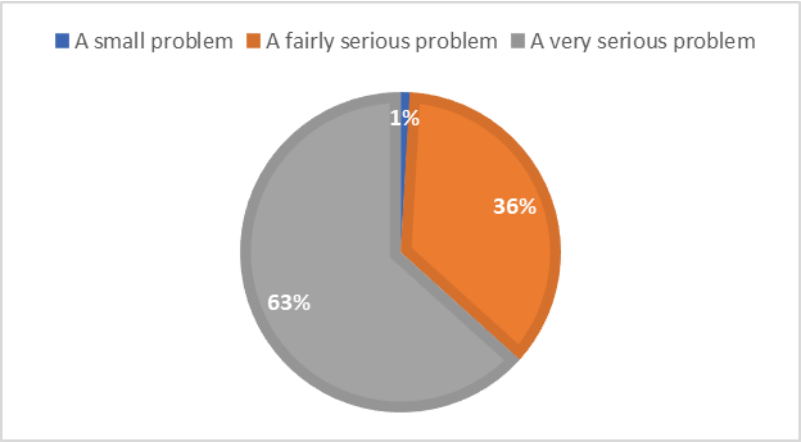


Figure 12: Perceptions on overcrowding in the ED.

1.7. Impact of ED overcrowding on patient care:

The surveyed emergency department physicians identified several negative impacts of ED overcrowding on patient care. These included staff burnout (87.96%), prolonged pain and suffering for patients (78.70%), long waiting times and delays in diagnosis and treatment (75.93%), and increased risk of errors in patient care (69.44%) (Figure 13).

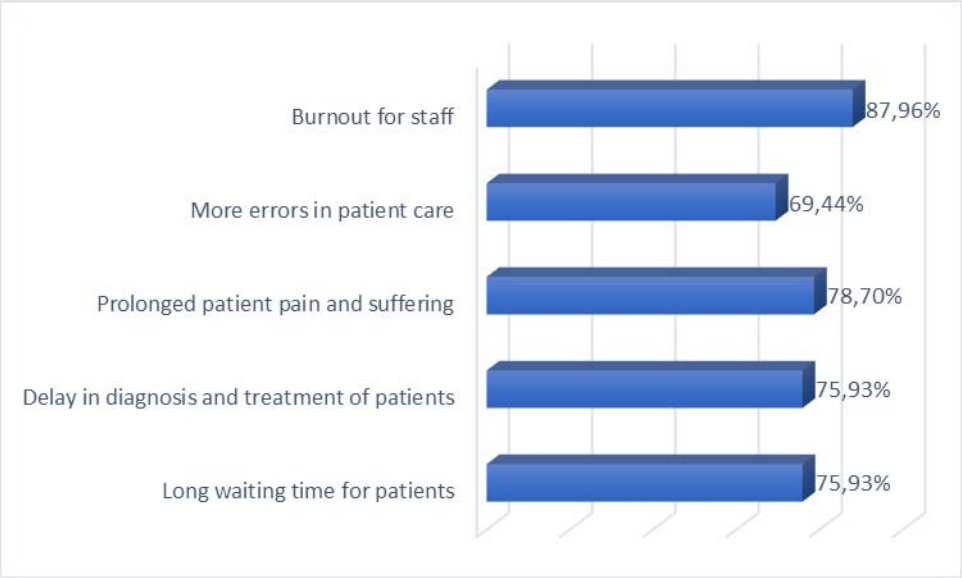


Figure 13: Perceptions on the effect of overcrowding in the ED on patient-care.

1.8. Contribution of lab result delays to ED overcrowding:

The surveyed emergency department physicians were asked to assess the extent to which waiting for lab results contributed to ED overcrowding. A majority (69.44%) considered lab result delays to be a major cause of ED overcrowding, while a smaller proportion (26.85%) considered them to be a moderate cause. Only a small fraction (3.70%) considered lab result delays to be a minor cause of ED overcrowding (Figure 14).

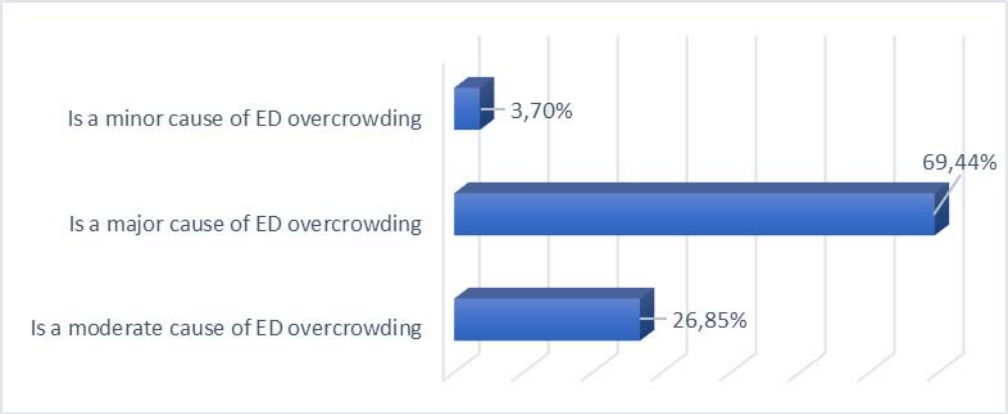


Figure 14: Perceptions on the contribution of laboratory results delay to the ED overcrowding.

1.9. Availability of POCT devices for the measurement of specific biomarkers:

The surveyed emergency department physicians were asked about the availability of POCT devices for the measurement of specific biomarkers including troponin, D-dimers, BNP/NT pro-BNP, CRP, procalcitonin, and S100B. The vast majority (97.22%, or 105 practitioners) reported that they did not have such devices in their practices, while a small minority (2.77%, or 3 practitioners) reported having POCT devices for the measurement of some or all of these biomarkers: 2 practitioners reported having POCT devices for the measurement of troponin, D dimer, BNP, CRP and PCT and 1 practitioner reported having POCT for the measurement of troponin, BNP, PCT and S100B (Figure 15).

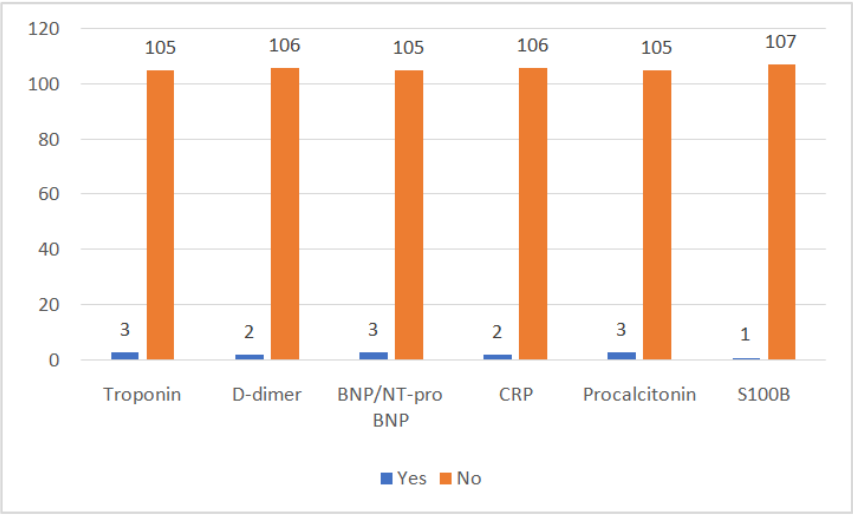


Figure 15: Availability of POCT for troponin, D dimer, BNP/NT pro-BNP, PCT, CRP and S100B

1.10. Interest in implementing POCT devices for the measurement of specific biomarkers:

The surveyed emergency department physicians were asked about their interest in implementing POCT devices for the measurement of the specific biomarkers mentioned above. A large proportion (92.59%, or 100 practitioners) reported that they would be interested in implementing such devices, while a small proportion (7.41%, or 8 practitioners) were not interested (Figure 16).

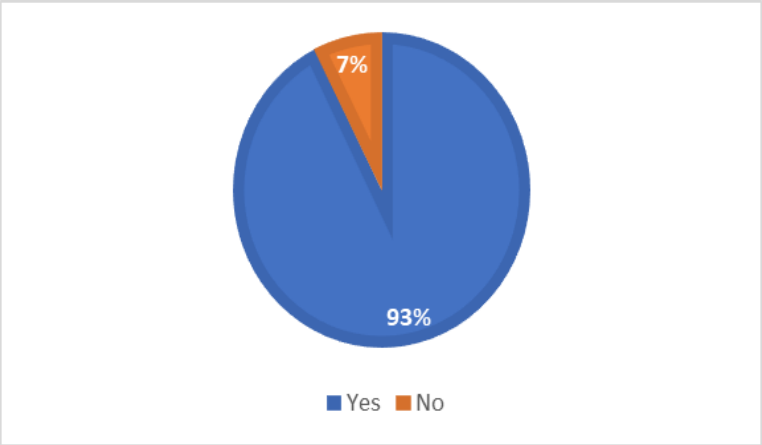


Figure 16: Interest in the implementation of POCT for troponin, D dimer, BNP/NT pro-BNP, PCT, CRP and S100B.

2. Biomarkers:

2.1. Awareness of the Term "Biomarker":

Of the 108 practitioners who completed the questionnaire, 71 (66%) had not heard of the term "biomarker", while 37 (34.26%) had (Figure 17).

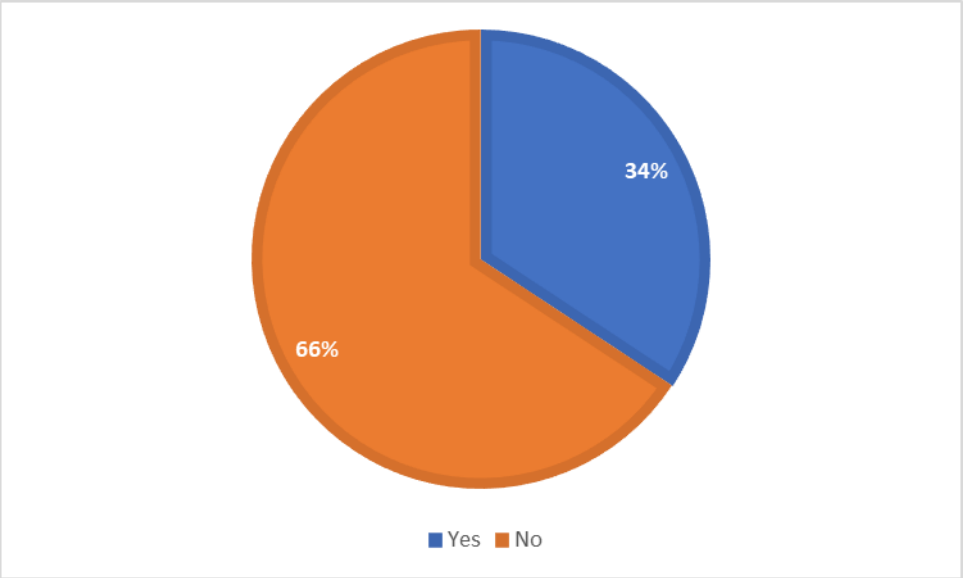


Figure 17: Awareness about the word "biomarker".

2.2. Self-Assessment of Knowledge on Biomarkers:

Of the 108 practitioners who completed the questionnaire, the majority of practitioners (91.67%) considered their knowledge about biomarkers to be insufficient, while 9 (8.33%) considered it sufficient (Figure 18).

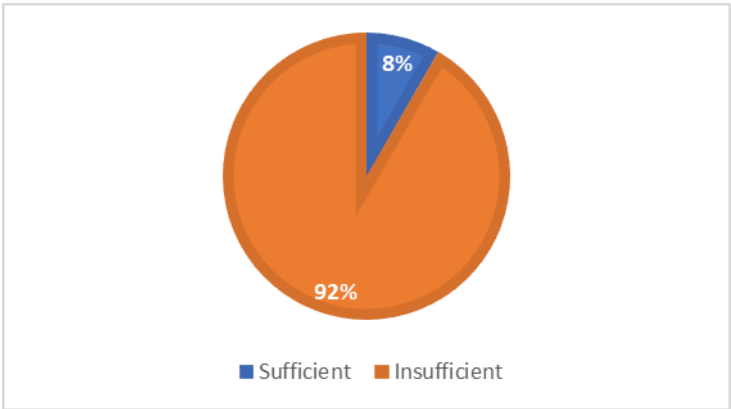


Figure 18: Personal estimation of knowledge about biomarkers.

2.3. Interest in Training or Receiving Information on Biomarkers:

A total of 99 practitioners (91.67%) expressed interest in receiving training or information about biomarkers, while 9 (8.33%) were not interested (Figure 19).

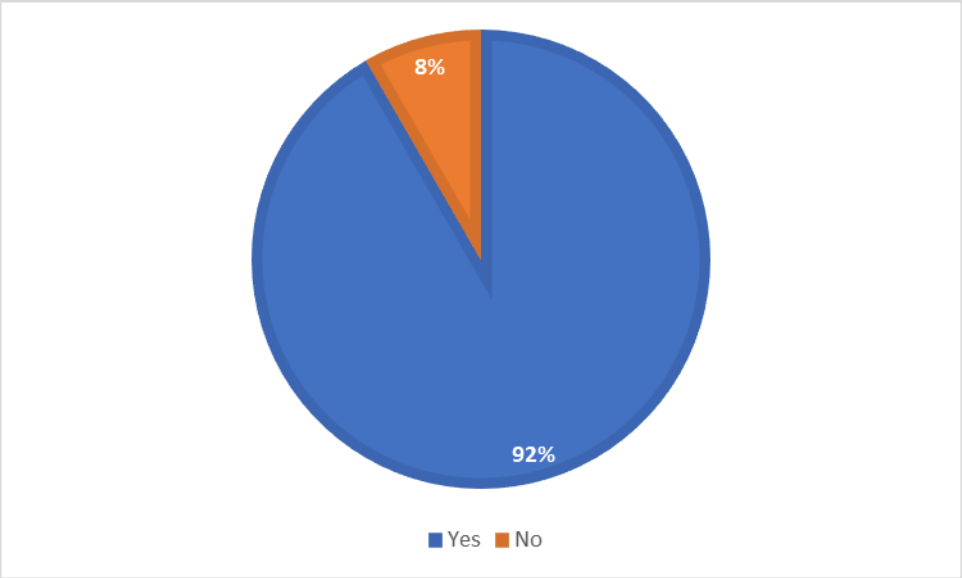


Figure 19: Degree of interest in receiving training or information on biomarkers.

2.4. Potential Applications of Biomarkers:

Of the practitioners surveyed, 92 (85.19%) recognized that a biomarker could be used in the diagnosis of a disease, 79 (73.15%) said it could be used for disease monitoring, 65 (60.19%) said it could be used to determine the prognosis of a disease, 53 (49.07%) said it could be used in predicting and monitoring the response to a therapy, and 48 (44.44%) said it could be used to determine prognosis. 11 practitioners (10.19%) said they did not know (Figure 20).

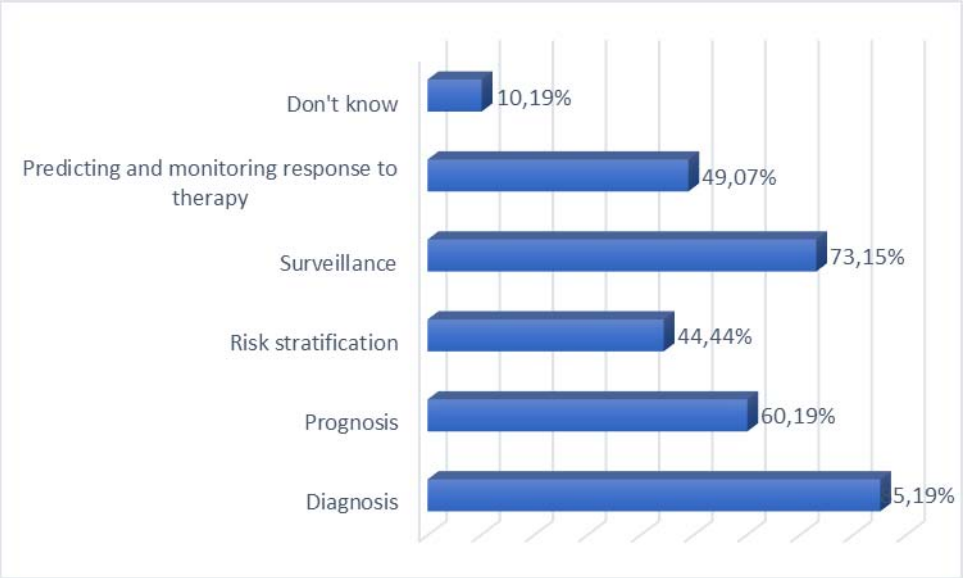


Figure 20: Perceptions on the applications of biomarkers.

2.5. Challenges in Using Biomarkers:

hat are some challenges you face when using biomarkers? In the sample, 88 practitioners (81.48%) reported difficulty interpreting results for biomarkers, 40 (37.04%) did not know which biomarker to use, and 13 (12.04%) reported no difficulties (Figure 21).

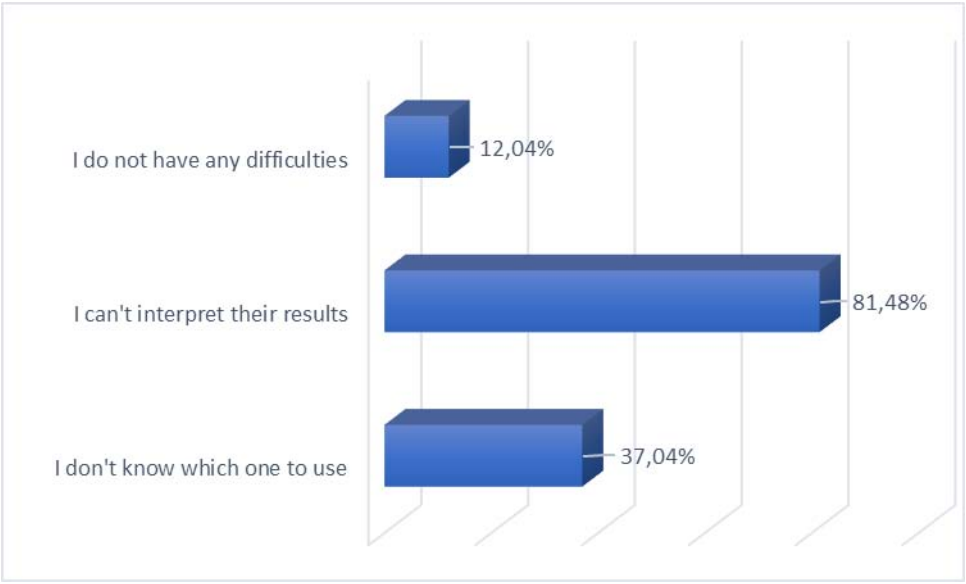


Figure 21: Perceptions on the challenges with the use of biomarkers.

III. Descriptive analysis:

1. Distribution of the overall scores:

The questionnaire included 75 graded questions. The scores of the evaluated physicians ranged from 0 to 29 with a mean of 11.05 a standard deviation of 6.648 and a median of 10.00 (Table 1, Figure 22).

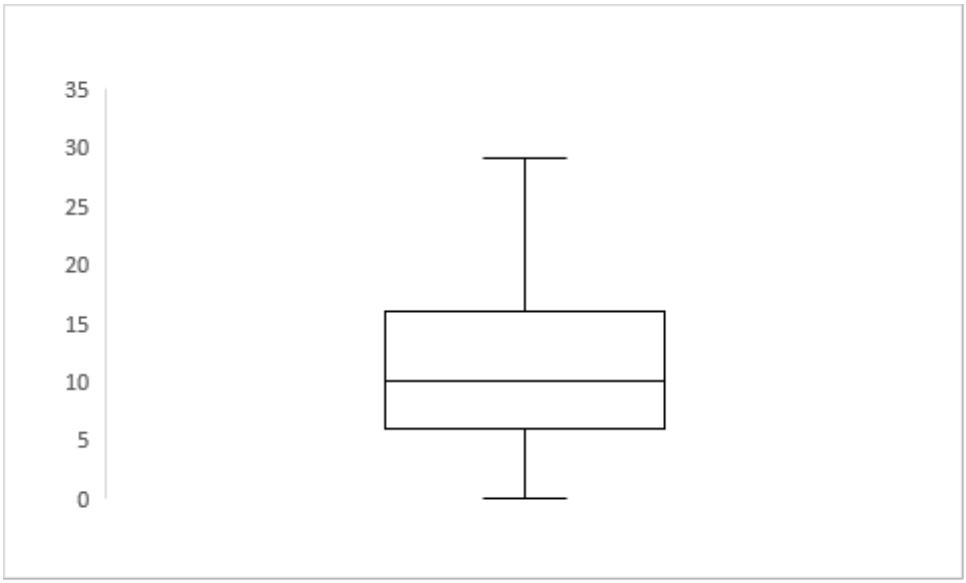


Figure 22: Box plot distribution of the overall scores.

Table I: Questionnaire score analysis.

	Number	Average	Median	Standard deviation	Minimum	Maximum
Score	108	11,05	10,00	6,648	0	29

29% of the subjects obtained an average score between 5 and 9, 22% had an average score between 10 and 14, 20% had an average between 15 and 19, 19% had an average between 0 and 4 and 10% had an average of over 20 (Figure 23).

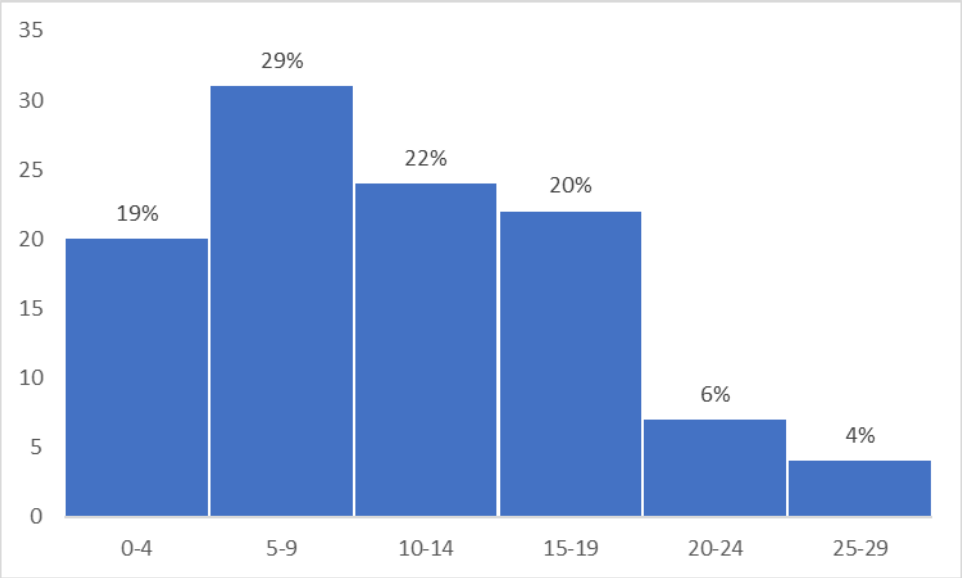


Figure 23: Bar graphical distribution of the overall scores.

2. Distribution of scores by subsection:

2.1. Biostatistics scores:

This subsection included 16 questions. The questionnaire scores of the evaluated physicians ranged from 0 to 14 with an average score of 4.45, a standard deviation of 3.187 and a median of 4 (Table 2, Figure 24).

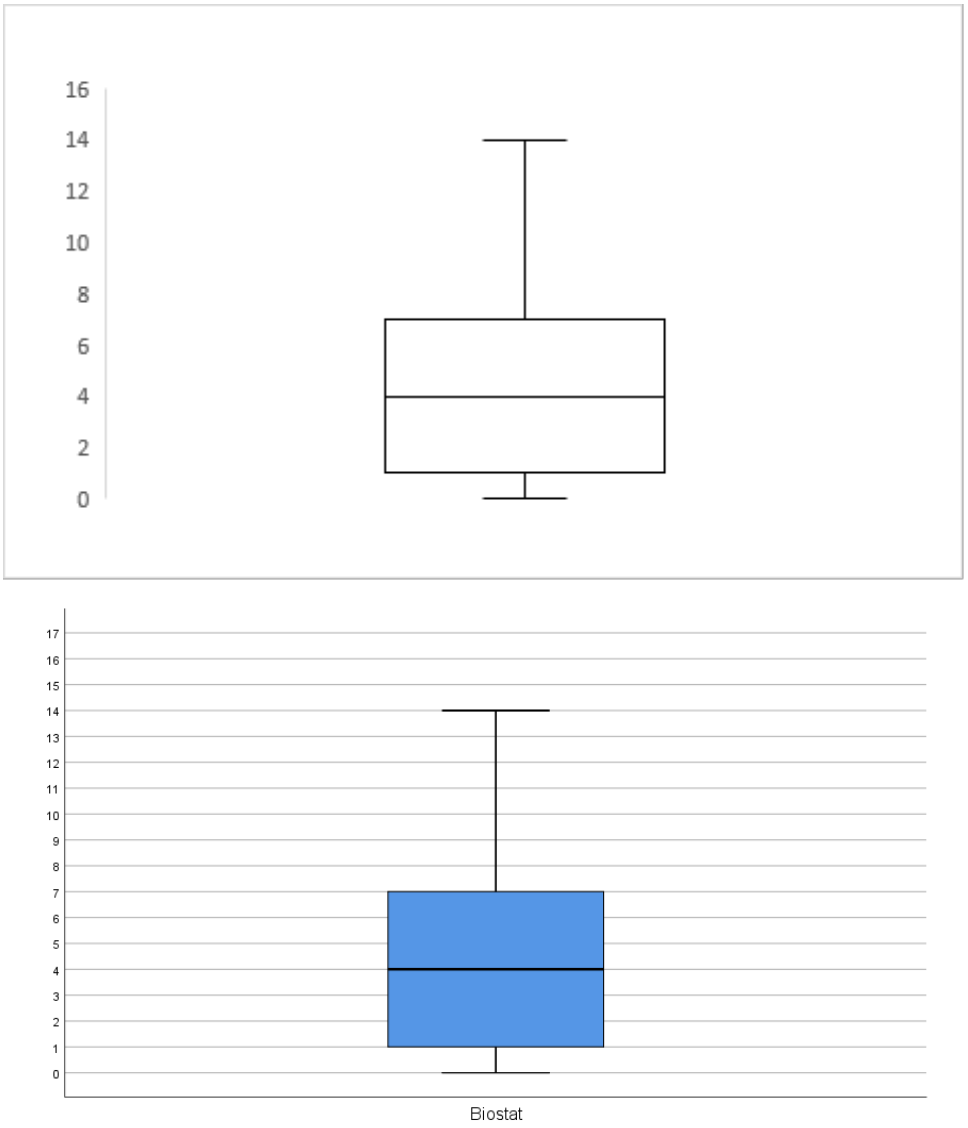


Figure 24: Biostatistics subsection – Box plot distribution of the scores.

Table I: Biostatistics score analysis.

	Number	Average	Median	Standard deviation	Minimum	Maximum
Score	108	4,45	4	3,187	0	14

26% of the subjects obtained a score less than 1, 57% obtained a score between 2 and 7, 19% obtained a score above 8 (Figure 25).

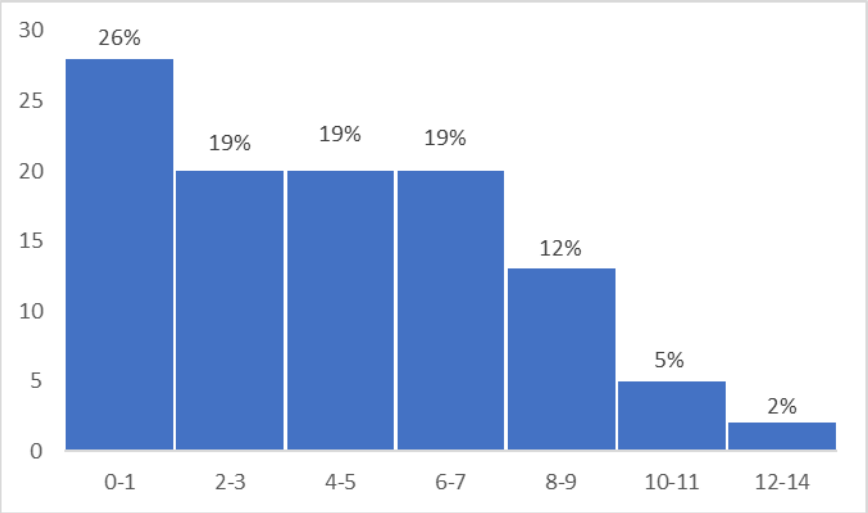


Figure 25: Biostatistics subsection – Bar graphical distribution of the scores.

2.2. Troponin:

This subsection included 19 questions. The scores of the evaluated physicians in this section ranged from 0 to 10 with an average of 2.74, a standard deviation of 2.492 and a median of 2.5 (Table 3, Figure 25).

Table II: Troponin score analysis.

Number	Average	Median	Standard deviation	Minimum	Maximum
108	2,74	2,5	2,492	0	10

2.3. D dimer:

The scores of the physicians in this section ranged from 0 to 2 with an average of 0.79, a standard deviation of 0.762 and a median of 1 (Table 4, Figure 26).

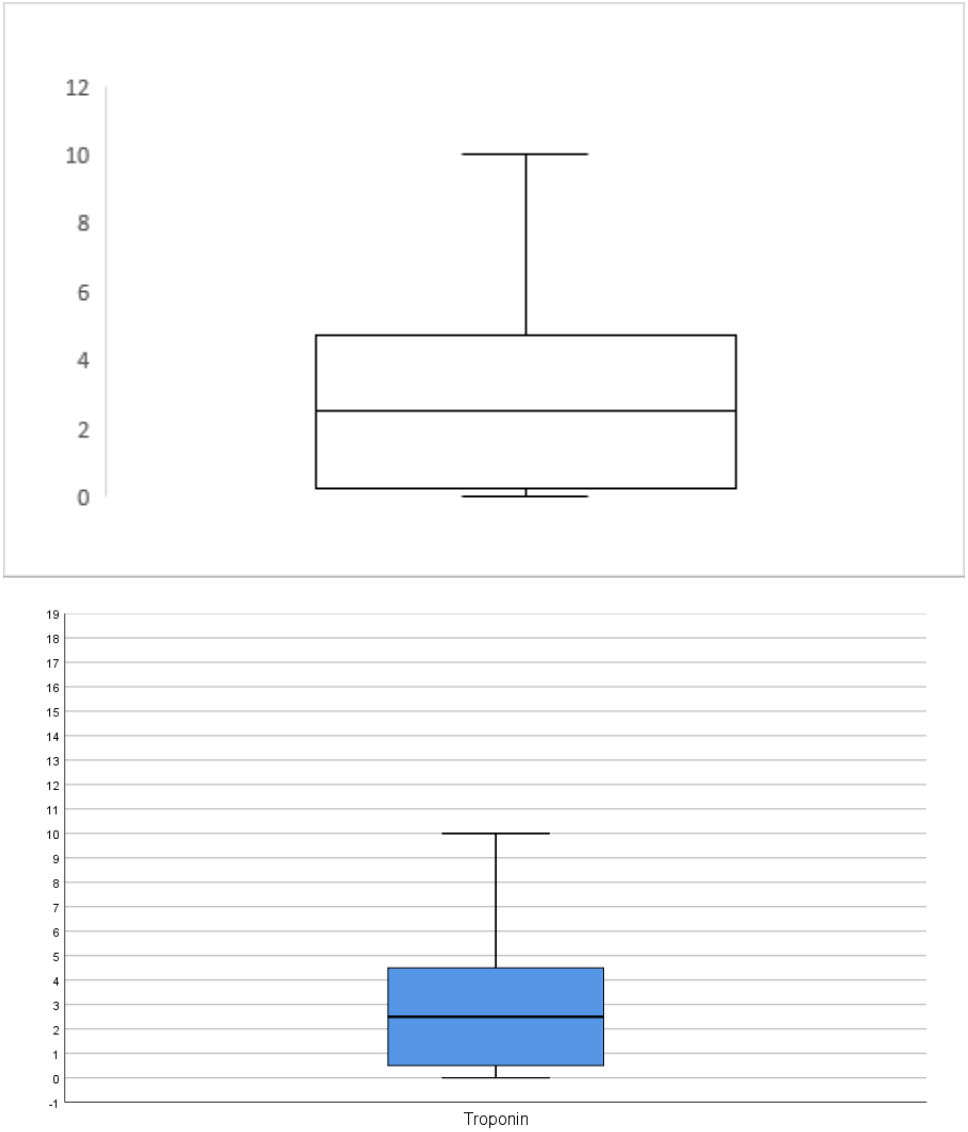


Figure 26: Troponin subsection – Box plot distribution of the scores.

Table III: D dimer score analysis.

Number	Average	Median	Standard deviation	Minimum	Maximum
108	0,79	1	0,762	0	2

38% of the physicians had a score less than 1, 54% of the physicians had a score between 2 and 5 and 9% had a score above 6 (Figure 27).

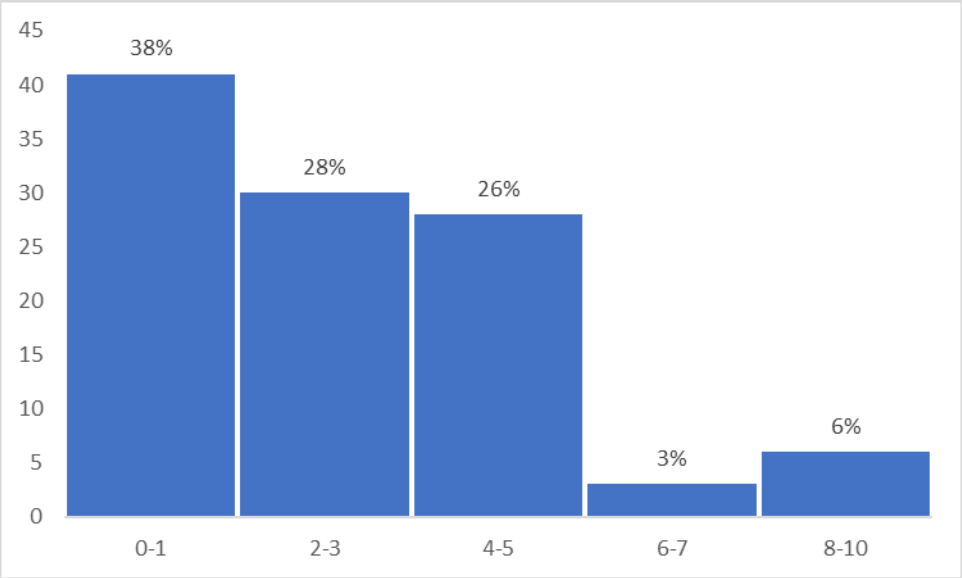


Figure 27: Troponin subsection – Bar graphical representation of the scores.

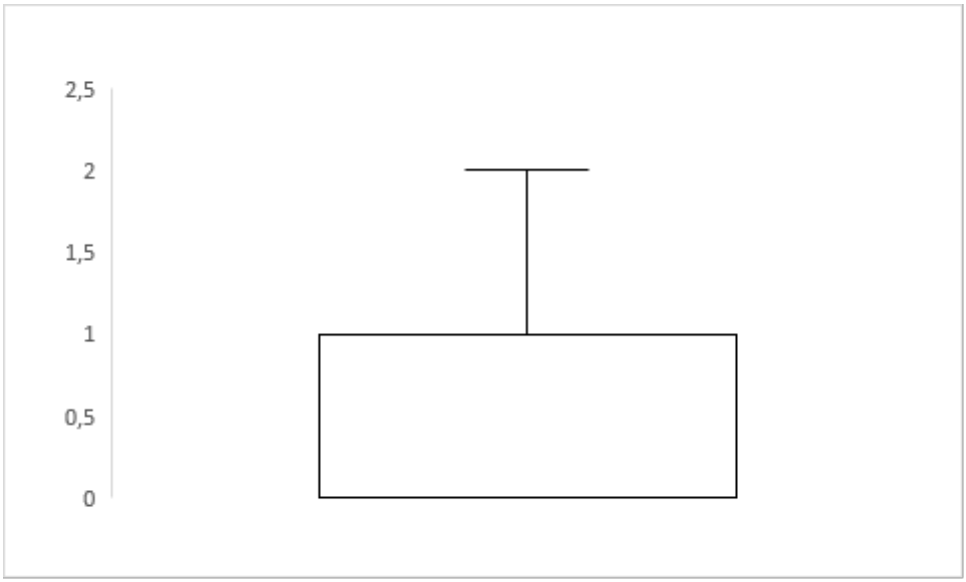


Figure 28: D dimer subsection – Box plot distribution of the scores.

42% of the physicians had a score of 0, 38% had a score in the 1 range and 20% had a score in the 2 range (Figure 29).

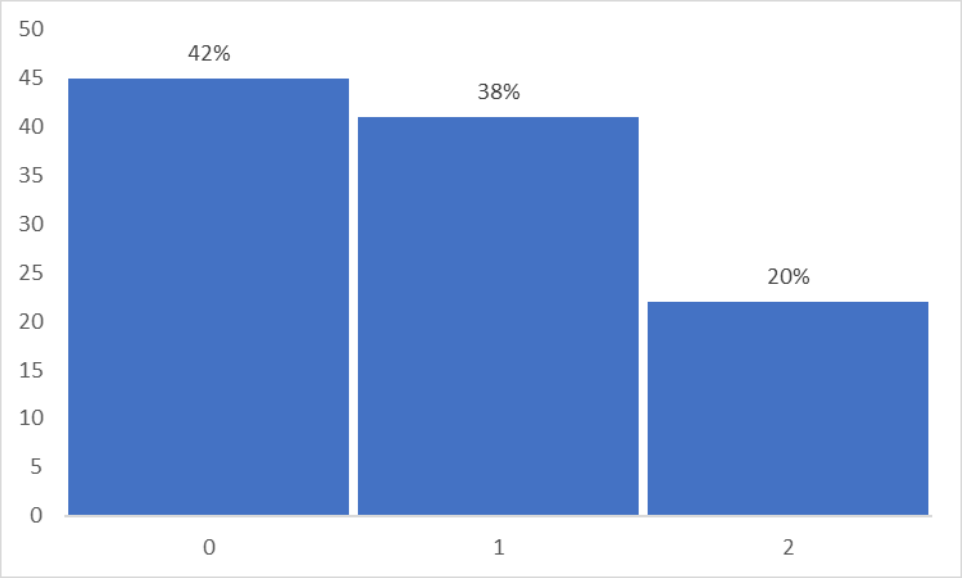


Figure 29: D dimer subsection – Bar graphical representation of the scores.

2.4. BNP, NT pro-BNP:

The scores of physicians in this section ranged from 0 to 4 with an average of 0.81, a standard deviation of 1.112 and a median of 0 (Table 5, Figure 30).

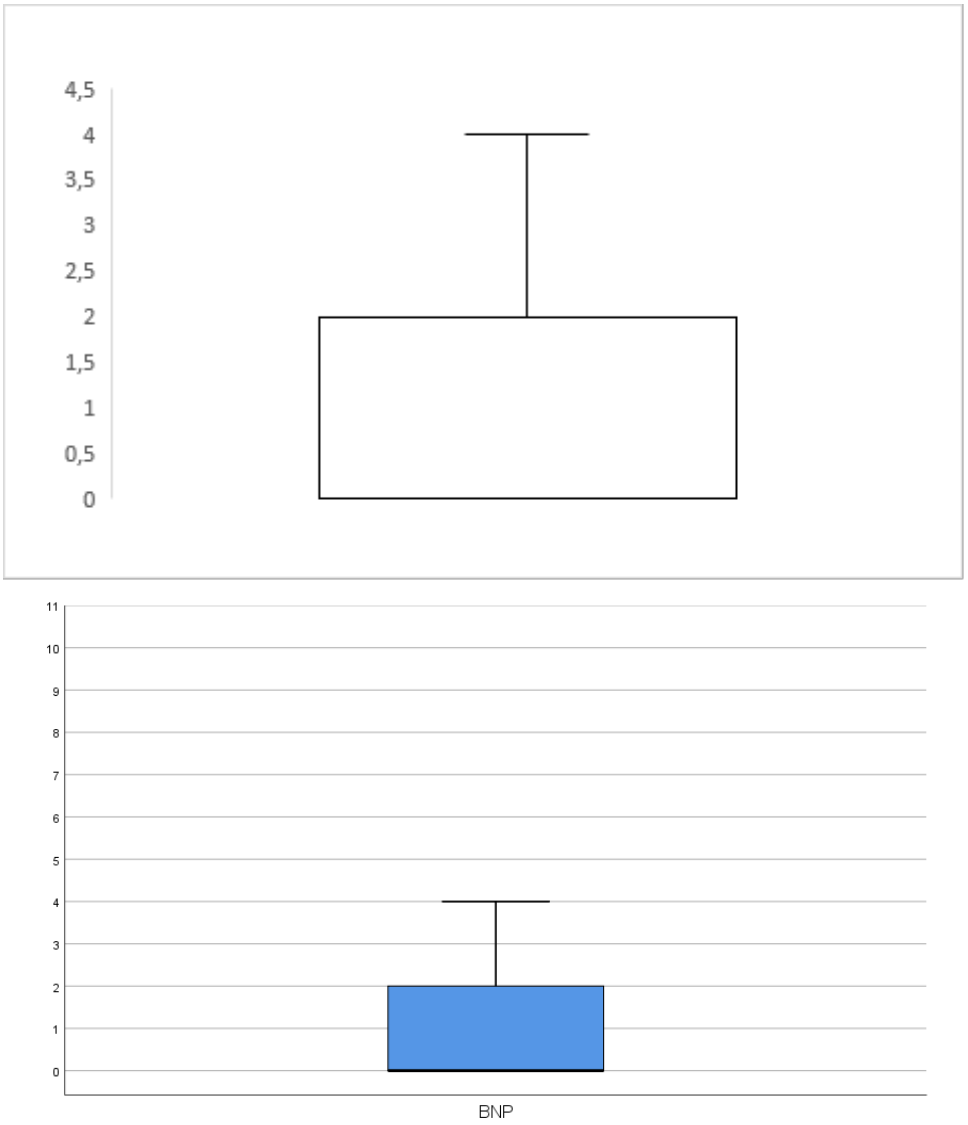


Figure 30: BNP/NT pro-BNP subsection - Box plot representation of the scores.

Table IV: BNP/NT pro-BNP score analysis.

Number	Average	Median	Standard deviation	Minimum	Maximum
108	0,81	0	1,112	0	4

More than half the physicians (59%) had a score of 0, 10% had a score in the 1 range, 23% had a score in the 2 range and 8% had a score above 3 (Figure 31).

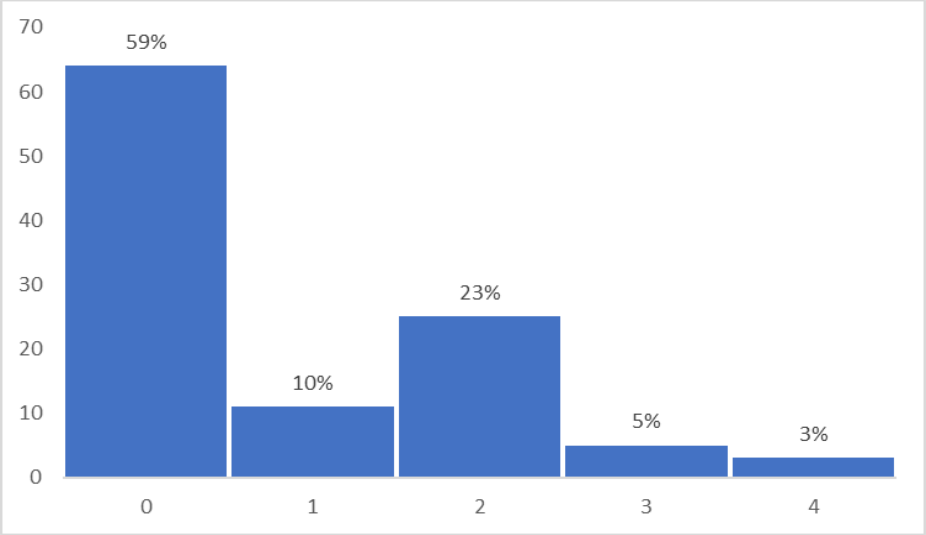


Figure 31: BNP/NT pro-BNP subsection – Bar graphical representation of the scores.

2.5. Procalcitonin:

The physicians' scores in this section ranged from 0 to 4 with an average of 0.58, a standard deviation of 1.024 and a median of 0 (Table 6, Figure 32).

Table V: PCT score analysis.

Number	Average	Median	Standard deviation	Minimum	Maximum
108	0,58	0	1,024	0	4

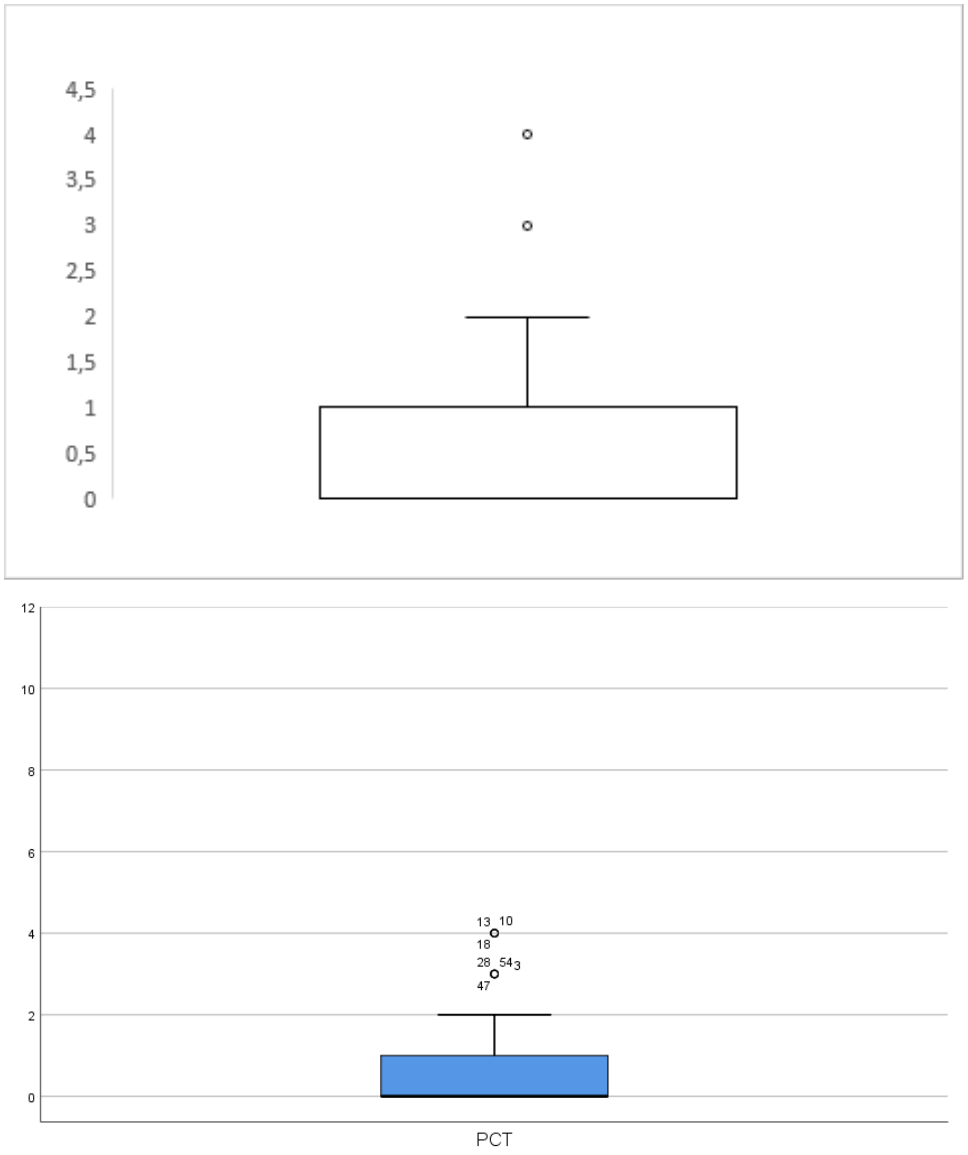


Figure 32: PCT subsection – Box plot representation of the scores.

67% of the physicians had a score of 0, 19% had a score in the 1 range, 6% had a score in the 2 range and 8% had a score above 3 (Figure 33).

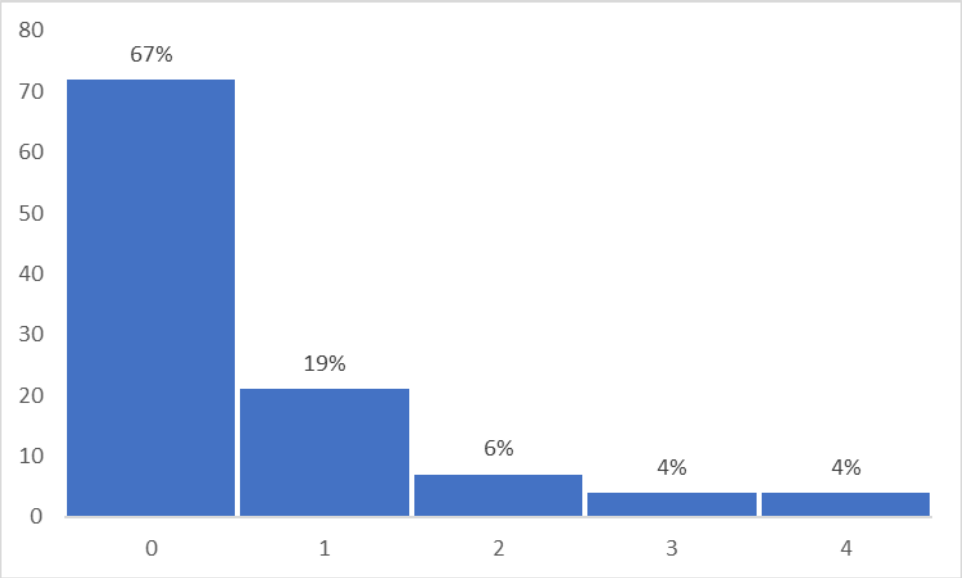


Figure 33: PCT subsection – Bar graphical representation of the scores.

2.6. CRP:

Physicians in this section had scores between 0 and 4 with an average of 0.56, a standard deviation of 0.878 and a median of 0 (Table 7, Figure 34).

Table VI: CRP score analysis.

Number	Average	Median	Standard deviation	Minimum	Maximum
108	0,56	0	0,878	0	4

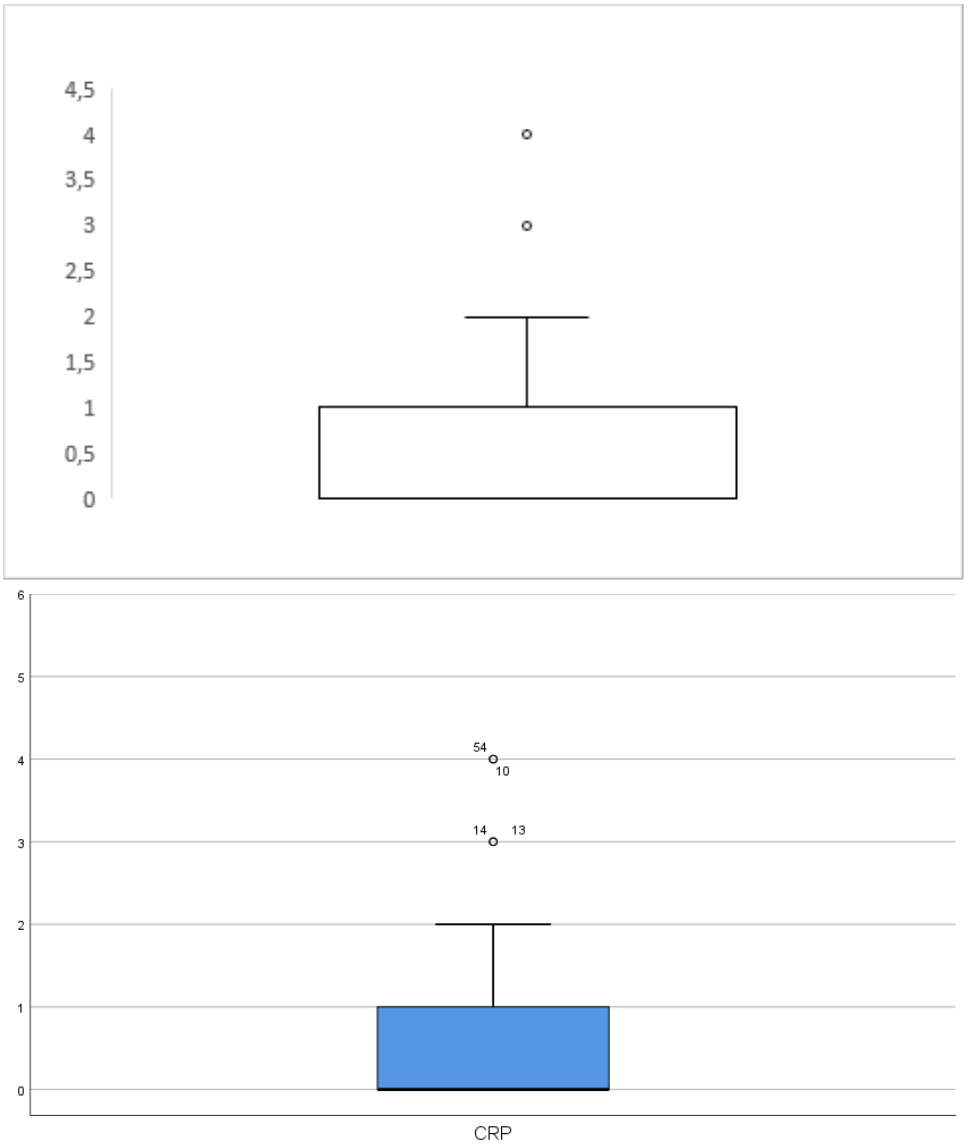


Figure 34: CRP subsection – Box plot representation of the scores.

62% of the physicians had a score of 0, 25% had a score in the 1 range, 9% had a score in the 2 range and 4 % scored above 3 (Figure 35).

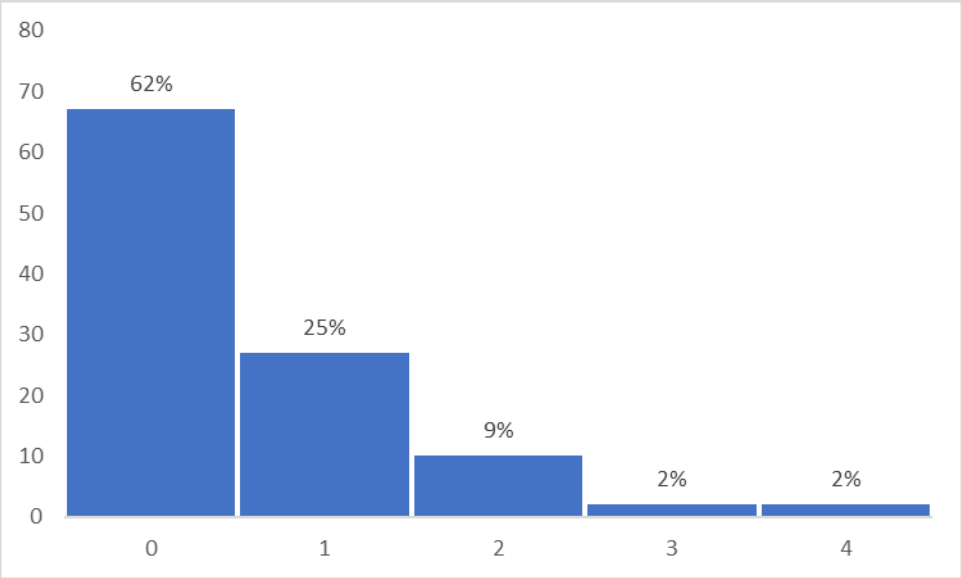


Figure 35: CRP subsection – Bar graphical representation of the scores.

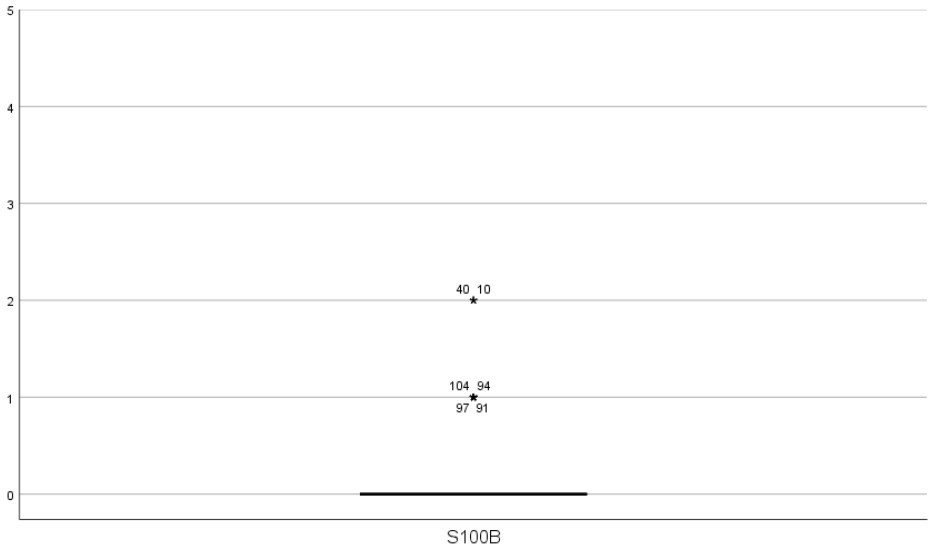
2.7. S100B:

Physicians in this section had scores ranging between 0 and 2 with an average of 0.19, a standard deviation of 0.456 and a median of 0 (Table 8).

Table VII: S100B score analysis.

S100B	Number	Average	Median	Standard deviation	Minimum	Maximum
	108	0,19	0	0,456	0	2

84% of the physicians had a score of 0, 13% had a score in the 1 range and 3% had a score in the 2 range (Figure 36).



S100B subsection – Box plot representation of the scores.

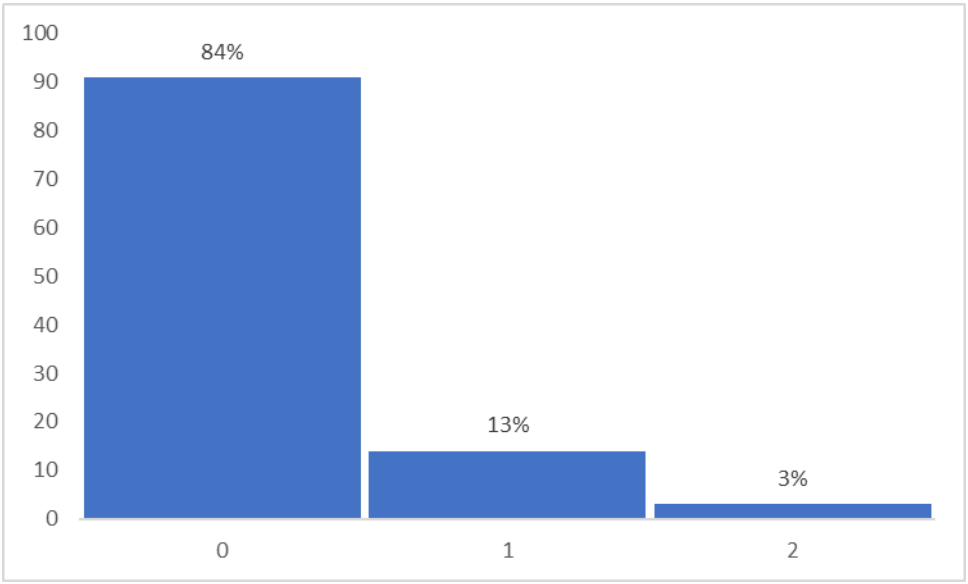


Figure 36: S100B subsection – Bar graphical representation of the scores.

IV. Statistical analysis

1. Effect of gender on the scores:

From the available information in the table and box plot below, we can observe that the scores were in the 10.73 range for and were less dispersed for females, while the scores were in the 11.55 range and were more dispersed in males (Table 9, Figure 37).

Table VIII: Statistical analysis of overall scores by gender.

	Gender	Number	Average	Standard deviation
Scores	F	66	10,73	6,446
	M	42	11,55	7,002

Figure 37: Box plot distribution of scores by gender.

The Shapiro Wilk normality test reveals that we cannot reject the hypothesis of normality of the scores in the two samples of men and women (P(F)=0.06>0.05 and P(M)=0.173>0.05), so we apply the Student's test to see if the difference found between the scores of men and women is significant.

Student's test for comparison of means:

We seek to test the following hypotheses:

- H0: The average score of men is equal to the average score of women.
- H1: The average score of men is different from the average score of women.

Table IX: Independent sample T-test analysis of means by gender.

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
score	Equal variances assumed	F 0,728	Sig. **0,396**	t -0,623	df 106	Sig. (2-tailed) **0,534**	Mean Difference -0,82	Std. Error Difference 1,316	Lower -3,429	Upper 1,789
	Equal Variance not Assumed			-0,612	82,088	0,542	-0,82	1,341	-3,487	1,846

Laveen's test reveals that we cannot reject the null hypothesis that the variances of the score variable are equal between men and women (P-value=0.396 > 0.05), so we can apply Welch's uncorrected Student's test (1st line) to test the equality of the score averages between men and women (Table 10).

The Student's test is not significant (p=0.534>0.05), so we fail to reject the null hypothesis (H0) of equal score averages between men and women (Table 10).

We then conclude that the scores do not differ significantly between men and women.

2. Effect of age on scores:

Physicians under 27 years of age have a mean score of 10.30 and a standard deviation of 0.983, whereas those over 27 years of age have a mean of 11.85 and a standard deviation of

0.826. Scores are more dispersed among those under 27 compared to those above 27 (Table 11, Figure 38) .

Table X: Statistical analysis of scores by age.

	Age group	Number	Average	Standard deviation
Scores	≥ 27	52	11.85	0.826
	< 27	56	10.30	0.983

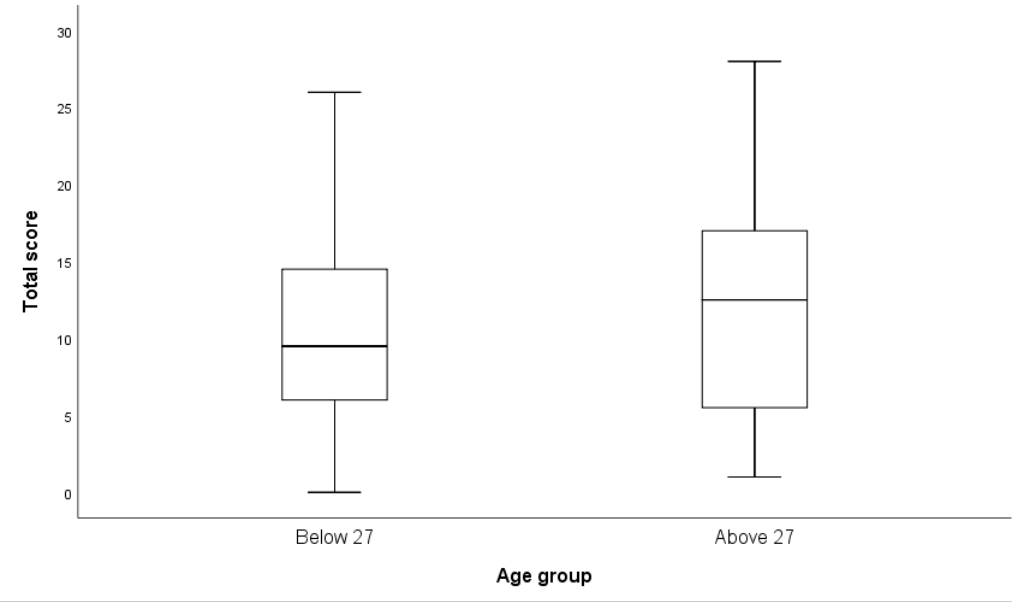


Figure 38: Box plot distribution of the scores by age group.

The Shapiro Wilk normality test reveals that we cannot reject the hypothesis of normality of the scores in the two samples of older than 27 and younger than 27 (P(≥27)=0.075>0.05 and P(<27)=0.098>0.05), so we apply the Student's test to see if the difference found between the scores of physicians younger than 27 and older than 27 is significant.

Student's test for comparison of means:

We seek to test the following hypotheses:

- H0: The average score of physicians younger than 27 years of age is equal to the average score of physicians older than 27 years of age.

- H1: The average score of physicians younger than 27 years of age is different from the average score of physicians older than 27 years of age.

Table XI: Independent sample T-test analysis of means by age.

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Score	Equal variances assumed	2,868	**0,093**	1,207	106	**0,230**	1,543	1,278	-,990	4,075
	Equal variances not assumed			1,201	101,519	0,232	1,543	1,284	-1,004	4,090

Laveen's test reveals that we cannot reject the null hypothesis that the variances of the score variable are equal between the two age groups (P-value=0.093 > 0.05), so we can apply Welch's uncorrected Student's test (1st line) to test the equality of the score averages between the two age groups (Table 12).

The Student's test is not significant (p=0.230>0.05), so we fail to reject the null hypothesis (H0) of equal score averages between the two age groups. (Table 12).

We then conclude that age does not significantly impact the physicians' scores.

3. Effect of personal estimation of knowledge:

Subjects who consider their knowledge to be sufficient have an average score of about 13.33. Those who consider their knowledge to be insufficient have an average of 10.84 (Table13, Figure 39).

Table XII: Statistical analysis of scores by personal estimation of knowledge.

	Estimation of knowledge	N	Mean	Std. Deviation
Total score	Insufficient	99	10,84	6,573
	Sufficient	9	13,33	7,450

Figure 39: Box plot distribution of the scores by personal estimation of knowledge.

The Shapiro Wilk normality test reveals that the normality of the scores in both samples of sufficient and insufficient knowledge is rejected (P(Sufficient)=0.038<0.05 and P(Insufficient)=0.013<0.05). Therefore, the appropriate test to explore if the difference between the two groups is significant is the Mann-Whitney U test.

Mann-Whitney U test for comparison of means:

We seek to test the following hypotheses:

- H0: The average score of physicians who judge their knowledge sufficient is equal to the average score of physicians who judge their knowledge insufficient.
- H1: The average score of physicians who judge their knowledge sufficient is different from the average score of physicians who judge their knowledge insufficient.

Table XIII: Independent sample Mann-Whitney U test analysis of means by personal estimation of knowledge.

	Total score
Mann-Whitney U	369,000
Wilcoxon W	5319,000
Z	-,851
Asymp. Sig. (2-tailed)	0,395

The Mann-Whitney test is not significant (p=0.395), so we cannot reject the null hypothesis (H0) of equal average scores between the two groups (Table 14).

It is then concluded that the perception of personal knowledge does not significantly influence the scores, those who perceive their personal knowledge as sufficient get the same average scores as those who do not.

4. Effect of status intern-resident:

From the available information in the table and box plot below, we can observe that the scores were in the 10.14 range for intern physicians and were more dispersed, while the scores were in the 11.50 range and were less dispersed in resident physicians (Table 15, Figure 40).

Table XIV: Statistical analysis of scores by status.

	Gender	Number	Average	Standard deviation
Scores	Intern physician	36	10,14	1,060
	Resident physician	72	11,50	0,800

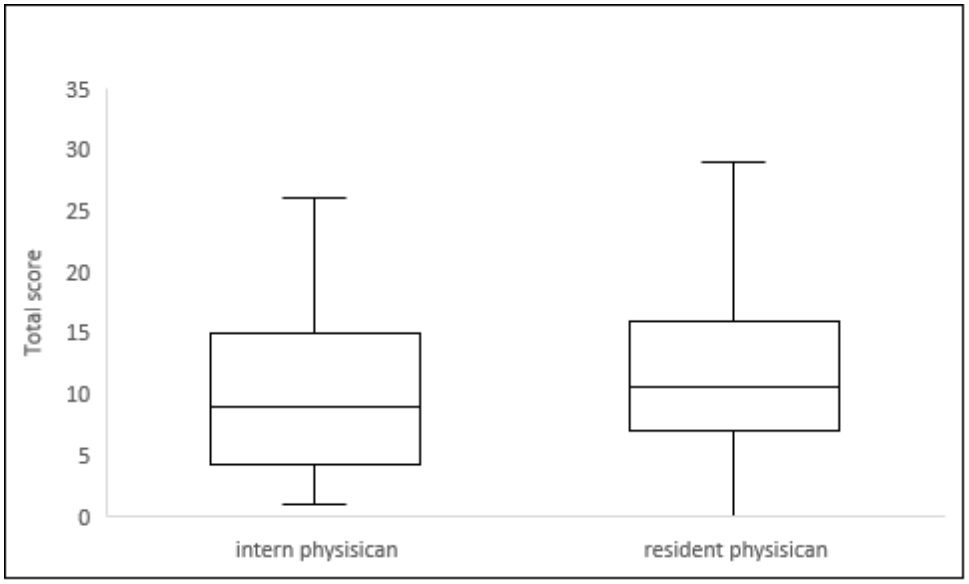


Figure 40: Box plot distribution of the scores by status.

The Shapiro Wilk normality test reveals that we cannot reject the hypothesis of normality of the scores in the two samples of interns and residents (P(interns)=0.188>0.05 and P(residents)=0.066>0.05), so we apply the Student's test to see if the difference found between the scores of residents and interns is significant.

Student's test for comparison of means:

We seek to test the following hypotheses:

- H0: The average score of interns is equal to the average score of residents.
- H1: The average score of interns is different from the average score of residents.

Table XV: Independent sample T-test analysis of means by status.

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Total score	Equal variances assumed	,062	0,803	-1,003	106	0,318	-1,361	1,357	-4,051	1,329
	Equal variances not assumed			-1,025	74,287	0,309	-1,361	1,328	-4,007	1,285

Laveen's test reveals that we cannot reject the null hypothesis that the variances of the score variable are equal between interns and residents (P-value=0.803 > 0.05), so we can apply Welch's uncorrected Student's test (1st line) to test the equality of the score averages between interns and residents (Table 16).

The Student's test is not significant (p=0.318>0.05), so we fail to reject the null hypothesis (H0) of equal score averages between interns and residents (Table 16).

We then conclude that the scores do not differ significantly between intern physicians and resident physicians.

5. Effect of years of training on scores for interns:

1st year interns have an average score of 10.61 and a standard deviation of 7.101, whereas 2nd year interns have a mean score of 9.31 and a standard deviation of 4.939. Scores are more dispersed among 1st year interns compared to 2nd year interns (Table 17, Figure 41).

Table XVI: : Statistical analysis of scores by years of training for interns.

	Years	Number	Average	Standard deviation
Scores	1st year	23	10.61	7.101
	2nd year	13	9.31	4.939

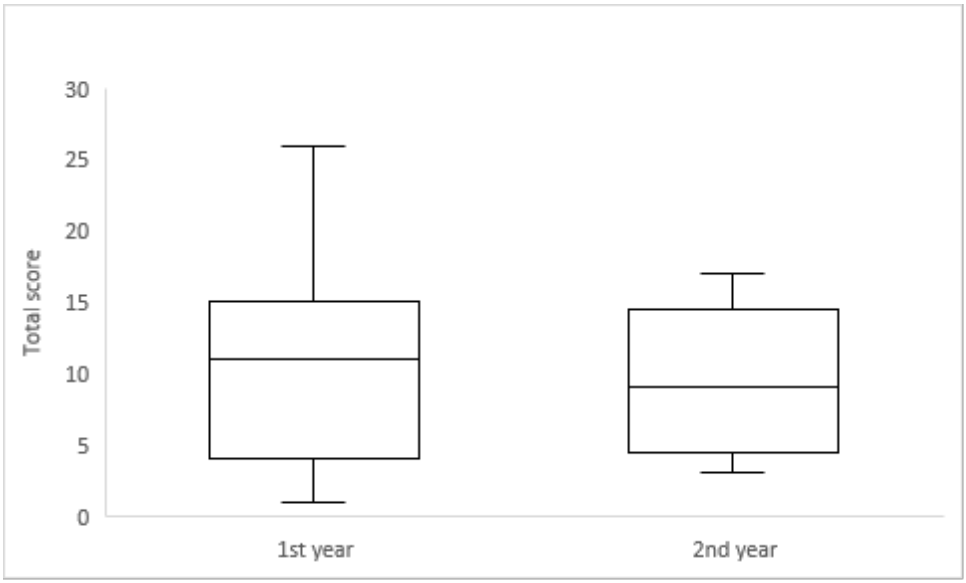


Figure 41: Box plot distribution of the scores for interns by years of training.

The Shapiro Wilk normality test reveals that we cannot reject the hypothesis of normality of the scores in the two samples 1st year interns and 2nd year interns (P(1st year)=0.368>0.05 and P(2nd year)=0.206>0.05), so we apply the Student's test to see if the difference found between the scores of 1st year interns and 2nd year interns is significant.

Student's test for comparison of means:

We seek to test the following hypotheses:

- H0: The average score of 1st year interns is equal to the average score of 2nd year interns.
- H1: The average score of 1st year interns is different than the average score of 2nd year interns.

Table XVII: Independent sample T-test analysis of means by years of training for interns.

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Total score	Equal variances assumed	2,792	**0,104**	0,584	34	**0,563**	1,301	2,228	-3,228	5,830
	Equal variances not assumed			0,645	32,341	0,524	1,301	2,017	-2,806	5,408

Lavene's test reveals that we cannot reject the null hypothesis that the variances of the score variable are equal between 1st and 2nd year interns (P-value=0.104>0.05), so we can apply Welch's uncorrected Student's test (1st line) to test the equality of the score averages between 1st and 2nd year interns (Table 18).

The Student's test is not significant (p=0.563>0.05), so we fail to reject the null hypothesis (H0) of equal score averages between 1st and 2nd year interns (Table 18).

We then conclude that the scores do not differ significantly between 1st year interns and 2nd year interns.

6. Effect of years of training on the scores of residents:

1st year residents have an average score of 11.63 and a standard deviation of 5.786, whereas 2nd year residents have a mean score of 12.48 and a standard deviation of 6.536, 3rd year residents have an average score of 8.82 and a standard deviation of 6.600, 4th year

residents have a mean score of 4.80 and a standard deviation of 5.263 and 5th year residents have a mean score of 23.67 and a standard deviation of 4.509. (Table 19, Figure 42).

Table XVIII: Statistical analysis of scores by years of training for residents.

Residents years of training			Statistic
Total score	1st year	Mean	**11,63**
		Std. Deviation	5,786
	2nd year	Mean	**12,48**
		Std. Deviation	6,536
	3rd year	Mean	**8,82**
		Std. Deviation	6,600
	4th year	Mean	**4,80**
		Std. Deviation	5,263
	5th year	Mean	**23,67**
		Std. Deviation	4,509

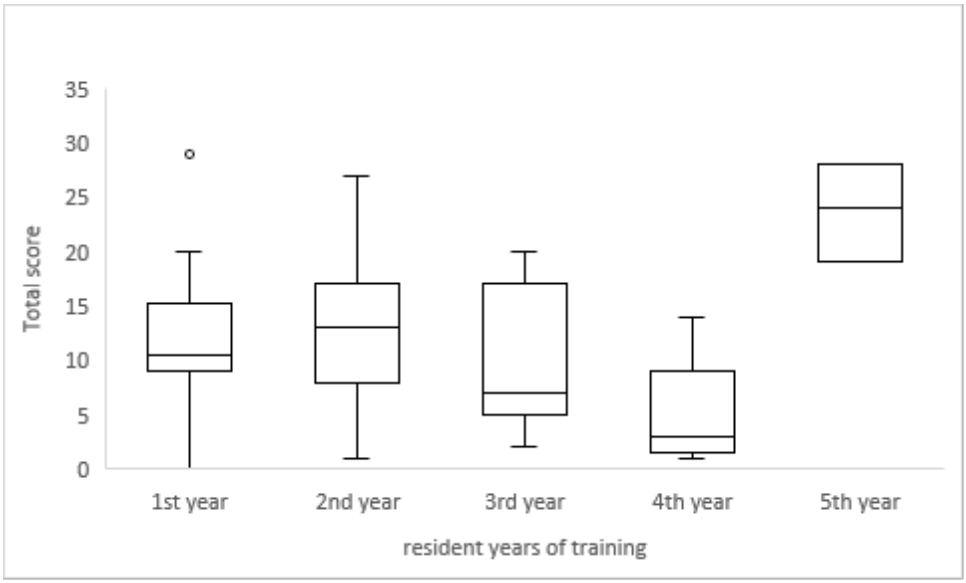


Figure 42: Box plot distribution of the scores for residents by years of training.

The Shapiro Wilk normality test reveals that we cannot reject the hypothesis of normality of the scores in the three samples of 1st,2nd and 5th year residents(P(1st year)=0.265>0.05, P(2nd year)=0.902>0.05, P(5th year)=0.878>0.05). However, it reveals that we can reject the hypothesis of normality of distribution of the scores in the two sample of 3rd and 4th year

residents (P(3rd year)=0.013<0.05, P(4th year)=0.031<0.05). Therefore, the appropriate test to explore if the difference between the five groups is significant is the Kruskal-Wallis test.

Table XIX: : Independent sample Kruskal-Wallis H test analysis of means by years of training for residents.

	Total score
Kruskal-Wallis H	0,164
df	1
Asymp. Sig.	0,686

The Kruskal-Wallis test is not significant (p=0.686), so we cannot reject the null hypothesis (H0) of equal score averages between the five groups (Table 20).

We then conclude than the number of years of training does not significantly impact resident physicians' scores.

7. Effect of frequency of use on the scores:

7.1. Troponin subsection, effect of frequency of use on the scores:

The Troponin subsection scores increase with frequency of use, from 0.29 within practitioners who never use it, to 0.43 within those who rarely use it, to 1.10 within those who sometimes use it, to 3.75 within those who often use it, and to 6.88 within those who always use it (Table 21, Figure 43).

Table XX: Statistical analysis of Troponin scores by frequency of use.

Frequency of use	7	Never	Mean	0,29
			Std. Deviation	0,488
	7	Rarely	Mean	0,43
			Std. Deviation	0,787
	42	Sometimes	Mean	1,10
			Std. Deviation	1,122
	36	Often	Mean	3,75
			Std. Deviation	1,052
	16	Always	Mean	6,88
			Std. Deviation	2,094

Figure 43: Troponin subsection – Box plot distribution of the scores by the frequency of use.

Correlation can be used to assess the degree of relationship between the ordinal variable of frequency of prescription of troponin tests (Never=1, Rarely=2, Sometimes= 3, Often=4, Always=5) and Troponin subsection scores.

Table XXI: Troponin subsection – Correlation study between the scores and the frequency of use.

Frequency of use	**Pearson Correlation**	**0,794**
	Sig. (2-tailed)	**<0,001**
	N	108

The correlation between Troponin subsection scores and frequency of its use was significant ($p<0.05$) with a high intensity ($r=0.794$) (Table 22).

It is concluded that there is a strong positive correlation between the frequency of use of troponin and the troponin subsection scores, those who use it frequently tend to have better scores.

7.2. D dimer subsection, effect of frequency of use on the scores:

The D dimer subsection scores increase with frequency of use, from 0.14 within practitioners who never use it, to 0.25 within those who rarely use it, to 0.63 within those who sometimes use it, to 1.20 within those who often use it, and to 1.55 within those who always use it (Table 23, Figure 44).

Table XXII: Statistical analysis of D dimer scores by frequency of use.

Frequency of use	**14**	**Never**	**Mean**	**0,14**
			Std. Deviation	0,363
	20	Rarely	Mean	**0,25**
			Std. Deviation	0,444
	32	Sometimes	Mean	**0,63**
			Std. Deviation	0,554
	20	Often	Mean	**1,20**
			Std. Deviation	0,616
	22	Always	Mean	**1.55**
			Std. Deviation	0,800

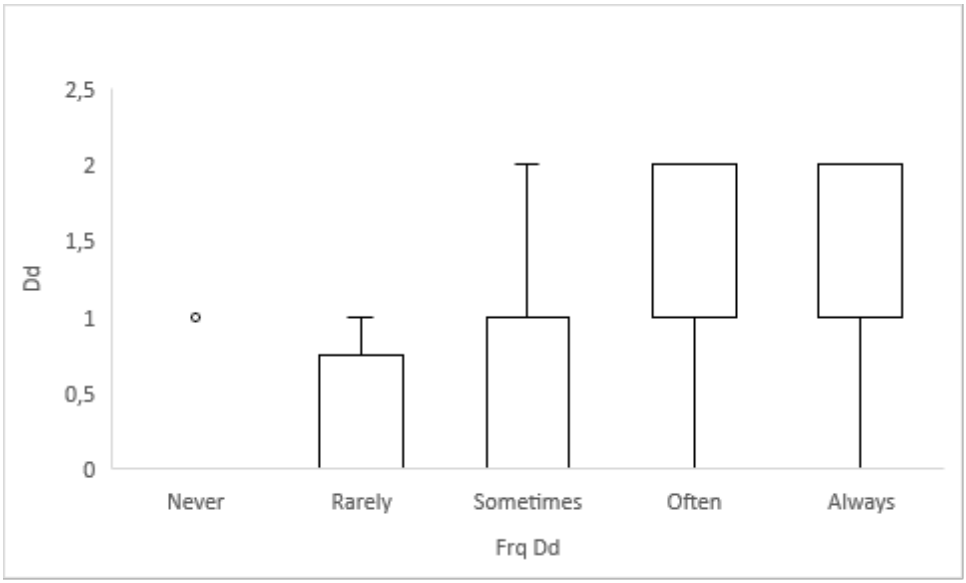


Figure 44: D dimer subsection – Box plot distribution of the scores by the frequency of use.

Correlation can be used to assess the degree of relationship between the ordinal variable of frequency of prescription of D dimer tests (Never=1, Rarely=2, Sometimes= 3, Often=4, Always=5) and D dimer subsection scores.

Table XXIII: D dimer subsection - Correlation study between the scores and the frequency of use.

Frequency of use	Pearson Correlation	0,653
	Sig. (2-tailed)	<0,001
	N	108

The correlation between D dimer subsection scores and frequency of its use was significant ($p<0.05$) with a high intensity ($r=0.653$) (Table 24).

It is concluded that there is a strong positive correlation between the frequency of use of D dimer and the D dimer subsection scores, those who use it frequently tend to have better scores.

7.3. BNP/NT pro-BNP subsection, effect of frequency of use on the scores:

The BNP/NT pro-BNP subsection scores are 0.29 within practitioners who never use it, 0.57 within those who rarely use it, 0.51 within those who sometimes use it, 1.64 within those who often use it, and 2.00 within those who always use it (Table 25, Figure 45).

Table XXIV: Statistical analysis of BNP/NT pro-BNP scores by frequency of use.

Frequency of use	28	Never	Mean	0,29
			Std. Deviation	0,460
	14	Rarely	Mean	0,57
			Std. Deviation	0,756
	37	Sometimes	Mean	0,51
			Std. Deviation	0,692
	14	Often	Mean	1,64
			Std. Deviation	0,497
	15	Always	Mean	2,00
			Std. Deviation	1,134

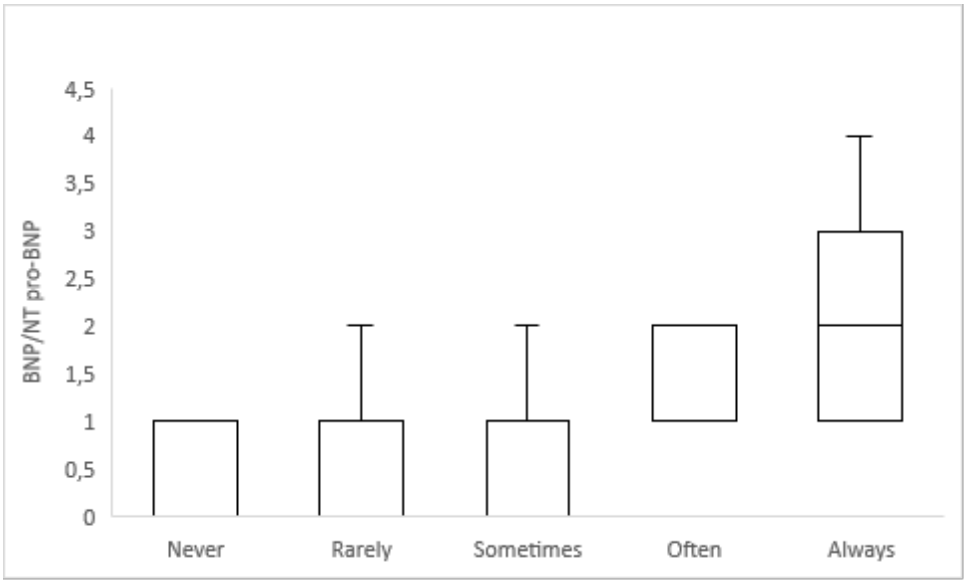


Figure 45: BNP/NT pro-BNP subsection - Box plot distribution of the scores by the frequency of use.

Correlation can be used to assess the degree of relationship between the ordinal variable of frequency of prescription of BNP/NT pro-BNP tests (Never=1, Rarely=2, Sometimes= 3, Often=4, Always=5) and BNP/NT pro-BNP subsection scores.

Table XXV: Troponin subsection - Correlation study between the scores and the frequency of use.

Frequency of use	**Pearson Correlation**	**0,593**
	Sig. (2-tailed)	**<0,001**
	N	108

The correlation between BNP/NT pro-BNP subsection scores and frequency of its use was significant ($p<0.05$) with a medium intensity ($r=0.593$) (Table 26).

It is concluded that there is a moderate positive correlation between the frequency of use of BNP/NT pro-BNP and the scores, those who use it frequently tend to have better scores.

7.4. Procalcitonin subsection, effect of frequency of use on the scores:

The PCT subsection scores increase with frequency of use, from 0.10 within practitioners who never use it, to 0.20 within those who rarely use it, to 0.54 within those who sometimes use it, to 1.30 within those who often use it, and to 3.38 within those who always use it (Table 27, Figure 46).

Table XXVI: Statistical analysis of PCT scores by frequency of use.

Frequency of use	**42**	**Never**	**Mean**	**0,10**
			Std. Deviation	0,297
	20	Rarely	Mean	**0,20**
			Std. Deviation	0,410
	28	Sometimes	Mean	**0,54**
			Std. Deviation	0.508,
	10	Often	Mean	**1,30**
			Std. Deviation	0,483
	8	Always	Mean	**3,38**
			Std. Deviation	0,744

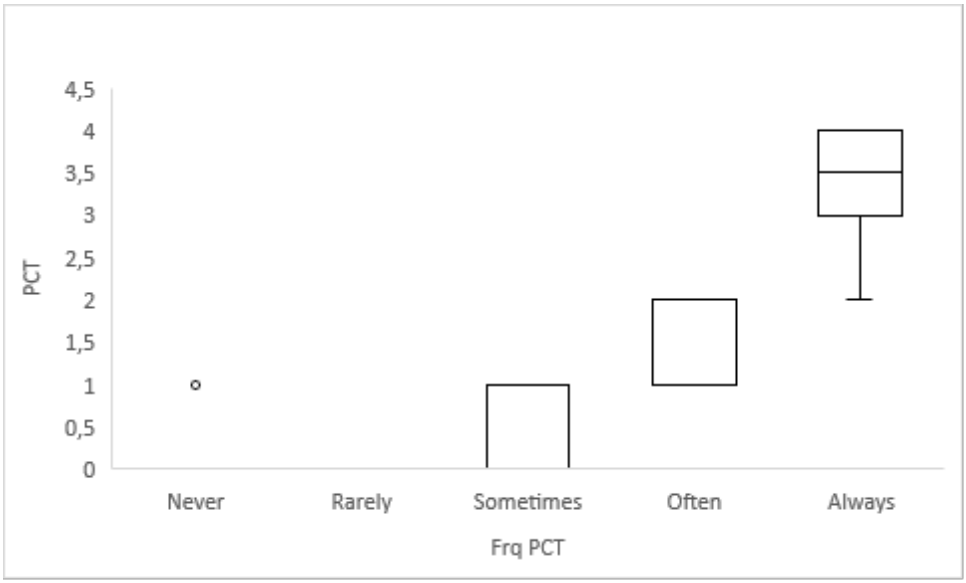


Figure 46: PCT subsection – Box plot distribution of the scores by the frequency of use.

Correlation can be used to assess the degree of relationship between the ordinal variable of frequency of prescription of PCT tests (Never=1, Rarely=2, Sometimes= 3, Often=4, Always=5) and PCT subsection scores.

Table XXVII: PCT subsection - Correlation study between the scores and the frequency of use.

Frequency of use	**Pearson Correlation**	**0,762**
	Sig. (2-tailed)	**<0,001**
	N	108

The correlation between PCT subsection scores and frequency of its use was significant ($p<0.05$) with a high intensity ($r=0.762$) (Table 28).

It is concluded that there is a strong positive correlation between the frequency of use of PCT and the PCT subsection scores, those who use it frequently tend to have better scores.

7.5. CRP subsection, effect of frequency of use on the scores.

The CRP subsection scores increase with frequency of use, from 0.20 within practitioners who never use it, to 0.29 within those who rarely use it, it drops to 0.37 within those who sometimes use it, it goes up to 0.58 within those who often use it, and to 0.85 within those who always use it (Table 29, Figure 47).

Table XXVIII: Statistical analysis of CRP scores by frequency of use.

Frequency of use	**5**	**Never**	**Mean**	**0,20**
			Std. Deviation	0,447
	7	Rarely	Mean	**0,29**
			Std. Deviation	0,488
	43	Sometimes	Mean	**0,37**
			Std. Deviation	0,578
	12	Often	Mean	**0,58**
			Std. Deviation	0,669
	41	Always	Mean	**0,85**
			Std. Deviation	1,131

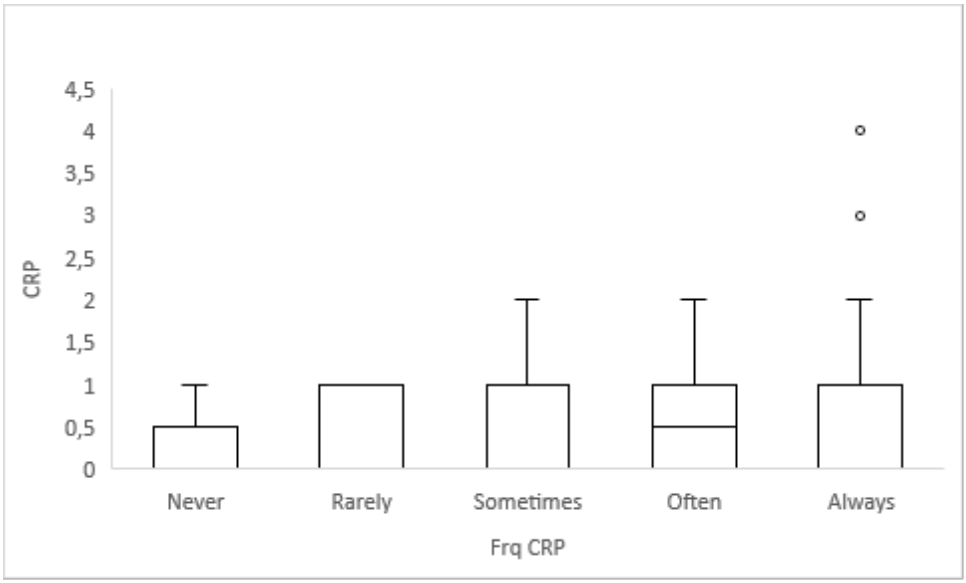


Figure 47: CRP subsection – Box plot distribution of the scores by the frequency of use.

Correlation can be used to assess the degree of relationship between the ordinal variable of frequency of prescription of CRP tests (Never=1, Rarely=2, Sometimes= 3, Often=4, Always=5) and CRP subsection scores.

Table XXIX: CRP subsection – Correlation study between the scores and the frequency of use.

Frequency of use	**Pearson Correlation**	**0,274**
	Sig. (2-tailed)	**0,004**
	N	108

The correlation between CRP subsection scores and frequency of its use was significant ($p<0.05$) with a weak intensity ($r=0.279$) (Table 30).

It is concluded that there is a weak positive correlation between the frequency of use of CRP and the scores, those who use it frequently tend to have better scores.

7.6. S100B subsection, effect of frequency of use on the scores:

The S100B subsection scores were 0.15 within practitioners who never use it, 0.00 within those who rarely use it, 0.75 within those who sometimes use it, 1.50 within those who often use it. (Table 31, Figure 48).

Table XXX: Statistical analysis of S100B scores by frequency of use.

Frequency of use	**94**	**Never**	**Mean**	**0,15**
			Std. Deviation	0,387
	8	Rarely	Mean	**0,00**
			Std. Deviation	0,000
	4	Sometimes	Mean	**0,75**
			Std. Deviation	0,957
	2	Often	Mean	**1,50**
			Std. Deviation	0,707
	0	Always	Mean	**#**
			Std. Deviation	#

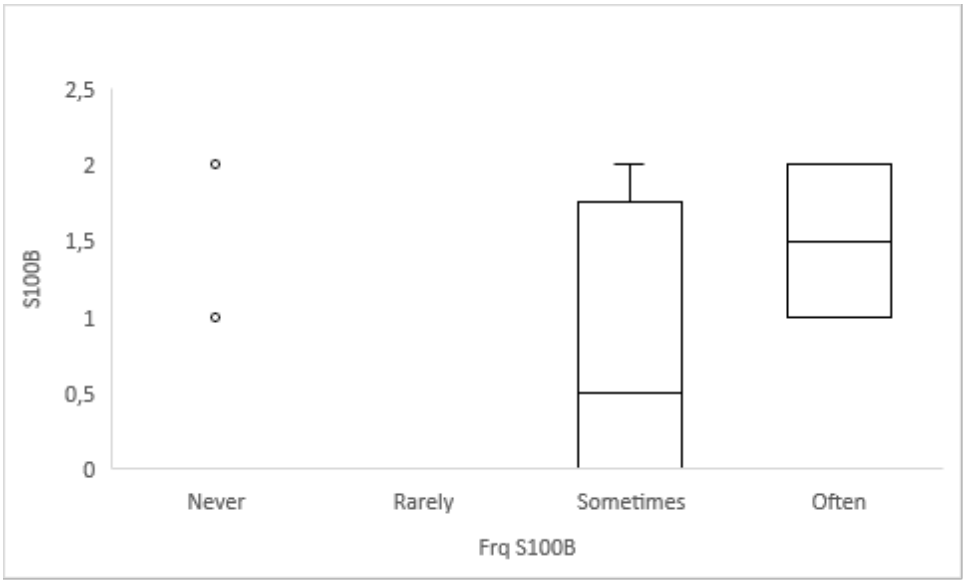


Figure 48: S100B subsection – Box plot distribution of the scores by the frequency of use.

Correlation can be used to assess the degree of relationship between the ordinal variable of frequency of prescription of S100B tests (Never=1, Rarely=2, Sometimes= 3, Often=4, Always=5) and S100B subsection scores.

Table XXXI: S100B subsection - Correlation study between the scores and the frequency of use.

Frequency of use	**Pearson Correlation**	**0,378**
	Sig. (2-tailed)	**<0,001**
	N	108

The correlation between Troponin subsection scores and frequency of its use was significant ($p<0.05$) with a low intensity ($r=0.378$) (Table 32).

It is concluded that there is a weak positive correlation between the frequency of use of S100B and the S100B subsection scores, those who use it frequently tend to have better scores.

V. Response analysis by question:

1. State of knowledge on biostatistics:

1.1. In your opinion, a biomarker can have an application in:

When asked about the applications of biomarkers, 85.19% of the practitioners said it can be used in diagnosis, 73.15% said it can be used in monitoring, 60.19% said it can be used in prognosis, 49.07% said it can be used to predict the response to a therapy, 44.44% said it can be used in risk stratification and 10.19% could not give an answer (Figure 49).

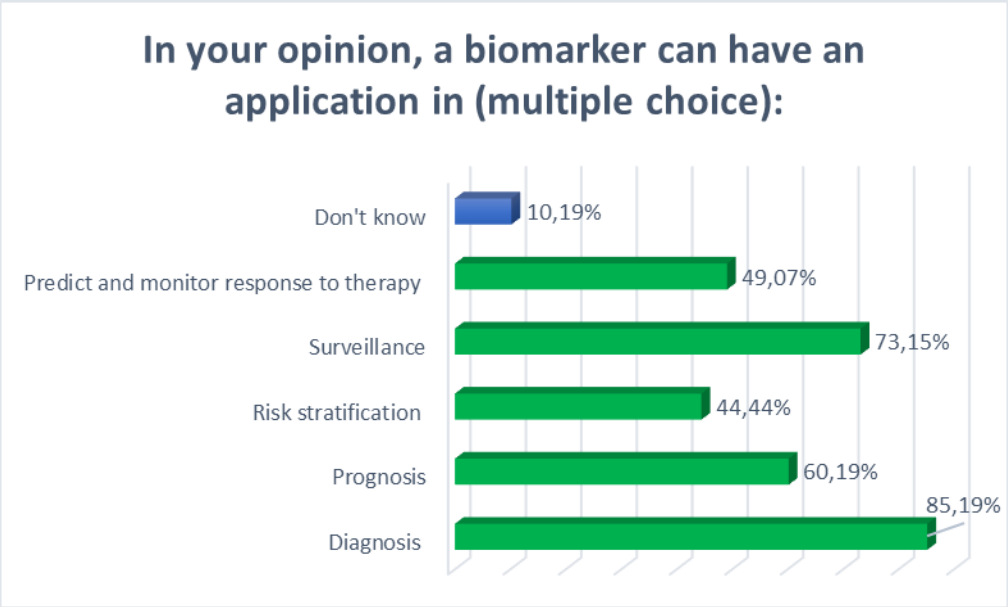


Figure 49: Question 24.

1.2. Biomarker sensitivity refers to:

More than half of the physicians (58 practitioners, 53.70%) did not know what biomarker sensitivity refers to, 19 practitioners confuse sensitivity with predictive values, accounting for 17.6% and 12 practitioners (11.1%) confuse sensitivity with specificity. 17.6% of the practitioners (19 practitioners answered the question right (Figure 50).

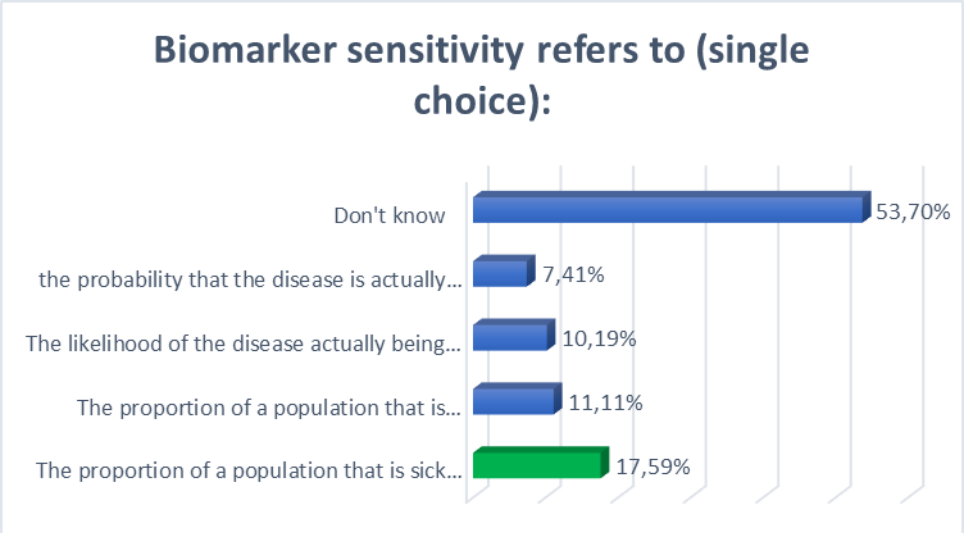


Figure 50: Question 26.

1.3. Biomarker specificity refers to:

More than half of the physicians (58 physician, 53.7%) did not know what specificity refers to, 20 practitioners confuse specificity with predictive values, accounting for 18.52%, and 10 practitioners (9.26%) confuse specificity with sensitivity. 18.5% of the practitioners (20 practitioners) answered the question right (Figure 51).

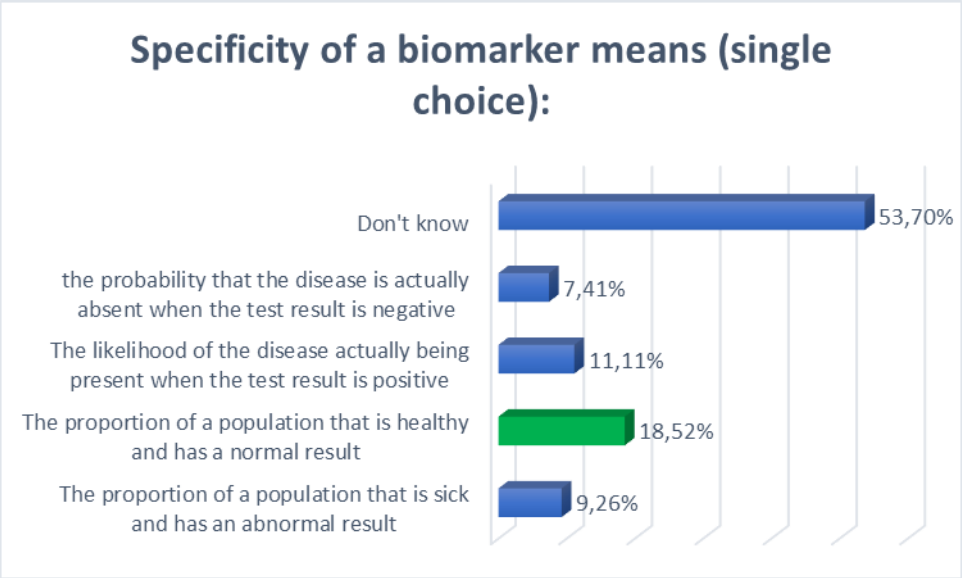


Figure 51: Question 27.

1.4. Positive predictive value of a biomarker means:

Almost half of the practitioners (51 practitioners, 47.22%) did not know what PPV of a biomarker refers to, 14 practitioners confused it with specificity and specificity, accounting for 12.96% and 1 practitioner (0.93%) confused it with NPV. 42 practitioners (38.9%) answered the question right (Figure 52).

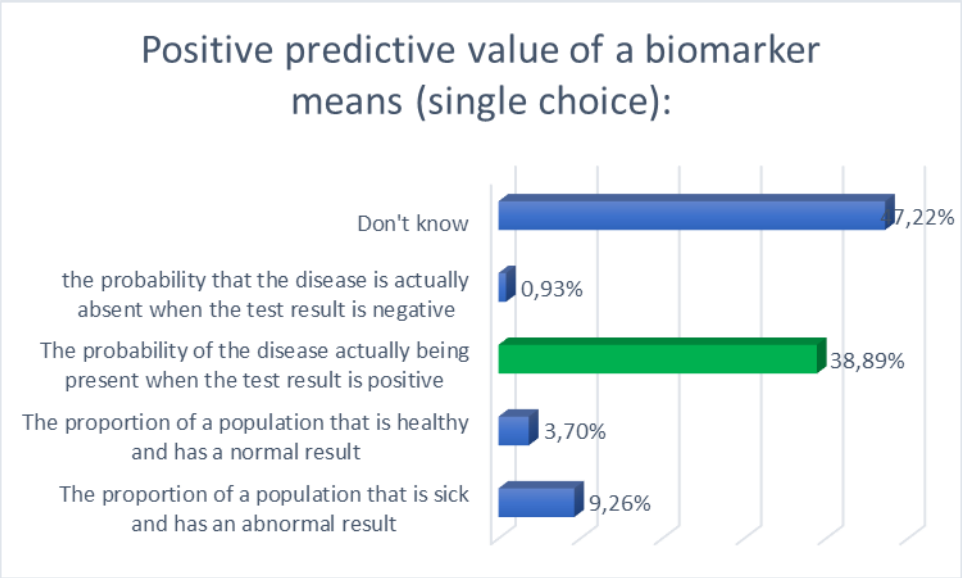


Figure 52: Question 28.

1.5. Negative predictive value of a biomarker means:

Almost half of the practitioners (49 practitioners, 45.4%) did not know what NPV means, 15 practitioners (13.89%) confuse NPV with specificity and sensitivity and 3 practitioners confuse it with PPV, making up 2.8%. 41 practitioners answered the question right, accounting for 37.96% (Figure 53).

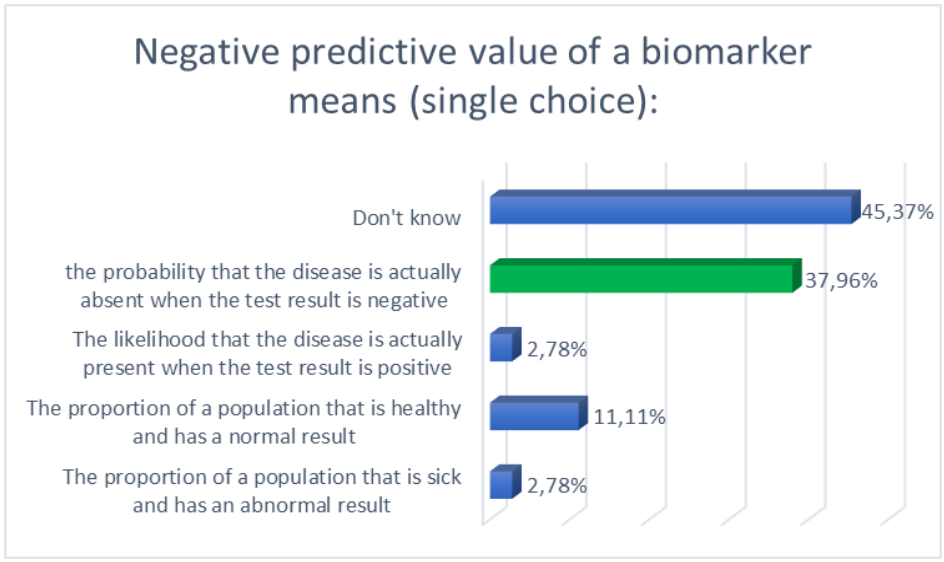


Figure 53: Question 29.

1.6. The NPV and PPV both depend on the prevalence of the disease and the intrinsic characteristics of the biomarker:

More than half of the practitioners (60 practitioners, 55.6%) did not know if NPV and PPV depended on the prevalence of the disease and the intrinsic characteristics of the biomarker, 4 practitioners said it did not accounting for 3.7% and 44 practitioners answered the question right accounting for 40.74% (Figure 54).

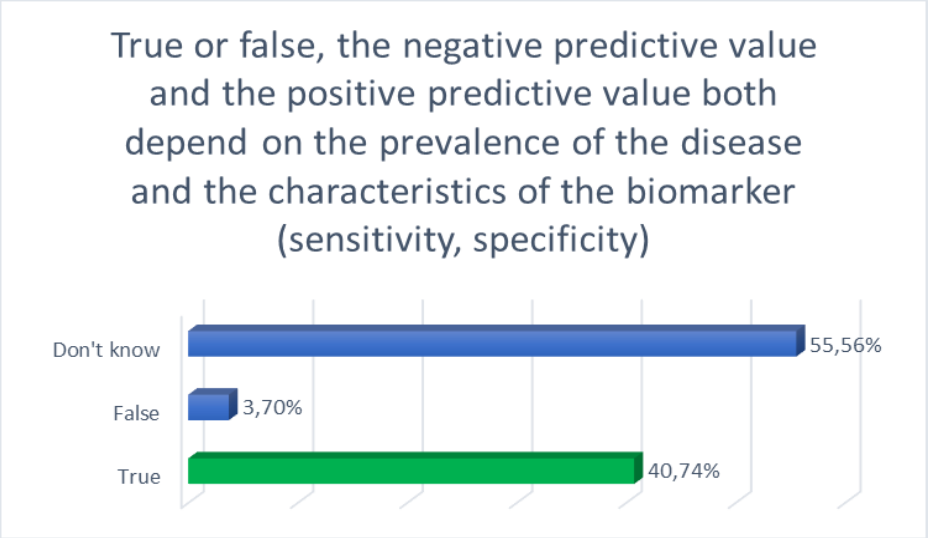


Figure 54: Question 30.

1.7. The Sn and Sp of a biomarker depend on the prevalence of the disease in the population:

More than half the practitioners (71 practitioners, 65.74%) did not know if Sn and Sp depended on the prevalence of the disease in the population. 18 practitioners said it did, making 16.67% and 19 practitioners answered the question right, accounting for 17.59% (Figure 55).

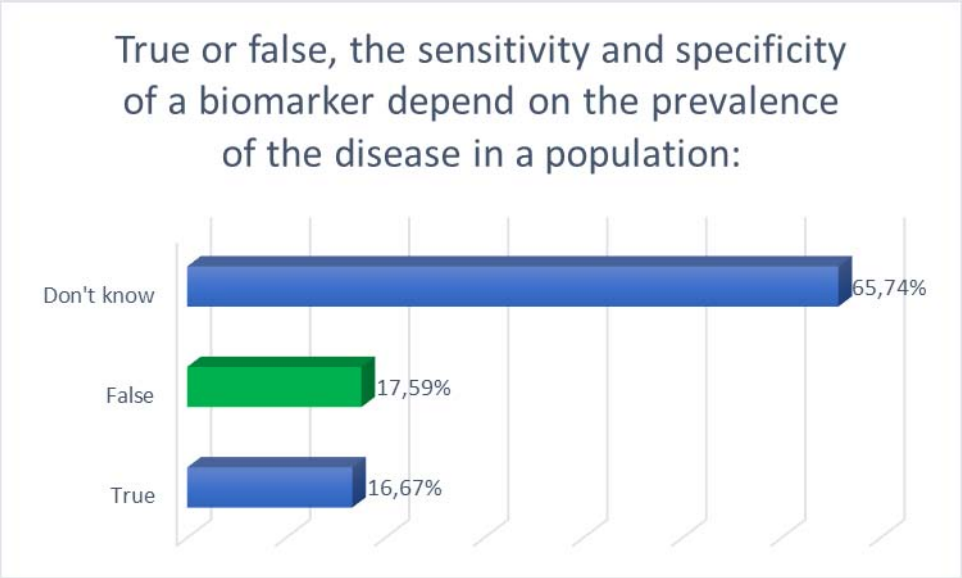


Figure 55: Question 31.

1.8. A biomarker that has a high sensitivity:

25 practitioners (23.15%) think that a biomarker that has a high sensitivity confirms the diagnosis when the result is positive, 18 practitioners (16.67%) think it will be more often positive in people with the disease than negative in people without the disease and more than half the practitioners (65 practitioners, 60.19%) answered the question right (Figure 56).

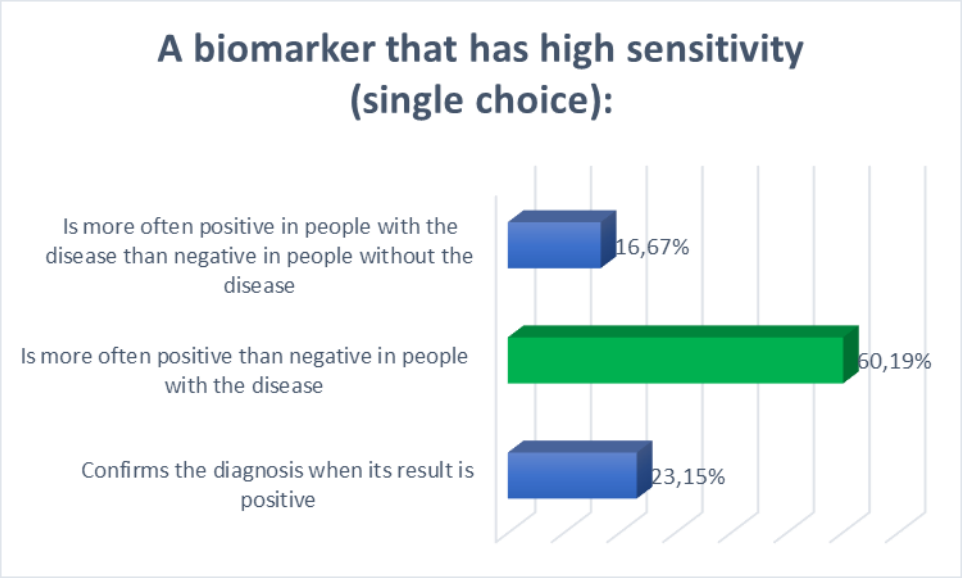


Figure 56: Question 32.

1.9. You request a test (biomarker) because you think your patient has a disease. The statistic that describes the proportion of a population with a positive result that is indeed sick is:

More than half the practitioners (66 practitioners, 61.11%), did not know the name of the statistic that describes the proportion of the population that has a positive test result and is indeed sick, 17 practitioners (15.74%) confuse it with Sn or Sp, 4 practitioners (3.7%) confuse it with 1-PPV or 1-NPV and 21 practitioners answered the question right, accounting for 19.44% (Figure 57).

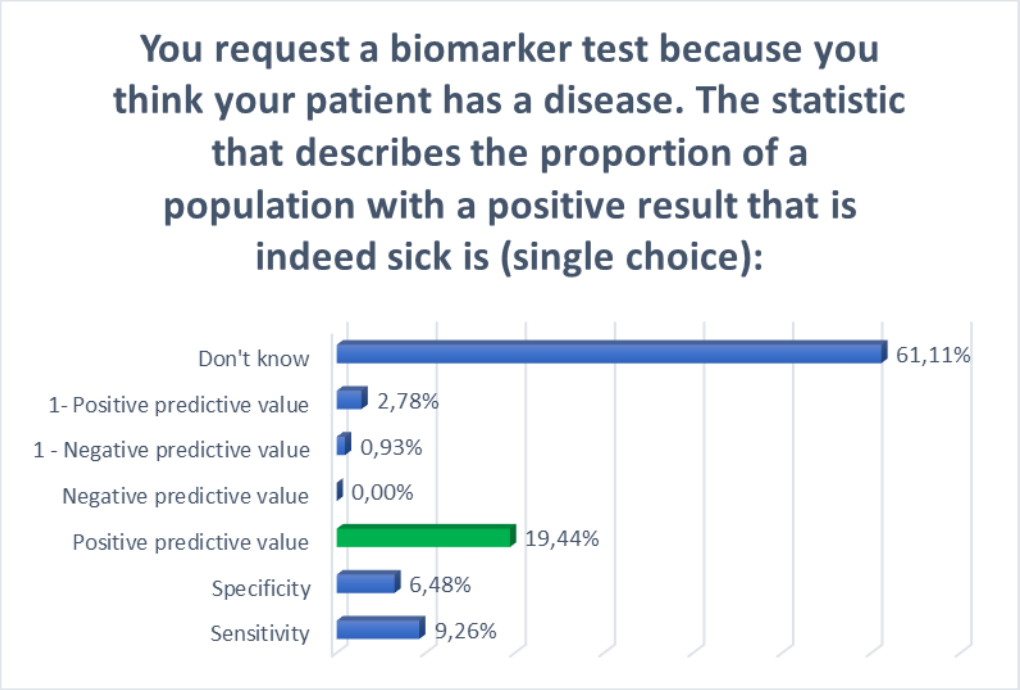


Figure 57: Question 33.

1.10. You order a biomarker test because you think your patient has a disease, but the test comes back negative. The statistic that describes the proportion of a population with a negative test result that nevertheless has the disease is:

More than half the practitioners (71 practitioner, 65.74%) did not know what statistic describes the population with a negative test (biomarker) result that nevertheless has the disease. 8 practitioners (7.4%) confuse it with Sp or Sn, 6 practitioners (5.56%) confuse it with

NPV, 4 practitioners (3.7%) confuse it with 1-PPV and 19 practitioners answered the question right, accounting for 17.59% (Figure 58).

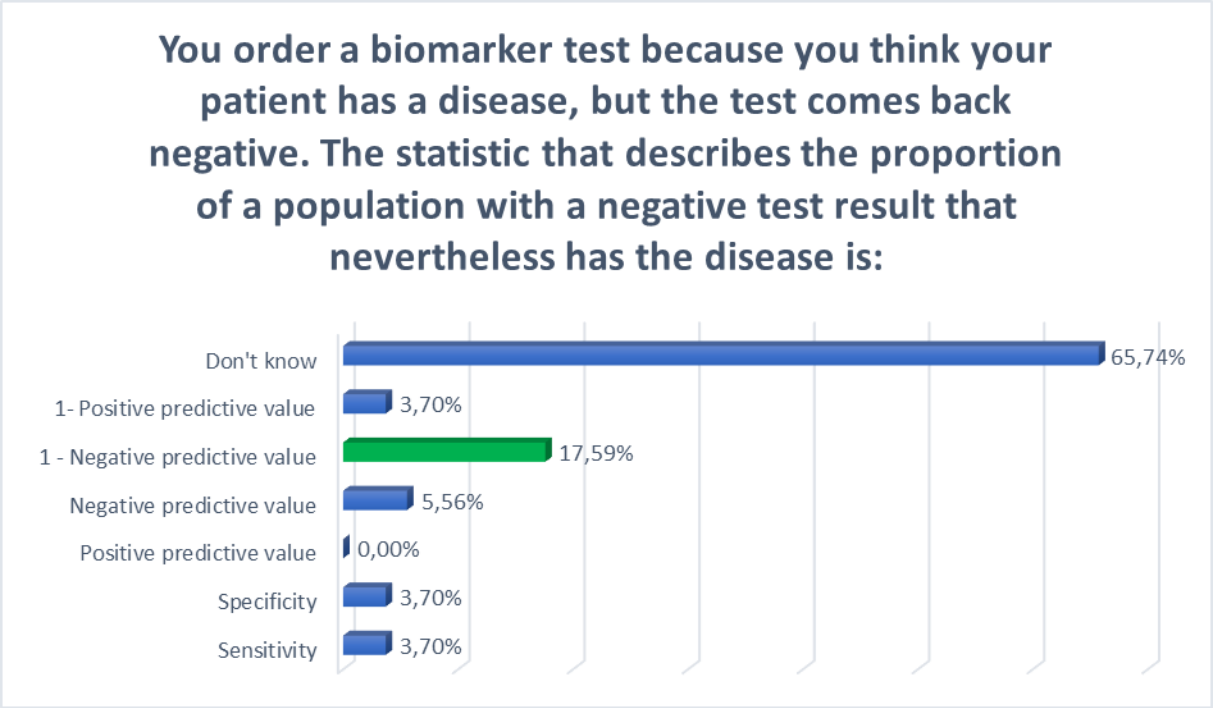


Figure 58: Question 34.

1.11. You request a biomarker assay to rule out a disease, but the test comes back positive. The statistic that describes the proportion of a population that has a positive result but is still healthy (single choice):

More than half the practitioners (72 practitioners, 66.67%) did not know what statistic describes the proportion of a population that has a positive test (biomarker result) but was nevertheless healthy, 8 practitioners (7.4%) confuse it with Sp or Sn, 3 practitioners (2.77%) confuse it with PPV or NPV, 2 practitioners (1.85%) confuse it with 1-NPV and 23 practitioners answered the question right, accounting for 21.3% (Figure 59).

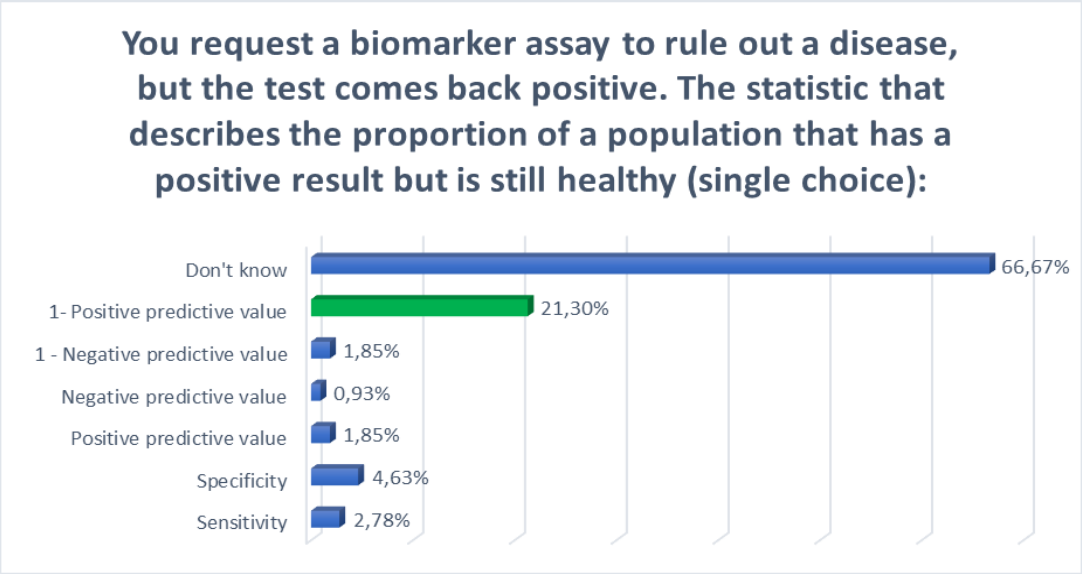


Figure 59: Question 35.

1.12. To assess the pre-test probability of a disease, you use:

When asked about how they assess pre-test probability of a disease, 26.85% of the participants said they do not think about it, 43.52% said they use clinical scores, 45.37% use the prevalence of the disease as a guide, 37.96% estimate it intuitively and 40.74% use the position of the hypothesis on the differential diagnosis list (Figure 60).

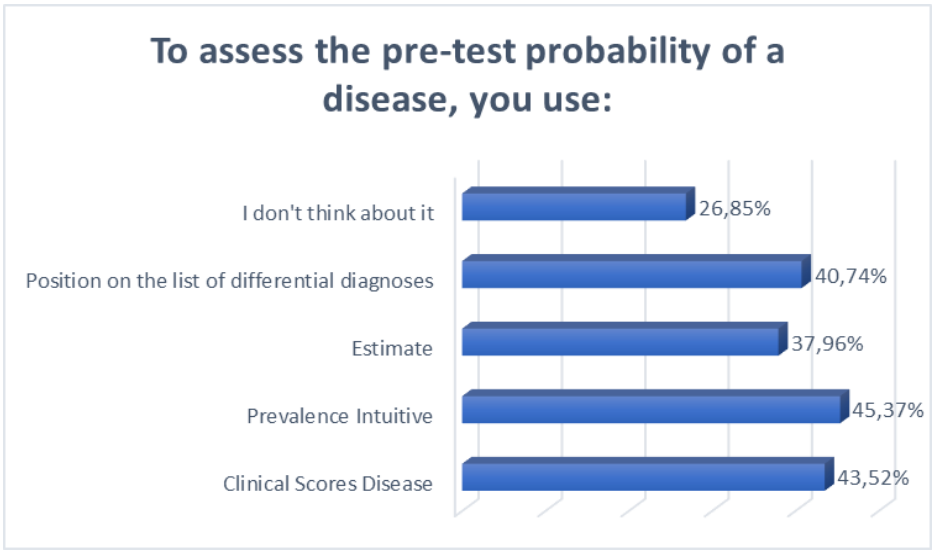


Figure 60: Question 36.

1.13. In terms of diagnosis, a biomarker has more contribution when the pre-test probability is:

39 practitioners (36.11%) said they did not know when a biomarker contributed more towards a diagnosis, 27 practitioners (25%) said it was when the pre-test probability was high, 13 practitioners (12.04%) said it was when the pre-test probability was low and 29 practitioners (26.85%) answered the question right (Figure 61).

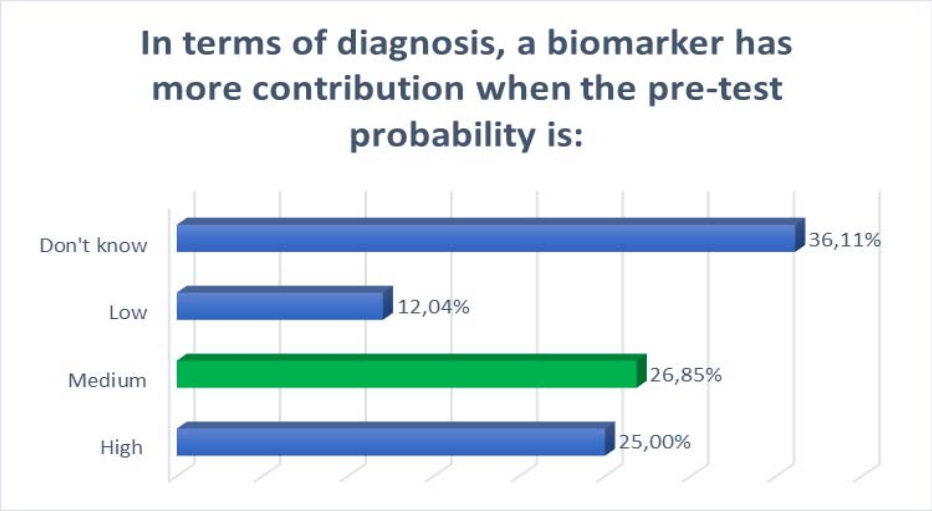


Figure 61: Question 37.

1.14. You want to eliminate a disease, you need a biomarker that has a high:

65 practitioners (60.19%) did not know on what test characteristic to base themselves on to choose biomarker that would eliminate a disease, 8 (7.41%) practitioners said they would choose a biomarker with a high specificity and 35 practitioners said they would choose a biomarker with high sensitivity, accounting for 32.41% (Figure 62).

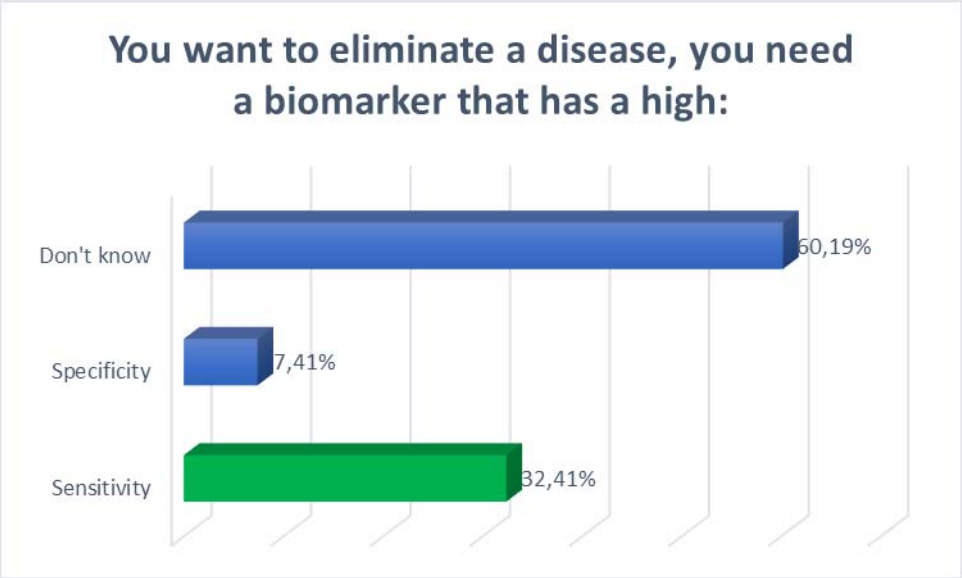


Figure 62: Question 38.

1.15. You want to confirm a disease, you need a biomarker that has a high:

When asked about what biomarker characteristic to choose in a biomarker to confirm a diagnosis, 65 practitioners (60.19% said they did not know, 6 practitioners (5.56%) said they would choose a biomarker with a high sensitivity and 37 said they would choose a biomarker with a high specificity accounting for 34.26% (Figure 63).

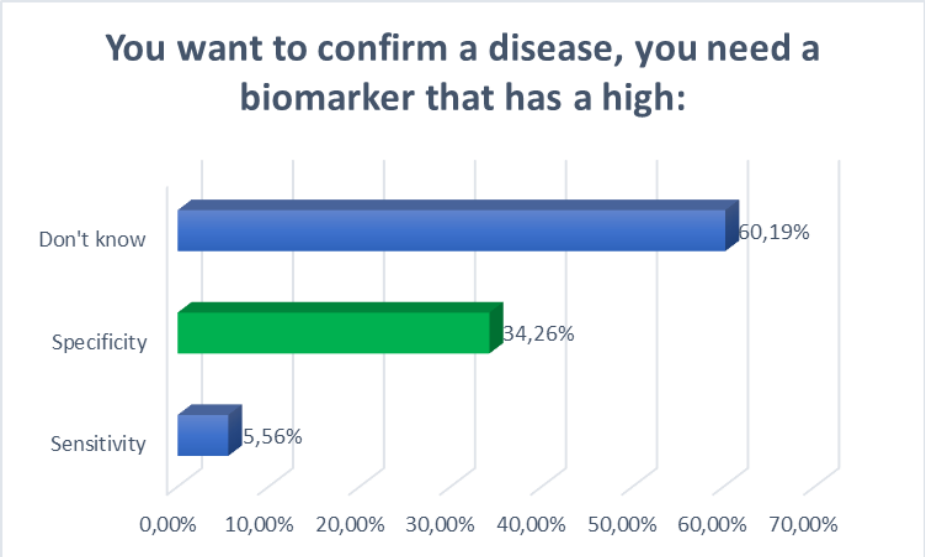


Figure 63: Question 39.

1.16. If you really need to exclude a disease regardless of the pretest probability, you should use a test that has a sensitivity greater than or equal to:

When asked about the degree of sensitivity needed to exclude a diagnosis regardless of the pretest probability, 61 practitioners (56.48%) said they did not know, 8 practitioners (7.4%) said they would need a sensitivity below 99% and 39 practitioners (36.11%) said they would need a sensitivity above 99% which was the right answer (Figure 64).

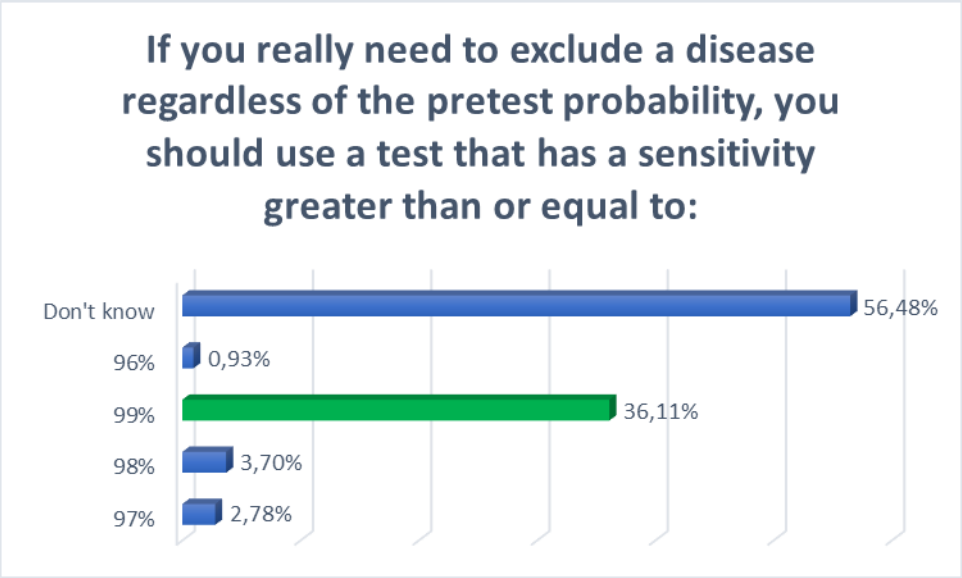


Figure 64: Question 40.

1.17. If you really need to confirm a disease regardless of the probability of the pre-test, you must use a test that has a specificity greater than or equal to:

When asked about the degree of specificity needed to confirm a diagnosis regardless of the pretest probability, 60 practitioners (55.56%) said they did not know, 11 practitioners (10.18%) said they would need a specificity below 99% and 37 practitioners (34.26%) said they would need a sensitivity above 99% which was the right answer (Figure 65).

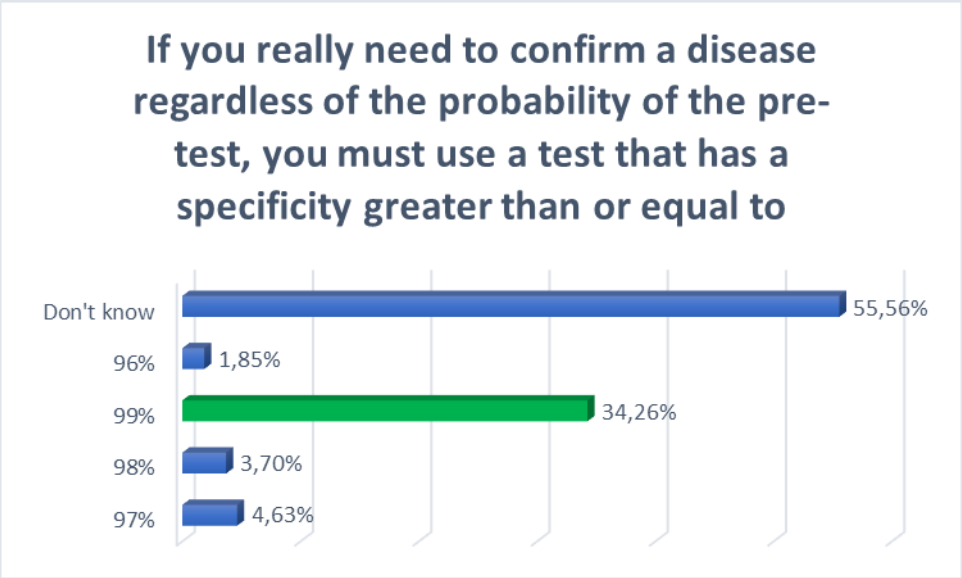


Figure 65: Question 41.

1.18. Have you ever heard of the ROC curve?

When asked about the ROC curve 102 practitioners (94.44%) said they have never heard of it while only 6 (5.56%) have previously heard of it (Figure 66).

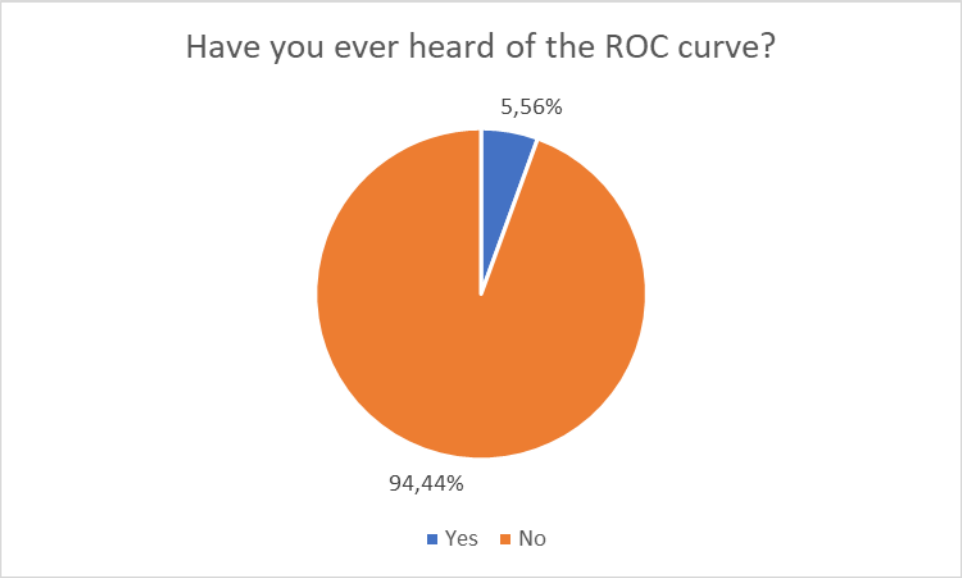


Figure 66: Question 42.

1.19. Have you ever heard of likelihood ratios?

When asked about the LR 102 practitioners (94.44%) said they have never heard of it while only 6 (5.56%) have previously heard of it (Figure 67).

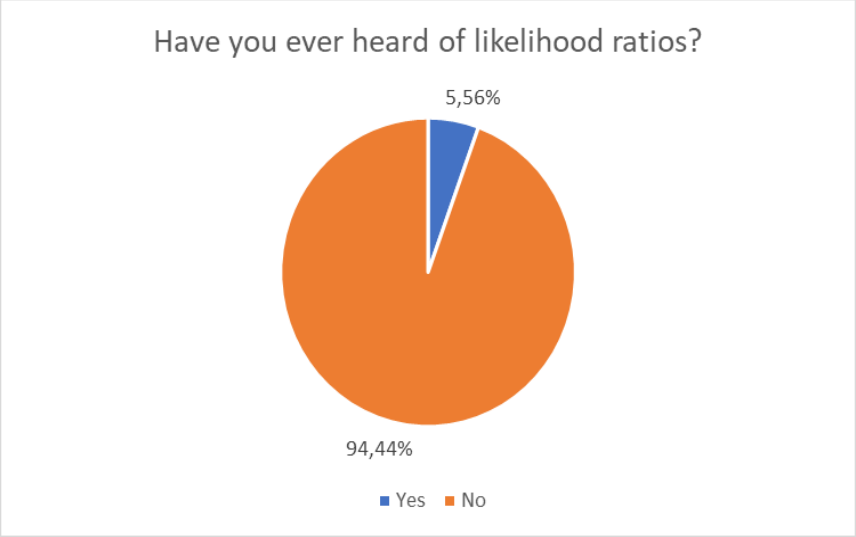


Figure 67: Question 44.

1.20. Have you ever heard of the Fagan nomogram?

When asked about the Fagan nomogram 106 practitioners (98.15%) said they have never heard of it while only 2 (1.85%) have previously heard of it (Figure 67).

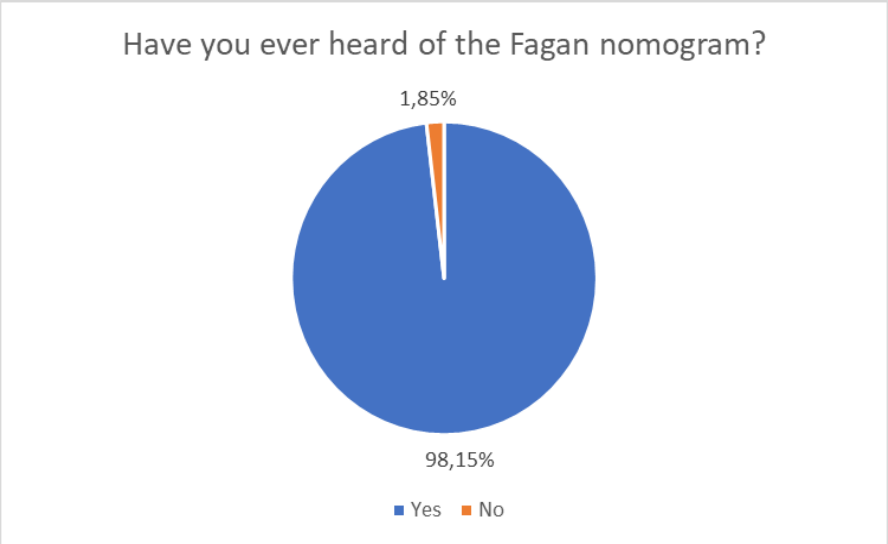


Figure 68: Question 46.

2. State of knowledge on troponins:

2.1. Regarding biomarkers of myocardial infarction, what are the Correct answers (multiple choice):

When asked about biomarkers of myocardial infarction, 17 (15.74%) practitioners think that CK-MB levels increase faster than myoglobin, 13 (12.04%) (practitioners think that ASAT is a biomarker of choice for the diagnosis of MI, 6 (5.56%) practitioners think that myoglobin is a cardio-specific biomarker, 63 (58.33%) think that cTnI allows for the retrospective diagnosis of MI, 62 (57.41%) practitioners think that cTnI is a cardio-specific biomarker and 30 practitioners could not give an answer (Figure 69).

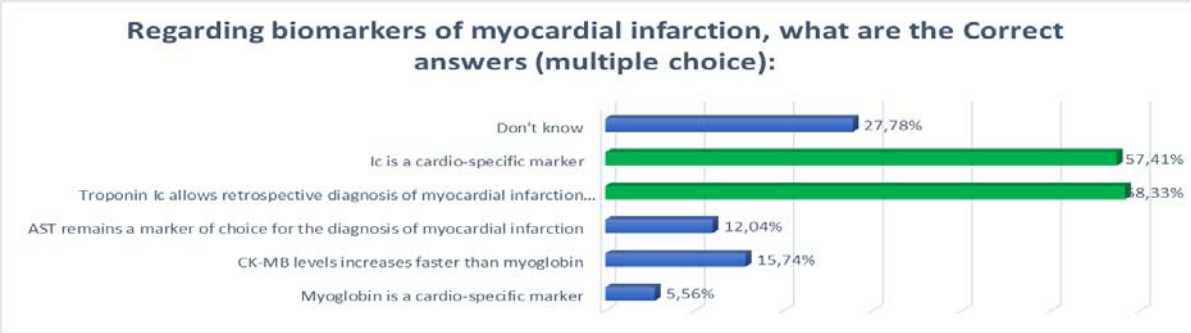


Figure 69: Question 49.

2.2. Of the following statements regarding cardiac biomarkers, which of the following are correct (multiple choice):

When asked about cardiac biomarkers, 13 practitioners (12.04%) think that troponins appear in the bloodstream 8 hours after MI, 35 practitioners (32.41%) adequately answered that myoglobin appears in the bloodstream earlier than troponins, 43 practitioners (39.81%) responded adequately that troponins are used to monitor reperfusion and evaluate the success of thrombolysis/angioplasty, 46 practitioners (42.59%) correctly answered that troponin is measured using immunoassays, and 58 practitioners (53.70%) appropriately chose the proposition that myoglobin is a non-specific marker for MI. 30 practitioners (27.78%) could not give an answer (Figure 70).

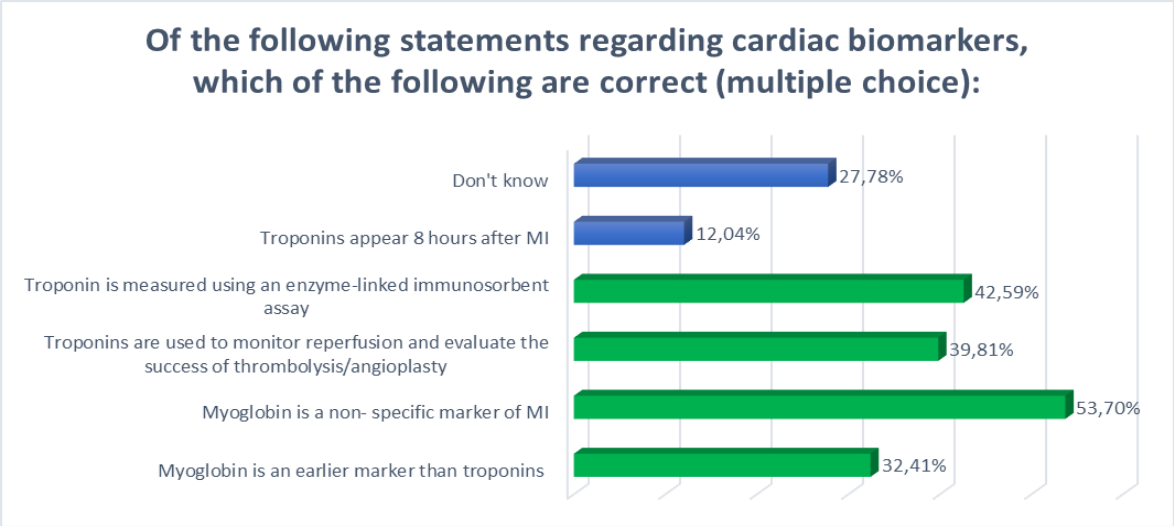


Figure 70: Question 50.

2.3. Which of the following statements is correct (single choice)?

When asked about troponins, 6 practitioners (5.56%) think that troponins are sensitive biomarkers for MI but are not very specific, 11 practitioners (10.19%) think that the decline of troponins is observed 48h after an MI, almost half of the practitioners (53 practitioners, 49.07%) could not give an answer and 38 practitioners (35.19%) correctly answered that troponins may become elevated in conditions other than coronary thrombosis (Figure 71).

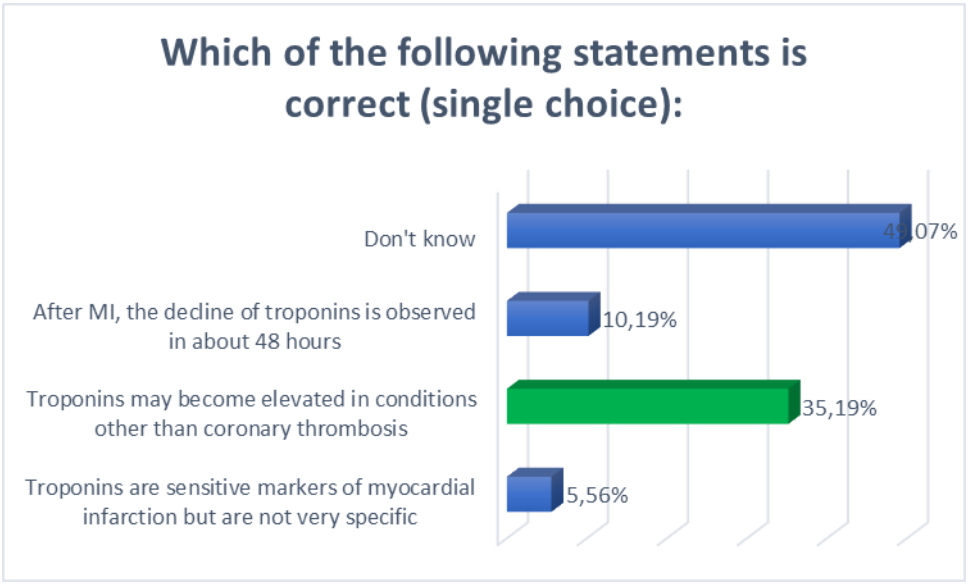


Figure 71: Question 51.

2.4. Which of the following statements about troponins are correct (multiple choice):

When asked about troponin physiology and kinetics, 36 practitioners (33.33%) think that troponins are the earliest markers to rise after an MI, 20 practitioners (18.52%) think that cTnC is of interest in the diagnosis of MI and 33 practitioners (30.56%) could not give an answer. 34 (31.48%), 36 (33.33%), 43 (39.81%) practitioners respectively chose the right answers stating that troponins are a set of contractile proteins, that they results are considered positive above the 99th percentile and that they persist in the blood for more than a week after an MI (Figure 72).

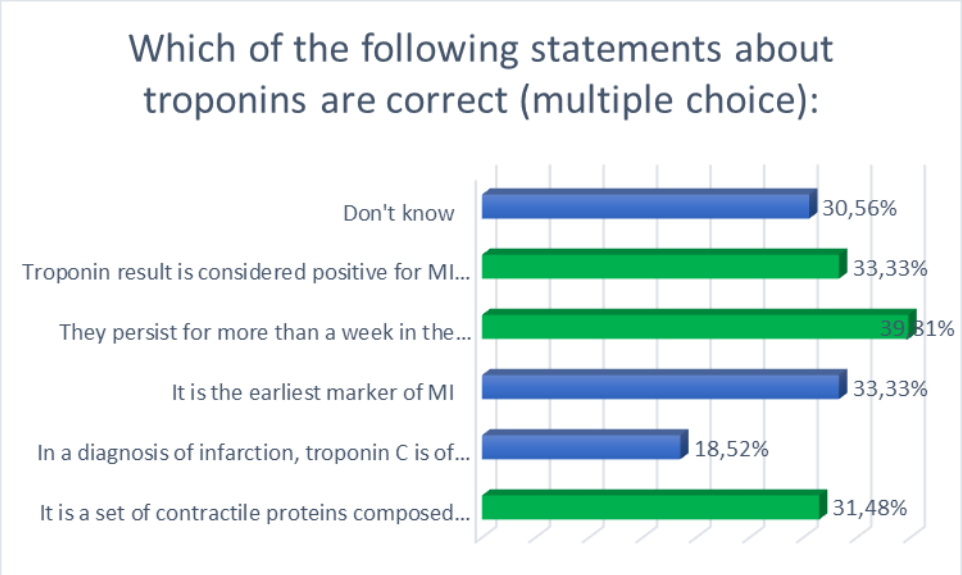


Figure 72: Question 52.

2.5. What is the earliest marker in myocardial infarction (single choice):

When asked about the earliest cardiac marker to rise after an MI, 20 practitioners (18.52%) said they did not know, 3 practitioners (2.78%) think it is CK-MB, more than half of them (59 practitioners, 54.63%) think that it is troponins, none of them chose ASAT or LDH and 26 of them correctly chose myoglobin, accounting for 24.07% (Figure 73).

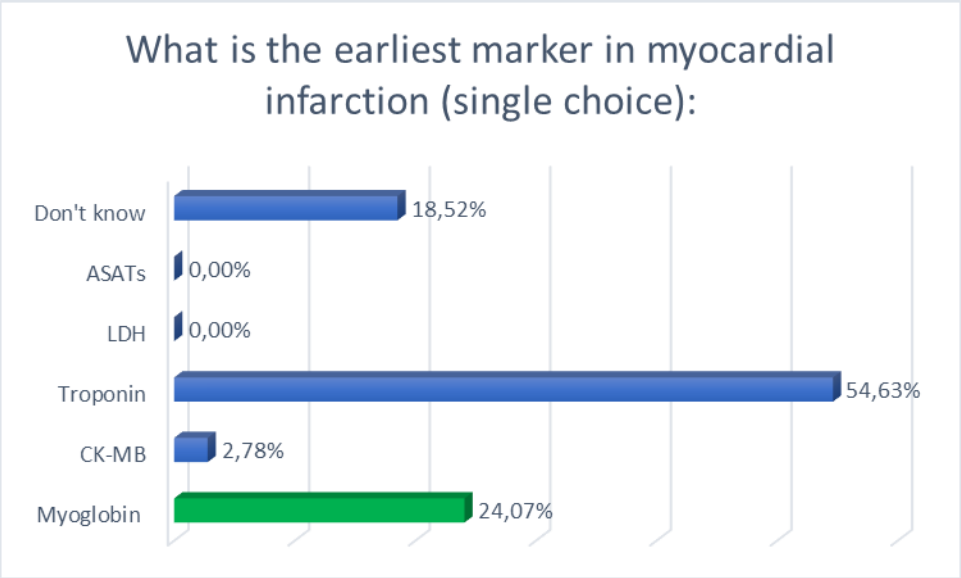


Figure 73: Question 53.

2.6. In case of chest pain with suspicion of myocardial infarction we monitor certain plasma proteins for different reasons (multiple choice):

When asked about cardiac biomarkers in MI, almost half of the practitioners (53 practitioner, 49.07%) could not give an answer, 26 practitioners (24.07%) think that troponin in the earliest marker to rise in the blood, 15 practitioners (13.89%) thin that myoglobin is a cardio-specific marker of myocardial necrosis, and 38 (35.19%), 15 (13.89%) and 13 (12.04%) practitioners respectively answered correctly that cTnI was the most specific marker of myocardial necrosis, CPKMB-mass was the most specific isoenzyme of the creatinine kinases and that myoglobin was the earliest marker to rise in myocardial necrosis (Figure 74).

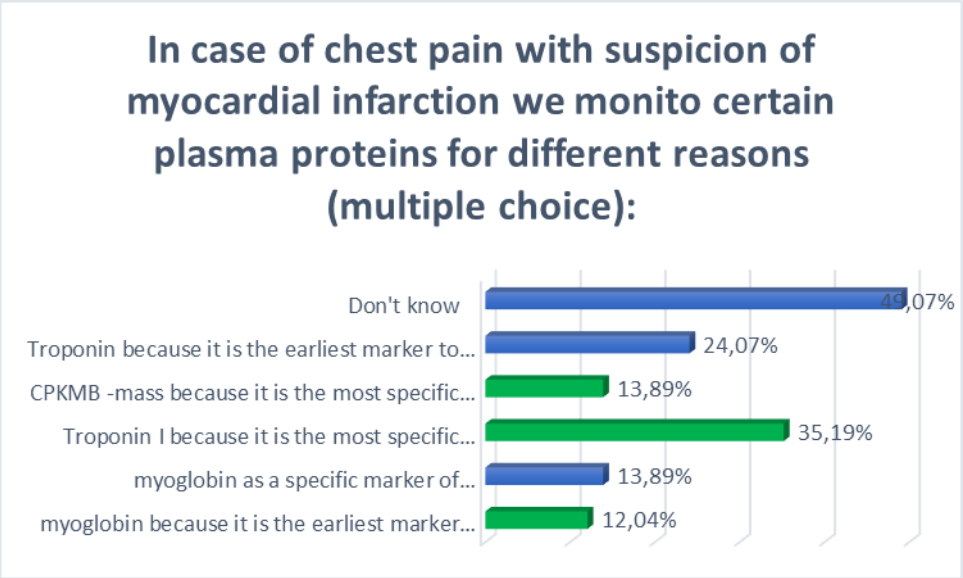


Figure 74: Question 54.

2.7. What elements are included in the definition of "myocardial injury" or "myocardial damage" introduced in the 4th universal definition of MI (multiple choice):

When asked about the elements of the 4th universal definition of MI, more than half the practitioners (68 practitioners, 62.96%) could not give an answer, 12 (11.11%) and 11 (10.19%) practitioners respectively think that the elevation or decrease of cardiac troponins can make the diagnosis on their own, 34 (31.48%), 28 (25.93%) and 11 (10.19%) practitioners respectively gave the correct answer that a clinical context was needed, that at least one value of troponins had to be above the 99th percentile and that either the elevation and/or the decrease of cardiac troponins were needed to make the diagnosis of MI (Figure 75).

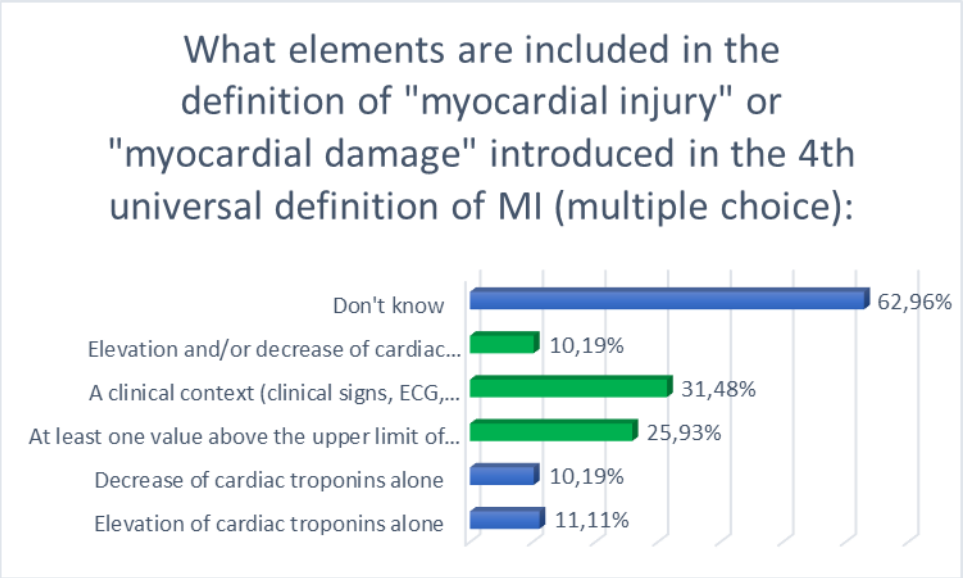


Figure 75: : Question 55.

2.8. Troponins can be elevated in (multiple choice):

When asked about the differential diagnosis possible in front of elevated troponins, 47 practitioners (43.52%) said they did not know, 6 practitioners (5.56%) chose “hypo and hyperthyroidism”, 20 practitioners (18.52%) chose “tachyarrhythmias”, 31 practitioners (28.70%) chose “Aortic dissection”, 40 practitioners (37.04%) chose “shock” and more than half the practitioners (59 practitioner, 54.63%) chose myocarditis which were all right answers (Figure 76).

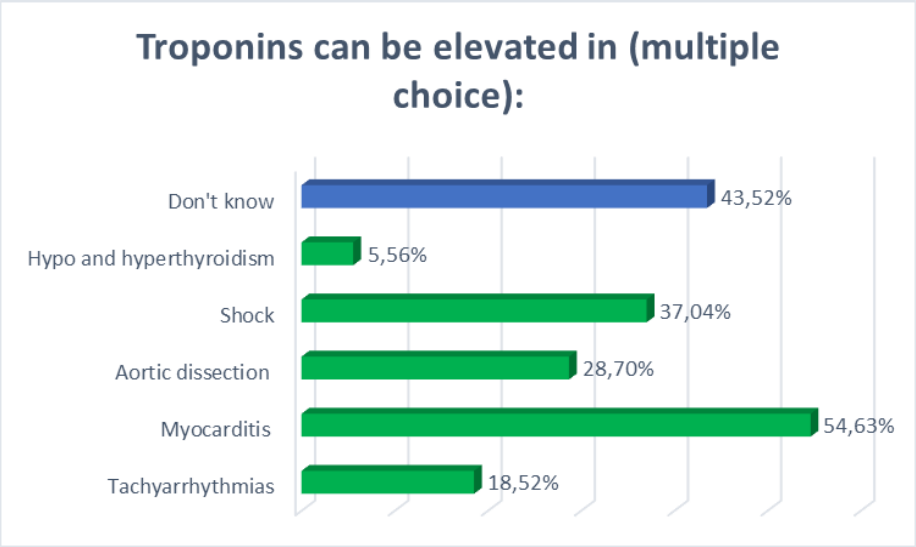


Figure 76: Question 56.

2.9. The most specific marker for myocardial infarction is (single choice):

When asked about the most specific marker for myocardial infarction, 36 practitioners (33.33%) said they did not know, no practitioner chose myoglobin or CRP-us, 24 practitioners (22.22%) chose troponin C and 48 practitioners chose cTnI which was the right answer, thus making up 44.44% (Figure 77).

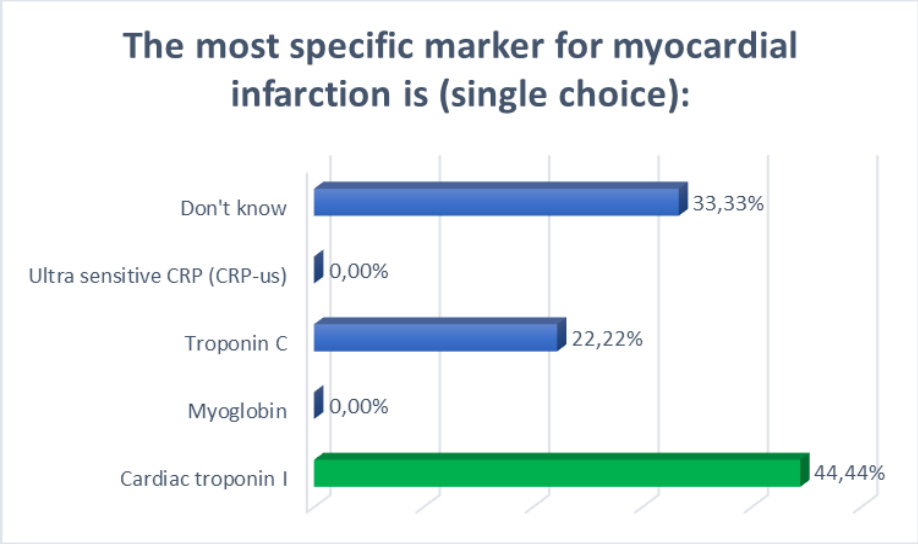


Figure 77: Question 57.

2.10. You receive a patient in the emergency room complaining of chest pain >3h, ECG is non-contributory and TnTc Hs result is < 14 ng/L ng/L. You decide to (single choice):

When asked about troponin algorithm, 68 practitioners (62.96%) said they did not know, 21 practitioners (19.44%) said they would ask for another troponin test after 2 hours and 19 practitioners said they would rule out MI, accounting for 19.59% (Figure 78).

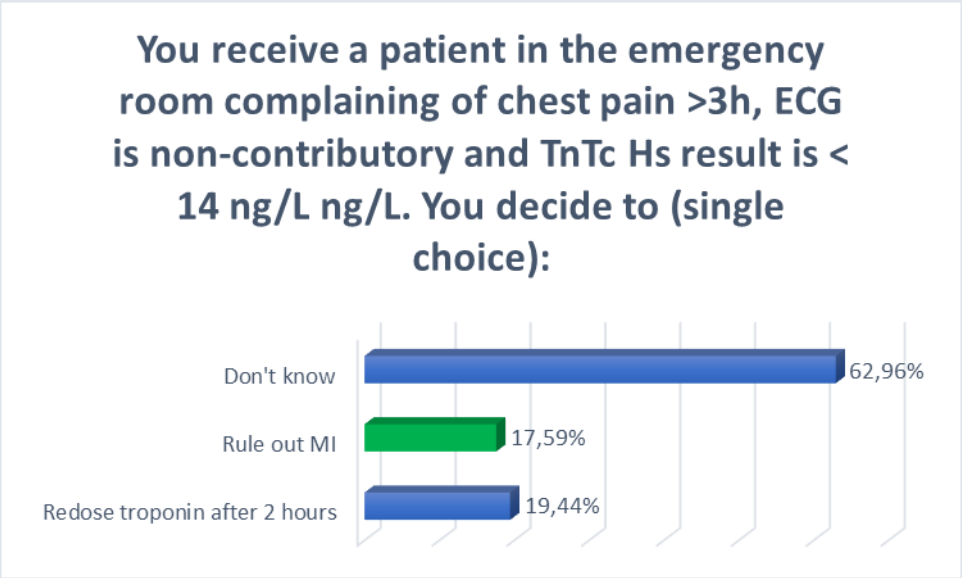


Figure 78: Question 58.

2.11. You receive a patient in the emergency room who complains of chest pain >3h, The ECG is non-contributory and the TnTc Hs result is between 14 and 50 ng/L. You decide to repeat the troponins after 2 hours (multiple choice):

When asked about troponin algorithm, 72 practitioners (66.67%) said they did not know, 9 practitioners (8.33%) said they would rule out the diagnosis of MI if there was a decrease of more than 30% in troponins, 30 (27.78%), 25 (23.15%) and 15 (13.89%) practitioners respectively chose to rule in the diagnosis of MI if there was an increase of more than 30% in troponins, if there was an increase of more than 7 ng/L in troponins and to rule out the diagnosis of MI if troponins did not increase. But only 6 practitioners (5.55%) chose all 3 (Figure 79).

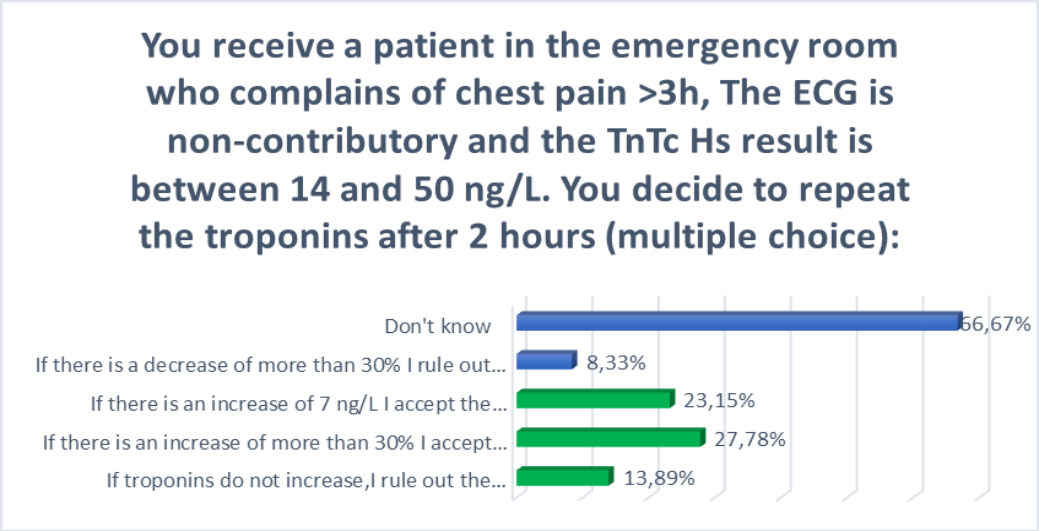


Figure 79: Question 59.

2.12. Factors that may influence the 99th percentile of ultrasensitive troponin are (multiple choice):

When asked about the factors that could influence the 99th percentile of the Tn-us, more than half the practitioners (64 practitioner, 59.26%) said they did not know, 37 (34.26%), 34 (31.48%), 29 (26.85%) and 16 (14.81%) practitioners respectively chose “determination method”, “renal insufficiency”, “age” and “gender” which were all correct answers (Figure 80).

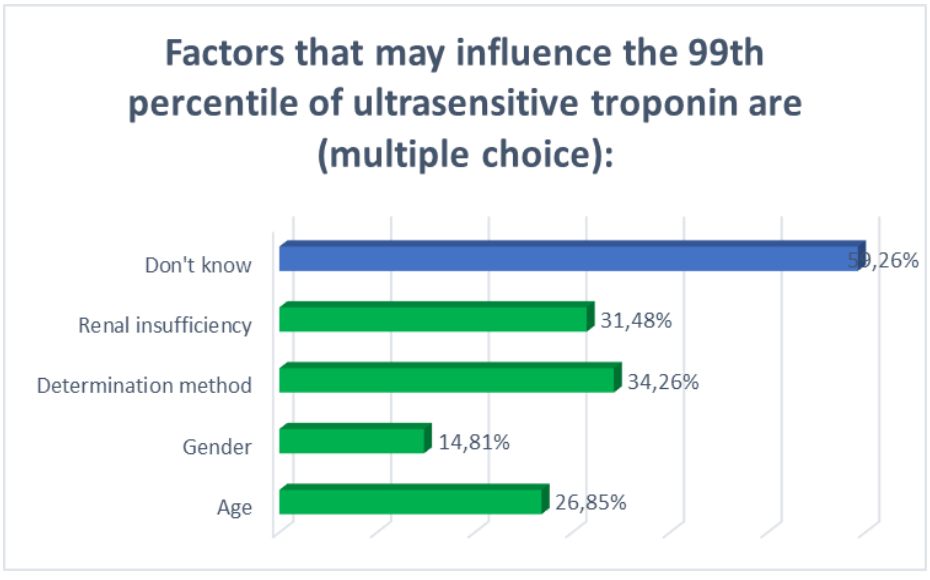


Figure 80: Question 60.

2.13. Even outside of MI, troponin elevation, however low, retains long-term prognostic significance:

When asked if troponin elevation had long term prognostic significance even outside of MI, more than half the practitioners (83 practitioner, 76.85%) could not give an answer, 7 practitioners (6.48%) said no and 18 practitioners (16.67%) said yes (Figure 81).

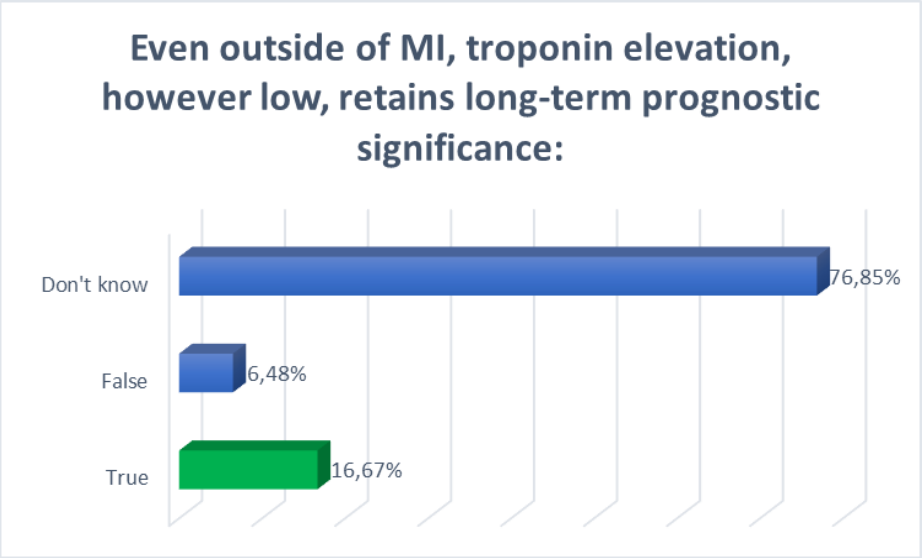


Figure 81: Question 61.

2.14. In myocardial necrosis, cTn elevation occurs between ..... after the onset of myocardial injury (single choice):

When asked about the kinetics of troponin elevation after an MI, more than half the practitioners (67 practitioner, 62.04%) said they did not know, 8 practitioners (7.41%) said it happened between 0 and 2 hours, 12 practitioners (11.11%) said it happened 4 and 8 hours and 21 practitioners (19.44%) said it happened between 2 and 4 hours which was the right answer (Figure 82).

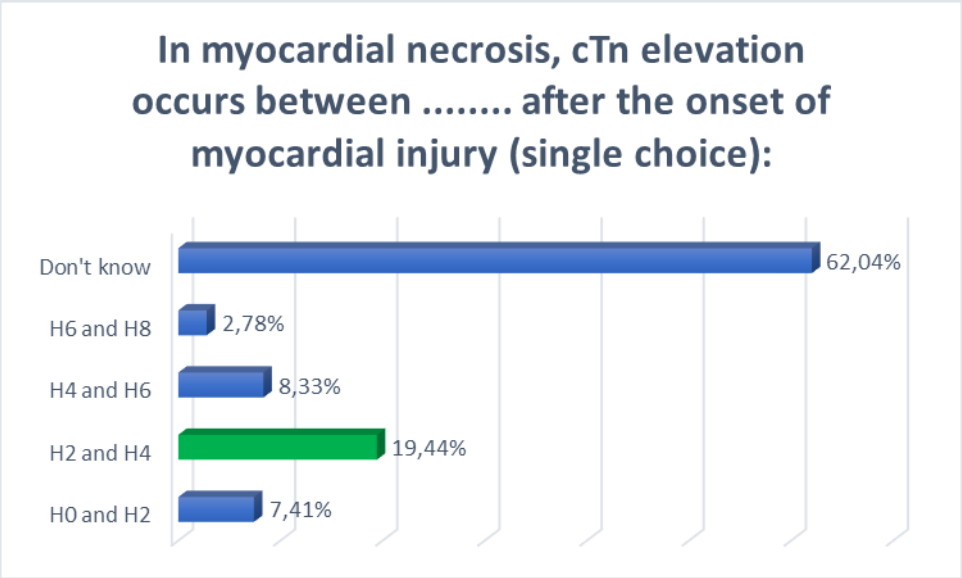


Figure 82: Question 62.

2.15. During myocardial necrosis, the maximum serum cTn level is reached between (single choice):

When asked about troponin kinetics, 88 practitioners (81.48%) said they did not know, 5 practitioners (4.62%) said it happened between 0 and 6 hours, 7 practitioners (6.42%) said it happened beyond 24 hours and 20 practitioners (18.52%) said it happened between 9 and 15 hours which was the right answer (Figure 83).

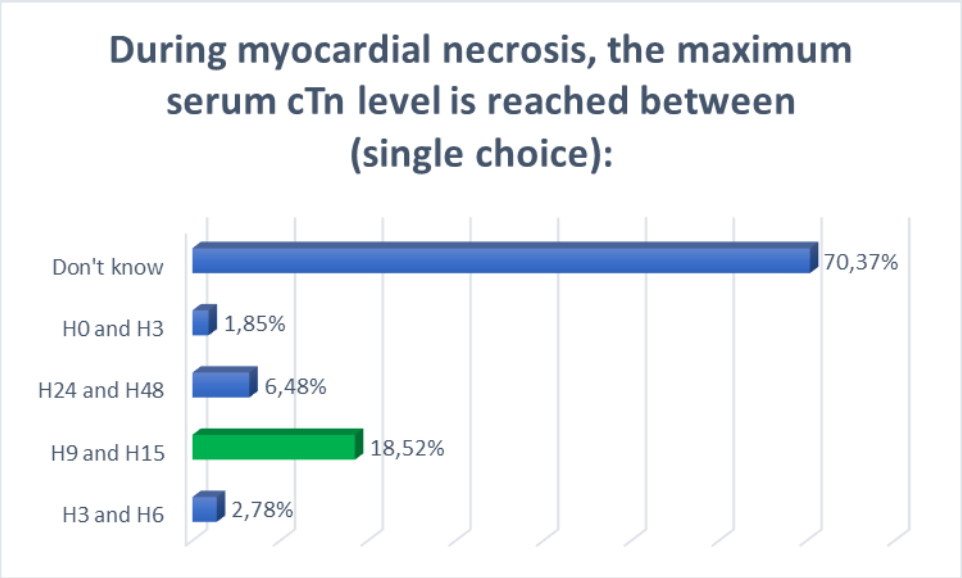


Figure 83: Question 63.

During myocardial necrosis, the return to normal cTn is between (multiple choice):

When asked about troponin kinetics, the majority of the practitioners (88 practitioner, 81.48%) said they did not know, 15 (13.83%) and 4 (3.70%) respectively said that cTnI returned to normal between the 10th and 14th day after MI and that cTnT returned to normal between the 4th and 7th day after MI, while 6 (5.56%) and 1 (0.93%) practitioners chose the correct answers which were the opposite of the previous two (Figure 84).

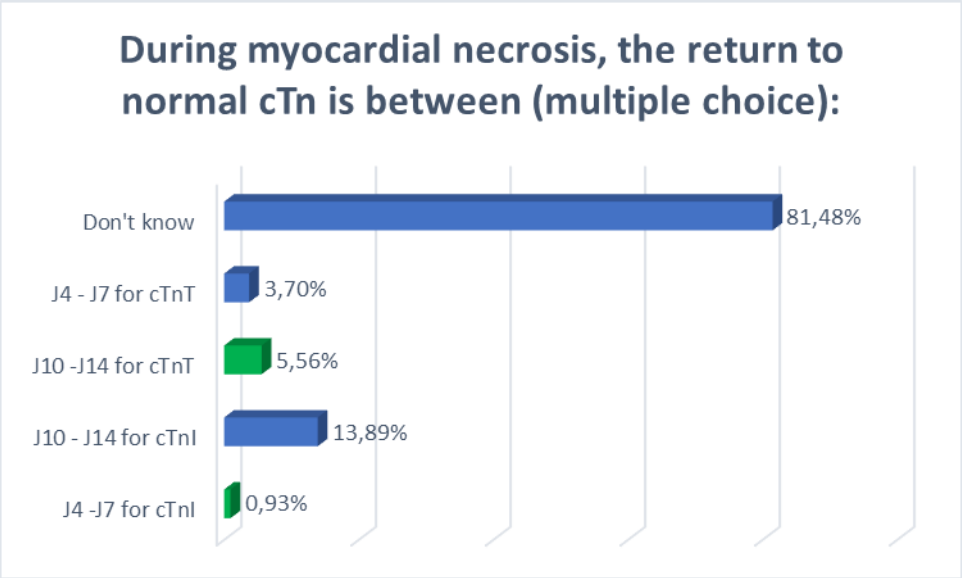


Figure 84: Question 64.

2.16. Cardiac troponins (multiple choice):

When asked about cardiac troponins, 74 practitioners (68.52%) said they did not know, 14 (12.96%) and 26 (24.07%) respectively said that they always reflected irreparable myocardial damage, that they were significantly elevated within 1 hour of myocardial damage, 24 and 13 practitioners, respectively representing 22.22% and 12.04% of the practitioners chose the right answers which were “troponins can be detected in the serum 5 days after the MI” and “troponins have a prognostic role in coronary, non-coronary and even non cardiac disease” (Figure 85).

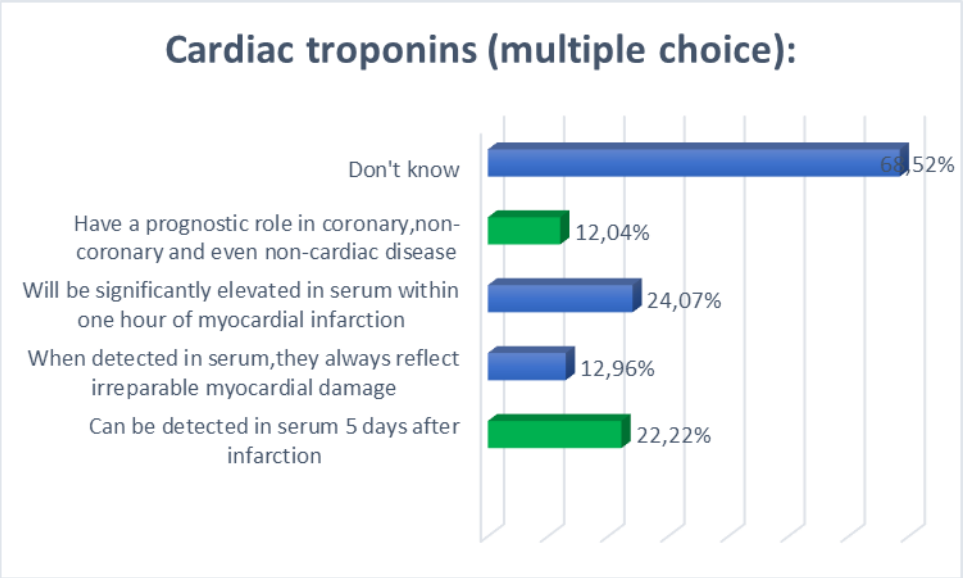


Figure 85: Question 65.

2.17. Cardiac troponins (multiple choice):

When asked about cardiac troponins, 76 practitioners (70.37%) could not give an answer, 3 practitioners (2.78%) thin that there is only 1 manufacturer of troponin assays, 29 (26.85%) practitioners correctly answered that their release could occur in the absence of CAD, and 19 practitioners (26.85%) correctly answered that the cut off values depended on the laboratory and the test manufacturer (Figure 86).

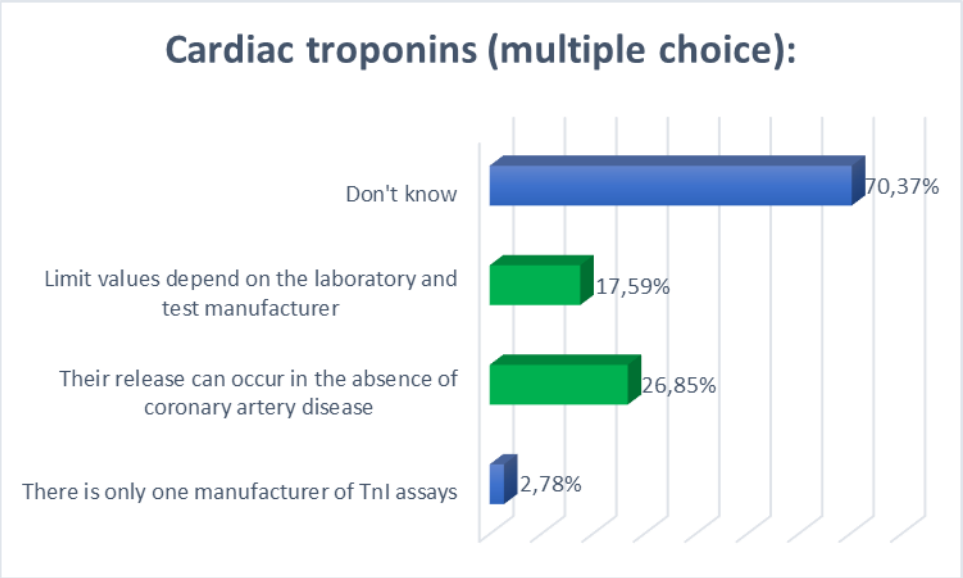


Figure 86: Question 66.

2.18. Cardiac troponins (multiple choice):

When asked about cardiac troponin physiology, 71 practitioners (65.74%) could not give an answer, 11 (10.19%) and 18 (16.67%) practitioners said that all 3 isoforms are useful in the diagnosis of cardiac lesions, that they could only be released in individual forms, 23 (21.30%), 12 (11.11%), 12 (11.11%) practitioners chose the right answer which were “troponin increase is not always synonymous with coronary thrombosis, “5-8% of troponin is unbound in the cardiomyocyte’s cytoplasm” and “the cytoplasmic fraction was the first to be released in the event of myocardial injury” which were the right answers (Figure 87).

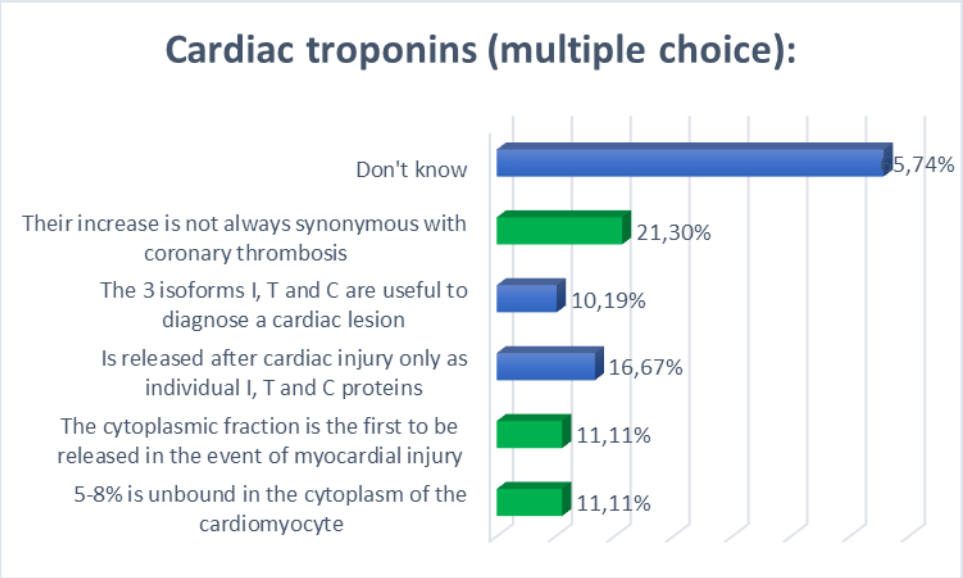


Figure 87: Question 67.

3. State of knowledge on D Dimer:

3.1. Concerning d-dimer (multiple choice):

When asked about D dimer, 22 practitioners (20.37%) could not give an answer, 15 practitioners (13.89%) think that a positive D dimer assay confirms the diagnosis of PE, 66 (61.11%), 28 (25.93%) and 53 (49.07%) practitioners respectively chose the correct propositions stating that “D dimer has a good NPV (99%) to exclude PE”, “a d dimer ELISA determination of less than 500 ug/L clearly rules out the diagnosis of PE” and “d dimer is a marker of coagulation activation and fibrinolysis” (Figure 88).

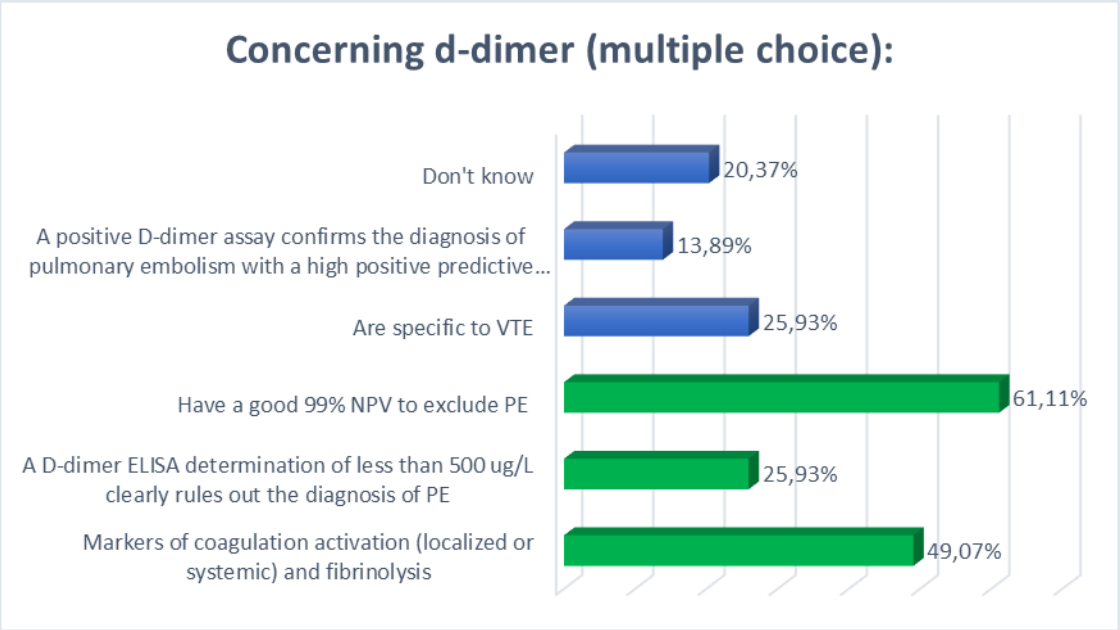


Figure 88: Question 68.

3.2. D-dimer levels may be elevated in the following situations (multiple choice):

When asked about differential diagnosis to site in front of d dimer elevation, 23 practitioners (21.30%) could not give an answer, 76 (70.37%) practitioners chose VTE, 40 (37.04%) practitioners chose pregnancy, 30 practitioners (27.78%) chose aortic dissection, 62 (57.41%) chose DIC, 26 (24.07%) practitioners chose renal insufficiency, 21 (19.44%) practitioners chose elderly subjects, which were all right answers (Figure 89).

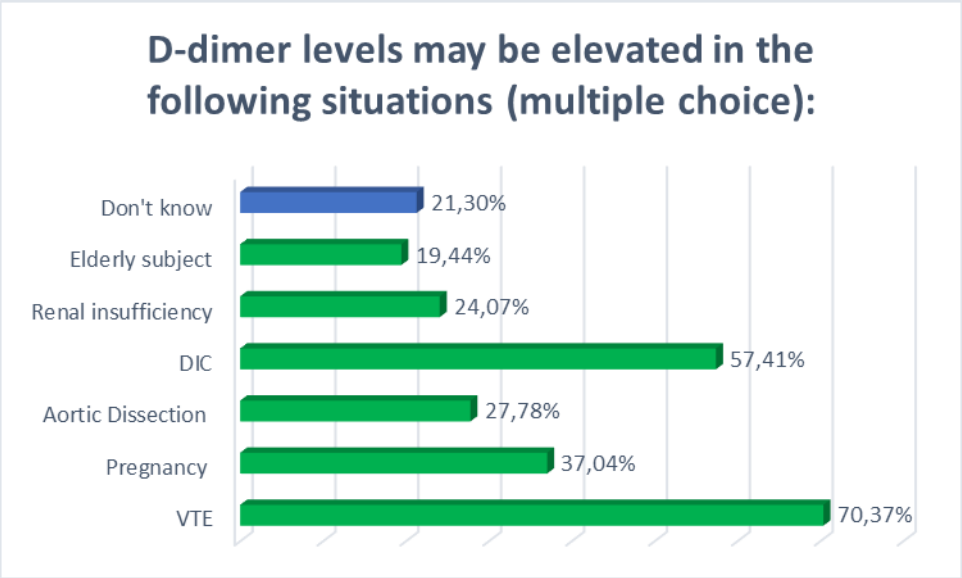


Figure 89: Question 69.

3.3. D-dimer testing is not recommended in situations where the pre-test probability of VTE is:

When asked about the pertinence of d dimer testing according to pretest probability, 34 (31.48%) practitioners could not give an answer, 30 (27.78%) said that d dimer testing was not recommended if pretest probability was low, 33 (30.56%) practitioners said it was not recommended if the pretest probability was intermediate and 11 practitioners (10.19%) said it was not recommended when the pretest probability was high, which was the correct answer (Figure 90).

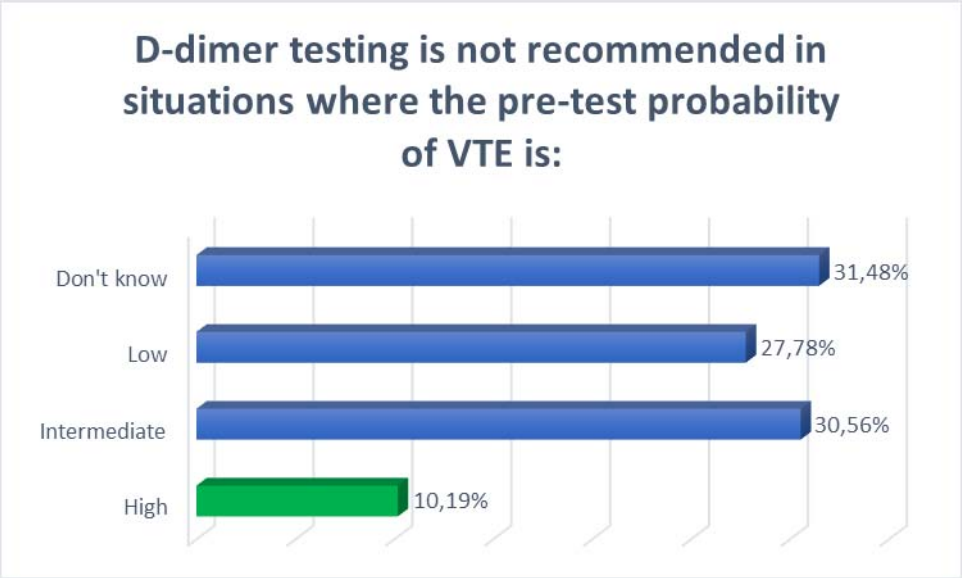


Figure 90: Question 70.

3.4. The threshold value of d-dimer in ug/L in a subject over 50 years old is calculated from his age according to the following formula:

When asked about the threshold value of d dimer in subjects above 50 years of age, 54 (50.00%) of practitioners said they did not know, 3 (2.78%) practitioners said it was age*3, 7 (6.48%) practitioners said it was age*20, 3 practitioners (3.78%) said it was age*12 and 41 (37.96%) practitioners chose the right answer which was age*10 (Figure 91).

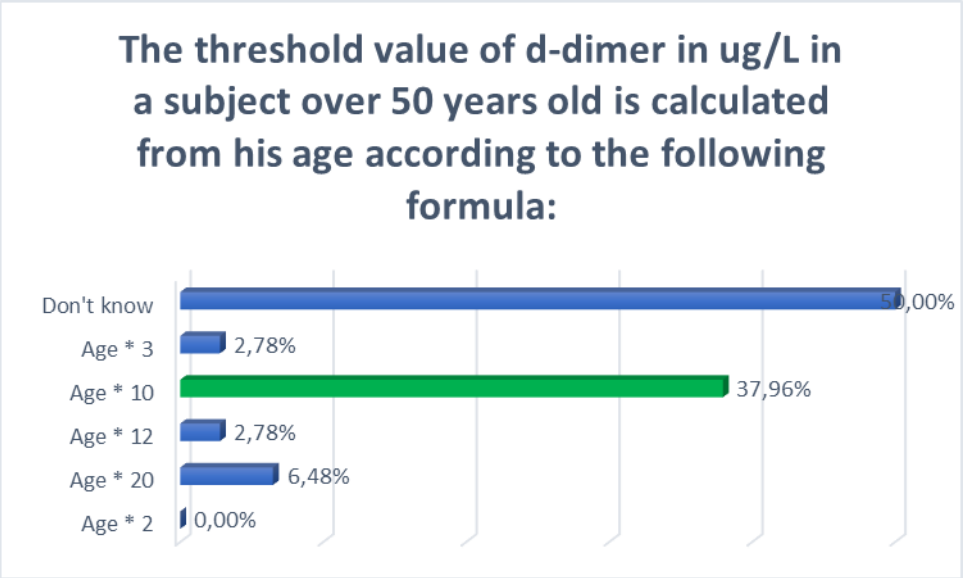


Figure 91: Question 71.

3.5. Signs that can predict early mortality in embolism pulmonary embolism are (multiple choice):

When asked about the signs that can predict early mortality in PE, 49 (45.37%) practitioners could not give an answer, 32 (29.63%) practitioners chose “obstruction of more than 70% of the lung vascular bed”. 37 (34.26%) practitioners chose “high BNP”, 35 (32.41%) chose “elevated troponins” and 45 (41.67%) chose “collapsed ejection fraction” which were all right answers (Figure 92).

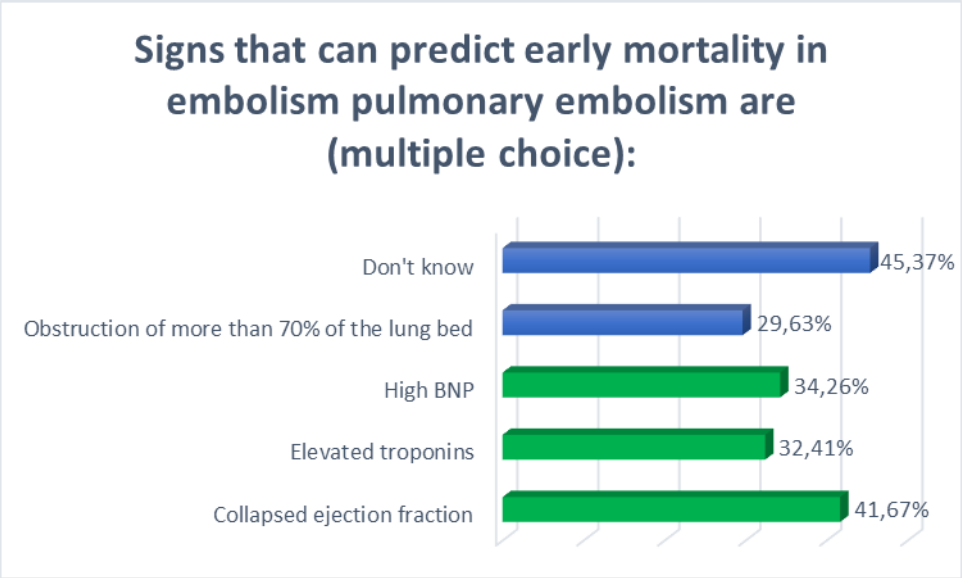


Figure 92: Question 72.

3.6. BNP and NT pro-BNP:

When asked about the physiology of BNP, 54 (50.00%) practitioners said they did not know, 28 (25.93%) practitioners think that BNP is secreted in response to increased atrial volume and pressure, 22 (20.37%) thin that BNP is secreted by the atrial myocardium. However, 30 (27.78%) practitioners said BNP was secreted by the ventricular myocardium, 32 (29.63%) said that BNP was secreted in response to increased ventricular strain/stretch and 12 (11.11%) said it had a half-life of 20 min which were all right answers (Figure 93).

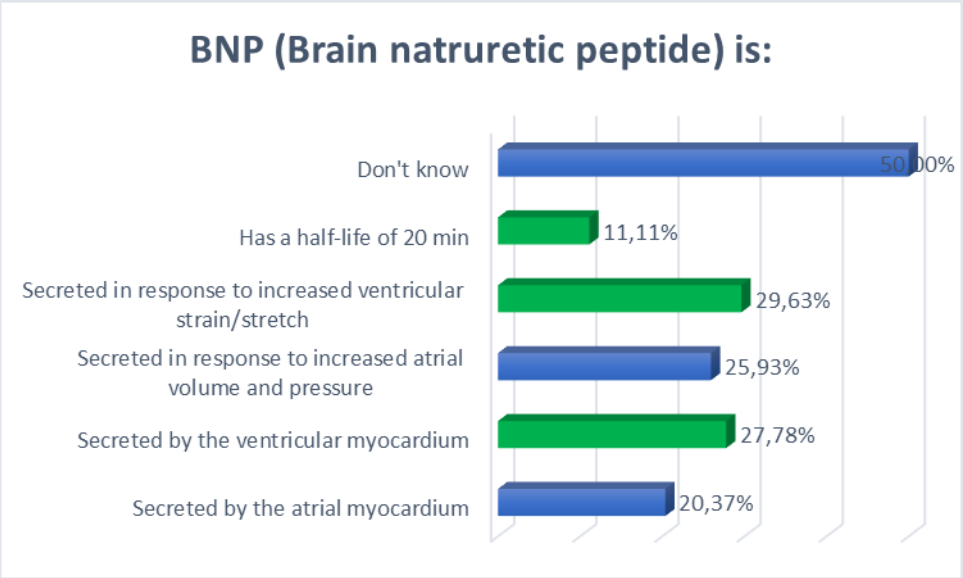


Figure 93: Question 73.

3.7. Concerning BNP and NT- pro BNP (multiple choice):

When asked about the uses of BNP and NT pro-BNP, 62 (57.41%) practitioners could not answer, 7 (6.48%) practitioners said that screening with NT pro-BNP allowed for the screening of patients with atrial fibrillation who were at risk of developing a stroke, 22 (20.37%) said that the threshold for inclusion depended on the age of the patient, 34 (31.48%) said that BNP and NT pro-BNP had a good NPV to exclude HF, 32 (29.63%) practitioners said that BNP and NT pro-BNP were used to exclude or diagnose HF in patients with dyspnea and 18 (16.67%) said that BNP and NT pro-BNP were secreted equimolecular which were all right answers (Figure 94).

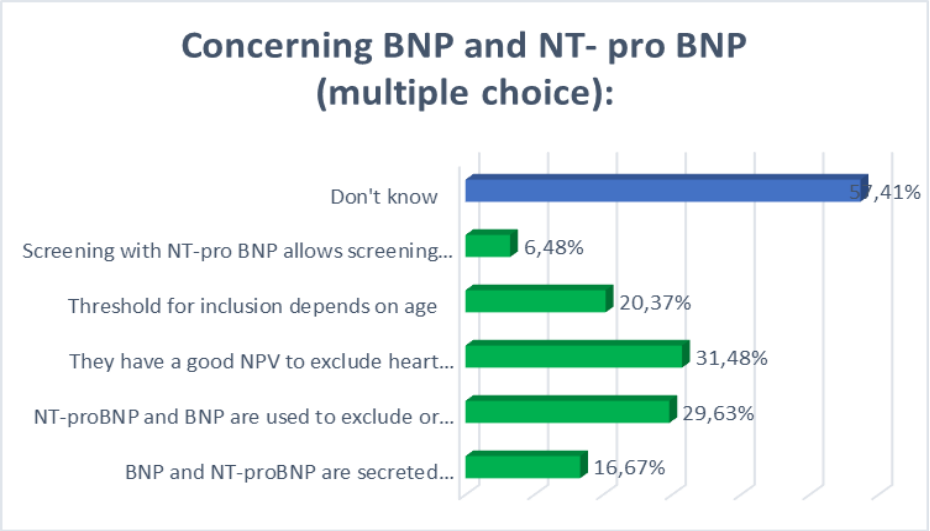


Figure 94: Question 74.

3.8. NT-proBNP (multiple choice):

When asked about NT pro-BNP, 80 practitioners (74.07%) could not give an answer, 8 (7.41%). 9 (8.33%), 9 (8.33%) and 23 (21.30%) practitioners respectively said that it had a half-life of 90 min, that it had a longer half-life than BNP, that its elimination was primarily urinary and that it was an inactive form which were all right answers (Figure 95).

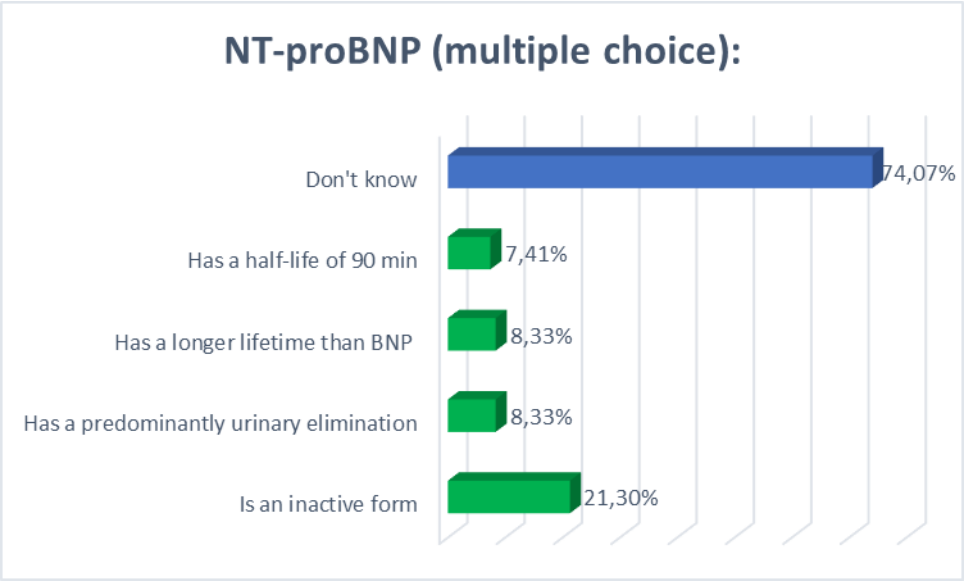


Figure 95: Question 75.

3.9. Among the factors that influence BNP (multiple choice):

When asked about the factors that could influence BNP levels in the blood, 77 (71.30%) practitioners could not give an answer, 22 (20.37%) practitioners said it decreased with age. However, 27 (25.00%), 19 (17.59%), 16 (14.81%) and 16 (14.81%) respectively said that it increased in case of renal failure, that it increased in case of lung disease, that it decreased in obese patients, that it decreased in female patients, which were all right answers (Figure 96).

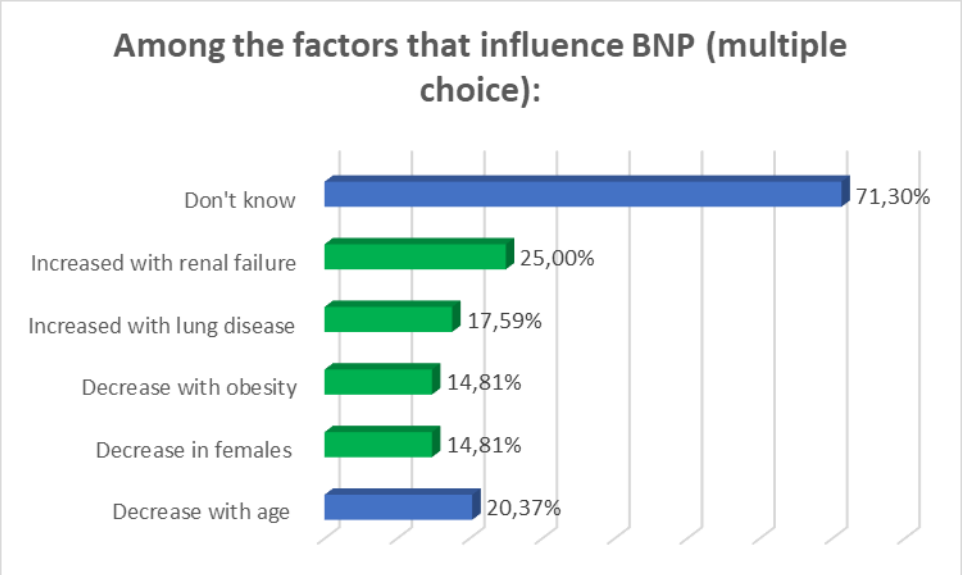


Figure 96: Question 76.

3.10. The exclusion threshold for heart failure for NT-pro BNP is less than (single choice):

When asked about the exclusion threshold of NT pro-BNP for HF, 54 practitioners (50.00%) could not give an answer, 11 (10.19%) practitioners chose 100 pg/ml, 1 practitioner (0.93%) chose 200 pg/ml, 7 practitioners (6.48%) chose 400 pg/ml. However, 35 practitioners chose the right answer which was 300 pg/ml accounting for 32.41% of the practitioners (Figure 97).

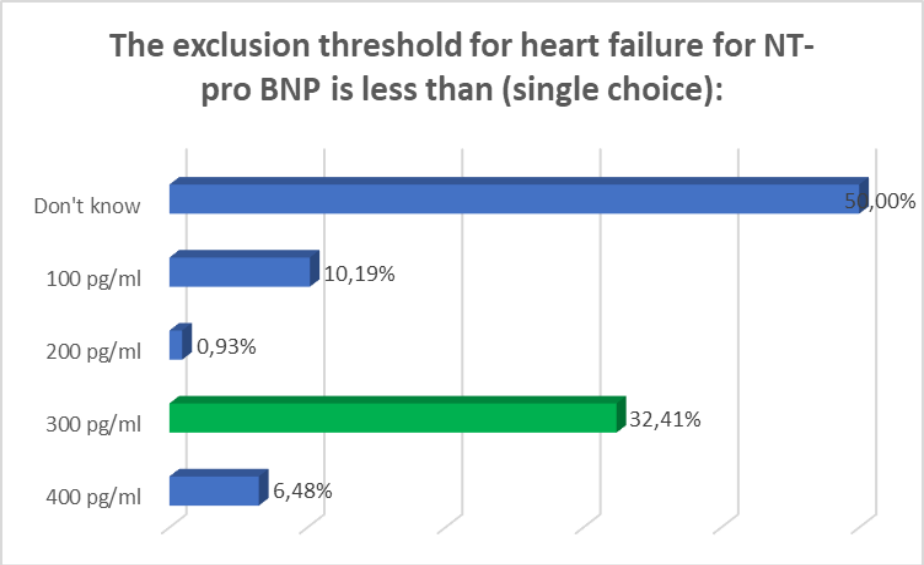


Figure 97: Question 77.

3.11. The exclusion threshold for heart failure for BNP is less than (single choice):

When asked about the exclusion threshold of BNP for HF, 56 practitioners (51.85%) could not give an answer, 14 (12.96%) practitioners chose 300 pg/ml, 3 practitioners (2.78%) chose 200 pg/ml, no practitioner chose 400 pg/ml. However, 35 practitioners chose the right answer which was 100 pg/ml accounting for 32.41% of the practitioners (Figure 98).

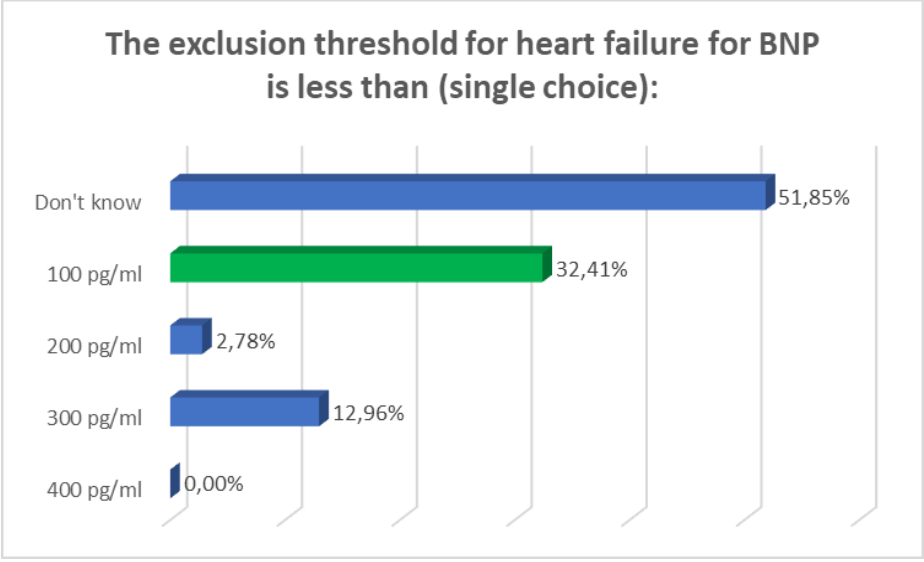


Figure 98: Question 78.

The cutoff for heart failure for NT-pro BNP is:

When asked about the cutoff for NT pro-BNP in HF according to age, 96 (88.89%) of the practitioners could not give an answer, 4 practitioners (3.70%) think it is the same for all ages. However, 4 (3.70%), 6 (5.56%) and 6 (5.56%) respectively chose "1800 pg/ml after 75 years of age", "900 pg/ml between 50 and 75 years of age" and "450 pg before the age of 50" which were all right answers (Figure 99) .

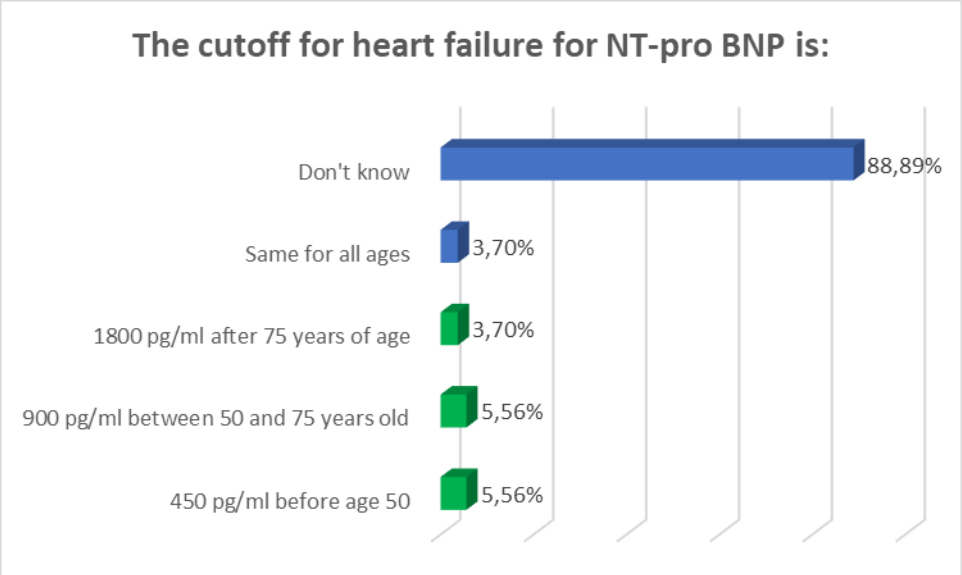


Figure 99: Question 79.

3.12. BNP (multiple choice):

When asked about the effect of BNP, 77 practitioners (71.30%) could not give an answer, 1 practitioner (0.93%) thinks that it leads to vasoconstriction, 21 (19.44%), 20 (18.52%), 16 (14.81%), 4 (3.70%) and 5 (4.63%) practitioners respectively chose the right answers which stated, that it causes diuresis and natriuresis, that it inhibited RAA system, that it was an active form, that it was eliminated by endopeptidases, kidneys and receptors A, B and C, that it had a shorter half-life compared to NT-pro BNP (Figure 100).

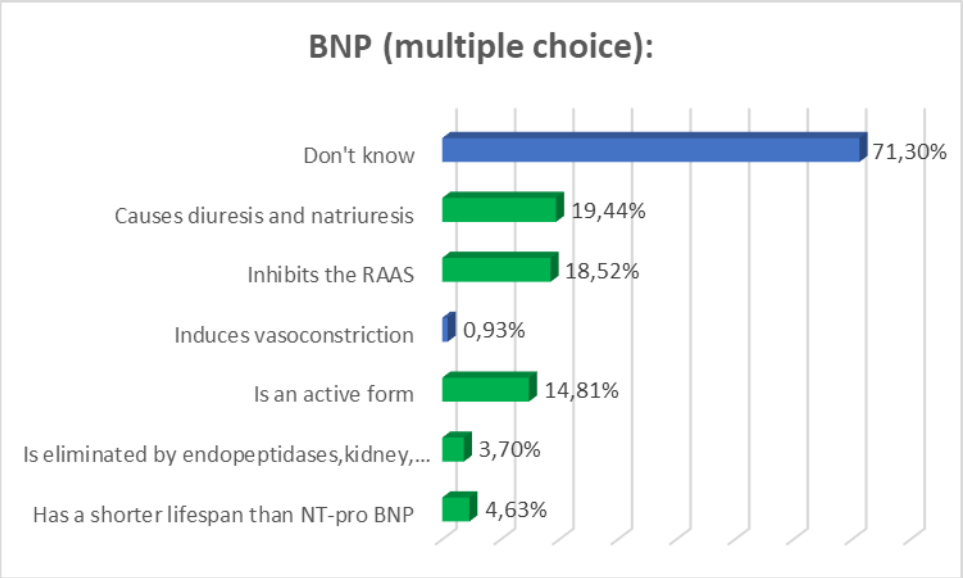


Figure 100: Question 80.

3.13. The factors that influence BNP and that necessarily require an adaptation of thresholds are (multiple choice):

When asked about the factors that necessarily required an adaptation of BNP thresholds, 72 (66.67%) practitioners could not give an answer, 20 (18.52%), 15 (13.89%) and 18 (16.67%) respectively chose lung conditions, obesity and female gender. However, 31 (28.70%) practitioners chose renal failre and 27 (25.00%) practitioners chose age, which were both correct answers (Figure 101).

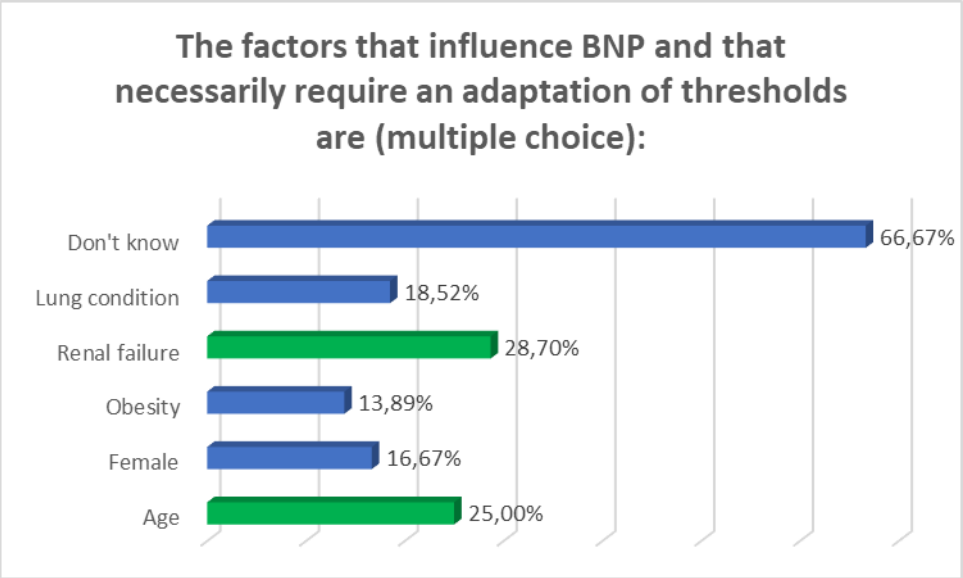


Figure 101: Question 81.

3.14. In terms of severity, there is a correlation between BNP/NT-pro BNP level and (multiple choice):

When asked about BNP and NT- pro BNP as a biomarker for prognosis, 87 (80.56%) practitioners could not give an answer, 2 (1.85%) said it had no correlation. However, 18 (16.67%), 10 (9.26%) and 14 (12.96%) respectively said it had a correlation with the severity of HF, the NYHA classification and the LV ejection fraction which were the 3 right answers (Figure 102).

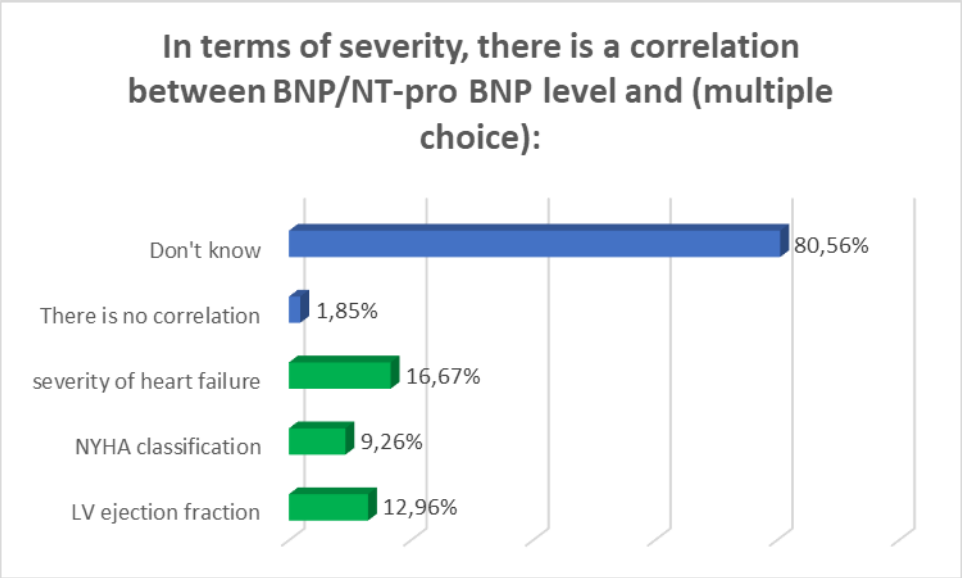


Figure 102: Question 82.

3.15. In terms of prognosis and therapeutic follow-up, BNP/NT-pro BNP (choice of choice):

When asked about BNP as a prognostic and therapeutic biomarker, 73 practitioners (67.59%) could not give an answer, 9 (8.33%), 22 (20.37%), 19 (17.59%), 7 (6.48%), 19 (17.59%) and 16 (14.81%) practitioners chose the right answers which were -respectively-: "provides prognosis for morbidity and mortality of ACS", "allows to anticipate cardiac decompensation", "reduces the frequency of acute events, rehospitalization and mortality", "the therapeutic goal should be less than 1000 pg/ml", "if they do not decrease during treatment or increase, mortality becomes high" and "predicts progression to chronic heart failure", which were the right answers (Figure 103).

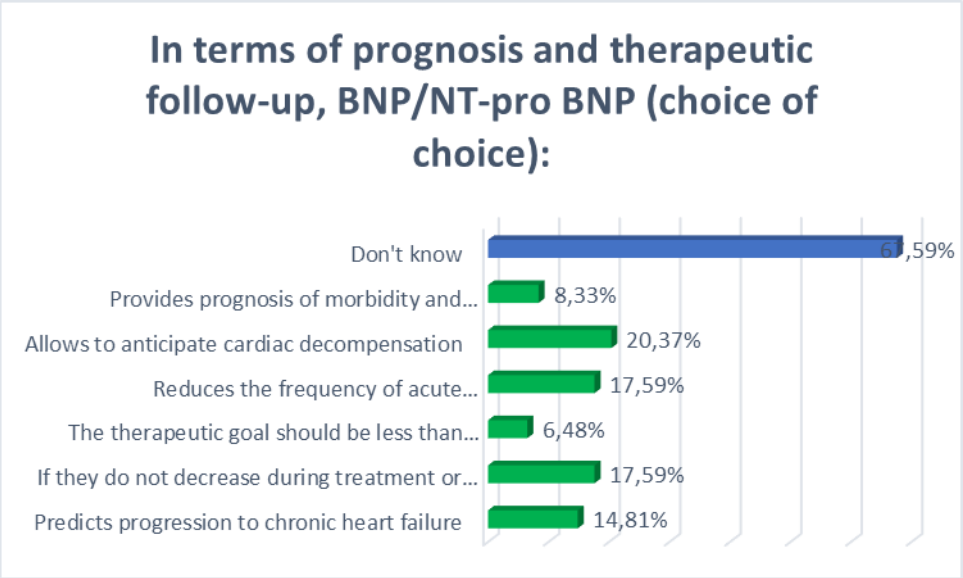


Figure 103: Question 83.

4. State of knowledge on procalcitonin:

4.1. Procalcitonin (multiple choice):

When asked about PCT, 68 (62.96%) practitioners think it is synthesized by the parathyroid cells,13 (12.04%) practitioners believe that age does not influence its levels. 53 (49.07%) practitioners believe it is better than CRP in the prognosis of sepsis, 51 (47.22%) practitioners believe it reduces the duration of antibiotic therapy and 53 (49.07%) believe it helps in the decision to start, maintain or stop antibiotics which were the 3 right answers (Figure 104).

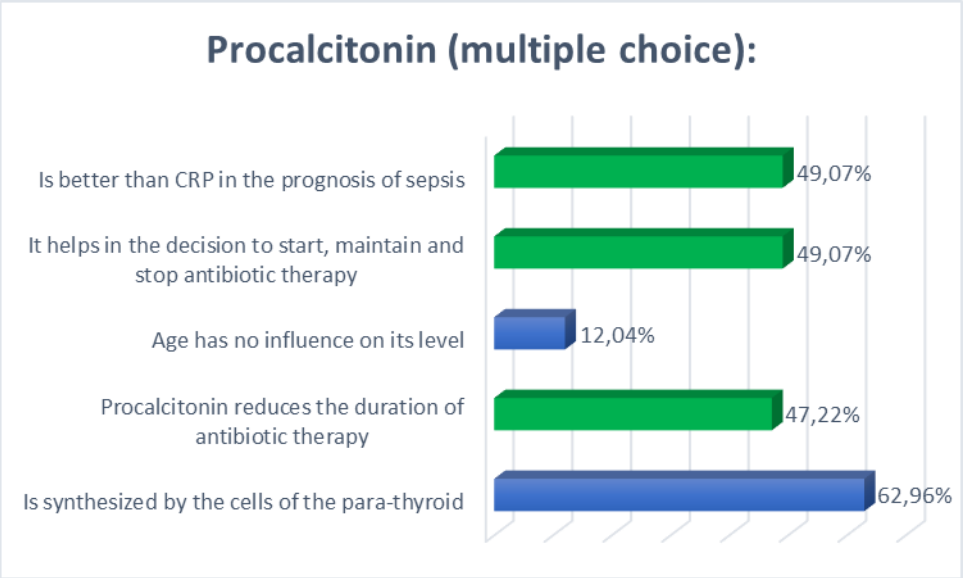


Figure 104: Question 84.

4.2. During infectious episodes, which of the following infectious agents are generally associated with a "low" or even "negative" PCT (multiple choice):

When asked about pathogens associated with low levels of PCT, 18 practitioners could not give an answer, 23 (21.30%) practitioners said it was gram negative bacteria, 32 (29.63%) practitioners said it was parasites and 1 (0.93%) practitioner said it was gram positive cocci. However, the right answers were “viruses” and “intercellular bacteria” which were checked respectively by 83 (76.85%) and 32 (21.30%) practitioners (Figure 105).

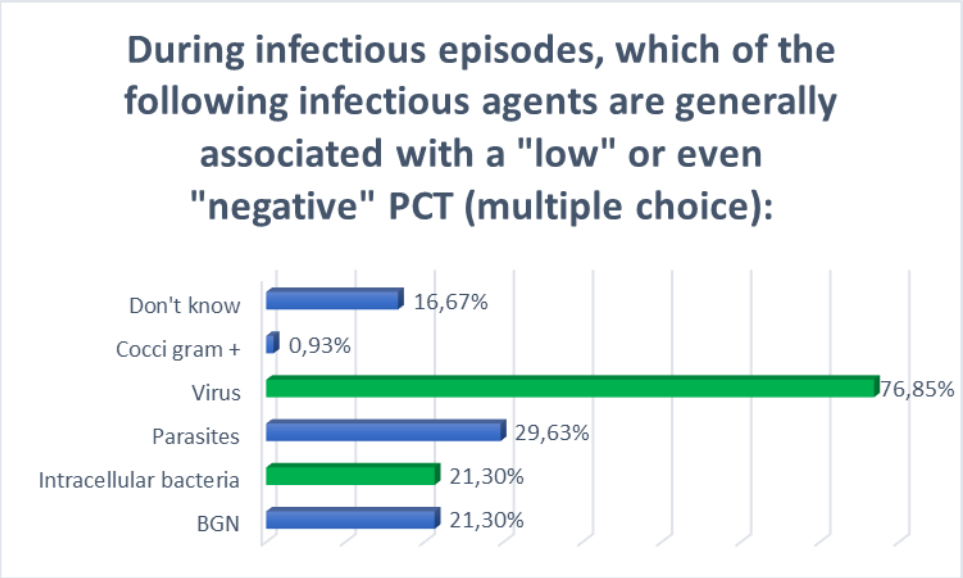


Figure 105: Question 85.

4.3. Procalcitonin may not increase in some situations where infection is present (False negative) as:

When asked about the limitations of PCT, 55 (50.93%) practitioners said they did not know. 47 (43.52%), 35 (32.41%), 30 (27.78%) and 12 (11.11%) practitioners respectively checked “an infection masked by antibiotics”, “compartmentalized infection”, “localized infection” and “early infection <3h” which were the right answers (Figure 106).

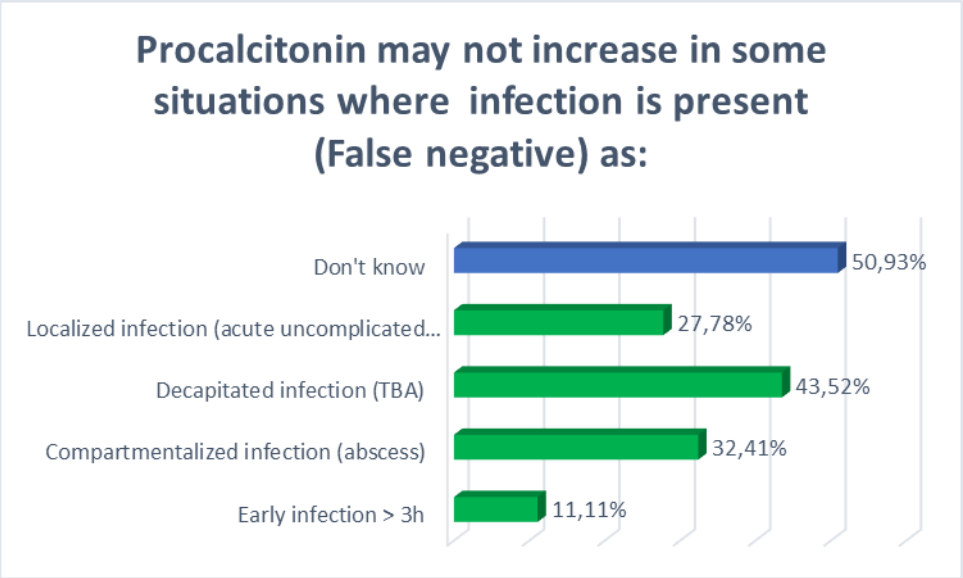


Figure 106: Question 86.

4.4. The half-life of the PCT is about (single choice):

When asked about the half life of PCT, 84 practitioners (78.70%) could not give an answer, 6 practitioners (5.56%) think it is 6 hours, 3 practitioners (2.78%) think it is 36 hours and 6 practitioners (5.56%) think it is 12 hours. However, 9 practitioners chose the right answer which was “24 hours” (Figure 107).

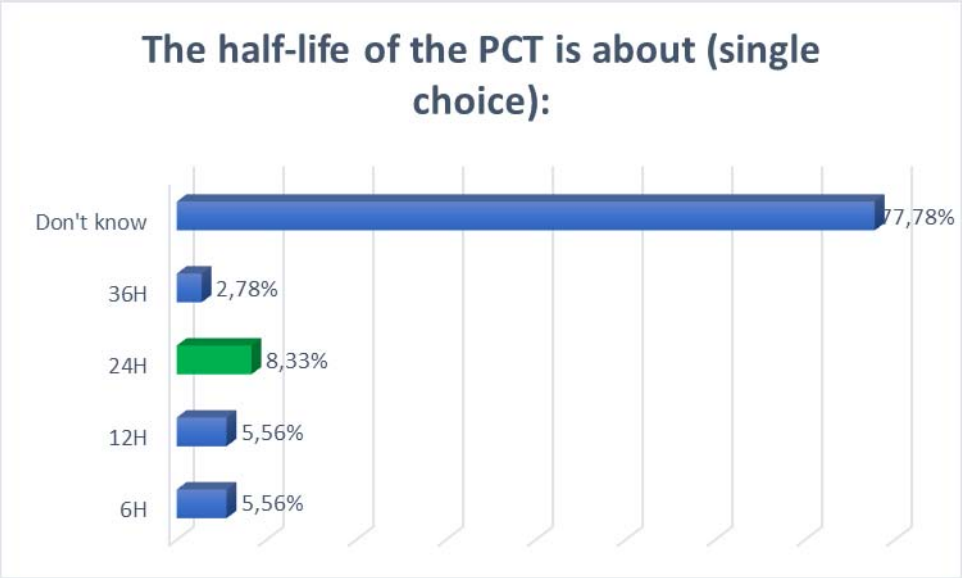


Figure 107: Question 87.

4.5. After endotoxin injection, PCT is detectable in serum as early as (single choice):

When asked about the delay in PCT increase, 85 practitioners (78.70%) said they did not know, 15 (13.88%) practitioners chose answers above 6 hours and 8 practitioners (7.41%) chose the right answer which was 3 hours (Figure 108).

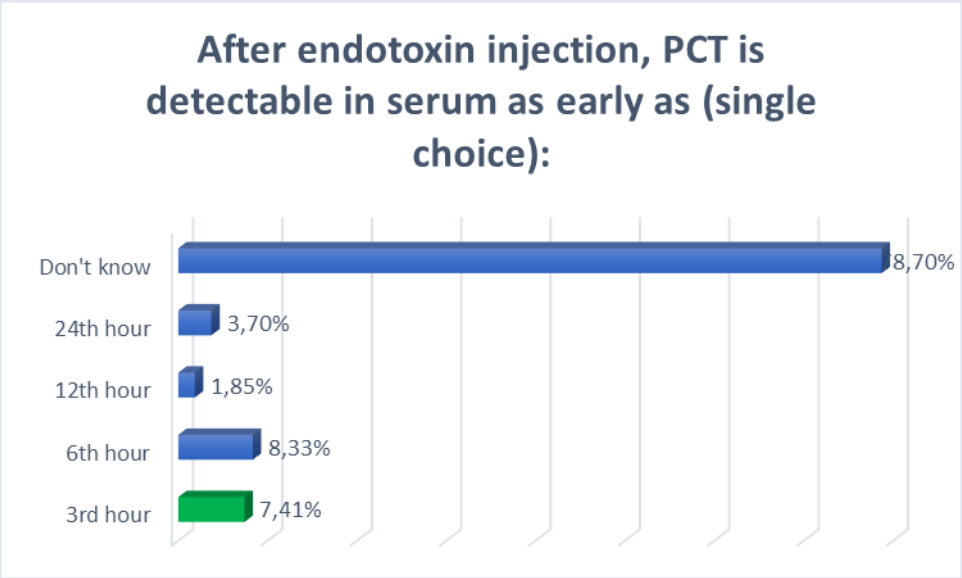


Figure 108: Question 88.

4.6. What non-septic situations can lead to a significant PCT increase (multiple choice):

When asked about non-specific situations that lead to an increase in PCT, 57 practitioners (52.78%) could not give an answer. 28 (25.93%),27 (25.00%), 26 (24.07%) ,18 (16.67%) ,17 (15.74%) ,17 (15.74%) and 3 (2.78%) practitioners respectively chose polytrauma and surgery, newborn<48h, medullary thyroid cancer, MAS, severe cardiogenic shock, small cell lung and bronchial carcinoma and heat stroke, which were all right answers (Figure 109).

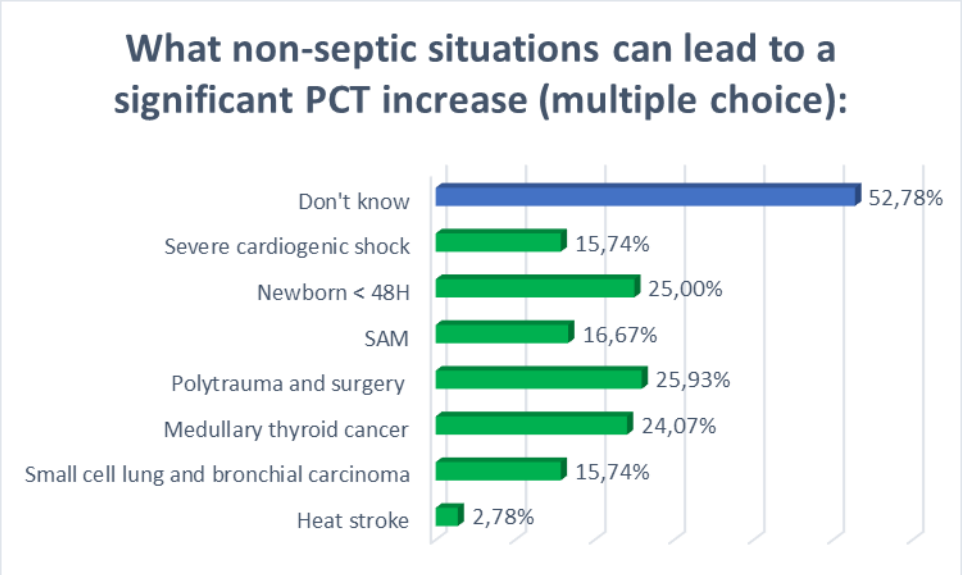


Figure 109: Question 89.

4.7. In lower respiratory infections, above which cut-off point is it recommended to repeat the PCT within 12 hours on average (6-24 hours depending on the situation), when the pre-test probability is high (single choice):

When asked about the recommended cutoff value of PCT below which it was recommended to repeat dosage within 12 hours when the pretest probability was high, 92 practitioners (85.19%) said they did not know, 14 practitioners chose values above 0.2 ng/ml. however, 2 practitioners chose the right answer “0.1 ng/ml” accounting for 1.85% (Figure 110).

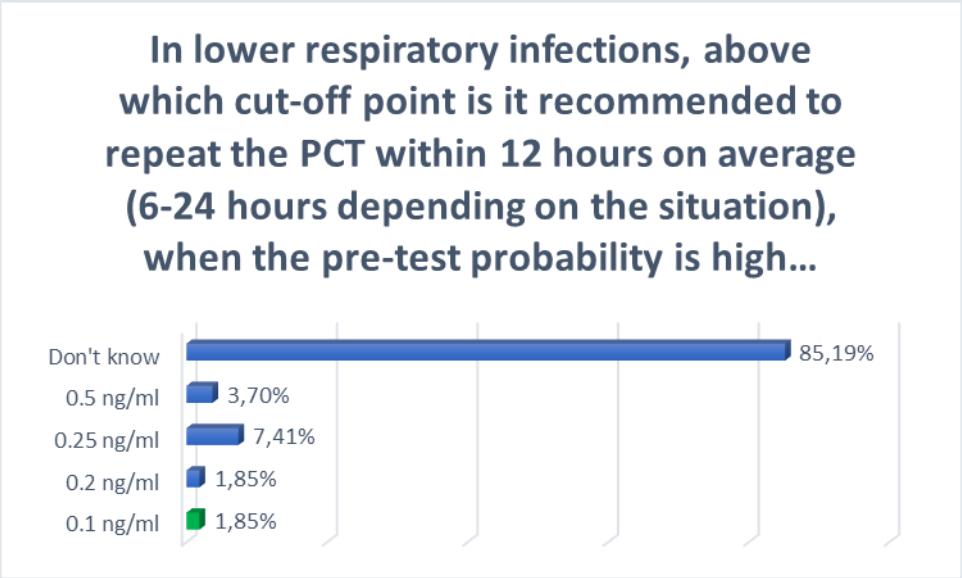


Figure 110: Question 90.

4.8. There is general agreement in the literature that PCT is a good marker of infection in the population over 75 years of age:

When asked about the age limitations of PCT, 88 practitioners (81.48%) said they did not know, 13 practitioners (12.04%) think that PCT is a good marker for infection in patients above 75 years of age while 7 practitioners think It is not, accounting for 12.04% (Figure 111).

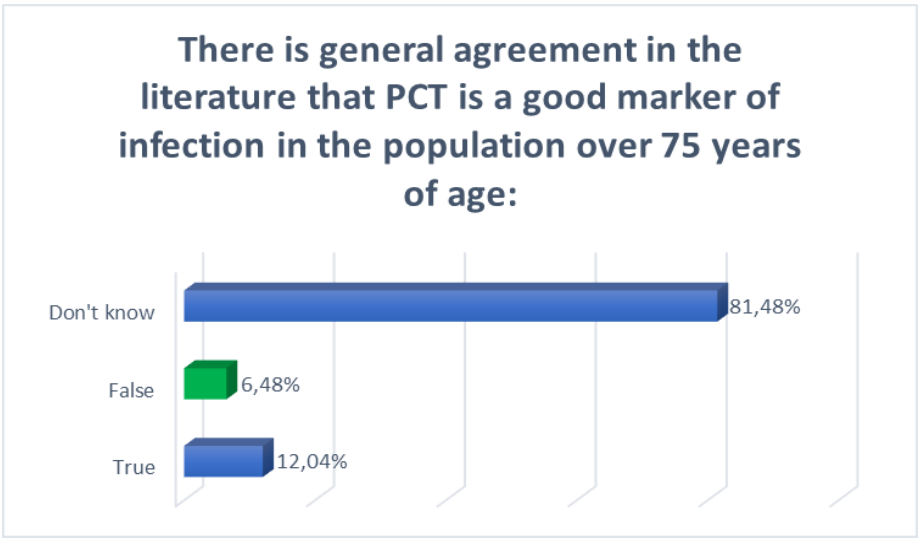


Figure 111: Question 91.

4.9. In the context of lower respiratory infections and sepsis, the discontinuation or initial non-prescription of antibiotics is recommended for PCT (single choice):

When asked about PCT in the context of lower respiratory tract infection, 91 (84.26%) could not give an answer, 10 practitioners chose values of "0.1 ng/ml" or "0.5 ng/ml" while 7 (6.48%) practitioners chose the right answer which was "0.25 ng/ml" (Figure 112).

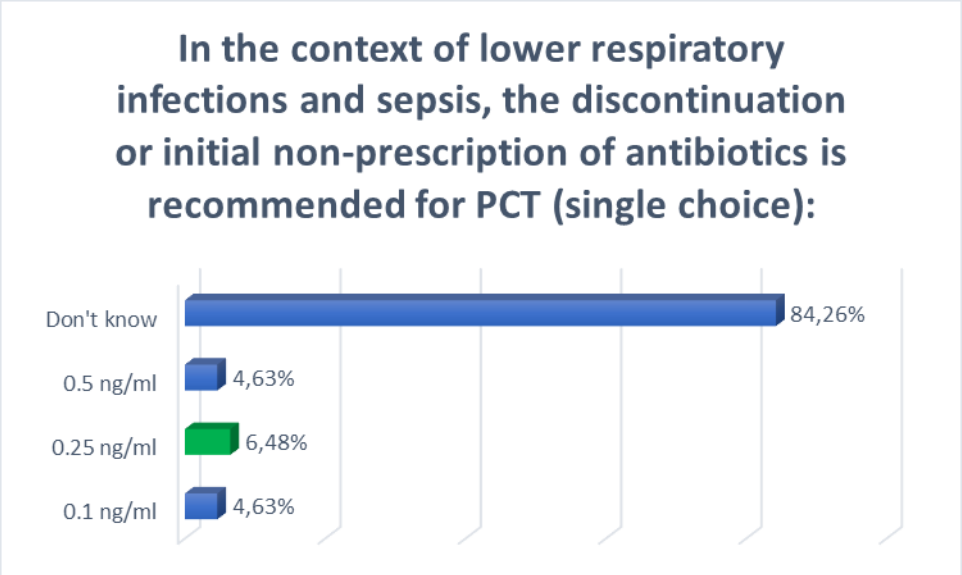


Figure 112: Question 92.

4.10. In general, at what threshold is PCT associated with a high risk of severe sepsis and/or septic shock (single choice):

When asked about PCT threshold associated with high risk of sepsis or septic shock, 93 (86.11%) practitioners could not give an answer, 4 (3.70%) practitioners chose "1ng/ml", 3 practitioners (2.78%) chose "4ng/ml", 2 practitioners (1.85%) chose "0.5 ng/ml". however, 6 practitioners (5.56%) chose the right answer which was "2ng/ml" (Figure 113).

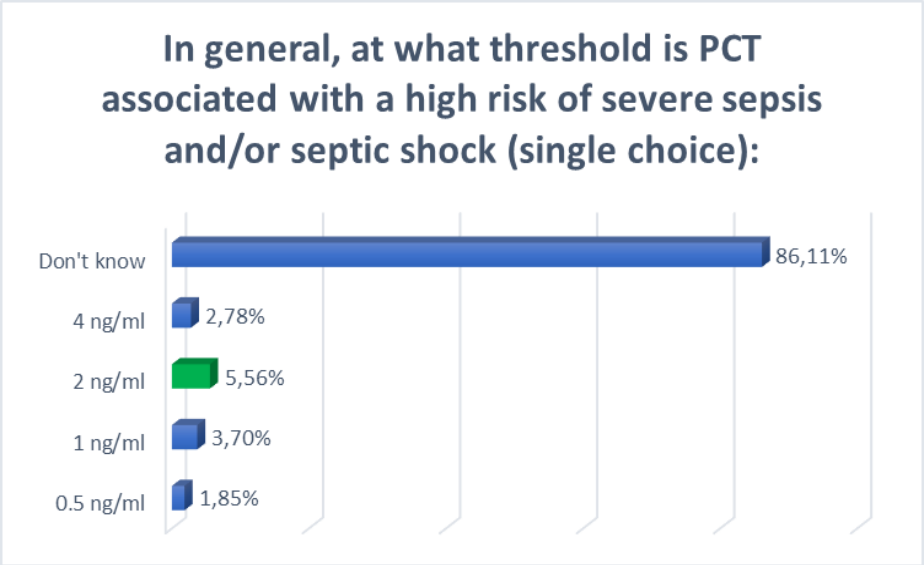


Figure 113: Question 93.

4.11. PCT has documented prognostic stratification utility at which of the following thresholds (single choice):

When asked about the utility of PCT in stratification of risk, 96 practitioners (88.89%) could not give an answer, 5 (4.63%) practitioners chose ">2ng/ml", and 7 (6.48%) practitioners chose >5ng/ml" which was the right answer (Figure 114).

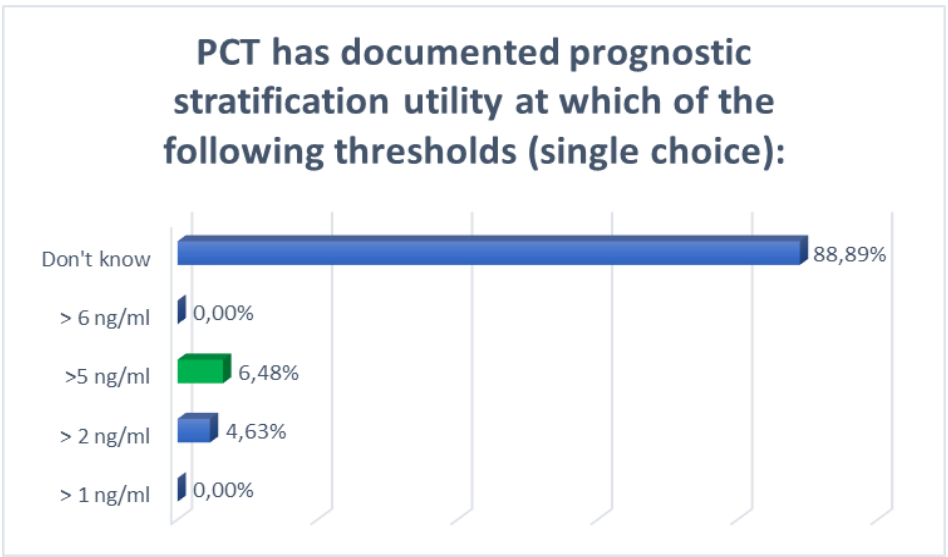


Figure 114: Question 94.

4.12. The PCT decision threshold for distinguishing between inflammation and infection for meningitis is (single choice):

When asked about the PCT threshold for distinguishing between inflammation and infection, 96 practitioners (88.89%) could not give an answer, 7 (6.48%) practitioners chose values above 1 ng/ml. 5 practitioners (4.63%) chose the right answer which was "0.5-1 ng/ml" (Figure 115).

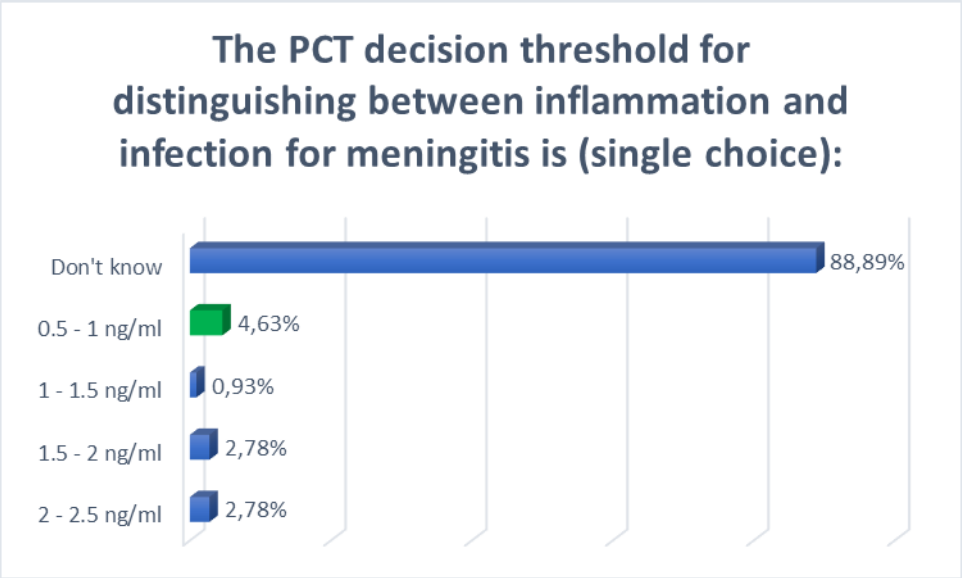


Figure 115: Question 95.

5. State of knowledge on CRP:

5.1. CRP (multiple choice)

When asked about CRP, 31 (28.70%) of practitioners could not give an answer, 10 (9.26%) practitioners think that CRP is synthesized by the hypothalamus, 19 practitioners (17.59%) think that CRP is specific to bacterial infections. 53 (49.07%), 42 (38.89%) and 8 (7.41%) practitioners respectively checked the following suggestions "Is a marker of inflammation of all causes", "Is a protein synthesized by the hepatocytes" and "Named for its property of precipitation upon contact with the pneumococcal C polysaccharide" which were the right answers (Figure 116).

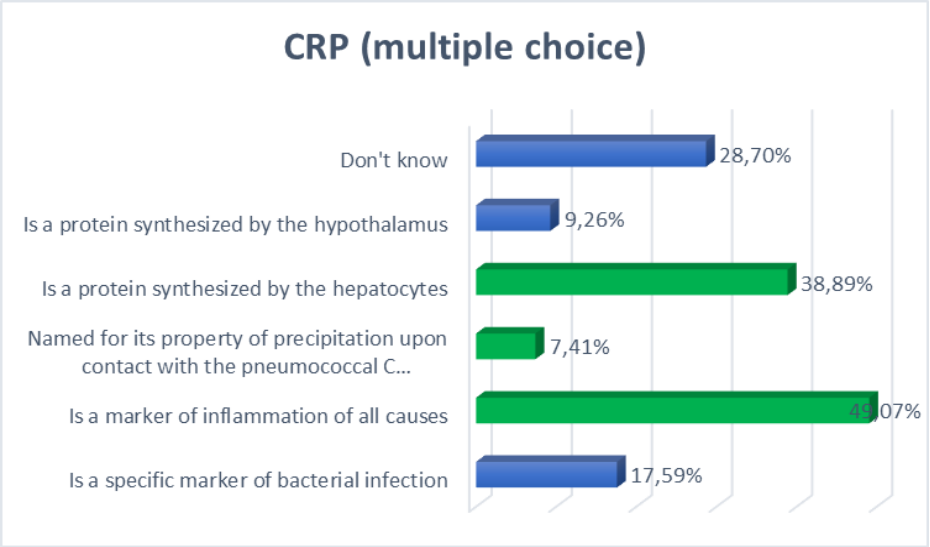


Figure 116: Question 96.

5.2. The half-life of CRP is (single choice):

When asked about the half-life of CRP, 77 (71.30%) practitioners did not know, 2 (1.85%) practitioners think it is 3 hours, 5 (4.63%) practitioners think it is 24 hours, 11 practitioners (10.19%) think it is 12 hours. However, 13 (12.04%) practitioners answered “6 hours” which was the right answer (Figure 117).

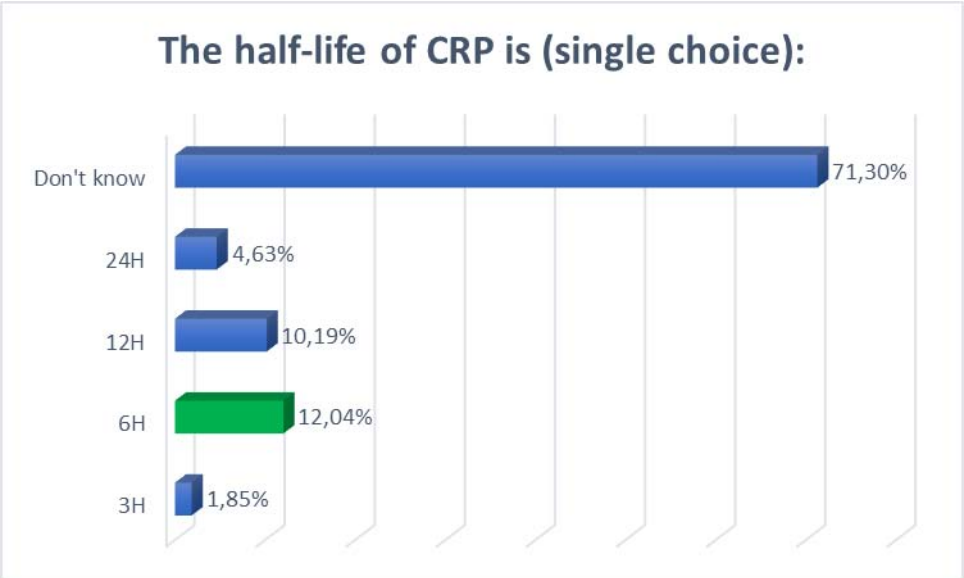


Figure 117: Question 97.

5.3. Based on the kinetics of CRP, it rises after the onset of the process inflammatory as soon as (single choice):

When asked about the kinetics of CRP, 77 practitioners (71.30%) could not give an answer, 20 practitioners (18.51%) believe that CRP rises within 24 hours, 13 (12.04%) practitioners think that it rises after 48 hours which was the correct answer (Figure 118).

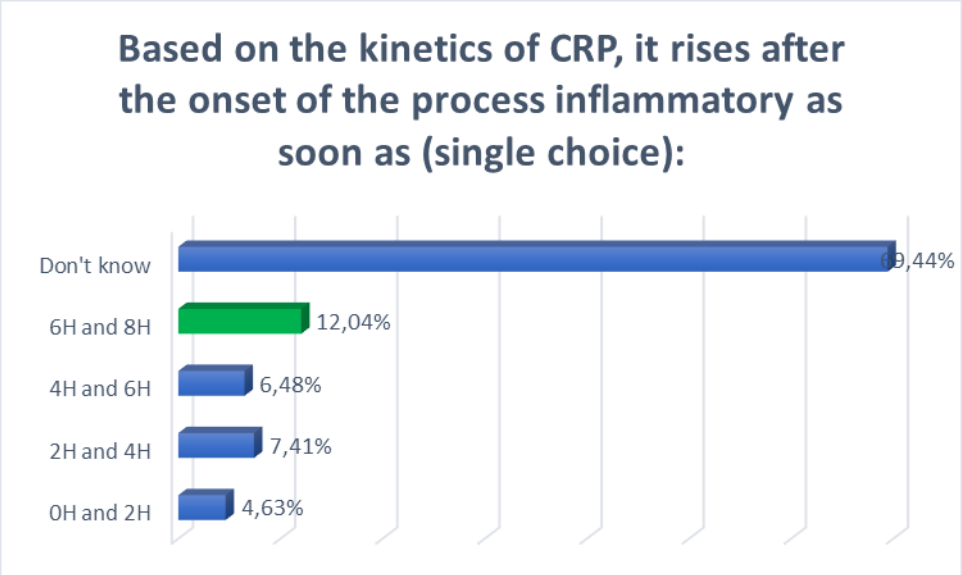


Figure 118: Question 98.

5.4. CRP reaches its maximum value in (single choice)

When asked about CRP kinetics, 77 practitioners (71.30%) could not give an answer, 18 (16.66%) practitioners believe it reaches its maximum before 24h and 13 practitioners (12.04%) believe it reaches its maximum in 48 hours which was the correct answer (Figure 119).

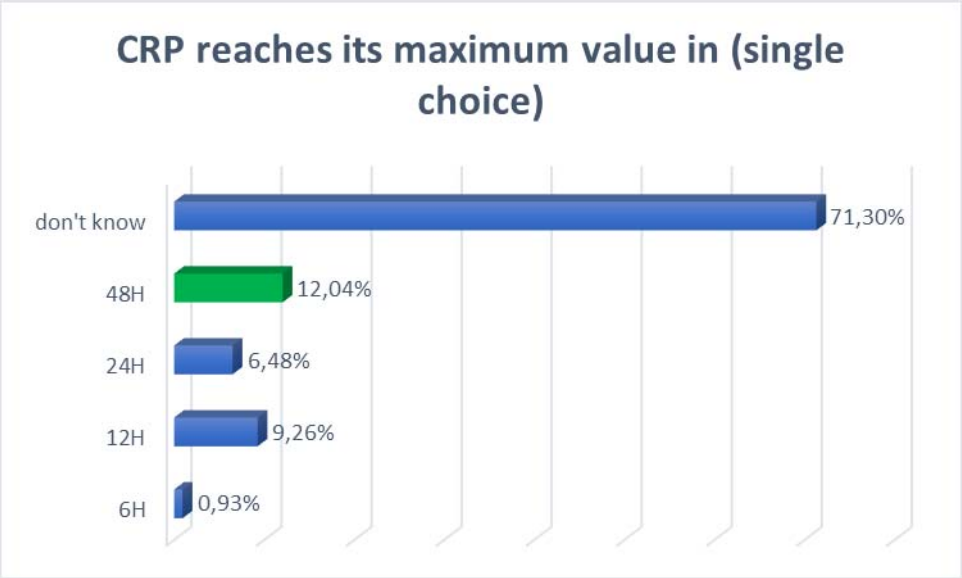


Figure 119: Question 99.

5.5. CRP concentration is influenced by (multiple choice)

When asked about the factors that influence CRP concentration, 57 practitioners (52.78%) could not give an answer. 39 (36.11%), 36 (33.33%), 33 (30.56%), 30 (27.78%), 16 (14.81%) practitioners respectively chose corticosteroid use, liver failure, pregnancy, age and chronic smoking (Figure 120).

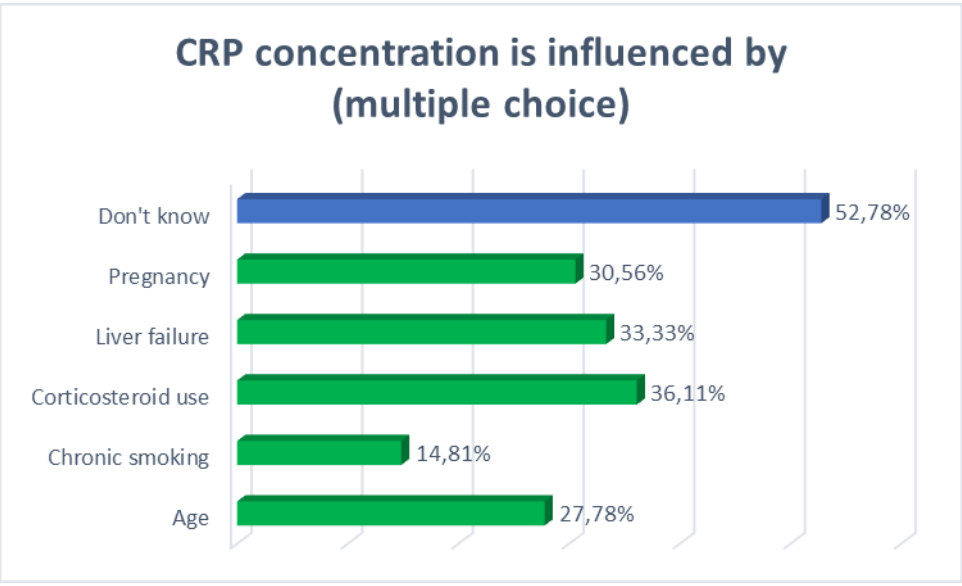


Figure 120: Question 100.

5.6. CRP (multiple choice):

When asked about the prognostic value of CRP, 66 (61.11%) practitioners could not give an answer, 10 (9.26%) practitioners think its value is not correlated with the severity of the SOFA score, 6 practitioners (5.56%) think CRP is better than PCT for prognosis of sepsis. However, 37 (34.26%) and 16 (14.81%) practitioners respectively think that PCT is better than CRP in the prognosis of sepsis and that CRP value is correlated with SOFA scores (Figure 121).

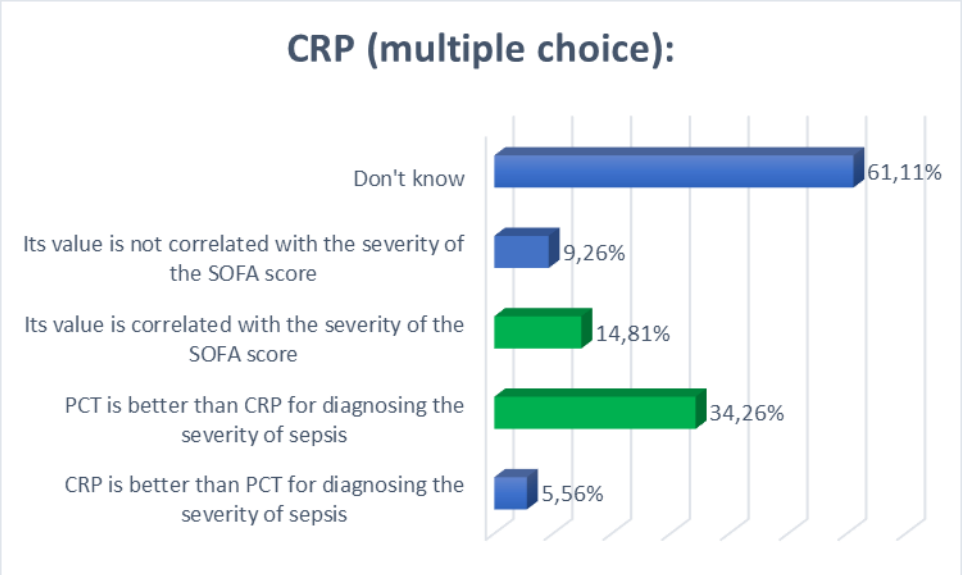


Figure 121: Question 101.

6. State of knowledge on S100B:

6.1. Regarding the localization of the S100b protein (single choice):

When asked about the physiology of S100B, 89 (82.41%) practitioners said they did not know, 3 (2.78%) practitioners think it is produced in the liver and 16 (14.81%) think it is produced in the brain tissue which was the right answer (Figure 122).

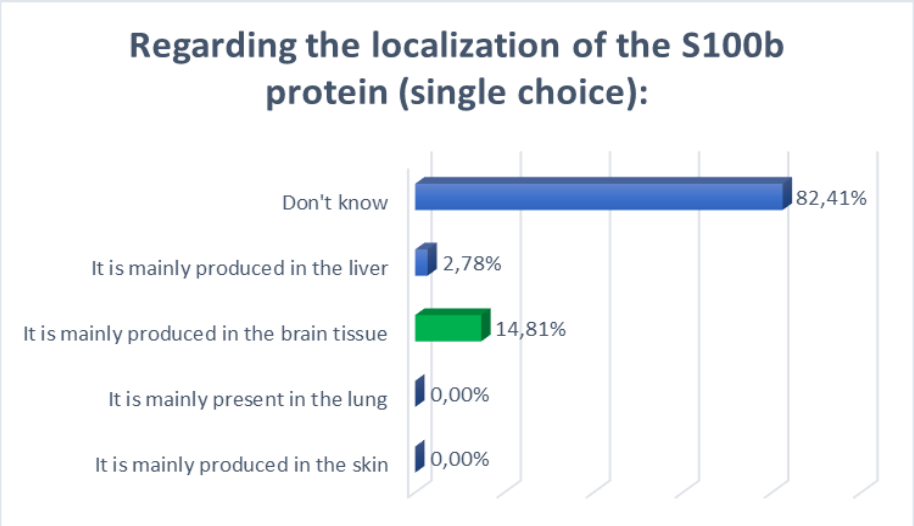


Figure 122: Question 102.

6.2. The S100b protein assay is indicated in the CT (single choice):

When asked about the indications of S100B protein, 94 practitioners (87.04%) could not give an answer, 10 practitioners (9.26%) think it is indicated when a patient has risk factors for intracranial lesions, 3 (2.78%) practitioners think it is indicated if the Glasgow score is < 13. However, 1 practitioner (0.93%) gave the right answer, which was "when the mild head injury was less than 3h old" (Figure 123).

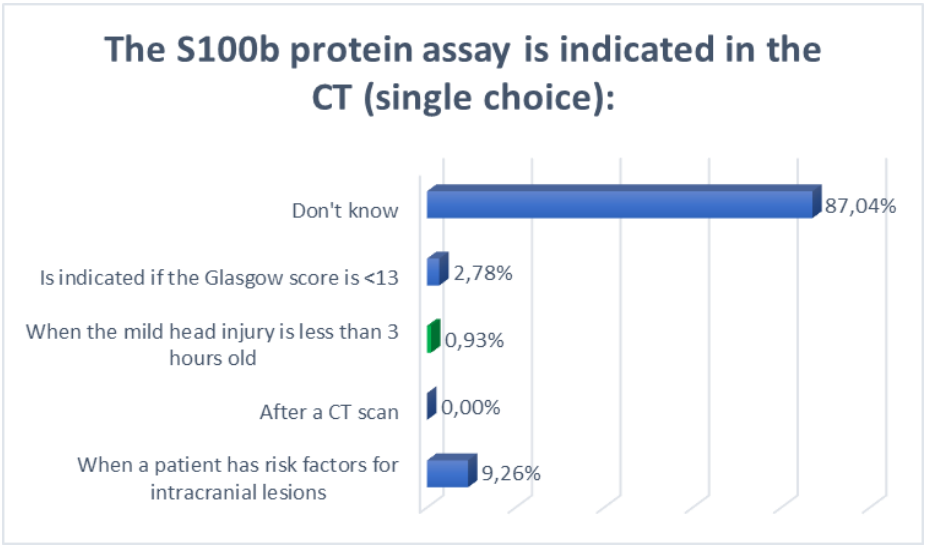


Figure 123: Question 103.

6.3. The S100b protein may be useful for (multiple choice):

When asked about the applications of S100B, 93 practitioners (86.11%) could not give an answer, 12 (11.11%), 10 (9.26%), 5 (4.63%), 2 (1.85%) practitioners respectively chose the following propositions: “Early assessment of the risk of neurological complications after head injury”, “The decrease in the number of brain scans prescribed after minor head trauma”, “Estimating neurological prognosis after stroke”, “Estimating the neurological prognosis after cardiac arrest”, which were all right answers (Figure 124).

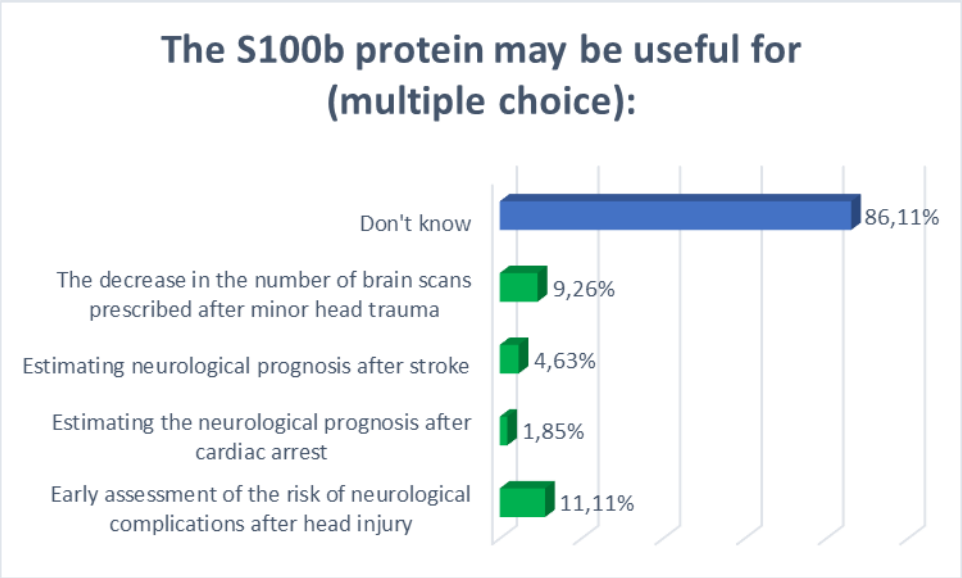


Figure 124: Question 104.

6.4. S100b protein may increase in the following citations (multiple choice):

When asked about the differential diagnosis of increased S100B protein increase. 92 (85.19%) practitioners said they did not know, 9 (8,33%), 2 (1,85%), 16 (14,81%), 12 (11,11%) practitioners respectively chose “Brain tumors (glioma, glioblastoma, neuroma)”,”Malignant melanoma”, “Head trauma with rupture of the blood-brain barrier”, “Stroke” which were all right answers (Figure 125).

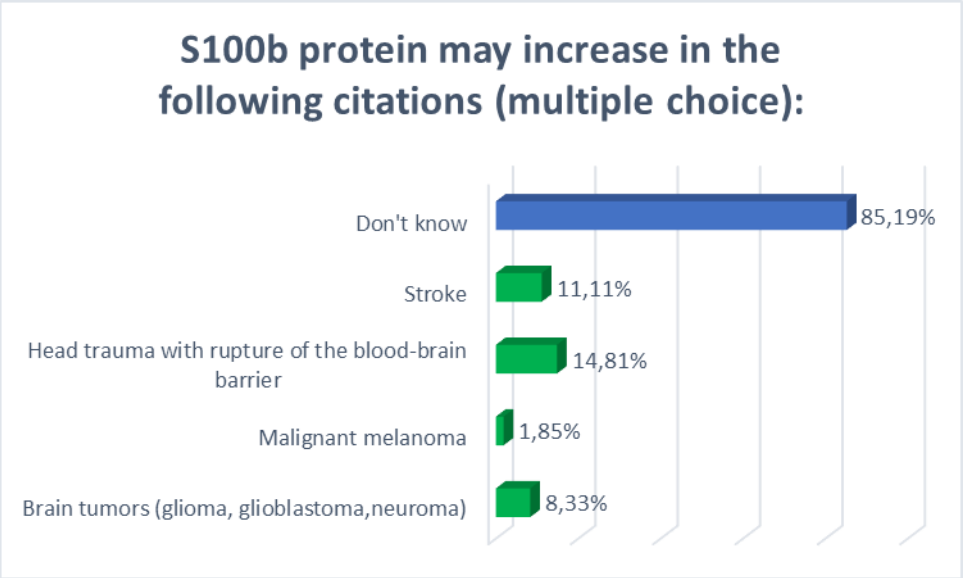


Figure 125: Question 105.

6.5. S100b protein (multiple choice):

When asked about S100B, 96 practitioners (88.89%) could not give an answer, 6 (5,56%), 3 (2,78%), 4 (3,70%), 10 (9,26%) and 1 (0,93%) practitioners chose the following propositions: "Has an excellent negative predictive value to rule out an intracranial hemorrhagic lesion", "Has an excellent positive predictive value to confirm an intracranial hemorrhagic lesion", "Can predict a normal CT scan (without brain lesions) if negative", "At high concentrations in patients with CT documented brain damage", "Is a marker of aggressiveness and response to treatment in malignant melanoma", which were all right answers (Figure 126).

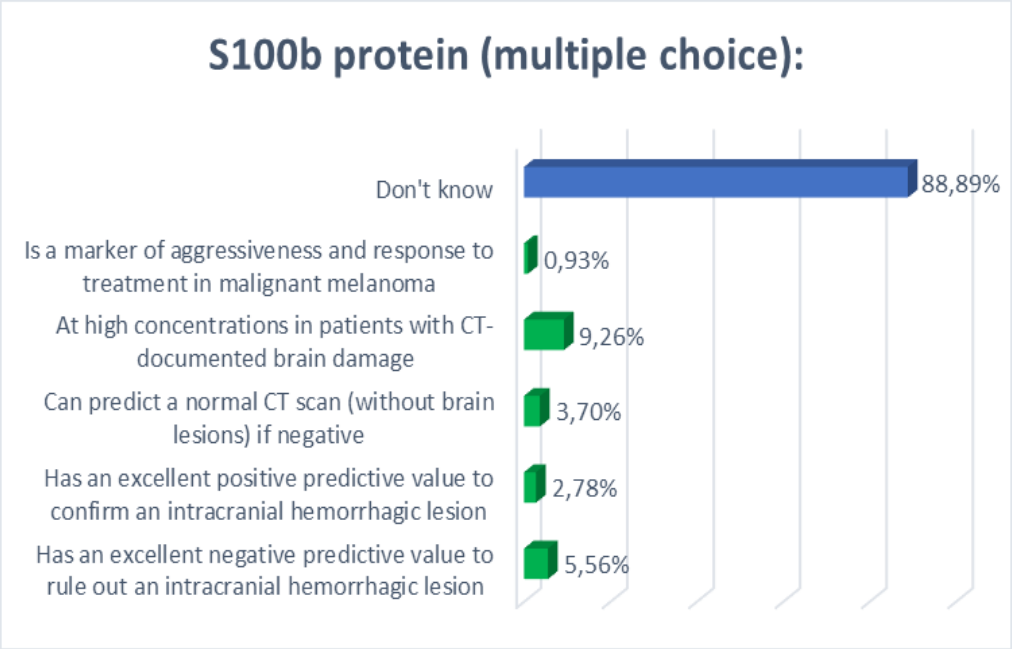


Figure 126: Question 106.

DISCUSSION

LITERATURE REVIEW

I. Literature review on biomarkers:

This review aims to provide clinicians with a comprehensive introduction to the use of biomarkers in emergency departments (EDs). In the first part, we will discuss the general concepts and principles of biomarkers, as well as the statistical methodologies that are used to evaluate their diagnostic properties. We will also explain the importance of understanding classic diagnostic indices like sensitivity, specificity, and predictive values, as well as newer concepts like likelihood ratios and ROC curves and the place they hold within the principles of Bayesian theory.

In the second part, we will focus on six specific biomarkers: cardiac troponin for myocardial infarction, natriuretic peptides for heart failure, D-dimers for venous thromboembolism, C-reactive protein as a marker of inflammation, procalcitonin for bacterial infection and antibiotic stewardship, and S100B protein for mild head injury. For each biomarker, we will provide an overview on physiopathology, historical evolution of evidence, strengths and limitations for a rational implementation into clinical algorithms with a special emphasis on the following elements: reference and/or threshold values, the metabolism of the biomarker (synthesis, release, clearance, kinetics, half-life), physiological effects, characteristics of the biomarker (sensitivity, specificity, PPV, NPV …) and also the most important possible variations of the results (limitations and confounders of the biomarker).

In the third part, we will examine POCT and its potential to address issues in the ED such as overcrowding and long turnaround times. We will discuss the benefits and challenges of POCT, as well as future perspectives.

We believe that having a thorough understanding of the characteristics of biomarkers allows for accurate interpretation and application of biomarker results in individual patients. And that familiarity with the statistical methodologies available is crucial to navigate the biomarker

revolution, whether you are a clinician, researcher or a consumer of scientific literature. Therefore, our objective is to offer a comprehensive guide on the use of biomarkers in emergency departments to aid readers in enhancing their diagnostic abilities and selecting appropriate tests.

II. Literature review on biomarkers:

1. Definition:

In 2001, the biomarker definitions working group of the National Institutes of Health (NIH) defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathological processes, or pharmacologic responses to a therapeutic intervention". When this characteristic is the result of an assay or measured from a biological sample, the term biomarker (short for biological marker) is used (1).

According to the NIH, biomarkers can be subdivided into "Type 0", "Type 1" and "Type 2" biomarkers. A type 0 biomarker provides a signal of the natural history of a disease that correlates longitudinally with known clinical indices (diagnosis, prognosis and outcome). A type 1 biomarker captures the effects of a therapeutic intervention in accordance with its mechanism of action (general efficacy of treatment). A type 2 biomarker is used as a surrogate for clinical endpoints (2). The relationship of each type with disease ranges from tenuous (type 0) to being mechanistically linked to the disease (type 2).

Clinical endpoint: a characteristic of variable that reflects how a patient feels, functions and survives. It is mainly used to reflect the effect of a therapeutic intervention (survival, patient reported outcomes such as pain, or ability to perform activities of daily life).

Surrogate endpoint: a biomarker that is intended to substitute for a clinical endpoint. it is therefore a direct measure of how a patient fells, functions or survives. They are expected to predict clinical benefit or harm based on epidemiological, pathophysiological, therapeutic or

other scientific evidence Therefore, changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinical endpoint. For example, if we can show that statins reduce cholesterol we can say that statins reduce death without showing directly that statins prevent death since elevated cholesterol levels increase heart disease. In this example, "death from heart disease" is the clinical endpoint while "levels of cholesterol in the blood" is the surrogate endpoint. Other examples include blood pressure in stroke prevention, QT interval in drug safety, time to progression in cancer, and plasma glucose in diabetes.

Biomarkers have many valuable applications in disease detection and monitoring of health status. The main applications in clinical practice include the following:

- Screening biomarker: a biomarker that discriminates between the healthy and asymptomatic disease state.
- Diagnostic biomarker: a biomarker used to detect or confirm presence of a disease or condition of interest or to identify individuals with a subtype of the disease.
- Monitoring biomarker: a biomarker measured repeatedly for assessing status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent.
- Response biomarker: a biomarker used to show that a biological response, potentially beneficial or harmful, has occurred in an individual who has been exposed to a medical product or an environmental agent.
- Predictive biomarker: a biomarker used to identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a medical product or an environmental agent.
- Prognostic biomarker: a biomarker used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest.

- ❖ Safety biomarker: a biomarker measured before or after an exposure to a medical product or an environmental agent to indicate the likelihood, presence, or extent of toxicity as an adverse effect.

- ❖ Risk biomarker: a biomarker that indicates the potential for developing a disease or medical condition in an individual who does not currently have clinically apparent disease or the medical condition.

Table XXXII: The main types of a biomarkers and their examples.

Type of biomarker	Examples
Diagnostic Biomarker	• Blood sugar or hemoglobin A1c (HbA1c) to identify patients with Type 2 diabetes mellitus (DM). • **Troponin Ic for the diagnosis myocardial infarction.** • **Procalcitonin for the diagnosis of bacterial infection.**
Monitoring Biomarker	• International normalized ratio (INR) or prothrombin time (PT) for assessing whether the desired effect of anticoagulation has been attained in patients on warfarin Prostate-specific antigen (PSA) when assessing disease status or burden in patients with prostate cancer. • **B-type natriuretic peptide (BNP) or N-terminal pro BNP (NT-pro BNP) during follow-up to supplement clinical decision making in pediatric patients with pulmonary hypertension.** • **Procalcitonin to guide antibiotic duration.**
Response Biomarker	• Blood pressure when evaluating patients with hypertension, to assess response to an antihypertensive agent or sodium restriction. • Serum LDL cholesterol when evaluating patients with hypercholesterolemia, to assess response to a lipid-lowering agent or dietary changes. • Hemoglobin A1c (HbA1c) when evaluating patients with diabetes, to assess response to antihyperglycemic agents or lifestyle changes. • **Brain natriuretic peptide when evaluating postoperative outcome in noncardiac surgery.** • **Troponin when evaluating long-term outcome in cardiac surgery.**
Predictive Biomarker	• Breast cancer genes 1 and 2 (BRCA1/2) mutations when evaluating women with platinum-sensitive ovarian cancer, to identify patients likely to respond to Poly (ADP-ribose) polymerase (PARP) inhibitors. • Human leukocyte antigen allele (HLA)-B*5701 genotype to evaluate human

	immunodeficiency virus (HIV) patients before abacavir treatment, to identify patients at risk for severe skin reactions. • Mutations in the BRCA1/2 genes to predict sensitivity to ionizing radiation.
Prognostic Biomarker	• Breast cancer genes 1 and 2 (BRCA1/2) mutations when evaluating women with breast cancer, to assess the likelihood of a second breast cancer. • Increasing prostate-specific antigen (PSA) when evaluating patients with prostate cancer during follow-up, to assess the likelihood of cancer progression. • **C-reactive protein (CRP) level to identify patients with unstable angina or a history of acute myocardial infarction with a greater likelihood of recurrent coronary artery disease events** • **Procalcitonin to identify severe outcome in septic patients.** • **Troponin Ic to identify severe outcome in patients with pulmonary embolism.**
Safety Biomarker	• Serum creatinine when evaluating patients on drugs that affect kidney function to monitor for nephrotoxicity. • Serum potassium when evaluating patients on diuretics (decreased levels), angiotensin-converting-enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or aldosterone antagonists (increased levels). • Neutrophil count when evaluating patients on cytotoxic chemotherapy to adjust dose, determine the need to interrupt therapy, or consider the use of growth. • Corrected QT interval (QTc) to assess the potential for drugs to induce torsade de pointes.
Risk Biomarker	• Breast cancer genes 1 and 2 (BRCA1/2) mutations as a susceptibility/risk biomarker to identify individuals with a predisposition to develop breast cancer. • Factor V Leiden as a susceptibility/risk biomarker to identify individuals with a predisposition to develop deep vein thrombosis (DVT). • Infection with certain human papillomavirus (HPV) subtypes as a susceptibility/risk biomarker to identify individuals with a predisposition to develop cervical cancer. • **C-reactive protein (CRP) level as a susceptibility/risk biomarker to identify adult patients with a greater likelihood of incident coronary disease.**

The two main applications of biomarkers in emergency medicine are:

- For diagnosis: when the history and clinical examination do not allow a decision to be made between two etiological hypotheses (e.g., troponin in case of atypical chest pain in a patient with cardiovascular risk factors and a non-contributory ECG).

- For prognosis: in order to identify patients who are either the most severe from the start, or who are at risk of worsening in the short term. It is probably in this last field that the added value of biomarkers is the clearest and the most likely to be developed, because assessing the clinical severity of a patient remains a difficult exercise in the emergency room, despite the existence of severity scores. However, this prognostic evaluation is one of the main decisions in emergency medicine (e.g., whether the patient should be hospitalized or treated as an outpatient).

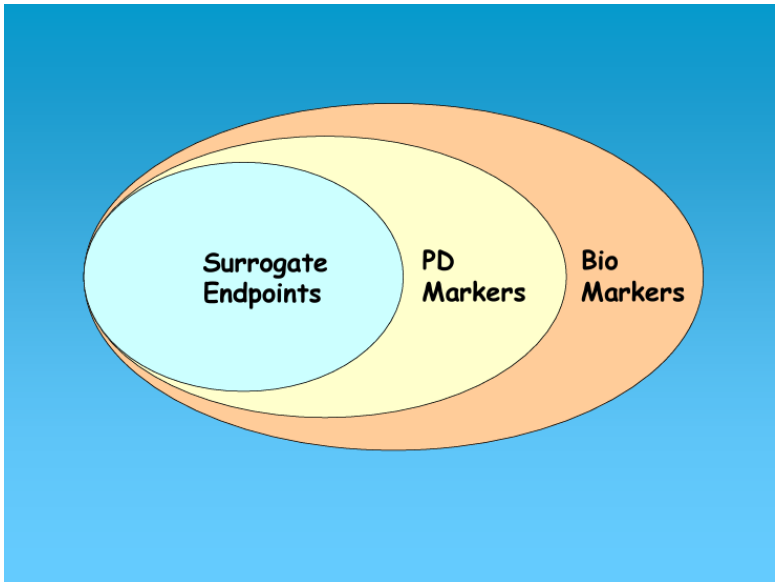


Figure 127: The relationship between surrogate endpoints, pharmacodynamic biomarkers and biomarkers (3).

1.1. History of biomarkers (4):

The term "biomarker" was first used in 1973 in an article title to indicate the presence of material of biological origin. This usage can also be found in the geological and ecological literature. However, the earliest clinical use of the term can be traced back to 1977 in a publication titled "Tumor biomarkers of value in the management of gynecologic malignancy will also be correlated with clinical course". It's worth noting that the concept of biomarkers is much older, with references to "biochemical markers" in 1949 and to "biological 'markers'" in 1957. The term "surrogate" comes from the Latin word "surrogare" (sub + rogare; supine surrogatus),

which literally means "asked in place of." It is defined as "a person or thing that acts for or takes the place of another". The earliest example of "surrogate endpoint" of which is aware dates from 1983, but in the context of competitive strategy. In 1989, the term was used in the context of clinical trials and was defined as "one that we elect to measure as a substitute for some other variable". The earliest use of "surrogate marker" in a biomedical sense was in 1985 in the context of AIDS diagnosis. Furthermore, the expression "surrogate response variable" was used in the same year in a textbook on clinical trials, where it was noted that a change in tumor size could be used as a surrogate for mortality.

1.2. Biomarker validation:

Biomarker validation refers to the process by which biomarkers are tested for their accuracy and consistency, as well as their ability to tell us something important about health or disease. Although there is no one single measure that can be used to determine the validity of all biomarkers, there are general criteria that all biomarkers must meet to be useful (5). According to the FDA, a biomarker needs to satisfy two criteria to be valid (6). First of all, it needs to have an established scientific framework or body of evidence that elucidates the physiologic, pharmacologic, toxicologic, or clinical significance of the test results. Secondly, it needs to be measured using an analytical test system with well-established performance characteristics.

Additional distinction is made between “known valid biomarkers” that have been accepted in the broad scientific community and “probable valid biomarkers” that appear to have predictive value for clinical outcomes but may not yet be widely accepted or independently verified by other investigators or institutions. When a biomarker generates or possesses sufficient data to establish a significant association between a pharmacogenomic test result and clinical outcomes, the biomarker represents a “probable valid biomarker”. It would be expected that this biomarker would meet the two criteria mentioned above, and its association with a meaningful outcome would have been demonstrated in more than one experiment.

There are several important hierarchical steps in demonstrating the clinical interest of a biomarker (7):

1. Demonstrate that the biomarker is significantly modified in diseased patients as compared to control.
2. Assess the diagnostic properties of the biomarkers.
3. Compare the diagnostic properties of the biomarker to existing tests.
4. Demonstrate that the diagnostic properties of the biomarker increase the ability of the physician to make a decision.
5. Assess the usefulness of the biomarker, which should be clearly distinguished to the quality of diagnostic information provided. Assessment of the usefulness mainly involves both characteristics of the test itself such as cost, invasiveness, technical difficulties, rapidity, and characteristics of the clinical context (prevalence of the disease, consequences of outcome, cost, and consequences of therapeutic options).
6. Demonstrate that the measurement of the biomarkers modifies outcome (intervention studies).

There are four main stages of test development and evaluation. These stages intend to answer a specific question about the biomarker following the previously mentioned steps. Diagnostic studies should match methods and take steps to answer these diagnostic questions, Sackett has summarized these steps into four questions that must be asked to validate a biomarker (8):

- Do test results in affected patients differ from those in normal individuals?
- Are patients with certain test results more likely to have the target disorder?
- Do test results distinguish patients with and without the target disorder among those in whom it is clinically sensible to suspect the disorder?
- Do patients diagnosed using the diagnostic test fare better than similar untested patients?

With the first question, we want to show that the value of the test is different in sick patients compared to non-sick patients. With the second question, we study the performance of the test in selected populations, it tells us whether the test shows diagnostic promise under ideal conditions. The last two questions refer to the notion of utility. They allow the test to be validated under the usual conditions of patient management and to evaluate the contribution of the test to the improvement of the patients' state of health in the real world setting of routine clinical practice.

III. Discrimination between two groups in an ideal situation:

First and foremost, there must be a link between the test and the condition of interest. This is translated as “scientific validity of an analyte” and is defined as 'the association of an analyte with a clinical condition or a physiological state'. This means that for a continuous test, the mean value of the test result should differ between patients with and without the disease of interest. This means that the percentage of positive or negative test results should be different in both groups for a categorical or dichotomous test result. This information may come from scientific literature, expert opinion, proof of concept studies, or clinical performance studies.

IV. Technical validity:

If a test appears to be capable of distinguishing patients with the target condition from patients who do not have the target condition, we must ensure that this is not a one-time result. Technical validity encompasses a very broad range of questions and outcomes. It is about research into the repeatability and reproducibility of laboratory tests, inter-rater test research (a measure of consistency used to evaluate the extent to which different judges agree in their assessment decisions), and analytical sensitivity (minimally detectable levels). Analytical performance is defined by outcome measures such as 'analytical sensitivity, analytical specificity, trueness (bias), precision (repeatability and reproducibility), accuracy (resulting from trueness

and precision), limits of detection and quantitation, measuring range, linearity, cut-off, including determination of appropriate criteria for specimen collection and handling, and control of known relevant endogenous and exogenous interference and cross-reactions.

V. Clinical validity and accuracy in a clinically relevant situation:

If the test appears to be capable of distinguishing patients with and without the target condition, and if the test results appear to be sufficiently robust, it is time to move from laboratory samples and extreme participant samples to a real-life situation in a prospectively planned and carried out study. Unless the test is intended as a screening test, the patients to be tested will be symptomatic in real life. Furthermore, the samples may not be as perfect as in a laboratory setting. Although this may also be true for a test's technical validity (reproducibility of blood pressure results, for example, may differ between healthy men and healthy pregnant women), our focus here is on diagnostic accuracy. This stage is destined to determine the device's clinical performance and requires the manufacturer to demonstrate it "in relation to diagnostic sensitivity, diagnostic specificity, positive predictive value, negative predictive value, likelihood ratio, and expected values in normal and affected populations." It does not distinguish between laboratory and real-world settings, but it does state that devices must be fit for their intended purpose. This step needs to provide answers for the following questions:

- Who will be tested?

The first question to be answered is who will be tested with the test under evaluation in real life. We need to know where these patients come from, through what referral route, in what healthcare setting they will be tested and what the management steps after a negative or a positive test result will be. Also, the same test may have different performance characteristics in a triage situation than in a confirmation setting where most patients who clearly do not have the disease of interest will be excluded.

- What to explain about the tests of interest?

Only providing the sensitivity and specificity (or predictive values) of the test of interest may not be helpful for clinical decision making. For example, if a new test may be used to replace an older test, you need to know how the new test compares to the older test. Is it more accurate? Or is it equally accurate combined with better feasibility or lower costs? Is there a choice between multiple tests at the same time? In that case, you may need to compare all tests available. If the test is going to be used as a triage test, then you may want to compare the accuracy of the current testing strategy with the testing strategy that includes the new test as a triage test. The way the tests were conducted is important as well. An integral part of assessing the sensitivity and specificity of a continuous diagnostic test is the threshold at which it is to be used. A higher positivity threshold will result in lower sensitivity and higher specificity. However, the same positivity threshold may not result in the same sensitivity and specificity. In a high-prevalence setting, more people may have higher levels without being diseased, resulting in a lower specificity. Choosing the optimal threshold may be done in different ways, but one has to realize that determining an optimal cut-off point based on the data at hand may lead to overoptimistic and therefore biased results.

- What is the target condition?

The target condition is a specific manifestation of the disease that the test is designed to detect. Each target condition may necessitate a different reference standard to determine the patient's true status. The gold standard was once used as a reference standard. There is no gold standard for most diseases, and if there is, it may not reflect the clinical decision that needs to be made for this patient. The reference standard is sufficiently reliable to select those patients who truly require treatment, whereas the gold standard may detect everyone with the slightest sign of disease, leading to over-diagnosis and unnecessary treatment. We must believe that the reference standard is sufficiently reliable to distinguish between people with and without the target condition. If that is not possible, then alternative solutions must be found. The simplest

solution is to account for the imperfection of the reference standard when interpreting the results (80% sensitivity means that of the 100 people with the disease, the test will be positive in 80 of them, not that 80 of them have the disease). Another option is to use composite reference standards (use all tests or clinical criteria available for a diagnosis). Expert opinion can also be used to determine who has the target condition, but they are not always reliable. Another approach is latent class analysis (a statistical technique in which a model estimates the likelihood of a patient having the target condition or not).

VI. Effect on outcomes important for the patient and on society:

The accuracy of a test tells us little about whether patients who had been tested do better than similar patients who have not been tested or who had a different test. As a result, in the following stage, researchers will look into how the test results affect diagnostic reasoning and decision making. The ultimate question, however, should be, 'Does the patient's situation improve as a result of testing?' As a result, the relevant outcomes should also reflect important health outcomes for the patient. Whether a test influences decision-making, changes treatment options, or improves the overall confidence of the doctor treating the patient is only relevant if the patient benefits from testing. Patient-relevant outcomes include disease risk, death risk, and patient quality of life. The randomized controlled trial is the most effective study design for determining the impact of a test on patients' health. In a randomized controlled trial, one patient group will have the test of interest and will be managed based on the results, while the other patient group will be managed differently. This alternative method could be a different test, a referral based on clinical signs and symptoms, or treatment based on a different algorithm than the test under consideration. However, such a design has drawbacks. Because the expected difference in outcomes between the two groups is typically small, such a randomized controlled trial requires a large sample size to detect existing differences. Furthermore, the protocol for both arms must be clear and strictly adhered to. The final step to consider is cost-effectiveness

and the potential societal effects of introducing the test. This can be estimated through modeling and monitored in real time through post-market surveillance and performance monitoring. Manufacturers are required to produce periodic safety and summary reports summarizing the results and conclusions of post-marketing surveillance under the new Regulation. In the event of potentially serious incidents, they must also take corrective action.

In conclusion, the purpose of a diagnostic test is to accurately predict the likelihood of a patient having a particular disease. However, the ultimate goal of testing should be to improve the patient's health status. Therefore, any diagnostic procedure, medical equipment, or test should be chosen based on its potential to benefit the patient. In order to ensure that only biomarkers with demonstrated value are used in clinical practice, it is recommended that they be tested through interventional or impact studies, comparing groups of patients with and without the biomarker assay

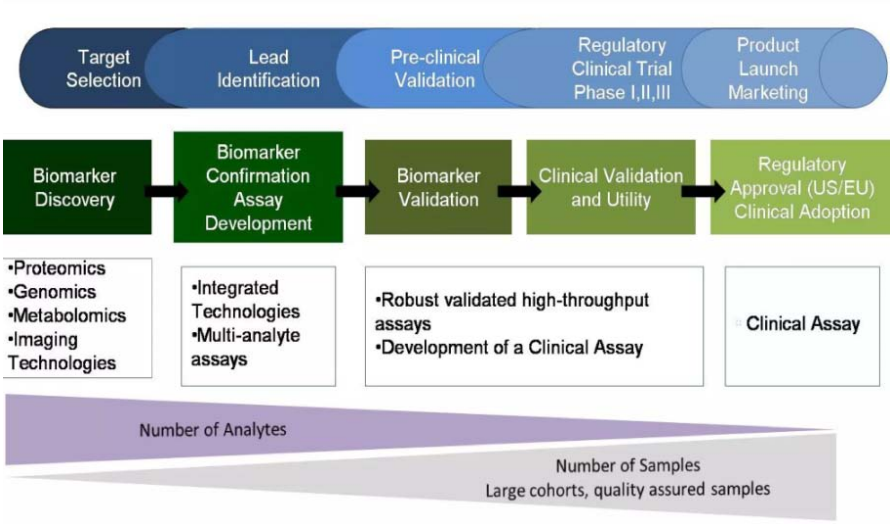


Figure 128: Biomarker discovery and evaluation.

1. Characteristics of an ideal biomarker:

A biomarker is considered to have a potential interest for routine clinical practice (9):

- The cellular and molecular mechanisms that explain the relationship between the biomarker and the phenotype it is intended to predict/diagnose are understood.
- The relationship between biomarker concentration and risk magnitude (or phenotype severity) is linear.
- The kinetics of biomarker concentration change should be known and reproducible for a given phenotype or therapeutic intervention.
- Safe and easy to measure (easily measurable in body fluids).
- Has great sensitivity, specificity, accuracy and a high predictive value.
- Is statistically associated with the occurrence of the disease and if it reclassifies a statistically significant number of patients into another risk category.
- Is modifiable with treatment.
- Whether interventions exist that would not be implemented if this biomarker was not considered and these interventions decrease morbidity and mortality.
- If it can be shown that the clinical benefit of acting on the biomarker levels is maintained even when traditional risk factors have been identified and treated.
- Cost efficient to follow up (assay techniques must be reproducible and inexpensive).
- Consistent across gender and ethnic groups.

For example, these would be the characteristics of the ideal cardiac biomarker. In general, biomarkers of acute coronary syndrome (ACS) include parameters that contribute to the diagnosis, follow-up, prognosis, and analysis of risk factors of this pathological entity. A cardiac marker should ideally have the following characteristics (10,11):

- It should be cardio-specific and cardio-sensitive: it should only be synthesized and released by the heart (absent in non-myocardial tissues) and absent (or in low concentrations) in the blood circulation of healthy subjects.
- It should appear very early in the circulation (released in the blood soon after the MI), allowing early detection of infarction or patients at risk of developing an infarction (while injury can be prevented/reversible).

- It should have a sufficiently long half-life to allow for late diagnosis.
- Its plasma concentration should be correlated with prognosis.
- It should be measured using a method adapted to the emergency setting (rapid, easily obtainable, and cheap).

Cardiac troponins, and more specifically hypersensitive troponins, meet the criteria of choice for a cardiac biomarker of ACS.

2. Bayesian reasoning:

Bayes' theorem, also referred to as Bayes' rule, is a mathematical principle that was first introduced by Reverend Bayes in “Essay toward solving a problem in the doctrine of chances,” which was published in the Philosophical Transactions of the Royal Society of London in 1764 (12). It describes the relationship between the conditional probability of an event (B) given the occurrence of another event (A), and the unconditional probability of those events. The theorem can be represented mathematically as: $Pr(A|B) = Pr(B|A)\ Pr(A) / Pr(B)$.

In simpler terms, the theorem can be interpreted as a way to update the probability of a diagnosis based on the results of a diagnostic test. The pre-test probability, or the level of belief that a patient has a particular diagnosis, is multiplied by a ratio that reflects the test results and the discriminative power of the test.

Diagnostic studies cover a broad range of patients, but when it comes to making a decision for a specific patient, Bayesian reasoning can be useful. This method allows you to integrate the patient's pretest probability with the diagnostic qualities of a given test using likelihood ratios (LR). In the end, this will give you a post-test probability for your patient.

One way to understand the usefulness of a biomarker is its value in enhancing our existing knowledge about predicting the probability of an outcome, such as a diagnosis or prognosis. Bayesian statistical methods provide a powerful system for updating our current information about the likelihood of a disease or prognosis.

Bayes' theorem uses two types of information to calculate the predicted probability of an outcome: the pretest probability of the outcome, and the predictive power of the biomarker. The pretest probability is similar to the general prevalence of the disease in the population being studied, or what we know about the base rate of the disease for a particular individual without additional information. This information is combined with the predictive power of the biomarker (i.e., the ability of the test to distinguish between different disease states) to adjust our prediction of the likelihood of the outcome.

In summary, the predicted probability of a patient having a disease (post-test probability) can be calculated as the post-test probability (pretest probability) multiplied by the predictive power of the evidence (likelihood ratio). Numerical examples of this calculation can be found in the concept of likelihood ratios.

3. Bayes theorem and VTE:

The use of biomarkers in the diagnosis of venous thromboembolic disease is an old story and probably one of the best illustrations of the application of Bayes' principles in evidence-based medicine. The main point of these diagnostic tests, D-dimer test in this case, is that none of them can absolutely exclude or confirm the diagnosis of VTE in all clinical situations.

The interpretation of the result will therefore depend on a fundamental parameter: the clinical probability or pre-test probability. This notion is known under the name of “Bayes theorem” where the diagnostic decision does not correspond to an absolute certainty but to a probabilistic approach based on an estimation of the risk of error.

When the risk of negative error is sufficiently low (<3-5%), PE can be excluded. When the risk of false positive is sufficiently low (<15%), the diagnosis of PE can be made. This risk, or post-test probability, depends on the pre-test clinical probability and the characteristics of the diagnostic test, which performance is estimated by its likelihood ratio. This post-test probability

can therefore be calculated using the a mathematical formula (discussed later) or more easily using the Fagan diagram (13,14).

This concept is valid for all diagnostic approaches but has been particularly studied in the context of VTE where the estimation of the pre-test probability or clinical probability has been modelled in the form of explicit rules. The best-validated and most widely used scores are the Wells score for DVT and PE and the revised Geneva score for PE (15,16).

4. Pretest probability:

While it might seem premature to introduce the topics of pretest and posttest probabilities and Bayesian theory without first discussing an appropriate mathematical foundation in biostatistics, they are nevertheless concepts with which physicians should have some familiarity with, at least in a qualitative way. A more robust mathematical explanation will come in later sections.

When clinicians decide to order a diagnostic test, they want to know which test (or tests) will best help them “rule in” or “rule out” disease in their patient. In the clinical language, they take the initial assessment of the likelihood of disease "pretest probability", perform a test to help shift their suspicion one way or the other, and determine a final assessment of the likelihood of disease "posttest probability".

Pretest probability is defined as “the probability of the target disorder before the application of the diagnostic test result”.

Posttest probability is the probability of the disease after the test result is known. Qualitatively, the higher a patient's pre-test probability was for having a disease the higher their post-test probability will be following a positive test result.

Pre-test probability is the starting point for all clinical decisions because it allows the patient to be positioned on a spectrum from low to high probability of having a disease. This approach allows the clinician to, first, to decide whether it is worth testing at all. If a test is

needed, select the most appropriate test (testing threshold), correctly interpret the results of a diagnostic test, choose to start treatment (treatment threshold) or abstain from treating. For example, the clinician may know that a certain test result increases the probability of disease 40%, but this information alone is unhelpful unless the clinician also knows the starting point: if the pre-test probability for the particular diagnosis was 50%, the finding is diagnostic (i.e. post-test probability 50% + 40% = 90%); if the pre-test probability was only 10%, the finding is less helpful, because the probability of disease is still akin to a coin toss (i.e. post-test probability 10% + 40% = 50%). So, for one patient with a relatively high pretest probability, the posttest probability will be high enough to rule in the diagnosis. While for a different patient, with a lower pretest probability, the same exact positive test result will not rule in the diagnosis. Unfortunately, this phenomenon is ignored far too often in practice.

Bayes theorem is a mathematical formula that is used to calculate the probability of an event based on prior knowledge and evidence. It is used to calculate the posttest probability of a disease or condition based on the pretest probability and the results of a diagnostic test. The basic idea behind Bayes' theorem for medical diagnosis is widely accepted. A positive test increases confidence in a diagnosis but does not necessarily indicate certainty. Whether this confidence exceeds a treatment (or action) threshold is a decision for the clinician and patient to make. Similarly, a negative test decreases confidence in a diagnosis, but rarely rules it out completely. It is up to those involved to decide whether further action is necessary.

Estimating pretest probability is an important first step in the diagnostic process. This can be done using clinical prediction rules, published estimates of disease prevalence, or through clinical reasoning. Once the pretest probability has been determined, the clinician can decide whether testing is necessary, select the appropriate test, interpret the test results, and make treatment decisions based on the posttest probability. By considering both pretest and posttest probabilities, clinicians can make more informed decisions for their patients.

There are several different ways to come up with a pretest probability for a disease, including:

1. Clinical prediction rules: Clinical prediction rules are decision-making tools that use a combination of patient characteristics and test results to predict the likelihood of a particular outcome. For example, a clinical prediction rule for deep vein thrombosis (DVT) might use factors such as the patient's age, gender, and medical history, as well as the results of a physical exam, to estimate the likelihood of DVT.
2. Published estimates of disease prevalence: The prevalence of a disease is the proportion of people in a population who have the disease at a given time. Published estimates of disease prevalence can be used to estimate the pretest probability for a particular patient. For example, if the prevalence of a disease is 1% in the general population, the pretest probability for an individual patient would be 1%. Although, the approach that is used will depend on the specific situation and the information that is available.
3. Clinical reasoning: Clinical reasoning is the process of using a patient's symptoms, medical history, and other factors to make a diagnosis. A clinician can use clinical reasoning to come up with a pretest probability by considering the patient's specific symptoms and other relevant factors and determining the likelihood of the patient having a particular disease.

VII. From published estimates of disease prevalence:

Pre-test probability can be found in published estimates of disease prevalence. Even so, clinicians must adjust these estimates with information from their own practice. For example, large studies based in emergency departments show that 12% to 35% of patients presenting with cough and fever have pneumonia (17). The probability of pneumonia, however, is certainly lower in patients presenting with cough and fever to an office-based practice, and it may be higher if cough and fever develops in patients with cancer or human immunodeficiency virus (HIV) infection. In fact, because the best estimate of pre-test probability incorporates information from the clinician's own practice (how specific underlying diseases, risks, and exposures make

disease more or less likely) the practice of evidence-based medicine is never "cookbook" medicine, but instead consists of decisions based on the unique characteristics of the patients the clinician sees.

VIII. From clinical prediction rules:

Clinical prediction rules (CPR) are tools which identify and quantify the contributions of the most helpful pieces of information related to a specific clinical scenario and reduce them to an algorithm or simple scoring system to help predict the probability of a specific diagnosis, of benefiting from a specific treatment, or experiencing adverse outcome (18).

These pieces of information can be features of a patient's demographic such as age and sex a patient's current symptoms their medical history exam findings or test results. There are a variety of alternative names for clinical prediction rules or for their subtypes such as: risk scores, decision rules, probability assessments, severity index, scoring systems, and risk stratification tools. While there is some variability in how these terms are used in practice it is more commonplace to use the term clinical prediction rule as an umbrella term.

The development of a clinical prediction rule has four stages (19):

- Derivation: first multivariate statistical methods are used to identify the set of useful independent pieces of data and their relative weights. In order for a piece of data to be useful it needs to not only be predictive but also needs to discriminate between those with and without the diagnosis or outcome of interest. It also needs to be relatively common within the population in which the rule will be applied otherwise if it included every predictive piece of data no matter how rare, the clinical prediction rule would easily become too unwieldy to be practical.
- Validation: the rule is then validated using a separate data set to ensure that the initially determined predictive variables were not a statistical anomaly. even for successfully validated rules the validation data set often demonstrates less predictive accuracy than

the derivation data sets which is to be expected and does not necessarily mean that mistakes were made along the way.

- Impact analysis: validation should be followed by an impact analysis to see if the clinical prediction rule actually improves patient outcomes and or reduces cost in real world situations, however this has not yet been done for many possibly even most rules currently in use.
- Implementation: the final stage is implementation in which a validated and impactful rule sees widespread adoption in clinical practice.

Clinical prediction rules that use scoring systems are often incorporated into diagnostic algorithms or flow charts that further simplify the cognitive burden for a clinician.

One of the most famous clinical prediction rules is the Wells' Score for Pulmonary Embolism. This score is an evidence-based tool which calculates the pre-test probability for pulmonary embolism using clinical data obtained during the primary examination, just prior to performing a confirmatory (CT Angiography) or exclusionary test (D dimer).

The Wells' Score is a tool used for assessing the risk of pulmonary embolism (PE) in patients. The tool comprises seven criteria, each with a score ranging from 1.0 to 3.0. By summing the positive findings for a patient, the tool assigns the patient to a risk category: low, moderate or high probability. Several studies have validated the Wells' Score for ruling in and ruling out pulmonary embolism. The low-risk group, with a prevalence of 1-2%, indicates that in a group of patients with 1 point, there is a 1-2% risk of pulmonary embolism. In other words, the prevalence for every category of risk is different, depending on the number of patients with the disease in each risk group. In this case, we will use data from the first study that validated the score (20). It suggests that patients with low-risk characteristics (0-1 points) have a 2% probability for pulmonary embolism. For moderate-risk patients (2-6 points), the probability of pulmonary embolism is 15%, and for high-risk patients (>6 points), the probability of having pulmonary embolism is 43%.

Unfortunately, nowadays, there are just a few scores and tools to calculate pre-test probabilities of common clinical problems, for example, the Alvarado score for appendicitis, TIMI risk score for ischemic heart events, or the 4T's score used to assess the Heparin-induced thrombocytopenia (Table 34). Therefore, in the absence of a broad existence of evidence-based tools for determining the pre-test probability of many diseases, clinicians may end up making an estimate based on their existing knowledge and observations.

Table XXXIII: Examples of clinical prediction rules.

Category	Rule	Purpose
Diagnostic	Wells score (PE & DVT)	Diagnosis of PE and DVT
	PERC rule	Diagnosis of PE
	Heart score	Diagnosis of ACS
	4T score	Diagnosis of heparin-induced thrombocytopenia
	CAGE questions	Diagnosis of alcohol abuse/dependence
Therapeutic	CHADS2 and CHADS2-VASC scores	Decision of use anticoagulation in patients with a-fib
	CURB65 score	Decision to admit patients with pneumonia
	PORT score/ Pneumonia severity index	Decision to admit patients with pneumonia
	Pulmonary severity index (PESI)	Decision to admit patients with PE
	San Francisco syncope rule	Decision to admit patients for syncope
Prognostic	TIMI score	Estimates short-term risk of death or ischemic events in patients with UA/NSTEMI
	APACHE II score	Estimates short-term death in critical illness
	HAS-BLED score	Predicts risk of major bleeding in patients on anticoagulation
	MELD score	Estimates long-term death in cirrhosis, determines rank on liver transplant list (US°
	Revised cardiac risk index	Estimates risk of cardiac complications after non-cardiac surgery
	Glasgow coma scale	Estimates short and long-term prognosis in a variety of acute neurological injuries

IX. The bigger picture, clinical reasoning:

The process of deductive thinking based on the clinical examination and history is known as clinical reasoning.

Trowbridge and al. define clinical reasoning as a cognitive and noncognitive process by which a healthcare professional consciously and unconsciously interacts with the patient and environment to collect and interpret patient data, weigh the benefits and risks of actions, and understand patient preferences to determine a working diagnostic and therapeutic management plan whose purpose is to improve a patient's well-being (21).

Higgs and al. define more comprehensively as "context dependent way of thinking and decision making in professional practice to guide practice actions. It involves the construction of narratives to make sense of the multiple factors and interests pertaining to the current reasoning task. It occurs within a set of problem spaces informed by the practitioner's unique frames of reference, workplace context and practice models, as well as by the patient's or client's contexts. It utilizes core dimensions of practice knowledge, reasoning and metacognition and draws on these 50 capacities in others. Decision making within clinical reasoning occurs at micro, macro and meta levels and may be individually or collaboratively conducted. It involves meta skills of critical conversations, knowledge generation, practice model authenticity and reflexivity" (21).

For the sake of practicality and simplicity, we can define clinical reasoning as a process by which a clinician hypothesizes the possible diagnosis a patient may have, selects appropriate tests to confirm or refute their hypothesis and develops treatment strategies for the diagnosis under consideration.

Clinical reasoning is very important for many reasons:

- Accurate diagnosis is the key to identifying the treatment that will restore the patient to good health. And while computers have been successfully able to generate lists of possible diseases, when different signs and symptoms are input into their search

engines (ex. Ddxof, DXplain, ILIAD, Quick Medical Reference, ISABEL). The computer's limited. This is a job that still only the clinician's mind can accomplish.

- Despite the widespread availability of diagnostic tests, most experts estimate still that an accurately taken history alone can lead to the correct diagnosis in the majority of cases, some say as much as 75% of cases. And when physical exam is taken into account, an additional 15% of cases can be diagnosed (22).
- When diagnosis is viewed as a processing pathway founded on a robust medical history, it becomes clear that in some situations, investigations may become unnecessary and in other circumstances, their impact will be enhanced.
- Even when tests are needed, the significance of their results cannot be really appreciated unless we know the likelihood of the disease in question before the test is obtained.

Broadly speaking, diagnostic reasoning has 5 steps (23):

1. Identification of the clinical information that is relevant to diagnosis.
2. Interpretation of its meaning.
3. Generation of hypotheses which provide a coherent explanation of the patient's problem.
4. Testing and refining of those hypotheses through further data collection.
5. Establishment of a working diagnosis.

Clinical reasoning incorporates analytic and non-analytic strategies of thinking, which interact at different phases in the patient encounter. Non-analytic strategies (unconscious/reflexive) include pattern recognition, heuristics, illness scripts, and semantic qualifiers. Analytic strategies (conscious) include causal reasoning and probabilistic reasoning, where logic and critical thinking are given importance. Meta-cognition, an awareness of one's own thinking, overarches the analytic and non-analytic processes of cognition directing the clinician to the diagnosis (24).

Since our focus is to demonstrate how we can arrive at a pretest probability for a disease in the absence of published data or clinical prediction rule, we will not discuss clinical diagnosis in its entirety, we will focus instead on differential diagnosis, but we will however give a brief statement on each element of clinical reasoning.

Data gathering: The physician needs to first obtain enough information from the patient to construct a good problem representation. The way to do that is to compose a problem list of the patient's issues, process that list to increase its impact and specificity, create a problem representation called "patient illness script" that facilitates comparison with the "disease illness scripts". And the elements of the illness script for the patient are very similar to the elements of the illness script for a disease. Elements of an illness script: Epidemiology (Exposures, demography, past disease history), Time course, Syndrome statement, Important medical history not otherwise included, almost identical to disease illness scripts)

Illness scripts: An illness script is an organized mental summary of the clinician's knowledge about a disease, it is initially shaped by reading and refined by clinical experience. Information is primarily categorized by pathophysiology, epidemiology, symptom characteristics, diagnostic tests and treatment. The complexity of an illness script varies depending upon disease prevalence and the clinician's experience, therefore, it is updated after each new encounter with the disease (25–27). This concept is important because cognitive psychologists hypothesize that scripts represent how physicians actually remember and process information (28). Script theory describes how information becomes structured and is retrieved from long-term memory to interpret and predict new information. Illness scripts are most helpful when they contain maximally distinguishing features rather than just those that are shared by diseases with similar presentations, these types of features are called key features and itself can be divided into two types: differentiating features and defining features.

- Discriminating feature: a sign or a symptom in a given constellation of diseases that only occurs in two out of those three diseases and allows us to exclude the possibility that the third disease is present.

- Defining feature: a feature that is present in a particular grouping of diseases in only one out of three conditions.

Subsets of these key features (not present in all conditions) whose presence or absence significantly alters the likelihood of the diagnosis are called "must have features" and "rejecting features":

- Must have features mean that in order to diagnose a particular disease in a particular patient we must have this particular sign or symptom "without it, the disease can't be diagnosed". An example of a must have feature would be jaundice in the diagnosis of cholangitis.
- Rejecting features, that is if a patient has this particular sign or symptom the diagnosis of this disease we are considering cannot be made "if present, this diagnosis cannot be made". An example of a rejecting feature would be hyperreactive reflexes rejecting the diagnosis of Guillain-Barre.

Problem representation: Problem representation means a way of describing a problem as fully and specifically as possible, before generating a differential diagnosis list. It aims to incorporate all significant symptoms and signs, describe them as accurately as possible, emphasize the most specific features, avoid distraction by minor signs or symptoms or non-specific markers of illness and match the patient's presentation to classic disease descriptions.

Differential diagnosis: a list of diagnoses which could reasonably explain a specific patient's presentation, based on information available at the time. It is used to identify the proper diagnosis from a set of possible competing diagnoses (29).

Since physicians understands the phenotypic expression of a disease using an illness script, they can prioritize the likelihood of a given diagnosis, by how well that patient's illness script matches the classic disease illness script. The more compatible the patients' illness script is with the disease illness script, the more likely it is that that disease is present.

Prioritization of the differential diagnosis is paramount. The most likely diagnoses should be at the top of the list, and because testing and treating for high priority diagnostic possibilities avoids unnecessary costs in treatment and prevents wasted time, they should be targeted first.

Most importantly, prioritization aids in the interpretation of subsequent diagnostic tests. There are really no tests that are 100% sensitive and 100% specific. So, test results can lead to a false positive, resulting in unnecessary follow-up tests or treatment, or false negatives, which may lead to erroneously discarding a disease that was a clinically correct diagnosis. The way to minimize these diagnostic errors is to understand going into the test, how likely a clinical diagnosis is. It is paramount to develop a tiered approach to clinical probability based on patient illness script matching to the disease illness scripts. M. Medow and C. Lucey (30) proposed a tiered approach to prioritize lists of differential diagnosis based on the following criteria:

- Tier 1 possibility: Clinically high likelihood
- Disease explains all the patient's major findings
- Patient has all major manifestations of the disease
- They have no rejecting features and may have a key feature
- Tier 2 possibility: Clinically moderate likelihood
- Disease explains most of the patient's findings
- Patient lacks some of the usual manifestations of the disease
- They have no rejecting features
- Tier 3 possibility: Clinically low likelihood
- Patient has single or few features of the disease in question
- Patient has a rejecting feature of the disease in question

When dealing with clinical problem solving and looking at how to use diagnostic tests, we are often told it is important to consider the pretest probability of disease based on the clinical presentation. And while there are some conditions, for instance CAD, PE and DVT where there is published information about the extent of the pretest probability or clinical prediction rules, in most cases we deal with clinical probabilities. To remedy this, we can assign to each of the 3

tiers a categorical probability from very likely to very unlikely. The difference between a likely and a very likely disease is that a disease is assigned very likely if there is a defining feature. Likewise, the presence of a rejecting feature puts a disease in the very unlikely category.

The next step is to connect the categorical probabilities to numerical probabilities in order to be able to use mathematical clinical decision tools like the Fagan nomogram in the assessment of the post-test probability of disease.

The post-test probability can be deduced from the tiered approach to clinical reasoning using a diagnostic test:

1. The first step is to determine the pretest probability of the disease being considered. Ideally this comes from an evidence-based source. If it is very likely (<10-20%) or very unlikely (>80-90%), in general, no further testing is needed.
2. If published data on the prevalence of a disease is lacking, the pretest probability can be categorized as likely, uncertain or unlikely.
3. Based on these tiers, clinicians can choose testing and treatment strategy. In general, tier I diseases should be tested and treat for before tier II and tier III diseases.
4. If the initial assessment is very unlikely or very likely, then in most cases it is not worth further testing according to Bayes' theorem, the results would either confirm what is already near certain or it would minimally move the post-test probability in the opposite direction. Either way, the clinician would not normally take additional actions.
5. If a moderately precise test is prescribed. If the test is positive, the post-test probability increases by one qualitative category (eg, unlikely to uncertain). If the test is negative, the post-test probability decreases by one qualitative category (eg, unlikely to very unlikely).
6. This process continues until the clinician is comfortable enough with the confidence in the diagnosis considering the patient's preferences, the risk of the disease and the effects of treatment.

Table XXXIV: Tiered approach to probabilities in clinical reasoning by M. Medow and C. Lucey (30).

Tier	Categorical probability	Numerical probability	Comment
1	Very likely Likely	>90% 67-90%	Defining feature
2	Uncertain	34-66%	
3	Unlikely Very unlikely	10-33% <10%	Rejecting feature

Threshold testing: the idea behind the threshold model is to put the probability of a specific disease in a particular patient with symptoms, signs and or lab abnormalities exists on a spectrum somewhere between 0% and 100%. There is a probability threshold at which a clinician decides to rule out the disease and discontinue further testing for it, and a threshold at which he decides to rule in and treat the disease.

The test threshold defines the boundary above which a clinician would order tests to evaluate the presence of a disease, and below which a clinician would decide that additional testing is not warranted due to all the reasons such as the disease being too improbable or not being particularly dangerous. The test threshold the probability of disease below which testing is unjustified is the point at which we would rule out the disease thus we can also call this the rule out threshold. The treatment threshold defines the probability of disease at which the benefits outweigh the risks of treatment. At probabilities below the treatment threshold the risks of treatment outweigh the benefits. The treatment threshold is generally the same as the rule in threshold. Finally, if a disease has neither been ruled in nor ruled out additional testing is usually warranted. Whether these thresholds are called “test” and “treatment” thresholds or the “rule in” and “rule out” thresholds, they define a region of probabilities in which testing is typically appropriate:

- Ruling out a diagnosis: a diagnosis is ruled out when the probability of that disease is low enough that the balance of anticipated benefit and anticipated harm argues against further testing for it. Ruling out a diagnosis does not mean that its probability is literally 0%.

- Ruling in a diagnosis: a diagnosis is ruled in when the probability of that disease is high enough that the balance of anticipated benefit and anticipated harm argues against further testing for it. ruling in a diagnosis it doesn't mean that its probability is literally 100%.

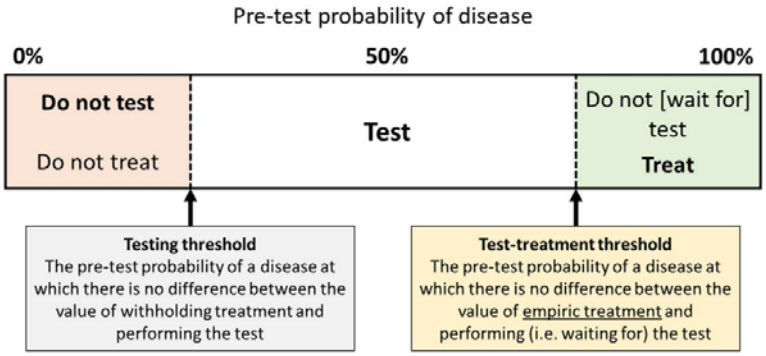


Figure 129: The threshold approach to testing and treatment decisions.

Test selection: When seeing a patient with an unknown disease the choice of diagnostic tests depends upon the test performance characteristics classically this includes the test sensitivity and specificity but at least as important are its positive and negative likelihood ratios for the disease under consideration. Other factors include the risk of harm from the test itself, the cost of the test (both the out-of-pocket cost for the patient and the cost to the health care system), the relative availability of different options, and lastly, the patient preference.

Influenced by the aforementioned considerations are three basic strategies to test selection when considering a strategy ask what you are trying to accomplish with the test:

- With a confirmation strategy, tests are selected which characteristics might rule in the leading diagnosis.
- With an elimination strategy, tests are selected which characteristics might rule out a relatively unlikely diagnosis (do not miss diagnosis).
- With a discriminatory strategy, tests are selected with the ability to discriminate between two or more equally likely diagnoses.

The revision of the differential diagnosis also obviously requires an accurate interpretation of the test itself; it requires knowledge of the test's performance characteristics that is the positive and negative likelihood ratios as mentioned before including an appreciation of the possibility of false positives and false negatives and last it requires the recognition of when a test result may be inaccurate. This will be the subject of the following section.

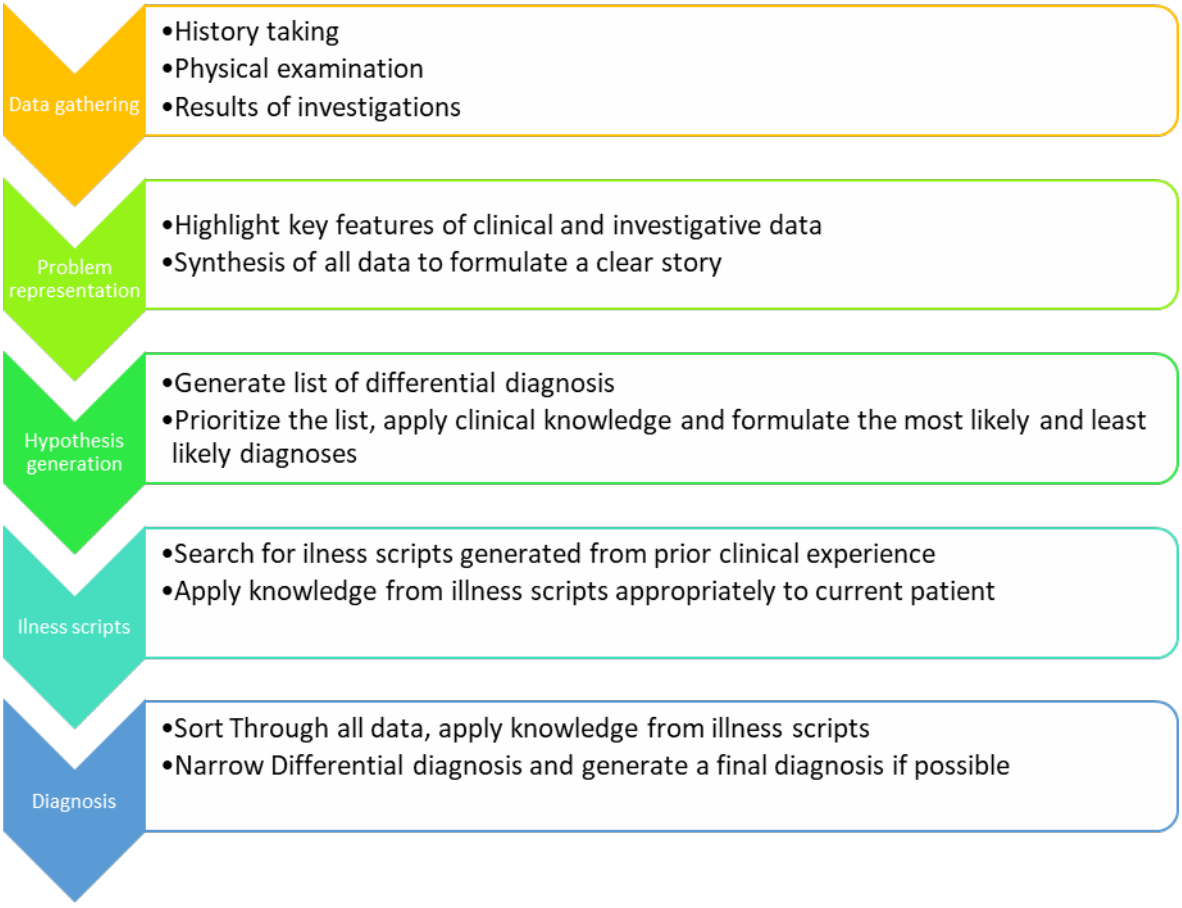


Figure 130: Steps and strategies for clinical reasoning. Adapted from Bowen JL. Educational strategies to promote clinical reasoning (31).

1. Biomarkers performance characteristics:

The study of the diagnostic performance of a biomarker is an important area of medical research that aims to evaluate the accuracy and utility of biomarkers in detecting and diagnosing diseases. The classic indicators used to assess the performance of a biomarker are sensitivity

and specificity. Unfortunately, they are the most widely used statistics to describe a diagnostic test and the most commonly provided variables in diagnostic studies. While, predictive values provide more information about the probability of disease in individuals with positive or negative test results and are therefore considered to be better than sensitivity and specificity in certain situations. Beyond these basic metrics, other statistical measures, such as likelihood ratios and receiver operating characteristic (ROC) curves, can be used to more accurately assess the performance of a biomarker. Likelihood ratios are considered to be better than predictive values in certain situations because they provide a more precise measure of how much a test result changes the probability of the disease being present. Finally, the area under the ROC curve (AUROC) is a measure of the overall diagnostic accuracy of the biomarker.

To demonstrate how these characteristics are calculated and used, we will be intimately referring to an imaginary case throughout this chapter. This will allow us to illustrate the key concepts and provide a clear understanding of how these metrics are applied in practice.

2. Sensitivity and specificity:

The terms sensitivity and specificity are used to describe the discriminatory power of a biomarker. Sensitivity is the proportion of patients with the diagnosis who have a positive result on the biomarker test, while specificity is the proportion of patients without the diagnosis who have a negative result on the test. These indicators can be calculated by constructing a 2×2 contingency table, where subjects are divided into true and false positives and true and false negatives based on the test result and their health status. The reference test, also known as the gold standard, is the best single test or combination of tests currently used to diagnose a particular disease. All other methods of diagnosing, including new biomarkers, must be compared against the gold standard. If a new biomarker is better than the current gold standard, it can be validated and potentially replace the current standard. For example, head CT is the gold standard for the detection of intracranial abnormalities against which S100B has been compared

(32), bacterial cultures are the gold standard for the diagnosis of bacterial infections against which procalcitonin has been compared (33), and the gold standard for the diagnosis of MI has been changed from CK-MB to troponin by first collaborative group of redefinition of MI in 2000 because it performed better (34).

The way to construct a 2x2 contingency table is the following:

- In cell A we enter those in whom the biomarker in question correctly diagnosed the disease (as determined by the gold standard). In other words, the biomarker is positive, as is the gold standard. These are the true positives (TP).
- In cell B we enter those who have positive results for the biomarker in question but do not have disease according to the "gold standard test". The biomarker has wrongly diagnosed the disease. These are false positives (FP).
- In cell C, we enter those who have disease on the "gold standard" test but have negative results with the biomarker in question. The biomarker has wrongly labeled a diseased person as "normal". These are false negatives (FN).
- In cell D we enter those who have no disease as determined by the "gold standard" test and are also negative with the biomarker. These are true negatives (TN).

Table XXXV: 2×2 contingency table.

		Health status		
		Diagnosis present	Diagnosis absent	
Test results	Positive	A (TP)	B (FP)	All the patients who test positive
	Negative	C (FN)	D (TN)	All the patients who test negative

2×2 TABLE: The total number of patients with the disease is the sum of the first column, A+C. The total number of patients without disease is the sum of the second column, B+D. The sensitivity of the biomarker is the proportion of patients with disease who test positive for the

biomarker, A/(A+C). The specificity of the biomarker is the proportion of patients without disease who test negative for the biomarker D/D+B.

Table XXXVI: Contingency table of astroglial protein S-100B concentration in systemic circulation according to CCT findings of intracerebral lesions.

S100B	CCT+	CCT-	
>0.10 µg/L	92	855	Post predictive value, 10% (7-13)
≤0.10 µg/L	1	361	Negative predictive value 99.68% (99-100)
Total	93 Sensitivity, 99% (96-100)	1216 Specificity, 30% (29-31)	1309

To recall how to calculate sensitivity and specificity, Sackett and others have suggested helpful mnemonics: Sensitivity is represented as "PID" for "positivity in disease" (an abbreviation normally associated with "pelvic inflammatory disease"), and specificity is represented as "NIH" for "negativity in health" (an abbreviation normally associated with the "National Institutes of Health") (35).

Sensitivity (Se) refers to the ability of a test to detect the disease, the proportion of sick patients with a positive test or the true positive rate:

$$\text{Sensitivity (Sn)} = \frac{A}{A+C} = \frac{TP}{TP+FN}$$

Specificity (Sp) refers to the ability of a test to detect subjects free of the disease, the proportion of healthy subjects with a negative test or the true negative rate:

$$\text{Specificity (Sp)} = \frac{D}{D+B} = \frac{TN}{TN+FP}$$

3. Demonstration:

Let's consider a study in which 1000 people with a suspected disease undergo an index test (biomarker) and a reference standard (gold standard). The prevalence of this disease in this group is 25%. 240 people tested positive on both the biomarker and the reference standard and 600 people tested negative on both tests, 10 tested negative for the biomarker but positive for the reference test and 150 tested positive for the biomarker and negative for the reference test . The first step is to draw a 2 x 2 table as shown below.

		Reference test	
		Sick	Not sick
Biomarker results	Positive	240	150
	Negative	10	600
	Total	250	750

$$\text{Sensitivity(Sn)} = \frac{A}{A+C} = \frac{240}{240+10} = 0.96 = 96\%$$

10 people (4%) with the disease were falsely identified as not having it. This means the biomarker is fairly good at identifying people with the condition.

$$\text{Specificity(Sp)} = \frac{D}{D+B} = \frac{600}{600+150} = 0.8 = 80\%$$

150 people (20%) without the disease were falsely identified as having it. This means the biomarker is only moderately good at identifying people without the disease.

4. Updating Probability of Disease using Sensitivity and Specificity:

Sensitivity and specificity can sometimes be helpful. Sackett et al introduced the acronyms "SpPIn" and "SnNOut" to help practitioners remember how to use these measures in clinical practice ((35).

A very high sensitivity, when negative, rules out disease. An easy way to remember this rule of thumb is the acronym proposed by Sackett and others Sackett and others (36): "**SnNOut**", which is taken from the phrase: "**S**ensitive tests when **N**egative rule **Out** disease". Conversely, a very specific test, when positive, rules in disease. The acronym for this kind of test is "**SpPIn**", which is taken from the phrase "**S**pecific tests when **P**ositive rule **In** the disease". Thus, sensitivity and specificity by themselves are only useful when either is very high (95% or higher (37)). Negative tests with sensitivities near 99% can almost certainly rule out a disease, since the post-test probability will be very unlikely even if the original pretest probability was likely. Similarly, positive tests with specificities near 99% can almost certainly rule in a disease, since the post-test sensitivity will be very likely even if the original pretest probability was unlikely.

Since this introduction, many practitioners have adopted these mnemonics as irrefutable standards. Despite the promotion by Sackett, the use of these descriptors has been questioned. In 2004, Pewsner et al (38) urged caution in the unqualified use of SpPIn and SnNOut, warning that potential weaknesses were present behind the singular use of SpPIn and SnNOut that might have unwanted clinical consequences.

5. Limitations of sensitivity and specificity:

Sensitivity and specificity are commonly used to evaluate the performance of a diagnostic test, but they have several limitations.

First, these measures are not very useful for clinicians trying to revise the probability of disease because they are derived from a defined population within a case-based, case-control design. This means that the knowledge of the state of health or illness of the sample precedes the estimation of sensitivity and specificity. In other words, sensitivity is only calculated in patients who have the disease, while specificity is only calculated in patients who do not have the disease. Clinicians do not usually know whether or not a patient has the disease, which is why they order the test in the first place. Next, there is generally a trade-off between sensitivity and

specificity in that as one parameter rises, the other falls. This codependent relationship makes the ranking of the usefulness of a specific test less than intuitive and makes the use of either one without the other-as in SpPIn and SnNOut where sensitivity only applies to individuals who have the disease, while specificity is applicable only to those who do not- potentially misleading. Furthermore, although mathematical calculation of sensitivity and specificity are not necessarily altered by prevalence (they can be estimated in isolation from a sample of sick (sensitivity) or healthy (specificity) subjects) (39,40), certain clinical situations may foster higher estimates. These indices can be influenced by the severity of the disease, by its risk factors, and by selection biases (41). In other words, the estimates of sensitivity and specificity produced by a given study are affected by the number of diseased subjects enrolled in that study and the severity of the disease. For example, a biomarker is likely to be more sensitive among more severe than among milder cases of the diseases. The sensitivity of procalcitonin to diagnose bacterial infection is greater in patients with meningitis than in patients with pyelonephritis (42).Finally, sensitivity and specificity cannot easily be used to convert a pre-test probability of a disease to a post-test probability of disease (43). Meaning, sensitivity and specificity do not give clinicians the information they need to interpret the test results, which is how much to increase the probability of disease according to the test result.

There are other characteristics of diagnostic tests which that are more useful to clinicians such as predictive values.

6. Predictive values:

The predictive value of a test is a measure of the times that the value (positive or negative) was the true value, i.e. the percent of all positive tests that were actually true positives or vice versa. Positive predictive value is the probability that subjects with a positive test (biomarker present) truly have the disease. Negative predictive value is the probability that

subjects with a negative test (biomarker absent) truly do not have the disease. They can be calculated using the same 2 × 2 contingency table above (Table 34):

The positive predictive value (PPV) is the proportion of patients with a positive test result that actually has the disease:

$$\text{PPV} = \frac{A}{A+B} = \frac{TP}{TP+FP}$$

The negative predictive value (NPV) is the proportion of the patients with a negative test result that actually does not have the disease:

$$\text{NPV} = \frac{D}{D+C} = \frac{TN}{TN+FN}$$

7. Demonstration:

We are told that the prevalence of the disease is 25% therefore we can fill in the last row of totals – 25% of 1000 people is 250 – so 250 people will have the disease and 600 will be free of said disease. We also know the number of people testing positive and negative on both tests and so we can fill in two more cells of the table.

		Reference test		
		Diagnosis present	Diagnosis absent	
Biomarker results	Positive	240	150	390 (All the patients who test positive)
	Negative	10	600	610 (All the patients who test negative)
	Total	250	750	1000 (All the people tested)

$$\text{PPV} = \frac{A}{A+B} = \frac{240}{240+150} = 0.62 = 62\%$$

This measure tells us how well the test performs in this population. It is dependent on the accuracy of the biomarker (primarily specificity) and the prevalence of the condition. In our example, of the 390 people who had a positive biomarker result, 62% will actually have the disease.

$$\text{NPV} = \frac{D}{D+C} = \frac{600}{600+10} = 0.98 = 0.98\%$$

This measure tells us how well the test performs in this population. It is dependent on the accuracy of the biomarker (primarily sensitivity) and the prevalence of the condition. In our example, of the 610 people with a negative biomarker result , 98% will not have the disease.

8. Updating Probability of Disease using predictive values:

The positive and negative predictive values answer the practical question that every physician asks: “If the test is positive (or negative), what is the patient’s probability of actually having the disease (or not having the disease)” Or more accurately "Given a positive (or negative) test result, what is the new probability of disease?”

The probability of disease given a positive test can therefore be called the "post-test probability of disease given a positive test", the "positive predictive value", or the "posterior probability of disease given a positive test". These names are interchangeable. Similarly, the probability of disease given a negative test is called the "post-test probability of disease given a negative test" or the "posterior probability of disease given a negative test"; this is equal to one minus the negative predictive value.

- Post-test probability of disease given a positive test:

Post-test probability of a disease given a positive test = PPV = $\frac{A}{A+B} = \frac{TP}{TP+FP}$

- Post-test probability of disease given a negative test:

Post-test probability of a disease given a negative test = $1 - NPV = \frac{C}{C+D} = \frac{FN}{FN+TN}$

PPV tells us how many of test positives are true positives, and if this number is higher (as close to 100 as possible), then it suggests that this new test is doing as good as “gold standard”.

NPV tells us how many of test negatives are true negatives, and if this number is higher (as close to 100 as possible), then it suggests that this new test is doing as good as “gold standard”.

9. Limitations of predictive values:

Predictive values might appear to be more useful for applying the results of a study because these values relate to the way these tests are used in clinical decision making : “given a test result (positive or negative),what is the probability that the result is correct?” Sensitivity and specificity values work in the opposite direction : “given the condition is present or absent , what is the probability that the correct test result will be obtained?”.

Despite their apparent usefulness, predictive values can be deceptive. First of all, like Sn and Sp, PPV and NPV are only calculated from a proportion of the population within a case based, case control design. PPV is calculated only from those who scored a ‘‘positive’’ on the test finding, whereas NPV is calculated only from those who score a ‘‘negative’’ on the test finding. Secondly because they are highly dependent on the prevalence of the disease in the sample, changing the prevalence (or changing pre-test probability) changes the predictive value in non-linear ways, positive predictive values will be lower and negative predictive values will be higher in samples with a low prevalence of the condition. If prevalence is high, the trends reverse (44). This is a significant limitation of using predictive values and/or post-test probabilities because each pair of predictive values or post-test probabilities is associated with a single pre-test probability. Meaning that the same test result may therefore give you one post-test probability in the emergency room, and a different one in your office, if the pre-test probabilities differ. The significance of this issue cannot be overstated as the prevalence of disease can vary significantly among different populations. Sepsis is more prevalent in intensive care units compared to

emergency departments, and the effectiveness of procalcitonin in detecting sepsis may also vary in these settings. For instance, a study by Falcoz et al. (45) found that a procalcitonin level of 1 ng/ml had a positive predictive value of 63% for predicting postoperative infection following thoracic surgery. However, the prevalence of infection in that study was only 16%. If the scope of the study was limited to only patients with systemic inflammatory response syndrome criteria, the prevalence would have been 63% and the positive predictive value would have been 90%.

In the next section we will discuss likelihood ratios, and how they overcome this and other limitations.

9.1. Likelihood ratios:

LRs are another way of describing the diagnostic value of a biomarker. The LR of a biomarker is the proportion of patients with disease who have a particular finding divided by the proportion of patients without disease who also have the same finding. Because tests can be positive or negative, there are two likelihood ratios for each test. The "positive likelihood ratio" (LR+) tells us how much to increase the probability of disease if the test is positive, while the "negative likelihood ratio" (LR−) tells us how much to decrease it if the test is negative. The formula for calculating the likelihood ratio is:

$$\text{LR} = \frac{\text{probability of an individual with the condition having the test result}}{\text{probability of an individual without the condition having the test result}}$$

Thus, the positive likelihood ratio is:

$$\text{LR} + = \frac{\text{probability of an individual with the condition having a positive test result}}{\text{probability of an individual without the condition having a positive test result}}$$

Similarly, the negative likelihood ratio is:

$$\text{LR} - = \frac{\text{probability of an individual with the condition having a negative test result}}{\text{probability of an individual without the condition having a negative test result}}$$

We can calculate the LR+ and LR− from the 2 × 2 contingency table above (Table 34):

The positive LR is the proportion of patients with disease who have a positive finding $(A/A+C)$ divided by the proportion of patients without disease who have a positive finding $(B/B+D)$, or $sensitivity/(1-specificity)$. The negative LR is the proportion of patients with disease who lack the finding $(C/A+C)$ divided by the proportion of patients without disease who lack the finding $(D/A+C)$, or $(1-sensitivity)/specificity$.

$$\text{LR+} = \frac{\text{Sensitivity}}{1-\text{Specificity}}$$

$$\text{LR-} = \frac{1-\text{Specificity}}{\text{Sensitivity}}$$

10. Updating probability of disease using likelihood ratios:

One of the most interesting features of LRs is that they quantify the increase in knowledge about the presence of disease that is gained through the diagnostic test, which is to say that LRs tell us how much we should shift our suspicion for a particular test result.

According to Bayes' theorem, if a test result is positive, the post-test probability becomes:

$$P(post) = \frac{P(pre) \times sensitivity}{(P(pre) \times sensitivity) + (1 - P(pre)) \times (1 - specificity)}$$

If the test is negative, the post-test probability becomes:

$$P(post) = \frac{P(pre) \times (1 - specificity)}{(P(pre) \times (1 - specificity)) + 1 - P(pre)) \times specificity}$$

In diagnostic reasoning, Bayes' theorem can be simplified to state that the post-test odds of a disease equals the pre-test odds of that disease multiplied by the likelihood ratio of a diagnostic test. It is important to note that this formulation assumes that the diagnostic test is independent of any previous tests or observations. Using LRs, post-test probability can be calculated by first converting pre-test probability P(pre) into pre-test odds O(pre):

$$O(pre) = \frac{P(pre)}{(1 - P(pre))}$$

The pre-test odds O(pre) is multiplied by the LR of the physical sign to determine the post-test odds O(post):

$$O(post) = O(pre) \times LR$$

The post-test odds O(post) converts back to post-test probability P(post), using:

$$P(post) = \frac{O(post)}{(1 + O(post))}$$

The first thing to understand about LRs is that an LR > 1 indicates an increased probability that the target disorder is present, and an LR < 1 indicates a decreased probability that the target disorder is present. Correspondingly, an LR = 1 means that the test result does not change the probability of disease at all! The following are general guidelines, which must be correlated with the clinical scenario:

Likelihood ratios (LR) are calculated from the full population represented in the case-based, case control design thus are considered metrics that influence clinical utilities (the ability to make rational diagnostic decisions). A LR+ above 1.0 influences post-test probability with a positive finding, whereas a low LR- (a value close to 0) influences post -test probability with a negative finding.8Both values are wedded to pretest probability and can be used to determine the post-test probability of a given diagnosis; whether ruling in or ruling out. Benchmark values have been provided to give clinicians perspective of individual meaningful levels. For example, LR+ >5 and LR- <0.2 is stated to moderately increase positive or negative post-test probability by approximately 30%.9But in reality, each likelihood ratio is dependent on the pretest probability and should be considered individually to guide decision-making.

Table XXXVII: Interpretation of likelihood ratios.

LR	Interpretation
> 10	Large and often conclusive increase in the likelihood of disease
5 – 10	Moderate increase in the likelihood of disease
2 – 5	Small increase in the likelihood of disease
1 – 2	Minimal increase in the likelihood of disease
1	No change in the likelihood of disease
0.5 – 1.0	Minimal decrease in the likelihood of disease
0.2 – 0.5	Small decrease in the likelihood of disease
0.1 – 0.2	Moderate decrease in the likelihood of disease
< 0.1	Large and often conclusive decrease in the likelihood of disease

The terms "odds of disease" and "probability of disease" are very often confused, but they are not the same. If we consider a group of 10 patients, 3 of whom have a disease and 7 of whom do not. If we randomly chose a patient from this group, the probability that they will have the disease is 3/10 or 0.3 or 30%. On the other hand, the odds of having the disease in this group are 3 : 7. To improve the clinical utility further, McGee (46) developed a table linking LRs to approximate percentage changes in post-test probability. McGee recommended that practitioners memorize 2, 5, and 10. With a LR+ of 2, 5, and 10, the percent increase in post-test probability is 15, 30, and 45, respectively. With an LR- , the practitioner uses the inverse version of the numbers or 1/2 (.50), 1/5 (.20), and 1/10 (.10) so that the percent decrease in post-test probability is 15, 30, and 45.

Here is a table which relates the odds to the probability:

Table XXXVIII: The relationship between odds and probability.

Probability	Odds
1%	1:99
5%	1:19
10%	1:9
20%	1:4
33%	1:2
50%	1:1
67%	2:1
80%	4:1
90%	9:1
99%	99:1

Stated as a mathematical formula this relationship is:

- for an odd of **a:b** , **probability** = $\frac{a}{a+b}$
- for a probability of **x%**, the odds are **x : (100-x)**

Thus, if the odds are 4:9, the probability is 4 / (4+9) = 4/13 = 0.31 (or 31%). Similarly, if the probability is 15%, then the odds are 15 : (100-15) = 15 : 85.

This is important to know because Likelihood ratios tell us how much we should shift our suspicion for a particular test result. But the formula uses odds not probability, and thus it is important to know how to convert probability into odds and vis versa.

post-test odds of disease = likelihood ratio × pre-test odds of disease

So, for positive and negative tests:

odds of disease for (+) test = odds of disease before testing × LR+

odds of disease for (-) test = odds of disease before testing × LR-

11. Demonstration:

If we estimate, based on our knowledge of the community, that the pre-test probability of the disease is approximately 25%. We then decide to use a diagnostic test with sensitivity of

96% and specificity of 80%. The LR+ and LR- are therefore 4.8 and 0.05. We can determine the likelihood of disease in our patient, in 3 simple steps. If the test is positive, we will use the LR+ of 4.8:

Step	Description	Calculation
1.	Convert the pre-test probability to odds form	25% = 25/(100-25) = 25:75 =1:3
2.	Multiply the pre-test odds by the LR to calculate the post-test odds	(1:3) x 4.8 = 1.6
3.	Convert the post-test odds back to a probability	160:100=160/(160+100)=160/260 = 0.62 or 62%

If the test is negative, we will use the LR- of 0.05 :

Step	Description	Calculation
1.	Convert the pre-test probability to odds form	25% = 25/(100-25) = 25:75 =1:3
2.	Multiply the pre-test odds by the LR to calculate the post-test odds	(1:3) x 0.05 = 0.02 = 2:100
3.	Convert the post-test odds back to a probability	2:100 = 2/(2+100) = 2/102 = 0.019 = 0.02 or 2%

Instead of just knowing that a positive test makes disease more likely, and a negative one makes it less likely (or worse yet, thinking that a positive test means the patient has disease and a negative test means they don't) we can estimate the specific likelihood of disease for our patient. This is truly "patient-centered" medicine, since our interpretation of the laboratory test is specific to our patient's pre-test probability of disease, which is in turn based on his or her age, symptoms, and signs.

In the above example, strictly from a mathematical standpoint, a positive test does not provide sufficiently convincing evidence of disease (62% probability), and you should be open to other causes for his or her symptoms. However, a negative test does provide substantial

evidence for not having the disease (2% probability). Let's consider another example with a pre-test probability of disease of 80%. By our estimate, if the test is positive, LR+ = 4.8:

Step	Description	Calculation
1.	Convert the pre-test probability to odds form	80% = 80/(100-80) = 80:20 = 4:1
2.	Multiply the pre-test odds by the LR to calculate the post-test odds	(4:1) x 4.8 = 192:10
3.	Convert the post-test odds back to a probability	192:10 = 192 / (192+10) = 192/202 = 0.95 or 95%

If the test is negative, LR- = 0.1:

Step	Description	Calculation
1.	Convert the pre-test probability to odds form	80% = 80/(100-80) = 80:20 = 4:1
2.	Multiply the pre-test odds by the LR to calculate the post-test odds	(4:1) x 0.05 = 0.2 = 2:10
3.	Convert the post-test odds back to a probability	2:10 = 2 / (2+10) = 2/12 = 1/6 = 0.17 or 17%

In this case, a negative test does not rule out disease (17% probability), and a positive test gives a high enough likelihood of disease (95% probability) that you would probably treat the patient. Consequently, we can deduce that calculations using likelihood ratios (LR) demonstrate greater clinical utility because the calculations incorporate both sensitivity and specificity and is a conduit for individualizing treatment for each patient, in this way, it is much more powerful than simply doing the same thing for every patient.

11.1. Fagan nomogram:

Bayesian statistical methods can be illustrated using Fagan's nomograms. These examples show how the post-test probability of a disease can be calculated using Bayes' theorem, given the pretest probability, the test result, and the test characteristics (sensitivity and specificity).

An alternative to odds ratio conversion was produced by Fagan in 1975 (14). Use of a nomogram allows the multiplicative analysis of pre-test probability and a LR to calculate post-test probability, without requiring a conversion to an odds ratio. Post-test probability calculations are associated with the probability of having or not having the condition when a test is positive (LR+) or negative (LR-).

In order to avoid converting fractions to odds, multiplying by the odds ratio, getting the post-test odds and converting back to a fraction, the Fagan nomogram is used. This nomogram is designed in three parallel longitudinal axes: left, center and right. The left axis represents the pre-test probability and is joined to the likelihood ratio, on the central axis, to read off the post-test probability on the third axis. To use it, you simply draw a line from the known pre-test probability, through either the LR+ (for a positive diagnostic test result) or the LR- (for a negative diagnostic test result) and read off the post-test probability.

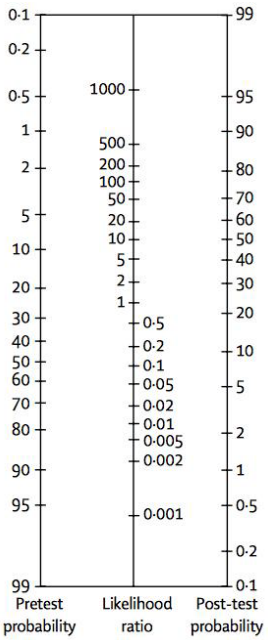


Figure 131: The nomogram showing Bayes' Theorem, produced by Dr Terrence J. Fagan in 1975.

Nowadays, there are more "modern" alternatives like the Two-Step Fagan Nomogram, which adds two extra axes between the LR axis that represents sensibility and specificity to calculate negative and positive likelihood ratios in the same nomogram.

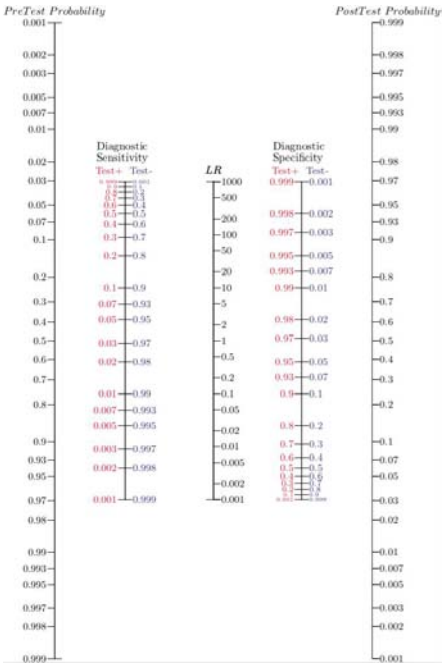


Figure 132: The two-step Fagan nomogram takes a step back, incorporating lines for test sensitivity and specificity, which are used to directly determine the Likelihood Ratios.

11.2. Demonstration:

A patient is suspected of having a certain disease, and the pre-test probability of the disease is approximately 25%. We decide to use a diagnostic test with a positive likelihood ratio (LR+) of 4.8 and a negative likelihood ratio (LR-) of 0.05. Using the Fagan nomogram, we can calculate the post-test probability of the disease (Figure 131).

1. If the test result is positive by following these steps:

1. Locate 25% on the vertical axis as the prior probability
2. Draw a line to the point on the LR+ line that corresponds to 4.8 (blue line)
3. Draw a vertical line down from that point to the LR- line
4. Read the post-test probability from the vertical axis. Between 60 and 70%

2. If the test result is negative by following these steps:

1. Locate 25% on the vertical axis as the prior probability
2. Draw a line to the point on the LR- line that corresponds to 0.05 (red line)
3. Draw a vertical line down from that point to the LR+ line
4. Read the post-test probability from the vertical axis. Between 1 and 2%

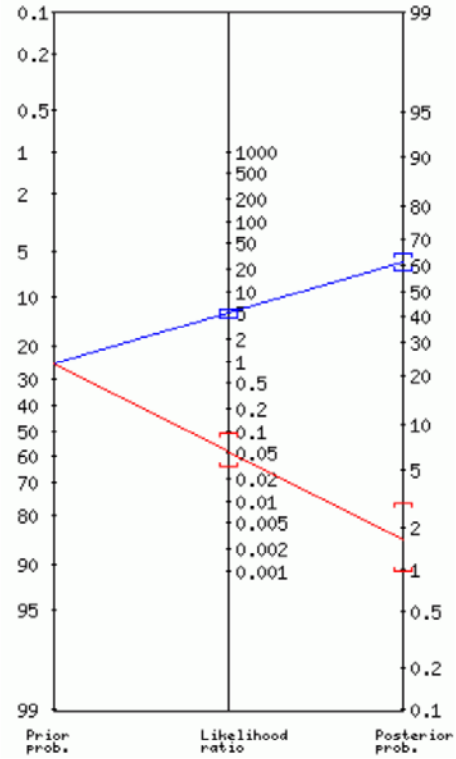


Figure 133: Calculating posttest probability using Fagan nomogram (Alan Schwartz's Diagnostic Test Calculator)

12. Advantages of using LRs:

Fortunately, likelihood ratios (LR), which combine sensitivity and specificity, alleviate many of the shortcomings of sensitivity and specificity and SpPIn and SnNOut. Furthermore, LRs are not dependent on disease prevalence and, thus, are considered as a robust global measure of the diagnostic properties of a test, and they can be used with tests that have more than two

possible results (see interval LR). positive setting to determine what level of increased likelihood is clinically relevant to improve the management of patients.

In a single number, the LR conveys to clinicians how convincingly a physical sign argues for or against disease. If the LR of a finding is large, disease is likely, and if the LR of a finding is close to zero, disease is doubtful. This advantage allows clinicians to quickly compare different diagnostic strategies and thus refine clinical judgment (46).

Using LRs to describe diagnostic accuracy is superior to describing it in terms of sensitivity and specificity, because the previously explained mnemonics, SpPin and SnNout, are sometimes misleading. For example, according to the mnemonic SpPin, a finding with a specificity of 95% should argue conclusively for disease, but it does so only if the positive LR for the finding is a high number. If the finding's sensitivity is 60%, the positive LR is 12 and the finding argues convincingly for disease (i.e., consistent with the SpPin mnemonic); if the finding's sensitivity is only 10%, however, the positive LR is 2 and the post-test probability changes only slightly (i.e., inconsistent with SpPin mnemonic). Similarly, a highly sensitive finding argues convincingly against disease when absent (i.e., SnNout) only when its calculated negative LR is close to zero.

Another advantage of LRs is that a biomarker measured on an ordinal scale (e.g., 0, 1+, 2+, 3+) or continuous scale (e.g., blood pressure) can be categorized into different levels to determine the LR for each level, thereby increasing the accuracy of the finding. Other examples include continuous findings such as heart rate, respiratory rate, temperature, and percussed span of the liver, and ordinal findings such as intensity of murmurs and degree of edema. For example, in patients with chronic obstructive lung disease (i.e., emphysema, chronic bronchitis), breath sounds are typically faint. If the clinician grades the intensity of breath sounds on a scale from 0 (absent) to 24 (very loud), based on the methods discussed in Chapter 30,29,30 he or she can classify the patient's breath sounds into one of four groups: scores of 9 or less (very faint), 10 to 12, 13 to 15, or greater than 15 (loud). Each category then has its own LR (Table 2.3): scores of 9 or less significantly increase the probability of obstructive disease (LR = 10.2),

whereas scores greater than 15 significantly decrease it (LR = 0.1). Scores from 10 to 12 argue somewhat for disease (LR = 3.6), and scores from 13 to 15 provide no diagnostic information (LR not significantly different from 1). If the clinician instead identifies breath sounds as simply "faint" or "normal/increased" (i.e., the traditional positive or negative finding), the finding may still discriminate between patients with and without obstructive disease, but it misses the point that the discriminatory power of the sign resides mostly with scores less than 10 and greater than 15. When findings are categorized into levels, the term specificity becomes meaningless. For example, the specificity of a breath sound score of 13 to 15 is 80%, which means that 80% of patients without chronic airflow limitation have values other than 13 to 15, though the "80%" does not convey whether most of these other values are greater than 15 or less than 13. Similarly, when findings are put in more than two categories, the LR descriptor negative is no longer necessary, because all LRs are positive for their respective category.

A final advantage of LRs is that clinicians can use them to combine findings, which is particularly important for those physical signs with positive LRs around 2 or negative LRs around 0.5, signs that by themselves have little effect on probability but when combined have significant effects on probability. Individual LRs can be combined— however, only if the findings are "independent."

13. The relationship between sensitivity and specificity/ROC/AUROC/ (47):

If an ideal test existed, it would have 100% sensitivity and 100% specificity, meaning that it would correctly identify all individuals with the disease and all individuals without the disease. In practice, this is impossible, and a threshold must be chosen for the test, leading to classification errors. Sensitivity and specificity are inversely related, so choosing a higher sensitivity will result in a lower specificity and vice versa. A higher threshold for a diagnostic test will result in a lower sensitivity, as fewer patients with the condition will be classified as positive. Conversely, a lower threshold will result in a higher sensitivity, as more patients with the

condition will be classified as positive. A higher threshold for a diagnostic test will result in a higher specificity, as fewer patients without the condition will be classified as positive. Conversely, a lower threshold will result in a lower specificity, as more patients without the condition will be classified as positive.

Therefore, by adjusting the threshold of a diagnostic test, we can trade-off sensitivity and specificity. The ROC curve is a visual representation of this trade-off, allowing us to see how sensitivity and specificity vary as the threshold changes.

A Receiver Operating Characteristic (ROC) curve is a graphical representation of the performance of a diagnostic test. It is used to evaluate the ability of a test to correctly distinguish between patients with a disease and those without it. The curve is created by plotting the true positive rate (sensitivity) against the false positive rate (1-specificity) at various threshold settings of the test.

To create the ROC curve, the threshold setting of the test is varied and the true positive rate and false positive rate are calculated for each threshold. These values are then plotted on a graph, with the false positive rate on the x-axis and the true positive rate on the y-axis.

A test with perfect discrimination will have a ROC curve that hugs the top left corner of the graph, while a test with no discrimination will have a ROC curve that is a diagonal line from the bottom left to the top right of the graph.

To interpret the ROC curve, we use the area under the curve (AUROC). A test with a high AUROC (close to 1) is considered to have good discrimination, while a test with a low AUROC (close to 0) is considered to have poor discrimination. Additionally, we can look at the position of the ROC curve relative to the diagonal line. A test that is above the diagonal line is considered to be better than a test that is on or below the diagonal line.

- The best possible test (100% sensitive and 100% specific) would have an area under the curve of: 1.0.

- A worthless test, which does not discriminate between patients with the disease and patients without the disease, would have an area under the curve of 0.5 (shown by the diagonal red line).

-

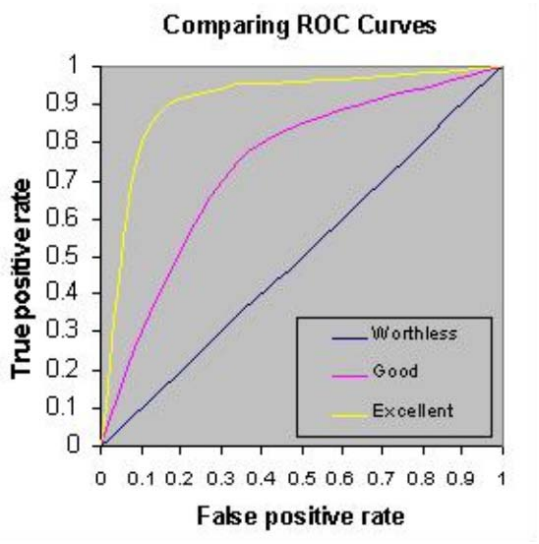


Figure 134: Comparison between tests using ROC and AUROC.

Table XXXIX: Important features of a diagnostic test.

Feature	Definition	Formula
Sensitivity	The probability that the test will correctly identify patients who have the disease or condition	sensitivity = true positives / (true positives + false negatives)
Specificity	The probability that the test will correctly identify patients who do not have the disease or condition	specificity = true negatives / (true negatives + false positives)
Positive predictive value	The probability that a patient with a positive test result actually has the disease or condition	positive predictive value = true positives / (true positives + false positives)
Negative predictive value	The probability that a patient with a negative test result does not have the disease or condition	negative predictive value = true negatives / (true negatives + false negatives)
Accuracy	The overall accuracy of the test, taking into account both true positive and true negative results	accuracy = (true positives + true negatives) / (true positives + true negatives + false positives + false negatives)
Positive likelihood ratio	The ratio of the probability of a positive test result in patients with the disease to the probability of a positive test result in patients without the disease	positive likelihood ratio = sensitivity / (1 - specificity)
Negative likelihood ratio	The ratio of the probability of a negative test result in patients with the disease to the probability of a negative test result in patients without the disease	negative likelihood ratio = (1 - sensitivity) / specificity
Receiver operating characteristic (ROC)	A graphical plot that shows the relationship between the true positive rate and the false positive rate at different threshold settings for a diagnostic test	N/A
Area under the ROC curve (AUROC)	A measure of the overall accuracy of a diagnostic test, calculated as the area under the ROC curve	AUROC = the area under the ROC curve

13.1. Key takeaways:

- Biomarkers are objectively measured characteristics that act as an indicator of normal biological processes, pathological processes, or pharmacologic response.
- Biomarkers in the ED can inform us on diagnosis, prognostication, risk stratification and monitoring of patients in critical and acute care settings.
- Biomarkers undergo rigorous analytical and clinical studies to ensure their validity. Impact studies are the most important of these studies, but they are rarely performed.
- Clinical reasoning refers to the cognitive processes and decision-making strategies used by healthcare professionals to formulate and evaluate possible diagnoses, select appropriate tests (biomarkers) and treatments, and monitor patient progress.
- The clinical reasoning process involves incorporating knowledge of pathophysiology, applying biostatistics and epidemiology, considering costs, integrating the patient's values and preferences, and communicating with other healthcare professionals.
- Determining pretest probability in the diagnostic process involves three main sources: disease prevalence, clinical decision rules, and physician's experience which contributes implicitly through intuition and explicitly through differential diagnosis.
- Clinical prediction rules are tools that identify and quantify the contributions of the most helpful pieces of information related to a clinical scenario. They reduce this information to an algorithm or scoring system to help determine a patient's diagnosis, treatment, and prognosis.
- Clinical prediction rules exist for only a minority of diagnoses and have several important limitations.
- In the absence of available published data and clinical prediction rules, a clinician can employ a combination of patient history, presenting symptoms, and clinical signs to generate a list of potential differential diagnoses. The clinician can then use this list to estimate the pretest probability of the patient's condition.

- A differential diagnosis is a list of diagnoses which could plausibly explain a specific patient's presentation based on the information available at the time usually placed in the order of estimated descending probability.
- The pretest probability of a disease depends on its position on the DDx list, which is influenced by the disease's prevalence in the population and the degree to which the patient's symptoms align with the illness script for the disease.
- To appropriately utilize diagnostic tests, it is essential to have knowledge of the pretest probability of the disease under consideration.
- Applying test results to revise the differential diagnosis requires estimation of the pre-test probability, accurate interpretation of the test, knowledge of the test characteristics, and the ability to identify possible inaccurate results.
- Tests are most helpful in ruling out a disease in cases of diagnostic uncertainty.
- A common mistake when using biomarkers is considering the result to be 100% accurate, rather than an aid to decrease uncertainty.
- Clinicians often fail to adequately consider pre-test probability when interpreting diagnostic test results. This can lead to the inappropriate ruling-in of diagnoses with low pre-test probabilities following positive tests or the premature ruling-out of diagnoses with high pre-test probabilities following negative tests, due to treating all items on the differential diagnosis list as having similar probabilities.
- When a diagnosis is unlikely, a positive test, even if its specificity is high, does not confirm the diagnosis. It only increases its likelihood from unlikely to uncertain.
- When a diagnosis is likely, a negative test, even if its sensitivity is high, does not eliminate the diagnosis. It only decreases its likelihood from likely to uncertain.
- The interpretation of a biomarker is based on its characteristics, such as sensitivity, specificity, predictive values, likelihood ratios, and others.
- The positive and negative predictive values depend on the intrinsic qualities of the test and the prevalence of the disease under consideration.

- The sensitivity and specificity of a biomarker are intrinsic qualities of the test and do not depend on the prevalence of the disease under consideration.
- The statistic that describes the proportion of people with a positive test that actually have the disease is the PPV.
- The statistic that describes the proportion of people with a negative test who still actually have the disease is 1-NPV, also known as false negative.
- LRs are not dependent on disease prevalence and are considered a robust global measure of a test's diagnostic properties. They can be used with tests that have more than two possible results to determine clinically relevant levels of increased likelihood.
- The threshold model provides a theoretical framework to guide clinical decisions despite the presence of uncertainty.
- Clinicians are exposed to new diagnostic tests and studies about their diagnostic properties. Understanding biostatistics can help clinicians critically assess these studies.
- Understanding biostatistics will enable clinicians to make more informed decisions about the use of diagnostic tests in their practice.

13.2. Review of the relevant literature on troponins:

a. Introduction:

Cardiovascular disease is a critical global health issue, with coronary artery disease (CAD) representing the leading cause of morbidity and mortality in industrialized nations (48,49). In Morocco, CAD is the primary cause of death, resulting in an estimated rate of 38% and nearly 70,000 deaths annually (50,51). Chest pain is a prevalent symptom of CAD and a frequent complaint in emergency medicine, but not all patients presenting with chest pain exhibit acute coronary syndrome (ACS) (52). To identify patients at high risk for ACS, assessing pre-test probability is crucial, and biomarkers such as troponin can play a pivotal role (53).

Troponin measurement has emerged as a standard diagnostic tool in the emergency department for patients presenting with chest pain or suspected ACS. Cardiac troponin I and T (cTnI and cTnT) have become indispensable proteins since 1990, not only for diagnosing myocardial infarction (MI) but also for risk stratification, guiding therapeutic strategies, and prognostic evaluation. The advent of highly sensitive immunoassays in 2010 has significantly expedited the diagnosis of ACS, enabling a prompt decision-making approach for patient management (54). The use of ultrasensitive troponin has rekindled the debate regarding ACS diagnosis, as the interpretation of results now necessitates a fresh approach that emphasizes clinical reasoning. The 2018 Universal Definition of Myocardial Infarction regulates the use of these immunoassays in 1-hour and 3-hour diagnostic algorithms (55).

b. Myocardial infarction:

Acute myocardial infarction (MI) is defined by the presence of myocardial necrosis in combination with the clinical presentation of myocardial ischemia. The diagnosis of acute MI requires the rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit in a healthy population. In addition, at least one of the following elements must be present: symptoms of ischemia; ECG changes indicative of active ischemia (such as new ST-T wave changes, new left bundle branch block, or the development of new pathologic Q waves); imaging evidence of new regional wall motion abnormality; or the loss of viable myocardium (56,57).

The classification of myocardial infarction (MI) types is based on the etiology of the ischemia (56):

- Type 1 MIs are due to a primary coronary event, such as the spontaneous rupture of an atherosclerotic plaque or dissection within the coronary artery, resulting in ST-segment elevation MI (STEMI) or non-ST-segment elevation MI (NSTEMI) (Figure 135).
- Type 2 MIs are the result of a non-thrombotic condition causing an imbalance between coronary oxygen supply and demand, leading to myocardial ischemia (such as anemia,

arrhythmias, hypertension, coronary artery spasm, and hypotension) in the presence of fixed coronary disease (Figure 135).

- Sudden cardiac death defines the third type of MI.
- The fourth type is composed of two subtypes: percutaneous coronary intervention (PCI)-associated MI (defined as a biomarker increase that exceeds three times the 99th percentile of the upper reference limit) and MI due to stent thrombosis.
- Type 5 MIs are secondary to coronary artery bypass grafting (CABG) and are defined as a biomarker increase that exceeds five times the 99th percentile of the upper reference limit, in combination with electrocardiographic, imaging, or angiographic evidence of ischemia.

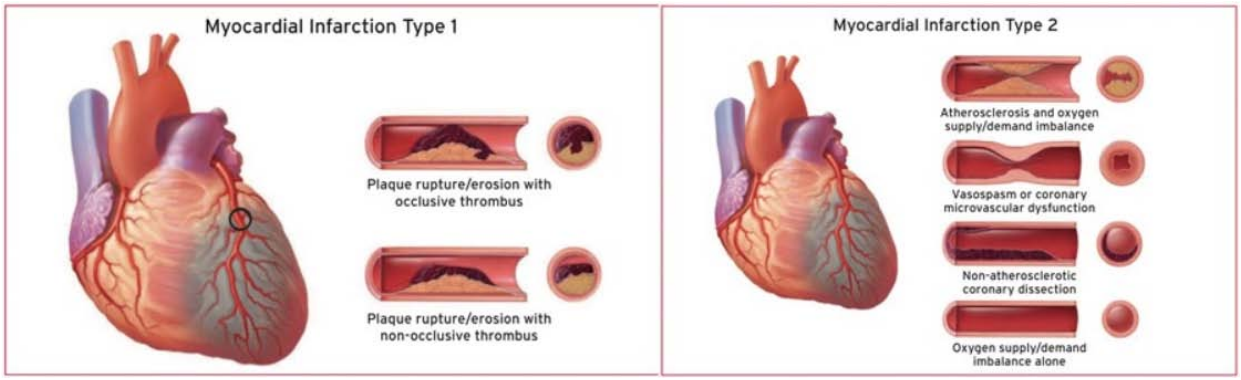


Figure 135: The key difference between Type I vs. Type II MI is the presence/absence of plaque rupture (55)

c. Metabolism, physiology and molecular aspects of troponin:

c.1. Troponin definition:

Troponins are proteins found in the contractile filaments of striated cardiac muscle. There are two types of filaments: the thick filament is made of myosin, and the thin filament is made of actin, tropomyosin, and the troponin complex.

The troponin complex consists of three subunits:

- Troponin C is a small polypeptide with a molecular weight of 18,000 Da and is found in both the myocardium and striated muscle.
- Troponin I, with a molecular weight of 24,000 Da, inhibits the adenosine triphosphatase (ATP) activity of the myosin head and exists in three different forms: two forms specific to slow and fast-twitch striated muscles and one form specific to the myocardium (cTnI).
- Troponin T, with a higher molecular weight of 37,500 Da, anchors troponins I and C to tropomyosin and exists in many different molecular forms, with two cardiac isoforms (cTnT) and 12 skeletal muscle isoforms.

The differentiation between cardiac and skeletal muscle isoforms is primarily characterized by a sequence similarity of 90%, with only 6 to 11 amino acids differentiating the two. Notably, each of the troponins (I, C, and T) exists as both skeletal and cardiac muscle isoforms. While the isoforms of troponin I and T exhibit high specificity for their respective muscle types, the absence of a cardiac muscle-specific isoform for troponin C explains the absence of an immunoassay targeting this particular form (58,59).

There are two distinct pools of troponins present within the cell (60,61):

- The first pool is the functionally free cytosolic pool, which contains the free forms of troponin I and T.
- The second pool is the major structural sarcomeric pool, also known as the myofibrillar pool, which comprises complexes.

In the absence of damage to myocardial cells, the presence of cardiac troponins in the general circulation is either negligible or present only in minimal amounts, depending on the sensitivity of the assay methods employed. Following damage to the myocyte, there is a biphasic increase in serum troponin levels, which corresponds to the initial release of free cytoplasmic troponin at first followed by the gradual dispersion of myofibril-bound troponin complexes. The forms of troponin released into circulation after myocardial necrosis can vary based on the intensity of the necrosis, including minor forms such as free troponin I and free troponin T, and

major forms such as the TnI-TnT (IT) binary complex, the TnI-TnC (IC) binary complex, and TnI-TnT-TnC (ITC) ternary complex. The diversity of circulating forms poses a challenge in standardizing assay methods (62).

Table XL: Intracardiac distribution of cardiac biomarkers

Marker	Tissue Level (mg/g)	Location in Cell	Percentage (%)
cTnI	4-6	Sarcoplasm	96-97
		Cytosol	3-4
cTnT	11	Sarcoplasm	92-94
		Cytosol	6-8

d. Function of the troponin complex:

The troponin complex is critical for regulating the contraction of the heart's myofilaments. When calcium binds to troponin C, it causes a conformational change in the complex, leading to the release of troponin I from its inhibitory interaction with actin. This displacement of tropomyosin exposes the binding sites of actin, allowing for the generation of force by the myosin head and the contraction of the myofibril (54).

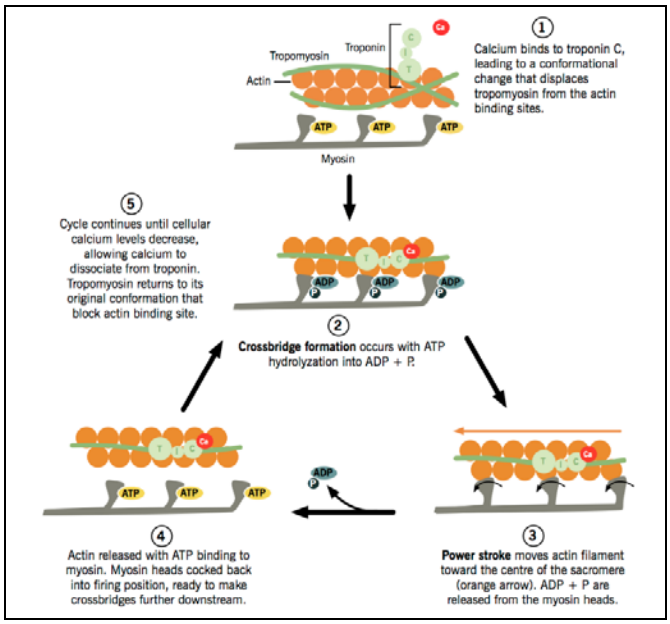


Figure 136: Schematic representation of the troponin complex during cardiomyocyte contractile cycle (63).

e. Troponin release:

There are 6 potential major pathobiological mechanisms for troponin elevations (64,65):

- **Myocyte necrosis** is the most common mechanism, and it can be caused by ischemic, inflammatory, infiltrative, direct trauma, and toxic factors, including sepsis.
- **Apoptosis**, on the other hand, is a type of programmed cell death that can be triggered by short-term ischemia or myocardial distension. It is associated with the activation of caspases and other intracellular proteinases that mediate the cleavage of structural proteins, leading to the release of troponin.
- **Normal myocyte cell turnover**, although limited in the myocardium, may also result in the release of troponin into the systemic circulation.
- **Proteolytic degradation of troponin**, on the other hand, can occur without cell death or membrane disruption. This can be triggered by the accumulation of lactic acid in cardiomyocytes, which activates proteolytic enzymes and leads to the creation of small fragments that can pass through the cell membrane.
- **Increased permeability of the cell membrane without necrosis** can also result in the release of troponin. This can be caused by myocardial stretch or ischemia, both of which damage the cell membrane and increase its permeability.
- **The formation and release of membranous blebs** has also been hypothesized as a mechanism for troponin release. This has been observed in liver cells and cultured cardiac myocytes, but there is little evidence supporting its occurrence in humans.

f. Kinetics of troponin release, half-life and elimination:

f.1. Conventional troponin:

Various biomarkers can be utilized to detect myocardial necrosis, also known as heart muscle damage, with myoglobin, CK-MB, and troponins being the most frequently employed. Myoglobin is the earliest biomarker to increase following injury and can be detected in the

bloodstream within 1-3 hours of the injury. CK-MB is also a useful biomarker and can be found in the bloodstream 4 hours after the injury, reaching its peak within 24 hours and returning to normal within 48-72 hours (66). However, troponins have now replaced myoglobin and CK-MB as the preferred biomarkers due to their high specificity for heart tissue and lower likelihood of producing false-positive outcomes in instances of skeletal muscle damage.

Troponins can be detected in the bloodstream between 4-6 hours after the injury, with peak concentrations occurring 8-24 hours after symptoms and requiring 5-9 days to return to normal levels. This expanded diagnostic window makes troponins more beneficial for detecting acute myocardial infarction, commonly known as a heart attack (67). The kinetics of troponin release during myocardial ischemia are comparable for both isoforms, cTnI and cTnT, with minor differences. Troponin I has a half-life of 1.08+/-0.63 days, with its serum levels remaining elevated for up to 4-7 days, while troponin T has a half-life of 2h , and its serum levels can remain elevated for 10-14 days (68,69). The prolonged half-life seen in ACS (acute coronary syndrome) may be due to continued breakdown of contractile proteins.

Although the mechanism of troponin elimination is not well understood, it is believed that the reticuloendothelial system clears it due to its relatively large molecular size. Recent evidence suggests that troponin T is fragmented into smaller molecules that can be excreted through the kidneys, which may explain its high prevalence in patients with renal failure (70).

Table XLI: Comparison of Biomarkers for Detecting Myocardial Necrosis

Biomarker	Time detectable from onset of ischemia	Peak	Return to baseline	Half-Life
Myoglobin	1-3 hours	8-10 hours	1-2 days	2-3 hours
CK-MB	4 hours	24 hours	48-72 hours	17-19 hours
Troponins	4-6 hours	8-24 hours	to 4-7 days for Troponin I and 10-14 days for Troponin T	cTnI: 1.08+/-0.63 days, cTnT: 2 h

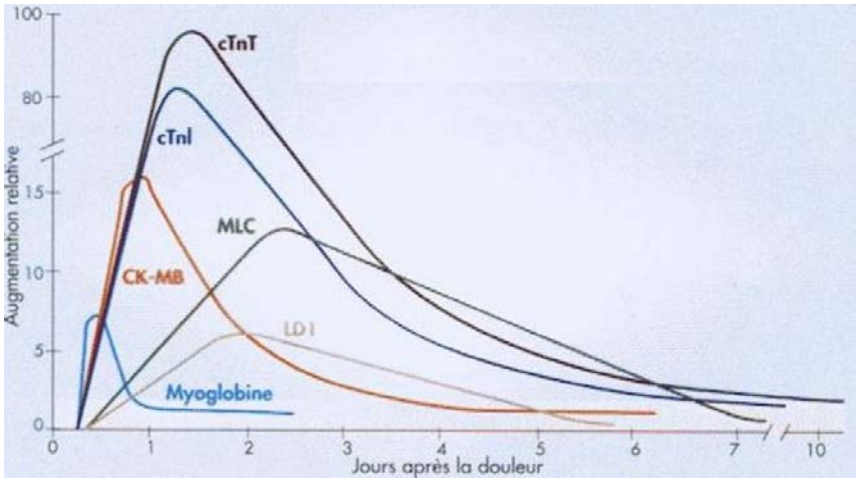


Figure 137: Kinetics of different cardiac markers after the onset of chest pain, Laboratory of biochemistry, Poissy Hospital.

f.2. Hypersensitive troponin:

Ultrasensitive methods have demonstrated that blood concentrations of cTnT and cTnI increase within 1-3 hours following a myocardial infarction, which is a considerable improvement compared to the 4-6 hours needed for conventional methods (71). Maximum plasma levels are reached at approximately 18-24 hours, with decay kinetics that are comparable to those observed using conventional assays. cTn concentrations remain elevated in circulation for 75-140 hours for cTnI and over 10 days for cTnT (72).

Biomarker	Time detectable from onset of ischemia	Peak	Return to baseline	Half-Life
Myoglobin	1-3 hours	8-10 hours	1-2 days	2-3 hours
CK-MB	4 hours	24 hours	48-72 hours	17-19 hours
Troponins	4-6 hours	8-24 hours	to 4-7 days for Troponin I and 10-14 days for Troponin T	cTnI: 1.08+/- 0.63 days, cTnT: 2 h
Hypersensitive Troponin	1-3 hours	6-9 hours	75-140 hours for cTnI and over 10 days for cTnT	3-5 hours

g. Assay technique:

The preferred approach to measure cardiac troponins is to use sandwich-type enzyme immunoassay methods. These techniques employ one or two "capture" antibodies that can selectively recognize the sequence of cardiac troponin, along with a "detector" antibody that is fused to a signal generator. The interaction between these elements results in a complex that can be visualized through luminescence, fluorescence, or colorimetry, depending on the specific technique utilized. The underlying principle of all these methods remains identical, which is to employ antibodies to trap cardiac troponin within a given sample and produce a signal that is directly proportional to its concentration (73).

Table XLII: Contemporary HighSensitivity Cardiac Troponin Assays (74).

	Limit of Detection (ng/L)	99 % (CV) (ng/L)	10% CV (ng/L)
Hs-cTn-T			
Roche Elecsys	5.0	14 (13%)	13
Hs-cTn-I			
Abbot ARCHITECT	1.2	16 (5.6%)	3.0
Beckman ACCESS	2 to 3	8.6 (10%)	8.6
Mitsubishi Pathfast	8.0	29 (5%)	14
Nanosphere	0.2	2.8 (9.5%)	0.5
Radiometer AQT90	9.5	23 (17.7%)	39
Singulex Erenna	0.09	10.1 (9.0%)	0.88
Siemens Vista	0.5	9 (5.0%)	3
Siemens Centaur	6.0	40 (10%)	30

h. Performance characteristics:

h.1. Conventional troponin:

The sensitivity of troponin T and troponin I tests increases over time, providing more accurate results for the diagnosis.

Upon admission to the hospital, the sensitivity of a troponin T test ranges from 25% to 65%. However, if the test is repeated 2 to 6 hours later, the sensitivity increases to 59% to 90% (75-77). By 6 to 12 hours after admission, the sensitivity of the test approaches 100%. Similarly,

the sensitivity of a troponin I test upon admission is less than 45%, but improves to 69% to 82% when measured 2 to 6 hours later and reaches 100% sensitivity between 6 and 12 hours after admission (75-77). These findings suggest that the most accurate results of a troponin test are obtained at least 6 hours after the onset of myocardial necrosis (78).

Therefore, to optimize the diagnosis of AMI, it is recommended to draw blood samples for troponin measurements at the time of presentation and again 6 to 9 hours later. Serial testing can also increase the positive predictive value of the troponin test, improving from 25% for troponin I and 35% for troponin T at presentation to 89% for troponin I and 57% for troponin T after 12 hours (76).

In contrast, specificity does not vary significantly over time. Troponin I has a specificity of around 83% to 98% with serial testing (76,77,79) and troponin T has specificities ranging from 86% to 98% (76,77). The negative predictive value of troponin I and T at presentation is 85% and 88% respectively and increases to 98% and 99% respectively after 12 hours (76).

Table XLIII: Troponin Test Performance Characteristics in the Diagnosis of Acute Myocardial Infarction

Troponin Test		Sensitivity	Specificity	NPV	PPV
Troponin T	Admission	25%	86-98%	88%	35%
	2-6 Hours Later	59-90%	86-98%	-	57%
	6-12 Hours Later	Approaches 100%	86-98%	99%	-
Troponin I	Admission	<45%	83-98%	85%	25%
	2-6 Hours Later	69-82%	83-98%	-	89%
	6-12 Hours Later	Approaches 100%	83-98%	98%	-

h.2. Performance characteristics of hypersensitive troponin:

The use of highly sensitive cardiac troponin (hs-cTn) assays has resulted in an improvement in the diagnostic accuracy for detecting myocardial infarction (MI) at presentation.

This improvement has facilitated the reduction in the time interval to the second cardiac troponin assessment, resulting in shorter stays in the emergency department and lower costs. It is recommended to employ the 0h/1h or 0h/2h algorithms, which have been developed and validated in large multicenter diagnostic studies that utilized central adjudication of the final diagnosis for all currently available hs-cTn assays.

The optimal thresholds for rule-out have been selected to ensure a minimum sensitivity and a negative predictive value (NPV) of 99%. The optimal thresholds for rule-in have been chosen to ensure a maximum positive predictive value (PPV) of 70%. The cut-off concentrations in the 0h/1h and 0h/2h algorithms are specific to the assay used. Several large validation cohorts have reported an NPV for MI in patients assigned "rule-out" that exceeded 99%. The PPV for MI in patients meeting the "rule-in" criteria is approximately 70-75%.

Table XLIV: Performance Characteristics of hs-cTn Assays

Performance Characteristics	Summary
NPV for MI in "rule-out" patients	Exceeded 99% in several large validation cohorts
PPV for MI in "rule-in" patients	Approximately 70-75%

h.3. Classic troponin vs hypersensitive troponin:

High sensitivity cardiac troponin (hs-cTn) assays have emerged as a superior diagnostic tool for acute myocardial infarction (AMI) when compared to standard cardiac troponin assays due to their enhanced negative predictive value. Additionally, the development of hypersensitive troponin assays has significantly reduced the "troponin-blind" interval, enabling earlier detection of AMI. This has enabled a shorter time for patient triage, as the values become higher than the threshold earlier in the case of a myocardial infarction. The time between assays can be reduced from 6 hours (conventional troponin) to 3 hours for the second ultrasensitive troponin assay, and even to 1 hour at present (75). Importantly, hs-cTn assays have been shown to result in a 4% absolute and 20% relative increase in the detection of type 1 myocardial infarction, leading to a

corresponding decrease in the diagnosis of unstable angina. However, these assays are also associated with a 2-fold increase in the detection of type 2 myocardial infarction (80).

Hypersensitive troponins are more frequently positive than standard troponins and are likely to detect myocardial micro-necrosis more accurately, allowing 20% of myocardial infarction diagnoses to be reclassified. Many more patients with clinical syndromes of myocardial ischemia will now meet the diagnostic criteria for MI and will benefit from treatment, especially early antithrombotic treatment(81).

h.4. Normal and critical findings:

- **Conventional troponin:**

In 2007, The National Academy of Clinical Biochemistry released a guideline which recommends the use of the 99th percentile of a healthy reference population as the decision limit for a "positive" cardiac troponin (cTn) result. This guideline has been widely accepted by various organizations including the European Society of Cardiology and the American College of Cardiology (82).

It is important to note that levels of high-sensitivity cardiac troponin (hs-cTn) should be interpreted as quantitative markers of cardiomyocyte damage, where higher levels are indicative of a greater likelihood of myocardial infarction (MI). Elevations that exceed 5-fold the upper reference limit have a high positive predictive value (>90%) for acute type 1 MI. Conversely, elevations that are within 3-fold the upper reference limit have a limited positive predictive value (50-60%) for AMI and may be associated with a broad spectrum of conditions.

h.5. Hypersensitive troponin:

Significant advances have been made in troponin assays, culminating in the development of ultrasensitive assays in 2007, which represented a major breakthrough (54). These assays possess the ability to detect troponin variations greater than the 99th percentile of a control population, with a coefficient of variation (CV) below 10%, as demonstrated in figure 138.

Hypersensitive troponin assays, which have been developed by several companies, are more precise and dependable than previous methodologies. Hypersensitive assays are capable of identifying troponin concentrations ten times lower than conventional methods, with a detection limit of 5 ng/l compared to the latest generation of troponin's limit of 10 ng/l. This advancement has had a substantial impact on acute coronary syndromes management (83).

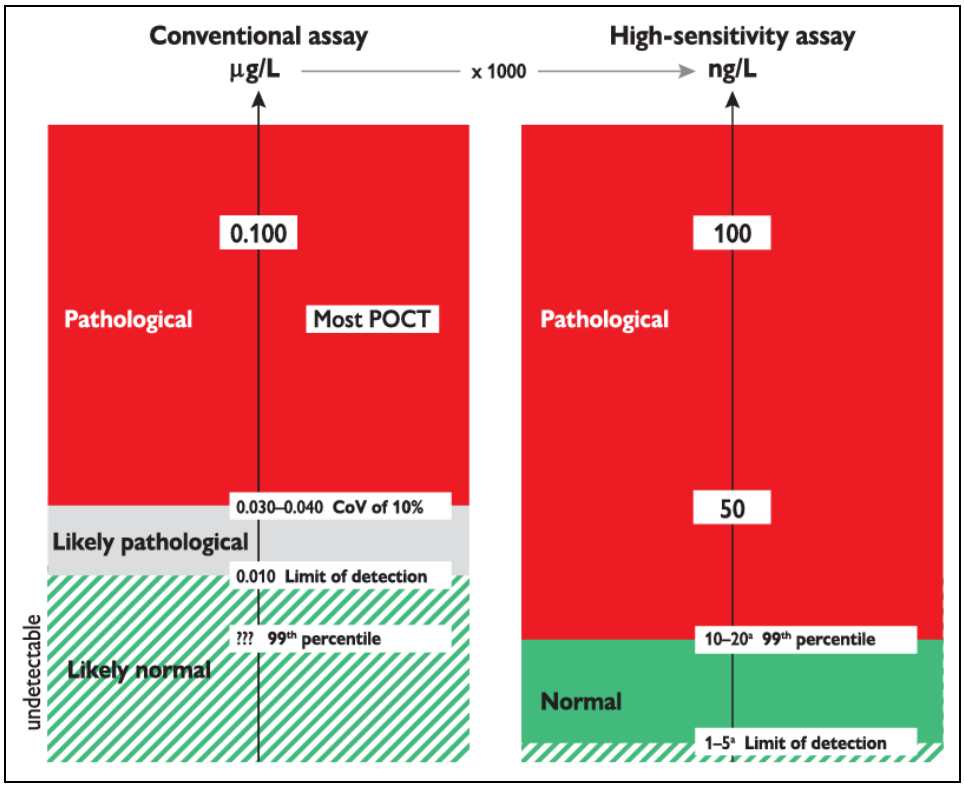


Figure 138: Conventional and high-sensitivity cardiac troponin (57).

i. Clinical application of troponin assay:

i.1.In the diagnosis of MI:

- Classic troponin:

The definition of MI combines clinical or ECG signs of myocardial ischemia with troponin elevation or decrease (55).

The use of troponin levels as a diagnostic tool for myocardial infarction (MI) has been established in the literature and is recommended by both American and European guidelines since 2000 (84,85). In the presence of chest pain suggestive of acute coronary syndrome (ACS), troponin testing is essential. If the clinical presentation is typical with ST-segment elevation on the electrocardiogram, treatment can be initiated without waiting for the troponin result. However, in cases where the electrocardiogram is non-contributing or difficult to interpret, the troponin result may be decisive for the immediate course of action.

The accurate diagnosis of acute coronary syndrome (ACS) is critical for determining the appropriate treatment course for patients. Troponin testing timing plays a crucial role in diagnosing ACS. Unlike other conditions with increased troponin, ACS requires two successive determinations due to the kinetics of troponin release and clearance in the presence of ischemic symptoms. A variation greater than 20% between consecutive determinations indicates a change in the patient's condition. Therefore, according to the recommendations, conventional troponin tests should be performed on admission and repeated 6 to 9 hours later if the first test is negative (86).

In this context, the timing of the initial troponin test is of utmost importance, as the troponin elevation typically appears 3-4 hours after the onset of symptoms. Therefore, a single negative assay may be sufficient to rule out MI if the patient is admitted 26 hours after the onset of symptoms. Conversely, a single positive troponin assay on arrival at the emergency department is sufficient to confirm the diagnosis of MI if the presentation is typical (87).

- **hypersensitive troponin:**

It is crucial to note that both conventional and hypersensitive troponin serve as a singular marker for myocardial infarction (MI), albeit with varying degrees of analytical precision (88). Conventional troponin assays have been limited in their diagnostic sensitivity when performed upon admission, necessitating a second troponin assay 4-6 hours later to enhance sensitivity. Hypersensitive troponin assays, on the other hand, exhibit greater sensitivity by being able to detect troponin in the bloodstream within the first hour of an MI event and In cases of negativity, can be repeated within 3 hours or even 1 hour later, (80). The superiority of hypersensitive troponin assays is even more significant in patients who are managed very early, as it enables earlier diagnosis of acute coronary syndrome (89).

The interpretation of kinetics after two troponin assays necessitates understanding the minimum change between values that would indicate a significant increase or decrease. For conventional troponins, the recommended variation is more than 20% between two assays, and for hypersensitive troponins, it is 30% (87,90). In addition to excluding MI when negativity is indicated, this kinetic approach also aids in the diagnosis of MI of coronary origin when the low value of the first assay rises sharply in the second.

In conclusion, it is recommended to perform measurements at admission and after 3 hours with hypersensitive troponins (57). If chest pain began within the previous 6 hours, a single test may suffice. Nonetheless, this strategy cannot exclude the diagnosis of acute coronary syndrome (ACS), as it does not rule out the possibility of unstable angina, though it can exclude the diagnosis of MI with a negative predictive value of 100%.

- **The 0/3h and 0/1h algorithms:**

The European Society of Cardiology has issued a Class I recommendation for both the 0/1 hour (0/1h) algorithm and the 0/3 hour (0/3h) algorithm as effective protocols for the early rule-out of AMI. Despite their shared recommendation, these algorithms differ significantly. The 0/1h algorithm utilizes hs-cTn concentrations at presentation and absolute changes within the first hour to optimize diagnostic accuracy, whereas the 0/3h algorithm relies on a fixed

threshold protocol based on the 99th percentile at presentation and 3 hours, in addition to clinical criteria such as a GRACE score below 140 and the absence of pain (91).

0/3h algorithm:

- Rule out: When a patient presents with chest pain, a troponin test is the first step in assessing the likelihood of MI. If the troponin level is below the upper limit of normal and the patient has had pain for more than six hours with a low GRACE score or no pain, a single high-sensitivity troponin test may be sufficient to rule out a cardiac event and safely discharge the patient.
- Rule in: When a patient presents with chest pain within six hours of symptom onset, a second troponin test is necessary to evaluate the delta change between the two troponin levels. If the second troponin test shows a delta change or if either of the troponin values is above the upper normal limit, the patient may require invasive management, such as coronary angiography or percutaneous coronary intervention. In cases where a patient presents with characteristic pain and has a qualifying ECG or a very high troponin level (above the ULN), immediate management by a cardiology team may be necessary.

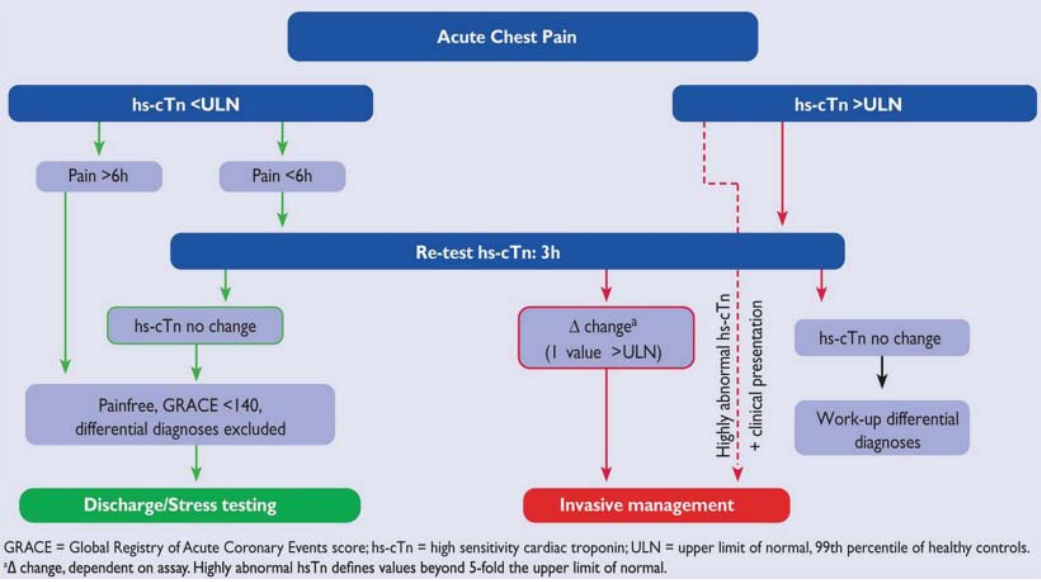


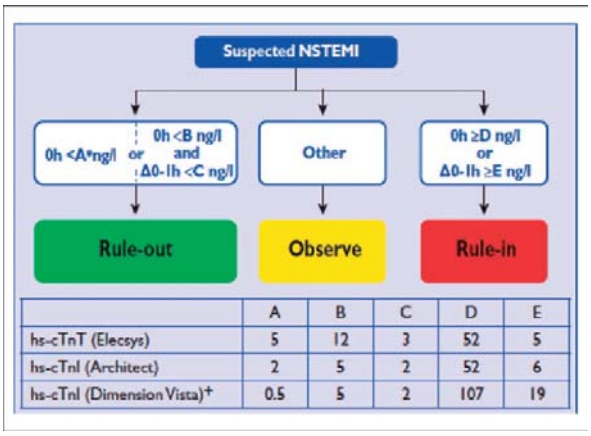
Figure 139: 0 h/3 h rule-out algorithms using high-sensitivity cardiac troponin assays in patients presenting to the emergency department with suspected non-ST-elevation myocardial infarction (92).

1h algorithm:

In March 2016, the European Society of Cardiology (ESC) proposed a new algorithm for the management of patients with chest pain by reducing the time to recheck ultrasensitive troponin from 3 hours to 1 hour according to the ESC 2015 algorithm (Figure 130). This algorithm incorporates the baseline level of ultrasensitive troponin and its absolute changes within 1 hour. The choice of this parameter is based on a diagnostic accuracy that is very high and has been published previously based on the combination of absolute levels and absolute changes.

The TnT us algorithm (Elecsys) has been obtained and validated in recent studies (93):

- The criteria for the "rule out" was defined as TnT us undetectable at presentation or a baseline concentration below 12 ng/l associated with an absolute change in the 1st hour below 3 ng/l.
- The "rule in" is defined by a baseline TnT us concentration of at least 52 ng/l or an absolute change in TnT us of at least 5 ng/l at the first hour. Patients with a TnT us concentration between these two levels (12 – 52 ng/l) were classified in the "observe" area.



	A	B	C	D	E
hs-cTnT (Elecsys)	5	12	3	52	5
hs-cTnI (Architect)	2	5	2	52	6
hs-cTnI (Dimension Vista)+	0.5	5	2	107	19

Figure 140: European Society of Cardiology 0/1-hour algorithm (94).

Risk stratification and prognosis:

The potential of troponin to predict short-term mortality and long-term morbidity has been recognized since the early 1990s (95,96). Nowadays, the measurement of cardiac troponin levels is considered a crucial aspect in the prognostication of acute coronary syndrome (ACS). Initial cardiac troponin levels not only provide diagnostic utility but also add prognostic information in conjunction with clinical and ECG variables.

Numerous studies have indicated a proportional relationship between the intensity of troponin release into the circulating blood and the extent of myocardial necrosis.

Any elevation above the 99th percentile has prognostic significance. A positive troponin is generally correlated with cardiovascular risk scores and predicts mortality at 5-10 years. The higher the hs-cTn levels, the greater the risk of death. In patients with suspected ACS, even moderate elevation of hypersensitive troponin on admission increases the risk of re-infarction and death at 30 days by a factor of 3 and is also associated with an increased risk of mortality at 6 months (97). The prognostic power of troponin seems to be independent of the causes of its elevation (98). The increase in cardiovascular risk is true even for low troponin values and even in the absence of chest pain (99,100).

Troponin, has also been demonstrated in acute heart failure to predict short- and long-term mortality in association with a natriuretic peptide and in chronic stable heart failure using low TnTc values determined by a high-sensitivity kit (101) (102).

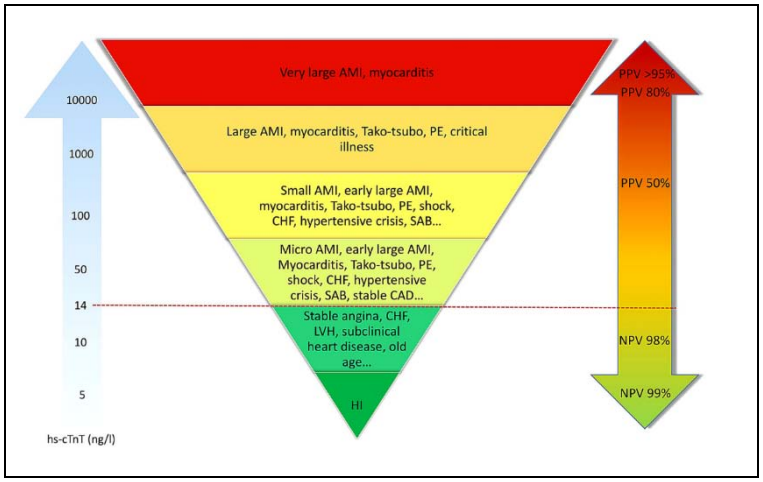


Figure 141: High-sensitivity cardiac troponin as a quantitative marker(54).

i.2.Pitfalls of troponin assay:

Confounders of cardiac troponin concentration:

The presence or absence of myocardial infarction (MI) is not the only factor that affects high-sensitivity cardiac troponin (hs-cTn) concentrations in patients presenting with suspected non-ST-elevation acute coronary syndrome (NSTE-ACS). Four clinical variables have an impact on hs-cTn concentrations: age (which is largely a surrogate for pre-existing cardiac disease), renal dysfunction (which is also largely a surrogate for pre-existing cardiac disease), time from chest pain onset, and sex. The effect of age (differences in concentration between healthy very young and healthy very old individuals can be up to 300%), renal dysfunction (differences in concentration between otherwise healthy patients with very high and very low estimated glomerular filtration rate can be up to 300%), and chest pain onset (>300%) is substantial, while the effect of sex is more modest (40%). Until information technology tools that allow the incorporation of the effect of all four variables are available, the use of uniform cut-off concentrations should remain the standard of care in the early diagnosis of MI (57).

When it comes to the serum concentration of hs-cTnT, there are several factors that can impact it, such as age, gender, and kidney function, independent of cardiac diseases. Despite this, the current upper reference limits don't take these factors into account, even though multiple studies have shown that they have a relevant effect on hs-cTnT.

The upper reference limit of 14 ng/L for the Elecsys® assay was derived from a population of 616 "apparently healthy volunteers" with an average age of 44 years. However, the majority of patients who present with acute chest pain or other heart-related complaints are considerably older. Consequently, several community-based studies have suggested an adjusted upper reference limit of >35 ng/L for cardiac-healthy males and >25 ng/L for cardiac-healthy females over 65 years, with the 99th percentile values increasing even more with age.

Moreover, several studies in different countries have shown that the sex of a patient can significantly influence the hs-cTnT serum concentration, with men showing significantly higher values, which is believed to be a result of their higher cardiac muscle mass, on average. In

contrast, the 99th percentile of hs-cTnT values in women aged <65 years was consistently below the commonly applied threshold of 14 ng/L.

Furthermore, troponin T levels increase with declining renal function measured by eGFR due to multiple reasons, such as reduced renal elimination and myocardial injury. However, specific hs-cTnT upper reference limits for different stages of renal insufficiency are still lacking.

It is also recommended to determine serum creatinine and eGFR in all patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS), as these factors affect prognosis and are included in the Global Registry of Acute Coronary Events (GRACE) risk score.

Differential diagnosis:

New: Not all troponin elevations are indicative of coronary artery disease. In fact, healthy individuals may have detectable levels of cardiac troponin. Moreover, multiple pathophysiological mechanisms can cause troponin elevation, particularly in the context of a hypersensitive assay method where sensitivity is improved at the expense of specificity. Because troponin elevation reflects myocardial injury, but is not synonymous with a coronary lesion.

It is important to note that not all troponin elevations are indicative of coronary artery disease. On one hand, it is common to detect circulating levels of cardiac troponin in healthy individuals. On the other, Multiple pathophysiological mechanisms can cause troponin elevation, particularly in the context of a hypersensitive assay method where sensitivity is improved at the expense of specificity because troponin elevation is a reflection of myocardial injury, but it is not synonymous with a coronary lesion (103). However, the degree of change in these levels can differentiate between acute and chronic cardiomyocyte damage, with more pronounced changes indicating a higher likelihood of AMI.

Troponin elevation can result from various cardiovascular and non-cardiovascular conditions. Pulmonary embolism, aortic dissection, heart failure, and cardiotoxicity can all lead to an increase in troponin levels due to myocardial injury. Additionally, non-cardiovascular conditions such as respiratory, infectious/immune, gastrointestinal, nervous system, renal,

endocrine, musculoskeletal, and inherited diseases can also cause troponin elevation. A non-exhaustive list of diseases associated with troponin increase can be found in the table below.

In the case of ACS, a dynamic troponin pattern can demonstrate the acuity of myocardial injury and help narrow the differential diagnosis. Analysis of troponin kinetics over several assays can differentiate between acute and chronic elevation. A 30% delta in kinetics over the course of 3 hours improves the specificity of the test in the diagnosis of ACS (55). An increase of 20% or more between two samples taken at the time of the onset of clinical signs and 3 to 6 hours later should be considered significant if these values are above the 99th percentile (56). This approach significantly improves specificity and may help differentiate myocardial infarction (MI) from other etiologies of elevated troponins, avoiding diagnostic misclassification.

Therefore, troponin assays should be performed primarily in contexts suggestive of ACS, and the interpretation of troponin results should be made in the context of clinical presentation and electrocardiographic arguments (104). Correlating biological data with the clinical context is paramount to avoid misinterpretation of troponin levels.

DISEASE	MECHANISM FOR Tn RELEASE
NON-TRHOMBOTIC CARDIAC TISSUE DAMAGE	
Congestive heart failure	• Release of cytokines • Destruction of contractile proteins • LVH • Global wall stretch • Impaired hemodynamic function • Concomitant renal disease
Coronary vasospasm	• Reversible/Irreversible tissue damage • Altered transient membrane permeability
Cardiac trauma	• Myocite damage • Altered myocite integrity • Trauma to coronary arteries
Myocarditis/Perimyocarditis	• Troponin spillage from myocardial cell necrosis • Damage of the outermost layer of the myocardium
Pulmonary embolism	• Right ventricular dilation • Right ventricular strain
Postcardiac surgery/ablation Cardioversion Cardiopulmonary resuscitation	• Prolonged hypotension and hypoxemia • Mechanical and electrical trauma (chest compressions, defibrillation)
Sepsis/critically ill patients	• Release of cytokines and reactive oxygen species • Direct effect of bacterial endotoxines • Concomitant myocarditis • Prolonged hypotension • Dysfunction of the coronary autorregulation
End-stage renal disease	• Decreased renal elimination • Uremic myo/pericarditis • Congestive heart failure • LVH • Hemoconcentration following dialysis
Arrhythmias (tachycardias, bradycardias)	• Hemodinamic compromise • Reversible myocite injury
Stroke	Neurally mediated myocite damage
Epileptic seizures	• Neurally mediated myocite damage • Transient supply-demand mismatch secondary to increased afterload by tonic skeletal muscle contraction
FALSE POSITIVE cTn TESTING	
Heterophile antibodies	Interference in several inmunoassays, cardiac Tn included
Reumatohid factor	
Macroenzymes	
Circulating antibodies (vacinnations, inmunotherapies, blood transfusions)	
Fibrin clots	
Malfunction of the analyzer	Analyzer error

Figure 142: Etiology of elevated troponin levels in the absence of MI (105).

13.3. Key takeaways:

- Chest pain is a common complaint in emergency medicine and is often evaluated for the possibility of acute coronary syndrome. However, not all patients with chest pain will have ACS, and the prevalence of ACS in emergency medicine is around 15%.
- The diagnostic approach for managing chest pain focuses on excluding life-threatening causes, particularly acute coronary syndrome because of its seriousness and the potential consequences of a diagnostic error.
- ACS refers to a group of clinical conditions that result from acute myocardial ischemia, often due to ruptured atheromatous plaque leading to coronary thrombosis. However, other mechanisms, such as an imbalance between oxygen supply and demand is also possible.

- The diagnosis of ACS typically involves a combination of a physical examination, electrocardiogram, and troponin assay. The ECG is sufficient to diagnose STEMI, but not NSTEMI, which requires the use of troponin.
- The troponin proteins (I, C, and T) have both skeletal and cardiac muscle isoforms, with troponin I and T being particularly specific to cardiac muscle. There is no cardiac muscle-specific isoform of troponin C, which is why there is no immunoassay for this form of troponin.
- Only a small fraction (5-8%) of troponin is unbound in the cytosol, and this is the first fraction to be released upon injury to the myocardium.
- In some cases, Troponin testing is not necessary. In the presence of a clinical examination that suggests acute myocardial ischemia and a contributory electrocardiogram, treatment should be initiated without waiting for the troponin assay result, which will later confirm the diagnosis.
- The Hs TnT assay is a cardio-specific troponin T assay that has been improved through the use of analytical signal amplification technology. This technology has increased the sensitivity of the assay and results are now expressed in ng/L rather than µg/L.
- The kinetics of troponin levels can be a crucial factor in medical decision-making. A value higher than the 99th percentile in the first 24 hours or two values higher than the 99th percentile, along with characteristic kinetics, is strong evidence of myocardial necrosis in the context of ischemia.
- Due to the large number of test suppliers and the lack of standardization of threshold values, each laboratory must define and validate its own threshold value.
- The cutoff value for Hs troponin is typically determined by the 99th percentile of the distribution in a reference population of healthy subjects and the assay should have a coefficient of variation $\leq$10% for the 99th percentile cutoff value. However, this level of precision is rarely achievable using conventional troponin assay techniques.

- The cut-off value for the Elycsys assay is to 14 ng/l, which corresponds to the 99th percentile of a healthy population aged 18-71, in accordance with recommendations for good analytical precision.
- Hypersensitivity assays can detect coronary events earlier and exclude the diagnosis of ACS more quickly, using a kinetic of 2 negative assays taken 3 hours or 1 hour apart instead of 6 hours with an increase of more than 30% between the 2 assays indicating an evolving myocardial infarction.
- Following a myocardial infarction, blood concentrations of cTnT and cTnI measured by ultrasensitive methods rise after 2-3 hours, compared to 4-6 hours with conventional methods. Peak plasma levels are reached around 18-24 hours and the decay kinetics are identical to those observed with conventional assays. Circulating cTn concentrations remain elevated for 75-140 hours for cTnI and more than 10 days for cTnT.
- Any gain in sensitivity comes at the cost of specificity, and there is a risk that new Hs-troponin assays will result in a higher prevalence of false positives.
- Troponin is specific to the heart muscle but not necessarily to coronary thrombosis. Its tissue specificity is distinct from the mechanism of myocardial injury, so if elevated troponins are found in the absence of myocardial ischemia, an evaluation for alternative causes of myocardial injury should be conducted.
- Elevated troponin levels are not necessarily indicative of coronary artery disease and can be seen in any situation where there is significant myocardial injury, such as tachyarrhythmias, myocarditis, aortic dissection, shock, hypothyroidism, or hyperthyroidism.
- Troponin results should be interpreted in the context of the clinical presentation and in combination with the clinical and electrocardiographic examination.

13.4. Summary on D-dimers:

a. Introduction:

Venous thromboembolic disease (VTE) is a serious medical emergency that can occur in any type of practice. It is characterized by the presence of deep vein thrombosis (DVT) and pulmonary embolism (PE). In fact, 50% to 80% of patients with symptomatic DVT also have either symptomatic or asymptomatic PE. Conversely, in patients with symptomatic PE, asymptomatic DVT is found in 80% of cases. VTE is a common pathology, affecting an estimated 5 to 20 cases per 10,000 individuals per year in the general population. It is also associated with a significant number of deaths, with an estimated 25,000 VTE-related deaths occurring annually. Chronic complications such as post-thrombotic disease and pulmonary hypertension can have a significant impact on a patient's quality of life. As a result, reducing VTE-related mortality and morbidity is a major public health priority.

D-dimers, a diagnostic tool introduced in the 1980s, are used to exclude the diagnosis of DVT and PE, and have since been extensively studied (106,107). D-dimers, along with other minimally invasive tests such as venous Doppler ultrasonography, CT pulmonary angiography, and scintigraphy, are included in international guidelines for managing suspected VTE (104). Unlike imaging tests, which can be invasive, expensive, and not always available, D-dimers can be easily obtained through a simple blood sample with quick results. Due to their high sensitivity, D-dimers can be used to exclude VTE diagnosis based on a negative test, thus avoiding imaging tests and their potential adverse effects such as radiation exposure, contrast material injection, and allergies (108,109). However, their low specificity precludes their use in confirming the diagnosis of VTE.

b. Pulmonary embolism:

Pulmonary embolism (PE) is an acute, life-threatening condition in which embolic material, usually a thrombus from one of the deep veins in the legs or pelvis, blocks one or more

pulmonary arteries, resulting in impaired blood flow and increased pressure in the right cardiac ventricle. Pulmonary embolism and deep vein thrombosis are two manifestations of the same condition, venous thromboembolism (110). The conditions responsible for venous thrombogenesis have been known since the famous Virchow Ŕ triad since the year 1860 associating blood stasis, endothelial wall injury, and altered hemostatic balance. In fact, the accident results from the complex entanglement of genetic factors, found in almost half of the patients with transient or persistent environmental (surgery, cancer, pregnancy...) and/or acquired factors (antiphospholipid syndrome). Thus, VTE is a multifactorial pathology.

PE is difficult to diagnose because the symptoms are not specific and the clinical presentation of patients with suspected PE is highly variable, ranging from asymptomatic patients to those in cardiogenic shock. Multiple clinical signs or circumstances should or may raise the suspicion of PE: chest pain, acute dyspnea, syncope-malaise, hemoptysis, desaturation, persistent fever, etc. PE should or may also be considered in the presence of chest pain in a patient with signs of venous thrombosis or thromboembolic risk factors: surgery within four weeks, trauma with limb immobilization, estrogen treatment, cancer, personal history of venous thromboembolic disease, etc.

c. Physiology, metabolism and molecular aspects of D-dimer:

D-dimers are a class of fibrin degradation products that play a significant role in the blood clotting process. They consist of a group of molecules with a molecular weight of approximately 195,000 Da and share a similar protein motif called the D-D motif, from which they derive their name. This motif is illustrated in Figure 144, which shows the process of fibrinolysis.

The presence of D-dimers indicates the concurrent activation of the coagulation and fibrinolysis pathways. The hemostatic clot produced by coagulation is only temporary, and it is gradually dissolved under the action of the fibrinolytic system once the tissue structure and function have been restored following a vascular breach. D-dimers are generated by the

sequential action of three enzymes (111), (112): thrombin (factor II), fibrin stabilizing factor (FXIIIa), and plasmin, the key enzyme of fibrinolysis.

During the coagulation phase, thrombin cleaves circulating fibrinogen into fibrin monomers, releasing four fragments from one fibrinogen molecule, including two fibrinopeptides A and two fibrinopeptides B. The soluble fibrin monomers then spontaneously form a protofibril polymer using hydrogen bonds to link with the polymerization sites that were unmasked by thrombin's action on neighboring fibrin monomers. FXIIIa, activated by thrombin, stabilizes soluble polymers by creating covalent bonds between the D domains of fibrin monomers. The fibrin network is then stabilized and becomes insoluble. The presence of fibrin triggers a process of reactive fibrinolysis leading to the generation of plasmin, the proteolytic enzyme of fibrinolysis.

Plasmin degrades fibrin into stabilized fibrin derivatives, including D-dimers, which are specific to the action of plasmin on fibrin (113). D-dimers are heterogeneous fibrin degradation products that possess the D-Dimer epitope formed by two covalently bonded fibrin monomers (linked by factor FXIIIa). They are thus distinguished from fibrin and fibrinogen degradation products (FDPs) (114). The half-life of D-dimers is 6-8 hours (115), and they are eliminated by renal clearance and the reticuloendothelial system (116).

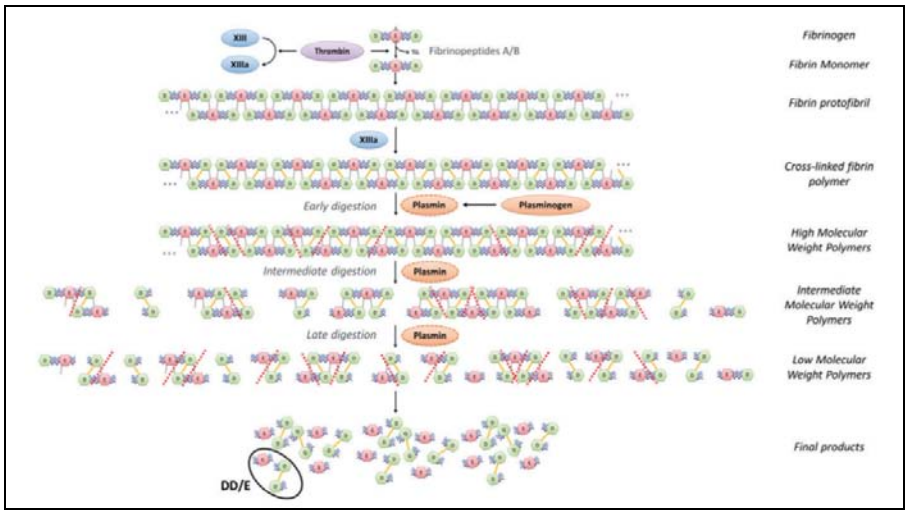


Figure 143: Mechanism of D-dimer production(116).

d. Performance characteristics:

The measurement of D-dimer levels in suspected cases of thromboembolism has been shown to have high sensitivity and negative predictive value, but low specificity. This makes the D-dimer an effective exclusion test for pulmonary embolism (PE), as a negative result can effectively rule out the presence of this condition. To achieve this, a threshold level of less than 500 ng/mL is typically used to dichotomize the test as negative or positive, with the former yielding high negative predictive value. However, when using this threshold, the specificity of the test is poor at only 45.1% (117) (118) (119).

The D-dimer test is known to have an excellent negative predictive value (94 to 99%) in patients with low or intermediate probability of venous thromboembolism (VTE), where a plasma D-dimer level of less than 500ng/mL can exclude the diagnosis of PE and eliminate the need for further imaging studies (120). However, when clinical probability is high, the test may be unnecessary due to the high number of positive results in this group. When the clinical probability is low or intermediate and D-dimer results are above 500ng/mL, the diagnosis of VTE cannot be affirmed due to the low positive predictive value (less than 50%) and lack of specificity. Further imaging studies are required (121,122) (123,124).

It is important to note that different D-dimer tests have varying performances, and the type of test used should be considered when interpreting results. Quantitative tests such as ELFA, classical ELISA, and 2nd generation latex agglutination assays have excellent sensitivities (95-99%) and negative likelihood ratios (0.09, 0.11, and 0.13, respectively) (114,115) (120,121), which make them useful in excluding the diagnosis of VTE in patients with a non-high pre-test clinical probability. Conversely, other D-dimer tests with a LR greater than 0.15 can only exclude VTE in patients with a low pre-test clinical probability.

In conclusion, combining a low clinical probability score for PE with a D-dimer level of less than 500 ng/mL can effectively rule out PE. Best practice guidance recommends combining the D-dimer result with a validated tool, such as the Wells or Geneva rule, to allow for structured risk quantification (15,125-127) (128). However, it is important to note that the D-dimer test is

useful for ruling out non-severe PE, but it is never sufficient to confirm the diagnosis. In cases of potentially severe PE with a high pretest probability, further diagnostic tests are necessary.

Table XLV: Performance Characteristics of D-dimer for Suspected Thromboembolism

Performance Characteristic	Value
Specificity	45.1%
Sensitivity	96.8%
Negative Predictive Value (NPV)	94% to 99%
Positive Predictive Value (PPV)	50%
Likelihood Ratio (LR)	0.1-0.13

e. D-dimer assay technique:

The principle of the assay is based on the recognition by a monoclonal antibody of the D-D epitopes. Hence, monoclonal antibodies, directed against these epitopes allow their detection in blood or plasma. These antibodies do not recognize fibrinogen molecules, fibrinogen degradation products, or soluble fibrin monomers.

There are many different D-dimer tests. They differ in the immunological technique used, the specificity of the monoclonal antibodies used, the material (plasma, whole blood, etc.), the units of presentation of the results (DDU: D Dimer unit or FEU: fibrinogen equivalent unit) and the positivity thresholds (129). All these differences have an impact on the characteristics and diagnostic performance of the tests, making direct comparison between two different D-dimer tests impossible (13,130). It is therefore necessary to know the performance of the test with which one is working. In practice, they can be grouped into six categories, each with advantages and disadvantages (123,131).

- **ELISA (Enzyme Linked Immunosorbent Assay) technique**: is a quantitative method with excellent sensitivity (considered the gold standard). Unfortunately, it is complex and requires a long time to perform (2-4 hours) on limited batches of samples. All of these conditions limit its usefulness in the context of the ED.

- **Rapid ELISA or ELFA (Enzyme Linked Immunofluorescent Assay)**: is a rapid technique (about 35 min) and fully automated. It is independently observable and has excellent sensitivity.
- **Membrane-based ELISA (immunodiffusion/immunofiltration)**: uses a monoclonal antibody that produces a color change in the presence of high levels of D-dimer. The test is rapid (about 20 min) and provides a semi-quantitative result with intermediate sensitivity.
- **Latex microparticle agglutination (first generation)**: This is a semi-quantitative method based on visible agglutination of latex particles covered with monoclonal antibodies. Rapid and easy to perform, it has a poor sensitivity and is not used for the exclusion of VTE but remains useful for the diagnosis of DIC because of its simplicity.
- **Latex microparticle agglutination (second generation)**: This is an identical method to the previous one but provides a quantitative result thanks to an immunoturbidimetric analyzer. It is independently observable and has excellent sensitivity. (Tinaquant®)
- **Hemagglutination tests on whole blood**: They are based on a method similar to that of 1st generation microparticle agglutination, with red blood cells being used instead of latex microparticles. It provides a qualitative result based on the presence or absence of visible hemagglutination. It is observer dependent and has an intermediate sensitivity. It has the advantage of being very rapid and can be performed at the patient's bedside in a few minutes.

These differences between tests show that only those whose performance is well known because they have been validated in large clinical trials can be reliably used. At present, these are essentially the Vidas® and Tinaquant® techniques (Table 43).

Table XLVI:Selected D-Dimer Assays (132)

Assay Name	Manufacturer	Methodology	Unit Type	Reported Units	Manufacturer Cut-Off	FDA Approval/Clearance for VTE Evaluation
Advanced D-Dimer	Dade Behring Diagnostics	Quantitative, latex enhanced immunoturbidimetricimmunoassay	FEU	mg/L	Instrument dependent	Aid in diagnosis
AQT90 FLEX D-dimer	Radiometer Medical ApS	Quantitative, time-resolved fluorometry	NA	mg/L	500 mg/L	NA
Auto Blue 400 Auto Red 700	Helena Biosciences	Latex enhanced immunoturbidimetric immunoassay	DDU	ng/mL	200 ng/mL	NA
D-Dimer Diazyme D-Dimer Assay	Diazyme Laboratories	Latex enhanced immunoturbidimetric immunoassay	FEU	mg/mL	<0.5 mg/mL	Aid in diagnosis
HemosIL AcuStar D-Dimer	Instrumentation Laboratory	Emzyme immunoassay, chemiluminescence	FEU	ng/mL	500 ng/mL	Exclusion
HemosIL D-Dimer	Instrumentation Laboratory	Latex enhanced immunoturbidimetric immunoassay	DDU	ng/mL	243 ng/mL	Exclusion
HemosIL D-Dimer HS	Instrumentation Laboratory	Latex enhanced immunoturbidimetric immunoassay	DDU	ng/mL	243 ng/mL	Exclusion
HemosIL D-Dimer HS 500	Instrumentation Laboratory	Quantitative, latex enhanced immunoturbidimetric immunoassay	FEU	ng/mL	500 ng/mL	Exclusion
INNOVANCE D-Dimer	Siemens AG	Quantitative, latex enhanced immunoturbidimetric immunoassay	FEU	ng/mL	500 ng/mL	Exclusion

MDAW D-Dimer	bioMe´rieux SA	Quantitative, latex enhanced immunoturbidimetric immunoassay	NA	NA	NA	Aid in diagnosis
Nordic Red D-dimer	Nordic Biomarker AB	Quantitative, latex enhanced immunoturbidimetric immunoassay	DDU	ng/mL	200 ng/mL	NA
Nordic Blue D-dimer	Nordic Biomarker AB	Quantitative, latex enhanced immunoturbidimetric immunoassay	DDU	ng/mL	200 ng/mL	NA
STA Liatest D-Dimer	Diagnostica Stago, Inc.	Quantitative, latex enhanced immunoturbidimetric immunoassay	FEU	mg/mL	<0.5 mg/mL	Exclusion
Tina-quant D-Dimer BM	F. Hoffman-La Roche Ltd.	Quantitative, latex enhanced immunoturbidimetric immunoassay	FEU	mg/mL	<0.5 mg/mL	Exclusion
TriniLIA D-Dimer	Tcoag Ireland Ltd.	Polystyrene microparticle agglutination assay	FEU or DDU	NA	NA	NA
VIDAS D-Dimer	bioMe´rieux SA	Quantitative, ELISA, sandwich type	FEU	ng/mL	500 ng/mL	Exclusion

f. Clinical application of D Dimer assay:

f.1. Diagnostic tool to rule out VTE:

The diagnosis of venous thromboembolism (VTE), comprising pulmonary embolism (PE) and deep vein thrombosis (DVT), relies on clinical, biological, and paraclinical evidence, including Doppler ultrasonography of the lower limbs and thoracic angiography (125,126). A diagnostic approach that considers the pretest probability, determined using clinical scores, and subsequent imaging and biological assessments, is recommended (133,134).

When pulmonary embolism (PE) is suspected, a thorough evaluation of the patient's clinical presentation and symptoms is crucial, including dyspnea, tachycardia, and chest pain. Clinical prediction rules, such as the Wells criteria, modified Wells criteria, Charlotte, and Geneva score, have been developed to assess pretest probability and standardize practices (135). Of these, the Wells criteria and revised Geneva score have been validated on a large scale, and allow categorization of patients into low, intermediate, or high probability groups (16),(136).

The clinical probability assessment method used in Europe has a significant impact on the prevalence of venous thromboembolism (VTE). Patients with low clinical probability have a prevalence between 5 and 15%, while those with intermediate probability have a prevalence between 25 and 50%. High clinical probability is associated with a prevalence above 60%. These findings have been supported by several studies (137–139).

When evaluating a patient with suspected PE, the initial step is to calculate their Wells score. Based on the score, patients are placed in one of three risk categories (140):

- Patients with a Wells score of 0 or 1 are in the lowest risk category. In this case, the PERC rule can be applied to determine whether any of eight features are present, all of which would increase the risk of PE. If none of the PERC features are present, a PE can be ruled out without additional diagnostic tests.
- Patients with an intermediate Wells score of 2 to 6 require a d-dimer test. If the d-dimer is normal, a PE can be ruled out. If the d-dimer is elevated, the next step is to perform a CT

pulmonary angiogram (CTPA), a ventilation-perfusion (VQ) scan, or bilateral lower extremity duplex ultrasound.

- Patients with a Wells score greater than 6 are in the highest risk category. A normal d-dimer is insufficient to decrease the probability of PE enough to rule it out. These patients should be referred to CTPA or one of the aforementioned alternatives. CTPA is an exceptionally sensitive test, and if it does not show PE, a PE has been ruled out for the vast majority of patients. If it does show PE, then the diagnosis is confirmed. For patients with minimal other lung disease, a VQ scan is the best option. However, for patients with chronic lung disease, VQ scans are frequently non-diagnostic, so bilateral leg duplex ultrasounds may be preferable.

There are additional caveats to this algorithm. If the patient is hemodynamically unstable and cannot safely go to the CT scanner, a bedside echo should be considered first, and a presumptive diagnosis of PE may be made if there is a high Wells score combined with evidence of acute right ventricular dysfunction. If there are physical exam signs of a deep vein thrombosis (DVT), the d-dimer can be skipped altogether, and an ultrasound may be performed instead, as the treatment of clinically mild PE and DVT are similar. If a patient has a high Wells score and a negative CTPA, and the post-test probability of a PE still feels too high to rule out the diagnosis, a VQ or ultrasound may be considered.

There is a common variation of the Wells score in which patients are placed into one of two categories instead of three. Algorithms that use this approach tend not to incorporate the PERC rule at all and therefore require all patients to undergo either a d-dimer or CTPA. Lastly, there is an alternative to the Wells score called the Geneva score, but it has not been widely used in practice.

The D-dimer test is a widely used tool in the diagnostic approach of venous thromboembolism (VTE), which includes pulmonary embolism (PE) and deep vein thrombosis (DVT). It is typically used as a screening test to exclude the possibility of VTE when the pretest probability is low. The test's objective is to rule out the diagnosis of VTE and therefore prevent

unnecessary imaging examinations with potential harmful effects, such as irradiation, injection of contrast products, and allergies. The use of the D-dimer test in the diagnostic algorithm can also reduce the length of stay in emergency departments, provided that the test used does not take too long.

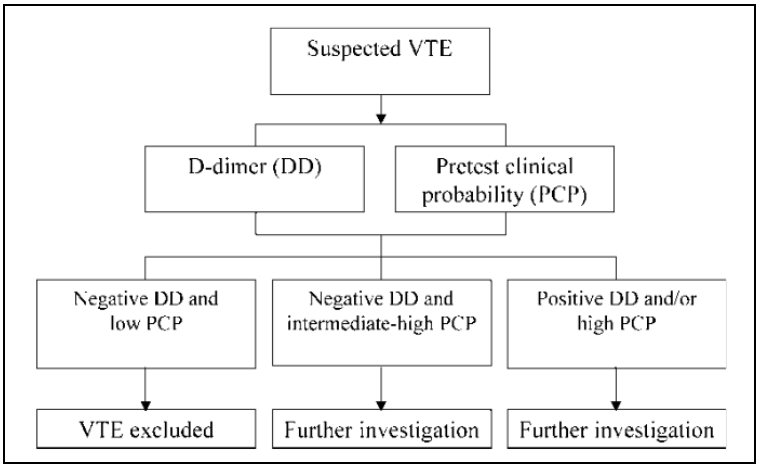


Figure 144: Diagnostic algorithm based on D-dimer testing integrated with pretest clinical probability(141).

g. Prognosis:

In a wide range of both benign and malignant diseases characterized by trauma, infection, ischemia, bleeding, or thrombosis, elevated levels of D-dimer have been observed. Extensive research has been conducted to investigate the potential diagnostic, prognostic, or therapeutic utility of D-dimer levels. For example, in patients with malignant tumors, gastrointestinal bleeding and necrosis, intracerebral hemorrhage, sickle cell disease, migraine headaches, traumatic brain injury, tuberculosis, Cushing's disease, asthma, membrane oxygenator failure, and several other conditions, D-dimer levels have been evaluated as an unfavorable prognostic and/or a risk factor for thrombosis (132).

In patients presenting with chest pain, elevated D-dimer levels serve as an early indicator of coronary ischemia and an independent prognostic factor for myocardial infarction (142).

Numerous studies have demonstrated that increased levels of plasma D-dimer are associated with unfavorable prognoses in patients with various types of cancer, including breast, colon, lung, gastric, ovarian, and prostate cancers, as well as cancers affecting other organs (143). Moreover, persistently elevated D-dimer levels at the end of anticoagulant therapy for a thromboembolic episode predict the risk of recurrence, but current knowledge does not justify prolonging anticoagulant therapy based on this factor alone (144). Similarly, if the D-dimer level is associated with the size of the clot, it is not a validated prognostic marker (145). Finally, there is no convincing evidence to support adjusting curative or preventive anticoagulant treatment doses based on D-dimer levels.

To date, there is no thrombotic situation or pathology other than the diagnosis of VTE in which D-dimer evaluation has been sufficiently evaluated to warrant a recommendation.

h. Pitfalls of the D-dimer assay:

h.1. Age:

D-dimer measurement is an essential part of diagnosing venous thromboembolism (VTE), allowing clinicians to rule out the disease in about 30% of patients with suspected deep vein thrombosis (DVT) or pulmonary embolism (PE). However, D-dimer levels are frequently elevated in older patients, regardless of the presence of VTE, making the test less useful in this demographic.

The usefulness of D-dimer in younger patients is higher. Approximately half of patients under 40 years old with suspected PE have a negative D-dimer result, which allows for the exclusion of around 50% of patients from further testing. However, this percentage decreases with age, and in patients over 80 years old, only 1 in 20 patients have a negative D-dimer result (146).

To address this issue, it is currently recommended to adjust the D-dimer cutoff value based on age for patients over 50 years old, with a formula of (age * 10). This approach

improves the specificity of D-dimers and excludes the diagnosis of pulmonary embolism in 30% of patients over 75 years old, compared to only 6.4% with the standard cutoff value of 500 ug/L (147). This adjustment in the cutoff value could increase the accuracy of VTE diagnosis in elderly patients and reduce the need for unnecessary imaging and diagnostic procedures.

h.2. Differential diagnosis:

Regardless of the biological specificity of monoclonal antibodies directed against D-dimer fragments, the multitude of clinical situations associated with thrombosis/fibrinolysis activation means that the clinical specificity of D-dimer for the diagnosis of VTE is low, in the order of 40%. This is due to the fact that many situations, both pathological and physiological, can lead to activation of coagulation or fibrinolysis processes, resulting in elevated levels of D-dimer in the blood (129,148).

These situations include non-thromboembolic diseases (149), physiological situations, cancers and various therapeutic treatments.

For example, physiological situations include age (150), normal pregnancies (151) (as the 2nd trimester). Therapeutic situations include certain preventive or curative treatments like thrombolytics which increase D dimer levels, whereas anticoagulant treatments decrease them, treatment with heparin (standard or low molecular weight) decreases the D dimers. Finally, high-dose estrogens increase their levels in the blood (141).

In addition, D-dimer levels can increase in, severe infectious and inflammatory reactions of various origins(152), recent surgery, trauma or intense and prolonged physical effort (153,154). Not to mention D-dimer levels are elevated in the plasma of patients with various types of cancers, including breast and ovarian cancers, lung cancers, pancreatic cancers, colorectal cancers and in leukemias in general (152). This is also the case for disseminated intravascular coagulation (DIC), which occurs in many etiologies (155): sepsis, trauma, burns, severe liver disease, eclampsia...

Furthermore, the location and age of a thrombus can also influence D-dimer levels, with lower levels observed in distal compared to proximal deep vein thrombosis, and levels that decrease over time (156). Despite this, the positivity of a D-dimer test can persist for nearly a week after the thromboembolic event, even with the initiation of anticoagulant treatment (157).

In summary, the clinical specificity of D-dimer for the diagnosis of VTE is low due to the many clinical situations associated with thrombosis and fibrinolysis activation. Therefore, the non-specificity of an increase in D-dimer levels should be taken into account when interpreting test results.

Nonpathologic	Pathologic
Age	Trauma
Race (black population)	Preeclampsia
Cigarette smoking	Malignancy
Pregnancy and puerperium	Infection
Postoperatively	Chronic inflammatory diseases
	Disseminated intravascular coagulation
	Sickle cell disease
	Arterial or venous thromboembolism
	Acute coronary syndromes
	Stroke
	Peripheral artery disease
	Atrial fibrillation
	Congestive heart failure
	Hemorrhages

Figure 145: Conditions associated with increased D dimer plasma levels(141).

i. Key Takeaways:

- D-dimers are specific degradation products of fibrin that are produced through the sequential action of coagulation and fibrinolysis. They reflect the entire

process of clot formation and dissolution and are specific to the action of plasmin on fibrin.

- The use of D dimer in the diagnosis of VTE is one of the best illustrations of the application of Bayes' principles in evidence-based medicine. Because The interpretation of the result will therefore depend on a fundamental parameter: the clinical probability or pre-test probability.
- This concept is valid for all diagnostic approaches but has been particularly studied in the context of VTE where the estimation of the pre-test probability or clinical probability has been modelled in the form of explicit rules. The best-validated and most widely used scores are the Wells score for DVT and PE and the revised Geneva score for PE
- D-dimers are used to rule out the diagnosis of PE in patients with a low or intermediate clinical probability
- D dimer assay should not be used in patients with a high clinical probability, instead, they should be investigated using other tests.
- A positive D-dimer result is not useful for making a diagnosis of VTE or even for suspecting VTE in an asymptomatic patient.
- D-dimer testing should only be performed in cases of clinical suspicion of VTE, after pre-test clinical probability assessment, as part of an exclusionary approach.
- Currently, it is recommended to adjust the D-dimer cut-off value according to the formula (age * 10), for patients over 50 years of age
- Plasma concentrations of D dimer rise in many physiological, pathological and therapeutic situations
- D dimer assay using ELISA method excludes VTE when it is < 500 ug/L
- D dimer has a good NPV to exclude PE approaching 99%.

- Predictors of early mortality in PE include, ejection fraction, high troponins, high BNP.

13.5. Summary on BNP/NT pro-BNP:

a. Introduction

In developed nations, acute heart failure (AHF) has a prevalence of 10% in individuals aged 75 years and older. France alone records 120,000 new cases of AHF annually. Among the elderly population, AHF is the primary cause of hospitalization and is associated with a severe prognosis. In-hospital mortality rates hover around 10%, with an even higher mortality rate of nearly 25% in patients over 70 years of age. Dyspnea is one of the primary reasons for emergency department visits, and AHF is a major contributor to this condition. However, dyspnea is not exclusive to AHF and may arise due to other pathological processes, and the etiological diagnosis of dyspnea can be complex in geriatric patients. Nonetheless, prompt diagnosis and treatment of AHF can improve patient outcomes. In a study involving over 500 dyspneic elderly individuals, appropriate treatment initiated in the emergency department reduced mortality (11% versus 26%), length of hospital stay, and admission to intensive care (25% versus 40%) (158).

Cardiac Doppler ultrasound is often used to confirm heart failure when dyspnea's etiology is uncertain. However, this examination is subject to several limitations, including the time required to perform the procedure and variability associated with the operator and patient factors such as obesity or emphysema (159). Therefore, there is a need for a reliable and rapid marker of acute heart failure. BNP measurement is a low-cost and highly sensitive test that can aid in diagnosing heart failure in hospital settings. Natriuretic peptides, such as BNP and NT-pro BNP, are serum markers of cardiomyocyte stress and are elevated during heart failure exacerbation and decompensation, irrespective of the cause. Elevated serum BNP levels are clinically useful in diagnosing and excluding congestive heart failure (CHF) exacerbation. The

primary indication for BNP measurement is to assist in the diagnosis of dyspnea in the emergency department, particularly in comorbid patients, such as those with cardiac insufficiency and chronic bronchopathy. The test is particularly helpful in elderly patients, where clinical presentation and chest X-ray findings are not adequately discriminating (160,161). Increased serum natriuretic peptide concentrations provide strong evidence for the diagnosis of AHF and can also predict adverse outcomes and prognosis in patients with cardiac disease.

b. Heart failure:

Heart failure is the inability of the heart to provide sufficient blood flow to meet the body's needs and/or abnormally high left ventricular filling pressures. More specifically, heart failure is a clinical syndrome characterized by a constellation of symptoms (dyspnea, orthopnea, lower limb swelling) and signs (elevated jugular venous pressure, pulmonary congestion) often caused by a structural and/or functional cardiac abnormality resulting in reduced cardiac output and/or elevated intracardiac pressures. HF is most often due to myocardial dysfunction: either systolic, diastolic, or both. However, other pathologies can cause it like pathologies of the valves, pericardium, and endocardium, and abnormalities of heart rhythm and conduction (162). These structural and/or functional cardiac abnormality must be corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion (162).

Heart failure (HF) is a complex and heterogeneous condition with multiple phenotypes and varied clinical presentations. Early diagnosis is crucial to prevent adverse outcomes and death. Patients with HF exhibit diversity in their cardiac structure and function, etiology, precipitating factors, comorbidities, and medications. Risk factors for HF include hypertension, renal disease, heart disease, diabetes, male gender, older age, and obesity, with advanced age and renal disease. Precipitating factors for AHF exacerbation can be either cardiac or non-cardiac causes. Dysrhythmias, uncontrolled hypertension, dietary or medication noncompliance, aortic dissection, dysrhythmias, and cardiac ischemia are among the cardiac causes, while pulmonary disease, endocrine disease, infection, worsening renal function, anemia, and

medication side effects are non-cardiac causes. Acutely, the most common symptoms associated with AHF include dyspnea, orthopnea, and edema, with elevated LV filling pressures being the underlying mechanism. However, these symptoms exhibit poor sensitivity and specificity. On examination, S3 heart sound, hepato-jugular reflux, and jugular venous distension possess high specificity, while lung auscultation and lower extremity edema have low specificity. Although no single sign or symptom is sufficient to rule out AHF, elevated jugular venous pressure, third heart sound, and lung crepitations are strongly suggestive of a diagnosis of AHF.

c. Physiology of natriuretic peptides:

Synthesis, structure and release:

The natriuretic peptide family includes at least 6 members, ANP, BNP and CNP. As the name suggests, they are formed by a number of amino acids united by peptide bonds, and they are able to induce urinary sodium elimination (natriuresis).

The type A peptide (ANP) was isolated from cardiac atria in 1984, the B type (BNP) from porcine brain in 1988 and the C natriuretic peptide (CNP) was also isolated from porcine brain in 1990 (163,164). Other members of this family include: vasonatrin, a synthetic natriuretic peptide, and urodilatin which is of renal origin (165). Although ANP was identified first, concentrations of BNP in the myocardial tissue were found to be higher than those of ANP, therefore, BNP has been studied more intensely than ANP as a clinically useful marker of increased ventricular pressure.

The gene involved in the synthesis of natriuretic peptides is located on chromosome 1 (1p36.2) and consists of three exons and two introns. This gene encodes a 134 amino acid (AA) protein called the pre-proBNP1-134 (166). After removing a 26 amino-acid signal peptide, 108 aa pro BNP1-108 is produced, another step requiring the action of proteases, Furin and Corin, generates equimolecular amounts of a C-terminal part, an active form, BNP1-32 (32AA), and an inactive N-terminal peptide made of 76 aa called NT pro-BNP (167) (Figure 147).

Other than myocardium, there are other sites of production like central nervous system, lungs, thyroid gland, spleen and ovaries. Under normal conditions however, BNP and NT-pro BNP

are secreted almost entirely by the left ventricle. The release of BNP into the bloodstream by ventricular myocytes is exclusively regulated through the modulation of its synthesis by transcriptional mechanisms, and not by the control of exocytosis of already produced and stored BNP in vesicles. BNP is produced by cardiomyocytes in the atria and ventricles in response to increased pressure and cardiac muscle stretch (168,169).

The concentrations of BNP and NT-pro BNP increase in heart failure (170). Plasma NT pro BNP levels are elevated in heart disease accompanied by an increase in ventricular end-diastolic pressures (except for tamponade) after its release into the systemic circulation through the coronary sinus(171).

The role of cardiac wall stretching seems to be major in the synthesis of natriuretic peptides, but this stretching may be associated with the effects of ischemia and local inflammation in unstable angina and myocardial infarction. The latter are accompanied by an increase in natriuretic peptides even when the hemodynamic changes are very discrete (172,173).

The presence of myocytes in the right ventricle is an important piece of information since it explains the increase in NT pro BNP levels in acute and chronic pathologies which accentuate right ventricular stress through pulmonary hypertension, but also in intracranial hemorrhage or sepsis (174). However, plasma levels will be lower than in left ventricular dysfunction. The increase in NT-pro BNP release is part of a phenomenon of hormonal activation that is characteristic of congestive heart failure to reduce cardiac preload and afterload by its vasodilatory and diuretic effects (175,176).

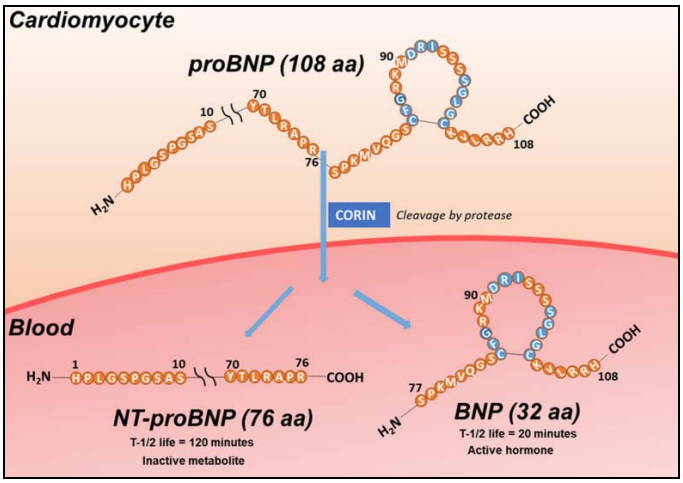


Figure 146: Pathways of NT pro-BNP and BNP synthesis from pro-BNP(177).

Mechanism of action:

As with all natriuretic peptides, the action of BNP requires the stimulation of membrane receptors on the surface of target cells, thus defining these molecules as hormones (Figure 138). Currently, three natriuretic peptide receptors have been identified(163,178):

- Natriuretic peptide receptor A (NPR-A).
- Natriuretic peptide receptor B (NPR-B).
- Natriuretic peptide receptor C (NPR-C).

NPR-A and NPR-B are found at the level of vascular endothelium and smooth muscle cells of various tissues, they are transmembrane proteins with 2 domains, one extracellular and one intracellular that catalyzes the conversion of guanosine triphosphate into guanosine monophosphates or into a cyclic form (cGMP) by the guanylate kinase to which it is linked. Another receptor, NPR-C, the most abundant, located mainly in the kidney and blood vessels, is responsible for the clearing of BNP. BNP can also be degraded by neutral peptidases that cleave its annular structure and transform BNP into an inactive peptide.

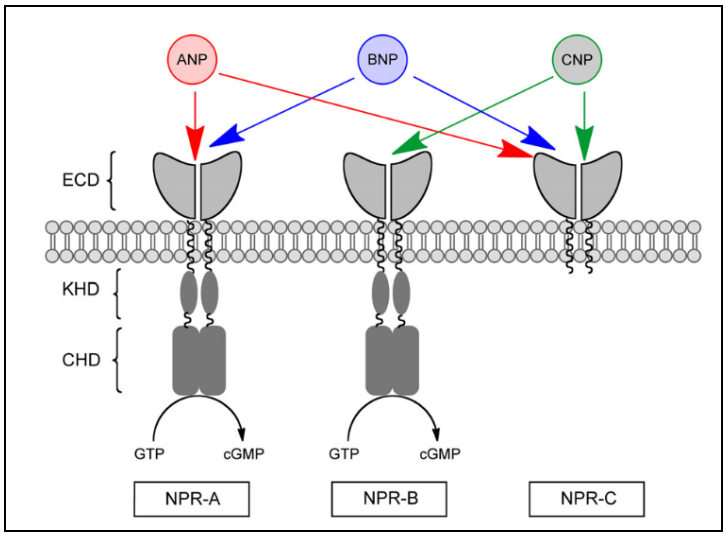


Figure 147: Diagrammatic representation of the natriuretic peptide receptors and their ligand selectivity(178).

Physiologic role of natriuretic peptides:

The effects of natriuretic peptides on the kidney are complex, direct and indirect. The main action of natriuretic peptides on the kidney is a rapid and transient increase of sodium and water excretion (diuresis and natriuresis). Similarly, it also induces an increase in the excretion of phosphate, calcium, magnesium, chlorine and cGMP (179).

Plasma natriuretic peptides increase filtration at the glomerular level by increasing intracellular cGMP concentration. Its effect at the glomerular level is explained on one hand by the elevation of the filtration coefficient (Kf) and on the other hand by the increase of the filtration fraction (FF). The natriuretic and diuretic effect of BNP may be independent from the modification of the glomerular filtration rate by acting directly or indirectly on sodium reabsorption in the different tubular segments. The endoluminal action of natriuretic peptides is summarized as an inhibitory effect on renin secretion (180).

Following systemic secretion, the natriuretic peptides activate transmembrane guanylate cyclase on the surface endothelial cells, thereby increasing intracellular levels of cyclic guanosine monophosphate (cGMP), which subsequently induces a decrease in intracellular calcium leading to relaxation of smooth muscle fibers leading to vasodilation.

The peptides have also demonstrated the ability to antagonize adverse pathways that are over-activated in the setting of heart failure, for example, the renin-angiotensin-aldosterone axis (RAAS), which has anti-diuretic effects, and the transforming growth factor-beta pathway, which increases cardiac remodeling and fibrosis. (Figure 139) (174).

Natriuretic peptide receptors and plasma endopeptidases actively clear BNP from the circulation; the plasma half-life is thus short, approximately 20 minutes. NT-pro BNP has a correspondingly prolonged half-life of 60-120 minutes and no receptor-mediated clearance of NT-pro BNP is known to occur. As a result, plasma levels of NT-pro BNP tend to be 3-5 times higher than BNP levels. Clearance of NT-pro BNP is primarily renal. Therefore, the renal clearance of NT-pro BNP confounds its diagnostic utility in patients with renal insufficiency.

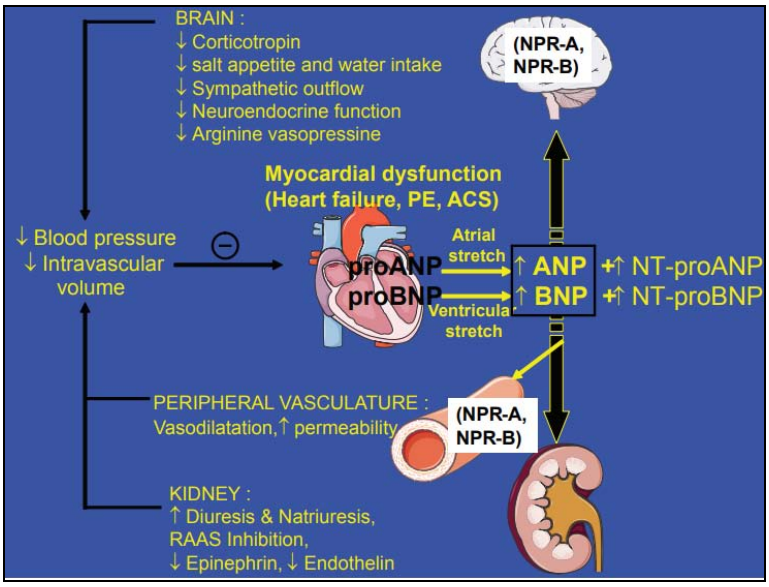


Figure 148: Summary on the actions of BNP and NT pro-BNP(174).

d. Assay technique:

The BNP assay technique of the first generation was a competitive radioimmunoassay using iodine-125 as a tracer and required the extraction and purification of the plasma sample. This technique was developed by Shionoria. In the 2000s, the first-generation assay was replaced by faster second-generation assays, which were sandwich techniques that utilized

monoclonal antibodies and radioisotope labels in the form of “capture” antibody and a “detection” antibody. Commercial versions of the monoclonal antibody assay first became available in 1994 and initially required 12-36 hours to complete. Third-generation assays, which provided results in as little as 15 minutes, became available in 2000. These rapid assays used immunofluorescent methods (181).

These techniques differ in terms of the marker used, the type of signal measured, and the nature of the targeted epitopes. Currently, several techniques for the measurement of BNP are marketed in France. However, in the United States, all commercially available assays for BNP and NT-proBNP used for clinical purposes are rapid immunoassays. These techniques utilize different antibodies that recognize distinct epitopes of the molecule. In addition, the antibodies directed against BNP also recognize the released proBNP1-108 in the bloodstream, in different ratios depending on the antibodies selected and the different circulating forms (182-185). The lack of standardization for BNP assays can make it difficult to interpret the results, which should obviously take into account the measurement techniques used.

e. Normal and critical findings:

Levels of B-type natriuretic peptide (BNP) vary according to age and gender in healthy individuals, with increasing levels seen in older people and on average in women. A normal BNP level is typically below 100 pg/mL, and a value below this cut-off makes heart failure unlikely. Conversely, a value above 300 pg/mL confirms heart failure if consistent with the clinical picture (161,186).

The cut-off for NT-proBNP is typically 300 pg/mL, below which the diagnosis of acute heart failure (AHF) is unlikely (149). Conversely, a value above 900 pg/mL for those aged between 50 and 75 years, and above 1800 pg/mL for those over 75 years of age, makes the diagnosis highly likely (162).

However, the "gray area" between these cut-offs represents a range of uncertainty, with nearly 30% of patients who require testing found in this category.

f.Performance characteristics:

B-type natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) are biomarkers that are commonly used to aid in the diagnosis of heart failure. The performance characteristics of these biomarkers were evaluated in a diagnostic meta-analysis (187).

B type natriuretic peptide (BNP) demonstrated high sensitivity and negative predictive value at a threshold of ≤100 ng/L, with sensitivity consistently above 95% and negative predictive value above 90%. Specificity and positive predictive value were lower, with specificity ranging widely from 52% to 73% and positive predictive value ranging from 63% to 75%. At a BNP level of 100-500 ng/L, sensitivity decreased to 85% (81% to 88%), while specificity increased to 86% (79% to 91%), and positive predictive value and negative predictive value remained relatively stable at 85% (78% to 90%) and 86% (82% to 89%), respectively. At a threshold of ≥500 ng/L, the reported sensitivity varied widely from 17% to 56%, with paired specificity ranging from 56% to 93%.

NT-pro BNP demonstrated high sensitivity and negative predictive value at a threshold of ≤300 ng/L, with sensitivity above 99% and negative predictive value above 98%. Specificity and positive predictive value were lower, with specificity ranging from 26% to 62% and positive predictive value ranging from 57% to 73%. At a threshold of 300-1800 ng/L, sensitivity decreased to 90% (86% to 93%), while specificity increased to 76% (69% to 82%), and positive predictive value and negative predictive value were 80% (74% to 84%) and 88% (82% to 92%), respectively. At a threshold of ≥1800 ng/L, the reported sensitivity varied from 60% to 73%, with paired specificity ranging from 63% to 80%.

Overall, as per the 2012 European Society of Cardiology guidelines, BNP and NT-pro BNP have comparable diagnostic accuracy in detecting acute heart failure. At the recommended rule-out thresholds of 100 ng/L for BNP and 300 ng/L for NT-pro BNP, both natriuretic peptides exhibit excellent ability to exclude the possibility of acute heart failure. The sensitivities of BNP and NT-pro BNP at these lower recommended thresholds are 95% and 99%, respectively, and

their negative predictive values are 94% and 98%, respectively, for the diagnosis of acute heart failure(188) (189,190)

Table XLVII: Performance Characteristics of BNP and NT-pro BNP in Diagnosis of Heart Failure.

Biomarker	Threshold	Sensitivity	Specificity	PPV	NPV
BNP	≤100 ng/L	**95%**	52-73%	63-75%	**90%**
	100-500 ng/L	85%	86%	85%	86%
	≥500 ng/L	17-56%	56-93%	-	-
NT-pro BNP	≤300 ng/L	**99%**	26-62%	57-73%	**98%**
	300-1800 ng/L	90%	76%	80%	8%
	≥1800 ng/L	60-73%	63-80%	-	

g. Clinical application of BNP and NT pro-BNP:

- **Diagnostic value:**

The differentiation between congestive heart failure (CHF) and respiratory pathology is often challenging in elderly and obese patients with acute dyspnea. In light of their characteristics, biomarkers such as B-type natriuretic peptide (BNP) and NT-proBNP are increasingly being utilized in emergency medicine, as numerous studies conducted worldwide have shown that BNP measurement is an effective tool in the diagnosis of CHF in patients presenting to the emergency department (ED) with dyspnea (160,170,191-193).

Multicenter studies have demonstrated that BNP and NT-proBNP are highly reliable diagnostic markers of CHF in the emergency setting, with similar accuracy (161,194), even in elderly patients (195,196). In practice, NT-proBNP appears to be gaining importance in rapid tests performed in EDs for the management of heart failure.

Additionally, the recommendations of the European Society of Cardiology have stated since 2001 that a normal level of NT-proBNP makes the diagnosis of heart failure unlikely (197). However, it should be noted that elevated NT-proBNP or BNP levels do not determine the cause or type (systolic or diastolic) of acute heart failure.

The diagnosis of heart failure typically involves a combination of physical examination, chest x-ray, electrocardiogram (ECG), and measurement of biomarkers such as B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP).

Laboratory testing is an important component in the diagnosis and management of patients suspected to have Acute Heart Failure (AHF). It can provide diagnostic and prognostic information. A complete blood count, basic metabolic panel, renal function testing, liver function tests, troponin, and a B-type natriuretic peptide (BNP) level should be included in laboratory testing.

Natriuretic peptides, specifically BNP and NT-pro BNP, may be a valuable adjunct in cases where the diagnosis is unclear. BNP levels below 100 pg/mL and NT-pro BNP levels below 300 pg/mL suggest that heart failure is very unlikely. Conversely, BNP levels above 500 pg/mL and NT-pro BNP levels above 1800 pg/mL indicate that heart failure is very probable. The cases where BNP levels fall between 100 and 500 pg/mL and NT-pro BNP levels are between 300 and 1800 pg/mL (grey zone) are non-specific and may require further testing such as echocardiography can be performed to evaluate left ventricular dimension and ejection fraction, diastolic filling, and the severity of mitral regurgitation, which can help confirm or rule out a diagnosis of heart failure (198) (Figure 151).

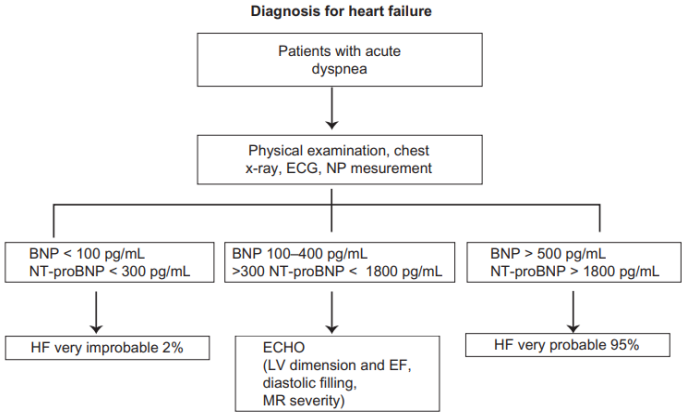


Figure 149: Decisional algorithm for HF diagnosis on the basis of NP measurement

h. Prognostic value:

Numerous studies have demonstrated a positive correlation between various indices of acute heart failure (AHF) severity, including clinical classification, functional indices, or echocardiographic scores, and the concentration of NT-proBNP (N-terminal pro-brain natriuretic peptide) (199). Specifically, NT-proBNP can also serve as a valuable prognostic marker in patients with established CHF, as elevated levels have been observed in patients with higher New York Heart Association functional class scores and have been correlated with mortality, morbidity, and repeated hospital admissions (200,201). Furthermore, short-term elevations in NT-proBNP levels in hospitalized patients with chronic heart failure (CHF) have been linked to extended hospital stays. Additionally, in patients with heart failure admitted to the hospital, short-term increases in NT-proBNP levels have been demonstrated to predict prolonged hospital stays (202).

NT-proBNP has alos prognostic importance in various cardiac conditions, such as unstable angina, myocardial infarction, aortic stenosis, and post-transplant follow-up (197,203,204). In pulmonary embolism, NT-proBNP levels that are lower than 150 pg/l (180-200 pg/ml) upon admission suggest a favorable outcome, with a highly accurate negative predictive value. Elevated initial levels, even without hemodynamic failure, are associated with an unfavorable outcome and a three-month mortality rate (205).

In acute coronary syndrome (ACS), Brain natriuretic peptide (BNP) has been shown to serve as a useful prognostic indicator. Studies have established an inverse correlation between left ventricular function and mortality in the aftermath of an acute myocardial infarction (AMI), with lower left ventricular ejection fraction (LVEF) associated with higher mortality rates. BNP can be used to predict a decrease in LVEF and New York Heart Association (NYHA) class. Furthermore, NT-proBNP monitoring can assist in assessing prognosis following an MI because it becomes elevated in patients with post-MI LV dysfunction with ejection fractions <40% (206). Multiple studies have supported the utility of BNP as a non-invasive and cost-effective prognostic marker in ACS (190) (203,207,208).

In septic shock, persistent high levels of NT-pro BNP, which are indicative of non-reversible systolic dysfunction, may be a marker of poor prognosis. Specifically, increased NT-pro BNP levels or sustained high concentrations on days 2 and 3 are poor prognostic indicators in patients with low LVEF (left ventricular ejection fraction) (203,207,209,210).

NT-proBNP may potentially become the "gold standard" for monitoring HF patients in order to identify those who should be referred early for heart transplantation (207).

NT-proBNP is part of a group of prognostic factors that can be influenced by medical intervention, and therefore can function as a dynamic marker that reflects the patient's management. Clinical trials investigating the use of biomarkers, specifically B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), to guide pharmacotherapy for heart failure with reduced ejection fraction (HFrEF) have yielded inconsistent results. While these biomarkers have been found to be useful prognostic indicators for HFrEF, it is not clear whether a biomarker-guided strategy would offer additional benefits compared to the cautious application of guideline-recommended therapies. Consequently, current evidence does not endorse the routine measurement of BNP or NT-proBNP as a means of guiding the titration of therapies for HFrEF (162).

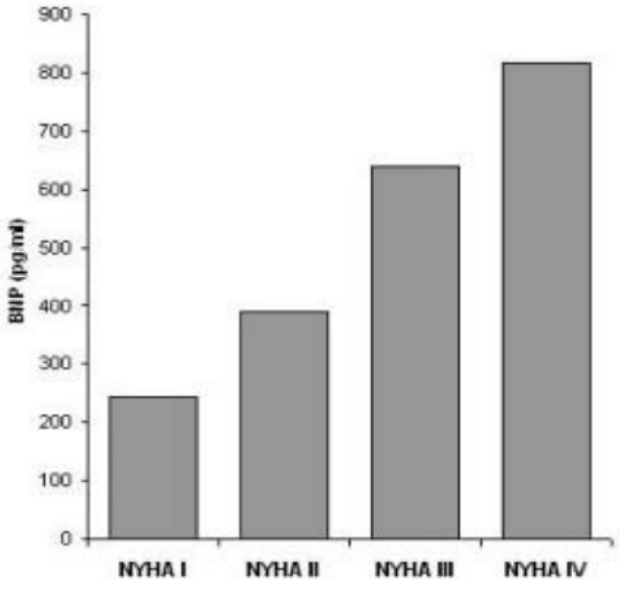


Figure 150: Median plasma levels of brain natriuretic peptide (BNP) in patients with heart failure according to their NYHA functional class(211).

i. Hallmark studies:

Breathing not properly study:

The evaluation of BNP and NT-proBNP in the ED is based on the Breathing Not Properly study and subsequent research (186). The Breathing Not Properly study was a multicenter, prospective study that included 1586 patients presenting to the ED with acute dyspnea. The study aimed to establish the diagnosis of CHF in cases where the clinical presentation was ambiguous or when there were confounding comorbidities present. The study was conducted at 7 centers, 5 in the US and 2 in Europe, from April 1999 to December 2000. BNP levels were measured using the Triage BNP Test and compared to the attending physician's assessment of clinical probability of CHF, as well as other conventional evaluation methods such as patient demographics, medical history, physical examination, and results of electrocardiography and chest x-rays. The study found that BNP levels had a high diagnostic accuracy for CHF and improved the diagnostic accuracy when used in conjunction with conventional evaluation methods. Specifically, BNP had the greatest diagnostic value in the intermediate probability group, where BNP levels of at least 100 picograms per milliliter correctly classified 74.0% of cases as having or not having CHF. The study also confirmed the value of a careful history and physical examination in diagnosing CHF but noted that these methods have limitations and can be improved upon with the use of BNP testing. The study suggests that BNP may be a sensitive and specific indicator of ventricular disorders and could be useful in the acute diagnosis of CHF in the ED. However, it should be noted that the study has several limitations, including the potential for misclassification of CHF status and the lack of generalizability to all patients with acute dyspnea. Despite these limitations, the results of the Breathing Not Properly study and subsequent research have indicated that BNP and NT-proBNP are useful diagnostic markers for CHF in the ED setting. Their high sensitivity and specificity, particularly in the intermediate probability group, make them valuable tools in the diagnosis of CHF in patients presenting with acute dyspnea. However, it is important to note that BNP and NT-proBNP should not be used as

standalone diagnostic tests, but rather as part of a comprehensive evaluation that includes a thorough history, physical examination, and other relevant tests.

- **BASEL study:**

There have been some impact or interventional studies that suggest the use of BNP assays in the emergency department for patients presenting with dyspnea may improve outcomes. Specifically, it has been shown to reduce length of stay in the emergency department, rehospitalization, and associated costs. In a Swiss study (BASEL study) (212), 227 patients aged 70 years on average were managed in the usual way and 225 patients received a BNP assay (Triage®) associated with therapeutic recommendations based on BNP levels. The use of BNP significantly reduced hospitalization rates (75% versus 85%), length of hospitalization (8 versus 11 days), and cost of hospitalization (27% less) in patients over 70 years of age, although no significant difference in mortality was observed (212). However, mortality was only reduced in the subgroup of patients over 70 years of age (9% versus 17%). The conclusions of other impact studies are less enthusiastic (213,214). However, the European Society of Cardiology has recommended testing for suspected CHF since 2007 (215). However, to optimize the diagnostic utility of BNP/NT-proBNP, it is important to reserve testing for more difficult-to-manage patients (e.g. elderly or those with COPD), interpret values correctly, and implement appropriate treatment.

- **PRIDE study:**

This prospective study enrolled 600 patients who presented to the emergency department with dyspnea. 35% of these patients (209 patients) were found to have acute congestive heart failure (CHF) according to the clinical diagnosis made by the study physicians, who were blinded to the NT-pro BNP results. The study was conducted at the Massachusetts General Hospital in Boston, Massachusetts. The study aimed to establish the utility of NT-pro BNP testing in the emergency department to rule out acute CHF and to determine the optimal cut points for this use. It also aimed to compare the results of NT-pro BNP testing with the clinical

assessment of the managing physician for identifying acute CHF, and to investigate whether NT-pro BNP testing alone or in combination with clinical judgment is superior for diagnosing acute CHF in patients who present with dyspnea in the emergency department.

The study found that NT-pro BNP testing is a valuable addition to standard clinical assessment for identifying and excluding acute CHF in these patients. The optimal cut points for this use were found to be >450 pg/ml for patients <50 years of age and >900 pg/ml for patients >50 years of age, with a negative predictive value of 99% for ruling out acute CHF. The study also found that NT-pro BNP testing alone was superior to clinical judgment alone for diagnosing acute CHF, and that NT-pro BNP plus clinical judgment was superior to either alone. The study also found that the optimal rule-in strategy using NT-pro BNP was an age-stratified approach with 2 cut points, whereas a single cut point of 300 pg/ml was of value for excluding the diagnosis (199).

j.Pitfalls:

Both BNP and NT-po BNP suffer from similar confounding effects of age, sex, and renal insufficiency. NT-pro BNP is most sensitive for the detection of mild LV dysfunction and structural heart disease, while BNP is less sensitive to the effects of renal insufficiency than NT-pro BNP.

Chronic heart failure:

In patients with chronic heart failure (CHF), it is the evolution of natriuretic peptide levels over time and their variation around the baseline value that can help overcome the challenge of accurately diagnosing CHF based on a single assay (an increase of more than 50% of this baseline value being in favor of the diagnosis of CHF). Therefore, measurement of natriuretic peptides is becoming an integral part of the long-term follow-up of CHF patients and is a key element in the adaptation of treatment by the cardiologist. This baseline value should be available to the emergency physician during an episode of acute dyspnea in order to best interpret the result of a new determination.

Age:

Like BNP, its concentrations vary by age; the normal threshold for those under 50 years of age is 450 pg/ml, while it is 900 pg/ml for those over 50 years of age to 75 years of age and 1800 pg/ml for those over 7 years of age (189).

Renal clearance:

Particular care is necessary to evaluate an elevated BNP in patients with multiple comorbidities, for example, those with renal failure, to identify the cause of the peptide's increase (216). Moderate renal insufficiency (>50 ml/mn) does not significantly affect the threshold values for BNP. BNP levels were inversely correlated with estimated glomerular filtration rate (GFR). For BNP assays, optimal cut-offs for ruling out CHF are 290 pg/mL for a GFR between 60 and 89 mL/min and 515 pg/mL for a GFR between 15 and 29 mL/min. For NT-pro BNP assays, optimal cut-offs were 1360 and 6550 pg/mL, respectively.

BMI:

Obesity, on the other hand, decreases serum natriuretic peptide concentrations. The mean BNP values are 3 times higher for lean patients with CHF than for obese patients with CHF (517 vs 176 mg/mL). Obese patients with BMIs ≥ 25 kg/m2 had median BNP levels below the recommended rule-in threshold of 500pg/mL.

Atrial fibrillation:

AF confounds the utility of BNP assay for diagnosing acute CHF exacerbation. AF was associated with increased BNP levels in the absence of acute CHF. A high cut off value to exclude CHF is required.

Differential diagnosis:

While elevated BNP levels are highly sensitive to heart failure, they are not specific to its cause; elevated BNP may be seen in a variety of other cardiac conditions, such as myocardial disease, valvular disease, arrhythmias, pulmonary hypertension, and myocardial injury due to cytotoxicity. Additionally, NT-proBNP elevation may also be present in non-cardiac conditions, such as gram-negative sepsis BNP and NT-proBNP levels may be affected by the presence of

specific comorbidities, such as chronic renal failure, type 2 diabetes, obesity, and acute coronary syndrome (217). Levels are higher in patients with renal failure, diabetes, acute coronary syndrome (ACS), and lower in obese individuals (189). It is noteworthy that while NT-proBNP may be elevated in non-HF contexts, the presence and degree of elevation are often significantly correlated with an increased risk of adverse outcomes. Therefore, it is crucial to consider the potential implications of elevated NT-proBNP levels, even in non-HF contexts, rather than dismissing them as "false-positive" findings (206).

These "false positive" and “false negative” natriuretic peptide situations should be well understood and always include a biological result in the precise clinical context. It would be potentially harmful to focus solely on an elevated BNP result during a severe sepsis and to adopt a therapeutic attitude of depletion rather than filling.

Table XLVIII: Summary of selected non- heart failure causes of NP elevation possible diagnoses.

Category	Subcategory
Heart muscle disease	Hypertrophic heart muscle diseases
	Infiltrative myocardiopathies (e.g. amyloidosis)
	Acute cardiomyopathies (e.g. apical ballooning syndrome)
	Inflammatory (e.g. myocarditis, chemotherapy)
Valvular heart disease	Aortic stenosis and regurgitation
	Mitral stenosis and regurgitation
Arrhythmia	Atrial fibrillation and flutter
Anemia	N/A
Critical illness	Bacterial sepsis
	Burns
	Adult respiratory distress syndrome
Stroke	N/A
Pulmonary heart disease	Sleep apnea
	Pulmonary embolism
	Pulmonary hypertension
	Congenital heart disease

13.6. Key takeaways:

- AHF has a prevalence of 10% in individuals aged 75 and plus. It is the main cause of hospitalization among the elderly and has a high mortality rate
- Dyspnea is a primary reason for emergency department visits. Dyspnea, is a common presentation of congestive heart failure (CHF).
- Prompt diagnosis and treatment of AHF can improve patient outcomes.
- HF is a clinical syndrome characterized by a constellation of symptoms and signs caused by structural and/or functional cardiac abnormalities.
- Increased serum natriuretic peptide concentrations provide strong evidence for the diagnosis of AHF and can also predict adverse outcomes and prognosis in patients with cardiac disease.
- BNP is produced by cardiomyocytes in the atria and ventricles in response to increased pressure and cardiac muscle stretch.
- BNP and NT-pro BNP are secreted almost entirely by the left ventricle in equimolecular amounts.
- Given the longer half-life of NT-pro BNP, its serum levels are higher than that of BNP.
- The main action of natriuretic peptides on the kidney is diuresis and natriuresis. Natriuretic peptides also exhibit vasodilatory effects in the cardiovascular system.
- A normal BNP level is typically below 100 pg/mL, while a normal NT-pro BNP level is typically below 300 pg/mL.
- BNP and NT-pro BNP have comparable diagnostic accuracy in detecting acute heart failure, with excellent ability to exclude the possibility of acute heart failure.
- BNP and NT-pro BNP have high sensitivity and negative predictive value
- A single NT-pro BNP cutoff of 900 pg/mL provides similar diagnostic performance as a BNP of 100 pg/mL; however, age-stratified cutoff points for NT-pro BNP (450 pg/mL

for ages less than 50 years, 900 pg/mL for 50-75 years, and 1800 pg/mL for more than 75 years) performed the best.

- Elevated levels of NT-pro BNP or BNP are associated with increased morbidity and mortality in patients with heart failure.
- BNP values in the grey zone require further investigation. Measurement of BNP concentrations and its variations is an important prognostic marker in heart failure.
- The heterogeneity of commercially available assay techniques makes knowledge of the method used essential for interpretation of the result, and requires that the patient be monitored with the same technique.
- BNP and NT-pro BNP levels vary among healthy populations based on age, gender, and BMI.
- Both BNP and NT-pro BNP levels are lower in patients with obesity than in patients with a normal BMI. Levels of the peptides are higher on average in females than males.

13.7. Summary on procalcitonin:

a. Introduction

Clinicians face a significant challenge in identifying infections due to the diverse and often atypical presentation of infectious diseases. This difficulty is exacerbated in overcrowded emergency departments, where early identification of infections is crucial. Although fever is an important symptom to consider, it is not a reliable indicator of infection or its bacterial etiology.

Physicians are faced with the dilemma of managing potentially life-threatening conditions such as sepsis and related syndromes that necessitate immediate administration of appropriate antimicrobial therapy, and the limitations of traditional methods for identifying the infectious agent. Direct microscopic examination, culture, or microbial genome detection can take 48 hours or more, rendering them unsuitable for urgent situations.

With the increasing concern over emerging bacterial resistance issues, medical professionals generally agree that antibiotics should not be prescribed for every suspected infection. Striking a balance between timely and accurate identification of infections and the judicious use of antibiotics is crucial for improving patient outcomes and preventing the development of antibiotic resistance.

Therefore, identification of a specific marker for bacterial infection is crucial for effective diagnosis and treatment. The ideal biomarker for bacterial infections should exhibit high sensitivity and specificity towards bacterial infections, enabling rapid and early diagnosis. It should also have the ability to predict the course and prognosis of the disease, and aid in guiding and rationalizing therapeutic decisions, particularly with respect to antibiotic stewardship. Among the available biomarkers for infection, procalcitonin (PCT) stands out as the sole biomarker fulfilling all the aforementioned criteria. PCT has demonstrated the highest specificity and prognostic value for infections, and it is the only biomarker for which numerous interventional studies have demonstrated utility in guiding rational antibiotic prescriptions.

b. Bacterial infection, sepsis, pneumonia, meningitis:

Sepsis is a life-threatening clinical syndrome that is caused by a dysregulated host response to infection resulting in a characteristic constellation of physiologic and biochemical abnormalities. This disorder has a spectrum of severity, ranging from mild vital sign abnormalities, such as fever, tachycardia, and tachypnea, along with leukocytosis, to more severe conditions that can lead to hypotension, responsive to infusions of IV fluids. Furthermore, organ dysfunction, including low urine output and increased creatinine, confusion or delirium, hypoxemic respiratory failure, liver failure, ileus, sepsis-induced cardiomyopathy, and secondary heart failure, and a variety of hematologic abnormalities can occur. In extreme cases, patients will experience hypotension that is resistant to IV fluids, which is accompanied by an elevation of serum lactate. This combination is what is currently required for a diagnosis of septic shock, and

when the physiologic and biochemical abnormalities become so severe as to be irreversible, death is inevitable.

c. Biosynthesis and metabolism of PCT:

The discovery of Procalcitonin (PCT) dates back to 1975 (218). It was during research on an early marker for thyroid cancer recurrence that the team of Professor Claude Bohuon at the Gustave Roussy Institute in the 1980s stumbled upon its potential role in bacterial sepsis. Further investigation by Assicot et al. in 1993 confirmed that PCT was a specific biomarker of bacterial infection, with minimal elevation in viral infections and non-infectious inflammatory syndromes (219).

PCT is a pro-hormone of calcitonin, a hypo-calcemic hormone, and a protein consisting of 116 amino acids (13 kDa). The CALC-1 gene on chromosome 11 generates several types of mRNA via an alternative splicing mechanism, with only the CT-1 and CT-2 mRNA transcripts encoding PCT. Translation of PCT results in the first product, pre-procalcitonin, which is a 141 amino acid protein with a 25 amino acid signal sequence. This protein is rapidly eliminated in the endoplasmic reticulum to yield a 116 amino acid protein, procalcitonin (218,220).

In the physiological state, PCT is secreted by the C cells of the thyroid and to a lesser extent by the pulmonary endocrine cells (214). In response to a hormonal stimulus, PCT undergoes specific proteolysis in the C-cells of the thyroid, resulting in the excretion of calcitonin but not PCT. In this case, the increase in procalcitonin is not associated with an increase in blood calcitonin levels (221). However, in sepsis, intact PCT is released into the bloodstream (222). The origin of PCT synthesis during sepsis is ubiquitous, but increased PCT has been observed in infected and thyroidectomized subjects, ruling out exclusive thyroid synthesis during sepsis. In vitro studies have demonstrated the presence of mRNA or PCT itself in monocytes as well as in most tissues, including adipocytes. Its secretion by parenchymal cells and monocytes probably occurs under the joint influence of bacterial toxins and inflammatory mediators. An experimental study of a sepsis model in hepatectomized baboons reported the inability of these animals to produce PCT, suggesting a critical role of the liver in its synthesis. In

bacterial sepsis, secretion becomes ubiquitous, although mainly from the liver and adipocytes (222) (Figure 141).

In the physiological state, it is secreted by the C cells of the thyroid and to a lesser extent by the pulmonary endocrine cells (223). PCT synthesis is under the influence (positive or negative) of certain pro-inflammatory cytokines released by cells of the immune system in response to microbial aggression and lipopolysaccharide released by the bacterial agent (224). Therefore, PCT secretion is absent in viral sepsis, which would result from a cytokine profile different from that of bacterial infection. The first two cytokines involved are Tumor Necrosis Factor α (TNFα) and Interleukin-6 (IL-6). PCT synthesis occurs shortly after cytokine synthesis in the inflammatory cascade (Figure 143).

In the context of severe bacterial infection, the expression of CGRP-I undergoes a massive increase in all parenchymal tissues of the body (225,226). There appears to be no tissue specificity of splicing, as mRNAs coding for procalcitonin and CGRP are found ubiquitously (227). Despite much debate about the site of PCT synthesis, high levels of PCT have been detected in septic thyroidectomized patients, indicating that thyroid C-cells are not a major site of synthesis. Alkalitonin-like immunoreactivity has been observed in pulmonary neuroendocrine cells, and PCT has been found in patients with small cell lung carcinoma, suggesting that the lung may be a site of PCT production (228). However, the liver is likely the primary site of PCT synthesis, as incubation of human liver sections with interleukin 6 (IL-6) and tumor necrosis factor (TNF-a) results in an increase in PCT in the medium, and hepatic secretion has been demonstrated in baboons (225).

Despite numerous studies, the biological function of PCT remains unclear. Animal models suggest that PCT is not only a sepsis marker, but also a mediator of the inflammatory cascade. Administration of PCT to healthy animals has little effect, whereas administration of PCT to animals in a septic state is associated with increased mortality (229). In various animal models of sepsis, neutralization of PCT significantly improves survival (230,231). Injection of PCT into septic or non-septic animals does not induce or increase TNF-a production, whereas TNF injection dramatically stimulates PCT production (232). These findings indicate that PCT is a secondary mediator that requires prior stimulation to play a role in the inflammatory process. In

a human model in which LPS was injected, the presence of PCT decreased the production of TNF-alpha, IL-12, and IFN-gamma, while increasing the production of IL-10, favoring a Th2 profile that characterizes post-septic immune depression (233).

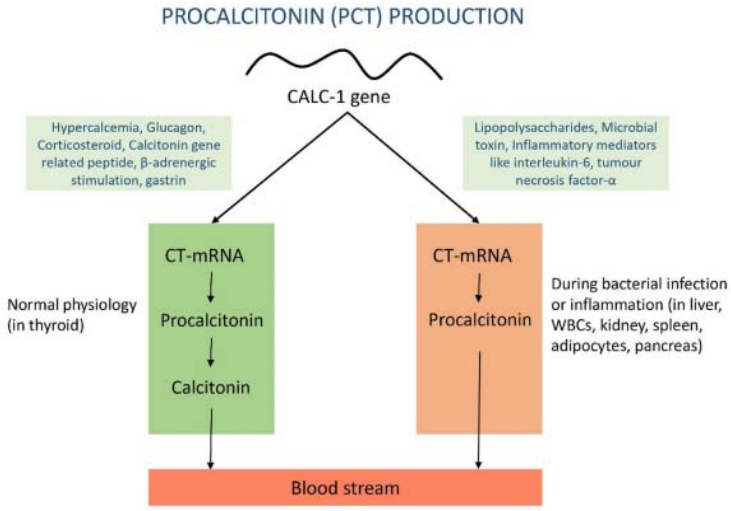


Figure 151: Specific mediators, metabolic pathways, and organs responsible for procalcitonin production(234).

d. Kinetics of PCT:

The kinetics of procalcitonin (PCT) have been extensively investigated since the groundbreaking experiment conducted by Dandona in 1994, where intravenous injection of Escherichia coli endotoxin was administered to healthy volunteers. Following endotoxin injection, the appearance of PCT in serum follows the peak of TNF-α chronologically. It is noteworthy that the peak of PCT concentration occurs subsequent to those of TNF-α and IL-6, which appear at the second and third hour, respectively. Studies have demonstrated that PCT secretion is induced by TNF-α and, to a lesser extent, by IL-6 (235).

Serum concentration of PCT increases as early as 3 hours after the onset of infection, with a peak observed between 6 and 8 hours, and subsequently plateauing from 8 to 24 hours (236). The half-life of PCT is estimated to be approximately 20 to 24 hours (Figure 143). The favorable correlation between PCT and the severity of inflammatory reaction permits daily assays to be performed, thus aiding in monitoring the evolution of infectious pathology and response to treatment (237).

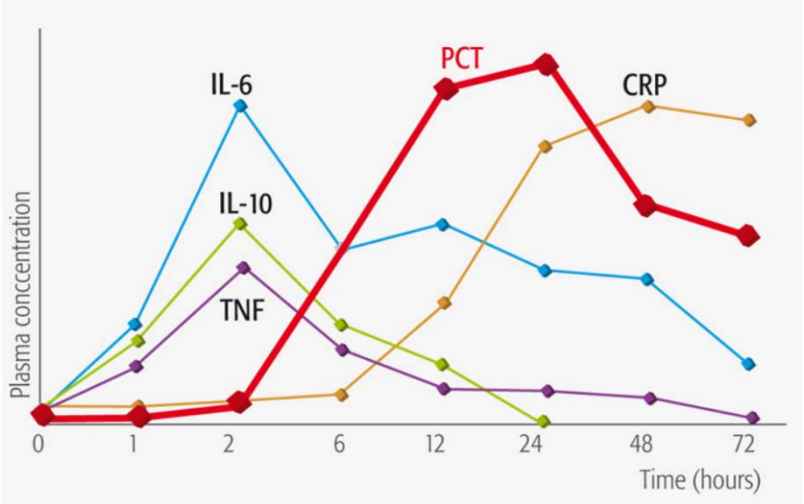


Figure 152: Kinetics of different biomarkers of bacterial infection(238).

e. Normal and critical findings:

Under physiological conditions, procalcitonin (PCT) is secreted by the C cells of the thyroid and, to a lesser extent, by the pulmonary endocrine cells, with a blood level below 0.05 ng/ml. The maximum limit considered as normal in healthy individuals varies from 0.05 to 0.1 ng/ml depending on the laboratory standards (223).

During viral infections and inflammatory states, a slight increase in PCT concentration may be observed, but it typically does not exceed 1.5 µg/L. Conversely, in cases of severe bacterial infection, PCT concentrations may increase up to 1000 µg/L (239).

f. Assay technique:

The first commercially available procalcitonin (PCT) test was the Brahms immunoluminometric technique, which was entirely manual and time-consuming, taking approximately two hours. Following this, various companies have developed automated techniques, all utilizing Brahms' patented anti-calcitonin and anti-katacalcin antibodies. These two antibodies are used in a sandwich method, either as capture or detector antibodies. Importantly, these techniques are highly specific and do not cross-react with molecules of similar structure, such as calcitonin or katacalcin.

The primary characteristics of the presently available PCT assays are listed below (Table 46).

Table XLIX: Overview of different PCT assays (240):

Assay Name	Time to Result/Incubation Time (min)	Upper Range of Measurement (µg/L)	Sample Volume Required (µL)	Sample Matrix	Maximum Number of Thaw Cycles	Lower Limit of Detection (µg/L)	Functional Assay sensitivity or Limit of quantification (µg/L)
B.R.A.H.M.S PCT sensitive KRYPTOR	19	50 (direct), 5000 (Auto Dil)	50	Serum; EDTA; Heparin	3	0.02	0.06 (FAS)
ADVIA Centaur B.R.A.H.M.S PCT	26 (CP), 29 (XP)	75 (direct), 1500 (Auto Dil)	100	Serum; EDTA; Heparin	5	0.04	0.05 (FAS)
ARCHITECT B.R.A.H.M.S PCT	22	100 (direct), 1000 (Auto Dil)	150	Serum; EDTA; Heparin	3	0.003	0.01 (LoQ)
ELECSYS B.R.A.H.M.S PCT	18	100 (direct), 1000 (Auto Dil)	30	Serum; EDTA; Heparin	1	0.02	0.06 (LoQ)
LIAISON B.R.A.H.M.S PCT II GEN	16	100	100	Serum; EDTA; Heparin; Citrate	3	0.02	0.04 (LoQ)
LUMIPULSE G B.R.A.H.M.S PCT	30	200	60	Serum; EDTA; Heparin; Citrate	1	0.0048	0.0079 (LoQ)
VIDAS B.R.A.H.M.S PCT	20	50	200	Serum; Heparin	3	0.03	0.05 (LoQ)
Diazyme PCT	10	100	20	EDTA	3	n.a.	0.17 (LoQ)
Maglumi PCT	15	100	20	EDTA whole blood	n.a.	n.a.	0.13 (FAS)

g. Performance characteristics

Distinguishing between bacterial and viral infections can be challenging based on clinical presentation alone, and the treatment strategies differ significantly. Traditional markers like C-reactive protein (CRP) and white blood cell count may not always provide reliable information on the etiology of the infection. However, Procalcitonin (PCT) levels remain low in viral infections and increase in severe bacterial infections. The sensitivity and specificity of PCT in identifying the bacterial or viral origin of sepsis are 92% and 73%, respectively, with positive and negative likelihood values of 6.05 and 0.1. PCT's statistical performance is notably better than CRP for this indication (241). For example, Schwartz et al. found that using a threshold of positivity of 0.5 µg/l, PCT had a specificity of 100% and a sensitivity of 69% for differentiating bacterial from non-bacterial meningitis (242).

In the emergency department, for the diagnosis of bacterial infection across all infectious sites, PCT is a reliable diagnostic marker of systemic infection. Its sensitivity ranges from 62-77%, and specificity ranges from 88-59%, with the area under the ROC curve ranging from 0.79 to 0.76. The optimal threshold for emergency medicine is approximately 0.2 ng/ml, which requires the use of a sufficiently sensitive assay technique (243,244).

Table L: Diagnostic characteristics of PCT:

Characteristic	Value
Sensitivity	92%
Specificity	73%
Positive Likelihood	6.05
Negative Likelihood	0.1

h. Clinical utility of PCT:

h.1. In diagnosis:

- **Bacterial vs non-bacterial:**

The emergency department is one of the hospital departments where the identification of sepsis is a frequent issue. Few studies have examined the contribution of PCT in the emergency department without targeting specific pathologies. In 2005, Hausfater et al. studied the diagnostic and prognostic value of PCT in 243 patients presenting to the emergency department with a temperature of 38.5°C or higher. At a threshold of 0.2 µg/L, PCT had a sensitivity of 77% and a specificity of 59% for the diagnosis of bacterial and/or parasitic infections. Moreover, they showed the prognostic value of PCT in this context: 54% of patients with PCT above 5 µg/l versus 15% of those with PCT below 0.2 µg/l had a poor prognosis (death or transfer to intensive care) (244).

Many studies have confirmed the role of PCT as a specific marker of severe bacterial or parasitic infections (mainly malaria and certain systemic fungal infections) (245). One of the main applications of PCT in emergency medicine is its capacity to differentiate between a bacterial infectious process and an inflammatory process, a capacity that neither ESR nor the CRP measurement have. In a meta-analysis systematically comparing the performance of CRP and PCT for the diagnosis of bacterial infection, Simon et al (241) concluded that PCT had better sensitivity and specificity than CRP: 88 versus 75% and 81 versus 67% respectively.

- **Etiological diagnosis of meningitis:**

In the etiological diagnosis of meningitis, both in adults and children, PCT has a sensitivity of 70-100% and a specificity of 100% for predicting bacterial origin, for positivity thresholds varying between 0.2 and 5 ng/mL according to numerous studies (242,246,247). In addition, the use of PCT for negative predictive value in epidemic periods of viral meningitis may

help to rationalize antibiotic prescriptions (248). The main indication for PCT in this context is in meningitis with negative direct CSF examination, especially if the CSF cell count is mixed.

- **Suspected LRTI and antibiotic stewardship:**

The management of suspected lower respiratory infection is another area of application for PCT, as this is a situation where neither the patient presentation nor standard radiology are discriminating, leading to over-treatment with antibiotics. Beat Müller's team in Switzerland was the first to report on the feasibility and benefits of antibiotic stewardship guided by PCT in suspected LRTI in the emergency department (249) (Figure154). The primary outcome of this study was that 83% of patients in the standard group received antibiotics versus only 44% in the PCT-guided group with a decision threshold of 0.25 µg/L (249). These hospital data were confirmed in ambulatory medicine in a study of 53 general practitioners who included 458 patients with a respiratory tract infection, with a 72% reduction in the use of antibiotics in the PCT group (250). Finally, by grouping all the patients included in these different studies, the same authors confirmed the absence of a negative effect associated with the use of an algorithm guided by PCT in suspected respiratory infections (251) particularly in COPD exacerbations, but also in community-acquired pneumonia, without any negative effect on the course of the disease (249,251,252).

However, once again, the kinetics of the biomarkers must be kept in mind, because if PCT has a faster onset kinetic than CRP in serum (6 hours on average versus 12 hours for CRP), a patient presenting shortly after the onset of symptoms may have concentrations detectable by a sensitive technique but below the threshold of 0.25 µg/L. In this case, if there is a strong clinical suspicion of community-acquired pneumonia, antibiotic therapy may be warranted and monitoring of the PCT 12-24 hours later may be discussed. Recently, two studies conducted in intensive care units reported, with the same type of methodology, that the use of PCT to guide the treatment of septic cases was able to reduce antibiotic exposure, without deleterious effect

on mortality (253,254). Finally, a recent literature review on impact studies involving PCT in respiratory infections clearly recommends its use (255).

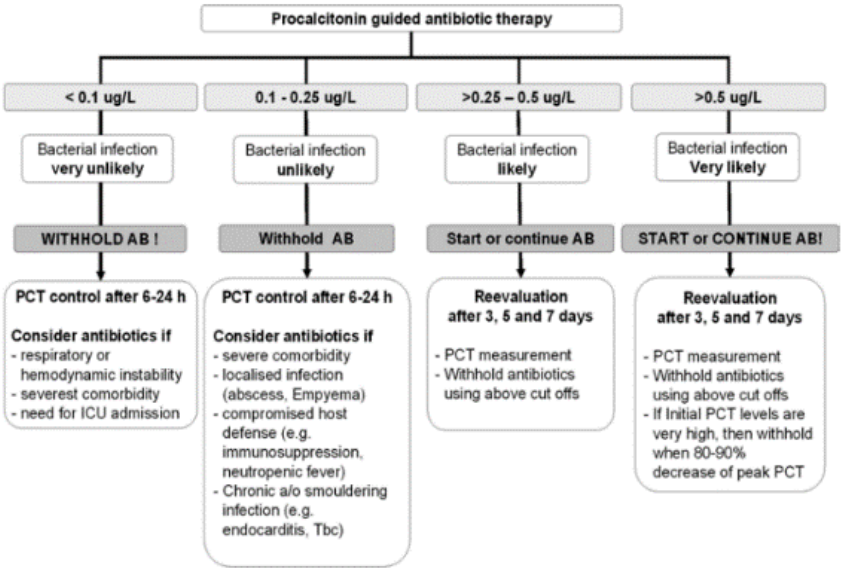


Figure 153: Antibiotic stewardship based on procalcitonin (PCT) cut-off(256).

Overall, in adults, the diagnostic relevance of PCT has been mainly demonstrated in:

- In pneumology, as part of the management of lower respiratory infections, significantly reducing exposure to antibiotics in patients hospitalized for pneumopathy (257). Its use also makes it possible to reduce the use of antibiotics in the context of asthma and COPD exacerbations (258,259), and to distinguish between lower tract respiratory infections induced by "classical" bacteria and "Atypical" intracellular bacteria (260,261).
- In neurology, when bacterial meningitis is suspected in adults (262). The PCT assay is included in the 2017 SPILF consensus recommendations on the management of meningitis. Thus, a PCT level < 0.25 ng/ml causes the bacterial etiology of meningitis to be reviewed (263).
- In gastroenterology, it is involved in the early diagnosis of pancreatic necrosis infections where it also has a severity value (264). Thus, a PCT >1.8 ng/ml for 2

consecutive days suggests a necrosis cast infection with a sensitivity of 95% and a specificity of 88%.

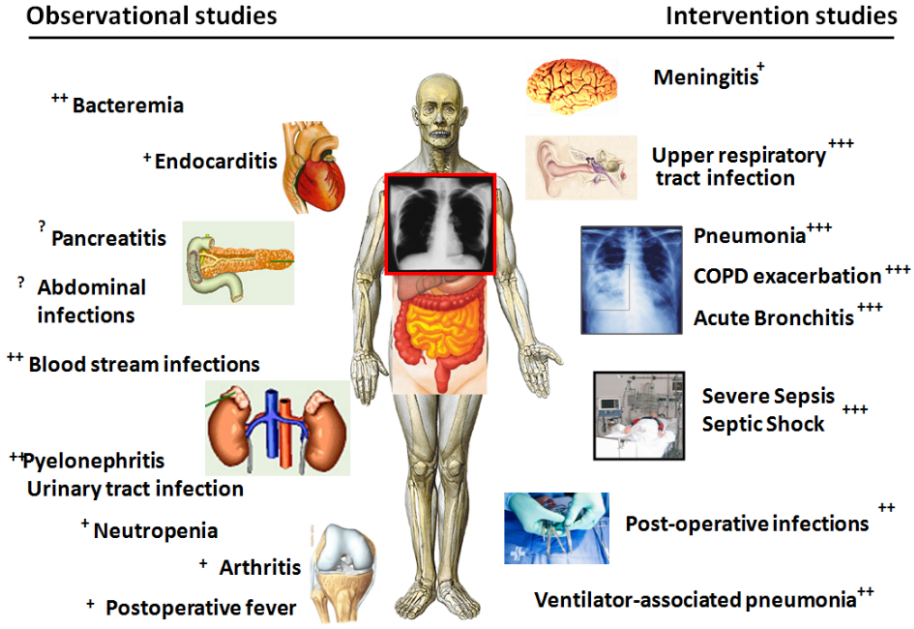


Figure 154: Available evidence concerning PCT in different infections (265).

- **In prognosis:**

Procalcitonin (PCT) has been demonstrated to have diagnostic and prognostic utility in clinical practice. Multiple studies have demonstrated that increased PCT concentrations are correlated with the severity of bacterial infection in septic states (266) and community-acquired pneumonia (267). It has also been shown to be useful for assessing the severity and predicting complications of bacterial sepsis (268), with a concentration of greater than 5 ng/ml having a prognostic risk stratification power as demonstrated by several studies including that of Professor Hausfater (244,269).

Furthermore, PCT has been shown to be a prognostic marker for identifying the most severe or potentially worsening septic patients in the emergency department (243,244). Early initiation of treatment has been shown to improve the prognosis of sepsis, and PCT elevation can aid in the decision-making process. Al-Nawas et al. observed a correlation between PCT concentrations on days 0 and 1 and the severity of sepsis in patients (270), and a study by (271)

found that a PCT threshold of 1.1 µg/L had a sensitivity of 97% and a specificity of 78% for differentiating sepsis from systemic inflammatory response syndrome. PCT is now generally considered a superior marker of sepsis compared to C-reactive protein, interleukin-6, interleukin-8, and tumor necrosis factor alpha (272). However, PCT alone cannot distinguish between different inflammatory and/or septic states and should be considered in conjunction with other biological and clinical criteria for differential diagnosis. In a small series of 15 patients, PCT was found to be only moderately elevated (average 1.4 µg/L) in cardiogenic shock compared to septic shock (range of 72-135 µg/L) (273).

The utilization of infection biomarkers for prognostic purposes is reasonable, as there is still room for improvement in the early identification and management of severe septic states in the emergency department, despite the widespread implementation of international criteria for defining these severe septic states. In addition, it is not uncommon to observe a discrepancy or delay between the intensity of the systemic inflammatory response and the onset of the first signs of organ failure. Conversely, some patients may be hospitalized due to the concern of developing septic shock (this is particularly true for community-acquired pneumonia and pyelonephritis). The prognostic value of PCT was initially identified in an original study, as the children with the most severe infectious conditions also had the highest PCT concentrations. Since then, numerous studies have confirmed the correlation between the absolute value of PCT and the severity of the infection. For example, several authors have reported that PCT levels progressively increase with the severity of sepsis (274). PCT levels also correlate with severity scores used in intensive care such as the APACHE score or the PSI index used to assess the severity of community-acquired pneumonia (266,267,275). We have also established that PCT is a prognostic marker, particularly in febrile patients, allowing the identification of the most severe septic patients or those at risk of worsening in the emergency department (253,255). Finally, the value of PCT in guiding decisions to admit patients from the emergency department was recently evaluated in two prospective multicenter studies, one on acute uncomplicated pyelonephritis and the other on low or intermediate severity community-acquired pneumonia

(276,277). In both studies, PCT performed better than C-reactive protein in identifying patients requiring hospitalization.

- **In antibiotic stewardship:**

Additionally, the kinetics of PCT evolution can be used to monitor the effectiveness of antibiotic therapy. PCT has a half-life of approximately 24 hours, and a decrease in concentration during treatment is indicative of its effectiveness. On the other hand, constant or increasing PCT concentrations suggest uncontrolled infection. Several studies have demonstrated that monitoring PCT can significantly reduce the duration of antibiotic therapy in patients with lower respiratory infections (249), exacerbations of chronic obstructive pulmonary disease, community-acquired pneumonia (252), and sepsis requiring intensive care (254). This "guided antibiotic therapy" approach has several benefits, including the reduction of bacterial resistance and cross-contamination, lower treatment costs, and shortened hospitalization duration and associated costs.

i. Limitations of procalcitonin:

PCT levels in newborns:

In newborns, there is a physiological peak in PCT levels at 48 hours of life, followed by levels similar to those in adults around the 5th day of life. This means that interpretation of PCT variations in newborns requires specific thresholds.

PCT levels in localized infections:

It is important to note that PCT levels do not increase in cases of localized infections, such as soft tissue abscesses or uncomplicated acute appendicitis. Additionally, PCT levels may not be elevated in the early stages of certain community-acquired pneumonias, and some infections caused by intracellular bacteria, such as atypical pneumonia, brucellosis, Lyme disease, and tuberculosis, also do not lead to increases in PCT.

PCT levels in renal failure and hemodialysis (278,279):

Chronic non-terminal renal failure does not affect baseline PCT levels, but patients with pre-terminal renal failure or undergoing iterative hemodialysis sessions may have PCT levels between 0.5 and 1.5 µg/L in the absence of infection.

Non-bacterial and non-septic etiologies of PCT elevation (220):

Several non-bacterial and non-septic etiologies of procalcitonin (PCT) elevation have been identified in the literature. These include certain immune system pathologies, such as macrophagic activation syndrome, Kawasaki disease, Wegener's and Goodpasture's syndrome, and ANCA vasculitis, as well as other conditions associated with systemic aggression and cytokine release, such as polytrauma, heat stroke, and burns. High PCT levels have also been observed in certain cancers, including small cell bronchial carcinomas and medullary thyroid cancers, Quervain's thyroiditis, and in cases of major hepatic cytolysis. Many immunomodulatory treatments can also lead to cytokine deregulation and elevated PCT levels.

In conclusion, limitations of PCT include false positive and false negative PCT results. False positive PCT results have been reported in certain conditions associated with abnormal inflammatory responses, including macrophagic activation syndrome, Kawasaki disease, heat stroke, neuroleptic malignant syndrome, drug hypersensitivity syndrome, and in the early stages of polytrauma or burns. False negative PCT results may occur in cases of localized infections, early stages of certain community-acquired pneumonias, and viral infections. In the event of discrepancies between clinical presentation and test results, repeating the PCT assay 12 to 24 hours later may be necessary.

j. Key takeaways:

- Identifying infections can be challenging due to their diverse and often atypical presentation, especially under the time constraints of the emergency department.

- Antibiotic stewardship is crucial to prevent the development of antibiotic resistance, but physicians also need to manage potentially life-threatening conditions such as with immediate administration of appropriate antibiotics.
- Procalcitonin is a specific diagnostic and prognostic biomarker of bacterial infection, making it an ideal biomarker for bacterial infection.
- PCT is a pro-hormone of calcitonin secreted by the C cells of the thyroid, but in infections PCT is secreted ubiquitously by parenchymal cells, monocytes and the liver.
- During infection, PCT release is under the joint influence of bacterial toxins and inflammatory mediators (TNF-α and IL-6)
- The value of PCT under normal physiological conditions is below 0.05 ng/ml. In cases of severe bacterial infection, PCT concentrations may increase up to 1000 µg/L.
- During viral infections and inflammatory states, a slight increase in PCT concentration may be observed, but it typically does not exceed 1.5 µg/L.
- PCT concentration increases as early as 3 hours after the onset of bacterial infection, with a peak observed between 6 and 8 hours, and subsequently plateauing from 8 to 24 hours. The half-life of PCT is approximately 20 to 24 hours.
- The correlation between PCT and the severity of infection permits daily assays to be performed, thus aiding in monitoring the evolution of infectious pathology and response to treatment.
- Procalcitonin has diagnostic relevance in suspected bacterial lower respiratory tract infections (LRTI) and meningitis, with high sensitivity and specificity for predicting bacterial origin.
- PCT can serve as a diagnostic tool of choice when distinguishing between bacterial and viral sepsis is challenging.
- PCT levels progressively increase with the severity of sepsis and correlate with severity scores used in intensive care.

- PCT-guided antibiotic stewardship allows for the reduction of unnecessary antibiotic prescriptions in suspected LRTI.
- It has also been shown to be useful for assessing the severity and predicting complications of bacterial sepsis.
- PCT is more effective at reflecting the response to antibiotic treatment compared to C-reactive protein, making it a useful marker for guiding antibiotic therapy and limiting the development of bacterial resistance and reducing treatment costs.
- PCT has been shown to be a prognostic factor, with its increase often correlating with the severity of the infection.
- The confounders and differential diagnosis of procalcitonin include localized infections, renal failure, non-bacterial etiologies like autoimmune diseases, trauma, heat stroke, and certain medications, among others. Clinicians should be aware of these potential confounders and consider them when interpreting PCT levels.
- PCT concentration is typically normal during localized bacterial infections and viral infections, making it specific to infection and useful in differentiating septic states from inflammatory or viral diseases.

13.8. Summary on CRP:

a. Introduction:

Sepsis is a life-threatening immune response that can occur in critically ill patients due to the presence of a pathogen in the body. The condition is associated with significant morbidity and mortality, and timely recognition and treatment are crucial for effective management.

When the diagnosis of sepsis is clear, such as in patients with bacteremia, shock, and multiple organ failure, biomarker testing may not be necessary before initiating treatment. However, in cases where the diagnosis is less certain, biomarkers may be useful, especially if the test is quick, inexpensive, and has high sensitivity and specificity for sepsis. It is important to

note that biomarker results should not be used as the sole basis for treatment decisions but should be considered in conjunction with clinical signs of infection. One commonly used biomarker in this context is C-reactive protein (CRP).

CRP is an acute-phase protein produced in response to inflammation. It was first discovered by William S. Tillet and Thomas Francis in 1930 while studying the immune response of patients with pneumonia caused by Streptococcus pneumoniae (280). They found that the serum of these patients precipitated with a soluble extract of pneumococcus pneumoniae, which was called fraction C. Later, it was identified as a cell wall polysaccharide (281). The precipitation reaction was strongly positive in patients with poor prognoses, and no reaction was observed in patients who had recovered from pneumonia. Tillet and Francis observed similar results in patients with staphylococcal osteomyelitis, rheumatoid purpura, subacute bacterial endocarditis, and pulmonary abscess. However, the test gave negative results when serum from patients with viral infection, malaria, and tuberculosis was mixed with fragment C.

In 1933, Rachel Welsh observed a strong precipitation reaction with Gram-negative microorganisms in a 6-month-old patient. From this experience, it was inferred that CRP was a non-specific chemical reaction to bacterial infection rather than an antigen-antibody reaction. This was based on two observations: the negativity of the test after resolution of the infectious episode, and a positive result at 6 months of life (282). In 1941, O.T. Avery and Theodore J. Abernethy discovered that the substance responsible for the precipitation reaction with fragment C was a protein, and later found that calcium is essential for the reaction (282,283).

b. Physiology and pathophysiology of CRP:

C-reactive protein (CRP) is a well-known marker of inflammation that is commonly used in clinical practice. CRP is a member of the Pentraxin family, which is highly conserved across species. It is composed of 206 amino acids and has a molecular weight of 118 kDa. The characteristic structure of CRP, and other Pentraxins, consists of five identical subunits, each

made up of two beta-pleated sheets, that are noncovalently associated in a symmetric, cyclic pattern around a central pore. This arrangement results in a pentameric, discoidal, and flattened configuration (284). The name CRP is derived from its property of reacting with the pneumococcal polysaccharide C in the presence of Ca++ ions, as historically described by Tillet and Francis in 1930 (285).

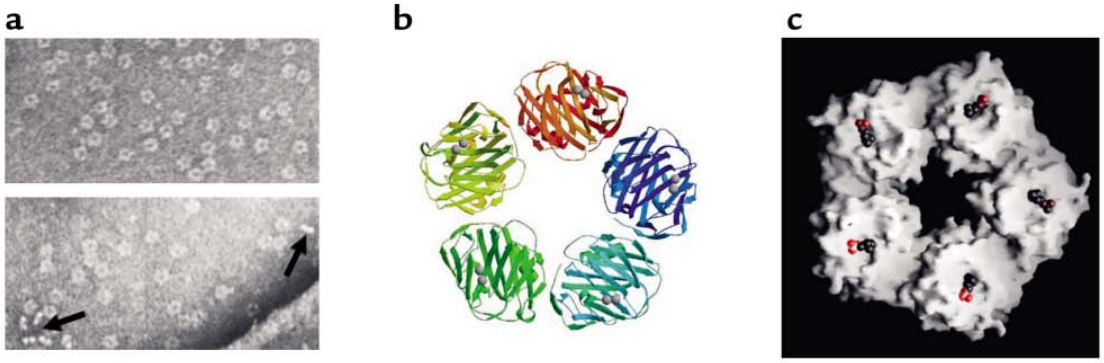


Figure 155: Molecular structure and morphology of human CRP. (a) Negatively stained electron micrograph. (b) Ribbon diagram of the crystal structure. (c) Space-filling model of the CRP molecule.

C-reactive protein (CRP) is a pentameric protein predominantly produced in liver hepatocytes, but it has also been observed to be synthesized in other cell types such as smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes. While such synthesis may be physiologically significant at local sites, it is unlikely that it contributes substantially to increased plasma concentration (286). The synthesis of CRP begins with the production of monomers, which are subsequently assembled into pentamers within the endoplasmic reticulum of the source cell. In hepatocytes, the pentameric form of CRP is retained within the endoplasmic reticulum by binding to two carboxylesterases, gp60a and gp50b. During non-inflammatory states, CRP is released slowly from the endoplasmic reticulum, but the binding of CRP to the carboxylesterases decreases during inflammatory conditions, leading to rapid secretion of CRP (287,288). The synthesis of CRP is largely stimulated by pro-inflammatory cytokines, particularly

interleukin-6, and to a lesser extent IL-1 and tumor necrosis factor alpha (289,290). Once released into the bloodstream, the protein is evenly distributed in the vasculature without significant sequestration at sites of inflammation (291). This could be explained by the detoxification hypothesis: to constrain and thereby neutralize harmful substances escaping from the site of inflammation to the circulation. Most of the CRP is taken up and also degraded by the same production site, the hepatocyte, and a small part is taken up and processed by neutrophils and macrophages (292).

C-reactive protein (CRP) is a protein with multiple functions in the body's immune response. These include:

- Binding to phosphocholine, a molecule found in certain microorganisms such as bacteria, parasites, and fungi. This binding results in the formation of a CRP-calcium phosphocholine complex that activates the classical human complement pathway. This pathway promotes the opsonization and phagocytosis of phosphocholine-containing microorganisms using a membrane attack complex (293).
- Calcium-dependent affinity for many other ligands, including damaged cell membranes, allowing CRP to recognize injured cells and activate the complement system through the classical pathway upon binding to C1q. The activation of the complement system leads to the production of anaphylatoxins C3a and C4a, and opsonin C4b and C3b (294).
- Ability to bind to the Fc receptor for IgG, which stimulates phagocytic cells and enhances the phagocytosis of damaged or dead microorganisms or host cells (295).

In summary, the main biological properties of CRP present in inflammatory foci are:

- to bind to altered or foreign structures, either endogenous (damaged membranes, exposed chromatin, cellular debris) or exogenous (bacteria, parasites).
- to trigger various host defense mechanisms: initiation of adhesion, activation of the complementary system, stimulation of opsonization and phagocytosis.

c. Kinetics of CRP:

The concentration of C-reactive protein (CRP) in circulation is primarily determined by its rate of synthesis, which can be significantly increased in cases of infection or inflammation. Following synthesis and release into circulation, CRP levels tend to increase significantly within a time frame of 6-8 hours post initial stimulation, CRP levels can increase to 50 to 1000 times its normal value peaking between 24-48 hours, with values sometimes exceeding exceed 300 mg/L (296,297).. The half-life of CRP is approximately 19 hours. Elevated levels of CRP may persist while the stimulus is present. However, after the resolution of an inflammatory or infectious episode, CRP levels decline rapidly with an estimated half-life of 4-9 hours (298–300). This rapid decline makes CRP an interesting marker of pathogenic activity, particularly when compared to other markers such as sedimentation rate.

Table LI: Timeline of C-reactive protein (CRP) concentration changes during infection/inflammation.

Event	Start of CRP increase	Peak CRP concentration	CRP half-life	Rapid decrease of CRP levels
Timeframe	Within 6-8 hours	Between 24-48 hours	Approximately 19 hours	Within 4-9 hours

d. Normal and critical findings:

The vast majority of CRP concentrations observed in normal individuals are below 5 mg/L and are below the detection limit of conventional methods. In the literature, the medians of the reference values are between 0.6 and 1 mg/L, with extremes between 0.07 and 29 mg/L (301). However, following an acute-phase stimulus, CRP values may increase dramatically, ranging from less than 50 µg/L to greater than 500 mg/L after approximately 48 h (302), a magnitude of increase of 10,000-fold (299).

Interpretation of CRP levels (303):

- Less than 0.3 mg/dL: Normal (level seen in most healthy adults).

- 0.3 to 1.0 mg/dL: Normal or minor elevation (can be seen in obesity, pregnancy, depression, diabetes, common cold, gingivitis, periodontitis, sedentary lifestyle, cigarette smoking, and genetic polymorphisms).
- 1.0 to 10.0 mg/dL: Moderate elevation (Systemic inflammation such as RA, SLE, or other autoimmune diseases, malignancies, myocardial infarction, pancreatitis, bronchitis).
- More than 10.0 mg/dL: Marked elevation (Acute bacterial infections, viral infections, systemic vasculitis, major trauma).
- More than 50.0 mg/dL: Severe elevation (Acute bacterial infections).

e. Assay technique:

C-reactive protein (CRP) quantification requires the use of immunochemical techniques. While a single reference technique does not exist, a secondary reference material (CRM 470) certified by the Community Bureau of Reference is available (304). This material is calibrated to a concentration of 39 mg/L, based on the World Health Organization's primary reference material (305).

Fast CRP measurement techniques are recommended due to the protein's short half-life and the frequent administration of the test in emergency settings. Quantitative liquid immunoprecipitation methods, including immunonephelometric and immunoturbidimetric techniques, are recommended for their speed and potential for automation. Immunoturbidimetry is the most commonly used technique, with 77.5% of laboratories using it in national quality control. However, semiquantitative methods using agglutination of latex particles coated with anti-CRP antibodies, as well as techniques using monoclonal antibodies bound to gold salt particles, should be avoided due to potential errors and lack of precision.

It is worth noting that before 1970, CRP was measured using qualitative or semi-quantitative techniques, such as latex agglutination, which limited its use for differential diagnosis as any degree of inflammation could result in false positives. Liquid-based immunoprecipitation techniques currently available have rapid turnaround times (less than 10

minutes) and good accuracy (CV < 5%) for measurements within the range of 20 to 150 mg/L. However, at lower concentrations, CVs are higher, and interferences from factors such as rheumatoid factor and heterophilic antibodies may be more significant (306), (307). The use of sensitized immunoprecipitation techniques, known as "immunolatex," can minimize the impact of these interferences by highly diluting the sample. These techniques have a lower limit of quantification of 0.11 to 0.31 mg/L and are linear between 0.3 and 10 mg/L, making them suitable for use in the cardiovascular clinical setting (308).

It is important to ensure that excess antigen is not present in the sample, as CRP concentrations of up to 600 mg/L can be observed in the serum. While the precision of CRP determination using a specific technique is generally acceptable, significant dispersion in inter-technique results still exists, even with the use of CRM 470. Closed systems tend to produce more consistent results, with CVs for nephelometry being slightly lower than those for turbidimetry. In terms of accuracy, some techniques may deviate from target values by 10-15%.

f. Performance characteristics:

Known since the 1930s and widely used as a diagnostic and monitoring tool, CRP belongs to the family of acute phase proteins. Its main advantage is its good sensitivity (71 to 100%) but its main drawback is its lack of specificity (66 to 85%), for the diagnosis of sepsis with thresholds varying from 40 to 100 mg/L (309,310).

g. Clinical application of CRP:

- **In diagnosis:**

CRP is a protein that is used as a marker of inflammation and is associated with the diagnosis of invasive bacterial diseases. However, there is conflicting data on the use of CRP for diagnostic purposes. Some studies argue that CRP is not specific enough to accurately differentiate between various sources of tissue destruction and that conclusive data has not been

consistently reproduced. Some criticisms of studies that support the use of CRP for diagnosis include small sample size study groups, inappropriate reference ranges and reporting of peak CRP levels instead of initial levels at presentation.

One way to get overcome the problem of specificity is to reason with decision thresholds rather than absolute value.

- **Bacterial vs nonbacterial etiology:**

It is generally accepted that CRP values above 60 or 80 mg/L are more suggestive of a bacterial origin than of any other etiology. However, here again, the real impact of CRP in the diagnostic process has been little studied, even though its measurement has become widespread. Moreover, despite early CRP synthesis after the initial stimulus, it should be kept in mind that in a patient seen rapidly after the onset of symptoms, the CRP may be initially low, which does not rule out the possibility of an early bacterial infection.

In practice however, apart from the diagnosis of appendicitis in abdominal pain, the added value of a CRP test in the emergency room is not obvious, especially in a febrile patient whose hyperthermia alone suggests that the test result will not be normal. It would be a delay management waiting for the results before undertaking more specific morphological and/or biological explorations.

- **LRTI and antibiotic stewardship:**

In one study, the CRP was found to be effective (area under the ROC curve of 0.83) compared to a clinical score in predicting the existence of pneumonia in a population of patients consulting an outpatient clinic for a recent onset cough (311). The authors suggest that for a threshold of 100 mg/L, CRP could be useful in deciding to perform a chest X-ray in this population. However, the small number of patients included (168 patients, of which only 20 had lung disease) is regrettable.

Conversely, in a randomized Danish study, whether or not general practitioners used a rapid test for CRP in the management of respiratory infections did not affect the rate of antibiotic prescription (43% in the CRP group versus 46% in the control group) (312).

- **In Pediatrics (313,314):**

CRP can also be used to differentiate between bacterial and viral infections in children under 6 years of age, with levels above 20 mg/L suggesting a bacterial infection and levels below 20 mg/L indicating a viral infection. For patients over 6 years of age, a decision threshold between 50 and 75 mg/L can be used for this purpose, particularly in the context of meningitis and pneumonia (315).

In neonatology, CRP levels above 20 mg/L at 12 hours of age may suggest the presence of an infection, while normal or low levels (below 5 mg/L at 24 hours of life) can help rule out infection and avoid unnecessary antibiotic therapy in newborns at risk.

However, normal or low CRP levels should be interpreted with caution in severe infections, particularly those caused by streptococcal B, as these newborns may not be able to mount an adequate acute phase response to fight the infection effectively.

- **Appendicitis (302):**

C-reactive protein (CRP) has been studied as a marker for postoperative complications and as a diagnostic tool for acute appendicitis. The sensitivity of CRP in studies ranges from 40-87% and specificity from 53-82%. Elevated CRP levels have been reported to be useful in the diagnosis of acute appendicitis after 12-24 hours of symptoms, especially when serial levels show an increase.

However, consistent data are lacking, and many studies report elevated CRP levels in patients with normal appendixes, as well as normal CRP levels in patients with gangrenous appendixes. A meta-analysis by Hallan et al. (316) exploring the accuracy of CRP in diagnosing appendicitis found a wide range of data for sensitivity and specificity and concluded that CRP is a test of medium diagnostic accuracy and is a little inferior to the total leukocyte count.

Therefore, CRP cannot accurately identify acute appendicitis, and should not be used to make management decisions in equivocal cases. There is no substitute for serial clinical examination during an observation period for abdominal pain.

- **Cholecystitis (302):**

In a study conducted by Juvonen (317), it was found that C-reactive protein (CRP) levels above 30 mg/L had a sensitivity of 78% in identifying patients with histologically diagnosed cholecystitis, while ultrasound had a sensitivity of 79%. Combining positive ultrasound findings with CRP levels above 30 mg/L resulted in a sensitivity of 97%. The study also found that CRP was a more sensitive marker than erythrocyte sedimentation rate (ESR), white blood cell count, or fever in identifying acute cholecystitis.

However, the study only included 18 patients with elevated CRP or ultrasound evidence suggestive of cholecystitis and no histologic evidence of disease, and also used peak CRP levels to calculate sensitivities, typically 2-5 days after hospital admission. Therefore, this study provides no compelling evidence that CRP would be useful in the emergency department, and routine CRP testing for cholecystitis cannot be recommended, as serial examinations and sonography provide sufficient diagnostic discrimination for this condition.

- **Pancreatitis (302):**

C-reactive protein (CRP) has been found to be a useful tool in the diagnosis and prediction of the severity of pancreatitis. Studies by Wilson et al.(318) have shown that high levels of CRP, with peak concentrations above 210 mg/L and 150 mg/L respectively, can discriminate between patients with clinically mild and severe pancreatitis with a high degree of sensitivity and specificity.

However, it is generally agreed upon that initial CRP values on admission to the emergency department are not a reliable marker of disease severity and have limited use in the diagnostic process.

- **PID (302):**

C-reactive protein (CRP) has been found by Lehtinen et al.(319) to be a useful tool in the diagnosis and prediction of the severity of Pelvic Inflammatory Disease (PID) but there is no significant difference between CRP levels in women who had endometritis only and those who had no PID.

The overall sensitivity and specificity of CRP in the diagnosis of PID is 74% and 67% respectively. CRP can be potentially useful for monitoring response to antibiotic therapy in patients who are not clinically improving. In the emergency department, there is no convincing data that CRP should influence patient disposition or antibiotic regimen in suspected PID.

- **UTI:**

C-reactive protein (CRP) has been found useful in urinary tract infections, with higher levels indicating pyelonephritis and antibiotic failures.

However, it is not useful in distinguishing between simple and complicated urinary tract infections in patients without clinical signs of acute pyelonephritis.

- **Meningitis:**

CRP has been found to accurately diagnose bacterial meningitis, but studies on its use to distinguish between bacterial and viral meningitis have inconclusive results.

CRP measurements in suspected meningitis should not influence patient management in the emergency department. Any clinical suspicion of meningitis should prompt early broad-spectrum antibiotic coverage.

- **Monitoring:**

CRP is also useful in monitoring the therapeutic response to antibiotic treatment in bacterial infections, as a rapid decrease (within 48 hours) in CRP concentrations can indicate the effectiveness of the treatment. In this case, serum CRP concentrations then decrease by a factor of about 2 per 24 hours until the value returns to normal. Regular monitoring of CRP levels can

help guide decisions on modifying antibiotic therapy if the CRP value remains high. CRP is not as useful in indicating complete healing from an infection.

- **Cardiac disease:**

In recent years, the use of highly sensitive methods has allowed for the exploration of very low concentrations of CRP (between 0.2 and 3 mg/L) in relation to cardiovascular disease. Chronic inflammation, which can be indicated by elevated CRP levels, is thought to play a role in the development and progression of atherosclerosis (320).

Epidemiological studies have found that increased CRP concentrations are associated with an increased risk of future coronary events (321). For example, a CRP level above 2.1 mg/L has been linked to a threefold increase in the risk of coronary events and a twofold increase in the risk of stroke. In addition, CRP is a predictive factor in patients with acute coronary disease (322). A CRP > 3.6 mg/L in a patient with unstable angina has a poor prognosis, with a twofold increase in the risk of coronary events.

The beneficial effect of aspirin in the prophylaxis of myocardial infarction appears to be directly related to circulating CRP levels. The treatment would be effective only in patients with a CRP > 2.1 mg/L. This application of CRP in cardiovascular risk requires the use of ultrasensitive techniques (308).

- **In prognosis:**

CRP and has limited abilities to predict outcome or distinguish sepsis from other inflammatory conditions. The 2003 international sepsis definitions conference recommended the incorporation of elevated levels of both CRP and PCT into the definition of sepsis. However, in the early part of the past decade, guidelines for the intensive "goal-directed" treatment of sepsis and septic shock began to rely on elevated lactate levels as a guide for therapy. Consequently, obtaining a lactate level when monitoring patients at risk of developing sepsis became standard practice (323).

Despite this, CRP is still used in conjunction with other biomarkers and clinical assessments to monitor and manage patients with sepsis. It is commonly accepted that the higher the CRP, the worse the outcome, this assertion is not based on solid scientific evidence (324). Thus, for the diagnosis of sepsis and for thresholds varying from 40 to 100 mg/L, the sensitivity of CRP widely ranges from 71 to 100% and the specificity from 66 to 85% depending on the study (302).

Conversely, as CRP is a very sensitive parameter, a patient with a negative CRP assay is unlikely to have a severe septic state, although here again the evidence is weak (325). It is also important to keep in mind that there can exist sepsis with normal CRP (326).

h. Pitfalls:

CRP testing has been applied to various disease entities commonly seen in the emergency department. CRP concentrations increase during most pathological processes causing an inflammatory response from the organism (except for systemic lupus): bacterial but also viral infections, polytrauma, immediate postoperative period, inflammatory systemic diseases, acute pancreatitis, acute appendicitis, etc. This lack of specificity makes it difficult to assess the real contribution of CRP measurement in practice, especially in emergency departments (302). In particular, in a febrile patient, hyperthermia itself is evidence of an inflammatory process and it is therefore rare that the CRP is normal. As such, CRP is not strictly speaking a marker of infection, but rather a reflection of the extent of the biological inflammatory syndrome (283,327).

i. Procalcitonin vs CRP:

A recent meta-analysis has observed that procalcitonin (PCT) levels are more accurate markers for bacterial infection than C-reactive protein (CRP) levels (310).

The kinetics of a prospective marker must be considered along with its sensitivity and specificity. PCT secretion begins within 4 hours after stimulation and peaks at 8 hours, clearing

when the insult is under control. PCT is stable in samples, and the assay is relatively easy to perform, with a moderate cost, and the result is available within 2 hours. In contrast, CRP secretion starts within 4–6 hours after stimulation and peaks only after 36 hours. The assay for determining CRP levels is easy to perform, often automated, and has a low cost.

PCT levels are more accurate markers for bacterial infection than CRP levels, both when differentiating bacterial infections from noninfective causes of inflammation and when differentiating bacterial infections from viral infections. While the meta-analysis is not without limitations, the results of this study provide valuable information for clinicians in their efforts to accurately identify and treat infections.

When considering which marker to use, it's important to note that PCT has been found to have higher sensitivity (77% vs 75%) and specificity (79% vs 67%) than CRP in differentiating bacterial septicaemia from noninfectious systemic inflammatory response syndrome. Additionally, PCT levels increase much earlier during an infectious process compared to CRP (4–12 hours vs 24–38 hours), allowing for earlier diagnosis. PCT can also be used as a prognostic marker, with levels correlating with bacterial load and infection severity. This is not the case for CRP. PCT has a plasma elimination half-life of 24–35 hours (compared to 48 hours for CRP), making daily measurement of PCT levels clinically significant. A daily drop of 30–50% in circulating PCT levels indicates that the infection is well-controlled. Multiple randomized controlled trials have shown that PCT measurements can guide the duration of antibiotic therapy in ICU patients with bacterial septicaemia. In these trials, antibiotics were discontinued in patients who showed clinical resolution plus either an 80% drop in PCT from peak level or a drop in PCT to below 0.5 ng/mL. Patients in the PCT arm had improved mortality rates, shorter hospital stays, and decreased antibiotic use. However, it's important to note that PCT is substantially more expensive than CRP (328).

Indications:

CRP:

- Differentiating likely bacterial from non-bacterial etiology in Type II and Type III exacerbations of chronic obstructive airway disease (COPD)
- Cases of acute respiratory illness when diagnosing community-acquired pneumonia (CAP) is uncertain

PCT:

- Differentiating systemic bacterial infection from noninfectious systemic inflammatory response syndrome (SIRS) as a diagnostic marker
- Ascertaining the severity of illness of bacterial sepsis as a prognostic marker
- Monitoring response to therapy of systemic bacterial infections
- Guiding discontinuation of antibiotics during systemic bacterial infections
- Excluding a bacterial etiology in cases of CAP and acute exacerbations of COPD if PCT is < 0.25 ng/mL

	CRP	PCT
Strengths	• Cheaper • Levels not influenced by: • renal disease • neutropenia • More likely to be raised by invasive fungal infections (in a patient with raised CRP and normal to low PCT: consider invasive fungal infection)	• Expensive • Improved sensitivity and specificity • Shorter induction time and elimination half-life • Diagnostic and prognostic marker • Can be used to monitor response to therapy and shorten antibiotic therapy • Levels not raised by: • viral infections • most autoimmune diseases • Transplant rejection • Allergic reactions
Limitations	• Diagnostic marker only • Non-bacterial causes of elevated levels: o trauma o surgery o most autoimmune conditions	• Levels not raised by local bacterial infections • Non-bacterial causes of elevated levels: • severe trauma • surgery, especially abdominal surgery • severe burns • prolonged cardiogenic shock • severe pancreatitis • severe renal insufficiency • severe liver cirrhosis • acute or chronic viral hepatitis • newborns (can still be used in this population as long as value is interpreted according to reference ranges) • following administration of anti-lymphocyte globulin, anti-CD3 or OKT-3 antibodies • heat stroke • some autoimmune diseases: Kawasaki syndrome, Goodpasture's syndrome, Wegener's granulomatosis, anti-neutrophil antibody positive vasculitis • paraneoplastic syndromes severe rhabdomyolysis

j. Key takeaways:

- C-reactive protein is a marker of acute inflammation.
- CRP is a pentameric protein synthesized by hepatocytes under the influence of IL-6.
- CRP functions include activation of the complement system, stimulation of opsonization, and stimulation of phagocytosis.
- In healthy individuals, CRP levels are normally less than 1 mg/L, and levels above 10 mg/dL may indicate infection, inflammation or tissue damage.
- CRP has been used as a screening test for inflammation, a biomarker of disease activity, and a predictive or prognostic tool for various acute and chronic diseases.
- Serial CRP measurements may be useful for monitoring a patient's response to medical intervention.
- CRP is a protein used as a marker of inflammation, but there is conflicting data on its use for diagnostic purposes.
- CRP is not specific for bacterial infections but decision thresholds, rather than absolute values, may help to overcome the problem of specificity.
- CRP can be used to differentiate between bacterial and viral infections in children with levels above 20 mg/L and a level above 60-80 mg/L in adults.
- In neonates, CRP levels above 20 mg/L at 12 hours of age may suggest the presence of an infection, while normal or low levels (below 5 mg/L at 24 hours of life) can help rule out infection and avoid unnecessary antibiotic therapy in newborns at risk.
- CRP can be used for the diagnosis of pneumonia, appendicitis, cholecystitis, meningitis, PID and others but with varying decision thresholds and varying sensitivity and specificity.

- In practice, the added value of a CRP test in the emergency room is not obvious, especially in a febrile patient whose hyperthermia alone suggests that the test result will not be normal.

13.9. Summary on S100B protein:

a. Introduction:

Traumatic brain injury (TBI) is a major public health issue that affects millions of people globally, with an incidence estimated between 64 to 71 million cases and a rate of 262 cases per 100,000 in Europe. TBI is a leading cause of emergency department admissions, accounting for 5% to 8% of all visits. While most patients with TBI recover within a short period, up to 15% of them may have abnormal findings on cranial computed tomography (CT) scans, which can lead to long-term disability or death due to intracranial complications. In addition, up to 1% may require neurosurgical intervention (329).

Mild TBI (mTBI) is the most common form of TBI, accounting for up to 94.5% of all TBI cases. It is defined as a TBI with a Glasgow Coma Scale score of 13 to 15. However, despite the prevalence of mTBI, cranial CT is still commonly used as a diagnostic tool, with up to 50% of patients receiving a head CT. Unfortunately, 80% to 99.5% of these scans show normal findings, leading to increased waiting times, length of stay, radiation exposure, and costs (330).

To address this issue, there is a need for biomarkers that can accurately identify TBI patients who do not require a CT scan. One such biomarker is S100B, a tumor marker protein that is commonly used to monitor patients with malignant melanoma. S100B has shown promise as a useful tool for improving clinical decision-making in the management of TBI patients, particularly as a pre-CT screening test for mTBI. By identifying patients who do not require a CT scan, S100B could help reduce costs, ease ED overcrowding, and minimize radiation exposure for patients with mTBI. Despite its potential benefits, however, S100B has not yet been widely implemented into standard care.

b. The problem with clinical screening tools:

Guidelines have been created to help doctors risk-stratify patients with TBI in the emergency department (ED) and identify who can be safely discharged versus who needs a cranial computed tomography (CCT) scan. These guidelines rely on clinical assessment of specific risk factors that can be recognized from a patient's history, symptoms, and physical examination, such as Glasgow Coma Scale (GCS), headache, vomiting, deficits in short-term memory, seizures, or loss of consciousness (LOC).

These guidelines include the Canadian CT Head Rule (CCHR) (331), New Orleans Criteria (NOC) (332), the CT in Head Injury Patients (CHIP) rule (333), and the National Institute for Health and Care Excellence (NICE) guidelines (334).

A recent study compared the performance of these four guidelines in patients with minor head injuries (335). The study found that the NICE guideline had the lowest sensitivity for an intracranial traumatic CT finding (73%) of the four criteria, but it was also the most specific (61%). Conversely, the NOC had the highest sensitivity (99%) but had extremely low specificity (4%). Sensitivity and specificity for a lesion potentially requiring neurosurgical management ranged from 85% (NICE) to 100% (NOC), and 4% (NOC) to 59% (NICE), respectively.

Although these guidelines help physicians identify patients who require a CCT scan versus those who can be discharged safely, the clinical presentation of TBI does not always correlate with its severity and the sensitivity and specificity of these guidelines were generally inadequate, and each had its strengths and weaknesses.

c. Physiology and ptochology of S100b:

The S100-β protein is a dimeric holoprotein that belongs to the S100 protein family. It was discovered in 1965 by Moore and is soluble in a saturated 100% solution of ammonium sulfate at neutral pH (336). The protein has a low molecular weight of approximately 21 kDa (10.5 kD for each monomer). Initially, the protein was thought to be specific to neuronal tissue, as it is mainly expressed in glial and Schwann cells. However, subsequent studies have shown

that the protein is widely distributed throughout brain tissue and is present at very low levels in histiocytes, adipocytes, skin dendritic cells, and normal melanocytes (337).

The S100-β protein consists of all dimers that have at least one β-subunit in their structure (ββ and αβ), among the two (α or β) found in S100 proteins. The β-subunit is highly expressed in the brain and is localized to glial cells and Schwann sheath cells. Within glial cells, αβ and ββ dimers coexist, while Schwann sheath cells express only the homodimer ββ. The β-subunit is encoded by chromosome 21 at the q22.2-22.3 region, while the genes for the majority of S100 family proteins are located on chromosome 1 at the 1q21 region. The brain specificity of the S100-β protein (or at least its neuro-selectivity) is related to the β-subunit, which is mainly synthesized by astrocytes.

The S100-β protein is able to bind calcium atoms via "main EF" type polypeptide domains, which are helix-loop-helix structures similar to those found in other intracytosolic calcium-binding proteins such as calmodulin and troponin (338). Dimerization and oligomerization seem to be important for the biological activity of the protein. Upon calcium binding, conformational changes occur in the protein to enable it to recognize its target proteins/receptors (e.g., RAGE). While the β-subunit is highly expressed in the brain and is localized to glial cells and Schwann sheath cells, about 5% of the protein is present at the extracellular level, allowing it to exert intercellular biological actions.

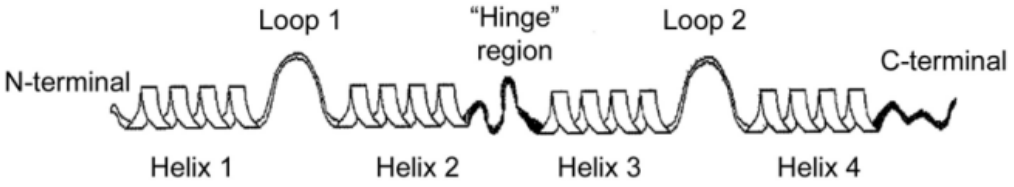


Figure 156: Helix-loop-helix arrangement of S100B protein.

Function:

The S100B protein has been shown to have both intracellular and extracellular effects in animal experimental studies (339). It plays a role in the regulation of the structural organization of cells by interacting with various proteins involved in the cytoskeleton, such as tubulin and tau, as well as glial fibrillary acidic protein (GFAP). At the extracellular level, S100B functions as a signal transducer, transmitting signals from receptors on the cell surface to target molecules within the cell. Some S100B proteins bind to the receptor for advanced glycation end products (RAGE), activating various intracellular signaling pathways. S100B has a paracrine effect that promotes the proliferation and regeneration of glial cells, as well as the growth and survival of neurons in vitro and in vivo.

S100B protein is selectively synthesized by certain cells in brain tissue, astroglial cells. It participates physiologically in the regulation of intracellular free calcium levels, and has neurotrophic activity towards neurons bordered by glial cells.

S100B is essential for the physiological development and maintenance of central nervous tissue and supporting glial tissue by exerting effects on the growth, differentiation, cell proliferation, and apoptosis of brain cells. Its effects on brain cells depend on the target cells and local concentration and can include regulation of phosphorylation mediated by protein kinases, modulation of enzymatic activation, maintenance of cell shape and motility, influence on signal transduction pathways, and promotion of calcium homeostasis.

An increase in the concentration of S100B protein in biological fluids in human pathology can have two origins (340). It can result from gene overexpression, most often of tumor origin, whether neurological (glioma, glioblastoma, neurinoma) or extracerebral (malignant melanoma). Alternatively, it can result from the release of intracellular S100B protein following cerebral cell lysis (e.g., head trauma, intracranial hemorrhage, stroke).

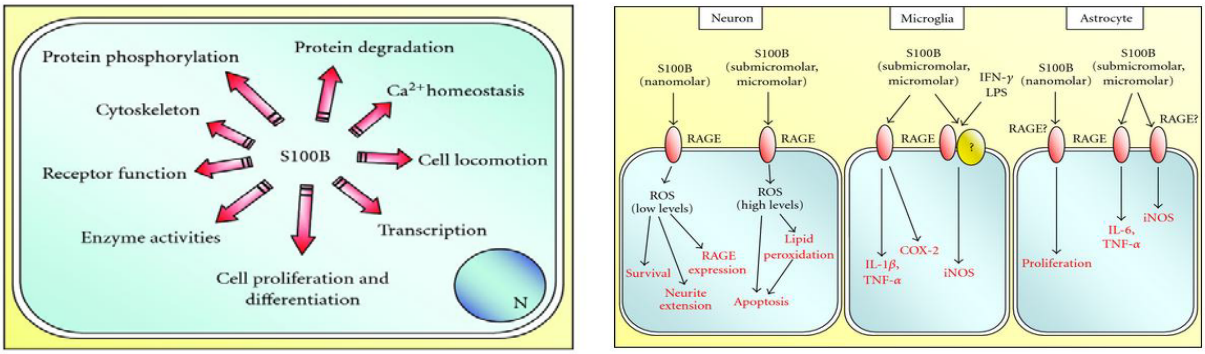


Figure 157: Schematic representation of intracellular (Left) and extracellular (Right) regulatory effects of S100B.

d. Assay technique:

S100B protein can be determined in various biological samples, including cerebrospinal fluid (CSF), plasma or serum, and urine. Samples should be collected in dry tubes, and if necessary, plasma or serum should be obtained after careful and prolonged centrifugation of the blood sample. Samples can be stored at +4°C for 48 hours, at -20°C for 3 months, and at -80°C for several years without affecting the analytical determination. It is worth noting that hemolysis of blood samples does not currently affect available assays (341).

In order to specifically determine S100B protein, immunometric techniques such as enzyme-linked immunosorbent assay (ELISA) are required. These techniques utilize a mixture of monoclonal antibodies specific to the β subunit. ELISA methods such as Liaison®, and Elecsys®, which are sensitive and widely available on immunochemistry analyzers, can detect concentrations as low as 20 ng/l. However, solid-phase ELISA is not suitable for rapid and punctual determination of the biomarker in emergency medical situations.

The threshold for normal values (or the cut-off for pathological values) varies between the available assay methodologies due to the differences in the anti-β antibody used by each technique. Although the values obtained by the methods differ significantly, they are correlated, and appear to be equally useful for monitoring the evolution of the marker in the same patient.

However, it is important to note that the results are not transferable between the available automated methods currently available.

Table LII: Examples of S100B assays (342).

Assay	Type	Capture Antibody	Tracer Antibody	Lower limit of detection (µg/L)	Measuring Range (µg/L)	Calibration
LIAISON® Sangtec®100	LIA	Paramagnetic particle coated 2 anti-S100B MoAbs	Isoluminol derivate-labeled anti-S100B MoAb	0.02	0.02-30	Gravimetrically determined concentration of purified bovine S100A1B and S100BB
Elecsys®S100 Sangtec®100	ECLIA	Biotinylated anti-S100B MoAb bound to streptavidin-coated microparticle	Ruthenium complex bound anti-S100B MoAb	0.005	0.005-39	Recombinant S100BB concentration of purified bovine S100A1B and S100BB
Sangtec®100 ELISA	ELISA	2 anti-S100B MoAbs bound to solid phase	anti-S100B MoAb conjugated with HRP	0.02	0.02-5	Gravimetrically determined concentration of purified bovine S100A1B and S100BB
CanAg S100 EIA	EIA	Biotinylated anti-S100B MoAb bound to streptavidin-coated well	anti-S100B MoAb conjugated with HRP	0.01	0.1-3.5	Recombinant S100BB concentration of purified bovine S100A1B and S100BB

e. S100b kinetics:

The concentration of S100B protein in biological media, particularly in the context of acute brain injury, can be significantly increased. For instance, after an intracranial hemorrhage, S100B concentrations may be 50 to 100 times higher than the normal physiological threshold value in the cerebrospinal fluid or blood. In this case, S100B levels tend to rise within 30 minutes of the injury due to its release from astroglia cells. However, the protein's relatively short half-life of 60-120 minutes limits its usefulness as a biomarker to patients who present within 3 hours of the injury (343,344).

S100B is eliminated through the kidneys. This has led some researchers to suggest using regular measurements of S100B protein in urine as a way of monitoring neurological disorders, particularly in newborns.

f. Normal and critical findings:

S100B protein is present in cerebrospinal fluid (CSF) at concentrations ranging between 1 and 2 µg/L, as it is eliminated from the brain following intra- or extracellular actions.

The concentrations of S100B in plasma are approximately 10 times lower than those in the CSF, ranging from 0.02 to 0.15 µg/L. The median concentration of S100B in healthy adults' blood is 0.05 µg/L, which is independent of age and gender.

The reference levels for S100B are also independent of age and gender, with a cut-off value of $\leq$ 0.10 µg/L being considered normal (within the 95th percentile). Reference levels for children are slightly higher than those for adults (345).

g. Performance characteristics:

The use of S100B testing as a pre-head computed tomography (CT) screening test has been included in several guidelines due to its high negative predictive value (NPV) of 99% for normal CT findings. At a clinical cutoff of 0.1 µg/l but its specificity is as low as 30-50% which is why it is only recommended as a “rule-out” test (346).

h. The clinical application of S100b:

- **In diagnosis:**

The interest of the S100B protein in clinical biology is linked to its significant increase in the blood following acute brain tissue injury, this injury can be of vascular origin (intracranial hemorrhage, ischemic stroke) or traumatic.

Thus, plasma S100B protein concentration is significantly increased in subjects with major traumatic brain injury, as well as in the majority of moderate or minor head injuries associated with brain contusion, confirming the diagnostic value of this biomarker. The most important contribution of S100-β protein in TBI should be the decision support in minor or moderate TBI to reduce the number of CT scans performed (347-350).

Finally, and entirely independent of the cerebral pathophysiological context, the synthesis of S100B protein by malignant melanocytes makes it of interest in the biological monitoring of malignant melanoma.

- **Screening for contusion in mTBI:**

Indeed, the presence of S100-β protein throughout the brain tissue under physiological conditions makes it a good marker of diffuse intracerebral injury, e.g. in relation to a concussion (351). In a German study condcucted by Biberthaler et al, 1309 subjects were included: 93 for whom the diagnosis of mTBI was made on the basis of head CT scan, and 1216 for whom the diagnosis was finally excluded (negative CT scan). Considering the CT scan as the gold standard for the diagnosis of TBI, the authors concluded that a low plasma concentration of S100-β protein has the almost absolute specificity for the exclusion of brain lesions secondary to TBI on CT scans, making it an excellent triage marker with a negative predictive value (NPV) close to 100%. Thus, an increased plasma concentration of S100-β protein in the first hours after the trauma would therefore allow, in an ED, a triage of patients suffering from cerebral contusion and therefore would be kept under medical observation or require hospitalization. Conversely, a

plasma concentration of S100-β protein remaining within the usual values indicates the absence of cerebral contusion and therefore allows not to perform a brain CT for this patient population. This original study by Biberthaler et al (351) has been confirmed in recent years by three other studies performed in France, by the hospital centers of Clermont-Ferrand and Marseille (352) and Bordeaux (353), and by a multicenter STIC-S100 study which results were in total coherence with the previous studies (354).

- **The Scandinavian Guidelines:**

The Scandinavian Guidelines for Initial Management of Minimal, Mild, and Moderate Head Injuries in Adults were developed to guide the management of head injuries using S100B protein in the Scandinavian emergency care setting. These guidelines prioritize the identification of patients who need neurosurgical or medical intervention, with identification of traumatic findings on CT scans being a secondary goal.

The evidence used to inform the guidelines was of reasonable quality, but many risk factors were not included due to poor predictive ability or high prevalence in the head injury population. These risk factors included amnesia, injury mechanisms, intoxication, trauma above the clavicles, nausea, vertigo, and headache. Older age was not included as a risk factor due to its moderate predictive ability and the potential for a high increase in CT scans in this population, but age ≥65 years in combination with antiplatelet medication was included as a risk factor due to the potential for increased complications after head injury in this group.

Recommendations for discharge instructions and observation routines were based on consensus. These guidelines have been validated in a retrospective study and have been shown to reduce the need for CT scans and costs. They have been approved by stakeholders and the working group (355).

A retrospective validation study conducted by Undén et al. found that the use of the Scandinavian guidelines with S100B had a sensitivity of 97% and a specificity of 34% for the detection of acute traumatic intracranial lesions and would result in a 32% reduction in CT scans.

This is the first time that S100B has been introduced into clinical practice guidelines, and it has demonstrated good ability to predict the absence of CT pathology and neurosurgical intervention when used with a low cutoff of 0.10 µg/l (355).

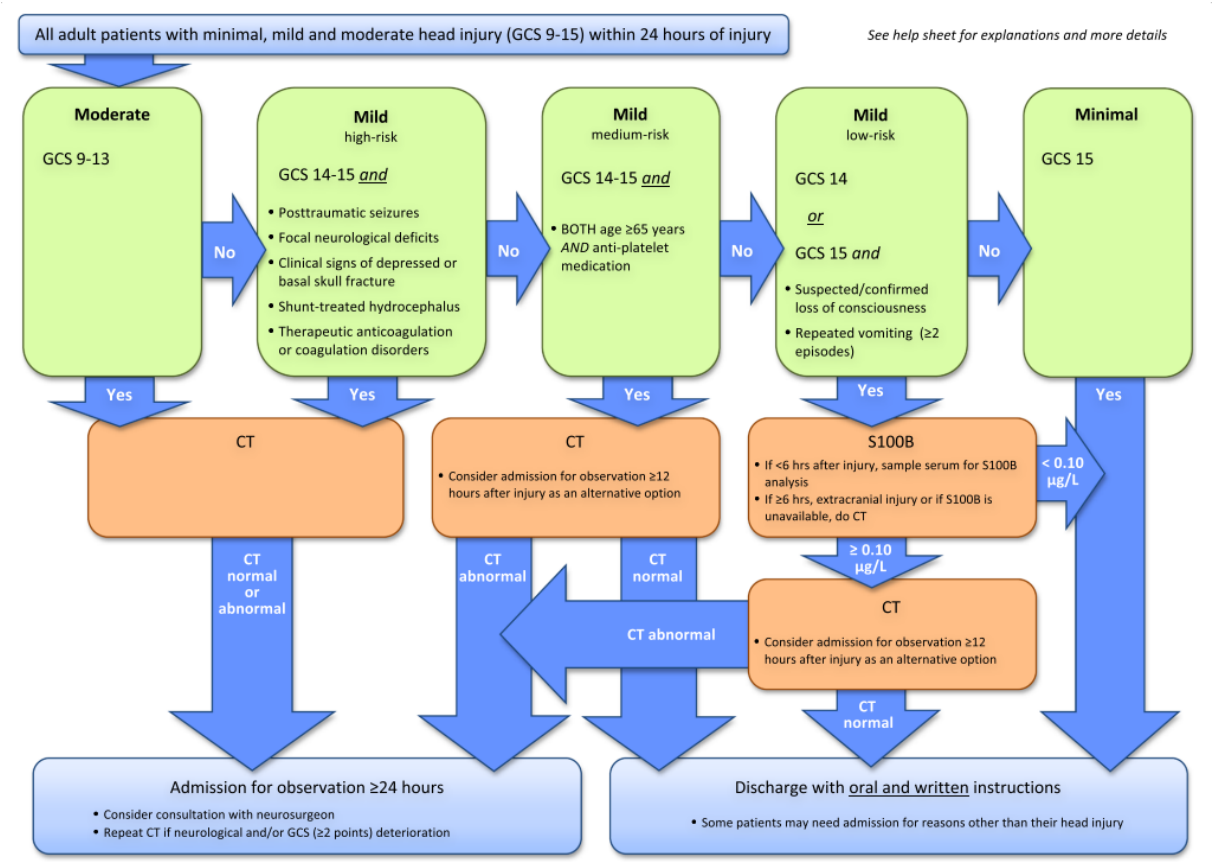


Figure 158: Flowchart of the updated Scandinavian guidelines for acute management of adult patients with minimal, mild or moderate head trauma (355).

In summary, all the international studies demonstrate the importance of early determination of the plasma concentration of S100-β protein and its integration among the other diagnostic elements (imaging in particular) to assess the severity of TBI and its short and long-term evolution.

- **In prognosis:**

One potential benefit of utilizing the plasma S100-β protein assay is its ability to predict the complications of traumatic brain injury (TBI) as well as the medical and social implications of cerebral contusion. Several studies have demonstrated a correlation between S100-β protein levels in plasma following a TBI and the clinical outcome of the patient (356,357). Increased S100-β protein is an excellent predictive marker of patient death or survival with major irreversible complications (358).

Furthermore, variations in plasma S100B following major surgical procedures such as cardiac surgery (359) can also serve as a biological marker of brain injury. This suggests that S100B could be utilized as a biomarker for predicting patient neurological outcomes after cardiac surgery (360,361).

The potential value of S100B protein as a predictive biomarker for patient outcomes, specifically in terms of survival following cardiac arrest, is also noteworthy. A small or moderate increase (<0.80 µg/l, using the Elecsys method®) in plasma S100B protein levels within minutes of cardiac arrest after resuscitation is associated with a favorable outcome. Conversely, low plasma S100B protein concentrations (with a steady decrease within 24 to 48 hours) appear to be predictive of a favorable outcome of the cardiac arrest (362).

i. Limitations of the biomarker:

It is important to be aware that values tend to be higher in healthy black subjects compared to Caucasian subjects due to increased gene expression of the protein in melanocytes. There is no significant difference in values between genders or age groups (363).

A study suggests that alcohol consumption may be a contributing factor to increased levels of the S100-β protein (364), which can complicate neurological deterioration in traumatic brain injury patients. This is especially interesting since 30 to 50% of TBI cases are associated with alcoholic intoxication (365,366).

S100B protein can be released in other contexts of brain injury, thus it has low specificity. Several studies have shown increased S100B protein in the subjects with stroke, epilepsy, meningeal hemorrhage, infectious meningoencephalitis, bacterial or viral meningitis, mental

retardation, or cerebral infirmity, or even in the amniotic fluid of fetuses with neurological abnormalities (367).

It is also possible that by abnormal perfusion of brain tissue, extracerebral pathologies may contribute to the systemic increase of S100B protein (339). An increase in plasma S100B protein has been observed during experimental hepatic, intestinal or renal ischemia/reperfusion and in patients admitted to the ICU for multiorgan failure (368).

Table LIII: Variations of S100B levels in the blood in different physiological/pathological conditions (369).

Condition	Variation in S100b
Intrauterine growth retard	Increase
Neonatal intraventricular hemorrhage	Increase
Acute brain injury	Increase
Major cardiac events	Increase
Brain metastases	Increase
Melanoma	Increase
Breast cancer	Increase
Multiple sclerosis	Increase
Neuromyelitis Optica	Increase
Alzheimer disease	Decrease
Amyotrophic lateral sclerosis	Decrease
Parkinson disease	Increase
Schizophrenia	Increase
Depressive/bipolar disorders	Increase
Obesity	Increase
Vigorous physical activity	Increase
Prolonged labor	Increase

j. Key takeaways:

- Traumatic brain injury (TBI) affects millions globally and is a leading cause of emergency department admissions.
- Mild TBI is the most common form of TBI, but cranial CT scans are still commonly used to rule out intracranial pathology, leading to increased costs and radiation exposure.

- Clinical guidelines for TBI risk-stratification are available, but their sensitivity and specificity are generally inadequate.
- The S100B protein is present in biological fluids and increases significantly in concentration after acute brain tissue injury.
- The β-subunit of S100B is mainly synthesized by astrocytes making it specific to neuronal tissue.
- S100B is a biomarker that could help identify low risk group of mTBI patients, thus reducing the number of CT scans by 30% and the costs and radiation exposure that comes with it.
- The diagnostic, prognostic and/or follow-up value of S100B protein after acute brain injury has been demonstrated by numerous experimental and clinical studies.
- S100B levels can predict the patient's short, medium, and long-term outcomes.
- The S100B test can be used to monitor the progression of severe traumatic brain injury.
- S100B levels are correlated with the severity of brain injury.
- S100B levels can indicate secondary neurological deterioration in patients with severe TBI.
- S100B levels tend to rise within 30 minutes of brain injury with a short half-life of 60-120 minutes, limiting its usefulness as it has to be measured within 3 hours of the injury.
- Reference levels for S100B are independent of age and gender, with a cut-off value of $\leq$ 0.10 µg/L considered normal.
- S100B testing has a high negative predictive value (99%) for the exclusion of intracranial lesions.

- Immunometric techniques such as ELISA are required to specifically determine S100B protein levels.
- A low plasma concentration of S100B protein has almost absolute specificity for the exclusion of brain lesions secondary to TBI on CT scans, making it an excellent triage marker: NPV close to 100%.
- S100B has the potential to improve clinical decision-making in the management of TBI patients, but has not yet been widely implemented into standard care.
- The Scandinavian Guidelines for Initial Management of Minimal, Mild, and Moderate Head Injuries in Adults are the first to incorporate the use of the biomarker S100B for mild traumatic brain injury management.
- S100B is present at very low levels in histiocytes, adipocytes, skin dendritic cells, and melanocytes.
- The S100B protein is specific to neuronal tissue but not specific to traumatic brain injury and can be released in other intracerebral and extracerebral pathologies. Therefore, it is crucial to interpret S100B protein levels in the context of the clinical situation.
- S100B is a useful tool for managing patients with malignant melanoma.
- The synthesis of S100B protein by malignant melanocytes makes it of interest in the biological monitoring of malignant melanoma.
- S100B is to mTBI what D dimer is to VTE, both have high NPV and both can only be used to rule out their respective pathologies.

13.10. Summary:

Table LIV: Recap on the commonly used biomarkers in the emergency department with indications and limitations.

Biomarker	Pathophysiology	Common clinical setting	Kinetics	Cut-off ranges	Rule-in	Caveats in ruling-in (False high, impaired specificity)	Rule-out	Caveats in ruling-out (false low, impaired sensitivity)
Troponin	Protein complex regulating myocardial contraction, released during cardiac necrosis. Cardio specific.	Suspected acute myocardial infarction (AMI) in patients presenting with chest pain and/or symptoms suggesting an anginal origin. Prognostic marker, levels	Can be detected 4 to 6 hours after the onset of necrosis and until 6 days after the event. Hypersensitive troponins allow detection	hs-cTnT <14 ng/l low risk, 14-52 ng/l intermediate, >52 ng/l high risk. But generally dependent on the laboratory. Value greater than the 99th percentile of a reference population with a coefficient of variation < 10%.	AMI	Myocardial wall stretch and cell necrosis of nonischemic origin (e.g.,Takotsubo, pulmonary embolism, myocarditis), demand ischemia (e.g. sepsis) persistently elevated level up to 14d, renal failure.	Consider alternative diagnosis to AMI, conservative therapy of symptoms and cardiovascular risk factors.	Time-lag of 1 to 3 h, rarely circulating antibodies.

		correlated with severity of MI.	as early as the 3rd hour.					
D dimer	Degradation product of fibrin. High levels in the event of a blood clot.	Suspicion of venous thromboembolic disease (VTE). Low or intermediate pre-test probability of pulmonary embolism as determined by the Geneva or Wells score.	Sensitivity 95%. Specificity 40% with ELISA techniques.	<500 µg/l: no imaging if low or intermediate (unlikely) clinical probability for VTE Imaging recommended if ≥500 µg/l independent of Ddimer if high VTE probability Patients >50 years: consider age-adapted cutoff ranges: cut-off = age x 10	Anticoagulation if VTE ruled in by imaging.	Low specificity. Age ≥80 years, all conditions associated with enhanced fibrin-turnover: e.g., systemic inflammation, vascular dissections, infection, trauma, surgery, cancer, pregnancy, inpatients. Unknown performance in patients on anticoagulants.	Consider alternative diagnosis to VTE, e.g., aortic dissection.	High clinical probability for VTE, upper-extremity deep vein thrombosis, pregnancy.
BNP/NT pro-	Hormones secreted by	Dyspnea and / or suspected	Immediately secreted,	BNP: <100 ng/l AHF unlikely, 100-400	AHF	Increased in elderly subjects,	Consider alternative	Obesity, flash pulmonary

BNP	ventricular myocytes during their stretching.	acute heart failure (AHF). Etiological diagnosis of acute dyspnea in the ED, in patients for whom an obvious etiology is ruled out: in practice, patients with CF or CRF, more broadly, elderly subjects with poor and non-specific presentation.	half-life of 90 to 120 minutes.	ng/l intermediate, >400 ng/l AHF likely NT-pro BNP: <300 ng/l AHF unlikely, 3 age-dependent cut-offs for rule-in of AHF (450 ng/l if <50 years, 900 ng/l between 50 and 75 years, 1800 ng/l if > 75 years)		women. Decreased in obese patients. Moderate elevation in anemia, arrhythmia due to atrial fibrillation, hypertension, ACS, right heart failure (pulmonary embolism), septic shock, acute renal failure, pulmonary hypertension, stroke.	diagnosis to AHF.	oedema, mitral valve disease, pericardial tamponade or constriction, BNP: limited stability of analyte
Procal citoni	Prohormone of calcitonin	Antibiotic Stewardship in	Can be detected by	Sepsis: < 0.05 ng/ml normal. < 0.5	Prescribe antibiotics in	New-borns, children, severe	Evaluate alternative	Early-course (24h) ,

n	produced by the C cells of the thyroid gland and intracellularly cleaved by proteolytic e nzymes. Absence of proteolysis during sepsis and release into plasma.	Infections , namely of the respiratory tract in ED and hospital ward antibiotic stewardship; Infectious etiology of SIRS in the ICU Meningitis with negative direct examination.	the 4th hour Half-life of 20 to 24 hours	ng/ml unlikely but localized bacterial infection possible. [0.5-2[sepsis possible. [2-10[sepsis likely. >10 severe sepsis or shock. Lower respiratory tract infections < 0.1ng/ml no bacterial infection. < 0.25 bacterial infection unlikely. > 0.25 probable bacterial infection and antibiotic treatment recommended.	LRTI in the ED and hospital - ward setting. In the ICU setting escalation of antibiotic therapy based on serial PCT measurement not recommended.	trauma, surgery and systemic inflammation, heat stroke, DRESS, MAS, malaria, medullary thyroid cancer and paraneoplastic hormone production.	diagnosis to systemic bacterial infection, discontinue antibiotics in LRTI and sepsis.	subacute, and localised infections, insensitive assay, should be applied in conjunction to clinical improvement
CRP	Inflammation, acute-phase protein.	Symptoms consistent with sepsis or	Synthesis 4 to 6 hours after the	Between 40 and 100 mg/l. > 60 to 80 mg/l likely bacterial	Inflammation.	Viral infections, polytrauma, immediate post-	SIRS	Time-lag to peak response (-72h),

		inflammatory disease. Abdominal pain, suspicion of acute appendicitis.	beginning of the inflammation. Half-life of 20 h. Sensitivity 71 to 100 %. Specificity 66 to 85 %.	origin.		operative, inflammatory system disease...		steroids, hepatic failure
S100B	Calcium-binding protein synthesized by astrocytes, its release in CSF and serum reflects injury to the brain and increased permeability of the blood brain barrier.	Screening for intracranial pathology in patients with mild TBI.	Half-life of 60 to 120min. secondary peaks from subsequent injuries.	0,10 µg/L	TBI and intracranial lesions that lead to blood-brain-barrier rupture in general.	Stroke, epilepsy, meningeal hemorrhage, infectious meningoencephalitis, bacterial or viral meningitis, melanoma.	Rule out an intracranial injury.	Highly influenced by the time from trauma

13.11. Summary on POCT:

a. Introduction:

Bedside biology can be traced back to the early days of medicine when our predecessor's identified glycosuria in diabetic patients by observing the attraction of flies to their urine around 1500 BC, it has evolved into the modern discipline of medical biology. Born out of Charles Darwin's work approximately 200 years ago, medical biology is often defined as the field of pharmacology and medicine that performs and interprets tests on human fluids or samples to characterize or monitor a disease, making it a fundamental element of diagnosis. In fact, over 60% of medical diagnoses rely on medical biology testing (370,371), which oftentimes has a radical impact on patient management.

To ensure timely and accurate test results, close collaboration between healthcare professionals and laboratory biologists is crucial in medical biology testing. However, even with a collaborative effort, medical laboratories may not always be able to provide results within the required timeframe, which can significantly impact patients. To address this issue, POCT has become increasingly important in recent years. POCT offers benefits such as availability, speed, flexibility, and adaptability, resulting in faster medical decisions on treatments, reduced hospital stays, earlier diagnosis and appropriate treatment, quicker referrals, and reduced waiting times in emergency departments. It can also lead to lower morbidity and mortality rates, making it an attractive option for emergency diagnostic strategies.

However, POCT has its limitations. One of the main drawbacks is the potential for lower accuracy and increased variability in test results between different devices or operators when compared to traditional laboratory testing methods. Another limitation is related to the availability and maintenance of equipment, as well as the need for trained personnel to perform the tests. Additionally, cost-effectiveness of POCT can be a concern, as individual tests or devices may be more expensive than those used in centralized laboratory settings. However, if

the potential for avoiding unnecessary hospital admissions, shortening the LOS and avoiding overcrowding in the ED is taken into account, the overall healthcare costs when using POCT can be lower.

As medical biology plays a crucial role in patient care, and with the increasing importance of POCT, it is essential to study its developments and evolution, particularly in the field of emergency medicine. However, despite its potential to revolutionize emergency diagnostic strategies and improve patient outcomes, careful consideration of its limitations is necessary to ensure that patient care is not compromised.

b. Definition:

Despite the widespread use of POCT, there has not been a consensus over a uniform definition for this type of testing. Instead, various terms such as near-patient laboratory testing, remote rapid testing, bedside testing, and decentralized testing are used to describe similar concepts, but POCT has emerged as the most commonly used term worldwide.

Generally, POCT is a method of performing medical tests using laboratory equipment located outside of the traditional laboratory setting, such as at the patient's bedside. This technique provides fast results, as the sample is not transported, the analytic process is simplified, and laboratory staff may not be required. One significant advantage of POCT over conventional methods is the shorter sample processing time. POCT achieves this by usually using whole blood and minimizing the sample transportation and preparation time. The results of POCT can be used for screening, monitoring, or diagnosis in various settings, such as hospitals, emergency departments, private clinics, ambulances, general practitioner’s office, during public health campaigns and even in patients' homes for self-monitoring.

Other definitions have been proposed (372):

- The Guideline of the German Medical Association defines POCT as a feasible option for use in hospitals only when the POCT is utilized as a singular determination with immediate consequences impacting treatment. POCT is not intended for series of regular, possibly automated tests, carried out close to the patient. The German Medical Association defines POCT methods with the term "unit-use reagents," which excludes more complex devices that do not operate with unit-use reagents from the POCT concept for rapid near-patient diagnostics. It is the operator's responsibility to check conventional laboratory test equipment in compliance with the regulations of the German Medical Association to assure quality control for optimal patient safety.
- The Laboratory Medicine Practice Guidelines introduced by the National Academy of Clinical Biochemistry (NACB) defines POCT as clinical laboratory testing conducted close to the site of patient care, typically by clinical personnel whose primary training is not in the clinical laboratory sciences, or by patients (self-testing). POCT refers to any testing performed outside of the traditional, core, or central laboratory.
- The College of American Pathologists (CAP) applies various definitions of POCT, depending on geography (hospital, outpatient services, etc.), function (in hospital intensive care units, outpatient departments, etc.), technology (simple hand-held devices, complex multi-parameter analyzers, etc.), or operational context (nurse, patient, etc. as user).
- O'Kelly et al. provide a pragmatic definition of POCT, defining it as a quality-assured pathology service that utilizes analytical devices (including test kits and analyzers, such as blood gas and critical care analyzers and meters for glucose, urinalysis, and other metabolites) provided near to the patient rather than in the traditional environment of a clinical laboratory.

Overall, the most important characteristics attributed to POCT are summarized here:

- Testing is performed in the direct proximity of the patient.

- Tests are performed outside of a central laboratory.
- Little or no sample preparation, i.e., mostly whole blood is used as test material.
- No pipetting steps.
- "Ready-to-use" reagents, e.g., as cassettes or single-use devices.
- Special devices intended or used exclusively for single sample measurement.
- No pertinent medical technical skill needed for operating the measuring device.
- Results available quickly.
- Results lead to a rapid diagnosis or have consequences for treatment.

c. Regulatory aspects of POCT:

Accreditation is a crucial process for assessing the quality of medical laboratory practices. In fact, medical biology laboratories are required to be accredited. A well-designed quality management system is essential for managing the risks posed to patients and facilities. This system should enable the evaluation of new or alternative POCT instruments and systems, as well as the approval of end-user proposals and protocols, purchase and installation of equipment, maintenance of consumable supplies and reagents, and training, certification, and recertification of POCT system operators. Quality control and assurance are also crucial components of this system.

In 2006, ISO 22870:2006 was introduced as a global standard specifically for POCT. This standard is carried out by medical biologists and ensures that the laboratory responsible for POCT examinations adheres to a suitable quality control framework. Instruments, protocols, maintenance, and consumables are closely monitored, as is the verification of user training and authorization. In conjunction with this standard, ISO 15189 outlines general requirements for quality and competence in medical laboratories (373,374).

Accreditation establishes a climate of trust between patients, prescribers, and laboratories:

- Instills trust between patients, prescribers, and laboratories.
- Recognition of laboratory competencies based on peer evaluation.
- Guarantee of exam reliability.
- Quality assurance in laboratory departments.
- Facilitation of the dialogue between the clinician and the biologist.
- Reduction of non-compliance issues.

d. Examples of Point of Care Testing:

The deployment of POCT is the result of the expression of a clinical need. The benefit of performing POCT is mainly found in the context of a medical emergency or an organizational need.

In the case of medical emergency, these devices allow us to perform tests that aid in the management of life-threatening emergencies for the patient. POCT in the ED mainly consists of emergency diagnostic tests. POCT becomes relevant when the availability of laboratory test results is not guaranteed within a given time frame, and when immediate and appropriate patient care depends on these results. Regarding organizational needs, it is easy to understand that a POCT test will help to guide the patient in their health journey, and by nature, streamline and decongest the emergency department.

In order to implement or maintain POCT, it is necessary for the authorities to reflect and develop a list of relevant tests to be carried out outside the laboratory, based on clinical urgency criteria, stability of samples, and logistical considerations. Medical societies have been studying this issue for years. In 2012, experts within a working group of the SFBC (French Society of Clinical Biology) defined the framework for POCT. They drew up a list of relevant medical biology exams to be performed remotely, due to their urgent nature (375). According to the SFBC, only certain emergency biology assays can be performed using POCT. We present below, by specialty, the main validated applications to date (376):

X. In the context of ABG analysis.

ABG test is the reference standard for diagnosis and management of acute dyspnea. It can indicate the presence of hypercapnia and/or hypoxia, and allows for early oxygen therapy and anticipates the need for ventilatory assistance. Blood gas analysis can also aid in diagnosing acidosis, both respiratory and metabolic, which can occur in cases of DKA. Lactate levels provide information on the degree of tissue hypoxia and are useful in cases of acute respiratory distress, sepsis, or shock.

EDs must be able to measure blood gases at the point of care if the laboratory cannot provide results in less than 10 minutes. Blood gas analysis must be immediate, and the results must be made known to the ED clinician as soon as possible. ABG analysis is also widely used in operating rooms, intensive care units, or delivery rooms (scalp pH, cord blood gas).

Rapidly measuring the levels of various electrolytes, including potassium, calcium, magnesium, sodium, and chloride, is important in the ED. A stand-alone electrolyte panel test is available, which provides results in less than 2 minutes, compared to the 40-45 minutes required in a traditional hospital laboratory. Some ABG devices are associated with the partial electrolyte panel (sodium, potassium, chloride, calcium) and some substrates (glucose, creatinine, lactate). These quickly performed tests allow for the rapid diagnosis and easy monitoring of acid-base and electrolyte imbalances.

In the management of septic shock, the rapid assessment of blood gas and lactate levels allows for the evaluation of the severity of shock and tissue perfusion status. Consequently, appropriate oxygenation and vascular filling can be initiated.

XI. In the context of inflammation biomarkers:

CRP is a widely used marker of inflammation, although its elevation can be non-specific. Its variations can help to evaluate a patient's condition. Procalcitonin is increasingly used in emergency medicine, particularly in cases of sepsis. Its elevation has great specificity for bacterial infection (377).

There are POCT systems for measuring CRP and PCT in emergency departments, allowing to make not only a rapid, but also informed decision on antibiotic prescription or patient discharge. An application of CRP in POCT is validated in pediatric emergencies.

XII. In the context of cardiac biomarkers:

Troponin is a protein that indicates myocardial injury and is essential in the management of chest pain and dyspnea. BNP or NT-pro BNP are biomarkers for left heart failure, especially in patients with acute dyspnea. A quick test can help in diagnosing the cause of the dyspnea (378). D-dimer analysis is useful for excluding thromboembolic disease, allowing for the early exclusion of pulmonary embolism in cases of acute dyspnea (with or without chest pain and a non-contributory ECG) when D-dimer levels are negative.

Thoracic pain is a frequent and daily reason for calling the ED and represents a significant proportion of mobilization of Mobile Emergency and Resuscitation Service (SMUR). In an emergency department, early troponin assay associated with an ECG will rapidly identify patients at risk of myocardial infarction and optimize their management. Additionally, in a hospital setting, troponin assay may help to monitor thoracic pain by following the evolution of troponin levels. The use of POCT can reduce turnaround time.

If the laboratory cannot provide results in a timely manner, POCT can be used, which optimizes diagnostic and therapeutic patient management in situations where vital prognosis

may be engaged or where the earliest possible therapeutic management conditions the prognosis. Among the situations where POCT provides important diagnostic assistance to the emergency physician and/or resuscitator are: shock, acute respiratory distress, chest pain.

POCT for troponin I or T are of interest in cardiology, especially when the laboratory cannot provide rapid results. In this context, both the American National Academy of Clinical Biochemistry and the European Society of Cardiology recommend the use of POCT devices to measure cardiac troponin (cTnI or cTnT) levels in clinical settings. The European recommendations for the management of NSTEMI advise implementing POCT troponin testing when obtaining laboratory results consistently takes longer than 1 hour (379). Several POCT options exist for cardiac enzymes (CPK, myoglobin, troponin) and/or BNP provide results within approximately 15 minutes, which significantly shortens the turnaround time for obtaining results, as described in the literature.

XIII. Contribution of POCT in the context of hematology:

In the context of emergency, If the recommended delays cannot be met, in situations of absolute emergency, POCT can be used.

Regarding hemoglobin measurement, there are various devices used for this purpose, with HemoCue being the most common. HemoCue® offers a widely used device: from capillary blood taken from the fingertip placed in an individual microcuvette, the hemoglobin level is obtained one minute after sampling. This device is widespread in emergency departments, SAMU vehicles, operating rooms, and maternity wards. Regardless of the etiology of shock states, rapid and effective patient management is essential. The value of POCT is evident, particularly in cases of hemorrhagic shock, enable the rapid assessment of the patient's condition and the initiation of appropriate therapeutic interventions such as transfusion. Bedside hemoglobin monitoring, particularly in the pre-hospital management of severe trauma, is also possible.

Various parameters can be detected using methods such as impedance, flow cytometry, cytochemistry, spectrophotometry, fluorescence, radio frequency, and calculations. The following parameters can be detected using methods such as chronometry, turbidimetry, nephelometry, immuno-turbidimetry, immuno-enzymatic, and ELISA: Prothrombin time (INR), Partial thromboplastin time (PTT), Activated clotting time (ACT), Thromboelastogram (TEG). Two devices for measuring the International Normalized Ratio (INR) are currently available and being studied for their usefulness in emergency medicine, particularly for managing severe bleeding in patients taking anticoagulants (380).

Regarding hemostasis, capillary INR measurement devices (Coaguchek XS Pro Roche® or INRatio ALERE®) can be used in emergency contexts (SAMU vehicles, emergency departments...) in patients taking vitamin K antagonists. In this case, capillary International Normalized Ratio (INR) measurement allows for the prompt determination of the patient's INR on arrival. In cases of overdose, rapid reversal with vitamin K and/or prothrombin complex concentrates can be initiated. Rapid post-reversal monitoring of INR efficacy can evaluate the success of the treatment and guide subsequent therapeutic interventions. The use of POCT in emergency situations provides significant time savings in patient management and contributes to early diagnostic support, particularly in critical phases of acute and complex conditions. It also enables close biological monitoring, close to the patient. However, these devices have only been validated for the follow-up of patients treated with vitamin K antagonists, they cannot be used to detect an acquired or congenital coagulation abnormality in untreated patients.

Thromboelastography devices (ROTEM® or TEG Haemonetics®) are used by some to Eds to assess coagulation in emergency contexts such as postpartum hemorrhage, multiple traumas, and hemorrhagic shock. The time gain stems from the absence of centrifugation (analysis is performed on whole blood) and the location of the automated machine at the patient's bedside. However, difficulties arise mainly from the need to allocate a member of the medical team (while the situation is critical) to perform the tests, the technical complexity of performing the tests,

and the lack of consensus and recommendations regarding the interpretation of these new parameters.

In cardiac surgery, activated clotting time (ACT) allows for a quick estimation of the effectiveness of heparin therapy and the effectiveness of protamine antagonization on whole blood and at the patient's bedside. Thus, in the face of peri- or post-operative bleeding in cardiac surgery, this test can implicate or rule out heparin as a potential cause. ACT does not have any other indications.

Figure 159: An example of POCT device available in our hospital: ABBOTT I-STAT. Measured parameters: Blood gas, electrolytes, hematocrit, glucose, lactate, creatinine, urea, cardiac biomarkers (Troponin I, BNP, and CK-MB), ionized calcium, coagulation (ACT and PT/INR) with 18 cartridges according to tests performed, 1 cartridge = 1 patient with Integrated quality control.

1. Benefits of POCT:

There are many studies that have reported on the benefit of POCT in reducing TAT and LOS in the ED:

- In a randomized French study (381) conducted in the emergency department, Renaud et al. compared the time between admission and treatment initiation fo NSTEMI. Out of 860 patients suspected of NSTEMI, 113 had confirmed diagnoses. In the first arm, 428 patients received POCT, and in the second control arm, 432 patients were included. The results showed that the turnaround time was reduced in the POCT arm (38 min vs. 109 min). The shorter turnaround time led to a decrease in the delay of treatment (151 min vs. 198 min).
- Several studies report that this time gain allows for shorter hospital stays. For instance, in an American randomized study (382), 263 patients suspected of NSTEMI were randomized to receive either POCT or standard testing in a cardiac emergency unit. The authors found a significant reduction in the duration of stay in the cardiac emergency unit (145 h vs. 80 h) and in the hospital (209 h vs. 150 h) for low-risk cardiovascular patients. Likewise, a randomized multicenter British study (383) that included 2,243 patients suspected of NSTE-ACS showed that the rate of returning home within four hours without adverse events was significantly higher in the POCT arm (32% vs. 13%).
- In a prospective Asian study (ASPECT study) (384), Than et al. validated a protocol for evaluating patients suspected of NSTEMI within two hours. The authors aimed to demonstrate that a score combining clinical (TIMI score), ECG, and POCT (troponin, myoglobin, CPK-MB) could safely accelerate the evaluation of suspected NSTEMI patients. The primary endpoint was the occurrence of a severe cardiac event at one month. For each patient, the TIMI score was evaluated, and the myoglobin, troponin, and CPK-MB levels were measured using a POCT device at 0 and 2 hours. Out of 3,582 patients, 370 were categorized as low-risk, and 3,260 were categorized as high-risk. Only three low-risk

patients had cardiac complications at 30 days. The sensitivity of the protocol was 99.3%, and the negative predictive value was 99.1%. Although it was not randomized, this prospective study was significant and demonstrated the benefits of POCT and the clinical-biological score for the rapid evaluation of patients with suspected NSTEMI.

- Other authors also report that the time savings are not significant. For example, a randomized study (385) conducted in two emergency departments in Australia included 1,194 patients suspected of ACS without ST segment elevation. The randomization was unique, as it was performed weekly, either with POCT or traditional laboratory testing. The authors found a trend toward a decrease in length of stay in the emergency department.

We discussed the relative time savings for patients with chest pain. The question arises as to whether this time savings can be generalized to all patients.

- In a randomized study conducted in South Korea (386), the authors included 10,244 patients who presented to the emergency department. In the first arm, patients received POCT (complete blood count and electrolyte panel) while in the second arm, patients received standard care. The primary outcome was length of stay in the emergency department. The results showed a median decrease of 22 minutes in length of stay (372 min vs. 350 min) across all patients, and a decrease of 12 minutes (256 min vs. 268 min) for patients who were discharged.
- In a non-randomized interventional study conducted in the United States (387), the authors investigated the use of POCT in triage for 300 patients presenting to the emergency department with chest pain, dyspnea, or infectious syndrome. In addition to standard triage by a nurse, patients with these symptoms received POCT, including electrolyte panel, hemoglobin, troponin, BNP, and lactate. The authors reported that POCT changed the management of care in 14% of cases and led to faster physician consultation in 6% of cases.

Another benefit of POCT is its ability to improve communication between biologists and clinicians, which enhances the interactions between the laboratory and the clinical department after the implementation of POCT equipment. Training and qualifications also contribute to improving communication and mutual understanding of professions. Biologists will be increasingly involved in visiting clinical departments, which allows them to better understand the functioning of these units. This proximity facilitates communication and is therefore beneficial for the laboratory, clinical departments, and ultimately, patients.

POCT can also contribute to the fluidity of clinical services, and thus improve patient care, particularly in emergency situations. Reduced waiting times contributes to reduced LOS and by extension to ED overcrowding the burden of care is lessened, it is also highly appreciated by patients.

The use of POCT in the infectious diseases department helps to reduce nosocomial transmission by detecting infections earlier, and therefore rapidly isolating the infected patient.

Performing POCT tests also allows for sparing a child from blood sampling in a pediatric department, thanks to POCT automation that enables analysis on a capillary sample.

2. Limitations of POCT:

Several limitations specific to POCT need to be highlighted.

First, evidence-based medicine is not formal on the usefulness of POCT. Several important prospective and/or randomized studies have shown good results, but as in many areas of medicine, the literature data are not all consistent and further impact studies are needed. In some cases, the literature reports results where the time savings are not clear. In a randomized, multicenter study (388) conducted in four emergency departments in the United States, 1,000 patients suspected of acute coronary syndrome were included in the POCT group and another 1,000 patients suspected of ACS were included in the control group. The hypothesis was that POCT would reduce the length of stay in the emergency department and/or the time to

transfer. The results were mixed, as one medical center saved time but another lost time. Overall, there was no difference, and the authors emphasized that the use of POCT should be considered on a case-by-case basis tailored to each institution's organization.

Second, although studies are positive, the question arises as to the clinical relevance of the results. A few minutes' time gain in a care process that lasts several hours is not of great interest, either for the patient or for the medical team.

Although the quality of some POCT tests in terms of sensitivity and specificity is equivalent to laboratory tests, this is not the case for all tests. Not all PCT automates are as efficient in terms of specificity and sensitivity as those in the central laboratory. Similarly, for CRP, the quantification threshold is 0.1 mg/L on laboratory automates whereas, for some POCT it is 10 mg/L. Therefore, healthcare personnel may make a therapeutic decision based on erroneous results. The impact on the patient's health can be dramatic. Some biologists, who are responsible for and guarantors of these examinations, will find them dangerous to implement.

Concerning the skills needed by the personnel to perform POCT, training is critical. The implementation of training, authorization, and user recertification is time and cost-consuming for all personnel involved, biologists and clinicians alike. Maintenance (including quality control) of the equipment, necessary for the proper functioning of the devices and for result reliability, is also time-consuming for biologists (380,389).The significant turnover of medical and paramedical teams in emergency departments exacerbates the difficulty of training. The implementation of POCT requires such organization that it is a necessary to reevaluate the organization and personnel competence of the ED, as they must acquire new skills and practice new methods. This is a paradigm shift.

The performance of POCT analyses is an additional task for healthcare providers. This has a direct impact on the workload of some caregivers, who are already regularly in a situation of work overload and stress. However, the time spent analyzing the sample is probably largely compensated for by the time gained in overall patient care.

It is necessary to ensure quality control of the automated equipment at a defined frequency and to be critical of the examination results. As the biologist is not present at the time of the tests to detect errors related to equipment dysfunction or to explain abnormal results, it is up to the caregivers to carry out this exercise. It is important to note that clinicians and nurses have a different view than biologists in terms of logistics and quality. Glucometers for example are calibrated daily by healthcare providers (with verification of appropriate strips).

Finally, the issue of financing remains a major obstacle to widespread adoption of POCT. The biggest difficulty today is the lack of financial resources for the purchase of very expensive software and hardware. In view of the requirements organizational standards, computer management software is necessary. Traceability of regular calibration of equipment is necessary to ensure the quality of results; this is even an obligation. For hospitals, software available via the hospital's intranet network is essential to receive information and/or remotely operate POCT equipment. This software would include reagent management, quality control, operator tracking, personnel training, and transmission of results to the laboratory.

Table LV: Factors Affecting Accuracy of POCT Results.

Workforce	Environment	Material (Sample)	Material (Reagents and Equipment)	Method
Untrained operator	Vandalism	Patient identification error	Lack of maintenance	Unperformed biological validation
Unauthorized access	Lack of confidentiality	Untrained sampler, non-conforming sample	Reactive management failure	Inappropriate technical confirmation
Untrained technician	Unstable power supply	Exceeded analysis deadline =sample degradation	Software failure	Unverified methods
Outdated documentation	Reactive storage	Interferences	Calibration or control failure	

2.1. The cost of POCT:

Another important limitation in these times of budget rationalization is the cost of POCT.. In addition, POCT assays are sometimes repeated and controlled a second time by traditional biology, thus multiplying costs.

When evaluating its cost-effectiveness of POCT compared to conventional laboratory testing. it is crucial to consider the need for POCT, machines, reagents, software, personal, turnaround time, hidden costs such as local laboratory support, user training, and maintenance.

In terms of saving time, POCT is performed near or at the bedside and provides the physician with the possibility of promptly intervening in the treatment, thus ensuring greater effectiveness in the diagnostic procedure. This makes POCT useful in situations where delayed outcomes could have a significant impact on the patient, such as in an intensive care unit (ICU) (390). The processing time of POCT is faster than equipment used in laboratories, which can take minutes to hours. POCT's processing time takes an average of 4.7 minutes, while sending a sample to the central laboratory can take 10,05 minutes if carried out by an individual or 8.1 minutes if a pneumatic tube is used (391,392).

Concerning personnel, the labor force used for POCT may be the same personnel already in place, such as the nursing team and the intensivist physician. However, this is a frequent misconception, and a fraction of the cost of these professionals should be considered in the cost of POCT since they would not be operating the equipment otherwise. Personal expenditures are the most relevant costs in POCT, accounting for two-thirds of total expenditures. However, in a comparative analysis of the total laboratory flow in POCT and a centralized laboratory, the former demonstrates a simpler and more dynamic flow than the latter (393).

Concerning consumable. It usually costs more than if the same test using the same reagent was performed in the central laboratory because tests can be done in series. Furthermore, there are other hidden costs that should be considered. For instance, a kit with 100 tests that costs 250$ may require 30 of those tests to perform quality control and calibration.

The cost of each test would then be $2.50 ($250/100 tests), which becomes 3.6$ (250$/70 tests) since only 70 tests are used to release patient results. To determine the total cost of the test per patient, labor and other consumables must be added to this amount (394).

Concerning wasting, POCT are to be performed by healthcare professionals trained in POCT, who are not professionals in medical biology. As a result, there could be repeated tests for the same patient due to different malfunctions, lack of practice (two or more measurements for a single result). This can lead to excessive use of consumables and long-term cost increases. The cost of equipment maintenance must also be taken into account.

Concerning the level of demand and volume, POCT can be at a disadvantage in terms of cost when compared to conventional equipment testing because of its low demand. As cost is inversely proportional to volume of use (395), hospitals need to have a clear view over why they are using POCT, as the financial impact may vary depending on the intended objective. To determine if there is a clinical need for POCT, it is important to investigate if there is real need for it. Furthermore, to date, it is not possible to bill POCT exams as a medical procedure.

Despite these many factors, a decision between POCT and central laboratory testing based solely on cost cannot be made by comparing the expenses of time, hardware, software, and personnel alone. Instead, the primary focus should be on assessing the overall impact on patient outcomes. This requires an evaluation of the efficiency and effectiveness of POCT in comparison to central laboratory testing. Additionally, it is essential to gather insights from the experience of institutions that have already implemented POCT to determine if they recommend it based on their experiences.

Lingervelder et al. conducted a systematic review (396) to examine the available evidence on the health economic impact of implementing POCT. The review categorized the studies into three categories: screening, diagnostics, and monitoring.

In terms of screening, out of eight publications, three evaluations reported a ratio of cost and effectiveness, with all of them recommending POCT implementation. Among the remaining

five evaluations that did not report a ratio, four found that POCT is less expensive and increases effectiveness, while one reported an increase in both costs and effectiveness. All but one of these evaluations concluded that the implementation of POCT is a cost-effective option.

In terms of diagnostics, out of 34 evaluations, 23 reported a ratio of cost and effectiveness, with 20 concluding in favor of implementing POCT. One evaluation concluded against its implementation based on a high probability that POCT is dominated by standard care. Of the 11 evaluations that did not report a ratio, all found an increase in effectiveness due to POCT, two found an increase in costs, while the rest reported cost savings.

In terms of monitoring, out of 14 evaluations, nine reported a ratio of cost and effectiveness, with three concluding in favor of POCT implementation, one concluding against its implementation, and five unable to reach a definitive conclusion. Two of these evaluations concluded that POCT is only likely to be cost-effective in settings without access to laboratory services. All evaluations that reported costs and effectiveness concluded in favor of POCT, with four reporting reduced costs due to POCT and all 5 reporting increased effectiveness.

Overall, the study found that POCT is recommended for implementation in more than 75% of the evaluations. Nonetheless, a detailed examination of the specifics is required, which will be discussed in the subsequent discourse.

To conclude, in order for POCT examinations to have a positive impact on the organization of care and patient management, it is necessary that the automates and analyzers be properly selected, that the quality of the implementation of the examinations on these automates and analyzers be respected, and that the appropriate examinations be prescribed.

Studies and surveys (397) have enabled the identification of the benefits and limitations of the use of POCT, this is a summary of the most important findings:

Table LVI: Comparison between the benefits and limitations of POCT

Theme	Benefits	Limitations
Time	Reduction of constraints related to sample transport. Faster results. Early diagnosis, rapid therapeutic decision-making.	Time requirements (test setup, daily/weekly/monthly maintenance) Delayed result validation by the biologist (in case of incorrect results)
Patients	Reduced sample volume (pediatrics) Improved patient outcomes Improved patient adherence	Patients may be uncomfortable with testing outside of a laboratory Accuracy concerns
Organization	Increased nursing efficiency Fluidity (especially in emergency departments)	
Sample	Reduction of constraints related to sample preservation	Additional sample processing may be required for some devices Concerns about sample quality or handling errors
Costs	Capital savings from avoiding setup of central laboratory and avoiding purchase of whole blood analyzers Laboratory employee savings Reduction in blood conservation cost Possible reduction of the overall cost of care	Capital costs from purchasing analyzers and information systems Higher cost of POCT (3 to 20 times more expensive than a classic biology exam): Higher reagent cost Software implementation Middleware implementation Need for repeats due to misdiagnosis or misuse Duplicate analysis due to verification using classic biology
Communication	Facilitation and improvement of communication between clinical services and laboratory (provision of advice, personnel training by the laboratory, etc.)	Connectivity or compatibility problems between laboratory and clinical departments
Accuracy	Some devices have accurate and reliable results	Some tests may have lower sensitivity or specificity compared to laboratory tests Concerns about accuracy of results due to user error or equipment malfunction
Personnel	Quality requirements Better training Accreditation Maintenance of skills	Rotation of healthcare personnel in clinical departments Salaries for testing coordinators

3. Implementation of POCT:

The implementation of a POCT device starts with adherence to regulatory requirements, involving the biologist and administration. After this necessary step, the hospital or department must consider four questions:

- Are the analytical characteristics of the test satisfactory? Installing a technique that does not meet certain quality requirements is not a viable solution.
- Can the test provide a benefit for the patient? If the desired test does not modify the patient's management or monitoring, its usefulness may be questioned. However, in the case of suspected ACS without ST-segment elevation, or the confirmation of an MI diagnosis with positive cTn, the added value of biology is significant. Similarly, in the case of acute dyspnea in an elderly patient, where early treatment is crucial for the prognosis of cardiogenic pulmonary edema, early measurement of NT-pro BNP or BNP is essential.
- Is it possible to organize this test through the central laboratory? Improved sample flow, constructive dialogue with the laboratory, or the use of a pneumatic system can sometimes solve certain delay problems and avoid the installation of a POCT machine. These organizational solutions only apply to intrahospital testing.
- Who will be responsible for maintenance? The installation of a POCT machine requires rigorous training and regular calibration, and the responsibility of biochemists in the reporting of results requires quality control.

To better integrate POCT, several steps are necessary, involving healthcare personnel and biologists:

- Clinicians or hospital practitioners must express a clinical need.
- Biologists then evaluate the request and select an analytical system. They ensure its proper implementation in the healthcare services and carry out its validation.

- They integrate the new device into the laboratory's quality system and establish an adequate document management system (procedures, technical sheets, etc.).
- Throughout the life of the device, biologists must train and empower healthcare personnel, manage non-conformities, and ensure quality control. They study the results of the analysis after the fact. Healthcare personnel must follow procedures and critically evaluate examination results.
- An annual review is conducted to evaluate the rationale for the equipment.
- Biologists may need to remove or replace a device.

4. Conclusion:

Certain POCT devices are of great assistance in life-threatening emergency situations. They provide a significant time-saving advantage and optimize diagnostic and therapeutic patient care, as well as simplify monitoring. The use of POCT devices is noteworthy for emergency departments. The use of POCT in these cases reduces waiting times for results.

However, despite their benefits, they still have limitations. The installation and operation of POCT devices have a significant financial cost. The use of such equipment requires appropriate training and regular updates for healthcare professionals. The cost of reagents and consumables is a financial constraint. Additionally, if these tests are confirmed by a laboratory, they represent an additional cost for the hospital. Finally, while POCT provides a time-saving advantage in terms of obtaining results and overall patient management in both inpatient and pre-hospital settings, the clinical relevance of time saved is not always clear, and the literature on this topic is not always consistent.

DISCUSSION

DISCUSSION

I. Strength and pertinence of our study:

Our study represents a pilot investigation of emergency department physicians' knowledge and opinions regarding the use of biomarkers and POCT in emergency care. To the best of our knowledge, this is the first study to explore this topic. The study aims to assess physicians' knowledge and identify areas where additional education and training may be required.

The significance of our study can be deduced from simple facts:

The use of biomarkers has become increasingly important in diagnosing and managing diseases in emergency departments. However, physicians must have the necessary knowledge to prescribe and interpret the results of biomarker tests. Therefore, assessing physicians' knowledge is crucial to identify areas where additional education and training may be required, particularly in the context of evolving standards of care.

Furthermore, our pilot study is relevant because it provides valuable insights into the trajectory of physician's cognitive skills. These results could serve as a baseline measurement for future studies to compare changes in physician's cognitive skills and identify patterns that may arise. Additionally, the results of our study could help identify trends and determine whether ongoing training and learning is effective in maintaining or improving physician's knowledge.

POCT has the potential to improve patient outcomes by providing rapid test results. However, cognitive and attitudinal barriers can impede the adoption of new standards of care. Therefore, longitudinal assessment studies can provide valuable insight into physicians' knowledge and opinions and promote the adoption of new standards of care. This can inform the development of educational programs to ensure physicians have the necessary knowledge and skills to use POCT effectively.

II. Response rate:

Our study was conducted using an online self-administered questionnaire and received responses from 108 physicians, representing a response rate of 63.52%. This sample size is sufficient to provide statistical power, as it represents a satisfactory proportion of the target population of 170 intern and resident physicians in the hospital at the time.

The high participation rate in the study could be due to a number of factors. One is that the target population of physicians were motivated to take part in the study, perhaps because they felt the topic was relevant to their work in the emergency department and that their responses would be valuable. Another reason may be that the design of the study made it easy for physicians to participate, as the use of an online self-administered questionnaire may have been more convenient than other methods of data collection such as in-person interviews. Additionally, an effective communication and awareness campaign, such as personal invitations and reminders, may have also contributed to the high participation rate.

III. Profile of the respondents:

The study population comprised primarily of young and female individuals. Female clinicians represented 61% of respondents, resulting in a sex ratio of 0.63.

The high proportion of young and female individuals in the study population is consistent with gender demographics in medical training, where women are often overrepresented. In Morocco, the percentage of female medical graduates has increased from 51.8% in 2000 to 63.3% in 2010 and 67.8% in 2019 (398).

The majority of the sample was made of resident physicians, accounting for 67% of the participants, followed by intern physicians, accounting for 33% of the participants.

The average age of all physicians in the study was 26.4 years, with interns averaging 24.9 years and residents averaging 27.4 years. The majority of physicians were in their first year of training, with 64% of intern physicians and 42% of resident physicians falling into this category.

Medical and surgical specialties accounted for most participants, with 49% currently training or planning to train in medical specialties and 28% in surgical specialties.

The youthfulness of the study population can be explained by the fact that the study took place in a teaching hospital which typically serves a younger population, and only included a specific group of practitioners: interns and residents which are typically of younger age. Additionally, the study population's youthfulness may be due to a sampling bias towards first-year residents, who were more likely to be connected to the interviewer. This type of selection bias is common in many studies that interview doctors locally, as the willingness to volunteer is often weaker for unrelated subjects than for subjects with a direct or indirect relationship with the interviewer.

IV. Analysis:

1. The state, opinions and perceptions on point of care testing:

1.1. Familiarity of healthcare practitioners with POCT:

The present study aimed to investigate the level of awareness regarding POCT among physicians. The results showed that the surveyed population had a significant lack of awareness regarding POCT. Specifically, 89% of the surveyed population had not even heard of POCT before, and only a small minority of 11% had heard of it, and only 6 practitioners were able to provide a definition.

Interestingly, our study's findings differ significantly from those of a previous study conducted by Sivakumar et al. (402) using the same methodology and a comparable sample size

of 100 residents. Sivakumar et al. found that 94% of the respondents were aware of POCT, but that only 11% of them had been exposed to POCT during medical school.

There are several reasons why practitioners may lack awareness of POCT. Firstly, some POCT methods, such as glucometers, are so commonly used in standard clinical examinations that practitioners may not even realize they are using POCT technology. It is crucial to recognize that familiarity with one type of POCT does not necessarily translate to familiarity with the concept of POCT.

Secondly, medical training curriculum does not adequately cover POCT education, as we confirmed by searching the university curriculum and finding zero instances where POCT has been mentioned. As a result, many healthcare practitioners may not be familiar with POCT despite its widespread use in clinical settings.

Thirdly, laboratory testing is a rapidly evolving field, with new technologies and applications emerging all the time. Keeping up with these developments can be challenging for practitioners who do not keep up with evolving standards or who lack interest. Recent advancements in analytical systems have led to a significant improvement in POCT, including cardiac biomarkers, infectious disease testing, coagulation monitoring, hematology testing, and blood-gas testing. Unfortunately, some healthcare practitioners may not be aware of these advancements, which may explain their lack of knowledge in this area.

In conclusion, addressing practitioners' lack of awareness of POCT will require a multifaceted approach, including improvements in medical training curriculum, greater access to POCT devices in practice settings, and increased awareness of the benefits of POCT. We suggest starting seminars or workshops on POCT among physicians, particularly during their training period. This will help bridge the knowledge gap and ultimately lead to better healthcare outcomes for patients.

1.2. The availability of POCT devices:

The present study aimed to assess the availability and access to POCT devices among practitioners.

The survey found that among the emergency department physicians who participated, the most commonly available POCT devices were urine dipsticks and blood glucose/ketone analyzers, available for 97.22% of practitioners. Urine pregnancy test kits and blood gas analyzers were each available for 50% of practitioners, while Hemoglobin analyzer (HemoCue) and RSV test kit were available for 19.44% and 11.11% of practitioners, respectively. The least available devices were INR coagulation analyzers (Coagucheck), complete blood count analyzers (Sysmex), and blood coagulation analyzers (TEG or ROTEM), which were available for 3.7%, 0.93%, and 0.93% of practitioners, respectively.

Our results present several similarities to those of Howick et al. (403) who conducted a cross-sectional survey of 2770 clinicians across Australia, Belgium, the Netherlands, the UK, and the USA. The survey aimed to evaluate the current use of POCT, the need for POCT and gather information on the conditions for which POCT could inform diagnosis, and desired future use of POCT.

Concerning blood Glucose/Ketone Meters, our study shows that the utilization of blood glucose/ketone meters is widely prevalent, with a rate of 97.22%. Across other countries, the utilization rates of blood glucose/ketone meters range from 69% in the UK, 74% in Australia, 82% in the USA, 87% in Belgium to 96% in the Netherlands. Similarly, the use of Urine Dipstick Test in our study is widely prevalent, with a rate of 97.22%. Across other countries, the utilization rates of urine dipstick tests range from 87% in Belgium to 96% in the Netherlands. This indicates a high degree of utilization of blood glucose/ketone meters and urine dipstick tests across countries.

The findings of this survey highlight the current state of POCT device availability in emergency department practices. The results show that the most commonly available POCT

devices were those that are commonly used for initial diagnostic purposes such as urine dipsticks and blood glucose/ketone analyzers. Their wide availability is due to the fact that they are often used to screen for a range of conditions from urinary tract infections, proteinuria, hematuria to diabetes, DKA, hypoglycemia among others.

Urine pregnancy test kits had a utilization rate of 50.93% in our study, while utilization rates in other countries ranged from 61% in Belgium, 68% in Australia, 80% in the UK, 86% in the USA to 94% in the Netherlands. This similarity across countries attests to the wide use of urine pregnancy tests. The relatively high availability of urine pregnancy test kits and blood gas analyzers is also noteworthy. These devices are often used to diagnose conditions such as ectopic pregnancy and respiratory failure, respectively.

In our study, the utilization rate of HbA1c analyzer was reported to be 0.00%. However, the utilization rates of HbA1c analyzer in clinics across other countries were reported to range from 2% in Belgium, 6% in Australia and the Netherlands, 17% in the UK, to 40% in the USA. Our study has the lowest utilization rate of HbA1c analyzer compared to these other countries, but even in those countries, the utilization rates were found to be low.

Similarly, the utilization rate of INR coagulation analyzer (Coaguchek) was 3.70% in our study, while the utilization rates in other countries ranged from 1% in the Netherlands, 12% in Belgium, 43% in the UK, 47% in the USA, to 48% in Australia. This disparity in utilization rates highlights the differences in utilization patterns between our study and other countries. While we are closer to the Netherlands in terms of utilization rates, the UK, USA, and Australia are far ahead. This could be explained by the fact that the least commonly available devices, which were the INR coagulation analyzers (Coagucheck), complete blood count analyzers (Sysmex), and blood coagulation analyzers (TEG or ROTEM), are often used for more specialized purposes such as monitoring anticoagulation therapy and assessing blood clotting disorders. The low availability of these devices may reflect a lack of training or expertise among emergency

department physicians in their use or a lack of demand for these tests in the emergency department setting.

Finally, the utilization rate of Hemoglobin analyzer (Hemocue) was found to be 19.44% in our study, while utilization rates in other countries ranged from 3% in Belgium, 10% in Australia, 16% in the UK, 50% in the USA, to 58% in the Netherlands. Our study falls in the middle compared to other countries, between Australia and the UK, in terms of the utilization of Hemocue. The relatively low availability of Hemoglobin analyzer (HemoCue) and RSV test kit is not surprising, as these devices are used to diagnose fewer common conditions such as anemia and respiratory syncytial virus (RSV).

Although both our studies aimed to determine the availability of different POC tests used by healthcare clinicians, it is crucial to note that our study population consisted of emergency department clinicians, while the other study used primary care doctors as participants. This difference in study population could have an impact on the results and limit the comparability of the findings.

Emergency department clinicians typically encounter different types of cases compared to primary care doctors, with a greater emphasis on acute conditions and emergencies. Consequently, their need for POC tests may differ in terms of the conditions they diagnose and the type of tests they use. However, it should be noted that many emergency cases that should be seen by the ED first present to primary care doctors, which explains their use of POC tests for diseases that represent emergencies.

Despite these limitations, we decided to conduct this comparison as we believed it would offer valuable insights into the differences in POC test utilization between different countries and clinical settings. Our findings may assist in guiding future research in this area, particularly in understanding how POC tests are used in emergency departments and how they could be optimized for this setting.

1.3. The discrepancy between desire and availability for certain POCT:

The present study aimed to assess the accessibility of POCT devices for specific biomarkers and identify any potential disparities between the requirements expressed by physicians and the current availability of these devices.

Our findings revealed a significant difference in the availability of POCT devices among practitioners for troponin, D-dimers, BNP/NT pro-BNP, CRP, procalcitonin, and S100B. Specifically, 97.22% of the total sample size did not possess any POCT devices for these biomarkers, while only 2.77% reported having POCT for some of them.

However, a striking contrast was observed between the limited availability of these devices and the overwhelming interest expressed by physicians in implementing them. In fact, 92.59% of practitioners expressed their interest in having access to these POCT devices, while only 7.41% were not interested. This discrepancy highlights the clear need to improve the accessibility of POCT devices for these specific biomarkers to meet the requirements expressed by practitioners.

Given the potential clinical implications of timely biomarker testing for specific emergency medical settings like ACS, CHF, PE, sepsis and TBI among others, it is crucial to address the existing gap in POCT device availability. Our study emphasizes the desire of improving the accessibility of POCT devices for troponin, D-dimers, BNP/NT pro-BNP, CRP, procalcitonin, and S100B to facilitate efficient and effective patient care.

1.4. The difference between Classic laboratory testing, point of care testing and rapid diagnostic orientation testing:

The finding that urine dipsticks and blood glucose/ketone analyzers are used by our practitioners is an opportunity to frame the subject of TROD within laboratory testing. According to French legislature, it is necessary to differentiate between POCT, and rapid diagnostic orientation tests.

Article L6211-1 of the French Public Health Code (CSP), modified by Law No. 2013-442 of May 30, 2013 (404), defines classic laboratory testing as a medical biology examination is a medical act that contributes to the prevention, screening, diagnosis or assessment of the risk of occurrence of pathological conditions, decision-making and therapeutic management, determination or monitoring of physiological or physiopathological states of the human being, excluding pathological anatomy and cytology acts, performed by specialist physicians in this field. The analytical phase of a medical biology examination cannot be carried out outside a medical biology laboratory except in the event that it is made necessary by an urgent therapeutic decision. ... However, the medical biologist remains responsible for validating the results obtained.

POCT in practice (subject to EN ISO 22870 accreditation) POCT are carried out under the responsibility of a medical biologist, outside the medical biology laboratory, only when necessary due to an urgent therapeutic decision. With some specificities: first, the locations where POCT can be performed: health establishments, medicalized transport vehicles. Second, the Authorized personnel that can perform POCT: physicians, midwives, nurses, medical laboratory technicians. The results of POCT must be validated by a medical biologist, but in this unique case, it is possible to validate these results after their emergency use by the prescriber, unlike laboratory testing performed within the central laboratory, which must be validated before any communication to the prescriber.

According to the Article L. 6211-3 of the French Public Health Code (405), TROD is a test, collection, and treatment of biological signals for screening, diagnostic orientation or immediate therapeutic adaptation purposes do not constitute a medical biology examination". "Tests or collections and treatments of biological signals mentioned in Article 1 of this decree constitute diagnostic orientation elements without substituting for the diagnosis made by means of a medical biology examination".

The TROD can be performed by an authorized healthcare professional in targeted indications. The regulatory framework provides a restrictive list of tests that can be performed by nurses, midwives, doctors, and community pharmacists, specifying the limited clinical indications for each test, this list mentions “Urinary test for the detection of proteinuria, ketonuria, glycosuria, bilirubinuria, urobilinogenuria, nitrituria, urinary pH, urinary density, leukocyturia, and hematuria. Capillary test for evaluating blood glucose levels and ketonemia. Vaginal test for the premature rupture of fetal membranes (amniotic cavity membranes). Transcutaneous test for evaluating bilirubinemia and oxygenation parameters. Oro-pharyngeal test for diagnostic guidance of streptococcus group A infections. Naso-pharyngeal test for diagnostic guidance of influenza. Capillary test for detecting immune status with respect to tetanus. Rapid diagnostic orientation test (TROD) for hepatitis C virus (HCV) and Human Immunodeficiency Virus (HIV).” The result is rendered under the responsibility of the healthcare professional performing the tests.

To summarize, the performance of a rapid diagnostic orientation test (TROD) involves the collection or processing of a biological signal, with the aim of screening, diagnosing, or immediately adapting therapy. These tests do not replace medical laboratory testing. The result of a TROD must be confirmed by medical laboratory testing.

In conclusion, the French legislation differentiates between classic laboratory testing, POCT, and TROD, and provides specific guidelines on where and by whom these tests can be performed, as well as the clinical indications for each test. It is important for healthcare

professionals to be aware of these regulations to ensure that they are following the correct procedures when conducting tests and interpreting results.

1.5. Conclusion:

In conclusion, our study revealed several similarities and disparities when compared to the cross-sectional survey of primary care clinicians across Australia, Belgium, the Netherlands, the UK, and the USA.

In terms of similarities, both our study and the cross-sectional survey by Howick et al. found high levels of availability of urine dipstick devices, blood glucose/ketone meters which could be considered rapid diagnostic orientation test rather than a POCT. In terms of disparities, our study reported lower levels of availability of urine pregnancy test kits compared to Australia, Belgium, the Netherlands, the UK, and the USA. Additionally, our study recorded no utilization of HbA1c analyzers, a low rate of utilization of INR coagulation analyzer (Coaguchek) and Hemoglobin analyzer (Hemocue) compared to the other five countries.

2. Opinions and perceptions of practitioners on the ED:

In addition to examining the opinions of practitioners on POCT devices, our study also explored the opinions of practitioners on overcrowding in the ED. The majority of practitioners (99%) considered the problem of overcrowding to be either very serious problem or fairly serious, and less than 1% considered it a small problem. This could be due to the negative effects of overcrowding on themselves and on their patients. In fact, our study found that a significant number of practitioners (78.70%) believe that overcrowding leads to prolonged pain and suffering for patients, while 75.93% report that it leads to long waiting times for patients and delays in diagnosis and treatment. Moreover, a large number of practitioners (69.44%) reported that overcrowding in the ED is associated with an increased risk of medical errors and

87.96% have acknowledged that overcrowding leads to staff burnout. To address these concerns, practitioners perceived POCT as a potential solution for overcrowding and its negative effects primarily due to its fast turnaround time. A vast majority of practitioners (87.96%) recognized the benefit of POCT devices in obtaining faster results, enabling earlier medical decisions. Additionally, 71.30% of practitioners saw their benefit in situations where patients required frequent testing, as it employed less manpower. Moreover, 45.37% of practitioners perceived POCT devices as an effective tool for reducing the cost of care.

While the majority of practitioners expressed enthusiasm for POCT, a small minority (7.41%) had reservations about its use. Our study found that these reservations were primarily related to device-related errors, including sampling errors, operator errors, reagent issues, calibration errors, and environmental factors. Specifically, 78.70% of practitioners attributed POCT device-related errors to sampling errors, 73.15% attributed them to their operators, 62.04% attributed them to the reagents being used, 58.33% attributed them to calibration errors, and 50.93% related them to the environment. These limitations may explain why some practitioners have reservations about the use of POCT.

In this discussion, we will explore how overcrowding represents a real problem in the emergency department, how it can negatively affect patients and healthcare workers, and how POCT, despite its limitations, can be a solution for overcrowding. We will also delve deeper into the concerns that practitioners have about the use of POCT devices and explore ways to address these concerns and ensure that POCT is used safely and effectively in clinical practice.

2.1. Comparison to other studies:

It is crucial to accurately identify the needs of healthcare professionals for which POCT would provide a significant advantage in terms of analysis time and performance (406). Therefore, one of the objectives of this study was to gather input from a panel of physicians regarding their need for biomarkers and POCT desired. In our sample of 108 practitioners,

92.59% stated that they would be interested in the implementation of POCT devices to measure six biomarkers, namely troponin, BNB/NT-pro BNP, D dimer, procalcitonin, CRP, S100B, while only 7.41% said they would not be interested. Based on these findings, it can be concluded that the majority of practitioners are interested in the implementation of POCT devices for measuring specific biomarkers while only a small minority of practitioners expressed disinterest in the implementation of POCT devices.

The results of our study are consistent with those of previous research. The findings of our study suggest that practitioners wish for the implementation of POCT devices to measure troponin, BNP/NT-pro BNP, D dimer, procalcitonin, CRP, and S100B. These biomarkers were also identified as being of high interest in the studies conducted by Vuillaume et al., Howick et al. and Turner et al.:

In a study conducted by Vuillaume et al. (407), 508 practitioners were asked to identify which biomarkers would be of great benefit to patients and improve the quality of care if they could obtain quick results in their daily practice. The study identified several biomarkers of interest, with the most frequently requested being troponin with 49.9%, D-dimers with 28.74%, and BNP or NT-pro BNP with 13.18% in relation to major cardiac emergencies such as myocardial infarction, cardiac respiratory distress, and pulmonary embolism. Furthermore, CRP was identified by 42.32% of participants in relation to inflammation, procalcitonin with 8.04% in relation to bacterial infection, and S100B with 2.75% in relation to traumatic brain injury. The surveyed participants acknowledged that the results of these biomarker tests can greatly impact patient management and treatment decisions.

In a study conducted by Howick et al. (403), 2770 practitioners across 5 countries, namely USA, UK, Netherlands, Belgium, and Australia, were asked to identify conditions for which POCT could help inform diagnosis, as well as to determine which POC tests they would like to use in the future. The study found a high demand for POC tests among practitioners. The most desired POC tests, which at least 50% of respondents in at least one country would use, were D-

dimer, troponin, B-type natriuretic peptide, and CRP with 68%, 66%, 59%, and 55% respectively. This desire for POC tests matched with the conditions for which clinicians would like to use a POC test to help make a diagnosis. The top 10 conditions for which clinicians most commonly reported wanting POC tests to help diagnose included PE/DVT with 53.03%, acute cardiac disease with 38.03%, and heart failure with 13.57%. Respondents in at least four countries included heart failure and PE/DVT among the top 10 conditions, while acute cardiac disease was included by all countries.

In a study conducted by Turner et al. (408), the objective was to determine the conditions for which POCTs would be most beneficial for Practitioners in terms of diagnosis and reduction of referrals. A total of 1635 practitioners were surveyed, and the results indicated that 43.1% of respondents identified pulmonary embolism/deep vein thrombosis (PE/DVT) as the most significant condition for which POCTs would be useful in diagnosis, making it the second most crucial condition overall. Acute cardiac disease was mentioned by 25.4% of practitioners, ranking it fourth. Heart failure was identified by 11.2% of participants, making it the eighth most significant condition, while lower respiratory tract infections (LRTI) came in tenth place with 9.2%. In terms of reducing referrals, PE/DVT was identified as the top condition by 46.6% of respondents, with acute cardiac disease coming in second at 24.4%. Heart failure was ranked fifth with 10.5%, while LRTI was tenth with 4.3%. The study highlights the importance of POCTs in the diagnosis and management of cardiac diseases, including acute cardiac disease, PE/DVT and heart failure, as well as infections.

In summary, our study and the three other studies by Vuillaume et al., Howick et al. and Turner et al. all indicate a high demand for POCTs among practitioners, with troponin, D-dimer, BNP/NT-proBNP, CRP, and procalcitonin being among the most desired biomarkers. The interest for these biomarkers aligns perfectly with the conditions for which practitioners want help diagnosing, such as PE/DVT, acute cardiac disease, and heart failure, were consistent across the studies. Our study contributes to the existing literature by providing further evidence of the high

interest in POCTs among practitioners and the specific biomarkers they would like to measure using these POCT devices.

2.2. Overcrowding in the emergency department:

a. Overview:

Over the years, there has been a significant increase in the number of emergency department visits in many countries such as the United States, France, and Morocco. While emergency department visits increased by 36% in the United States between 1993 and 2003 (409), there was a 3.5% annual increase in France between 1996 and 2018 (410,411). The situation is more severe in Morocco, with 11 million individuals seeking emergency care nationwide in 2015/2016, equivalent to one out of every three Moroccans (412). Our study took place at the Marrakesh teaching hospital, which receives an overwhelming number of 700 patients daily. The COVID-19 pandemic further highlighted the problem of healthcare system saturation, emphasizing the need to address the issue of overcrowding in emergency departments.

ED overcrowding occurs when there are more patients requiring emergency services than the available medical staff can handle in a reasonable timeframe (413–415). Several metrics, such as prolonged waiting times, lack of available beds, and increased ambulance diversions, are used to determine the extent of ED overcrowding (416). This problem not only affects the ED but also the wider hospital environment as it can lead to a decrease in efficiency and quality of care, and most importantly, an increase in patient mortality rates (417).

Many factors contribute to the issue of ED overcrowding, including an aging population, an increase in referrals from primary care facilities, and the lack of available resources. The lack of alternative care options and inadequate outpatient resources also contribute to the problem.

Additionally, a shortage of nursing and medical staff, as well as an increased number of uninsured individuals seeking emergency care, can exacerbate the issue.

b. Impact of ED overcrowding:

The results of our study provide a unique perspective on the reasons why overcrowding is perceived negatively by practitioners in the ED. By soliciting input directly from those who experience the impact of ED overcrowding on a daily basis, we gain valuable insights into the challenges faced by medical staff.

- **Practitioners have concerns for their patients:**

The impact of overcrowding on the quality of healthcare services provided in emergency departments (EDs) has been a subject of concern for healthcare providers. 78.70% of practitioners in our study believe that overcrowding leads to prolonged pain and suffering for patients, 75.93% believe it leads to long waiting times for patients and delays in diagnosis and treatment, and 69.44% believe it increases the risk of errors in patient care.

Indeed, overcrowding has been associated with prolonged waiting times, delays in treatment, and increased morbidity and mortality rates. This discussion will review the evidence supporting the negative effects of overcrowding on patient outcome.

- **Effects of Overcrowding on Patient Outcomes:**

Numerous studies have reported a correlation between overcrowding in EDs and poor patient outcomes. For instance, a retrospective study conducted in Australia (418) found a significant linear relationship between ED overcrowding and patient mortality on days 2, 7, and 30. The study estimated that approximately 120 deaths per year may be attributed to overcrowding. Similarly, another retrospective cohort study (419) evaluated data from all EDs in the greater Ontario area over a 5-year period, using length of stay in the ED as a metric for overcrowding. The study found a significantly greater risk of death with increasing length of stay

in the ED. Finally, on the bigger scale, large database studies (420–422) have also found that patients presenting during times of overcrowding have higher mortality rates and longer hospital stays than those presenting during periods without overcrowding.

These findings suggest that overcrowding in the ED should be considered an issue of public health and safety, rather than simply a problem of ED efficiency.

- **Effects of overcrowding on the timeliness of treatment:**

Overcrowding can lead to delays in treatment, which can have detrimental consequences for time-dependent illnesses. The duration of time between the onset of a medical condition and the initiation of effective treatment is a significant predictor of patient outcomes for various conditions where late diagnoses may result in permanent disability or death.

The time between the onset of a medical condition and the initiation of effective treatment is a critical factor in predicting patient outcomes for several conditions. Catchphrases such as "time is cure," "time is muscle," and "time is brain" have been coined for patients with acute myocardial infarction (AMI) (423), strokes (424), and sepsis (425). Timely initiation of appropriate treatment, such as fluid resuscitation and antimicrobial therapy, has been shown to improve outcomes for patients with septicemia (426) and community-acquired pneumonia (CAP) (427).

Studies have found a correlation between prolonged waiting times during overcrowding and substantial delays in the administration of antibiotics (428),(408) and pain medication (429), (409). This delay can have a negative impact on patient outcomes and increase the risk of morbidity and mortality.

Overall, the evidence points towards the associated between overcrowding and increased morbidity and mortality, as well as a deterioration of care (411). And the need for effective strategies to manage and mitigate the negative effects of overcrowding in EDs to ensure patient safety and optimal health outcomes.

- **Practitioners have concerns about medical errors:**

Medical errors represent a critical issue in hospital systems, and they can arise from various complex issues within these systems. One of the significant issues leading to medical errors is overcrowding in the Emergency Department (ED), which can seriously compromise the quality of care that patients receive. This problem is due to the fact that ED staff find it challenging to meet the needs of incoming patients and those already being treated, particularly in an overcrowded environment. Our study revealed a prevailing opinion within practitioners that overcrowding in the ED is associated with an increased risk of medical errors.

Several studies have shown that overcrowding negatively impacts the quality of care provided (430) (431) and threatens patient safety (432) (433) with a high risk for medical errors (434). This issue arises from errors of omissions (435) because ED staff must prioritize new patients arriving at the department over patients already in the ED. Boarded admissions, where patients are not assigned to a bed but placed in a shared area, are also at a higher risk of adverse events or errors (436).

These findings highlight the pervasiveness of the issue of overcrowding in the ED and the need for effective interventions to address this problem. This study provides valuable information for policy makers, healthcare providers, and researchers, and can inform future research in this area. By revealing the extent to which overcrowding is perceived as a serious problem by practitioners, our study underscores the urgency of developing strategies to mitigate this issue and improve patient safety in the ED.

- **Practitioners have concerns about burning out:**

Overcrowding not only affect the physical health of physicians and nurses, but also their mental health and well-being. The findings of our study are significant, as they demonstrate that a majority of 87.96% of healthcare practitioners recognize the negative impact of overcrowding in emergency departments (EDs) on staff burnout.

Overcrowding has become a major contributor to physician and nurse burnout, which has been exacerbated by the increasing number of patients requiring care in the ED, despite the efforts of healthcare professionals. In fact, studies shows that overcrowding is a significant contributor to high ED physician burnout, approaching 75% of physicians between 2011 and 2017 (437). Additionally, the American Medical Association's report that 62.8% of physicians experienced burnout in 2021 (438) and a study published in the Mayo Clinic Proceedings that revealed a dramatic spike in physician burnout during the first two years of the COVID-19 pandemic (439). Furthermore, a study conducted locally (440) reveiled that 20% of residents in the Mohammed VI Marrakech teaching hospital experienced severe burnout during this period.

This issue cannot be ignored, it has caused many healthcare professionals to retire early or leave the profession entirely, exacerbating the shortage of skilled healthcare professionals and increasing the burden on those who continue to practice. Exposure to infectious diseases, violence in the ED, shift work, and scheduling are among the many factors that contribute to the burnout of healthcare professionals.

The manpower challenges imposed by ED overcrowding can largely be offset through POCT. A rapid turnover of non-critical patients will help to reduce overcrowding, and a lower incidence of critical or deteriorating patients in the ED will free up costly time that nurses and staff would otherwise spend attending to these high-risk patients

Our study's findings highlight the effects of overcrowding on the ED staff and emphasize the need to break the cycle of burnout in EDs to ensure that the healthcare workforce can effectively meet the needs of the patient population.

In conclusion, our study reveals that ED physicians consider overcrowding to be a significant problem that negatively impacts patient care, hospital efficiency, patient outcomes, and physician well-being.

3. The need to speed up care by quickly obtaining biology results:

The purpose of our study was to investigate the impact of delays in laboratory test results on emergency department overcrowding, as perceived by ED practitioners. In this discussion, we will review the findings of our study and examine the existing literature on this topic.

Our study found that delays in laboratory test results were considered a significant contributor to ED overcrowding by 69.44% of ED practitioners. This finding is consistent with the literature analysis of factors contributing to length of stay in emergency departments and by extension to overcrowding.

Turnaround time (TAT) in medicine refers to the time interval from when a test order is written to when the results are available (441). TAT encompasses the entire process from the time the sample is taken to the point at which appropriate clinical action is taken based on the test results.

The brain-to-brain loop was introduced by George Lundberg (442) as a concept for laboratory testing. It involves the physician selecting laboratory tests, followed by a long period of waiting for results, the final step being the transmission of test results to the ordering physician who will decide on the appropriate next step. This concept has served as the useful framework for clinical laboratory testing.

The potential impact of conducting POCT instead of laboratory testing is not limited solely to shortening of TAT. Waiting for laboratory results is the main cause of the time lag and delay of several hours between the decision of the emergency physician to perform a medical laboratory analysis and the action resulting from the outcome of this same analysis (brain to brain time) (Figure 160). Specifically, an emergency physician rarely has the opportunity to carry out a patient's diagnostic process in one go and in the vast majority of cases, will be interrupted in the process and take care of other patients before becoming aware of the biological results that will allow them to conclude the case. This "chopping up" of the diagnostic process is a major

factor hindering the efficiency and speed of work for emergency physicians. The implementation of POCT, to be effective, must not be limited to just reducing TAT, but must be integrated into a patient circuit reorganization in order to optimize the availability of the result as soon as possible in the diagnostic decision loop.

Over the time, efforts have been made to close the brain-to-brain loop in laboratory testing and improve the diagnostic process. By using POCT, the physician who ordered the test is also the one who will perform and interpret the test. This effectively closes the brain-to-brain loop and avoids the numerous steps that typically consume the majority of time and this reduce TAT to a minimum.

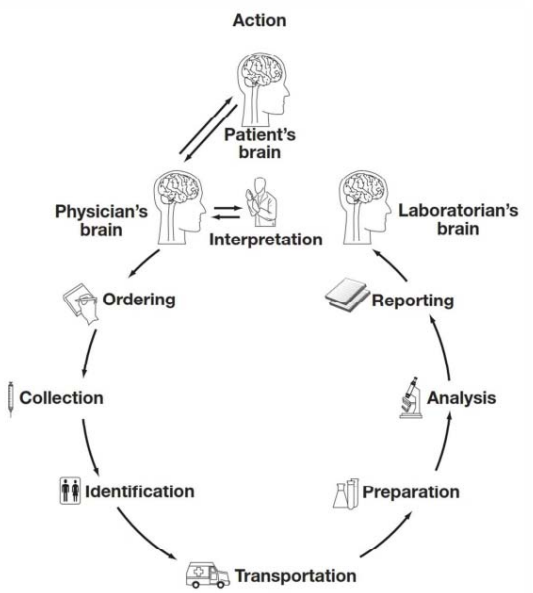


Figure 160: The "Brain-to-Brain" loop, depicting the steps in the process of considering, performing, and using laboratory tests for diagnosis (443)

The process of obtaining test results involves three phases: preanalytical, analytical, and postanalytical. The preanalytical phase starts from the time the test is ordered until it is analyzed on an instrument. The analytical phase involves preparing the sample, analyzing it, and implementing quality control measures. The postanalytical phase involves further validation and

interpretation of the results. The development of novel POCT technology has the potential to greatly reduce these delays (444) since one of the strengths of POCT is that it reduces the preanalytical phase to a minimum and brings test results closer to the decision-making process (445).

Blood testing have been found to add significant time to a patient's length of stay (LOS) in the ED. For instance, a study conducted in the United States through a National Hospital Ambulatory Medical Care survey (446) found that among different types of testing, blood tests were associated with the longest ED length of stay. Obtaining a blood test had a time cost of 72 minutes which represented 25% of the total LOS. It was also linked to an increased odds ratio of experiencing a LOS of more than 4 hours. The study suggests that improving the efficient use of blood tests in the ED could reduce LOS and improve patient and provider satisfaction. Likewise, a study conducted in 2008 at Ibn Rochd Hospital in Casablanca found the duration spent waiting for laboratory test results in the ED can account for 70 minutes on average (30min to 3 hours) (447).

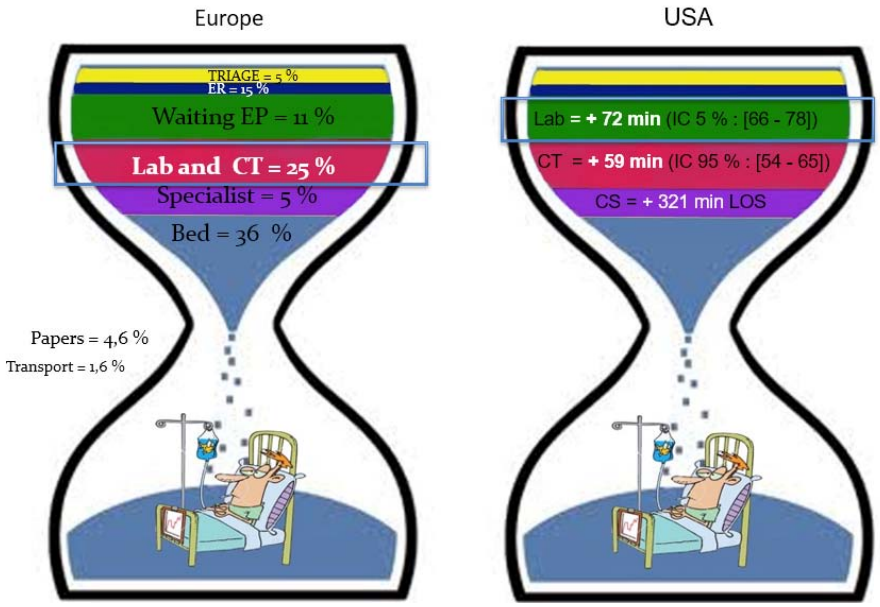


Figure 161: Illustration of the effect of testing and treatment on emergency department length of stay, adapted from Kocher et al. (446).

In conclusion, delays in laboratory test results have been identified as a significant contributor to ED overcrowding by a majority of ED practitioners in our study. This finding is substantiated by the scientific literature. This underscores the importance of reducing turnaround times to alleviate ED overcrowding and improve patient outcomes. Streamlining the laboratory testing process is essential to achieving these goals.

4. POCT as a possible solution to speed up decision making in an overcrowded ED:

Time is a critical factor in urgent medical situations such as heart attacks, strokes, severe infections, and acute heart failure. The current recommended timeframes for treating these conditions are stringent, with door-to-balloon time for heart attacks and door-to-needle time for strokes being less than 90 minutes and 4.5 hours, respectively. Achieving these deadlines requires rapid triage in the emergency room and the availability of efficient diagnostic and risk assessment techniques, such as troponin, procalcitonin or natriuretic peptides, to identify patients who require urgent revascularization or treatment. However, the reliance on central laboratory testing can be a challenge in providing efficient laboratory diagnostics (448). It is true that historically, the size and complexity of equipment required for medical testing necessitated the use of centralized hospital laboratories. But with advancements in technology, it has become increasingly feasible to perform common clinical investigations at the point of care (449) with a reasonable level of accuracy, as long as essential quality specifications are met (450).

POCT refers to the administration of diagnostic tests outside of a central laboratory, at or near the location of the patient. The primary advantages of POCT devices include increased portability and speed. Caregivers can perform, analyze, obtain, and act on test results at the bedside within minutes, significantly faster than if samples were sent to a central laboratory. When used effectively, POCT has the potential to facilitate clinical decision-making in the

diagnostic process, including rule-in or rule-out, treatment selection, decrease delays in treatment initiation, increase efficiency in the emergency department, positively influence patient management, and alleviate the negative effects of overcrowding.

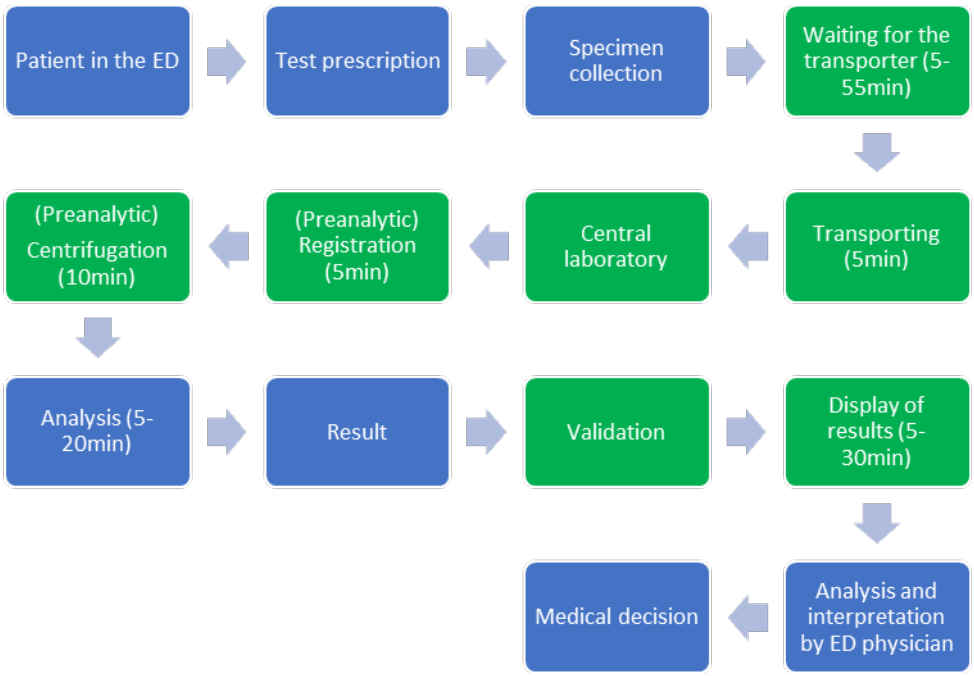


Figure 162: Comparison of laboratory testing workflows: central laboratory testing versus point-of-care testing with reduced steps highlighted in green (451).

POCT has the potential to minimize TAT by providing quicker decisions regarding patient admission and discharge, earlier and more accurate diagnosis, fewer tests, and shorter length of stay (452). Numerous reports have highlighted decreases in TATs for test results with the use of POCT in an emergency setting (453,454):

- One study compared TATs between POCT and laboratory testing when a tube transport system was implemented for the rapid transport of samples. It concluded that even under circumstances that sought to minimize sample transit times, POCT results were available an average of 46 minutes earlier than from the central laboratory (455).

- Another study has compared POCT and central laboratories and have found that at least 60 minutes can be saved through the use of POCT. Additionally, POCT can help to reduce errors related to tube labeling, sampling methods, and other issues, leading to time and cost savings, demonstrating a significant reduction in sample handling and decision-making steps. For example, POCT for cardiac markers has been found to reduce turn-around-time from 72 minutes (in a central laboratory) to 20 minutes (456).
- Several studies evaluating POC pregnancy testing in the emergency department (ED) found that regardless of whether ED staff evaluated pregnancy status by using urine or a qualitative human chorionic gonadotropin immunoassay kit, POCT could yield sufficiently sensitive results faster than if samples were sent to a central laboratory (457) as processing and handling delays inherently extended laboratory TATs.
- Simulation studies of ED activity have demonstrated the impact of reducing the time-to-result for cardiac marker tests from 120 minutes to 10 minutes on the length of stay, average number of diversion days, average number of diversion hours per day, and percentage of diversion days, while also increasing ED productivity (458). Observations before and after the implementation of POCT have shown a reduction in the median length of stay, with a greater effect on admitted patients compared to those discharged (459).
- A study by Jarvis et al. compared a "nurse-led triage model" with laboratory-analyzed samples to a "consultant-supported rapid assessment model" with POCT, resulting in a reduction in the median time for patients to be declared ready to leave the ED of 53 minutes (460).
- Kankaanpää conducted a larger study of an ambulatory ED population in three phases: (i) current practice supported by laboratory testing, (ii) POCT implementation, and (iii) the introduction of an "early assessment team." The results showed that POCT reduced the median length of stay by 29 minutes, with the addition of the early assessment team reducing the total median time saved to 46 minutes (461).

- Holden et al. found in a critical review that POCT in EDs leads to a reduction in the length of stay, waiting time, and the number of patients leaving without being seen (462).
- Interfacing POCT equipment with a clinical order communication system has also reduced the time to report results, with POCT results available in 23 minutes compared to laboratory results available in 60 minutes (463).
- The use of an air tube system for rapid return of laboratory results has been reported, although Nørgaard and Mogensen found that POCT still delivered results faster (by 46 minutes) (464).

5. Practitioners' perceptions of point of care testing: positive and negative Opinions:

5.1. Positive opinions:

The results of our study showed that a large majority of practitioners (92.58%) were in favor of implementing POCT and provided various reasons to justify their favorable position. Specifically, 87.96% of practitioners saw the benefit of POCT devices in obtaining faster results, enabling them to make earlier medical decisions. Additionally, 71.30% of practitioners saw the benefit of POCT devices in the setting where patients required frequent testing since it employed less manpower, and 45.37% of practitioners saw the benefit of POCT devices in lowering the cost of care.

Our findings are consistent with those of L. Vuillaume et al. (407), whose study revealed that 98% of physicians believed that obtaining faster results for certain biomarkers would be beneficial to their patients and the quality of care provided to them.

Our results are also consistent with a UK study conducted by P. Turner et al., (408) which provided qualitative data indicating mixed attitudes towards POCTs, similar to our study. Some

respondents felt that POCTs would enable faster decisions, stating that "Quick results enable fast decisions".

The high interest in POCT devices among the majority of practitioners could be attributed to their potential for more efficient and accessible testing, which allows for faster diagnoses and treatment decisions. As a result, this could lead to improved patient outcomes and increased satisfaction with the healthcare experience.

5.2. Negative opinions:

In our study, we found that the majority of practitioners (92.64%) saw added benefits to POCT devices, whereas only 5 practitioners (4.36%) reported not seeing any added benefit. The minority's disinterest in POCT devices could suggest that they are aware of the potential disadvantages associated with implementing such devices, such as limitations in accuracy and reliability compared to traditional laboratory testing methods. Additionally, the costs and infrastructure requirements of implementing POCT devices may also pose challenges.

One of the most significant limitations, as identified by practitioners in our study, was related to errors caused by POCT devices. Specifically, 85 practitioners (78.70%) attributed POCT device-related errors to sampling errors, 79 practitioners (73.15%) attributed them to their operators, 67 practitioners (62.04%) attributed them to the reagents being used, 63 practitioners (58.33%) said they were caused by calibration errors, and 55 practitioners (50.93%) related them to the environment. These results highlight the importance of properly training operators and ensuring accurate calibration of devices to minimize errors.

Our study's findings align with those of a UK study conducted by P. Turner et al. (408). Although this study did not provide quantitative data, it did provide qualitative data that revealed that both facilitators and barriers affected the adoption of POCTs in primary care, according to Turner et al. clinicians have concerns about of POCT devices. Some clinicians expressed concerns about the potential for excessive testing of patients, driven by both doctors and patient demand.

Others expressed concerns about the accuracy of results obtained from POCTs, particularly for diagnostic purposes. Additionally, some clinicians felt that there was no point in doing a test if you did not know how to interpret and explain it, indicating the need for proper training and education on the use of POCT devices and biomarkers.

Concerning errors related to POCT, the challenges associated with implementing POCT in the emergency department (ED) can be addressed through the use of internal quality control and external quality assessment (EQA) methods. Internal quality control methods help to ensure that devices are producing accurate and consistent results by analyzing the output of a control sample. Device manufacturers may provide the necessary control materials, or other control samples can be used. Likewise, many devices offer internal quality control functionality and may require quality control checks to be performed and documented before releasing patient results. If the POCT device has network access, then quality control measurements can be integrated into a central data management system. EQA involves the use of samples containing an unknown-to-the-operator value of reagent received from an external source, such as from an accredited EQA program or device manufacturer.

In conclusion, our study's findings suggest that practitioners generally see added benefits to the use of POCT devices, although a minority expressed disinterest. Practitioners also identified potential limitations associated with the implementation of POCT devices, such as the risk of errors. These findings emphasize the importance of properly training operators and ensuring accurate calibration of devices to minimize errors. Furthermore, the facilitators and barriers to POCT identified in our study align with those previously reported in the literature, indicating that these are common concerns among clinicians.

6. Investigating healthcare practitioners' levels of training prior to using POCT:

The contemporary advancements and continuing developments in clinical laboratory technology have a significant influence on the requirements of healthcare personnel. Therefore, one of the objectives of our study was to investigate the level of training that healthcare practitioners received prior to using POCT devices.

The results of our study showed that a significant proportion of healthcare practitioners (79.63%) who use POCT devices did not receive any training prior to their usage, only a minority of practitioners (20.37%) received training before using POCT devices.

Our results are consistent with a previous study conducted in Rabat and Casablanca, which found that POCT training was not provided to staff in 92% of cases (465).

These findings highlight the concerning issue of the absence of training provided to the healthcare practitioners in the use of POCT devices, which may potentially result in inaccurate and unreliable test results, leading to inappropriate clinical decision-making and patient management.

6.1. Overview on the literature in POCT training and legislature:

It is crucial to consider the issue of training in POCT because POCT, like any other laboratory process, can be subject to errors. A study conducted by Cantero, et al. (466) compared the error rates between POCT and central laboratory testing. The study revealed that POCT had a higher rate of errors in the pre-analytical phase compared to central laboratory testing. The study emphasizes the need for adequate training and monitoring of practitioners to ensure the accuracy and reliability of POCT results.

The implementation of POCT in the emergency department is associated with important challenges that need to be addressed. POCT places additional responsibilities on ED healthcare providers. These individuals must undergo regular training and meet certification requirements

for quality assurance purposes, which can place additional burdens on an already heavy workload. However, expediting patient flow through POCT might help to reduce this strain on staff. Additional oversight and regulatory challenges will exist for any substantial implementation of POCT in the ED. These costs must be weighed against the potential gains in efficiency and patient care that can realistically be expected to be achieved with POCT.

As of today, the Moroccan legislature has not addressed the topic of POCT. Instead, all current laws and regulations focus solely on central laboratory testing (467). Consequently, in the present discussion, we will refer to the legislative frameworks and international standards established by France, the USA, the International Organization for Standardization (ISO), and recommendations made by relevant medical societies.

There exist a multitude of standards and guidelines that officially outline how POCT should be implemented, managed, and monitored for performance quality. These professionally-based guidelines usually follow a similar format, providing comparable information, such as staff training and competency assessments (468–470).

Organizations with a centralized biomedical laboratory should adhere to POCT-specific requirements for quality and competence based on ISO 22870:2016, which must be used alongside ISO 15189:2012 in hospitals, clinics, and ambulatory care facilities.

To help meet the POCT training and competency assessment requirements, Table 42 provides a list of selected International Organization for Standardization (ISO) standards to consider (373,374,471–476).

Table LVII: International Standards for Medical Laboratory and POCT Competency and Training.

Standard	Definition	Scope of the Document
ISO 17593:2007	Requirements for in vitro monitoring systems for self-testing of oral anticoagulant therapy	Specifies requirements for in vitro monitoring systems for self-testing of oral anticoagulant therapy, including performance, quality assurance, and user training and procedures for the verification and validation of performance by the intended users under actual and simulated conditions of use. The standard is applicable only to PT measuring systems used by individuals for monitoring their vitamin-K antagonist therapy and reporting results as international normalized ratios (INR).
ISO 15189:2012	Medical laboratories – particular requirements for quality and competence	Specifies requirements for quality and competence in medical laboratories. It can be used by medical laboratories to develop their quality management systems and assess their competence. The standard can also be used to confirm or recognize the competence of medical laboratories by laboratory customers, regulating authorities, and accreditation bodies.
ISO 15197:2013	Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus	Specifies requirements for in vitro glucose monitoring systems that measure glucose concentrations in capillary blood samples, including design verification procedures and the validation of performance by intended users for self-measurement by laypersons for managing diabetes mellitus. The standard applies to manufacturers of such systems and other organizations, such as regulatory authorities and conformity assessment bodies, that have the responsibility for assessing the performance of these systems.

Table LVIII: International Standards for Medical Laboratory and POCT Competency and Training. (suite…)

Standard	Definition	Scope of the Document
ISO 22870:2016	POCT – requirements for quality and competence	Gives specific requirements for POCT and is intended to be used in conjunction with ISO 15189. The standard applies to POCT carried out in a hospital, clinic, and by a healthcare organization providing ambulatory care. The requirements of this standard apply to transcutaneous measurements, the analysis of expired air, and in vivo monitoring of physiological parameters. Patient self-testing in a home or community setting is excluded, but elements of this standard can be applied.
ISO/TS 22583:2019	Guidance for supervisors and operators of POCT devices	Provides guidance to supervisors and operators of POCT services that lack medical laboratory training, supervision, or support. The guidance outlines the essential components that must be taken into account to ensure the provision of accurate and secure POCT results.
ISO/TS 20914:2019	Practical guidance for the estimation of measurement uncertainty	Provides practical guidance on how to estimate and express measurement uncertainty for quantitative measurand values produced by medical laboratories, including those generated by POCT systems near the medical decision threshold. It also covers the estimation of measurement uncertainty for results obtained through qualitative (nominal) methods that involve a measurement step. However, it is not recommended to routinely include estimates of measurement uncertainty with patient test results, but they should be made available upon request.
ISO 15190:2020	Requirements for safety	Specifies requirements to establish and uphold a secure work environment in a medical laboratory. As is the case with all safety protocols, the requirements are outlined to define the laboratory safety officer's role and duties in guaranteeing that each employee takes accountability for their safety and the safety of others who may be impacted.

To have an effective POCT program, it's crucial to plan thoughtfully and oversee and supervise it continuously (477–479). The US's Joint Commission International (JCI) mandates that a qualified individual should be responsible for supervising and overseeing the POCT program

(480). The leadership team can be involved in the planning process by approving the resources allocated to the POCT program and the policies and procedures related to its management and oversight (481,482).

It's essential to note that many countries have licensure laws that restrict non-technical staff from conducting certain testing procedures (483,484). In the US, CLIA requirements do not permit non-technical staff to conduct some testing procedures related to moderate- and high-complexity tests (485).

6.2. Training requirements for POCT:

The majority of the staff performing POCT are not laboratory staff and may not be knowledgeable about testing processes, such as patient preparation, sample collection, instrument calibration, maintenance, and quality control. Therefore, it's crucial that staff performing POCT receive proper training and competency assessments to ensure the accuracy and reliability of test results. Alternatively, laboratory staff may take responsibility for some POCT activities, such as managing instrument maintenance and responding to instrument failures.

Before training for POCT, staff members must have their qualifications verified. Each qualified POCT user must complete initial training and orientation on each test method before testing initiation and after any changes or updates in instrumentation, kits, or test methods. Initial training must include direct observation, documented, and retained in the individual's training record. Following any changes or updates in methodology, personnel must receive training and documentation before performing patient testing.

All training must be performed by a qualified individual, such as a certified laboratory technical staff or the manufacturer/company representative, and the competency of the tester verified before performing patient testing. A qualified trainer must have demonstrated competency for all methods for which training is being conducted (486).

6.3. Competency assessment requirements for POCT:

Competency refers to the ability of staff to perform their job duties effectively and safely. In the context of training, competency assessment evaluates how well employees have learned the skills taught in training and how well they can apply these skills in their job. The objective being to ensure that they are producing accurate and reliable results and providing high-quality patient care.

The process of competency assessment should be outlined in policies and procedures, which must be approved by the laboratory director and reviewed periodically. Each employee must have their competency assessed and documented after training and before performing patient testing. Ongoing competency assessment must also be completed at designated intervals for each test method that the employee performs.

To comply with regulations, competency must be assessed for each non-waived POCT at six and 12 months following initial training and annually thereafter. Competency assessment should cover all phases of testing, including pre-analytic, analytic, and post-analytic phases.

Various assessment tools can be used for competency assessment, such as checklists, case studies, quizzes, and review of retained records. The appropriate tools should be selected and applied to evaluate each employee's competency, with the results evaluated, reviewed with the employee, and documented for record-keeping purposes.

One of the significant challenges of POCT is managing the training and competency assessments of multiple operators in different locations, many of whom are not laboratory professionals (487). To report outpatient results, every operator must receive documented training on each device. Ongoing assessments are performed at the first six months and then annually thereafter. In a large healthcare organization, there may be several device types and thousands of operators, making it challenging to track their training and assessments.

To address this challenge, facilities may opt to use an online training tool such as a learning management system (LMS) to track a large number of POCT operators. POCT

management software can also automate reminders for users who are due for their competency assessment. Additionally, when devices are capable, the POCT management software can prevent users from using a device until their certification is valid (488).

6.4. Personnel qualified to perform competency assessment:

The ISO 22870:2016 standard recommends that organizations establish a multidisciplinary committee to oversee POCT services. This committee is responsible for designating staff to perform POCT and implementing a training and competency assessment program for POCT operators. The technical consultant is responsible for assessing the competency of personnel performing moderately complex testing, which is required for CLIA compliance.

The laboratory director can serve as the technical consultant and perform competency assessment if they meet the qualifications for the position. The technical consultant is not required to undergo annual competency assessment. However, the laboratory director is responsible for ensuring that all testing personnel are competent and consistently report accurate results (489).

6.5. The multidisciplinary aspect of POCT testing:

Medical biology exams that are performed outside of traditional laboratory settings are subject to regulations outlined in the ISO 22870 standard requirements for quality and competence. It provides specific requirements for POCT and emphasizes a shared clinical and biological management approach by mandating the creation of an advisory committee and a disciplinary committee, each with their own respective missions. Therefore, POCT involves a group of medical and paramedical professionals (Figure163) to ensure optimal patient care. The organizational chart is as follows:

- The advisory committee (consisting of healthcare professionals) is responsible for defining the scope of use of POCT.
- The multidisciplinary supervisory group (representatives from the laboratory, administrative members, and clinical teams) is responsible for the field of use of POCT. The scope of use, missions, and responsibilities of each group are defined in clinical and biological contracts.
- Within the laboratory, each actor has responsibilities and tasks in accordance with their job description. The laboratory is responsible for ensuring analytical quality through maintenance and internal and external quality controls. It is also responsible for training healthcare personnel and maintaining their competencies to ensure safety in result reporting.
- Within the clinical department, the categories of healthcare professionals authorized to perform POCT outside of a medical biology laboratory are set. The department agrees to respect the laboratory's specifications to preserve the conformity of the sample, which ensures reliable results for the clinician.
- Support services: The quality control department establishes the quality policy through a Quality Management System and ensures that it constantly meets normative requirements and improves continuously. The IT department ensures continuity of result reporting between laboratory, supplier, and clinical service software. IT system qualification is required by the ISO 22870 standard. The procurement/logistics unit is responsible for implementing the "procurement" process for consumables and reagents in compliance with laboratory or clinical service procedures, establishment policies, and public procurement regulations. The biomedical engineering department is responsible for managing the POCT equipment, maintenance, and metrology.

This multidisciplinarity creates an intrinsic complementarity of disciplines, allowing each party's needs to be met in order to offer a tailored solution to the patient's needs, as well as a collaborative approach to problem-solving.

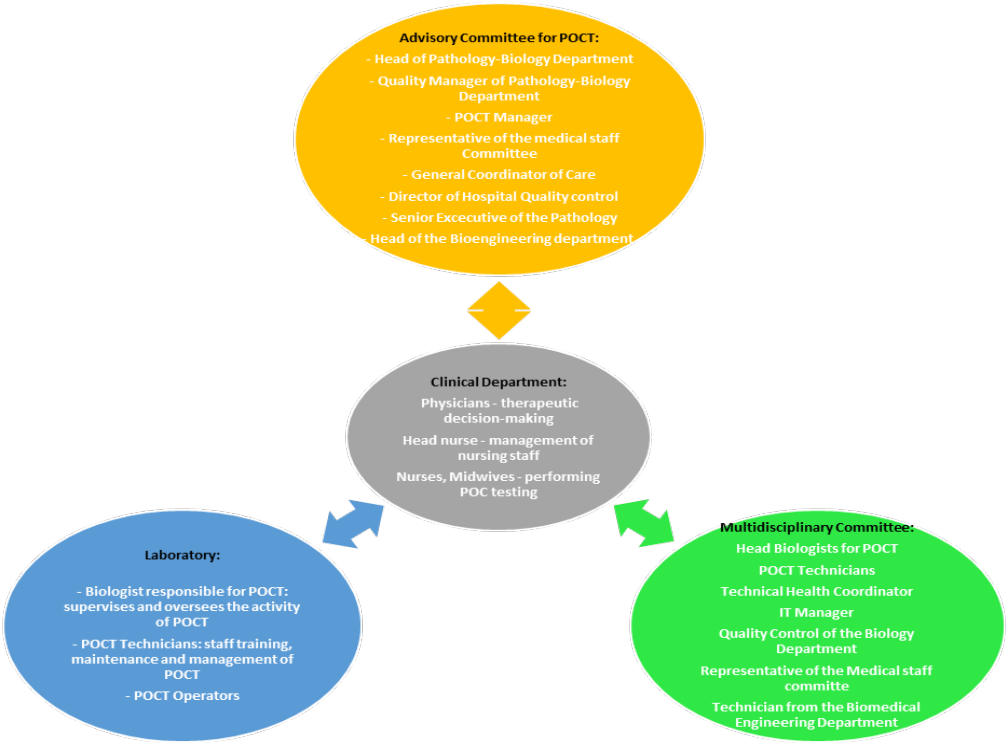


Figure 163: Navigating the multidisciplinary aspects of point of care testing implementation and adoption in hospitals.

6.6. Conclusion:

The most important finding of our study is that healthcare practitioners possess and use POCT devices despite not being fully aware of the term "point of care testing". Most of these devices could be classified as TRODs, rapid diagnostic orientation tests such as glucometers, urine dipsticks, and pregnancy tests.

Our study highlights the high level of interest among healthcare practitioners in implementing POCT devices to measure other biomarkers. This high level of interest is motivated by the perceived negative effects of overcrowding in the ED and the believe that lab results

significantly delay patient care and contribute to overcrowding in the ED. Therefore, practitioners are also motivated to implement POCT because they perceive added benefits of convenience, faster TAT, and lower costs.

While the majority of practitioners expressed enthusiasm for POCT, a small minority had reservations related to device-related errors. These findings underscore the importance of addressing these concerns and inform practitioners about quality control for POCT.

While POCT devices are available for some of the most frequent pathologies in the ED, practitioners express a need for POCT for specific biomarkers for certain pathologies, such as troponin for ACS, d-dimer for PE, BNP/NT-pro BNP for CHF, CRP and Procalcitonin for sepsis, and S100B for TBI. These are pathologies where time is of the utmost importance, and where most patients will test negative using exclusion biomarkers, which allows for early discharge.

Unfortunately, the enthusiasm for POCT is met with a concerning finding that the majority of practitioners have not received any training for POCT

It is important to note that POCT is not a panacea for all of the issues related to laboratory result delays and ED overcrowding. There are several challenges that must be addressed in order to effectively implement POCT in the ED. These include ensuring the accuracy and reliability of POCT devices, training staff to properly use and maintain the equipment, and developing protocols for integrating POCT results into patient care.

These findings suggest that in order for the implementation of POCT devices to be successful, it will be necessary to prioritize education and training for practitioners to ensure safe and effective use of POCT devices in clinical settings. This may require policy changes, such as mandating POCT training for healthcare practitioners, ensuring that the training is standardized and consistent, and providing ongoing support and education to practitioners to maintain their skills and knowledge.

Clinical pathways and ED logistics may need to be substantially modified in order to maximize the clinical and economic benefits of the rapid turnaround times (TATs) provided by

POCT. Additionally, the direct cost per analysis for the majority of POCT devices is higher than the cost per analysis in centralized laboratories. However, when taking into account the numerous manual steps required for transferring a blood sample to the central laboratory and retrieving the results consecutively, the total costs of POCT devices are comparable to those of central analysis. Clinical trials in academic hospitals did not reveal clear disadvantages of POCT compared to central analysis, while trials in rural regions were in favor of POCT.

7. Knowledge and Use of Biomarkers:

7.1. Familiarity of healthcare practitioners with the term 'Biomarker':

Biomarkers are crucial components of modern medicine, and their usage has increased significantly over the last few decades (490). However, it is uncertain whether healthcare practitioners are aware of the term and its significance. The aim of this question was to investigate the familiarity of healthcare practitioners with the term "biomarker".

In our study, we found that a significant proportion of participants (65.74%) were unfamiliar with the term "biomarker", only 34.26% were familiar with it.

This disparity could be attributed to the fact that the term "biomarker" is relatively novel, and healthcare practitioners may be more familiar with analogous terms such as "laboratory tests", “biological assays” or "biomolecules".

To contextualize these findings, we conducted a search of faculty course materials and found that the term "biomarker" was used in only 6 instances, 2 of which in cardiology, 3 in neurology and 1 in pediatrics. In its place, we found instances where the term "marker" was employed 329 times, such as in the case of "biochemical markers" and "cardiac markers" in Biochemistry courses.

Moreover, we identified specific biomarkers and their corresponding titles within the course materials. For instance, troponin was listed under the heading "Biological assays," while

D-dimers were categorized under "Paraclinical assessment." B-type natriuretic peptide (BNP) and N-terminal pro b-type natriuretic peptide (NT-pro BNP) were classified under "Biology," while C-reactive protein (CRP) and procalcitonin were listed under "Complementary assessment" or "Biology."

Another explanation could be that despite being a common part of modern science and medicine, the terms "biomarker," "surrogate marker," and "surrogate endpoint" only became more widespread in the 1980s and have only seen a recent increase in usage in recent years (491,492). A review of papers indexed in PubMed shows a surge in interest in biomarkers since 2005, with a particularly significant increase since 2010. Prior to this, the number of papers citing the word "biomarker" was in the tens or low hundreds. Approximately half of all publications on the topic have only been produced since 2014.

Studies have shown that it can take a significant amount of time for medical knowledge to be incorporated into clinical practice. For instance, a study by Putera et al. (493) found that it took a median of 16 years for pivotal clinical trial publication to result in meaningful uptake of class IA ACS therapies into clinical practice. Similarly, Morris et al. (494) conducted a broader study that aimed to synthesize existing knowledge on the time lag in health research. The study estimated that the time lag in the translation process of research to practice was 17 years. However, this time varied widely depending on the study and aspect of the process being measured. Notably, one study reported a time lag of up to 50 years.

Given the relatively new nature of the term "biomarker", the long-time lag that is often present in the adoption of new medical knowledge and the absence of this term from our university courses. it is reasonable to expect that many practitioners may not yet be familiar with this term. Nevertheless, more than a third of practitioners in our study were aware of it and the increasing interest in biomarkers and the significance of their role in modern medicine suggests that it is only a matter of time before the term becomes more widespread in the medical community.

7.2. Perceptions and awareness of the utility of biomarkers:

Biomarkers have become an increasingly important tool in modern medicine, with potential applications in disease diagnosis, prognosis, monitoring and response to therapy (1,9,491,495). Despite their potential, the extent to which medical practitioners recognize their utility remains unclear. This question aimed to investigate the extent to which medical practitioners recognize the potential applications of biomarkers in healthcare.

In the survey, 85.19% of the practitioners recognized that a biomarker can aid in the diagnosis of a disease. Additionally, 73.15% reported that biomarkers could be used in monitoring the disease, and 60.19% said it could be used to determine the prognosis of a disease. Furthermore, 49.07% believed in the potential of biomarkers in predicting and monitoring the therapeutic response. Only 44.44% recognized the potential of biomarkers in risk stratification, while 10.19% of participants reported not knowing about the use of biomarkers in medicine. Interestingly, 38.88% of the participants selected all the applications of biomarkers listed in the survey, suggesting a comprehensive understanding of the role of biomarkers in healthcare.

Traditionally, biomarkers have been taught in medical education primarily for their diagnostic use and sometimes for prognostic use. However, the results of our study suggest that there is an increasing understanding and appreciation of the multi-faceted role that biomarkers play in healthcare. This is a promising finding as it indicates that the medical community is beginning to recognize the importance of precision medicine and the role of biomarkers in personalized healthcare.

While the results of our study are encouraging, it is important to note that only a minority of participants recognized the potential of biomarkers in risk stratification. Given that biomarkers can aid in identifying individuals at higher risk of developing a disease, this highlights an area where further education and awareness among medical practitioners may be needed.

In conclusion, our study highlights the increasing understanding and appreciation of the multi-faceted role that biomarkers play in healthcare among medical practitioners. The results suggest that a significant proportion of practitioners recognize the use of biomarkers beyond just diagnosis and that there is an increasing awareness of their potential in monitoring disease progression and prognosis. However, the study also highlights an area where further education and awareness among medical practitioners may be needed, specifically in the potential of biomarkers for risk stratification and predicting therapeutic response.

7.3. Difficulty in interpretation and selection of biomarkers:

Biomarkers play a crucial role in the diagnosis and management of various diseases. However, interpreting biomarker results can be challenging and requires specialized knowledge and training. In this study, we aimed to evaluate healthcare practitioners' self-reported experience with biomarker interpretation. Participants were asked to choose from three options regarding their perceived experience with biomarker interpretation.

Of the sample, 81.48% indicated that they had difficulty interpreting biomarkers' results, while 37.04% reported difficulty in choosing biomarkers to test for. Interestingly, 29.62% selected both options "cannot interpret results for biomarkers" and "don't know which one to use". In contrast, 12.04% reported not facing any difficulties with biomarker interpretation.

The results of this study highlight the challenges that practitioners face when it comes to selecting and interpreting biomarker tests. This finding is consistent with previous studies that have identified a lack of knowledge and training among healthcare professionals when it comes to choosing and interpreting biomarker test results. Hickner et al. (496) found that primary care physicians commonly encounter challenges and uncertainties when it comes to requesting and interpreting diagnostic laboratory tests. Specifically, they reported experiencing uncertainty in requesting tests in 14.7% of encounters and uncertainty in interpreting the results in 8.3% of encounters. The difference in the population studied between our study and that of Hickner et al.

may have contributed to the observed differences in rates of uncertainty. Our study focused on training physicians in the emergency department, who may have different levels of experience, training, and familiarity with diagnostic laboratory tests compared to physicians who have completed their training, as studied by Hickner et al.

Proper test selection and interpretation have a significant impact on patient outcomes, morbidity, mortality, and healthcare costs (497). Clinicians need to be aware of various methods available to them to improve test selection and interpretation and utilize them to optimize patient care. To improve laboratory test selection and interpretation, reviewed methodologies such as the use of sensitivity, specificity, predictive values and likelihood ratios to estimate the ability of a test to identify a clinical condition, and receiver operating characteristic (ROC) curves can be applied (498). In this study, we also explored the knowledge of participants on Sn, Sp, predictive values, ROC and likelihood ratios, and the results will be discussed later.

Our study highlights the challenges faced by healthcare practitioners in selecting and interpreting biomarker tests, which is particularly concerning given the growing number of available tests with varying levels of accuracy and clinical utility. Without adequate guidance and education, practitioners may struggle to choose the most appropriate test for their patients, potentially leading to suboptimal treatment decisions. Therefore, there is a need for better guidance and decision-making tools, as well as increased education and training for practitioners, to improve patient outcomes and reduce healthcare costs. Clinicians should be aware of reviewed methodologies that can improve test selection and interpretation to optimize patient care.

8. Overall performance on the questionnaire:

In this subsection, we aimed to assess the knowledge of medical practitioners on biostatistics and six biomarkers, including troponin, BNP/ NT-pro BNP, D-dimer, procalcitonin,

CRP, and S100B, through a questionnaire consisting of 75 graded multiple-choice questions (MCQs).

Our study revealed significant knowledge gaps among medical practitioners regarding biomarkers. The average score obtained on the questionnaire was 11.05 out of 75, with a standard deviation of 6.648 and a median score of 10.00, indicating that medical practitioners scored poorly on the biomarker knowledge test. Only 30.56% of respondents scored at least half of the maximum score which was 29 out of 75.

The prevalence of "don't know" responses in the MCQs provided valuable insight into the state of knowledge among medical practitioners. A high rate of "don't know" responses in specific sections highlighted a lack of comprehension on specific topics and served as a reliable metric for identifying knowledge gaps.

In our study, a large percentage of responses in various biomarker and biostatistics sections were "Don't know." Specifically, "Don't know" accounted for 85.79% of responses in the S100B section, 66.32% in the BNP/NT pro-BNP section, 65.97% in the PCT section, 59.10% in the CRP section, 54.04% in the troponin section, 33.70% in the D-dimer section, and 29.37% of responses in the biostatistics section. Overall, "Don't know" represented 42.71% of responses, indicating a lack of knowledge or understanding about the biomarkers and biostatistics being studied.

The high rate of "don't know" responses in specific sections, such as the S100B section, indicates that there is a lack of awareness among medical practitioners regarding the use of certain biomarkers in clinical practice. S100B is a protein that has been identified as a potential biomarker for brain injury, and the high rate of "don't know" responses in this section suggests that healthcare professionals may not be aware of its clinical significance. Similarly, the high rate of "don't know" responses in the BNP/NT pro-BNP section indicates that there may be a lack of knowledge regarding the use of these biomarkers in heart failure.

In conclusion, our study highlights the need for targeted educational interventions to address the knowledge gaps among medical practitioners regarding biomarkers. The results of our study can serve as a valuable guide for the development of educational programs to enhance the competency of medical practitioners in the field of biomarkers.

9. Analysis of clinician's knowledge on biostatistics:

Based on our study results, it appears that the participants' performance in the biostatistics subsection was suboptimal. The mean score of 4.45 out of 16 suggests that, on average, participants answered only about 28% of the questions correctly. The standard deviation of 3.187 indicates that there was a wide range of scores among the participants, with some scoring much higher or lower than the mean. Additionally, the median score of 4.00 suggests that the distribution of scores was skewed, with more participants scoring towards the lower end of the scale. This is further supported by the fact that 81% of participants scored less than half of the maximum score on this subsection, indicating that a significant proportion of the participants struggled with the biostatistics questions.

9.1. Pretest probability:

The results indicate that there is a lack of consensus among physicians on how to assess pre-test probability of a disease. Approximately 26.85% of the participants reported that they do not consider pre-test probability in their practice, while the majority of the participants reported using different methods to estimate it. The most common methods reported were using clinical scores (43.52%) and the prevalence of the disease (45.37%) as a guide. Approximately 37.96% of the participants estimated pre-test probability intuitively, and 40.74% used the position of the hypothesis on the differential diagnosis list.

It is concerning that a significant proportion of the participants, 26.85%, did not consider pre-test probability when making diagnostic decisions, as pretest probability plays a crucial role in the interpretation of any diagnostic tests, including biomarker. The post-test probability of a disease, after a diagnostic test is performed, depends not only on the test's characteristics (499) but also on the pretest probability. Failure to adequately consider pretest probability can lead to incorrect diagnostic conclusions. A positive test result with a low pretest probability, for example, may result in a premature ruling-in of a diagnosis, even though the likelihood of the disease being present was initially low. Similarly, a negative test result with a high pretest probability may result in a premature ruling-out of a diagnosis, even though the likelihood of the disease being present was initially high. These types of errors inform us on the potential for physicians to place too much importance on diagnostic tests and assume they are 100% accurate and highlight the need for physicians to be aware of the limitations of diagnostic tests and to consider pretest probability in their interpretation. By doing so, they can avoid over-reliance on test results and ensure that diagnostic decisions are made in a comprehensive and accurate manner.

A study conducted by Agoristas et al. aimed to assess whether physicians correctly estimate post-test probability according to various levels of prevalence (500). They used a randomized trial involving a population-based sample of 1,361 physicians of all clinical specialties using a mail survey among physicians of all clinical specialties working in Geneva, Switzerland. The study found that most physicians do not take into account the prevalence of disease when interpreting a positive test result. In a previous investigation, Lyman et al. used a cohort consisting of 50 medical professionals affiliated with the university of South Florida to assess the post-test likelihood of disease based on three levels of prevalence (501). The respondents exhibited a general tendency to disregard information regarding prevalence. Other studies have observed that the pretest probability of disease is often ignored. Namely, Other studies have corroborated the notion that physicians possess limited proficiency in estimating

post-test probabilities. For instance, Steurer et al. found that 78% of Swiss general practitioners failed to select the correct range of post-test probability when presented with a positive screening test and a disease prevalence of 1% (502). Similarly, Sox et al. found that only 83% of American pediatricians wrongly estimated post-test probability when presented with a negative test result and a disease prevalence of 30% (503). In a third study by Schwartz et al. ,that encompassed US students, house officers, and physicians, more than 50% of the respondents greatly overestimated post-test probability (>50%, while the correct response was 9%) in the context of a positive screening test and a disease prevalence of 0.5% (504).

The results from these five studies were found to be consistent with our own, indicating a worrisome trend among physicians regarding their ability to accurately estimate probabilities in clinical settings. Specifically, our study revealed that a little more than one in four participants self-reported not taking pre-test probability into consideration when making diagnostic decisions. The five studies we referenced, utilizing diverse methodologies, similarly discovered that a considerable proportion of physicians did not incorporate pretest probability of disease when interpreting test outcomes.

On the other hand, the results of our study are encouraging in the sense that the majority of the participants reported considering pretest probability in their diagnostic decision-making process. The use of different methods to estimate pretest probability, such as using clinical scores, the prevalence of the disease, intuitive estimation, and the position of the hypothesis on the differential diagnosis list, demonstrates that physicians are aware of the importance of this concept. Each may have its own strengths and limitations, and the choice of method may depend on the individual case and the information available.

9.2. Clinical scores:

In our study, 43.52% of clinicians reported using clinical scores. Some examples of validated clinical scores for pretest probability include: Wells score for deep vein thrombosis

(DVT), CHADS2 score for stroke risk in atrial fibrillation, HEART score for acute coronary syndrome, PERC score for pulmonary embolism, Modified Alvarado score for appendicitis, CURB65 Score for Pneumonia severity.

Their advantages in general include:

- They reduce the need for burdensome biostatistical calculations that are rarely done in practice.
- They aid clinicians in recalling the most informative diagnostic and clinical features.
- They standardize decision-making among different clinicians.
- They are less prone to bias than conventional decision-making.
- Disadvantages include (505):
- They exist only for a minority of diagnoses and clinical situations.
- They do not incorporate uncommon yet strongly predictive features.
- They do not all prediction rules are sufficiently validated or have been shown to improve outcomes.
- They can inadvertently incorporate author biases into the standard of care
- They may underperform compared to expert opinion.
- They do not take into account patient preferences or different risk tolerances.

In summary, validated clinical scores for pretest probability can be a helpful tool for clinicians, but they should be used in conjunction with clinical judgement and individual patient factors. Despite their name, clinical prediction rules should be viewed as guides rather than strict rules that must be followed dogmatically. Clinicians should be aware of the limitations and potential biases associated with clinical scores and use them appropriately.

9.3. Disease prevalence:

In our study, 45.37% used the prevalence of the disease as a guide intuitively. Pretest probability is the probability of a patient having a particular disease or condition before any

diagnostic tests are conducted. Prevalence, defined as the proportion of individuals in a population with a particular disease or condition at a given point in time, is commonly used to estimate pretest probability in clinical practice. In this section, I will discuss how doctors use prevalence to estimate pretest probability, its advantages and disadvantages, and how it affects clinical decision-making.

One of the primary advantages of using prevalence to estimate pretest probability is that it is a readily available and easily understandable metric. Doctors can use population-level prevalence estimates to get a sense of the likelihood of a particular disease in a patient, which can help guide further diagnostic testing or treatment decisions.

However, there are also several disadvantages to relying solely on prevalence to estimate pretest probability. For one, prevalence estimates may not be representative of the patient population in question. Different populations may have varying prevalence rates of certain diseases, such as those presenting to the GP's office or the ED. Prevalence may also change over time due to changes in diagnostic criteria or treatment options. Another issue with relying on prevalence is that it does not account for individual patient characteristics or risk factors. For example, a patient with multiple risk factors for a particular disease may have a higher pretest probability than the general population, even if the disease is relatively rare in the population as a whole. Conversely, a patient without any risk factors may have a lower pretest probability, even if the disease is prevalent in the population.

In summary, prevalence is a useful metric for estimating pretest probability in clinical practice, but it has its limitations. Doctors should use prevalence in conjunction with other patient-specific risk factors and clinical presentation to arrive at a more accurate estimate of pretest probability, which can guide diagnostic testing and treatment decisions.

9.4. Differential diagnosis:

In our study, 40.74% used the position of the hypothesis on the differential diagnosis list. Estimating pretest probability based on the position of a hypothesis on the differential diagnosis list is another commonly used method in clinical practice. The differential diagnosis list is a list of possible diagnoses based on the patient's symptoms, medical history, and physical examination findings. In this section, I will discuss how doctors use the position of the hypothesis on the differential diagnosis list to estimate pretest probability, its advantages and disadvantages, and how it affects clinical decision-making.

One of the primary advantages of using the position of the hypothesis on the differential diagnosis list to estimate pretest probability is that it allows for the incorporation of patient-specific risk factors and clinical presentation. The differential diagnosis list is generated based on the patient's symptoms and medical history, and hypotheses are ranked based on their likelihood given the available information. Thus, a hypothesis that is high on the differential diagnosis list may have a higher pretest probability than one that is lower on the list. Another advantage of this method is that it allows for the integration of clinical reasoning and expert judgement. This approach can help to identify rare or atypical presentations of diseases that may not be captured by population-level prevalence estimates.

However, there are also several disadvantages to relying solely on the position of the hypothesis on the differential diagnosis list to estimate pretest probability. One potential issue is that the differential diagnosis list may not be comprehensive, and some hypotheses may be missed. Additionally, the position of a hypothesis on the differential diagnosis list may be influenced by biases or heuristics, such as availability bias or anchoring bias, which can lead to errors in clinical reasoning.

In summary, the position of the hypothesis on the differential diagnosis list is a useful method for estimating pretest probability in clinical practice, but it has its limitations. Doctors should use the position of the hypothesis on the differential diagnosis list in conjunction with

other patient-specific risk factors and clinical information to arrive at a more accurate estimate of pretest probability, which can guide diagnostic testing and treatment decisions. Furthermore, ongoing refinement of clinical reasoning and diagnostic processes can help to reduce errors and biases associated with this method.

9.5. Intuition:

In our study, approximately 38% of the participants reported using intuition to estimate pretest probability. This phenomenon can be attributed to the widespread use of intuition in clinical decision-making, known as decision-making by gestalt. This approach involves using clinical experience and knowledge to make an educated guess without relying on explicit algorithms or rules.

Intuition is a type of non-analytical thinking that involves the rapid processing of information based on past experience and knowledge. In clinical practice, doctors may use their intuition to arrive at a preliminary estimate of pretest probability based on the patient's clinical presentation, medical history, and other relevant factors. One advantage of using intuition to estimate pretest probability is that it can be a quick and efficient way to arrive at a preliminary diagnosis. Doctors may be able to quickly identify patterns and associations based on their past experiences, which can help guide their initial diagnostic workup.

However, there are also several disadvantages to relying solely on intuition to estimate pretest probability. One potential issue is that intuition can be influenced by cognitive biases, these biases, such as availability, anchoring, premature closure, and framing, can affect the accuracy and reliability of pretest probability estimates based on intuition (506). Furthermore, intuition may not be reliable in cases where the patient's presentation is atypical or rare, or when the doctor has limited experience with a particular disease. Another issue is that relying solely on intuition may lead to overconfidence or complacency in clinical decision-making.

In summary, using intuition to estimate pretest probability can be a quick and efficient way to arrive at a preliminary diagnosis in clinical practice, but it has its limitations. Doctors should use their intuition in conjunction with more objective methods of estimating pretest probability and remain vigilant for cognitive biases and errors in clinical reasoning.

In conclusion, our findings indicate that approximately one-third of healthcare practitioners do not consider pretest probability of disease in their clinical decision-making, while the other two-thirds make their estimation using different approaches. The estimation of pretest probability is a critical step in the diagnostic process, and usually involves three major sources (507,508): the examiner's experience, prevalence of the disease at the time of patient presentation, and clinical decision rules. While each method has its advantages and disadvantages, using multiple methods can help improve diagnostic accuracy. It is important for doctors to remain aware of limitations and potential sources of error, including cognitive biases. Continued education and training in diagnostic reasoning and clinical decision-making can improve estimation of pretest probability and lead to better patient outcomes.

9.6. The contribution of a biomarker towards a diagnosis:

When asked “Depending on the pretest probability, when does a biomarker contribute more towards a diagnosis?”. The results of our study suggest that 36.11% of the participants were unsure about when a biomarker contributes more towards a diagnosis. 25% believed that a biomarker contributes more towards a diagnosis when the pretest probability is high, while 12.04% believed that it contributes more when the pretest probability is low. Only 26.85% of the participants answered correctly.

Biomarkers are most useful for diagnosis when the pretest probability is in the mid-range. This is because when the pretest probability is close to 0% or 100%, the changes in probability are minimal and the diagnostic test has limited additional value. When the pretest

probability is close to 50%, however, the changes in probability are significant and the diagnostic test is more useful.

Empirical evidence supports the theoretical understanding that diagnostic tests are most valuable when pretest probability is in the mid-range. One such instance comes from the Breathing Not Properly trial (186), in which a nomogram was implemented to estimate the likelihood of congestive heart failure (CHF) based on pretest probability and B-type natriuretic peptide (BNP) levels. The trial demonstrated that BNP exhibited the highest diagnostic value in patients with intermediate pretest probability, where a BNP level of 100 pg/mL or greater accurately identified 74.0% of cases as having or not having CHF. Conversely, in instances where emergency department clinicians were certain that CHF was present before ordering the test, BNP levels exceeded 100 pg/mL in almost 90% of cases. Indicating that BNP served as a confirmatory test for what the clinicians were already certain about.

9.7. Biomarker performance characteristics:

Our study aimed to evaluate the understanding of diagnostic test metrics among healthcare professionals.

The results of the study indicate that a significant proportion of physicians have limited knowledge of the concepts of sensitivity and specificity in medical biomarkers. Over half of the physicians (53.7%) did not know what sensitivity refers to, with 17.6% confusing it with predictive values. Similarly, over half of the physicians (53.7%) did not know what specificity refers to, with 18.5% confusing it with predictive values. Only 17.6% of the practitioners correctly answered the question about sensitivity, and 18.5% correctly answered the question about specificity.

The results also showed that a significant proportion of participants had limited knowledge of metrics such as positive and negative predictive values (PPV and NPV), which are crucial in calculating the probability of a specific diagnosis based on test results and the patient's pre-test probability. 47.22% of participants were unaware of the meaning of PPV, while

3.70% and 9.26% confused it with specificity and sensitivity, respectively. The results were similar for NPV, with 45.37% of participants being unaware of its meaning and 11.11% and 2.78% confusing it with specificity and sensitivity, respectively.

The investigation revealed that a fraction of medical professionals exhibited confusion between sensitivity and negative predictive value, and specificity and positive predictive value. Our hypothesis is that this confusion arises from a lack of comprehension regarding the role of prevalence in predictive values. Although it is understandable that physicians may assume that a test with high sensitivity will have a high negative predictive value, as both measures indicate the test's capacity to exclude a disease, and a test with high specificity will have a high positive predictive value, as both measures represent the test's ability to diagnose the disease, the relationship between these values is more complex. A test with high specificity does not guarantee high positive predictive value, nor does a test with high sensitivity guarantee high negative predictive value, because the predictive values of a test depend on the disease prevalence. Our study corroborates this hypothesis, as more than half of the practitioners (55.6%) were unaware of the dependency of negative predictive value (NPV) and positive predictive value (PPV) on disease prevalence.

The incorrect answers given by the physicians in the study can be attributed to a lack of understanding of the key concepts of sensitivity and specificity. Despite the well-established convention of reporting test performance in studies using sensitivity and specificity, only a minority of the study participants were capable of selecting the right definition. And in fact the underutilization of these measures has been demonstrated in clinical practice in general (509). Instead of attributing this deficiency in aptitude to physicians, diagnostic test data authors should reassess their communication strategies. Notably, one research demonstrated that presenting positive likelihood ratios using simple and non-technical language significantly enhanced the participants' ability to accurately estimate the probability of disease (502).

9.8. High sensitivity and high specificity:

When the practitioners were asked about the degree of sensitivity and specificity needed to either exclude or confirm a diagnosis regardless of the pre-test probability, 50.41% did not know the degree of sensitivity needed to exclude a diagnosis, while 32.2% answered that it needs to be above 99%. Similarly, 49.59% did not know the degree of specificity needed to confirm a diagnosis, while 30.58% answered correctly that it needs to be above 99%.

If you need to exclude a disease regardless of the pretest probability, you should use a test that has a sensitivity close to 100%. This means that the test correctly identifies all cases of the disease and has no false negatives. Likewise, if you need to confirm the presence of a disease regardless of the pretest probability, you should use a test with a specificity close to 100%. This means that the test correctly identifies all true negative cases and has no false positives.

There are 2 problems however:

Firstly, there is a trade-off between sensitivity and specificity. It is difficult to find a test that satisfies both sensitivity and specificity to a high degree simultaneously. Ideally, a test should have a sensitivity close to 100% (able to detect all cases of the disease) and a specificity close to 100% (minimal false positive results). However, in practice, it is challenging to achieve both high sensitivity and high specificity simultaneously as increasing sensitivity often leads to decreased specificity and vice versa. A test with 100% sensitivity may not have high specificity, meaning that it may also have false positive results and produce positive results in healthy individuals. And a test with 100% specificity may lack sensitivity, leading to false negative results.

Secondly, it is difficult to find a test that is scores 99% on either metric in general. The only tests that are known to have high sensitivity and specificity include: Polymerase chain reaction (PCR) for detecting genetic material from infectious diseases Electron microscopy for detecting viral particles in a sample Enzyme-linked immunosorbent assay (ELISA) for detecting

antibodies in the blood. However, even these tests may not be perfect, and the ideal test will depend on the specific use case, the target population, and the available resources.

9.9. False negative and false positive rate:

According to the study, a significant proportion of practitioners in the medical field are not familiar with important statistical measures in medical testing. Specifically, more than two-thirds of the practitioners surveyed (66.67%) were unable to correctly identify the definition of FPR. Additionally, a similar proportion of practitioners (65.74%) were not able to correctly identify the definition of FNR. In both cases, only a minority of practitioners were able to provide the correct answer, with a mere 21.3% and 17.59% of respondents able to identify the definition of FPR and FNR, respectively. Some practitioners made incorrect associations, confusing these statistics with measures such as sensitivity and specificity, positive predictive value, and negative predictive value.

The false positive rate (FPR) and false negative rate (FNR) are important measures in medical testing. The FPR refers to the proportion of people in a population who have a positive test result but are actually healthy. On the other hand, the FNR refers to the proportion of people in a population who have a negative test result, but actually have the disease. These measures can be confusing to practitioners because they are related to, but distinct from, other important measures such as sensitivity, specificity, positive predictive value, and negative predictive value.

Understanding the relationships between these measures and the implications of test results is essential for properly interpreting and using the results of medical tests. Teaching practitioners about false positive and false negative rates can help dispel the illusion that medical tests are always accurate and that decisions can be made based solely on the results of a biomarker. When practitioners understand the concept of FPR and FNR, they can better appreciate the limitations of a medical test and understand that even highly sensitive and specific tests will still produce some false results.

9.10. the relationship between disease prevalence and biomarker performance characteristics:

The findings from our study suggest that a significant proportion of practitioner's lack understanding of the relationship between disease prevalence and the parameters used to evaluate the performance of medical tests.

More than half of the practitioners (55.6%) did not know if negative predictive value (NPV) and positive predictive value (PPV) are dependent on the prevalence of the disease and the intrinsic characteristics of the biomarker. Similarly, more than half of the practitioners (65.74%) did not know if sensitivity (Sn) and specificity (Sp) are dependent on the prevalence of the disease in the population.

However, it is encouraging to see that 40.74% of practitioners were able to correctly answer the question about NPV and PPV and that 17.59% of practitioners were able to correctly answer the question about Sn and Sp.

Positive predictive value (PPV) and negative predictive value (NPV) can change with the prevalence of the disease. When the prevalence of the disease is high, a positive test result is more likely to indicate the presence of the disease, and thus, PPV is generally higher. In this case, a test with high sensitivity and high specificity will have a high PPV. For example, consider a population in which the prevalence of a disease is 30%. A test with 80% sensitivity and 90% specificity will have a PPV of 77.42%. On the other hand, when the prevalence of the disease is low, a positive test result is less likely to indicate the presence of the disease, and thus, PPV is generally lower. For example, consider a population in which the prevalence of a disease is 1%. A test with the same characteristics will have a PPV of only 7.48%.

Sensitivity and specificity are independent of disease prevalence, meaning that they do not change with the proportion of individuals in a population who have a particular disease. Sensitivity is calculated as the proportion of true positive results out of all individuals with the disease. Sensitivity is determined by the test's performance and is not influenced by the

proportion of individuals with the disease in the population being tested. Specificity is calculated as the proportion of true negative results out of all individuals without the disease. Similar to sensitivity, specificity is determined by the test's performance and is not influenced by the proportion of individuals with the disease in the population being tested.

9.11. Test selection:

The selection of an appropriate diagnostic test is a crucial aspect of patient management and can greatly impact the outcome of a clinical evaluation. To make an informed decision, clinicians must consider the sensitivities and specificities of the available biomarkers, as these characteristics are fundamental indicators of the test's ability to accurately diagnose or rule out a condition.

The results of our study, however, highlight a concerning trend among medical practitioners. When asked about the choice of a biomarker to eliminate a disease, 60.19% of practitioners did not know what test characteristic to base their decision on. However, 7.41% of practitioners held the wrong believe that a biomarker with high specificity would be the best choice, while 32.41% correctly identified that a biomarker with high sensitivity is more suitable for this purpose. In the context of confirming a disease, the results were similar. 60.19% of practitioners did not know what biomarker characteristic to choose, while 5.56% wrongly believed that a high sensitivity biomarker would be the best choice. In contrast, 34.26% correctly identified that a biomarker with high specificity is the most appropriate choice for confirming a diagnosis.

The practitioners who answered incorrectly may not have fully understood the significance of these biomarker characteristics because it is well known that a biomarker with high sensitivity is more suitable for eliminating a disease because it has the ability to accurately identify individuals who have the disease (i.e., it has a low rate of false negatives). On the other hand, a biomarker with high specificity is more appropriate for confirming a disease because it

has the ability to accurately identify individuals who do not have the disease (i.e., it has a low rate of false positives).

Furthermore, the majority of participants were unfamiliar with other concepts such as likelihood ratios and the Fagan nomogram. 94.44% of participants had never heard of likelihood ratios, and 98.15% had never heard of the Fagan nomogram. These results highlight a need for additional education and training for healthcare professionals to improve their understanding of diagnostic test metrics and to effectively utilize and interpret biomarker test results in their clinical practice.

9.12. Synthesis:

At the crux of evaluating clinical test performance is the ultimate goal of calculating a posttest probability for a given disease and utilizing this probability to inform subsequent management decisions.

In our study, we questioned clinicians on various parameters, including sensitivity, specificity, predictive values, likelihood ratios, Fagan nomograms, and ROC in order to assess their understanding and application of these fundamental concepts in clinical decision-making.

In essence, the conclusion of the study highlights the lack of a comprehensive understanding of these various tools and metrics.

The impact of inaccurate estimation of post-test probability on patient care remains uncertain and may depend on subsequent clinical decision-making processes. While prior research has indicated a positive correlation between accuracy in post-test probability estimates and appropriate patient management, non-probabilistic cognitive processes, both analytical and non-analytical, may hinder clinicians from utilizing Bayes' theorem (510–513). Despite the efficacy of these alternative approaches, diagnostic errors remain prevalent, ranging from less than 5% in radiological or pathological specialties to 10–15% in most other clinical fields (512). Such errors are commonly attributed to inaccurate probability estimation (510,511,514–516).

Previous research suggest that incorrect probability estimation contributes significantly to diagnostic errors and unnecessary testing, particularly in situations where pre-test probability is low and positive predictive value is overestimated, or where pre-test probability is high and negative predictive value is overestimated. Although clinical decisions typically involve multiple tests and providers, errors in post-test estimation may still result in superfluous testing, heightened patient anxiety, and diagnostic inaccuracies (510,514,517,518).

Moreover, inadequate comprehension of probability thinking may hinder providers' ability to appropriately interpret and apply available evidence regarding novel diagnostic procedures (514,519).

Our findings suggest that there may be a lack of understanding among some practitioners about the importance of these characteristics when choosing a diagnostic test, and the need for further education and training to increase awareness of the significance of these biomarker characteristics in the diagnostic testing process.

9.13. Conclusion:

In summary, this study reveals that there is a lack of a comprehensive understanding of the various tools and metrics available to evaluate the effectiveness of a diagnostic test and implement them. The mean score of 4.45 out of 16 suggests that, on average, participants answered only about 28% of the questions correctly, indicating that a significant proportion of physicians have limited knowledge of the concepts of sensitivity, specificity, and predictive values. These misconceptions culminated in the inability of practitioners to select tests appropriately to rule in or rule out disease based on sensitivity and specificity.

The highlights of the study include the fact that approximately a third of the participants reported not considering pre-test probability in their practice. A majority of the participants were unfamiliar with other concepts such as likelihood ratios and the Fagan nomogram. On the other hand, the results of our study are encouraging in the sense that the majority of the

participants reported considering petest probability in their diagnostic decision-making process using different methods.

In conclusion, this study emphasizes the need for ongoing education and training programs to enhance physicians' understanding and knowledge of diagnostic test evaluation and selection. The findings underscore the importance of implementing these tools and metrics to improve diagnostic accuracy, ultimately resulting in better patient outcomes. It is imperative that physicians have a thorough understanding of these concepts to ensure that they are accurately selecting and interpreting biomarkers to diagnose and manage their patients' effectively.

10. Analysis of clinicians' knowledge on troponin:

The purpose of this subsection was to evaluate the knowledge and understanding of troponin among medical professionals. We conducted a survey comprising 19 questions on troponins and analyzed the responses from a sample of medical professionals. The mean score on this subsection was 2.74 out of 19 with a standard deviation of 2.492, and the median score was 2.50. Furthermore, 95.37% of the participants in our study scored less than half of the maximum score.

10.1. Troponin's physiology and its place in the diagnosis of MI:

In the present study, the knowledge and understanding of the participants regarding the function of troponins.

The results indicated that only 31.48% of the participants were aware that troponins are a class of contractile proteins. 18.52% of the participants held the misconception that TnC is a reliable biomarker for the diagnosis of myocardial infarction (MI), when in actuality TnC is not specific to the heart as it is found in identical form in both the myocardium and striated muscle. Hence, TnC is not utilized in the clinical assays for the detection of cardiac injury (59).

In this study, it was found that only 11.11% of participants were aware of the fact that 5-8% of troponin exists in an unbound state in the cytoplasm of cardiomyocytes. Similarly, only 11.11% of participants knew that the cytoplasmic fraction of troponin is the first to be released in the event of cardiac injury. This information is of great significance as it can contribute to a better understanding of the mechanism of troponin release and detection in myocardial injury. Moreover, this understanding is crucial for improving the diagnostic accuracy of high-sensitivity troponin assays, which have been shown to have low specificity. Thus, a deeper knowledge of the mechanism of troponin release and detection in myocardial injury can help us address this issue and improve the accuracy of these assays (61).

10.2. Troponin kinetics:

In the present study, we aimed to evaluate the knowledge and understanding of healthcare practitioners regarding the kinetics of serum troponin levels following a myocardial infarction (MI).

The study found that only 19.44% of participants were able to accurately determine the time frame in which cardiac troponin levels typically peak post-MI. This highlights a significant knowledge gap among healthcare practitioners. Further analysis revealed that only 18.52% of participants correctly identified the maximum elevation of serum troponin levels to occur 9 to 15 hours post-MI. Additionally, only 6.48% of participants were aware of the time frame in which troponin levels return to normal values. These findings indicate a need for improved education and training on the kinetics of troponin levels in the diagnosis and management of MI.

It is important to note that, in addition to the absolute cardiac troponin level, the kinetics of troponin elevation play a critical role in the diagnosis of MI. This aspect has been emphasized in every MI definition since the 2018 universal definition of myocardial infarction (55). Healthcare practitioners must have a solid understanding of the kinetics of troponin levels to accurately diagnose and manage MI.

10.3. MI diagnostic criteria:

The results of our study indicate that a substantial proportion of medical professionals lack adequate knowledge of the diagnostic criteria for myocardial infarction (MI) according to the fourth universal definition. Specifically, 62.96% of the participants were unable to accurately identify the criteria for MI diagnosis, and a small proportion of practitioners (10.19% and 11.11%) held incorrect beliefs that elevated cardiac hypersensitive troponins alone or a decrease in cardiac troponin levels alone were sufficient indicators of MI. Furthermore, 8.33% of practitioners stated that they would rule out the diagnosis of MI if there was a decrease in troponin levels greater than 30%. However, previous studies have established that both increases and decreases in serial troponin levels may be indicative of an acute cardiac injury such as MI (520).

Our findings are in line with the results reported by Jain et al. (521) in their study conducted at the University of Colorado. The purpose of their study was to assess the knowledge and understanding of medical professionals regarding the use of troponin, the definition of myocardial infarction, and the evaluation of elevated troponin levels. The study used a methodology similar to ours, including a multiple-choice questionnaire with eight questions and a sample size of 114 clinicians. Jain et al. found that 46% of clinicians were unable to identify the fourth Universal Definition of Myocardial Infarction, and 3% of participants could not identify that troponin levels alone cannot rule in or rule out coronary artery disease.

Comparing the results of both studies, it is evident that there is a knowledge gap among medical professionals regarding the diagnostic criteria for MI with 62.96% unable to identify the criteria for the fourth universal definition of MI in our study compared to 46% in Jain et al' study, and the lack of knowledge is not limited to a particular geographical location. Moreover, a slightly higher proportion of participants in our study (10.19% and 11.11%) held the incorrect belief that troponin levels alone are sufficient indicators of MI compared to 3% in the other study, indicating a greater need for education and training among medical professionals.

These findings suggests that there is room for improvement in the understanding of the diagnostic criteria for MI among medical professionals. Both of our studies highlight the importance of continued education and training for medical professionals to ensure accurate and effective diagnosis and treatment of patients. The lack of adequate knowledge of MI diagnostic criteria could result in misdiagnosis or delayed treatment, which could have severe implications for patient outcomes. Therefore, it is crucial to provide regular training programs, continuing medical education, and access to updated guidelines to ensure that medical professionals have access to the latest knowledge and best practices.

10.4. Has troponin replaced other markers:

This study evaluated practitioners' knowledge regarding biomarkers for the diagnosis of myocardial infarction, with a particular focus on troponins. The findings showed that 57.41% of participants correctly identified cTnI as a cardio-specific biomarker, indicating a good level of understanding among practitioners. However, there was still some confusion between cTnI and TnC, with 22.22% of participants selecting troponin C as the most specific marker for myocardial infarction.

When asked about the most specific marker for myocardial infarction, 33.33% of participants were unsure, while 44.44% correctly selected cTnI. Myoglobin and CRP-us were not selected by any of the participants, suggesting that troponins have become the preferred biomarker for the diagnosis of myocardial infarction due to their high sensitivity and specificity compared to other biomarkers.

These results reinforce the conclusion that troponins, particularly cTnI, have become the standard for the diagnosis of myocardial infarction among practitioners, owing to their superior diagnostic accuracy compared to other biomarkers. However, continued education is needed to clarify the differences between cTnI and TnC and to ensure that healthcare professionals have a clear understanding of the most specific biomarkers for the diagnosis of myocardial infarction.

Improved understanding and knowledge of biomarkers can help healthcare professionals make more accurate and timely diagnoses, which can ultimately lead to better patient outcomes.

10.5. Factors influencing 99th percentile of high-sensitivity troponin:

In the survey, practitioners were asked about factors that may affect the 99th percentile of high-sensitivity troponin (HsTn). A significant number (59.26%) reported that they did not know the answer. Of those who provided responses, 34.26%, 31.48%, 26.85%, and 14.81% correctly identified "determination method," "renal insufficiency," "age," and "gender," respectively, as potential influencers.

Previous research has established that the 99th percentile of the reference range for high-sensitivity troponin I and T immunoassays tends to increase with age (522), this is relevant because Currently available estimations based on age-specific ED admission rates suggest that the aging of the population will result in a substantial increase in the number of ED visits from elderly patients (523), and the specificities of elderly patients is their comorbidities, Additionally, the impact of demographic characteristics and comorbidities such as renal insufficiency on the diagnostic performance of biomarkers in this setting should be considered (524).

In patients with renal insufficiency, troponin levels may be elevated due to reduced clearance of the biomarker by the kidneys. Therefore, using a universal decisional threshold for HsTn may result in false positives cases of myocardial infarction in patients with renal insufficiency. Adjusting decisional thresholds for HsTn based on the patient's estimated glomerular filtration rate (eGFR) may be necessary to improve diagnostic accuracy in this population.

As for gender, women generally have lower levels of troponin than men, which means that using the same decisional threshold for both genders may result in a higher rate of false negative results in women. the use of a single threshold value for the entire population, rather than gender-specific cut-offs, may result in an increase misdiagnosis of MI.

These trends present significant challenges to the appropriate use of laboratory diagnostics in the emergency department. In this rapidly evolving environment, the diagnostic performance of some biomarkers may be severely impacted by the use of universal decisional thresholds.

10.6. Assay technique:

The findings of the study indicate that only 42.59% of the surveyed practitioners were cognizant of the fact that measurement of troponin is accomplished through immunoassays, while only 33.33% were aware of the fact that results are considered positive if they exceed the 99th percentile. A smaller proportion (26.85%) was knowledgeable about the fact that cut-off values can differ depending on the laboratory and test manufacturer. Additionally, only 2.78% of the respondents held the belief that there is a single manufacturer of troponin assays.

It is essential to highlight that although the production of troponin T assays is limited to a single manufacturer (525), which allows for comparability of results, there is considerable heterogeneity in the methodologies employed for troponin I assays across multiple manufacturers. In particular, the lack of standardization in the antibodies used by different manufacturers of cTnI assays leads to a disparity in the absolute concentrations of cTnI obtained from different analyzers or laboratories. Although some laboratories calibrate using National Institute of Standards and Technology standards, this does not necessarily eliminate interlaboratory variations. To achieve complete standardization, all manufacturers would need to utilize the same antibodies, however, this is a difficult goal to achieve due to intellectual property and economic considerations. This absence of calibration standardization has led to substantial disparities in the results of troponin I assays produced by different manufacturers (526).

These facts carry significant implications. The clinical diagnosis of myocardial infarction can be significantly impacted by certain facts. One such fact is the variability in cut-off values, which can differ based on the troponin I assay used by different manufacturers like Abbott,

Beckman, Siemens, or BioMerieux. Due to the lack of standardization, inconsistent results may occur, potentially affecting the accuracy of diagnosis and treatment plans. Furthermore, disparities in results across different assays may compromise the comparability of results and the validity of conclusions drawn from them. Therefore, it is crucial to take into account the differences in cut-off values and deltas while interpreting the results of troponin I assays for the diagnosis of myocardial infarction.

In conclusion, it is important to acknowledge that despite advancements in the field of troponin assays, there is still a significant need for improvement in certain areas such as assay standardization. The absence of standardization in the production of troponin I assays presents a significant challenge to the accurate and reliable diagnosis of myocardial infarction. In light of this, it is advised that clinicians not base their clinical judgment solely on the results obtained from different analyzers or laboratories in the absence of cTnI standardization (527).

10.7. Differential diagnosis:

The purpose of this study was to assess healthcare practitioners' understanding of the relationship between cardiac troponin levels and various medical conditions.

The study found that 26.85% of practitioners were aware that the release of troponin can occur in the absence of coronary artery disease (CAD). Similarly, 21.30% knew that an increase in troponin levels is not always synonymous with coronary thrombosis, and 35.19% knew that troponin levels can be elevated in conditions other than coronary thrombosis.

When asked about the specific conditions that can cause elevated troponin levels, 43.52% said they did not know indicating a significant knowledge gap, 5.56% identified hypo- and hyperthyroidism, 18.52% identified tachyarrhythmias, 28.70% identified aortic dissection, 37.04% identified shock, and 54.63% identified myocarditis.

These findings suggest that while practitioners may be aware of the potential for non-specific elevation of troponin, they have a limited understanding of the underlying causes. It is

important to note that an elevated level of troponin is not entirely specific for the diagnosis of myocardial infarction (MI). In fact the overall positive predictive value of troponin for acute coronary syndrome is only 56% (528). Nonetheless, an elevated troponin level remains a valuable clinical indicator of myocardial injury irrespective of its underlying etiology. An elevated troponin level has been shown to increase the risk of short-term major adverse cardiovascular events (MACE) and mortality (529). This holds true even in cases where the underlying cause of the elevated troponin is due to conditions such as sepsis, pulmonary embolism, chronic kidney failure, or heart failure (530).

The increasing sensitivity of cardiac troponin assays can paradoxically make them a less reliable test due to decreasing specificity. Clinicians must carefully consider the potential non-cardiac causes of troponin elevation in order to maintain the usefulness of these high-sensitivity assays in clinical decision making. It is crucial to understand the limitations of troponin testing and to interpret results in the context of the patient's overall clinical presentation (531).

10.8. Conclusion:

Our study found that the knowledge and understanding of medical professionals regarding troponins is generally poor. Many participants were unaware of important facts and concepts related to these biomarkers, such as the fact that troponin C is not cardio-specific, or the kinetics of troponin levels after a myocardial infarction. Additionally, a significant proportion of participants were unable to correctly identify the diagnostic criteria for myocardial infarction according to the fourth universal definition. These results suggest that there is a need for improved education and training on the use of troponins as diagnostic markers, in order to ensure their optimal use in clinical decision making.

In conclusion, it is important for medical staff to be educated on the performance characteristics, threshold limits, and interpretation of troponin assay results to facilitate understanding and accurate diagnosis. The combination of troponin levels, kinetics, and clinical

assessment, along with history and ECG findings and potentially adjunctive imaging, is essential for the rapid and accurate diagnosis of MI.

11. Analysis of Clinicians Knowledge on D dimer:

The D dimer subsection included 5 questions. The average score for this subsection was 0.79 with a standard deviation of 0.762 and a median of 1,00. All the participants scored less than half of the possible maximum score, and 42% scored zero.

11.1. The use of D-dimer assays in the diagnosis of venous thromboembolism:

In this study, we aimed to evaluate the level of understanding among medical practitioners regarding the use of D-dimer assays in the diagnosis of pulmonary embolism (PE).

The findings of the study indicate that a substantial proportion of participants were unable to provide an accurate response regarding the diagnostic utility of D-dimer assay in detecting venous thromboembolism (VTE). Specifically, 20.37% of respondents were unable to provide an answer, while 13.89% believed that a positive D-dimer assay confirms the diagnosis of PE and 25.95% believed that D-dimer is specific to VTE. However, these responses are not entirely accurate.

Although D-dimer is a sensitive marker for detecting thrombosis, its low specificity means that it should not be relied upon to confirm a diagnosis of VTE. Instead, it should only be used in suspected cases of VTE after estimating the clinical probability. An elevated D-dimer level does not confirm the diagnosis, but rather should be followed up with a diagnostic strategy to confirm or rule out VTE. Therefore, relying solely on a D-dimer assay to diagnose VTE can lead to incorrect diagnoses, unnecessary testing, and treatment, resulting in increased healthcare costs and patient harm.

One of the most common errors encountered in the emergency department is to diagnose VTE based solely on a positive D-dimer test in a non-suspect patient during routine evaluation. This highlights the importance of proper understanding and interpretation of D-dimer tests in clinical practice. D-dimer tests have low specificity since elevated levels of D-dimer can occur in various physiological and pathological situations. Of the practitioners surveyed, 21.30% could not provide an answer regarding these situations, while 37.04% selected pregnancy, 27.78% selected aortic dissection, 57.41% selected disseminated intravascular coagulation (DIC), 24.07% selected renal insufficiency, and 19.44% selected elderly individuals.

However, the correct understanding of D-dimer was demonstrated by a majority of practitioners. Specifically, 61.11% acknowledged that D-dimer has a good negative predictive value (NPV) of 99% to exclude PE, 25.93% recognized that a D-dimer level of less than 500 ug/L clearly rules out the diagnosis of PE, and 49.07% acknowledged that D-dimer is a marker of coagulation activation and fibrinolysis.

Overall, these findings highlight the need for adequate training and education of healthcare providers regarding the interpretation and use of D-dimer tests in clinical practice. Specifically, healthcare providers should be aware of the limitations of D-dimer tests and use them judiciously in conjunction with clinical assessment and imaging to establish an accurate diagnosis. Proper education and training can prevent errors and improve patient outcomes while reducing unnecessary healthcare costs.

11.2. Threshold value of d-dimer in subjects above 50 years:

The objective of this study was to evaluate practitioners' knowledge regarding the threshold value of D-dimer in individuals over 50 years of age. The findings showed that a significant number of respondents were not aware of the correct threshold value. In particular, 50% of the practitioners surveyed responded that they did not know the threshold value. Additionally, a substantial proportion of practitioners (12.04%) answered the question

incorrectly. Only 37.96% of the practitioners provided the correct answer, which is age multiplied by 10.

The age-adjusted D-dimer cutoff value, which is used to assess the likelihood of pulmonary embolism, is established as a value less than 500 µg/L for patients under 50 years of age and less than (age x 10) µg/L for patients over 50 years of age (147).

These findings underscore the importance of providing practitioners with up-to-date and accurate information about D-dimer testing and the age-adjusted cutoff value. Appropriate education and training can help reduce errors and improve the quality of patient care, particularly in older patients, who are at a higher risk for pulmonary embolism and for whom the use of this age-adjusted cutoff, in combination with a clinical probability assessment, can significantly improve the ability to exclude pulmonary embolism.

11.3. Mortality in PE:

The aim of this study was to assess the knowledge of practitioners on the predictors of early mortality in pulmonary embolism (PE). However, the results showed that a considerable proportion of respondents were uncertain about the correct answers. Nearly half of the practitioners, 45.37%, could not provide an answer to the question. While some practitioners gave correct answers, others gave incorrect ones. Approximately 30% of practitioners correctly identified "obstruction of more than 70% of the lung vascular bed" as a sign of early mortality in PE. Additionally, 34.26% of practitioners correctly chose "high BNP" and 32.41% chose "elevated troponins" as early mortality indicators. Moreover, 41.67% of practitioners correctly chose "collapsed ejection fraction" as a sign of early mortality in PE.

The use of biomarkers to identify patients with PE at higher risk of adverse outcomes has been an area of active research. The use of B-type natriuretic peptides (BNP) and troponins has been investigated as prognostic markers in patients with pulmonary embolism. Research shows that high levels of BNP identified a subset of patients with PE at higher risk of adverse outcomes.

Among these patients, increased troponin levels were found to be an independent prognostic marker (532,533).

However, it is important to note that the use of biomarkers alone should not be relied upon for clinical decision-making. Instead, biomarker results should be interpreted in the context of other clinical factors and used as part of a comprehensive risk assessment strategy.

The lack of consensus on the best markers for predicting early mortality in PE and the rapidly changing landscape of medical research may contribute to the inconsistent answers given by some practitioners.

11.4. Knowledge of the pertinence of D-dimer testing according to pretest probability:

The use of the D-dimer test depends on several factors, including the pretest probability of VTE. The aim of this study was to assess the knowledge and understanding of healthcare practitioners regarding the pertinence of D-dimer testing based on pretest probability. This question aimed to explore the knowledge on the correct use of D-dimer testing based on the pretest probability of VTE.

The results showed that 31.48% of practitioners could not give an answer when asked about the pertinence of D-dimer testing according to pretest probability. only 10.19% practitioners gave the correct answer, which was that D-dimer testing was not recommended when the pretest probability was high. On the other hand, 27.78% practitioners answered that D-dimer testing was not recommended if the pretest probability was low, while 30.56% practitioners answered that it was not recommended if the pretest probability was intermediate. We will explain why this is wrong:

The determination of clinical pre-test probability is critical in the diagnostic evaluation of venous thromboembolism (VTE). Validated scoring systems such as the Wells score for deep vein thrombosis (DVT) and the Wells or Geneva score for pulmonary embolism (PE) are commonly utilized to categorize pre-test probability as likely or unlikely, or as high, intermediate, or low

(533,534). Pre-test probability assessment guides further testing and aids in determining the appropriate diagnostic approach (534,535).

It is essential to analyze and interpret the study results and compare them with existing literature to draw meaningful conclusions. In this context, it is important to note that D-dimer testing in patients with a high clinical probability should not be performed in the first place. When the pre-test probability is greater than 20% the NPV of the D-dimer test is reduced due to the high prevalence of VTE in these patients and the post-test probability of VTE after a negative D-dimer result exceeds the safety threshold of 3% (536,537). The vast majority (approximately 60%) of patients with high pretest probability will have VTE and it is more logical to move towards a diagnostic test which, in the event of a positive result, will allow rapid confirmation such as ultrasonography for DVT and pulmonary angiography for PE.

It is worth noting that even if D-dimer testing is performed with the intention of ruling in VTE, the results are unlikely to be conclusive. This is because the clinical specificity of D-dimer for the diagnosis of VTE is low, at around 40%. Although the specificity increases with the level of D-dimer in the blood, even values as high as or above 7000 µg/L still have only about 80% positive predictive value. Therefore, D-dimer is not a diagnostic tool to rule in VTE (537).

Unjustified and inappropriate D-dimer testing is a major clinical problem. In cases where the assay is performed without any real clinical suspicion of VTE, three situations may arise (538):

1. The requested D-dimer assay is negative, which reassures the clinician but at the cost of additional examination and possible extension of the duration of emergency care.
2. The assay is positive but does not lead to a diagnostic approach and investigations, causing anxiety for the physician who decides to ignore it. This situation represents 45% of the situations where D-dimer values were positive.
3. The positive result triggers a diagnostic strategy and the performance of additional tests that are not clinically motivated, exposing the patient to potential adverse effects, the

discovery of incidentaloma, and prolongation of the length of stay in the emergency department, not to mention the anxiety caused to the patient and his relatives, and the financial cost involved. This situation represents 18 to 25% of D-dimer prescriptions.

Thus, testing without clinical suspicion is unnecessary and dangerous!

In conclusion, regardless of the test used, D-dimer testing in patients with a high clinical probability is inappropriate. Only if VTE is unlikely, D-dimer test is the next step to perform. D-dimer testing is an essential component of established protocols for diagnosing DVT and PE. Efficient diagnostic pathways are necessary to minimize the use of expensive and potentially harmful radiologic tests, as well as to reduce the burden on the healthcare system. To safely rule out suspected PE in low- to moderate-risk patients, it is important to assess their clinical probability and measure their D-dimer levels.

11.5. Conclusion:

In conclusion, the results of the studies highlight the need for improved education and training for healthcare practitioners in the diagnosis and treatment of Venous Thromboembolism (VTE) and. The incorrect use of D-dimer tests and the lack of knowledge regarding the age-adjusted D-dimer cutoff value and the signs that predict early mortality in PE, represents a major clinical problem. A comprehensive understanding of these aspects is essential for ensuring accurate and effective patient care. Further education and training programs are needed to update healthcare practitioners on the latest developments in D-dimer testing and interpretation, and to improve their knowledge and understanding of the appropriate use of D-dimer testing and the diagnosis of VTE. An informed and well-educated healthcare workforce is crucial for providing optimal patient care.

12. Analysis of Clinicians Knowledge on BNP and NT-pro BNP:

The BNP/NT pro-BNP subsection included 11 questions. The average score for this subsection was 0.81 with a standard deviation of 1.112 and a median of 0,00. 100% scored less than half of the maximum possible score which was 5.5, and 59% scored a zero.

12.1. BNP and NT-pro BNP physiology:

In this study, we examined practitioners' knowledge on the physiology of BNP. Concerning the secretory mechanisms of BNP, the results showed that a significant portion of practitioners lacked knowledge regarding BNP. Specifically, 50% of practitioners were unaware of the physiology of BNP, while 28% believed that it is secreted in response to increased atrial volume and pressure, and 20% thought it was secreted by the atrial myocardium. However, 27.78% of practitioners correctly believed that BNP is secreted by the ventricular myocardium, 29.63% correctly believed that it is secreted in response to increased ventricular strain/stretch and 11.11% were correct in stating that BNP has a half-life of 20 minutes. Finally, the 18 (16.67%) practitioners who said that BNP and NT pro-BNP are secreted equimolecular demonstrated a good understanding of the biological processes involved in the production of BNP and NT pro-BNP. BNP and NT pro-BNP are derived from the same precursor molecule, pro-BNP, and are secreted equimolecularly.

Furthermore, when asked about the effects of BNP, 72.23% of practitioners could not answer or answered incorrectly, indicating a lack of understanding of this important hormone. However, 19.44%, 18.52%, 14.81%, 3.70%, and 4.63% of practitioners respectively chose correct answers BNP causes diuresis and natriuresis, inhibits the renin-angiotensin-aldosterone system, is an active form, is eliminated by endopeptidases, kidneys and receptors A, B and C, and has a shorter half-life compared to NT-pro BNP.

These results suggest that there is a limited understanding among practitioners regarding the properties of N-terminal pro-BNP. It is concerning that 74.07% had poor knowledge on NT-pro BNP physiology. The 7.41% practitioners who correctly identified its half-life of 90 minutes demonstrated a good understanding of the kinetics of this biomarker. The 8.33% practitioners who correctly stated that NT pro-BNP has a longer half-life than B-type natriuretic peptide, the 8.33% practitioners who correctly stated that the elimination of NT pro-BNP is primarily urinary and the 21.30% practitioners who correctly stated that NT pro-BNP is an inactive form demonstrated a good understanding of the physiology of this biomarker.

As a brief summary of the physiology of natriuretic peptides, BNP and NT-pro BNP are primarily secreted by the ventricular myocardium in response to wall stress such as volume expansion and pressure overload. BNP has a half-life of 20min and NT-pro BNP has a longer half-life of 90min. BNP exhibits antagonistic effects against angiotensin II via diuretic/natriuretic actions, vasodilatory actions, and inhibition of aldosterone secretion while NT-pro BNP is biologically inactive. BNP and NT-pro BNP are filtered by the kidney and degraded by NPR A, B and C (167).

The results of this study indicate a mixed understanding among medical practitioners regarding the physiology of BNP and NT-pro BNP. While a relatively small proportion of practitioners had a good understanding of their physiology, the majority of practitioners showed a lack of knowledge in various aspects. Specifically, many practitioners were unable to correctly identify their secretion location and trigger, as well as the effects of BNP, and a significant portion were unaware of their half-life.

These findings suggest that there is a need for further education and awareness regarding BNP and NT-pro BNP physiology among medical practitioners. Improving knowledge in this area may lead to better patient outcomes and more effective treatment strategies for cardiovascular conditions.

12.2. Clinical application of BNP/NT-pro BNP:

BNP and NT pro-BNP are biomarkers used to help diagnose and manage heart failure (HF), so it is important for practitioners to have a basic understanding of their use. Therefore, this study aimed to assess physicians' knowledge about the clinical applications of BNP and NT-pro BNP.

The results are concerning, 57.41% of the practitioners could not answer the question about the uses of BNP and NT pro-BNP. Showing a big knowledge gap.

The study found that only 29.63% of practitioners recognized the use of BNP and NT pro-BNP in excluding or diagnosing heart failure in patients with dyspnea. Additionally, only 31.48% of practitioners recognized the good negative predictive value of BNP and NT pro-BNP in excluding heart failure. These results demonstrate a lack of understanding among practitioners regarding the main clinical application of BNP and NT-pro BNP in diagnosing heart failure, especially in patients with dyspnea. This lack of awareness is concerning since previous research (199,539) has established the diagnostic role of these biomarkers in patients with shortness of breath, which is a common presenting symptom in emergency rooms. Dyspnea is not a specific symptom of heart failure, and it can also present in other pathologies such as myocardial infarction and community-acquired pneumonia. Therefore, the use of BNP and NT pro-BNP can be helpful in differentiating between these conditions. Overall, this study highlights the need for increased awareness and education among practitioners regarding the role of BNP and NT pro-BNP in diagnosing heart failure in patients with dyspnea, which can lead to improved patient outcomes by facilitating earlier and more accurate diagnoses.

The study showed that practitioners' understanding of the use of NT pro-BNP in screening patients with atrial fibrillation (AF) who are at risk of developing a stroke was poor, with only 6.48% of practitioners correctly identifying this use of NT pro-BNP. While this demonstrates good understanding among the practitioners who answered correctly, it also suggests that practitioners may not be aware of this application of natriuretic peptides. This lack

of awareness may be due to the fact that this area of research is still developing, and practitioners may not be following its progress closely.

Atrial fibrillation (AF) is a common cardiac arrhythmia that increases the risk of ischemic stroke. AF-related strokes are more severe and have higher mortality rates compared to strokes from other causes (540). Brain natriuretic peptide (BNP) has been shown to be elevated in patients with acute ischemic stroke (AIS), particularly those with AF (541). Recent studies suggest that elevated BNP levels may also indicate a higher risk for AF and future stroke, and patients with BNP levels greater than 100 pg/mL may benefit from early prolonged AF monitoring to detect undetected AF (542,543). Despite the potential clinical significance of BNP in identifying high-risk stroke patients, it is not currently included in AF guidelines. Further research is needed to fully understand the implications of elevated BNP levels in stroke patients.

The study's overall findings indicate a discouraging level of awareness among practitioners regarding the main clinical application of BNP and NT pro-BNP, with only approximately one-third of practitioners demonstrating awareness of their use in diagnosing HF in patients presenting with dyspnea. Additionally, only a small minority of practitioners are aware of the ongoing research into potential future applications of these biomarkers.

These results suggest that more efforts are needed to educate practitioners on the role of BNP and NT pro-BNP in the diagnosis of heart failure, particularly in patients presenting with dyspnea, which is a common but not specific symptom of heart failure. It is also important to increase awareness of the potential future applications of these biomarkers, as ongoing research is uncovering their potential use in screening for atrial fibrillation and identifying high-risk stroke patients.

12.3. Confounders of natriuretic peptides plasma concentration:

The use of natriuretic peptide testing has now become a common practice in diagnosing and predicting the outcome of patients with shortness of breath. It is important for clinicians to

be well-informed about the various common disease processes, which can cause increased levels of natriuretic peptides, to prevent misdiagnosis of heart failure in such cases. Therefore, this study sought to examine the knowledge of practitioners on the differential diagnosis for elevated natriuretic peptide levels.

The results indicate that there is a limited understanding among practitioners regarding the factors that can influence B-type natriuretic peptide (BNP) levels in the blood. It is concerning that 71.30% of practitioners could not provide an answer when asked about the factors that could influence BNP levels.

The percentage of practitioners who answered the question correctly but incompletely varied between 15 and 25%. Specifically, 20.37% correctly identified that BNP decreases with age. 25.00% practitioners correctly stated that BNP increases in case of renal failure. 17.59% practitioners correctly stated that BNP increases in case of lung disease. 14.81% practitioners correctly stated that BNP decreases in obese patients. 14.81% practitioners correctly stated that BNP decreases in female patients.

In another question, practitioners were asked about the factors that necessarily required an adaptation of BNP thresholds. The results suggest that a significant number of practitioners (66.67%) were unable to answer. Of those who answered, some practitioners (18.52%, 13.89%, and 16.67%) chose factors that are not necessarily known to affect BNP levels and therefore may require more education on the subject. On the other hand, a smaller percentage of practitioners (28.70% and 25.00%) correctly chose renal failure and age as factors that require an adaptation of BNP thresholds, indicating a general understanding of the factors that impact BNP levels.

BNP and NT pro-BNP levels may be affected by the presence of comorbidities such as chronic renal failure, obesity. They are generally higher in patients with renal failure and lower in obese individuals (217).

Natriuretic peptides are released by the heart muscles in response to stretching and strain. However, it is essential to note that several other disease processes besides primary left

ventricular failure can lead to increased levels of circulating NP. These processes include heart muscle disease, valvular heart disease, arrhythmia, anemia, critical illness, stroke, and pulmonary heart disease and even non-cardiac diseases. Clinicians should be aware of these common non-heart failure causes of NP elevation to avoid misdiagnosis of heart failure in such cases. Elevated levels of NP should not always be considered a sign of heart failure, and all possible diagnoses should be taken into consideration when interpreting test results (544),(545).

12.4. BNP and NT-pro BNP thresholds:

The measurement of B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT pro-BNP) has become a widely used tool for the diagnosis and management of heart failure (HF). To ensure accurate interpretation of these biomarkers, practitioners must have a good understanding of their exclusion thresholds.

Unfortunately, our study has revealed limited understanding among practitioners regarding the exclusion thresholds of BNP and NT pro-BNP for HF diagnosis. Specifically, 50.00% of participants were unable to accurately respond to the query regarding the exclusion threshold of NT pro-BNP, with only 32.41% correctly selecting the value of 300 pg/mL. Similarly, 51.85% of participants were unable to accurately respond to the query regarding the exclusion threshold of BNP, with only 32.41% correctly selecting the value of 100 pg/mL.

Notably, numerous studies have demonstrated the robust negative predictive value of both BNP and NT pro-BNP for ruling out HF. For example, BNP levels below 100 pg/mL suggest a low likelihood of acute heart failure (AHF) in patients presenting with dyspnea. Similarly, an NT pro-BNP cutoff level of less than 300 pg/mL is optimal for ruling out a diagnosis of AHF (546).

The study's results indicate a need for improved education and training regarding the use of BNP and NT pro-BNP in the diagnosis and management of HF. Practitioners must be aware of the exclusion thresholds for these biomarkers to accurately interpret results and provide optimal care for their patients.

12.5. NT-pro BNP age-adjusted threshold:

The incidence of heart failure is strongly associated with age. Roughly 1% of individuals over 50 years old are affected by heart failure, with rates doubling with each subsequent decade of life, meaning that its incidence goes from 0.04% in patients under 44 years to 20.9% in those aged 85 years or older (547,548). Therefore, it is crucial for practitioners to have a good understanding of NT-pro BNP cutoffs based on patient age to accurately diagnose older patients with heart failure.

Our study aimed to assess practitioners' understanding of the age-adjusted cutoff for N-terminal pro-BNP (NT pro-BNP) in the diagnosis and management of heart failure. The results showed a significant gap in knowledge among practitioners, with the majority (88.89%) unable to provide an answer regarding the appropriate cutoffs based on age. Furthermore, of the practitioners who provided an answer, only a small proportion (14.81%) selected the correct cutoffs for different age groups.

A review of the literature reveals that age-related cut-points of 450, 900, and 1800 ng/L are commonly used to rule-in heart failure for ages less than 50, between 50 and 75, and over 75 years, respectively (194). Therefore, practitioners need to have a good understanding of these cutoffs based on age to accurately diagnose and manage heart failure in their patients.

In conclusion, our study highlights the significant gap in knowledge among practitioners regarding the age-adjusted cutoff for NT pro-BNP in the diagnosis and management of heart failure. There is a need for improved education and training for practitioners to enhance their understanding of the appropriate cutoffs based on age to accurately diagnose and manage heart failure in their patients. This could lead to better patient outcomes and reduced healthcare costs associated with heart failure management.

12.6. Natriuretic peptides for severity and prognosis:

The results of the survey indicate that a large proportion of practitioners (80.56%) were unable to answer the question about the role of BNP and NT-pro BNP as a biomarker for prognosis. Of those who did answer, only a small number (1.85%) answered incorrectly by stating that there was no correlation.

On the other hand, a number of practitioners (16.67%, 9.26%, and 12.96%) correctly identified the three factors that BNP and NT-pro BNP are correlated with, which are the severity of heart failure, NYHA classification, and LV ejection fraction.

A similar pattern is observed when practitioners were asked about BNP as a prognostic and therapeutic biomarker. The majority of practitioners (67.59%) were unable to give an answer, while a significant number (8.33%, 20.37%, 17.59%, 6.48%, 17.59%, and 14.81%) answered correctly by identifying various benefits of using BNP as a biomarker in the prognosis and treatment of acute coronary syndrome and heart failure.

Many studies have indicated that patients with heart failure who have elevated levels of BNP are at a higher risk of death or cardiovascular events. A 100 pg/mL increase in BNP levels resulted in a 35 percent increase in the risk of death. BNP tests have shown to be potentially more useful than traditional predictors of mortality such as age, ischemic etiology, left ventricular ejection fraction, NYHA classification, and serum creatinine levels, as BNP was the only statistically significant independent predictor of mortality in these studies. These findings suggest that BNP testing can be a useful tool in predicting the risk of adverse outcomes in heart failure patients, and clinicians should take this into consideration when assessing their patients' clinical status (549,550).

The short half-life of BNP, a volume-sensitive hormone, may make it useful in guiding diuretic and vasodilator therapy for patients with decompensated CHF. Falling BNP levels during hospitalization were observed in patients who did not have readmissions in the 30 days following discharge. In contrast, patients who were readmitted or died during this period showed

no such decrease in BNP levels despite overall clinical improvement. Changes in wedge pressures were found to correlate strongly with dropping BNP levels and clinical improvement in patients undergoing hemodynamic monitoring. In the future, BNP levels could potentially be used as a surrogate for wedge pressure, and noninvasive cardiac output measurements may be used as a measure of cardiac output, eliminating the need for Swan-Ganz catheterization (549).

It is likely that the lack of knowledge among practitioners about the role of BNP and NT-pro BNP as a biomarker for prognosis and treatment may be due to limited exposure to these biomarkers in their training and clinical practice. Furthermore, the field of cardiovascular medicine and biomarker use is constantly evolving and advancing, and practitioners may need to update their knowledge and skills to stay current.

12.7. Conclusion:

The results of this study suggest a significant gap in the understanding of BNP and NT-pro BNP among healthcare practitioners, particularly in the use of these biomarkers for the diagnosis and exclusion of heart failure in patients presenting to the emergency department. The mean score on the BNP/NT pro-BNP subsection was 0.81, with a majority of participants scoring less than half of the maximum possible score. These results highlight the need for further education and training to improve practitioners' understanding of these biomarkers and their role in the diagnosis and management of heart failure.

The study also highlights the need for improved education and training on the properties of NT-pro BNP, the factors that can influence BNP levels in the blood, the exclusion thresholds for BNP and NT-pro BNP for heart failure, and the cutoff for NT pro-BNP in heart failure according to age. A good understanding of these concepts is essential for accurate interpretation of these biomarkers and effective management of patients with heart failure and other cardiovascular diseases.

In conclusion, this study emphasizes the importance of continuing education and training efforts in the field of BNP and NT pro-BNP, as they can help to improve practitioners' knowledge and skills, leading to better patient outcomes.

13. Analysis of Clinicians Knowledge on PCT:

In the present study, the procalcitonin subsection comprised of 12 questions. It appears that the participants had relatively low levels of knowledge about procalcitonin. The mean score on the procalcitonin subsection was only 0.58 out of a possible maximum of 12 points, and the median score was 0. Additionally, the standard deviation of 1.024 indicates that there was a significant degree of variability in the scores.

13.1. Misconceptions about PCT physiology and pathophysiology:

Regarding the synthesis of PCT, 62.96% of the practitioners in the sample believed that it is synthesized by the cells of the parathyroid gland, which is incorrect as it is actually synthesized by the C cells of the thyroid gland. The site of PCT synthesis in case of infection and/or inflammation is not completely understood. During a severe infection, PCT is likely secreted by extrathyroidal cells. In fact, patients who have had a thyroidectomy can synthesize PCT in case of infection. Monocytes as well as liver cells could be involved in PCT synthesis in case of infection (218).

When asked about the pathogens associated with low levels of PCT, a small proportion of practitioners were unable to provide a response (16.66%), while others mistakenly identified gram negative bacteria (21.30%), parasites (29.63%), or gram-positive cocci (0.93%) as potential causes. However, the correct answers were viruses and intracellular bacteria (551), chosen by only 76.85% and 21.30% respectively. This is concerning since and any prescription of PCT should be unthinkable without this information.

13.2. Procalcitonin half-life and kinetics:

In regard to the half-life of PCT, the majority of practitioners (78.70%) were unable to provide an answer, while smaller proportions believed it to be 6 hours (5.56%), 36 hours (2.78%), or 12 hours (5.56%). Only 8.33% of practitioners selected the correct answer of 24 hours (551). Understanding the half-life of procalcitonin is essential for clinicians in guiding antibiotic therapy. Procalcitonin has a set half-life, and when a proper host immune response and antibiotic therapy are in place, PCT levels decrease by 50% over 24 hours. Therefore, knowing the timeline for when the levels of procalcitonin should begin to decrease can help monitor the effectiveness of antibiotic therapy and provide valuable information about the patient's prognosis (552).

When asked about the delay in PCT increase, the majority of practitioners (78.70%) were unable to provide an answer, while a small proportion (13.88%) selected answers above "6 hours" and only 7.41% chose the correct answer of "3 hours" (224). Understanding the kinetics of procalcitonin is vital as it provides clinicians with timely insights to support clinical decisions when it comes to diagnosing systemic bacterial infections and assessing their course and severity. Procalcitonin kinetics are unique from other conventional inflammatory markers as they provide timely information specific to systemic bacterial infections. Unlike other tests, procalcitonin rises and falls in response to a bacterial insult, while other markers like cytokine IL-6 rise and fall too quickly, and C-reactive protein (CRP) levels rise much later and decline much slower than the actual resolution of the episode. Moreover, procalcitonin is not subject to stimulation by competing causes of inflammation. Therefore, understanding procalcitonin kinetics can be highly beneficial in diagnosing bacterial infections promptly and accurately, enabling timely initiation of antibiotic therapy, and guiding the course of treatment for the patient's condition.

13.3. Procalcitonin clinical application:

Nearly half (49.07%) of the practitioners in the sample believed that PCT is superior to C-reactive protein (CRP) in determining the prognosis of sepsis, and similar proportions believed that it reduces the duration of antibiotic therapy (47.22%) and helps in the decision to start, maintain, or stop antibiotics (49.07%). These findings suggest that a significant proportion of participants understand the role of PCT in antibiotic stewardship and its superiority over CRP in the prognosis of sepsis.

As a review for the clinical applications of procalcitonin, the secretion of PCT is primarily observed during bacterial, parasitic, or fungal infections, making it an excellent biological marker. An increase in PCT concentration in the blood is indicative of an infectious state. Clinicians sometimes find it challenging to diagnose the infectious origin of a disease, given the nonspecific symptoms like inflammation, fever, and others. The PCT produced specifically during microbial infection is, therefore, of particular interest, as its concentration is not increased during viral infections or non-infectious inflammatory pathologies. Numerous studies have demonstrated that the concentration of PCT in the blood is generally proportional to the concentration of infectious agents. As a result, its measurement allows for the assessment of the severity of an infection. After the eradication of the infectious focus, the concentration of PCT decreases very rapidly. In contrast, if the infection persists, its production is maintained. The usefulness of measuring PCT, compared to C-reactive protein (CRP), is its rapid elevation during bacterial infection. CRP remains a good biological marker of the acute phase of inflammation, but its utility in distinguishing bacterial infection from viral infection is not demonstrated.

The Procalcitonin (PCT) test is a useful tool in various clinical situations:

- The PCT test can differentiate between bacterial and viral respiratory tract infections and determine the appropriate length of antibiotic treatment for respiratory infections.
- PCT is useful in diagnosing, risk stratifying, and monitoring patients with sepsis and septic shock.

- It can monitor the response to antibacterial therapy.
- PCT can diagnose systemic secondary infections in patients who have undergone surgery, organ transplant, or who have severe burns, multiorgan failure, or severe trauma.
- The test can diagnose bacteremia and sepsis in adults and children, including neonates.
- It can differentiate between bacterial and viral meningitis.
- PCT is helpful in diagnosing renal involvement in pediatric urinary tract infections and bacterial infections in neutropenic patients.
- Finally, PCT can diagnose septic arthritis.

In conclusion, this study found that physicians have a knowledge gap regarding the clinical applications of procalcitonin (PCT), which is a barrier to its optimal use.

13.4. Procalcitonin thresholds:

When asked about the recommended cutoff value of PCT below which it is recommended to repeat the measurement within 12 hours in cases of high pretest probability, the majority of practitioners (85.19%) were unable to provide an answer, while a small proportion (12.96%) selected values above 0.2 ng/ml and only 1.85% selected the correct answer of 0.1 ng/ml.

Similarly, when asked about the PCT threshold in the context of lower respiratory tract infection, the majority of practitioners (84.26%) were unable to provide an answer, with only 6.48% selecting the correct answer of 0.25 ng/ml.

When asked about the PCT threshold associated with a high risk of sepsis or septic shock, the majority of practitioners (86.11%) were unable to provide an answer, with only 5.56% selecting the correct answer of 2 ng/ml.

When asked about the utility of PCT in stratification of risk, the majority of practitioners (88.89%) were unable to provide an answer, with only 6.48% selecting the correct answer of >5 ng/ml.

Finally, when asked about the PCT threshold for distinguishing between inflammation and infection, the majority of practitioners (88.89%) were unable to provide an answer, with only 4.63% selecting the correct answer of 0.5-1 ng/ml.

Recommendations for antibiotic use depend on the initial procalcitonin (PCT) values for patients with lower respiratory tract infections (LRTIs). A PCT value of less than 0.1 µg/L strongly discourages antibiotic use. If antibiotics have not been started and there is no clinical improvement, a repeat PCT should be done after 6-12 hours (553).

For initial testing in patients with lower respiratory tract infections (LRTI), a PCT value between 0.1-0.24 µg/L discourages the use of antibiotics. On follow-up testing, if the PCT value falls between this range, it encourages early cessation of antibiotics. For initial testing in patients with sepsis, a PCT value below 0.25 µg/L strongly discourages the use of antibiotics. On follow-up testing, if the PCT value falls below 0.25 µg/L, it strongly encourages early cessation of antibiotics.

In patients suspected to have sepsis, procalcitonin (PCT) levels can be used to predict the likelihood of sepsis and septic shock. A PCT value of >2.0 µg/L indicates sepsis, while a value of >10 µg/L indicates likely septic shock. In patients with suspected sepsis, it is strongly recommended to consider initiating antibiotics in all unstable patients, and if a PCT value is greater than 2.0 ng/mL, antibiotics are strongly encouraged (553,554).

Higher PCT levels have been shown to be associated with a worse prognosis, therefore PCT is a marker of infection severity, with a threshold of severity at more than 5 ng/ml.

The first validated clinical application of PCT test a diagnostic tool for distinguishing between bacterial and viral infections. The test can differentiate between inflammation and infection with a decision threshold of 0.5 ng/ml. At least two types of infections can be detected using the PCT test: meningitis (threshold between 0.5-1 ng/ml) and lower respiratory tract infections (decision threshold of 0.25 ng/ml) (552).

These findings suggest that while the participants in the sample somewhat understand the utility and importance of PCT, they lack the practical knowledge of its thresholds, cutoffs, and recommendations for proper application.

13.5. Procalcitonin limitations:

When asked about the limitations of PCT, 50.93% of practitioners in the sample were unable to provide an answer. A smaller proportion identified an infection masked by antibiotics (43.52%), compartmentalized infection (32.41%), lack of sensitivity in early stages of infection (27.78%), and lack of specificity in differentiating between inflammation and infection (26.85%) as potential limitations. These findings suggest that while a significant proportion of practitioners in the sample are aware of the limitations of PCT, they lack a comprehensive understanding of the various limitations of this biomarker.

When asked about non-specific situations that lead to an increase in PCT, 52.78% of practitioners were unable to provide an answer. A smaller proportion identified polytrauma and surgery (25.93%), newborns under 48 hours (25.00%), medullary thyroid cancer (24.07%), SAM (16.67%), severe cardiogenic shock (15.74%), small cell lung and bronchial carcinoma (15.74%), and heat stroke (2.78%) as potential causes, all of which are correct.

It is important to understand the limitations of procalcitonin (PCT) as a diagnostic tool. While PCT can be useful in identifying bacterial infections, false positive and false negative results can occur with any test. Therefore, it is important to consider the clinical context when interpreting PCT results.

There are several situations in which PCT levels may be elevated due to non-bacterial causes. In newborns under 48-72 hours old, PCT levels may be elevated even in the absence of infection. Additionally, situations such as massive stress (including severe trauma, surgery, cardiac shock, and burns) and treatment with cytokine-stimulating agents (such as OKT3, anti-lymphocyte globulins, alemtuzumab, IL-2, and granulocyte transfusion) can also cause PCT

levels to be elevated. Some fungal infections, malaria, prolonged severe cardiogenic shock or organ perfusion abnormalities, some forms of vasculitis, and acute graft vs. host disease may also cause elevated PCT levels.

On the other hand, there are situations where there is an infection, but PCT levels may be low. In these cases, the infection may be masked by antibiotics, compartmentalized or localized, or in the early stages (less than 3 hours). It is also important to note that certain types of cancers, such as medullary thyroid cancer and small cell lung and bronchial carcinoma, can cause high PCT levels even in the absence of infection.

Overall, understanding the limitations of PCT and considering the clinical context can aid in interpreting PCT results accurately and effectively.

In addition, when asked about age limitations of PCT, 81.48% of the practitioners in the sample were unable to provide an answer, while 12.04% believed that age does not influence PCT levels (which is incorrect) and only 12.04% correctly identified that PCT is not a reliable marker for infection in patients over 75 years of age.

According to the available literature, there is no consensus on whether procalcitonin (PCT) can be considered a reliable marker of infection in individuals aged 75 years and above. While some studies have suggested that PCT is a useful biomarker for detecting infection in elderly patients (555,556), others have found that its diagnostic accuracy is limited (557–559), especially in the context of comorbidities and age-related changes in the immune system.

Therefore, the effectiveness of PCT as a diagnostic tool for infection in individuals over the age of 75 remains a topic of debate in the medical community. More research is needed to better understand the role of PCT in the diagnosis and management of infection in this population.

13.6. Comparison:

Christensen et al. conducted a qualitative investigation using semi-structured interviews at Østfold Hospital Trust in south-eastern Norway (560). The study included 14 physicians and found that they expressed uncertainty about when it was appropriate to use the test and how to interpret test results. This lack of clarity resulted in a reluctance to trust and use the test because of infrequent use and diverse confusing guidelines.

Overall, the study suggests that there is a need for clearer education about the appropriate use and interpretation of the PCT test to increase physicians' confidence and trust in the test.

Our study and Christensen et al.'s differ in their focus, methodology, sample size. But both studies suggest a need for increased education and clarity about the appropriate use and interpretation of procalcitonin.

13.7. Conclusion:

Antibiotic resistance is a major public health concern, and it is widely accepted that the use of antibiotics is a major driver of its development. Unfortunately, inappropriate and excessive use of antibiotics is common in emergency departments, as shown by both international studies (561,562) and local research. For example, a study conducted in the same hospital where this research was conducted (563) found that 15.8% of antibiotic prescriptions in the ED were not justified. Given the unique challenges posed by the ED, including time constraints and diagnostic uncertainty, improving antimicrobial prescribing practices in this setting is crucial to address the inappropriate use of antibiotics and combat the rise of antibiotic resistance.

One potential solution is to use procalcitonin, which may help alleviate clinicians' anxiety and encourage more judicious antibiotic use, provided it is used correctly. However, our research shows that practitioners have generally poor knowledge on PCT and specifically uncertainty

about the interpretation of PCT according to decision thresholds. This may result in the prescription of antibiotics as a precaution, thus overruling PCT algorithms.

Many studies point to the fact that PCT is used inappropriately and adherence to procalcitonin (PCT) algorithms is commonly low (564–566), but the explanatory factors remain relatively unknown (567,568). Systematic reviews of antibiotic prescription determinants have consistently shown that physicians may over-prescribe antibiotics out of anxiety for missing serious infections (569–571). This aligns with studies where physicians have prescribed antibiotics despite the PCT value being low when they felt clinical uncertainty (568,572). However, studies have failed to show any independent association between patients' clinical severity and PCT algorithm compliance (567,573). Consequently, low adherence cannot be explained solely by the severity of patients' clinical condition, but may be driven by other factors.

This study might have identified one factor that might provide insight into low adherence to PCT algorithms which is poor knowledge about these algorithms. Another factor might be the scarcity of clear guidelines and relatively short-term experience with procalcitonin. To date, respiratory tract infections (RTI) and sepsis are the only diagnoses in which meta-studies confirm the benefits of routine PCT use (574). PCT is recommended in LRTI to guide the decision to withhold or stop antibiotics and, in sepsis, to guide the discontinuation of antibiotics (574). Furthermore, the inconsistent recommendations across various studies, including indications, timing, and cut-off values, have further complicated optimal use of PCT (575).

Recently, two consensus reports have been published on PCT-guided antibiotic therapy, providing updated recommendations (576,577). These reports recommend evaluating PCT cut-off values along with disease severity, and other test findings such as microbiological data to individualize decision-making (576,577). However, the recommendations are comprehensive and not straightforward for all clinicians (575).

Optimizing adherence to PCT algorithms is a priority, given the well-documented reduction in inappropriate antibiotic use (578,579). However, evidence points to the fact that

PCT implementation should be accompanied by an educational program that includes clear instructions. There has been mixed results regarding PCT implementation (580–582). One study found increased days of antibiotic use in patients in which PCT was used without prior training, while others demonstrated significantly reduced antibiotic days of therapy when PCT implementation was incorporated into an antibiotic stewardship program (580–582). Therefore, PCT implementation should be accompanied by clear instructions, given the physicians' admissions of uncertainty over the selection and interpretation of biomarkers in this study and their call for more explicit guidance. Additionally, the poor results regarding thresholds recommended by guidelines underscores the need for education on the current evidence.

A logical consequence may be that antimicrobial stewardship program teams should be formed and should put their attention to targeted education on when PCT is indicated and when it is not and how to interpret it. Also, this team should allocate time to fulfil their paramount role in actively guiding and following up with physicians during their years of training.

14. Analysis of Clinicians Knowledge on CRP:

C-reactive protein (CRP) is a biomarker commonly used in the diagnosis and management of various medical conditions, including infections, inflammation, and cardiovascular diseases. In this study, we aimed to assess the knowledge of doctors on CRP and its clinical applications.

This subsection comprised of 6 questions. The mean score of the CRP subsection was 0.56 with a standard deviation of 0.878 and a median of 0.00, indicating that the majority of practitioners had limited knowledge on this topic. 96.29% scored less than half of the possible score, and 62% scored zero, suggesting that there is a significant knowledge gap in this area.

14.1. CRP half-life and kinetics:

The study revealed that a large percentage of practitioners lack knowledge about the kinetics of CRP. Specifically, 71.30% of practitioners could not answer questions about the half-life of CRP and when it reaches its peak value. Additionally, when asked about the onset of CRP rise after it has been triggered, 69.44% of practitioners could not provide an answer. Among those who did provide an answer, most of them gave incorrect responses. Only 12.04% of practitioners provided correct answers regarding the half-life of CRP (6 hours), when it reaches its peak value (48 hours), and when it starts to rise (6 to 8 hours). These findings highlight a knowledge gap among practitioners regarding important aspects of CRP that may have implications for patient care.

As a review of CRP kinetics. In disease states, CRP levels can increase rapidly within the first 6 to 8 hours and reach peak levels of approximately around 48 hours later. However, when inflammation or tissue damage resolves, CRP levels rapidly decline with an estimated half-life of 6 hours (302).

The results of our study suggest a lack of knowledge among practitioners regarding the kinetics of CRP. This is a cause for concern as accurate interpretation of CRP kinetics is critical for effective management of inflammatory conditions. This indicates a need for increased education and awareness and training regarding this biomarker.

Interestingly, some practitioners did provide the correct answer for certain questions, indicating that there may be differences in education and training among practitioners. It is possible that those who provided correct answers received more specialized education or training in this area.

14.2. CRP physiology:

In the physiology section, 28.70% of practitioners could not give an answer to the questions asked, and those who provided an answer gave a mix of correct and incorrect

responses. For example, 9.26% incorrectly thought that CRP is synthesized by the hypothalamus, and 38.89% correctly thought it is synthesized by the hepatocytes.

The results of our study suggest a lack of knowledge among practitioners regarding the physiology of CRP. This is a cause for concern as accurate understanding of the physiology of CRP is essential for effective diagnosis and management of inflammatory conditions.

The fact that almost 30% of practitioners could not provide an answer regarding the physiology of CRP indicates a need for increased education and awareness in this area. Similarly, the fact that some practitioners provided incorrect answers highlights the need for further education and training.

Interestingly, a relatively large proportion of practitioners correctly identified that CRP is synthesized by the hepatocytes. This may suggest that there are differences in education and training among practitioners, with some receiving more specialized education in this area.

As a review of CRP physiology. CRP was initially discovered in the blood of patients with acute pneumococcal pneumonia, it gets its name from its property of precipitating upon contact with the pneumococcal C polysaccharide. It is produced by the liver in response to various clinical conditions such as infection, inflammation, and trauma and is considered the prototypical acute phase reactant in humans. It is important to note that CRP is not produced by the hypothalamus. However, interleukins that induce its production by the liver can also influence the hypothalamus (280).

14.3. Prognostic value of CRP:

The aim of this study was to evaluate the knowledge of practitioners regarding the prognostic value of C-reactive protein (CRP) in sepsis. CRP is an acute-phase protein that is elevated in response to inflammation and has been studied for its potential to predict the severity and prognosis of sepsis.

Our study found that 61.11% of practitioners could not provide an answer when asked about the prognostic value of CRP in sepsis. Among those who did, 9.26% believed that its value is not correlated with the severity of the Sequential Organ Failure Assessment (SOFA) score. Interestingly, 34.26% of practitioners identified that procalcitonin (PCT) is better than CRP for the prognosis of sepsis, and 14.81% believed that CRP value is correlated with SOFA scores. In contrast, only 5.56% of practitioners believed that CRP is better than PCT for prognosis of sepsis.

Our study highlights a lack of knowledge among practitioners regarding the prognostic value of CRP in sepsis. The fact that 61.11% of practitioners could not provide an answer indicates that this is an area where increased education and awareness is needed. The fact that a significant proportion of practitioners identified PCT as being better than CRP for prognosis of sepsis may reflect the growing body of evidence supporting the use of PCT in this context. Similarly, the fact that some practitioners believed that CRP value is correlated with SOFA scores suggests that they may be aware of studies supporting this correlation. The fact that only a small proportion of practitioners believed that CRP is better than PCT for prognosis of sepsis may reflect the current state of the literature on this topic, which generally supports the use of PCT over CRP.

14.4. CRP clinical application:

The aim of this question was to evaluate the knowledge of practitioners regarding the clinical applications of C-reactive protein (CRP). CRP is an acute-phase protein that is elevated in response to inflammation and has been studied for its potential as a diagnostic and prognostic marker in various conditions, including infection.

Our study found that 17.59% of practitioners incorrectly believed that CRP is specific to bacterial infections. This is a common misconception, as CRP can be elevated in response to inflammation of any cause, including bacterial, viral, and non-infectious inflammatory conditions. In contrast, 49.07% of practitioners correctly identified CRP as a marker of

inflammation of all causes. This is an important concept, as it highlights the broad clinical applications of CRP as a biomarker for a wide range of conditions.

Our study underscores the need for increased education and awareness among practitioners regarding the clinical applications of CRP. The fact that almost one-fifth of practitioners incorrectly believed that CRP is specific to bacterial infections suggests that there may be a need for targeted education in this area. On the other hand, the fact that nearly half of practitioners correctly identified CRP as a marker of inflammation of all causes is encouraging. This indicates that many practitioners are aware of the broad clinical applications of CRP and the potential utility of this biomarker in a wide range of conditions.

14.5. CRP confounders:

The aim of this question was to evaluate the knowledge of practitioners regarding the factors that influence C-reactive protein (CRP) concentration. CRP is an acute-phase protein that is elevated in response to inflammation and understanding the factors that can influence its concentration is important for its appropriate use as a biomarker.

Our study found that 52.78% of practitioners could not provide an answer when asked about the factors that influence CRP concentration. This suggests a knowledge gap among some practitioners in this area. Of those who did provide an answer, the majority gave correct responses. For example, 33.33% of practitioners correctly identified liver failure as a factor that can influence CRP concentration. This is because the liver is responsible for synthesizing CRP, and liver failure can impair this process. 36.11% of practitioners correctly believed that corticosteroid use influences CRP concentration. This is a common knowledge, as corticosteroids can actually suppress CRP production and lead to lower levels of CRP. Other factors identified by practitioners as potentially influencing CRP concentration included pregnancy (30.56%), age (27.78%), and chronic smoking (14.81%). These factors have been studied to varying degrees, with some evidence suggesting that they may influence CRP levels.

Our study highlights a knowledge gap among some practitioners regarding the factors that can influence CRP concentration. The fact that over half of practitioners could not provide an answer in this area suggests that there may be a need for targeted education and training in this area. On the other hand, the fact that the majority of practitioners who did provide an answer gave correct responses is encouraging. This suggests that many practitioners are aware of the key factors that can influence CRP concentration and are well-informed in this area.

14.6. Conclusion:

In conclusion, the study highlights the need for improved education and training on CRP and its clinical applications among medical practitioners. The results indicate that there are knowledge gaps among practitioners regarding the physiology, prognostic value, clinical applications, and factors that influence CRP concentration. It is essential for doctors to have a good understanding of CRP and its role in the diagnosis and management of various medical conditions in order to provide optimal care to their patients.

15. Analysis of Clinicians Knowledge on S100B:

S100B protein is a biomarker used in the diagnosis and management of various medical conditions, including head injuries, strokes, and neurological disorders. In this subsection, we aimed to assess the knowledge of doctors on S100B and its clinical applications.

This subsection included 6 questions. The mean score was 0.19 with a standard deviation of 0.456 and a median of 0.00, indicating that the majority of practitioners had limited knowledge on this topic. 100% scored less than half of the possible score, and 97% scored zero, suggesting that there is a significant knowledge gap in this area.

15.1. S100B physiology:

In our study, we aimed to evaluate the knowledge of practitioners about the physiology of S100B and report on their responses.

The results of our study show that the majority of practitioners lacked knowledge about the physiology of S100B. Of the 108 practitioners who participated in the survey, 82.41% said they did not know the tissue of origin of S100B. 2.78% of practitioners incorrectly thought it is produced in the liver, while 14.81% thought it is produced in the brain tissue, which was the correct answer.

As a review of S100b physiology. The S100β protein is a small (21 kDa) homo- or heterodimer (alpha-beta subunits). The beta subunit confers to the protein its cerebral specificity, so S100β protein is selectively synthesized by astrocytes (very weakly by melanocytes, adipocytes, etc.). Its intracellular biological functions are diverse: modulation of metabolism, participation in cellular ultrastructure and motility, regulation of intracytosolic free calcium and interaction with p53. At the extracellular level, it acts in an autocrine and paracrine manner with adjacent astrocytes and neurons, exerting a growth, survival, or apoptotic effect (338).

15.2. S100B indications:

This question evaluated the knowledge of practitioners regarding the indications of S100B protein. The study found that the majority of practitioners were unable to provide an answer regarding the indications of S100B protein. However, a small percentage of practitioners provided correct answers.

The study found that the majority of practitioners lack knowledge regarding the appropriate indications and potential clinical uses of S100B protein. Specifically, 87.04% of practitioners were unable to provide an answer regarding the indications of S100B testing, and only 0.93% provided the correct answer that it is indicated when the time since head injury is less

than 3 hours. Similarly, 93 (86.11%) practitioners could not provide an answer when asked about the applications of S100B protein. However, some practitioners correctly identified early assessment of neurological complications (11.11%) and decreased brain scans (9.26%) prescribed after minor head trauma as potential applications of S100B. A small percentage of practitioners also identified potential uses of S100B in predicting neurological outcomes in other clinical settings beyond head injury, such as stroke (4.63%) and cardiac arrest (1.8%). These findings suggest a need for education and training for practitioners to improve their knowledge of the appropriate indications and potential clinical uses of S100B protein.

Mild traumatic brain injuries (TBI) are a major public health concern due to their high incidence, short-term risks (such as the risk of death), and long-term consequences (such as post-concussion syndrome), as well as the significant cost associated with their management. Mild TBI is defined as TBI with a history of loss of consciousness and a Glasgow Coma Scale (GCS) score of 13 or higher. Until recently, the decision to perform a CT scan in the management of minor TBI was based on clinical criteria, such as the presence of neurological symptoms (progressive headaches, deteriorating consciousness, amnesia, etc.) or concomitant intoxication. However, despite these criteria, almost 90% of CT scans do not show any lesions. Thus, an objective parameter that can be easily and quickly measured would be of great benefit in optimizing decision-making regarding the use of cerebral CT scans in these patients.

S100β protein is physiologically present in the brain and is released into cerebrospinal fluid and blood in response to brain injury. Its levels start to rise within the first hour and then decline steadily over the next 6 to 48 hours. Therefore, the concept of measuring S100B levels for TBI that occurred less than 3 hours ago seems crucial, as animal and human studies indicate a half-life of approximately 97 minutes. Patients who have suffered a minor TBI within the last 3 hours and are directed to an emergency department could benefit from S100B measurements. A CT scan would only be recommended for patients with a concentration greater than 0.1 µg/L (352,354).

S100B levels can help physicians avoid ordering unnecessary head CT scans in patients with minor head injuries. S100B levels have a negative predictive value of 97%, which means that when S100B levels are low, the likelihood of TBI is also low. Using S100B as a screening tool could reduce the frequency with which head CT scans are performed up to 30%, and 24% of patients could be discharged from the ED without waiting for a CT scan. This would decrease the burden on emergency department resources and potentially improve patient outcomes (583–587).

Reducing the frequency of head CT scans can have several benefits for patients. It can decrease their exposure to radiation, which is a significant concern in the medical field. It can also reduce the time patients spend in the emergency department waiting for their head CT scan. As patients often endure lengthy delays before undergoing CT scans.

S100B is a protein that can be used in stroke. Research studies have shown that following a stroke, there is an elevation of S100B levels in the serum. This increase in S100B serum levels has been associated with poor prognosis and an increased risk of in-hospital mortality after a stroke. Therefore, S100B levels can be used as a diagnostic tool for assessing the extent of brain damage after a stroke, as well as predicting the likelihood of negative outcomes (588–590).

S100B protein is a biomarker that can serve as a reliable tool for early prognostication and predict neurological outcomes after cardiac arrest. Specifically, S100B can predict the occurrence of brain injury following a cardiac arrest. This makes it a valuable diagnostic tool for assessing the likelihood of negative neurological outcomes in patients who have experienced cardiac arrest(591–593).

15.3. S100B differential diagnosis:

In this study, we investigated the knowledge of medical practitioners regarding S100B protein. One of the questions asked was about the differential diagnosis of increased S100B protein levels. It was found that the majority of practitioners (85.19%) did not know the answer,

indicating a lack of knowledge regarding this aspect of S100B protein. However, a small percentage of practitioners (8.33%, 1.85%, 14.81%, and 11.11%) correctly chose various options for the differential diagnosis of increased S100B protein levels, such as brain tumors, malignant melanoma, head trauma with rupture of the blood-brain barrier, and stroke.

It is important for practitioners to have knowledge of the differential diagnosis of increased S100B protein levels, as it can aid in the diagnosis and management of various neurological conditions. The fact that the majority of practitioners did not know the answer to this question highlights the need for continuing education and training in this area.

S100B protein has been widely used to monitor the progression and assess the effectiveness of therapy for melanocytic tumors, originating from extracranial sources. It is worth noting that individuals with darker skin have been found to have higher levels of S100B in their serum compared to individuals with lighter skin. This is likely due to a higher metabolic activity in melanocytes in individuals with darker skin. This finding may have implications when evaluating TBI outcomes in patients with darker skin, as higher serum levels of S100B may be erroneously interpreted as elevated, leading to unnecessary CT scans in cases of mild TBI (594).

Elevated levels of S100B protein can signify various clinical conditions, making it crucial for medical practitioners to understand the differential diagnosis of increased levels. While S100B is commonly used to indicate blood-brain barrier damage, other brain injury contexts like stroke, epilepsy, meningeal hemorrhage, infectious meningoencephalitis, bacterial or viral meningitis, mental retardation, and cerebral abnormalities in fetuses can also lead to elevated S100B protein levels. In addition, extracerebral pathologies may indirectly contribute to the increase of S100B protein, due to abnormal perfusion of brain tissue. Plasma variations in S100B protein are also observed in patients following major surgical procedures such as cardiac surgery and can predict patient outcomes after cardiorespiratory arrest. Therefore, a practitioner's knowledge of the differential diagnosis of elevated S100B protein levels is crucial in determining appropriate treatment plans and predicting patient outcomes.

15.4. Conclusion:

The results of the study demonstrate a lack of knowledge among medical practitioners about S100B and its clinical applications. The majority of practitioners were unable to answer questions related to the physiology, indications, applications, and differential diagnosis of increased S100B protein.

The low level of knowledge among medical practitioners about S100B protein may be attributed to several factors, including the limited exposure to this biomarker in medical education and training programs, and the limited availability of S100B testing in clinical settings which is understandable since it is anew biomarker only used in certain countries.

These findings suggest a need for improved education and training on S100B among medical practitioners.

16. Conclusion:

The findings of our study regarding biostatistics and biomarkers namely, troponin, D dimer, NP, PCT, CRP and S100B, suggest that the majority of practitioners in the emergency department have limited knowledge on these six biomarkers and biostatistics in general. However, there is a high level of interest in receiving training and information on the use of biomarkers. Our study also reported on several challenges that practitioners face when using biomarkers, including difficulty in interpretation and selection. These findings suggest that additional education and resources may be necessary to improve the use of biomarkers in the emergency department setting.

Based on the findings of this study, some potential recommendations for improving the use of biomarkers in emergency department settings could include:

- Providing education and training on biomarkers to emergency department physicians: This could involve incorporating information about biomarkers into medical education

and training programs, as well as providing continuing education and training opportunities for practicing physicians.

- Increasing the availability and use of biomarkers in emergency department settings: Increasing the availability and use of biomarkers could involve implementing policies and protocols to guide the use of these tools, as well as providing the necessary equipment and resources to support their use.
- Developing guidelines and resources for the use of biomarkers: This could include developing standardized protocols for the use of specific biomarkers, as well as providing resources such as reference ranges and interpretation guides to help physicians understand and use the results of biomarker tests.

V. Correlation Analysis:

1. Correlation between knowledge and experience:

The present study aimed to investigate the correlation between physicians' experience and their overall scores. Experience was quantified in two ways, first by using age, and second by using of years of training.

With regards to the measurement of experience using age, the results showed that for physicians under 27 years of age, the mean score was 10.30 with a standard deviation of 0.983, while for those over 27 years of age, the mean score was 11.85 with a standard deviation of 0.826. Scores were more dispersed among the younger physicians in comparison to their older counterparts. A statistical analysis revealed that there was no significant difference in the variances of the scores between the two age groups (P-value=0.093 > 0.05). Consequently, it can be deduced that age does not have a significant impact on physician scores.

When experience was evaluated more specifically by years of training, the study found that the average score for first-year interns was 10.61 with a standard deviation of 7.101, while the average score for second-year interns was 9.31 with a standard deviation of 4.939. The scores of first-year interns were more dispersed compared to second-year interns. The statistical analysis indicated that there was no significant difference in scores between the two groups of interns ($p=0.563>0.05$).

As for residents, the study found that the average scores for residents from first to fifth year were 11.63, 12.48, 8.82, 4.80, and 23.67, respectively, with respective standard deviations of 5.786, 6.536, 6.600, 5.263, and 4.509. A statistical analysis revealed that there were no significant differences in scores between residents of different years of training ($p=0.686>0.05$). Hence, it can be concluded that the number of years of training does not have a significant impact on resident physician scores.

Our findings challenge the widely accepted notion that experience in medicine correlates positively with knowledge. Initially, this came as a surprise to us, however, our study findings are consistent with previous research.

Choudhry et al. (596) conducted a systematic review of 62 studies, evaluating the relationship between years in practice, physician age and aspects of care, such as medical knowledge, adherence to standards of practice, clinical performance, and patient outcomes. The results revealed that 52% of evaluations reported a decline in performance with increasing experience, 21% reported a decline in performance with experience for some outcomes, but no association for others, while 21% reported no association. Even when accounting for other predictors of quality, such as patient comorbidity and physician volume or specialization, the findings remained unchanged. The conclusion was that physicians with more experience may need quality improvement interventions as they are at risk of providing lower-quality care.

However, it should be noted that Choudhry et al.'s study focuses on physicians who have completed their medical training, whereas the present study examines the ongoing training and development of physicians who are still in the process of acquiring knowledge and skills.

There are several factors that could explain the lack of correlation between experience and knowledge about biomarkers:

- Healthcare professionals' knowledge and use of biomarkers can vary based on their specialty and level of experience. Professionals in certain fields may have more exposure and familiarity with specific biomarkers regardless of their experience or training. For instance, cardiologists are likely to have more knowledge about cardiac biomarkers than those in other specialties. Experienced and trained healthcare professionals may not have worked with or learned about certain biomarkers, while those with less experience or training may have had more exposure to specific biomarkers.
- Medical education may not provide extensive training on some biomarkers, resulting in limited biomedical education. As a result, healthcare professionals may not have the necessary knowledge and skills to effectively utilize biomarkers in medical practice. This limited education may also lead to confusion about the clinical relevance of certain biomarkers and their interpretation.
- Continuing education is necessary to ensure that physicians stay up to date with the latest advancements in biomarker research. However, doctors may not always keep up with these changes, leading to a lack of awareness regarding new biomarkers. Furthermore, older physicians may be less willing to adopt new standards of care and practice innovations.
- The field of biomarkers is in a state of constant evolution, with new developments emerging at a rapid pace. As a result, some physicians may struggle to stay up to date with the latest advancements in this field. In our study, some of the lowest scores were observed when practitioners were asked about relatively new information, such as the age-adjusted

threshold for D-dimer and s100b which is an entirely new biomarker that has not yet been widely adopted.

- A lack of standardization in the use and interpretation of biomarkers in medical practice can lead to confusion among physicians. There are often multiple guidelines and contradicting research findings, which can further complicate matters. As a result, physicians may be uncertain about how to use biomarkers effectively and interpret their results accurately.

  In summary, the findings of this study indicate a lack of correlation between years of experience and physicians' knowledge of biomarkers. This raises significant concerns about the current structures of medical education and training, emphasizing the pressing need for ongoing education and training programs to enhance physicians' knowledge of biomarkers throughout their careers.

2. Correlation between knowledge and frequency of use of biomarkers:

In the present study we studied the correlation between the frequency of prescribing different biomarkers and practitioners' scores for each subsection, namely troponin, d-dimer, BNP/NT pro-BNP, CRP, procalcitonin and S100b.

We found a positive, but varying degrees of correlation between the frequency of prescribing biomarkers and their subsection scores. A strong correlation was observed for troponin (p-value < 0.001, $r = 0.794$), D dimer (p-value < 0.001, $r = 0.653$), PCT (p-value < 0.001, $r = 0.762$), and a moderate correlation was observed for BNP/NT pro-BNP (p-value < 0.001, $r = 0.593$). In contrast, a weak correlation was found for CRP (p-value 0.004, $r = 0.274$) and S100B (p-value < 0.001, $r = 0.378$).

These findings suggest that there is a relationship between the frequency of prescribing a particular biomarker and the degree of knowledge about that biomarker. In other words,

physicians who prescribe a particular biomarker more frequently tend to have a stronger knowledge about that biomarker.

These findings can be explained from a cognitive standpoint. It is known that the process of storing and consolidating information in memory, even at the smallest unit of organization known as a chunk (597), is influenced by the frequency of its use (598). The brain lacks a specific memory center, and different memories are stored in separate neural networks that work in tandem. The hippocampus is believed to play a critical role in temporary and permanent information storage. Memory formation is thought to occur through modifications in the connections between neurons in memory systems through synaptic plasticity (599). When a neuron receives information, proteins are produced and sent to synapses to strengthen or establish new connections, leading to the formation of a specific neural network in the cortex associated with the memory. Repetitive activation of this network can lead to strengthening of these connections, resulting in memory consolidation. The release of neurotransmitters such as glutamate and NMDA, as well as the expression of proteins enhancing glutamate release, has been linked to synaptic plasticity (600).

In conclusion, the regular and repeated activation of the neural network associated with a memory can lead to the strengthening of the connections between neurons, ultimately leading to the consolidation of the memory.

In conclusion, our study showed that experience, as measured by age or years of training, does not correlate with knowledge on biomarkers. However, experience measured specifically using the frequency of use of each biomarker was correlated to their scores. A physician with many years of general experience but limited exposure to certain biomarkers may not have the same level of knowledge as compared to a physician with specific experience with such biomarkers. Therefore, it is important for physicians to seek out opportunities for specific experience with a wide range of biomarkers in addition to accumulating general experience. This will enable them to provide the best possible care for their patients.

The need for physician assessment and clinical judgment:

3. Cognitive skills need to be kept current:

In the context of our study, it is essential to consider the broader issue of ongoing training and education for healthcare practitioners. It is well-established that physicians must engage in ongoing training and study to maintain their cognitive skills, as these skills can decline over time if not kept current. The decline in cognitive skills can lead to lower quality care, which can negatively impact patient outcomes. Moreover, the evolving nature of standards of care presents a challenge for physicians to remain up-to-date with the latest knowledge and practices. In this context, our study has the potential to not only evaluate physicians' knowledge and skills but also promote learning and retention to maintain existing levels and increase awareness of new standards of care. This approach has been supported by many studies, which have shown that education and training can lead to improved patient outcomes and better quality of care.

Vandergrift et al. conducted a study (601) to investigate the relationship between clinical knowledge, and quality of care among physicians. The results of the study showed that a doctor's exam performance significantly affects the relationship between practice infrastructure and care quality. For example, if a doctor had a top quintile practice infrastructure score, they provided higher quality care if they also scored in the top quintile on their exam. However, if the doctor scored in the bottom quintile on the exam, the quality of care they provided was lower and not related to the practice infrastructure score. Overall, the study found that clinical knowledge moderated the relationship between care quality and practice infrastructure, such that better care was associated with higher-quality practice infrastructure, but only among physicians with high levels of clinical knowledge. These findings suggest that practitioner's knowledge is a critical factor in the delivery of high-quality care.

Vandergrift et al. conducted a study (602) to evaluate the impact of state-mandated continuing medical education (CME) requirements on physician clinical knowledge. The results of the study showed that the implementation of continuing medical education (CME) requirements was correlated with an improvement in physician clinical knowledge. This association was statistically significant and equivalent to an increase in examination scores from the 50th to the 54th percentile. This study was the first to demonstrate a link between state-level CME requirements and improvements in clinical knowledge in the USA. Overall, this study supports the idea that ongoing education are essential for physicians to maintain and improve their clinical knowledge.

Norcini et al. conducted a study (603) to investigate the relationship between physician characteristics and patient outcomes. Specifically, the influence of education and experience, with a particular emphasis on the duration since the physician completed medical school and their most recent experience. The study found that there was no significant association between a physician's experience and adjusted mortality. On the other hand, time since medical school graduation was significantly associated with higher mortality for all conditions examined. Specifically, each decade since graduation was associated with a 4.5% increased relative risk for patient mortality, even after adjusting for hospital, patient, and physician characteristics, including initial specialty board certification. The study suggests that structured educational interventions and assessments may be necessary to help physicians maintain their skills and provide optimal patient care, as recent experience alone does not seem to overcome the increase in patient mortality that comes with a physician's time since formal training.

The study concludes that the reasons for the decline in patient outcomes are likely complex and multifaceted, one plausible factor is the failure of physicians to stay up-to-date with advancements in the treatment of specific medical conditions, including clinical therapeutics and imaging techniques. This suggests that some kind of organized educational

intervention, along with proper assessments, is necessary to help physicians maintain their competencies and provide the best possible care for their patients.

In conclusion, the three studies we reviewed provide evidence that ongoing education and training are essential for physicians to maintain their clinical knowledge and skills, and to provide high-quality patient care. The study by Vandergrift et al. highlighted the importance of individual physician knowledge in delivering high-quality care. The second study by the same author showed that state-mandated continuing medical education (CME) requirements are associated with an improvement in physician clinical knowledge. The third study by Norcini et al. found that time since medical school graduation was associated with an increased relative risk for patient mortality, highlighting the importance of structured educational interventions and assessments to help physicians maintain their skills and provide optimal patient care.

Overall, these studies support that ongoing education and training are essential for physicians to provide high-quality patient care. They also demonstrate that maintaining clinical knowledge and skills requires ongoing education and training, and that this is necessary even for experienced physicians. The studies also highlight the importance of structured educational interventions and assessments to ensure that physicians are able to keep up with changes in treatment approaches and maintain the necessary skills to provide optimal care to their patients. Therefore, it is important for medical professionals to recognize the significance of continuing education and training and make a commitment to lifelong learning to ensure the best possible outcomes for patients.

4. Self-Assessment is not enough:

Physicians may wonder if they can maintain their cognitive skills through self-assessment and self-directed remediation in areas of weakness.

Our study investigated the relationship between individuals' self-assessment of their and their overall scores. The mean score for the group who proclaimed sufficient knowledge (N=9) was 13.33 with a standard deviation of 7.450, while the mean score for the group who proclaimed insufficient knowledge (N=99) was 10.84 with a standard deviation of 6.573. Statistical analysis showed that there was no significant difference in the scores between those who considered their knowledge to be sufficient and those who considered it to be insufficient ($p=0.395>0.05$). Personal knowledge perception did not significantly impact practitioners' scores as both those who believed they had sufficient personal knowledge and those who did not scored similarly.

In this discussion, we will talk about a framework from cognitive psychology, define key terms, and look at relevant evidence.

Definition:

Defining self-assessment requires an understanding of the different processes that it entails. According to Nelson and Narens' influential framework from 1990, self-assessment involves two crucial processes: monitoring and control (604). The first process, monitoring, refers to an individual's ability to assess their current level of knowledge and performance. The second process, control, involves selecting appropriate learning and performance strategies based on the self-assessment. Together, these two processes form metacognition, which refers to an individual's ability to reflect on their own thinking and knowledge.

The importance of being accurate in self-assessment:

The cruciality of self-assessment cannot be overemphasized in medical research. According to research in cognitive psychology, accurate self-assessment plays a critical role in

effective learning. The evidence suggests that monitoring is causally related to learning decisions, and those decisions, in turn, alter the type and amount of learning that occurs.

For instance, learners tend to study material they perceive they do not know well, which is known as the discrepancy reduction strategy introduced by Dunlosky & Hertzog (605). Decisions about what to study impact long-term retention, as learners who focus on difficult material end up with better overall mastery than those who only study easy material as shown by Tullis & Benjamin (606).

Additionally Ohtani & Hisasaka (607) have found that metacognition, or having awareness of one's own thinking, is a predictor of academic success even when controlling for general intelligence. It would be ideal for doctors to have accurate self-assessment abilities when evaluating their medical expertise over time.

Empirical evidence of flaws in self-assessment:

People tend to have an illusion of personal accuracy in self-assessment, believing they are more accurate in their self-assessments than others. This illusion of personal accuracy in self-assessment has been observed in numerous studies and appears to be a widespread phenomenon (608).

To assess the accuracy of physicians' self-assessment, Davis et al. conducted a systematic review (609) that compared self-assessments to external observations of competence. Out of 20 comparisons, the review found that 13 demonstrated little or no relationship between self- and external assessment, in some cases an inverse relationship, indicating that physicians do not accurately self-assess. These findings are not new, as previous studies by Sibley et al., Gordon, and Dunning et al. decades ago reported similar conclusions.

Sibley et al. reported similar findings decades ago (610) and concluded that special scrutiny should be given to the assumption that adult learners are aware of gaps and deficiencies in their performance. Gordon also found that the validity of self-assessment was low to

moderate (611). Dunning et al. similarly found that physicians tend to overestimate their skills and knowledge (612). These findings are consistent with studies in other disciplines, such as law, engineering, guidance counseling, behavioral science, psychology, and medicine, where correlations for self-assessments of knowledge were poor, as found by Falchikov and Boud (613).

Explanation for the flaws in self-assessment:

Research indicates that self-assessment can contain errors and biases. We will explore key biases before discussing theoretical explanations for these biases in metacognitive monitoring.

One bias that affects self-assessment accuracy is underestimation. Koriat, Bjork, Sheffer, & Bar (614) found that people often greatly underestimate how much they will forget between the time they learn something and the time they need to use it. This is likely because newly acquired knowledge feels strong and prominent in the moment.

The stability bias , coined by Kornell & Bjork (615) , refers to people's tendency to assume that their current level of knowledge will remain the same indefinitely. This bias can affect physicians' self-assessment of their medical expertise in two ways. First, physicians may underestimate how much they could forget after their initial training, leading to overestimation of their self-assessment accuracy. Second, physicians may also underestimate how much they can improve their skills and knowledge, even in areas where they are weak or when practices need updating to conform to advancements in medicine. As a result, physicians may choose not to pursue valuable training or review opportunities unless prompted externally.

Another significant bias is known as the ease-of-processing heuristic, which refers to people's tendency to consider material as better understood and learned if it is subjectively fluent or easy to process at the time of evaluation. This phenomenon has been studied by a number of researchers, including Kornell, Rhodes, Castel, and Tauber (616), Alter and

Oppenheimer (617), Begg, Duft, Lalonde, Melnick, and Sanvito (618), and Oppenheimer (619). This bias is closely related to the heuristic of easily learned, early remembered, which was studied by Koriat (620).

Explanation for the causes of biases in self-assessment:

In the field of cognitive psychology, the factors that cause biases have been extensively studied.

According to research conducted by Koriat et al., learners do not have direct access to their memory strength when monitoring their own knowledge (621,622). This means that they cannot simply rely on their memory traces to judge their own level of skill or knowledge. In addition, the relationship between confidence and accuracy can be reversed in certain situations, such as when answering difficult questions with a high rate of incorrect responses, meaning that more confident answers are actually less likely to be correct (623). These findings suggest that self-assessments cannot be considered objective measures of knowledge.

According to cognitive psychology, learners use an inferential approach to judge their own memory abilities, as demonstrated by research conducted by Schwartz, Benjamin, & Bjork, and Koriat (621,624). They rely on various heuristics or mental shortcuts to make an educated guess about their level of skill and knowledge. However, these heuristics are not always reliable, even though they can be correct, as noted by Benjamin, Bjork, & Schwartz (625). For instance, learners may use the quantity of information that comes to mind as a strong indicator of their memory confidence, regardless of whether it is correct or not (626).

4.1. Conclusion:

Our findings indicated that physicians have limited ability to accurately self-assess, and this seems to be a ubiquitous finding that is supported by many other studies. In fact, some

studies have even found that in certain situations, absolute accuracy diverges from the ideal in the direction of physicians being overconfident.

There are various reasons why self-assessment may fail to be accurate, including the presence of biases. Some of these biases include the ease of processing bias, stability bias. All of these biases have explanations in cognitive psychology, where people rely on heuristics or mental shortcuts to make judgments and decisions.

When physicians are unable to accurately assess their level of knowledge, it can result in suboptimal decisions regarding continuing education programs and the information they use for their daily clinical practice. This can ultimately lead to poor patient outcomes.

Hence, it is recommended that current methods of professional development and competence evaluation place greater emphasis on external assessment. External assessors are often better equipped to evaluate a physician's performance and identify areas where continuing medical education may be necessary to improve their skills.

Studies such as ours are crucial in identifying areas where physicians may not be performing up to standard, encouraging improvement and ultimately provide better patient care.

a. The link between knowledge about biomarkers and over testing:

Over-testing is a well-established issue in healthcare that can result in further invasive procedures, unnecessary treatments, and complications. These negative consequences can eventually lead to patient harm and increased costs for the health system. Therefore, it is crucial to examine the role of physicians in test ordering and the evaluation of their decision-making processes to mitigate the risk of over-testing.

Our study explored the challenges physicians face when using biomarkers. Results show that a significant number of physicians struggle with interpreting the results of biomarker tests and selecting the appropriate tests to use. Specifically, the majority of physicians reported

difficulty in interpreting biomarker results in 81.48% of cases and uncertainty in selecting biomarkers in 37.04% of cases.

Our hypothesis is that physicians who lack knowledge in selecting appropriate biomarkers for testing may over-order tests as a compensatory measure. This is often driven by the belief that more testing is better to avoid missing any relevant information. However, this approach may lead to over-testing and potential patient harm. Furthermore, if physicians do not know how to interpret the test results or if the test does not lead to any change in diagnostic or therapeutic approach, then it becomes a wasteful and unnecessary procedure.

Clinicians are ultimately responsible for test requests and are ideally positioned to prevent overtesting. By the same token, we believe that providing physicians with education on appropriate biomarker selection and interpretation can help alleviate the problem of over-testing.

In light of the above, we will review the relevant literature on over-testing, defining the concept and highlighting its prevalence. We will also discuss the various causes and consequences of over-testing, as well as potential remedies to mitigate its negative effects. Through this review, we hope to shed light on the importance of addressing the issue of over-testing and the need for increased awareness and education on appropriate test selection and interpretation among healthcare practitioners.

4.2. Definition:

Overtesting is a term used in medical practice to describe the excessive use of non-recommended screening tests in asymptomatic patients or the use of more diagnostic tests than necessary to diagnose symptomatic patients (627). This practice involves the excessive use of diagnostic methods that are unlikely to benefit the patient due to the associated harms, costs, that can lead to various problems, such as false positives, and patient anxiety, among others. This practice is becoming an increasingly significant concern in the medical field, and many

discussions and debates are ongoing on how to avoid unnecessary medical tests and prevent overdiagnosis and overtreatment (628).

4.3. Evidence for over testing locally:

The study conducted in Avicenna Hospital in Marrakech, Morocco (399), aimed to assess the prescription strategy of diagnostic tests, including ECG, chest X-ray, and cardiac enzymes, by emergency physicians in terms of benefit, cost-effectiveness, and indication.

The study's findings showed that 68% of the requested tests were not justified, only 32% had a clear indication within the context of an emergency. This highlights the potential risk of over-testing and unnecessary tests in emergency departments, where physicians may feel pressured to order tests out of a desire to be thorough or due to time constraints.

Additionally, the study found that 41% of the doctors believed that the requested tests were always justified, indicating a potential lack of awareness or education on appropriate test ordering and interpretation. This finding is consistent with the results of our study which showed that many physicians struggle with interpreting test results and selecting appropriate tests.

In addition to the 41% of doctors who believed that the requested tests were always justified, 28% of doctors believed that the tests were correctly interpreted, and 11% believed that even if the test did not impact decision-making, it was still a necessary part of the screening process. These findings suggest that some physicians may order diagnostic tests without a clear understanding of their clinical utility or the potential risks associated with over-testing. Similarly, our study found that many physicians struggle with interpreting test results and selecting appropriate tests, highlighting the need for physician education and training on appropriate test ordering and interpretation.

4.4. The consequences of overtesting:

Although doctors may think that ordering numerous tests is a good idea and patients may believe that receiving them is beneficial, over-testing can negatively impact our healthcare system in several ways. Firstly, tests can be expensive, and both doctors and patients may have financial incentives to order more tests than necessary. However, if a doctor decides to over-test a patient, the patient or their insurance will ultimately have to pay for it. Additionally, unnecessary tests waste valuable time and resources within our healthcare system.

Secondly, irrelevant or superfluous testing increases the likelihood of false-positive results. False-positives can then lead to a series of additional tests to disprove the false-positive, which can be costly and time-consuming for the patient and/or insurance. Moreover, a false-positive may result in a misdiagnosis, leading to unnecessary treatments such as prescriptions or even surgery. This can also come at a significant cost to the patient and/or insurance.

Thirdly, certain tests have inherent risks, such as radiation exposure during imaging tests. Although if a test is necessary, the benefits may outweigh the risks, an unnecessary test can be dangerous.

A framework can be developed to categorize the rationale behind a person's behavior into external pressures and an internal motivating factor. External pressures provide context and opportunity for the behavior, while the internal motivating factor determines whether the individual will act upon the external pressure.

4.5. Is over testing driven by lack of knowledge

Development of a thematic framework for overtesting:

The utilization of excessive diagnostic testing by physicians is a complex issue that has been investigated by many researchers.

Greenberg and Green postulated that there are five primary reasons for this phenomenon (629), including the belief that an extensive battery of tests improves subclinical disease detection and patient prognosis, defensive medicine practices, patient requests, financial incentives or pressures from healthcare institutions and employers, and insufficient knowledge or confidence. It is possible that physicians may order more tests than necessary due to a lack of necessary knowledge or confidence in their abilities, with the two factors frequently intertwined. In such cases, physicians may opt for a "better safe than sorry" approach and order more tests rather than acknowledging their knowledge deficit.

Rowe and colleagues (630) have also observed that physicians may misjudge the consequences of over-testing due to a belief that more testing is better and that it can help identify previously missed condition. Consequently, the potential harms that may arise from over-testing are not given sufficient consideration.

Lam et al. (631) conducted a systematic review to investigate the reasons why clinicians tend to overtest. They analyzed 65 articles and identified direct and indirect factors that contribute to overtesting. Direct factors included a lack of knowledge and understanding of disease natural history and appropriate management pathways. Unnecessary testing was found to be a compensatory measure for this lack of understanding in 25 of the analyzed articles.

Similarly, a randomized trial by Wegwarth et al. (632) involving 412 physicians found that a lack of understanding of statistics, the significance of test properties, and results led to overtesting. Similarly, in our study, practitioners lacked knowledge of biostatistics and biomarkers.

Education and training as a possible solution for overtesting:

If overtesting in medicine stems from a lack of knowledge among practitioners, then it is reasonable to assume that education is a potential solution to the issue.

Fonseca et al. (633) found that greater training and experience helped cardiologists and non-cardiologists better understand when to perform additional tests and in which patients to perform the tests.

Additionally, educational intervention programs, such as the one conducted by Caverly et al. (634), were shown to positively impact clinical decision-making and test ordering behavior by increasing awareness of overuse drivers. This emphasizes the need for continuing education and training to prevent unnecessary testing. Overall, addressing the lack of knowledge and understanding among clinicians can play a critical role in reducing the overtesting that is prevalent in medicine.

Ease of access and overtesting:

One of the factors that may contribute to overtesting is the ease of access to medical tests.

Lam et al. (631), in their systematic review, identified the ease of access to medical tests as one of the factors that may contribute to overtesting. Specifically, they found that availability and ease of access to tests were significant indirect factors leading to overtesting in ten out of the 65 articles they reviewed. This idea has also been supported by other researchers in the field. Specifically, some studies have found that tests are more likely to be ordered during day shifts, when in close proximity, or when there is little resistance to test ordering (635–638).

Fonesca et al. (633) noted that the availability of technology and equipment also predicted test ordering in tertiary hospitals (639).

In a separate study of internal medicine residents, Vrijsen et al. (640) discovered that the electronic interfaces used for ordering tests had a significant impact on overtesting. The ease with which medical tests can be accessed may contribute to doctors ignoring or remaining unaware of the potential risks associated with over-testing, resulting in overestimating the benefits of testing while underestimating the harm it may cause.

Implications for our study:

The question of whether overtesting is related to the ease of access to medical tests is not without merit. This question is particularly relevant to our study, which focuses on the practitioners' knowledge and opinions on POCT. The availability and ease of access to tests are significant factors contributing to overtesting, and POCT devices could significantly improve the ease of access to tests. However, this convenience may also lead to overtesting as clinicians may order unnecessary tests due to the ease of access and the immediate availability of results.

The lack of standardization and regulation in POCT is a significant concern that can contribute to overtesting. This is because clinicians may use POCT devices without proper training or knowledge of the limitations of the test. Our study found that practitioners do not receive training in POCT, which can lead to inaccurate or misinterpreted results. Additionally, our study found that practitioners lack knowledge on biomarkers and self-admittedly have problems selecting appropriate biomarker tests and interpreting the results. Local studies have also shown that tests were inappropriately ordered in the ED by practitioners who thought they were always justified. These issues can all culminate and lead to inaccurate or misinterpreted results, which can result in unnecessary testing or treatment. Therefore, it is essential to address these issues by providing proper education and training to practitioners and implementing standardization and regulations to promote the safe and effective use of POCT devices in clinical settings.

Therefore, it is critical to address the factors that contribute to overtesting in POCT, such as the need for appropriate training, standardization, and regulations, to ensure appropriate and effective use of POCT devices. By doing so, we can promote the appropriate use of POCT and ensure that it is not contributing to the problem of overtesting in healthcare.

4.6. Overtesting during training:

The phenomenon of over-testing is frequently perpetuated through education and mentorship, sometimes stemming from a historical belief that "more is better" without sufficient

evidence to support it. Although some training programs are now placing greater emphasis on the judicious use of testing (641), it will likely take several years for this to significantly impact the overall value of healthcare services in the US. It is therefore the responsibility of healthcare providers to regularly evaluate their own practices and engage in discussions with colleagues and trainees regarding the issue of over-testing. Additionally, factors such as lack of knowledge or confidence can contribute to over-testing, and these can often be interrelated. In instances where a provider lacks knowledge, it may be more comforting to order multiple tests rather than address the knowledge deficit (642). To avoid unnecessary testing, it may be necessary to humble oneself and seek advice from colleagues.

Medical professionals are highly trained individuals who possess vast knowledge and experience in their field of practice. However, it is not uncommon for them to experience feelings of insecurity about their skills and knowledge. This insecurity may lead some physicians to rely on over-testing as a means of compensating for their doubts and fears. This is because they may find it embarrassing to seek assistance from their colleagues (629).

However, over-testing can also be seen as a learning opportunity for physicians. For example, when a doctor is unsure of a patient's prognosis, they may order a variety of tests to gain more insight. By analyzing the results of the tests, the physician can gain a better understanding of which tests were necessary and which were not. This can help the physician develop better judgment in the future regarding which tests to order for patients with similar presentations. This process of learning from over-testing is commonly observed in residents who are still in the process of learning. Vrijsen et al. (640) found residents supervisors were aware of this phenomenon and that the benefits of over-testing as a teaching tool were acknowledged by supervisors of residents who were prone to over-test their patients. These supervisors noted that although over-testing can waste clinical time, the benefit of "knowledge by over-testing" outweighs the issue of lost time.

On the other hand, over-testing can become a reflexive behavior that persists even after a physician has gained adequate experience as has been shown by Vaughn et al. (643). This behavior is known as reflexive testing, where a physician orders a test in response to a patient's signs or symptoms without considering their medical history or other relevant information. Reflexive testing is not based on knowledge gained through over-testing but rather on a physician's preference for routine testing over conducting deeper patient evaluations.

The two previously mentioned studies by Vaughn et al. and Vrijsen et al. have also shown that doctors are impressionable when it comes to over-testing, and this behavior can be deemed appropriate if it is observed and endorsed by coworkers and supervisors. Therefore, healthcare providers must ensure that they promote appropriate testing behaviors to help prevent over-testing and its potential consequences.

4.7. Solutions for overtesting:

The categorization of solutions into interpersonal, educational, technological, and policy-based solutions is common. However, it is crucial to acknowledge that these solutions may not be universally applicable. Factors such as the size of the medical practice and the level of experience of its physicians must be taken into account when selecting and implementing solutions. Moreover, implementing solutions entails significant investments of both time and financial resources, and a considerable amount of training is often necessary. Therefore, choosing an ill-suited solution not only risks wasting resources but may also disrupt the practice's stability and hinder the ability of doctors to provide prompt care to their patients.

Since over testing can be a compensatory measure for lack of knowledge and understanding, and given the rising costs of healthcare, an appropriately designed physician education program could be an effective method for reducing unnecessary laboratory tests and associated costs. To design such a program, it will be necessary to first identify areas of

weakness in physicians' knowledge, and studies such as the one described in this text will be crucial in this process.

The results of surveys conducted among physicians in the United States and Japan (644,645) indicated a comparable ranking of perceptions regarding the top three perceived solutions to the issue of overtesting. Among the solutions that were identified: training residents in the use of appropriateness criteria and the provision of additional practice guidelines. Effective remediation strategies are likely to be multifaceted and may encompass educational initiatives such as Choosing Wisely Japan, systems-level changes to enable the sharing of medical data, and potentially, revisions to healthcare payment systems.

Healthcare providers should adopt the following four strategies to mitigate excessive testing:

1. Refrain from ordering diagnostic tests without a clear medical indication, particularly "baseline" or "screening" tests.
2. Avoid ordering preoperative tests that lack a clinical rationale, as this results in unnecessary blood draws, anxiety, costs, and exposure to ionizing radiation.
3. Familiarize themselves with evidence-based guidelines for testing and apply them in clinical practice.
4. Clearly communicate to patients the reasons for avoiding excessive testing.

In addition to individual efforts, the following collective actions can also support the reduction of over-testing:

1. Task forces representing each specialty should address systemic factors contributing to excessive testing. Physicians should assess options for improving performance benchmarks. Surgeons and anesthesiologists should explore ways to eliminate non-indicated preoperative testing requirements at surgery centers.
2. Organizations responsible for training students and residents should prioritize education on responsible testing practices.

3. Each medical society should establish a digital platform for members to provide feedback and suggestions to reduce over-testing. A guidelines committee or ad-hoc panel will regularly review these suggestions and prioritize those with supporting evidence. If necessary, the committee may initiate research to address important questions.

It is imperative for healthcare providers and patients to work together to adopt a targeted and rational approach to testing, leading to improved care within a more efficient and effective healthcare system.

VI. Limitations and Biases:

1. Demographics and characteristics of the study population:

One limitation of this study is that it only included interns and residents who are in the early stages of their medical careers. Although this sample is representative of the primary providers of patient care in the ED, it does not represent the entire medical personnel of the ED, as professors, assistant professors, and attendings are also involved in ED patient care and their knowledge and perspectives may be different.

Future research could include physicians who have completed their training to better gave physicians knowledge on biomarkers and further enhance our understanding of POCT implementation in the ED. Additionally, future research could also explore differences between doctors in training and those who have completed their training. This could help identify any differences in experiences, perspectives, or challenges faced by medical professionals at different stages of their careers, and inform the development of targeted strategies to enhance the use of biomarkers and POCT implementation in the ED setting.

Another limitation of this study is that it only included doctors, and it would have been beneficial to include biologists and nurses as well. Biologists could have contributed their expertise on technical aspects, such as laboratory processes, quality control, and instrument maintenance. Meanwhile, nurses could have provided insight into the practical aspects of implementing POCT, including coordinating care, preanalytical steps, and how POCT would impact their workflows and responsibilities. Including all stakeholders in the healthcare pathway, such as doctors, biologists, and nurses, would have provided valuable insights for the successful implementation and maintenance of POCT programs.

2. Selection and Social Desirability Bias:

Our study is subject to several biases, including self-selection bias and social desirability bias, which are common in surveys that use self-administered questionnaires.

The questions used in the study were phrased in an objective manner rather than tailored to a particular subgroup with specific characteristics, opinions, or experiences to avoid selection bias.

The study may have been affected by social desirability bias. An example of a result that might have been affected by social desirability bias is that when asked about how they perceive their knowledge, most practitioners chose "insufficient," and a small number chose "sufficient." This bias could arise because it may feel arrogant to some practitioners to claim sufficient knowledge. In reality, the number of people who consider their knowledge sufficient might be higher than what was reported.

However, it is unlikely that this bias impacted other results as the survey questions focused on the participants' knowledge and understanding of biomarkers and POCT, which are less likely to be subject to social desirability bias. In contrast, if the questions had been subjective or sensitive in nature, such as asking participants about their efforts to reduce their

environmental impact or how frequently they donate to charity, social desirability bias could have had a more significant impact on the study's outcomes.

Overall, while our study is not immune to biases, the impact of these biases on the results of the study is likely to be minimal, as they are not directly related to the research question or the variables under investigation.

3. Qualitative Study Limitations:

Our study has some limitations related to its methodology. One of the main limitations is the reliance on qualitative methods, which tend to have smaller sample sizes compared to quantitative methods. Additionally, some of the data collected is based on individuals' perceptions and opinions rather than on objective measurements.

Despite these limitations, qualitative methods were chosen as they are well-suited to address the research question, as they permit the collection of a wide range of data, including attitudes, opinions, beliefs, and values, from a relatively small number of respondents.

4. Subjectivity Bias in Question Selection and Scoring:

In this study, there is a possibility that the design of the survey questionnaire may have introduced biases. Several factors can contribute to such biases, including the selection of questions and the information they were based on, the scoring system, the grouping of propositions, and the number of questions. These factors have the potential to impact how participants respond to the questions, and the manner in which the collected data is analyzed and interpreted.

4.1. Selection of Questions:

When designing the questionnaire for our biomarker study, we aimed to include questions that were relevant to the topic at hand. However, it could be argued that the questions were selected arbitrarily, since it can be challenging to determine which specific knowledge is most essential for utilizing biomarkers effectively in our field. Despite this potential issue, we made an effort to approach the selection process in a thoughtful manner. Specifically, we took into account factors such as experience, empirical evidence, existing research, guidelines, and feedback from previous conferences on the subject. Furthermore, to ensure the suitability and appropriateness of the chosen questions, my supervisor carefully evaluated them.

One of the challenges we encountered in our study was the lack of precedent, which made it difficult to select appropriate items for comparison. Although there are studies on biomarker prescription practices in emergency departments, including two that were conducted locally (399,400), none of them specifically focused on physicians' knowledge of biomarkers. It is noteworthy that the two local studies primarily centered on the prescription of biomarkers, such as CRP, BNP, and Troponin, whereas our study aimed to evaluate physicians' knowledge on these biomarkers. While prescription and knowledge of biomarkers may be related, they do not fully capture the same information.

4.2. Grouping of propositions:

The manner in which we group the propositions can impact the score that students receive. If the propositions are arranged in a clear and logical manner, it can facilitate the correct identification of the answer. Conversely, if the propositions are arranged in a random manner, it can make it more challenging for participants to identify the correct answer.

In the biostatistics subsection for example, there was a cluster of 4 questions and another cluster of 3 questions, all of which had the same set of propositions to choose from. It is possible that participants used a process of elimination as they progressed through these

questions, since the answer to one question could not be the answer to the next. This may have contributed to the relatively high success rate for these questions.

In other sections, different grouping strategies have been utilized. For instance, propositions for certain questions were categorized based on either physiology or kinetics, among others. Meanwhile, for other questions, propositions were randomly grouped and may consist of items from different categories such as physiology, kinetics, or indication. Individuals with strong knowledge in physiology may have had an advantage when the propositions were organized based on that specific topic. Conversely, they may have been at a disadvantage when the propositions were grouped randomly, which may explain the lower success rate for these types of questions.

Overall, we used diverse grouping methods to prevent the study results from being skewed in one particular direction. However, it is essential to acknowledge that irrespective of the diversity of the grouping methods, there is a risk of introducing bias into the findings. Therefore, it is crucial to consider the impact of the grouping methods used and their potential influence on the overall outcome when interpreting the study's findings.

4.3. Length of Questionnaire:

Prolonged questionnaires containing challenging questions can have a negative impact on the quality of responses. As participants progress further, their attention and motivation can decrease, leading to lower quality responses or even non-completion of the survey.

Our study included more than 100 questions, which may have resulted in survey fatigue bias among the participants. Additionally, feedback from participants indicated that the questionnaire was not only lengthy but also challenging, potentially exacerbating the issue of survey fatigue bias. However, we believed that a large number of questions was necessary to conduct a detailed and comprehensive assessment of physicians' knowledge and opinions on biomarkers and POCT.

To avoid such issues in future studies, researchers might consider conducting separate studies for each biomarker to reduce response burden and enhance the validity of the findings. By reducing the number of questions per survey, researchers can help prevent survey fatigue bias and increase the chances of obtaining valid and reliable results. This approach can also help ensure that participants remain engaged throughout the survey, leading to more accurate and meaningful data.

4.4. Assessment Tools and Their Impact on Scores:

The questionnaire used in the study comprised of both multiple-choice questions (MCQs) and single-choice questions (SCQs). SCQs are generally easier to answer as participants know that only one option is correct, they are more susceptible to random selection. On the other hand, MCQs require the selection of multiple propositions and are comparatively harder to answer.

The ratio of MCQs to SCQs in the questionnaire might have influenced the scores of each subsection as well as the overall score. It is possible that if a different proportion of MCQs to SCQs were used, or if only one type of question was utilized, the scores may differ. Therefore, it is crucial to consider the impact of this factor on the study's results, as the choice of assessment tools can affect the validity and reliability of the findings.

4.5. Scoring system:

The way we grade questions can have a significant impact on participants' scores. There are various scoring methods available, including the "plus one" method where one point is awarded for each correct answer and no points are deducted for incorrect answers, and the "minus one" method where one point is awarded for each correct answer but one point is deducted for each incorrect answer. Another option is the "partial credit" system, where partial

points are awarded for selecting the correct answer among the choices provided. Each method has its own advantages and disadvantages.

Our study utilized the plus one method for scoring, and it should be noted that alternative grading methods could produce different scores due to their subjective nature. However, it is important to recognize that while scores may vary, the study's outcomes may remain the same, as scores are only numerical values that reflect one dimension of knowledge and not necessarily the underlying trends and patterns in the data.

Moreover, it is crucial to acknowledge that our analysis did not solely depend on the quantitative data obtained from the scores. Instead, we conducted a comprehensive qualitative analysis of each question or cluster of questions to gain a better understanding of our participants' knowledge. This approach aligns with best practices in medical research, as it integrates both quantitative and qualitative data to allow for a more nuanced interpretation of the results.

4.6. Open ended questions:

Open-ended questions were not scored in this study because they do not have a fixed set of answers, making it difficult to assess the responses in a standardized way. In contrast, multiple-choice and single-choice questions have predefined answer options that can be scored easily, allowing for a more objective and standardized evaluation of responses.

Furthermore, the number of physicians who answered open-ended questions in this study was very low. Therefore, it was not possible to conduct a quantitative analysis of the responses. Instead, the responses to open-ended questions were used as qualitative data and were analyzed thematically to identify recurring patterns or themes.

5. The choice to include “Don’t know” in the choices:

The "Don't know" response option in surveys can be problematic because it is often chosen by individuals who genuinely do not possess the necessary knowledge to answer, but also by those who seek to minimize their effort in answering through a behavior known as "satisficing” (401).

Allowing respondents to skip questions may seem like a solution, but it also brings its own set of problems. There would be an increase in "missing values," some of which may be from individuals who genuinely do not know the answer, while others may be from those who do not want to take the time to think of a response. This was especially manifest in our investigation, when we offered the option to skip (which was the case in five questions). The majority of the participants, with percentages ranging from 79.62% to 100%, opted to skip the questions. Specifically, 94.44% chose to skip the first question, 79.62% chose to skip the second, 100% chose to skip the third, 99.07% chose to skip the fourth, and 100% chose to skip the fifth.

Additionally, if the "don't know" option was not available and respondents were not allowed to skip questions, they would be faced with two options: abandoning the survey resulting in high dropout rates or providing a random answer resulting in low quality data. Both of these scenarios would result in representativeness issues.

In view of several factors such as the type of questions, the characteristics of the surveyed population, and the study's objectives, we decided not to allow participants to skip questions and instead include a "Don't know" alternative.

Concerning, the potential loss of data, the inclusion of a "Don't know" response option helps in reducing noise created by individuals who have not reflected deeply on the question or lack relevant experience or knowledge. Their arbitrary responses would not provide significant information and would distort the data. Thus, we prioritize clean data over a large quantity of data.

Concerning the demographics of the surveyed individuals and the type of questions posed, it is clear that many of the questions were centered around in-depth information from physiology and pathophysiology that may have been forgotten since medical school. Over time, information tends to be forgotten, and relatively new information like information on POCT and S100B may not be familiar to respondents.

Concerning the objectives of our study, we concluded that not knowing was not only plausible, but also essential for us to evaluate. Accordingly, a statement was incorporated in the survey introduction, stating, "We ask of you to answer according to your current knowledge and without assistance, in order to best assess the need for training".

In the future, similar studies could be designed with participants who have undergone an educational intervention. In such cases, there would be an expectation for them to possess knowledge of the answers, and a "Don't know" option would not be necessary.

6. The impact of the covid-19 pandemic on education and training:

The COVID-19 pandemic has significantly disrupted the education and training of medical students and physicians. There has been a loss of instructional time, disruption to the continuity of learning, and potential long-term impacts on educational outcomes.

In March 2020, Morocco reported its first case of COVID-19 infection and hospitals across the country began preparations as the number of cases rapidly increased. On March 12, the World Health Organization declared the situation a pandemic. This resulted in changes to the roles of resident physicians, with some being deployed to areas of greatest need in hospitals and others having core rotations cancelled. Opportunities to practice and develop technical skills were also limited due to a focus on minimizing resident exposure to aerosol-generating medical procedures.

The pandemic has also had a significant impact on academic life, with universities and other educational institutions continuously modifying curricula, educational content, and activities in response to the uncertainty caused by the crisis. This has affected all levels of education, from undergraduate to postgraduate and doctoral programs, as well as research and administrative activities.

Medical students in clinical training have also been affected by the disruption caused by the pandemic. In Morocco, the pandemic led to the sudden shift to exclusive distance learning for medical education without prior preparation. A recent study in Morocco found low engagement with distance learning among medical students during confinement, with 53.3% studying one hour or more per day, 46.4% having access to multimedia learning resources, and 20.9% being offered interactive online sessions with their teachers (595). This lack of engagement can exacerbate the uncertainty and frustration already present during the pandemic. It is likely that the months of disrupted learning will continue to have a significant impact on the training experiences of these students and training physicians.

It is plausible that the current pandemic context, including the suspension or cancellation of various training programs, seminars, and research projects other than those related to SARS-CoV-2, has had a biased effect on the knowledge of physicians and, by extension, on the results of this study.

7. Limitations of language used in the questionnaire:

One potential source of bias is the interpretation of answer options by respondents. This can be particularly true for answer options such as "always," "sometimes," and "rarely," which may have different meanings to different individuals. It is important to recognize that each respondent may have their own interpretation of these terms, which could result in varying responses and lead to inaccurate conclusions.

8. Limited generalizability of study results:

One potential limitation is that all data were collected from a single site, which may not represent the perspectives and experiences of physicians in other settings where biomarkers have been used for a longer period or where physicians have received more comprehensive training.

Furthermore, this study was conducted on physicians in North Africa, and there is a possibility that the experiences and challenges they face differ from those encountered by physicians in Europe and North America, which would hinder the comparison with other countries.

Despite this limitation, our study's findings are still relevant to many hospitals in Morocco, where biomarker use is prevalent but knowledge about them is rarely evaluated. We believe that this situation may exist in other countries as well.

9. Lack of comparative data:

In this study, our goal was to address a gap in knowledge in a specific area by conducting a pilot study. However, we encountered the challenge of limited comparative data.

To overcome this limitation, we broadened our search scope to include related fields and similar studies that could provide valuable context. While we recognize that direct comparison was not possible, we have taken steps to acknowledge the limitations of our study in the conclusions.

CONCLUSION

In summary, our study revealed significant knowledge gaps among emergency department physicians in Morocco regarding the use of biomarkers and Point-of-Care Testing (POCT). Key findings include:

1. Limited awareness: A substantial 89% of surveyed physicians were unfamiliar with POCT.
2. Lack of training: Nearly 80% of practitioners lacked prior training in POCT device operation.
3. Device availability: Only 96.2% of practitionners had no access to POCT devices for troponin, BNP, D dimer, procalcitonin, CRP or S100B protein.
4. Overcrowding concern: 99% of practitioners identified overcrowding as a significant issue in healthcare facilities.
5. Biomarker awareness: 65.74% of participants were unfamiliar with the term "biomarker," highlighting a knowledge gap in this essential concept.
6. Biomarker utility: While 85.19% of healthcare practitioners recognized the potential of biomarkers in disease diagnosis and monitoring, challenges in interpreting results and selecting appropriate tests were prominent, affecting 81.48% and 37.04% of participants, respectively.
7. Knowledge deficiency: The study revealed a significant knowledge deficiency in biomarker-related areas, with an average questionnaire score of only 11.05 out of 75.
8. Challenges in Biostatistics: Our study highlighted suboptimal performance in biostatistics-related questions, with an average accuracy rate of approximately 28% in this domain.
9. Specific Biomarker Knowledge Gaps: Participants exhibited notable deficiencies in understanding specific biomarkers such as troponin, D-dimer, BNP/NT pro-BNP, procalcitonin, CRP, and S100B, with most scoring below half of the maximum attainable score in these areas.

10. Age and Training Impact: Our analysis did not reveal statistically significant differences in knowledge scores based on the age or years of training among the participating physicians.
11. Biomarker Prescription and Knowledge Correlation: We found that physicians who prescribed specific biomarkers more frequently tended to possess a significantly deeper understanding of those biomarkers, with robust positive correlations between prescription frequency and knowledge in certain cases.
12. Self-Assessment vs. Actual Knowledge: Interestingly, participants' self-assessed knowledge levels did not significantly impact their overall scores, indicating that personal perception of knowledge did not correlate with actual proficiency.
13. Challenges in Over-Testing: The study highlighted the issue of over-testing in healthcare, driven by factors such as a lack of knowledge and understanding among physicians regarding appropriate test selection and interpretation, financial incentives, patient requests, and the potential ease of access to medical tests. This finding is particularly relevant to Point-of-Care Testing (POCT) because it simplifies access to medical tests, raising concerns about the potential for over-testing. Therefore, there is a crucial need for careful and strategic implementation of POCT to prevent the exacerbation of over-testing.

RECOMMENDATIONS

1. Education and training: Implement comprehensive training programs for emergency department physicians on the use of POCT devices and biomarkers.
2. Device accessibility: Increase the availability of POCT devices, especially for critical biomarkers, to enhance timely testing.
3. Address overcrowding: Develop strategies to mitigate overcrowding in healthcare facilities, potentially through the use of POCT for rapid diagnostics.
4. Regulatory framework: Establish regulatory guidelines for POCT implementation and quality assurance in Morocco's healthcare system.
5. Biomarker education: Develop educational programs to enhance healthcare practitioners' understanding of biomarkers, their applications, and interpretation.
6. Interpretation support: Provide resources and training to assist clinicians in interpreting biomarker results accurately.
7. Targeted education: Tailor educational interventions to address specific knowledge gaps in biomarker-related areas.
8. Objective assessments: Emphasize objective assessments and training rather than relying solely on self-assessment for knowledge improvement.
9. Promote evidence-based decision-making and educate healthcare practitioners about the appropriate use of diagnostic tests to reduce over-testing and its associated negative consequences.
10. Leverage the potential of POCT to streamline access to tests, making them readily available for timely and necessary diagnostics, while simultaneously discouraging unnecessary testing.

ABSTRACT

Abstract

Evaluating Emergency Department Physicians' Knowledge and Attitudes Towards Biomarkers and Point-of-Care Testing in Morocco

Background: The use of biomarkers in emergency medicine is essential for prompt diagnosis and patient care. The COVID-19 pandemic underscored the significance of rapid diagnostic technologies such as Point-of-Care Testing (POCT), which depend on clinician expertise and training.

Objective: This study aims to assess the knowledge and attitudes of emergency department physicians toward biomarkers and POCT, identify educational gaps, and propose improvements for patient care standards in Morocco.

Methods: A cross-sectional observational study was conducted at Marrakech teaching hospital, enrolling interns and residents in the emergency department through a 101-question survey to evaluate their knowledge and attitudes.

Results: The study engaged 108 physicians with a 63.52% response rate. Our findings revealed a critical lack of awareness and formal education about POCT, with 89% of physicians unfamiliar with it and 79.63% having no training in operating POCT devices. The scarcity of POCT devices for crucial biomarkers was notable, with only 3.7% availability, despite 92.59% of physicians recognizing their importance in emergency care.

Physicians acknowledged the challenges of healthcare facility overcrowding and expressed interest in POCT as a solution, considering its rapid results and potential for cost savings. However, concerns were raised about the reliability of POCT due to potential device-related errors.

Knowledge gaps were apparent among healthcare practitioners, with 65.74% unfamiliar with the term "biomarker." Challenges in biomarker result interpretation affected 81.48% of

participants, and test selection impacted 37.04%. The average score of physicians on the questionnaire was notably low, indicating a need for targeted educational interventions.

Conclusion: There is an imperative need to enhance awareness and training in POCT among healthcare practitioners in Morocco to align with international standards. Our study highlights the potential of POCT to mitigate overcrowding challenges in emergency departments and improve diagnostic efficiency. Additionally, significant knowledge gaps concerning biomarkers necessitate educational improvements. A multifaceted approach, including policy changes, educational reform, and cultural shifts within the medical community, is required to promote appropriate diagnostic test use and improve healthcare outcomes.

Résumé:

Évaluation des connaissances et des attitudes des médecins du service d'urgence sur les biomarqueurs et les tests de biologie délocalisée au Maroc

Contexte : L'utilisation de biomarqueurs en médecine d'urgence est essentielle pour un diagnostic rapide et des soins aux patients. La pandémie de COVID-19 a souligné l'importance des technologies de diagnostic rapide telles que les tests au point de soin (POCT), qui dépendent de l'expertise et de la formation des cliniciens.

Objectif : Cette étude vise à évaluer les connaissances et les attitudes des médecins du service d'urgence envers les biomarqueurs et les POCT, à identifier les lacunes éducatives et à proposer des améliorations pour les normes de soins aux patients au Maroc.

Méthodes : Une étude observationnelle transversale a été menée à l'hôpital universitaire de Marrakech, en enrôlant des internes et des résidents du service d'urgence à travers une enquête de 101 questions pour évaluer leurs connaissances et attitudes.

Résultats : L'étude a impliqué 108 médecins avec un taux de réponse de 63,52 %. Nos résultats ont révélé un manque critique de sensibilisation et de formation formelle concernant les POCT, avec 89 % des médecins ne les connaissant pas et 79,63 % n'ayant aucune formation pour utiliser les dispositifs POCT. La rareté des appareils POCT pour des biomarqueurs cruciaux était notable, avec seulement 3,7 % de disponibilité, bien que 92,59 % des médecins reconnaissent leur importance dans les soins d'urgence.

Les médecins ont reconnu les défis de la surpopulation des établissements de santé et ont exprimé leur intérêt pour les POCT comme solution, compte tenu de leurs résultats rapides et de leur potentiel d'économies de coûts. Cependant, des préoccupations ont été soulevées concernant la fiabilité des POCT en raison d'erreurs potentielles liées aux appareils.

Des lacunes de connaissances étaient apparentes parmi les professionnels de la santé, avec 65,74 % ne connaissant pas le terme "biomarqueur". Les défis dans l'interprétation des

résultats des biomarqueurs ont affecté 81,48 % des participants, et la sélection des tests a impacté 37,04 %. Le score moyen des médecins sur le questionnaire était notablement bas, indiquant un besoin d'interventions éducatives ciblées.

Conclusion : Il est impératif d'améliorer la sensibilisation et la formation en POCT parmi les professionnels de santé au Maroc pour se conformer aux normes internationales. Notre étude met en évidence le potentiel des POCT pour atténuer les défis de surpopulation dans les services d'urgence et améliorer l'efficacité du diagnostic. De plus, des lacunes significatives de connaissances concernant les biomarqueurs nécessitent des améliorations éducatives. Une approche multifacette, incluant des changements de politique, une réforme éducative et des changements culturels au sein de la communauté médicale, est requise pour promouvoir l'utilisation appropriée des tests diagnostiques et améliorer les résultats de santé.

ملخص

تقييم معرفة ومواقف أطباء أقسام الطوارئ حول العلامات البيولوجية واختبارات الرعاية الصحية عند نقطة الرعاية في المغرب

الخلفية:

استخدام العلامات البيولوجية في الطب الطارئ أساسي للتشخيص السريع ورعاية المرضى. وقد أكدت جائحة كوفيد- 19 على أهمية التقنيات التشخيصية السريعة مثل اختبارات الرعاية الصحية عند نقطة الرعاية (POCT)، التي تعتمد على خبرة وتدريب الأطباء.

الهدف:

تهدف هذه الدراسة إلى تقييم معرفة ومواقف أطباء قسم الطوارئ تجاه العلامات البيولوجية واختبارات الرعاية الصحية عند نقطة الرعاية، وتحديد الفجوات التعليمية واقتراح تحسينات لمعايير رعاية المرضى في المغرب.

الطرق:

أُجريت دراسة ملاحظاتية عرضية في مستشفى تعليمي بمراكش، شملت 108 أطباء من المتدربين والمقيمين في قسم الطوارئ عبر استبيان من 101 سؤال لتقييم معرفتهم ومواقفهم،

النتائج:

بلغ معدل استجابة 63.52%.أظهرت النتائج نقصاً حرجاً في الوعي والتعليم الرسمي حول اختبارات الرعاية الصحية عند نقطة الرعاية، حيث لم يكن 89% من الأطباء على دراية بها، و 79.63% منهم لم يتلقوا تدريباً على استخدام أجهزة الرعاية الصحية عند نقطة الرعاية. كما كان نقص توافر أجهزة الرعاية الصحية عند نقطة الرعاية للعلامات البيولوجية الحاسمة ملحوظاً (3.7% فقط)، على الرغم من أن 92.59% من الأطباء أقروا بأهميتها في الرعاية العاجلة.

أقر الأطباء بتحديات الاكتظاظ في مرافق الرعاية الصحية وأبدوا اهتماماً بـ اختبارات الرعاية الصحية عند نقطة الرعاية كحل لسرعة نتائجها وإمكانية توفير التكاليف. لكن، كانت هناك مخاوف بشأن موثوقية اختبارات الرعاية الصحية عند نقطة الرعاية بسبب أخطاء محتملة تتعلق بالأجهزة.

كانت الفجوات المعرفية واضحة بين الممارسين الصحيين، حيث كان 65.74% منهم غير مُلمين بمصطلح "العلامة البيولوجية". وأثرت تحديات تفسير نتائج العلامات البيولوجية على 81.48% من المشاركين، وأثر اختيار

الاختبار على 37.04%. كما كان المعدل الذي حصل عليه الأطباء في الاستبيان منخفضاً بشكل ملحوظ، مما يشير إلى الحاجة لتدخلات تعليمية مستهدفة.

الاستنتاج:

هناك حاجة ملحة لتعزيز الوعي والتدريب في اختبارات الرعاية الصحية عند نقطة الرعاية بين الممارسين الصحيين في المغرب لمواكبة المعايير الدولية. تسلط دراستنا الضوء على إمكانية اختبارات الرعاية الصحية عند نقطة الرعاية في التخفيف من تحديات الازدحام في أقسام الطوارئ وتحسين كفاءة التشخيص. كما أن الفجوات المعرفية الكبيرة بشأن العلامات البيولوجية تتطلب تحسينات تعليمية. يتطلب الأمر نهجاً متعدد الأوجه يشمل تغييرات السياسة، وإصلاحات تعليمية، وتحولات ثقافية ضمن المجتمع الطبي لتعزيز استخدام الاختبارات التشخيصية المناسبة وتحسين نتائج الرعاية الصحية.

APPENDIX

Les marqueurs biologiques aux urgences

Dans le cadre d'un travail de recherche intitulé [Les marqueurs biologiques aux urgences. Etat de connaissance des praticiens et perspectives], une enquête transversale est menée par le service des Urgences SAMU CHU Mohammed VI de Marrakech. Elle concerne les médecins résidents, médecins internes et médecins enseignants

Objectifs à court terme:
1. Evaluer les connaissances sur les biomarqueurs aux urgences
2. Evaluer le besoin de formation sur les biomarqueurs aux urgences
3. Diffuser auprès des praticiens des informations sur les marqueurs biologiques et leurs rôle dans la médecine d'urgence.

Objectif à moyen et long terme:
Permettre une meilleure prise en charge des patients aux urgences en utilisant ces biomarqueurs.

Ce questionnaire est anonyme et dure environ 15 minutes. Je vous prie d'y répondre qu'une seule fois.
Je vous demande également de répondre selon vos connaissances actuelles et sans aide, afin d'évaluer au mieux le besoin de formation.

Les réponses seront communiquées ultérieurement, après analyse des données , afin de ne pas fausser l'évaluation.

Je vous remercie pour votre aide et précieuse collaboration.

* Indique une question obligatoire

Identification du répondant:

1. Vous êtes: *

Une seule réponse possible.

- ◯ Femme
- ◯ Homme

2. Votre âge *

3. Vous êtes: *

Une seule réponse possible.

- ◯ Médecin interne
- ◯ Médecin résident

4. Si vous êtes un médecin interne, vous êtes en quelle année?

Une seule réponse possible.

- ◯ 1ère année
- ◯ 2ème année

5. Si vous êtes un médecin résident, vous êtes en quelle année?

Une seule réponse possible.

- ◯ 1ère année
- ◯ 2ème année
- ◯ 3ème année
- ◯ 4ème année
- ◯ 5ème année

6. Quelle est votre type de spécialité ou votre futur type de spécialité ? *

Une seule réponse possible.

- ◯ Anesthésie et réanimation
- ◯ Urgentiste
- ◯ Médecine
- ◯ Chirurgie
- ◯ Biologie

La biologie délocalisée:

7. Avez-vous déjà entendu parler de "biologie délocalisée" *

Une seule réponse possible.

- ◯ Oui
- ◯ Non

La biologie délocalisée désigne tout examen de biologie médicale, dont la phase analytique est réalisée à proximité du patient, en dehors des locaux du laboratoire de biologie médicale, au sein d'établissements de soins publics ou privés et par du personnel extérieur au laboratoire.

8. Si oui, donnez une définition et quelques exemples:

9. Lequel des exemples suivants s'applique à la définition de biologie délocalisée? *

Une seule réponse possible.

- ◯ Prélever du sang dans l'ambulance et l'envoyer au laboratoire de l'hôpital
- ◯ Obtention d'hémocultures aux urgences
- ◯ L'usage d'un glucomètre pour obtenir une glycémie capillaire
- ◯ Obtention d'une température rectale à l'aide d'un thermomètre électronique
- ◯ Ne sait pas

0 Quel appareil de bio ogi délocalisée utilisez-vous dans votre domaine clinique ?

Plusieurs réponses possibles.

- [ ] Analyseur de gaz du sang
- [ ] Lecteurs de glycémie/cétone
- [ ] Analyseur d'hémoglobine (Hemocue)
- [ ] Appareil de lecture de la coagulation INR (Coaguchek)
- [ ] Analyseur de formule sanguine complète (Sysmex)
- [ ] Analyseur de l'HbA1c
- [ ] Kit de test urinaire de grossesse
- [ ] Kit de test VRS (virus respiratoire syncytial)
- [ ] Bandelette urinaire (dipstick)
- [ ] Analyseur de coagulation sanguine (TEG ou ROTEM)

11. Pour les items que vous avez coché, avez vous reçu une formation avant leurs utilisation? *

Une seule réponse possible.

- ◯ Oui
- ◯ Non

12. A votre avis quelles sont les plus grandes causes d'erreurs dans l'exactitude d'outils de biologie délocalisée? *

Plusieurs réponses possibles.

- [ ] Erreurs liées à l'échantillonnage
- [ ] Erreurs liées à l'opérateur
- [ ] Erreurs liées au réactif
- [ ] Erreurs liées au calibrage
- [ ] Erreurs liées à l'environnement

3 A votre avis, quels sont l s bénéfices de la biologie délocalisée? *

Plusieurs réponses possibles.

- [ ] Un coût moins cher
- [ ] Obtention plus rapide de résultats, qui permet aux médecins de prendre des décisions médicales plus tôt
- [ ] C'est plus convenable pour les patients nécessitant des tests fréquents, une diminution de la main-d'œuvre
- [ ] Je ne vois pas de bénéfice ajouté

14. Pour vous: l'encombrement aux urgences (overcrowding) constitue: *

Plusieurs réponses possibles.

- [ ] Un léger problème
- [ ] Un problème assez sérieux
- [ ] Un problème très sérieux

15. D'après votre expérience, quel est l'effet de l'encombrement aux urgences sur vous et sur la prise en charge des patients? *

Plusieurs réponses possibles.

- [ ] Une longue période d'attente pour les patients
- [ ] Un retard dans le diagnostic et le traitement des patients
- [ ] Douleur et souffrance prolongées des patients
- [ ] Plus d'erreurs dans la prise en charge des patients
- [ ] Un épuisement (burnout) pour le personnel

16. D'après votre expérience, à quel point, l'attente des résultats du laboratoire serais une cause d'encombrement aux urgences? *

Une seule réponse possible.

- ◯ Est une cause majeure d'encombrement aux urgences
- ◯ Est une cause importante d'encombrement aux urgences
- ◯ Est une cause mineure d'encombrement aux urgences

7 Disposez-vous d'out l d biologie délocalisée pour mesurer les biomarqueurs suivants?

Une seule réponse possible par ligne.

	Oui	Non
Troponine	◯	◯
D-dimères	◯	◯
BNP/NT-pro BNP	◯	◯
CRP	◯	◯
Procalcitonine	◯	◯
Protéine S100b	◯	◯

18. Serez-vous intéressés par l'implémentation d'outils de biologie délocalisée pour la mesure des biomarqueurs précédents? *

Une seule réponse possible.

◯ Oui
◯ Non

Généralités sur les biomarqueurs:

19. Avez vous déjà entendu parler de "biomarqueur"? *

Une seule réponse possible.

◯ Oui
◯ Non

20 Si oui, donnez-en une d éfinition:

Un biomarqueur (ou marqueur biologique) est une caractéristique définie qui est mesurée comme un indicateur des processus biologiques normaux, des processus pathogènes ou des réactions à une exposition ou une intervention, y compris les interventions thérapeutiques.

21. Concernant les biomarqueurs, considérez-vous vos connaissances: *

Une seule réponse possible.

- ◯ Suffisantes
- ◯ Insuffisantes

22. Seriez-vous intéressé(e) par une formation ou des informations sur les biomarqueurs?

Une seule réponse possible.

- ◯ Oui
- ◯ Non

23. A votre avis, un biomarqueur peut avoir une application dans (choix multiple): *

Plusieurs réponses possibles.

- ☐ Diagnostic
- ☐ Pronostic
- ☐ Stratification de risque
- ☐ Surveillance
- ☐ Prédire et monitorer la réponse à une thérapeutique
- ☐ Ne sait pas

4 Quelles sont les difficultés que vous rencontrez lors de l'utilisation de biomarqueur?

Plusieurs réponses possibles.

- [ ] Je ne sais pas lequel utiliser
- [ ] Je n'arrive pas à interpréter leurs résultats
- [ ] Je ne rencontre pas de difficultés

25. La sensibilité d'un biomarqueur désigne (choix unique): *

Une seule réponse possible.

- ◯ La proportion malade d'une population et qui a un résultat anormal
- ◯ La proportion saine d'une population et qui a un résultat normal
- ◯ La probabilité que la maladie soit réellement présente lorsque le résultat du test est positif
- ◯ la probabilité que la maladie soit réellement absente lorsque le résultat du test est négatif
- ◯ Ne sait pas

26. La spécificité d'un biomarqueur désigne (choix unique): *

Une seule réponse possible.

- ◯ La proportion malade d'une population et qui a un résultat anormal
- ◯ La proportion saine d'une population et qui a un résultat normal
- ◯ La probabilité que la maladie soit réellement présente lorsque le résultat du test est positif
- ◯ la probabilité que la maladie soit réellement absente lorsque le résultat du test est négatif
- ◯ Ne sait pas

7 La valeur prédictive positive d'un biomarqueur désigne (choix unique): *

Une seule réponse possible.

- ◯ La proportion malade d'une population et qui a un résultat anormal
- ◯ La proportion saine d'une population et qui a un résultat normal
- ◯ La probabilité que la maladie soit réellement présente lorsque le résultat du test est positif
- ◯ la probabilité que la maladie soit réellement absente lorsque le résultat du test est négatif
- ◯ Ne sait pas

28. La valeur prédictive négative d'un biomarqueur désigne (choix unique): *

Une seule réponse possible.

- ◯ La proportion malade d'une population et qui a un résultat anormal
- ◯ La proportion saine d'une population et qui a un résultat normal
- ◯ La probabilité que la maladie soit réellement présente lorsque le résultat du test est positif
- ◯ la probabilité que la maladie soit réellement absente lorsque le résultat du test est négatif
- ◯ Ne sait pas

29. Vrai ou faux, la valeur prédictive négative et la valeur prédictive positive* dépendent de la prévalence de la maladie et des caractéristiques du biomarqueur (sensibilité, spécificité)

Une seule réponse possible.

- ◯ Vrai
- ◯ Faux
- ◯ Ne sait pas

0 Vrai ou faux, la sens bilité et spécificité d'un biomarqueur dépendent de la prévalence de la maladie dans une population

Une seule réponse possible.

- ◯ Vrai
- ◯ Faux
- ◯ Ne sait pas

31. Un biomarqueur qui a une grande sensibilité (choix unique): *

Une seule réponse possible.

- ◯ Confirme le diagnostique quand son résultat est positif
- ◯ Est plus souvent positif que négatif chez les personnes atteintes de la maladie
- ◯ Est plus positif chez les personnes atteintes de la maladie que négatif chez les personnes non atteintes de la maladie

32. Vous demandez le dosage d'un biomarqueur car vous pensez que votre patient a une maladie. La statistique qui décrit la proportion d'une population avec un résultat positif et qui est en effet malade est (choix unique): *

Une seule réponse possible.

- ◯ Sensibilité
- ◯ Spécificité
- ◯ Valeur prédictive positive
- ◯ Valeur prédictive négative
- ◯ 1 - Valeur prédictive négative
- ◯ 1 - Valeur prédictive positive
- ◯ Ne sait pas

3 Vous demandez le dosage d'un biomarqueur car vous pensez que votre patient a une maladie, mais le test revient négatif. La statistique qui décrit la proportion d'une population avec un résultat négatif mais qui est néanmoins malade est (choix unique):

Une seule réponse possible.

- ◯ Sensibilité
- ◯ Spécificité
- ◯ Valeur prédictive positive
- ◯ Valeur prédictive négative
- ◯ 1 - Valeur prédictive négative
- ◯ 1 - Valeur prédictive positive
- ◯ Ne sait pas

34. Vous demandez le dosage d'un biomarqueur pour éliminer une maladie, mais le test revient positif. La statistique qui décrit la proportion d'une population qui a un résultat positif mais qui est quand même saine (choix unique): *

Une seule réponse possible.

- ◯ Sensibilité
- ◯ Spécificité
- ◯ Valeur prédictive positive
- ◯ Valeur prédictive négative
- ◯ 1 - Valeur prédictive négative
- ◯ 1 - Valeur prédictive positive
- ◯ Ne sait pas

35. Pour évaluer la probabilité pré-test d'une maladie, vous utilisez: *

Plusieurs réponses possibles.

- [ ] Scores cliniques
- [ ] Prévalence de la maladie
- [ ] Estimation par intuition
- [ ] Position sur la liste des diagnostics différentiels
- [ ] Je n'y pense pas

6 En terme d diagnostic, un biomarqueur a plus d'apport quand la probabilité pré-test est:

Une seule réponse possible.

- ◯ Forte
- ◯ Moyenne
- ◯ Faible
- ◯ Ne sait pas

37. Vous voulez éliminer une maladie, vous avez besoin d'un biomarqueur qui a une haute *

Une seule réponse possible.

- ◯ Sensibilité
- ◯ Spécificité
- ◯ Ne sait pas

38. Vous voulez confirmer une maladie, vous avez besoin d'un biomarqueur qui a une haute: *

Une seule réponse possible.

- ◯ Sensibilité
- ◯ Spécificité
- ◯ Ne sait pas

9 vous av z vraiment besoi d'exclure une maladie quelle que soit la probabilité du pré-test, vous devez utiliser un test qui a une sensibilité supérieure ou égale à:

Une seule réponse possible.

- 97%
- 98%
- 99%
- 96%
- Ne sait pas

40. Si vous avez vraiment besoin de confirmer une maladie quelle que soit la probabilité du pré-test, vous devez utiliser un test qui a une spécificité supérieure ou égale à:

Une seule réponse possible.

- 97%
- 98%
- 99%
- 96%
- Ne sait pas

41. Avez vous déjà entendu parler de la courbe ROC? *

Une seule réponse possible.

- Oui
- Non

2oui, quell est a définit › e on utilité?

43. Avez vous déjà entendu parler du rapport de vraisemblance? *

Une seule réponse possible.

- ◯ Oui
- ◯ Non

44. Si oui, quelle est sa définition et son utilité?

45. Avez-vous déjà entendu parler nomogramme de Fagan? *

Une seule réponse possible.

- ◯ Oui
- ◯ Non

6oui, qu ll est a définit › e on utilité?

47. Parmi les marqueurs biologiques suivants, quels sont ceux que vous utilisez le plus souvent dans votre pratique: *

Une seule réponse possible par ligne.

	Toujours	Souvent	Parfois	Rarement	Jamais
Troponine	◯	◯	◯	◯	◯
D-dimères	◯	◯	◯	◯	◯
CRP	◯	◯	◯	◯	◯
Procalcitonine	◯	◯	◯	◯	◯
Protéine S100B	◯	◯	◯	◯	◯
BNP et NT-proBNP	◯	◯	◯	◯	◯

Les biomarqueurs aux urgences: Troponines

48. Concernant les biomarqueurs de l'infarctus du myocarde, quelles sont les réponses exactes (choix multiple): *

Plusieurs réponses possibles.

- ☐ La myoglobine est un marqueur cardio-spécifique
- ☐ La CK-MB augmente plus rapidement que la myoglobine
- ☐ L'ASAT reste actuellement un marqueur de choix pour le diagnostic de l'infarctus du myocarde
- ☐ La troponine Ic permet un diagnostic rétrospectif de l'infarctus du myocarde
- ☐ La troponine Ic est un marqueur cardio-spécifique
- ☐ Ne sait pas

9 Parmi les propo itions su van e concernant les biomarqueurs cardiaques, quelles sont les réponses exactes (choix multiple): *

Plusieurs réponses possibles.

- [ ] La myoglobine est un marqueur plus précoce que les troponines
- [ ] La myoglobine est un marqueur non spécifique de l'IDM
- [ ] Les troponines permettent de faire le suivi de reperfusion et d'évaluer le succès d'une thrombolyse/angioplastie
- [ ] Le dosage de la troponine est réalisé par une technique immuno-enzymatqiue
- [ ] Les troponines apparaissent 8 heures après un IDM
- [ ] Ne sait pas

50. Parmi les affirmations suivantes, quelle est celle qui est exacte (choix unique): *

Une seule réponse possible.

- ( ) Les troponines sont des marqueurs sensibles de l'infarctus du myocarde mais sont peu spécifiques
- ( ) Les troponines peuvent devenir élevées dans des pathologies autres que la thrombose coronaire
- ( ) Après un IDM, la disparition des troponines s'observe en 48h environ
- ( ) Ne sait pas

51. Parmi les propositions suivantes concernant les troponines, lesquelles sont exactes (choix multiple): *

Plusieurs réponses possibles.

- [ ] Il s'agit d'un ensemble de protéines contractiles composé de troponine C, I et T
- [ ] Dans un diagnostic de l'infarctus, ce sont les troponines C qui ont un intérêt
- [ ] Elles sont les marqueurs les plus précoces de l'IDM
- [ ] Elles persistent plus d'une semaine dans le sang après l'IDM
- [ ] Le résultat du dosage de troponine est considéré comme positif pour l'IDM au-delà du 99ème percentile
- [ ] Ne sait pas

2 Quel est l marqueur le plus précoce dans l'infarctus du myocarde (choix unique) *

Une seule réponse possible.

- ◯ La myoglobine
- ◯ Les CK-MB
- ◯ La troponine
- ◯ La LDH
- ◯ Les ASAT
- ◯ Ne sait pas

53. En cas de douleur thoraciques avec suspicion d'infarctus du myocarde on dose certaines protéines plasmatiques pour différentes raisons (choix multiple): *

Plusieurs réponses possibles.

- ☐ la myoglobine car c'est le marqueur le plus précoce de la nécrose
- ☐ la myoglobine car c'est un marqueur spécifique de la nécrose myocardique
- ☐ la troponine I car c'est le marqueur le plus spécifique de la nécrose myocardique
- ☐ la CPKMB - masse car c'est l'iso enzyme le plus spécifique des créatines kinases
- ☐ la troponine car c'est le marqueur le plus précocement élevé
- ☐ Ne sait pas

54. Quels sont les éléments inclus dans la définition de "dommage myocardique" ou "myocardial injury" introduit dans la 4ème définition universelle de l'IDM (choix multiple): *

Plusieurs réponses possibles.

- ☐ Elévation seule des troponines cardiaques
- ☐ Diminution seule des troponines cardiaques
- ☐ Au moins une valeur supérieure à la limite supérieure du 99ème percentile
- ☐ Un contexte clinique (signes cliniques, ECG, imagerie ...) évident d'ischémie myocardique aiguë
- ☐ Elévation et / ou diminution des troponines cardiaques
- ☐ Ne sait pas

5 Les troponines peuvent être élevés dans les (choix multiple) : *

Plusieurs réponses possibles.

- [ ] Tachyarythmies
- [ ] Myocardites
- [ ] Dissection aortique
- [ ] Etat de shock
- [ ] Hypo et hyperthyroidies
- [ ] Ne sait pas

56. Le marqueur le plus spécifique de l'infarctus du myocarde est (choix unique): *

Une seule réponse possible.

- ◯ La troponine I cardiaque
- ◯ La myoglobine
- ◯ La troponine C
- ◯ La CRP ultra sensible (CRP-us)
- ◯ Ne sait pas

57. Vous recevez un patient aux urgences qui se plaint de douleur thoracique > 3h, * L'ECG est non contributif et le résultat des TnTc Hs est de <14 ng/l ng/L. Vous décidez de (choix unique):

Une seule réponse possible.

- ◯ Redoser la troponine après 2h
- ◯ Ecarter le diagnostic d'IDM
- ◯ Ne sait pas

8 Vous rec vez un patient aux urgences qui se plaint de douleur thoracique > 3h, * L'ECG est non contributif et le résultat des TnTc Hs est de entre 14 et 50 ng/L. Vous décidez de redoser les troponines après 2 heures (choix multiple):

Plusieurs réponses possibles.

- [ ] Si les troponines n'augmentes pas, j'écarte le diagnostic d'IDM
- [ ] Si il y a une augmentation de plus de 30% je retiens le diagnostic d'IDM
- [ ] S'il y a une augmentation de 7 ng/L je retients le diagnostic d'IDM
- [ ] Si il y a une baisse de plus de 30% j'écarte le diagnostic d'IDM
- [ ] Ne sait pas

59. Les facteurs qui peuvent influencer le 99ème percentile de troponine ultrasensibles sont (choix multiple):

Plusieurs réponses possibles.

- [ ] Age
- [ ] Sexe
- [ ] Méthode de dosage
- [ ] Insuffisance rénale
- [ ] Ne sait pas

60. Même en dehors de l'IDM, l'élévation de la troponine, aussi faible soit-elle , * conserve une importance pronostique à long terme :

Une seule réponse possible.

- ◯ Vrai
- ◯ Faux
- ◯ Ne sait pas

61 Lors d'une nécrose myocardique, l'élévation de la cTn se fait entre ..... après le début de l'atteinte myocardique (choix unique) : *

Une seule réponse possible.

- ◯ H0 et H2
- ◯ H2 et H4
- ◯ H4 et H6
- ◯ H6 et H8
- ◯ Ne sait pas

62. Lors d'une nécrose myocardique, le taux sérique maximal de la cTn est atteint entre (choix unique) : *

Une seule réponse possible.

- ◯ H3 et H6
- ◯ H9 et H15
- ◯ H24 et H48
- ◯ H0 et H3
- ◯ Ne sait pas

63. Lors d'une nécrose myocardique, le retour à la normale de la cTn se fait entre (choix multiple): *

Plusieurs réponses possibles.

- ☐ J4 -J7 pour la cTnI
- ☐ J10 - J14 pour la cTnI
- ☐ J10 -J14 pour la cTnT
- ☐ J4 - J7 pour la cTnT
- ☐ Ne sait pas

64 es troponines cardiaques (choix multiple): *

Plusieurs réponses possibles.

- [ ] Peuvent être détectés dans le sérum 5 jours après l'infarctus
- [ ] Lorsqu'ils sont détectés dans le sérum, ils reflètent toujours des lésions myocardiques irréparables
- [ ] Seront significativement élevé dans le sérum dans l'heure suivant l'infarctus du myocarde
- [ ] Ont un rôle pronostique dans les maladies coronaires, non coronaires et même non cardiaques
- [ ] Ne sait pas

65. Les troponines cardiaques (choix multiple): *

Plusieurs réponses possibles.

- [ ] Il n'y a qu'un seul fabricant de dosages de TnI
- [ ] Leur libération peut survenir en l'absence de maladie coronarienne
- [ ] Les valeurs limites dépendent des laboratoires et des fabricants de test
- [ ] Ne sait pas

66. Les troponines cardiaques (choix multiple): *

Plusieurs réponses possibles.

- [ ] 5-8 % est non lié dans le cytoplasme du cardiomyocyte
- [ ] La fraction cytoplasmique est la première à être libérée en cas de lésion myocardique
- [ ] Est libérée après une lésion cardiaque uniquement sous forme de protéines individuelles I, T et C
- [ ] Les 3 isoformes I, T et C sont utiles pour diagnostiquer une lésion cardiaque
- [ ] Leur augmentation n'est pas toujours synonyme de thrombose coronaire
- [ ] Ne sait pas

Les D-dimères

67 Conc rnant les d-dimères (choix multiple): *

P usie rs réponses possibles.

- [ ] Des marqueurs de l'activation de la coagulation (localisée ou systémiques) et de la fibrinolyse
- [ ] Un dosage des D-dimères par méthode ELISA inférieur à 500 ug/L élimine formellement le diagnostic d'EP
- [ ] Ont une bonne VPN à 99% pour exclure l'EP
- [ ] Sont spécifiques des MTEV
- [ ] Un dosage de D-Dimères positif affirme le diagnostic d'embolie pulmonaire avec une forte valeur prédictive positive
- [ ] Ne sait pas

68. Les d-dimères peuvent être élevés dans les situations suivantes (choix multiple):

Plusieurs réponses possibles.

- [ ] MTEV
- [ ] Grossesse
- [ ] Dissection aortique
- [ ] CIVD
- [ ] Insuffisance rénale
- [ ] Sujet âgé
- [ ] Ne sait pas

69. Le dosage des d-dimères n'est pas recommandé dans les situations ou la probabilité pré-test de MTEV est: *

Une seule réponse possible.

- ( ) Forte
- ( ) Intermédiaire
- ( ) Faible
- ( ) Ne sait pas

0 a val ur seuil des d-dimère en ug/L chez un sujet âgé de plus de 50 ans est calculée à partir de son âge selon la formule suivante:

Une seule réponse possible.

- ◯ Age * 2
- ◯ Age * 20
- ◯ Age * 12
- ◯ Age * 10
- ◯ Age * 3
- ◯ Ne sait pas

71. Les signes qui peuvent prédire la mortalité précoce en cas d'embolie pulmonaire sont (choix multiple):

Plusieurs réponses possibles.

- ☐ Fraction d'éjection effondrée
- ☐ Troponines élevées
- ☐ BNP élevés
- ☐ Obstruction de plus de 70% du lit pulmonaire
- ☐ Ne sait pas

La BNP et NT-pro BNP

72. La BNP (Brain natruretic peptide) est: *

Plusieurs réponses possibles.

- ☐ Sécrétée par le myocarde atrial
- ☐ Sécrété par le myocarde ventriculaire
- ☐ Sécrété en réponse à une augmentation du volume et la pression atriale
- ☐ Sécrété en réponse à une augmentation de la tension/étirement du ventricule
- ☐ A une demi-vie de 20 min
- ☐ Ne sait pas

3 Conc rnant le BNP et NT- pro BNP (choix multiple): *

P usie rs réponses possibles.

- [ ] Le BNP et NT-proBNP sont secrétés de façon équimoléculaire
- [ ] Le NT-proBNP et le BNP sont utilisés pour exclure ou diagnostiquer l'insuffisance cardiaque chez les patients qui présentent une dyspnée
- [ ] Ils ont une bonne VPN pour exclure l'insuffisance cardiaque
- [ ] Le seuil d'inclusion dépend de l'âge
- [ ] Le dépistage avec le NT-pro BNP permet le dépistage de malades en fibrillation auriculaire à risque d'AVC
- [ ] Ne sait pas

74. La NT-proBNP (choix multiple) : *

Plusieurs réponses possibles.

- [ ] Est une forme inactive
- [ ] A une élimination essentiellement urinaire
- [ ] A une durée de vie plus longue que la BNP
- [ ] A une demi vie de 90 min
- [ ] Ne sait pas

75. Parmi les facteurs qui influencent le BNP (choix multiple): *

Plusieurs réponses possibles.

- [ ] Diminution avec l'âge
- [ ] Diminution chez le sexe féminin
- [ ] Diminution avec l'obésité
- [ ] Augmentation avec l'affection pulmonaire
- [ ] Augmentation avec l'insuffisance rénale
- [ ] Ne sait pas

6 e seuil d'exclusion d'insuffi ance cardiaque pour la NT-pro BNP est inférieur à (choix unique):

Une seule réponse possible.

- ◯ 400 pg/ml
- ◯ 300 pg/ml
- ◯ 200 pg/ml
- ◯ 100 pg/ml
- ◯ Ne sait pas

77. Le seuil d'exclusion d'insuffisance cardiaque pour la BNP est inférieur à (choix unique): *

Une seule réponse possible.

- ◯ 400 pg/ml
- ◯ 300 pg/ml
- ◯ 200 pg/ml
- ◯ 100 pg/ml
- ◯ Ne sait pas

78. Le seuil d'inclusion de l'insuffisance cardiaque pour la NT-pro BNP est : *

Plusieurs réponses possibles.

- ☐ 450 pg/ml avant 50 ans
- ☐ 900 pg/ml entre 50 et 75 ans
- ☐ 1800 pg/ml après 75 ans
- ☐ Le même pour tout âge
- ☐ Ne sait pas

9 L BNP (choix multiple) : *

P usie rs réponses possibles.

- [ ] A une durée de vie plus courte que la NT-pro BNP
- [ ] Est éliminée par les endopeptidases, rein, récepteur A,B et C
- [ ] Est une forme active
- [ ] Entraine la vasoconstriction
- [ ] Inhibe le SRAA
- [ ] Entraine la diurèse et natriurèse
- [ ] Ne sait pas

80. Les facteurs qui influencent le BNP et qui nécessitent forcément une adaptation des seuils sont (choix multiple):

Plusieurs réponses possibles.

- [ ] Age
- [ ] Sexe féminin
- [ ] Obésité
- [ ] Insuffisance rénale
- [ ] Affection pulmonaire
- [ ] Ne sait pas

81. En terme de gravité, il y a une corrélation entre le taux de BNT/NT-pro BNP et * (choix multiple):

Plusieurs réponses possibles.

- [ ] Fraction d'éjection du VG
- [ ] Classification NYHA
- [ ] sévérité de l'insuffisance cardiaque
- [ ] Il n'y a pas de corrélation
- [ ] Ne sait pas

2 En terme de pro ostic et de uivi thérapeutique le BNP/NT-pro BNP (choix multiple):

Plusieurs réponses possibles.

- [ ] Est prédictif de l'évolution vers l'insuffisance cardiaque chronique
- [ ] Si ils ne diminuent pas durant le traitement ou qu'ils augmentent, la mortalité devient élevée
- [ ] Il faut viser comme objectif thérapeutique un seuil inférieur à 1000 pg/ml
- [ ] Permet de diminuer la fréquence des événements aigus, les réhospitalisassions et la mortalité
- [ ] Permet d'anticiper la décompensation cardiaque
- [ ] Permet de connaitre le pronostic de morbidité et de mortalité des SCA
- [ ] Ne sait pas

La procalcitonine

83. La procalcitonine (choix multiple):

Plusieurs réponses possibles.

- [ ] Est synthétisée par les cellules de la para-thyroïde
- [ ] La procalcitonine permet de réduire la durée de l'antibiothérapie
- [ ] L'âge n'a pas d'influence sur son taux
- [ ] Elle aide quand à la décision de débuter, maintenir et arrêter l'antibiothérapie
- [ ] Est mieux que la CRP dans le pronostic du sepsis

84. Lors d'épisodes infectieux, quels agents infectieux parmi ceux-ci sont généralement associés à une PCT «basse» voire «négative » (choix multiple): *

Plusieurs réponses possibles.

- [ ] BGN
- [ ] Bactéries intracellulaires
- [ ] Parasites
- [ ] Virus
- [ ] Cocci gram +
- [ ] Ne sait pas

5 L procalcitonine peut ne pas augmenter dans quelques situations où l'infection est présente (Faux négatif) comme:

Plusieurs réponses possibles.

- [ ] Infection précoce > 3h
- [ ] Infection compartimentalisée (abcès)
- [ ] Infection décapitée (ATB)
- [ ] Infection localisée (appendicite aigue non compliquée)
- [ ] Ne sait pas

86. Le temps de demi vie de la PCT est de l'ordre de (choix unique): *

Une seule réponse possible.

- ◯ 6H
- ◯ 12H
- ◯ 24H
- ◯ 36H
- ◯ Ne sait pas

87. Après injection d'endotoxine, la PCT est détectable dans le sérum dès la (choix unique): *

Une seule réponse possible.

- ◯ 3ème heure
- ◯ 6ème heure
- ◯ 12ème heure
- ◯ 24ème heure
- ◯ Ne sait pas

8 Quelles situat o s non septiques peuvent conduire à une augmentation significative de la PCT (choix multiple):

Plusieurs réponses possibles.

- [ ] Coup de chaleur
- [ ] Carcinome bronchique et pulmonaire à petites cellules
- [ ] Cancer médullaire de la thyroide
- [ ] Polytraumatisé et chirurgie
- [ ] SAM
- [ ] Nouveau-né < 48H
- [ ] Choc cardiogénique sévère
- [ ] Ne sait pas

89. Dans les infections respiratoires basses, au-dessus de quel seuil cut-off est-it recommandé de redoser la PCT dans les 12H en moyenne (6-24H selon les situations), quand la probabilité pré test est élevée (choix unique): *

Une seule réponse possible.

- ◯ 0.1 ng/ml
- ◯ 0.2 ng/ml
- ◯ 0.25 ng/ml
- ◯ 0.5 ng/ml
- ◯ Ne sait pas

90. L'ensemble de la littérature s'accorde à dire que la PCT est un bon marqueur d'infection dans la population des plus de 75 ans: *

Une seule réponse possible.

- ◯ Vrai
- ◯ Faux
- ◯ Ne sait pas

1 D ns le cadre des infections respiratoires basses et du sepsis, l'arrêt ou la non prescription initiale des ATB est recommandée pour une PCT (choix unique):

Une seule réponse possible.

- 0.1 ng/ml
- 0.25 ng/ml
- 0.5 ng/ml
- Ne sait pas

92. De manière générale, à partir de quel seuil la PCT est associée à un risque élevé de sepsis sévère et/ou choc septique (choix unique):

Une seule réponse possible.

- 0.5 ng/ml
- 1 ng/ml
- 2 ng/ml
- 4 ng/ml
- Ne sait pas

93. La PCT a une utilité de stratification pronostique documentée à partir de quel des seuils suivants (choix unique):

Une seule réponse possible.

- > 1 ng/ml
- > 2 ng/ml
- >5 ng/ml
- > 6 ng/ml
- Ne sait pas

4 Le seuil décis o nel de la PCT pour la distinction entre inflammation et infection pour la méningite est (choix unique):

Une seule réponse possible.

- ◯ 2 - 2.5 ng/ml
- ◯ 1.5 - 2 ng/ml
- ◯ 1 - 1.5 ng/ml
- ◯ 0.5 - 1 ng/ml
- ◯ Ne sait pas

La CRP

95. La CRP (choix multiple) *

Plusieurs réponses possibles.

- ☐ Est un marqueur spécifique de l'infection bactérienne
- ☐ Est un marqueur d'inflammation toute causes confondues
- ☐ Doit son nom à sa propriété de précipitation au contact du polysaccharide C du pneumocoque
- ☐ Est une protéine synthétisée par les hépatocytes
- ☐ Est une protéine synthétisée par l'hypothalamus
- ☐ Ne sait pas

96. La durée de demi-vie de la CRP est de (choix unique): *

Une seule réponse possible.

- ◯ 3H
- ◯ 6H
- ◯ 12H
- ◯ 24H
- ◯ Ne sait pas

7 Concérnant la cinétique de la CRP, elle s'élève après le début du processus inflammatoire dès (choix unique):

Une seule réponse possible.

- ◯ 0H et 2H
- ◯ 2H et 4H
- ◯ 4H et 6H
- ◯ 6H et 8H
- ◯ Ne sait pas

98. La CRP atteint sa valeur maximale dans (choix unique) *

Une seule réponse possible.

- ◯ 6H
- ◯ 12H
- ◯ 24H
- ◯ 48H
- ◯ ne sait pas

99. La concentration de la CRP est influencée par (choix multiple) *

Plusieurs réponses possibles.

- ☐ L'âge
- ☐ Tabagisme chronique
- ☐ La prise de corticoïdes
- ☐ Insuffisance hépatique
- ☐ Grossesse
- ☐ Ne sait pas

100. La CRP (cho x multiple): *

Plusieurs réponses possibles.

- [ ] La CRP est mieux que la PCT pour diagnostiquer la sévérité du sepsis
- [ ] La PCT est mieux que la CRP pour diagnostiquer la sévérité du sepsis
- [ ] Sa valeur est corrélée avec la sévérité du score SOFA
- [ ] Sa valeur n'est pas corrélée à la sévérité du score SOFA
- [ ] Ne sait pas

La protéine S100 beta

101. Concernant la localisation de la protéine S100b (choix unique): *

Une seule réponse possible.

- ◯ Elle est principalement produite dans la peau
- ◯ Elle est principalement présente dans le poumon
- ◯ Elle est principalement produite dans le tissu cérébral
- ◯ Elle est principalement produite dans le foie
- ◯ Ne sait pas

102. Le dosage de la protéine S100b est indiqué dans le TC (choix unique): *

Une seule réponse possible.

- ◯ Lorsqu'un patient présente des facteurs de risques de lésions intracrâniennes
- ◯ Après la réalisation de TDM
- ◯ Quand le traumatisme crânien léger date de moins de 3h
- ◯ Est indiqué si le score de Glasgow est <13
- ◯ Ne sait pas

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103. La protéine S100b peut être utile pour (choix multiple): *

Plusieurs réponses possibles.

- [ ] L'évaluation précoce du risque de complication neurologique après un traumatisme crânien
- [ ] L'estimation du pronostic neurologique après un arrêt cardiaque
- [ ] L'estimation du pronostic neurologique après un accident vasculaire cérébral
- [ ] La diminution de nombre de scanner cérébraux prescrit après traumatisme crânien mineur
- [ ] Ne sait pas

104. La protéine S100b peut augmenter dans les citations suivantes (choix multiple):

Plusieurs réponses possibles.

- [ ] Tumeurs cérébrales (gliome, glioblastome, neurinome)
- [ ] Mélanome malin
- [ ] Traumatisme crânien avec rupture de la barrière hémato-encéphalique
- [ ] Accident vasculaire cérébral
- [ ] Ne sait pas

105. La protéine S100b (choix multiple): *

Plusieurs réponses possibles.

- [ ] A une excellente valeur prédictive négative pour éliminer une lésion hémorragique intracrânienne
- [ ] A une excellente valeur prédictive positive pour confirmer une lésion hémorragique intracrânienne
- [ ] Peut prédire un scanner normal (sans lésions cérébrale) si elle est négative
- [ ] A des concentrations élevées chez les patients avec lésions cérébrales documentées par scanner
- [ ] Est un marqueur d'agressivité et de réponse au traitement au cours du mélanome malin
- [ ] Ne sait pas

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بسم الله الرحمن الرحيم

قسم الطبيب

أقْسِمُ باللَّهِ الْعَظِيمِ
أنْ أُرَاقِبَ اللَّهَ فِي مِهْنَتِي
وَأنْ أَصُونَ حَيَاةَ الإِنْسَانِ فِي كَافَّةِ أَطْوَارِهَا؛ فِي كُلِّ الظُّرُوفِ وَالأَحْوَالِ، بَاذِلاً وُسْعِي فِي اسْتِنْقَاذِهَا مِنَ الْهَلاَكِ وَالْمَرَضِ وَالأَلَمِ وَالْقَلَقِ.
وَأنْ أُحْفَظَ لِلنَّاسِ كَرَامَتَهُمْ، وَأَسْتُرَ عَوْرَتَهُمْ، وَأَكْتُمَ سِرَّهُمْ.
وَأنْ أَكُونَ عَلَى الْدَّوَامِ مِنْ وَسَائِلِ رَحْمَةِ اللَّهِ، بَاذِلاً رِعَايَتِي الصِّحِّيَّةَ لِلْقَرِيبِ وَالْبَعِيدِ، لِلصَّالِحِ وَالطَّالِحِ، وَالصَّدِيقِ وَالْعَدُوِّ
وَأنْ أُثَابِرَ عَلَى طَلَبِ الْعِلْمِ أُسَخِّرُهُ لِنَفْعِ الإِنْسَانِ لاَ لأَذَاهُ
وَأنْ أُوَقِّرَ مَنْ عَلَّمَنِي، وَأُعَلِّمَ مَنْ يَصْغُرُنِي، وَأَكُونَ أَخًا لِكُلِّ زَمِيلٍ فِي الْمِهْنَةِ الصِّحِّيَّةِ، مُتَعَاوِنِينَ عَلَى الْبِرِّ وَالتَّقْوَى
وَأنْ تَكُونَ حَيَاتِي مِصْدَاقَ إِيمَانِي فِي سِرِّي وَعَلاَنِيَتِي، نَقِيَّةً مِمَّا يُشِينُهَا تُجَاهَ اللَّهِ وَرَسُولِهِ وَالْمُؤْمِنِينَ
وَاللَّهُ عَلَى مَا أَقُولُ شَهِيدٌ

كليـــــــة الطب
و الصيدلة - مراكش
FACULTÉ DE MÉDECINE
ET DE PHARMACIE - MARRAKECH

MARRAKECH
جامعة القاضي عياض
UNIVERSITÉ CADI AYYAD

سنة 2023 أطروحة رقم 295

المؤشرات الحيوية في قسم الطوارئ: حالة المعارف وآفاق المستقبل

الأطروحة

قدمت ونوقشت علانية يوم **2023/10/13**

من طرف

السيد يكيردا سنأ

المزداد في 16 مارس 1995 بمراكش

لنيل شهادة الدكتوراه في الطب

الكلمات الأساسية:

العلامات الحيوية، قسم الطوارئ، اختبارات الرعاية على نقطة الرعاية، معرفة الطبيب، الإحصاءات الطبية، تروبونين، دي- ديمر، ببتيد الناتريوريتيك النوع ب، ببتيد الناتريوريتيك النوع ب برو النهائي، البروتين الالتهابي سي-رياكتيف، البروكالسيتونين، بروتين اس100ب

اللجنة

السيد	ه. نجمي أستاذ في طب العناية المكثفة وعلم التخدير	الرئيس
السيد	ت.أبو الحسن أستاذ في طب العناية المكثفة وعلم التخدير	المشرف
السيد	ع.هشيمي أستاذ في طب العناية المكثفة وعلم التخدير	الحكام
السيد	أ.غ.الأديب أستاذ في طب العناية المكثفة وعلم التخدير	