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What Open-Lung biopsy teaches us about ARDS in severe COVID-19 patients: Mechanisms, pathology and therapeutic implications.

THESIS

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BY

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Born on 30 August 1996 in Marrakech

TO OBTAIN THE DEGREE OF DOCTOR OF MEDICINE

KEYWORDS

COVID-19 ARDS – Open-Lung Biopsy – Microthromi – Diffuse Alveolar Damage.

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I SOLEMNLY PLEDGE to dedicate my life to the service of humanity;
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DEDICATIONS

"Nothing in life is to be feared, it is only to be understood.
Now is the time to understand more, so that we may fear less."

— Marie Curie —

I dedicate this thesis to...

To the memory of my grand-parents:
Malika Hadhoumi, Halima Koundi, Mohammed Abourida.

I wish I could go back in time and spend more time with you. I hope I could honour you today by dedicating this work to you. You were my role models and my source of benediction and blessing.

May your souls rest in peace.

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To Professor Hichame Fenane,

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Judge of my thesis

Associate Professor of Anaesthesiology & Intensive Care

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ABBREVIATIONS

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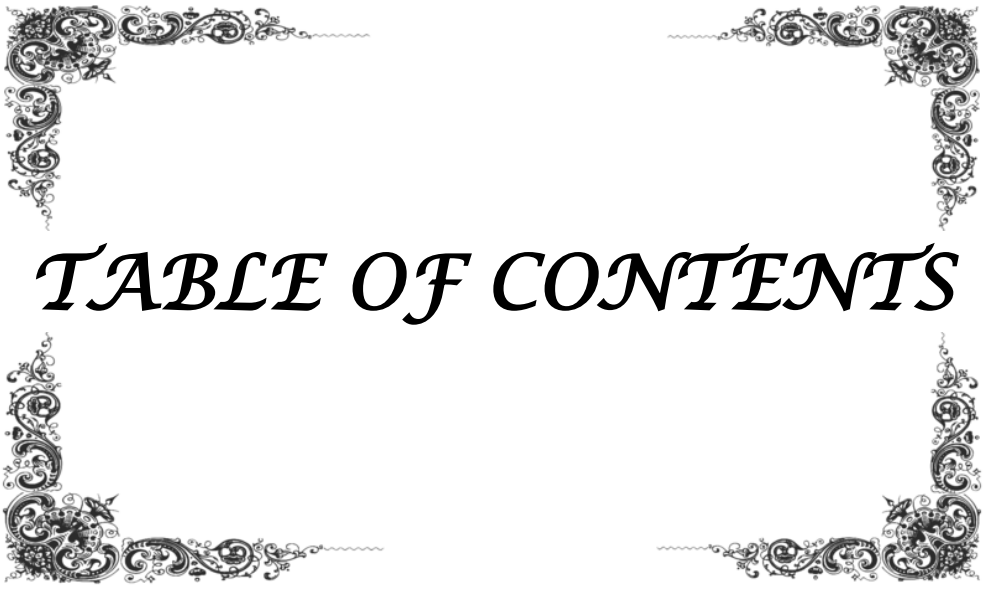
SARS-CoV-2: Severe Respiratory Coronavirus 2
COVID-19 : Coronavirus Disease 2019
ICU : Intensive Care
ARDS : Acute Respiratory Distress Syndrome
DAD : Diffuse alveolar damage
CT : Computed tomography
PPE : Personal Protective Equipment
RR : Respiratory Rate
HR : Heart Rate
SpO2 : Pulsed Oxygenation Saturation
Bp : Blood Pressure
CPAP : Continuous Positive Airway Pressure
IV : Invasive Ventilation
µg : Microgram
ML : Millilitre
pg : Picogramm
Mg : Milligram
IL : Interleukin
RT-PCR : Reverse Transcription Polymerase Chain Reaction
PEEP : Positive End-Expiratory pressure
ALI : Acute Lung Injury
PaO2 : Partial pressure of oxygen
FiO2 : Fraction of inspired oxygen
MmHg : Millimetre of mercury
AECC : American-European Consensus Conference
MERS : Middle East Respiratory Syndrome
ACE 2 : Angiotensin-converting enzyme 2
AT1-R : Angiotensin II type 1 receptor
TNF : Tumour Necrosis Factor
VWF : Von Willebrand factor
CRP : C-reactive protein
LMWH : Low-molecular-weight heparin
RNA : Ribonucleic Acid



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INTRODUCTION

In the early months of 2020, the world witnessed an outbreak of the Severe Respiratory Syndrome Coronavirus (SARS-CoV-2), which caused a tremendous flood of coronavirus-related pneumonia. In most cases, coronavirus disease 2019 (COVID-19) was rapidly resolved, whereas 26% require intensive care unit admission (ICU) (2). Clinical manifestations of COVID-19 vary from mild pneumonia to progressive Acute Respiratory Distress Syndrome (ARDS). Its singular features are severe hypoxemia often associated with near-normal respiratory system compliance at the beginning (3). On these distinctive grounds, a crucial question rose: How does COVID-19 damage the lungs to cause a rapidly progressive onset of profound hypoxemia?

In 1967, Ashbaugh et al. assumed that Diffuse Alveolar Damage (DAD) on lung histology was the pathological hallmark of ARDS (4). However, recent shreds of evidence point out that DAD is only a phenotype of ARDS among others, but with higher mortality (5). COVID-19 is a systemic disease that affects multiple organs, including the lungs, pharynx, heart, liver, brain, and kidneys (6). Very little is known about the "weaponry" of COVID-19; however, its main target seems to be the vascular endothelium. Initial reports documented clinically significant coagulopathy in critically ill patients (7) (8). According to the Berlin definition (9), diagnosing ARDS does not take into account pathologic findings which leaves a considerable gap in categorizing COVID-19 related ARDS (C-ARDS) and its peripheral vascular changes. On the other hand, previous work studied the co-infection rate between SARS-CoV-2 and other respiratory pathogens and focused only on nasopharyngeal swabs (10) but failed to address it in the lower respiratory tract.

Understanding the precise pathophysiology of C-ARDS will assist researchers and physicians in tailoring a timely-appropriated therapeutic approach. Here, we conducted a descriptive study performing an open-lung biopsy (OLB) in invasively ventilated patients with C-ARDS; taking into account the benefit-to-risk ratio. This study is aimed at determining C-ARDS pathological characteristics and co-infection with other pathogens in lung tissue.

MATERIALS AND METHODS

I. Patients and diagnosis

We selected patients with laboratory-confirmed SARS-CoV-2 infection -admitted to the COVID-19 ICU of the Moammed VI University Hospital of Marrakech, from the 25th of April to 25th June 2020- who later developed ARDS that met the Berlin definition (9) and were put under mechanical ventilation. Initial chest Computed Tomography (CT) scans revealed bilateral diffused ground-glass opacities in different percentages. Informed written consent from the next of kin was obtained. The ethics committee of the University Hospital approved this research respecting the regulations of the Helsinki declaration.

II. Surgical Technique

An open lung mini-thoracotomy with rib spreading was performed using the wedge resection technique from the anterolateral segment with a stapler *(Fig 1).* The anterior end of the incision was placed 3 to 4 cm lateral to the middle line of the breastbone. Pleural space was entered above the fifth rib. A chest tube was placed through another incision and the muscle layers were loosely closed with a running absorbable number 0 suture. A lung tissue fragment was immediately soaked in 4% formalin solution and the other fragments along with pleural effusion fluid were put in a culture environment. The surgical team wore level 3 personal protective equipment (PPE) during the invasive procedure *(Fig 2)*

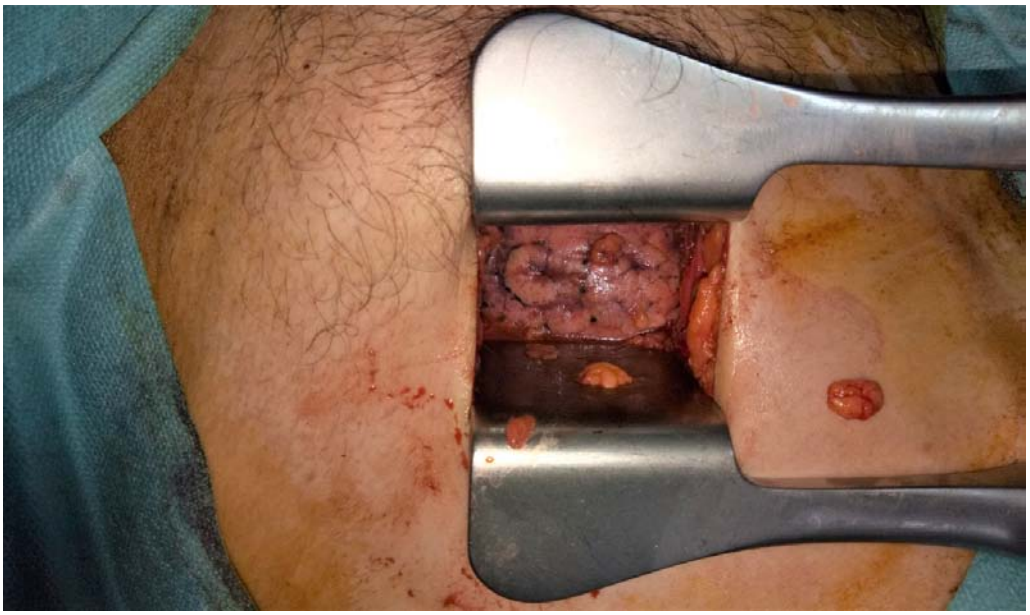

Figure 1: Rib spreading during mini-thoracotomy.

Figure 2: Surgical team performing open-lung biopsy while wearing appropriate PPE.

III. Specimen's analysis

Rigorous steps were respected to assure biosecurity of pathological tissue samples and to minimize staff contamination, as portrayed (*Fig. 3*). Biopsy lung tissue was analyzed with hematoxylin-eosin, Periodic Acid Schiff for detecting bacterial and fungal infection, and also Masson Trichrome staining to identify pulmonary interstitial fibrosis. The slides have been digitized using Leica SCN400 Slide Scanner, and then images of tissue sections were captured. Pleural effusion fluid and biopsy lung tissue were tested for SARS-CoV-2 by RT-PCR and a panel of non-SARS-CoV-2 respiratory viral pathogens (Adenovirus, Coronavirus Metapneumovirus, Enterovirus, Rhinovirus, MERS-CoV, Parainfluenza virus, Syncytial respiratory virus, Flu virus A & B), along with standard bacterial and fungal respiratory cultures as shown (*Fig 4*).

Figure 4: Specimen collection materials (A: Pathology vial, B: Virology PCR vial, C: Sars-CoV-2 PCR vial, D: Bacteriology vial).

Figure 3: Biosecurity of pathological tissue samples (A: Photographing the pathological examination request form; B: Placing the vials containing the samples in a container; C: Spraying the bottle with a disinfectant solution; D: Packaging in a level II biological safety cabinet without removing the sample from the vial; E: Leaving to set for at least 24 hours in 4% formalin solution; F: Using a microbiological safety station and PPE.)

RESULTS

I.

Clinical features

An open lung biopsy in 3 patients with C-ARDS was carried out. All of them were male and tested positive for SARS-CoV-2 by nasopharyngeal swab at the time of hospital admission. The median age was 65 years (range, 57-72 years). The median duration from symptoms to admission is 10 days (range, 7-13days), and the median duration from admission to death was 9.6 days (range, 5-15 days). Initial symptoms in 3 patients were mainly fever, dry cough, and shortness of breath, whereas Case 3 reported anosmia.

Hypertension was found in all patients as pre-existing comorbidity, Case 1 had hyperthyroidism and benign hypertrophy of the prostate, and Case 3 reported being a chronic smoker for 20 years with dyslipidemia. *(Table I).*

All patients were managed with the same national Moroccan protocol, which is hydroxychloroquine combined with azithromycin, Zinc, Vitamin C, and a therapeutic dose of Low Molecular Weight Heparin (LMWH), in addition to acetylsalicylic acid. Two patients had A^+ blood type and Case 1 had O+. The median duration of non-invasive ventilation management was 6.3 days (range, 3-10 days) and the median duration of mechanical ventilation was 3.3 days (range, 2-5 days). Open lung biopsy was performed on the first day of endotracheal intubation in all patients.

Table I. Clinical, radiological and microbiological characteristics of patients, and treatment received during ICU stay.

	Case 1	Case 2	Case 3
Age,years	72	68	59
Gender	Male	Male	Male
Known comorbidities	Hypertension Hyperthyroidism Benign hypertrophy of the prostate	Hypertension	Hypertension Chronic Smoker Dyslipidemia
Symptoms	Fever 38,7 °C Dry cough Shortness of breath Thoracic pain	Fever 38,9 °C Dry cough Shortness of breath Fatigue	Fever 38,5°C Dry cough Anosmia
Symptom duration before admission, (days)	13	7	10
Admission to death, (days)	15	5	9
Physical examination in admission	RR=33cpm SpO_2=73% HR = 95 bpm BP: 110/60 mmHg Blood sugar: 1.44g/L	RR=36cpm SpO_2=84% HR=95cpm BP=120/60 mmHg Blood sugar: 1.7g/L	RR=34cpm SpO_2=83% HR=88cpm BP=130/80 mmHg Blood sugar: 3.5 g/L
THORACIC CT SCAN	Ground glass Crazy paving >70%	Ground glass >75%	Ground glass >80%
Blood culture	Multiresistant Acinetobacter Baumani Gram-Positive Bacteria sensitive to Colistin (Catheter-related infection)	Sterile	Sterile
Duration of ventilator management,(days)	CPAP = 10 IV= 5	CPAP = 3 IV=2	CPAP = 6 IV = 3
Treatment	Hydroxychloroquine *200mg x 3/24h* Antibiotics (Azithromycin *250mg/24h* + Ceftriaxone *2g/24h* + Moxifloxacine *400mg/12h*) Therapeutic dose of LMWH (enoxaparin *1 mg/kg x 2 /24h*) Acetylsalicylic acid *160mg/24h* Methylprednisolone *120mgx2/24h* Zinc *220mg /24h* Vitamin C *1,5g /24h* Acetaminophen *500mg /6h*		
	Carbimazole *10mg/24h* Nebulised Colistin *2Million Unit x3/24h* Tocilizumab *8 mg/kg ONCE*		

Table I. Clinical, radiological and microbiological characteristics of patients, and treatment received during ICU stay." suite"

	Case 1	Case 2	Case 3
Blood type	O+	A+	A+
Microbiology (lung tissue and pleural fluid)	NEGATIVE	NEGATIVE	NEGATIVE
SARS-CoV-2 on Pleural fluid	Negative	Positive	Positive
SARS-CoV-2 on lung biopsy	Negative	Positive	Positive

RR: Respiratory rate, HR: Heart Rate SpO_2: Pulsed Oxygenation Saturation, BP: Blood Pressure, CPAP: Continuous Positive Airway Pressure, IV: Invasive Ventilation

II. Biological results

D-dimer serum levels at the admission of case 1,2, and 3 were 7.41 µg/mL, 2.27 µg/mL and 0.31 µg/mL respectively, whereas at their last day were elevated to 21.27 µg/mL , 22.95 µg/mL and 5 µg/mL *(Fig. 5)* . It's difficult to claim that none of the patients had thromboembolic events as no autopsy was performed.

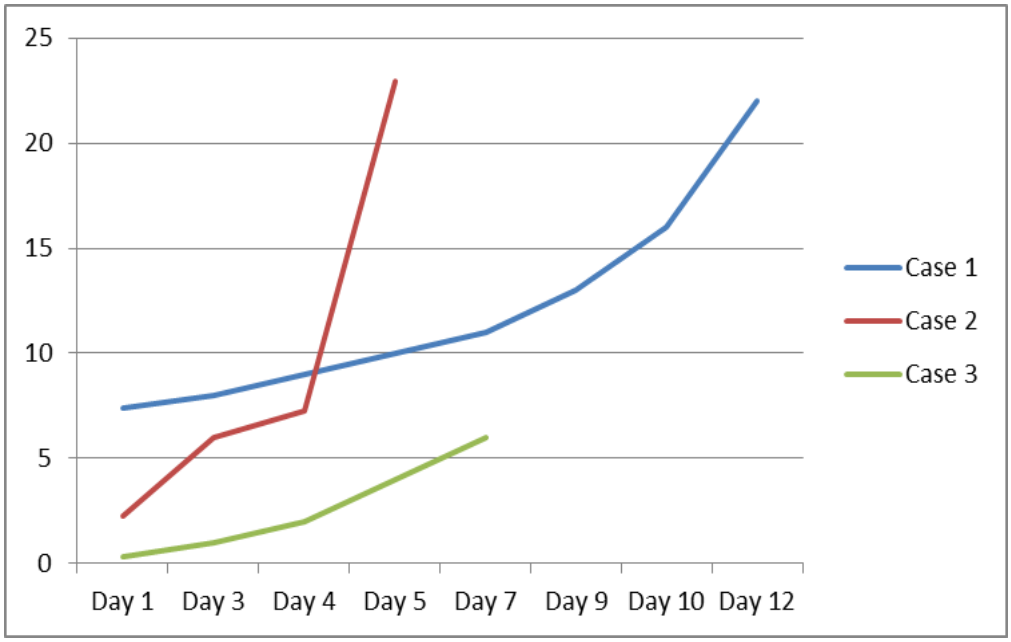

Figure 5: D-dimer level in patient's serum during ICU stay (µg/mL).

IL-6 serum levels at the admission of case 1,2, and 3 were 201 pg/mL, 107 µg/mL and 31 pg/mL respectively, whereas prior to their last day were elevated to 675 pg/mL , 325 pg/mL and 280 pg/mL *(Fig. 6).*

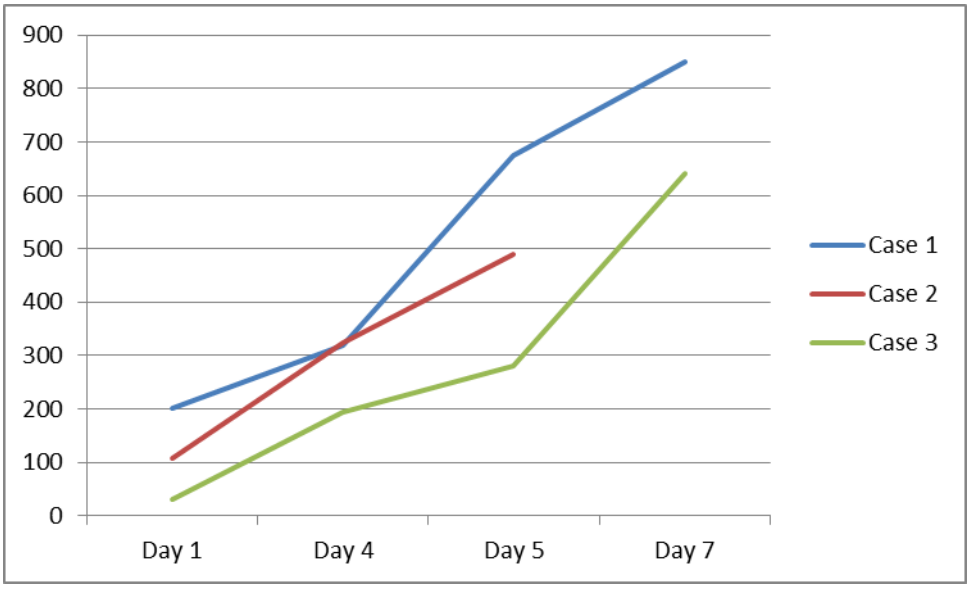

Figure 6: IL-6 level in patient's serum during ICU stay (pg/mL).

III. Microbiological results

Bacterial and viral (other than SARS-CoV-2) culture returned negative. Qualitative RT-PCR detected SARS-CoV-2 in the pulmonary parenchyma and pleural fluid of Case 2 and 3.

IV.

Histological results

Histological examination showed diffuse alveolar damage with collapsed alveoli (Fig. 8) and intensified thickening of the intercellular septa in Case 1 and 2, whereas Case 3 exhibited enlarged airspaces (Fig. 7), consistent with emphysema. The lumen was filled with proteinaceous and fibrin exudates (Fig. 12). Type II pneumocytes were found hyperplasic with an atypical appearance, multinucleated with enlarged and prominent nuclei (Fig. 10). There were significant focal points of pneumocyte desquamation, multinucleated giant cells, and hyaline membrane formation on the alveolar wall (Fig. 11). The interstitial tissue displayed oedema (Fig. 9) and widespread inflammatory infiltrates (Fig. 15) marked with lymphocytes mainly but also plasma cells, macrophages, and eosinophilic polynuclear cells. Prominent microthrombi (Fig. 16) and vascular congestion (Fig. 17) were the major pathological finding in all cases. Also, fibrin deposits (Fig. 14) were found in the vessel intima with a thickened vessel wall. Anthracosis deposit was also seen in Cases 1 and 2. No malignant tumour proliferation and no alveolar fibrosis (Fig. 18) were found in the 3 cases.

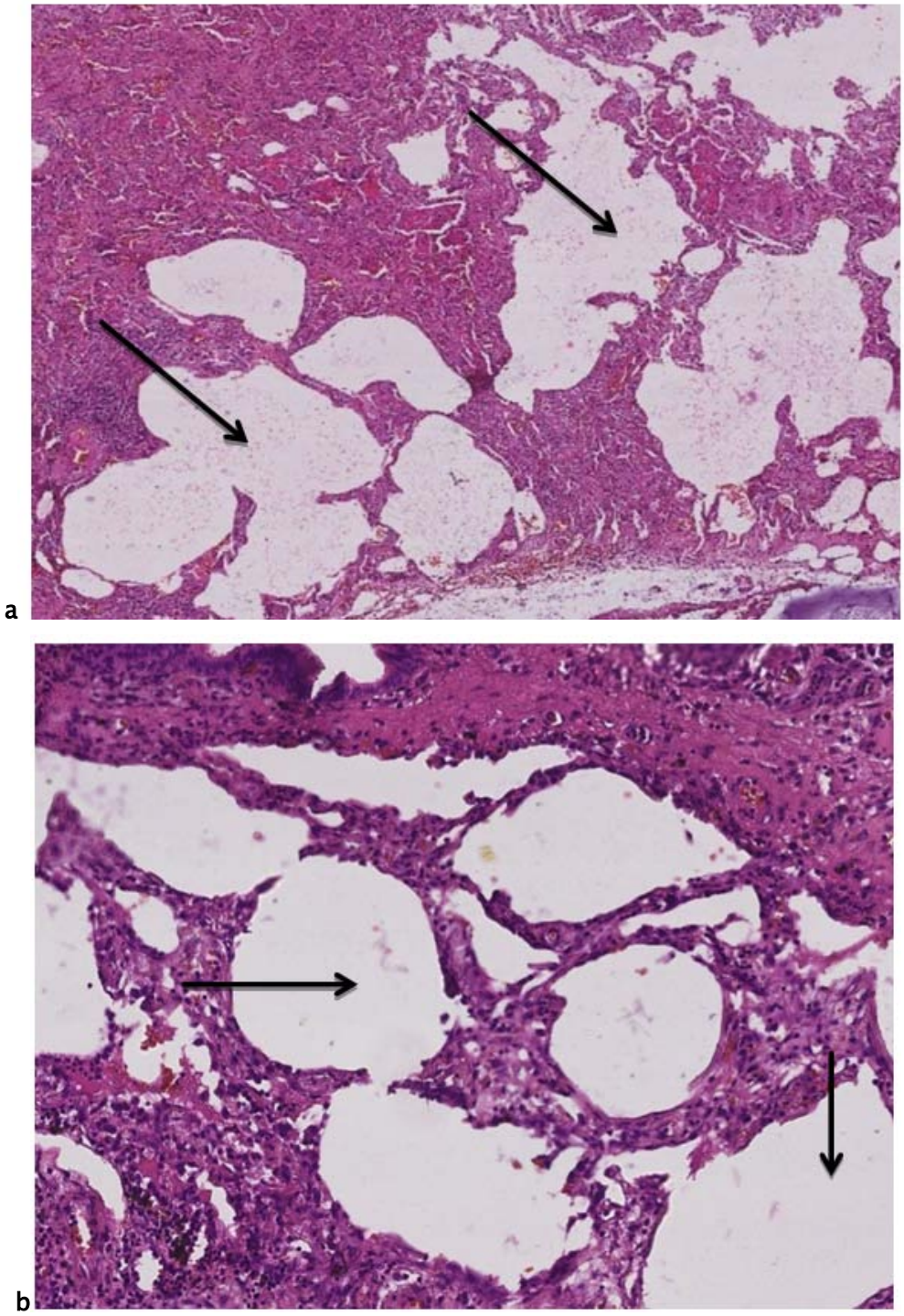

Figure 7: Alveolar dilatation (×20 magnification)

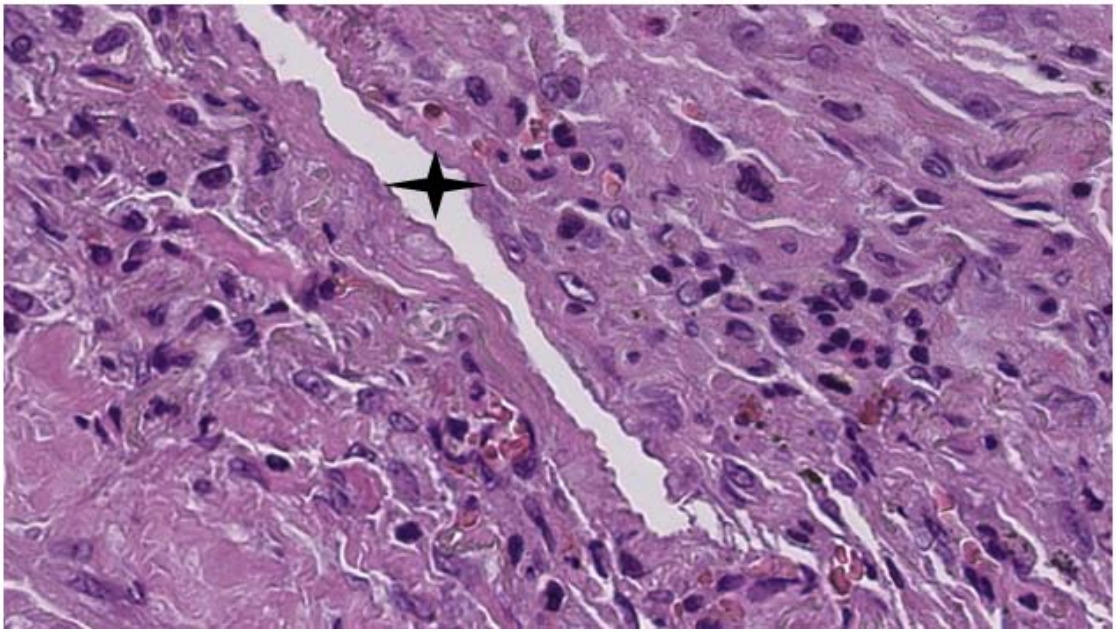

Figure 8: Collapsed alveoli. (×40 magnification).

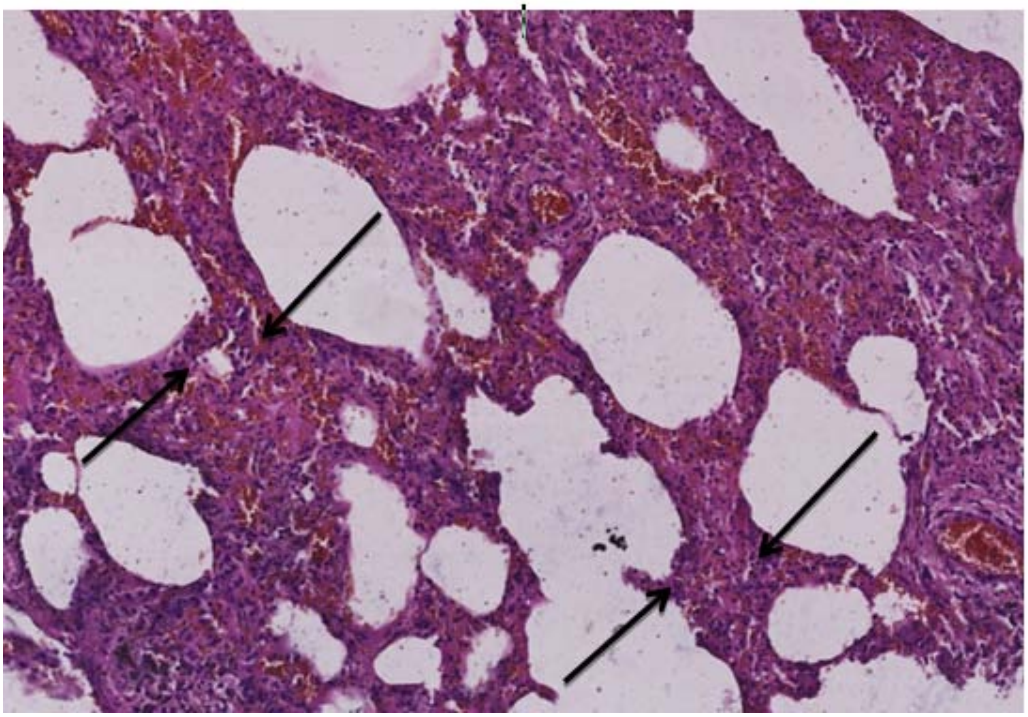

Figure 9: Inter-alveolar septum thickening (x20 magnification).

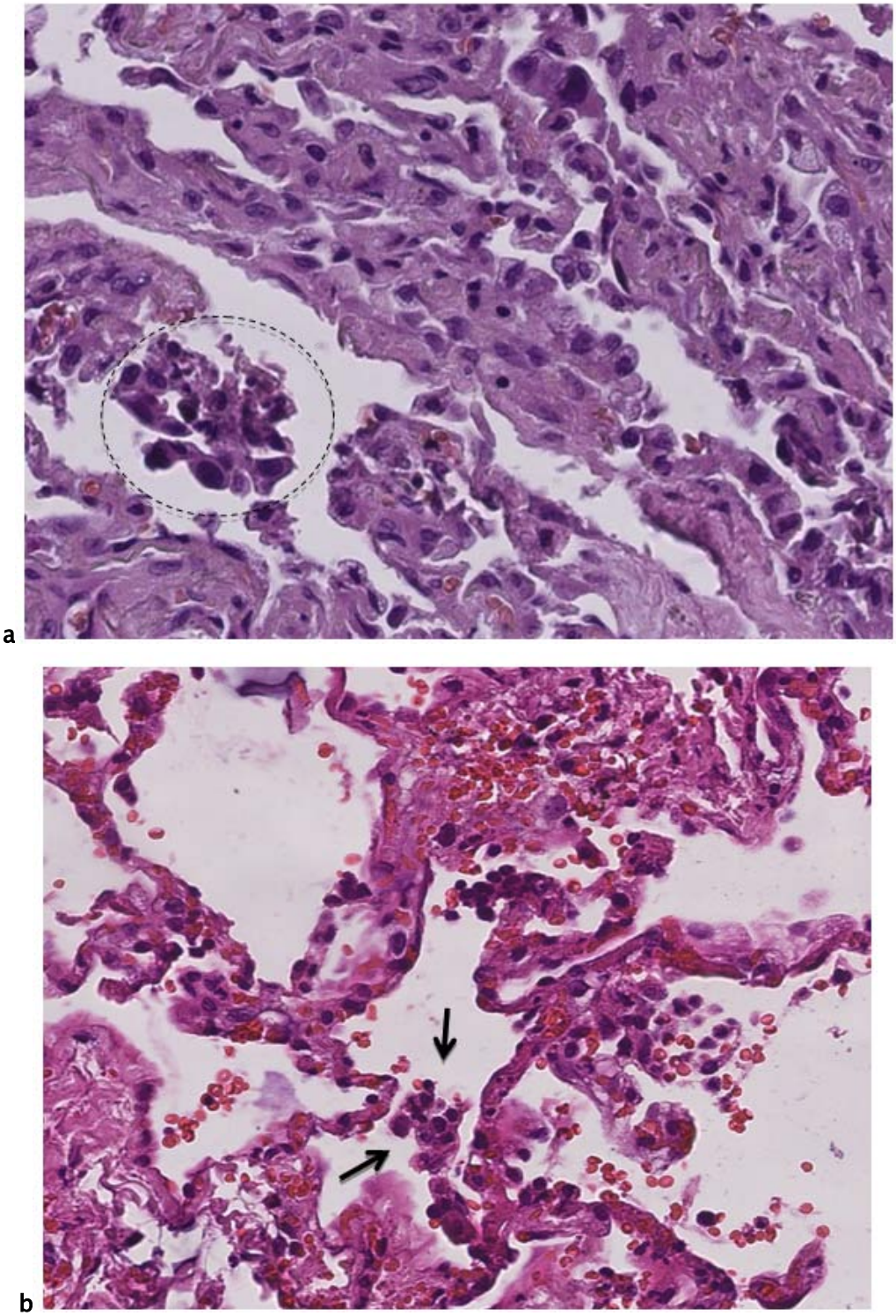

Figure 10: Epithelial desquamation and Type II pneumocyte hyperplasia (a,b x30 magnifications).

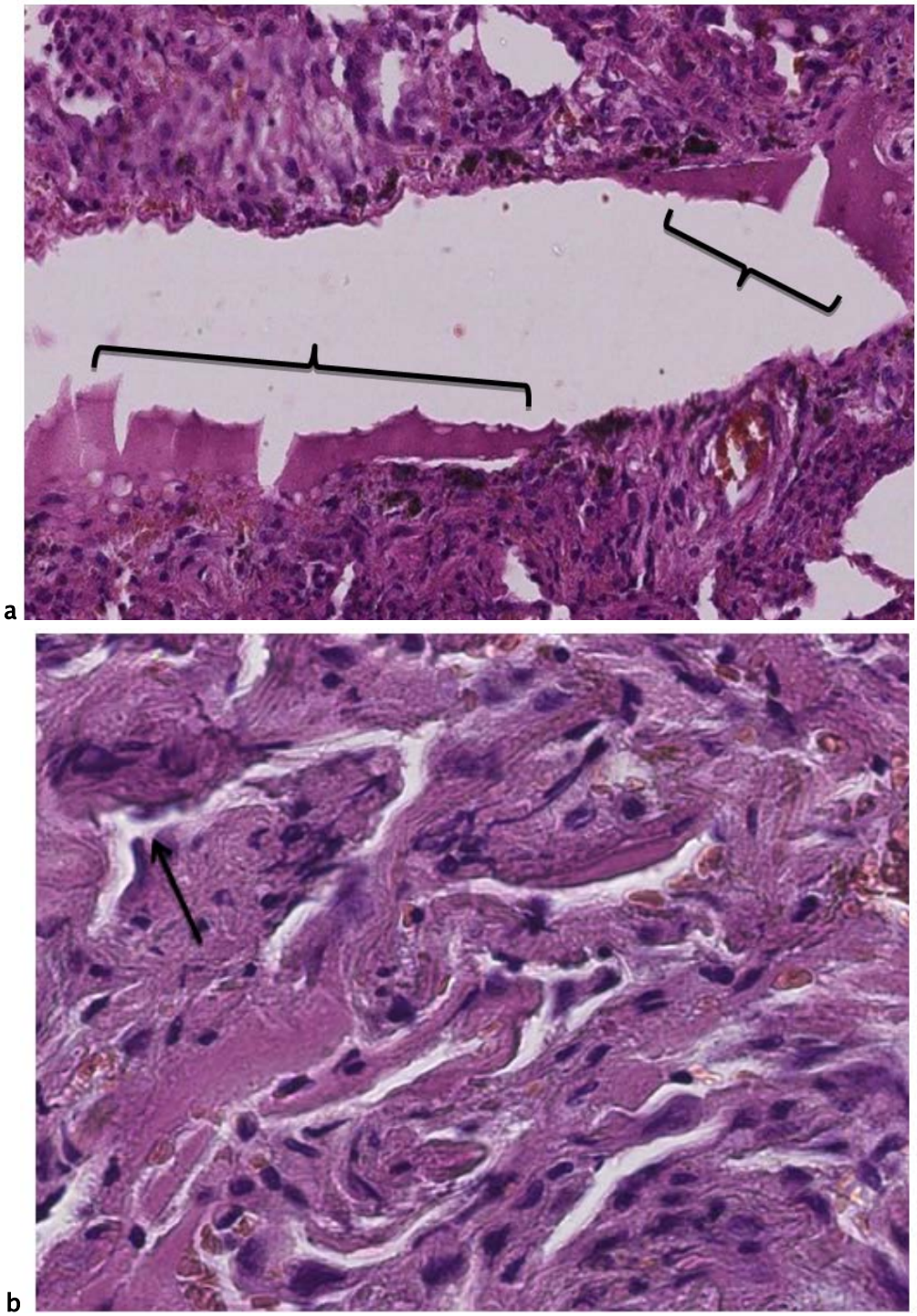

Figure 11: Hyaline membranes made of dead pneumocytes, surfactant and protein exudates. (a: x30magnification, b : x40 magnification)

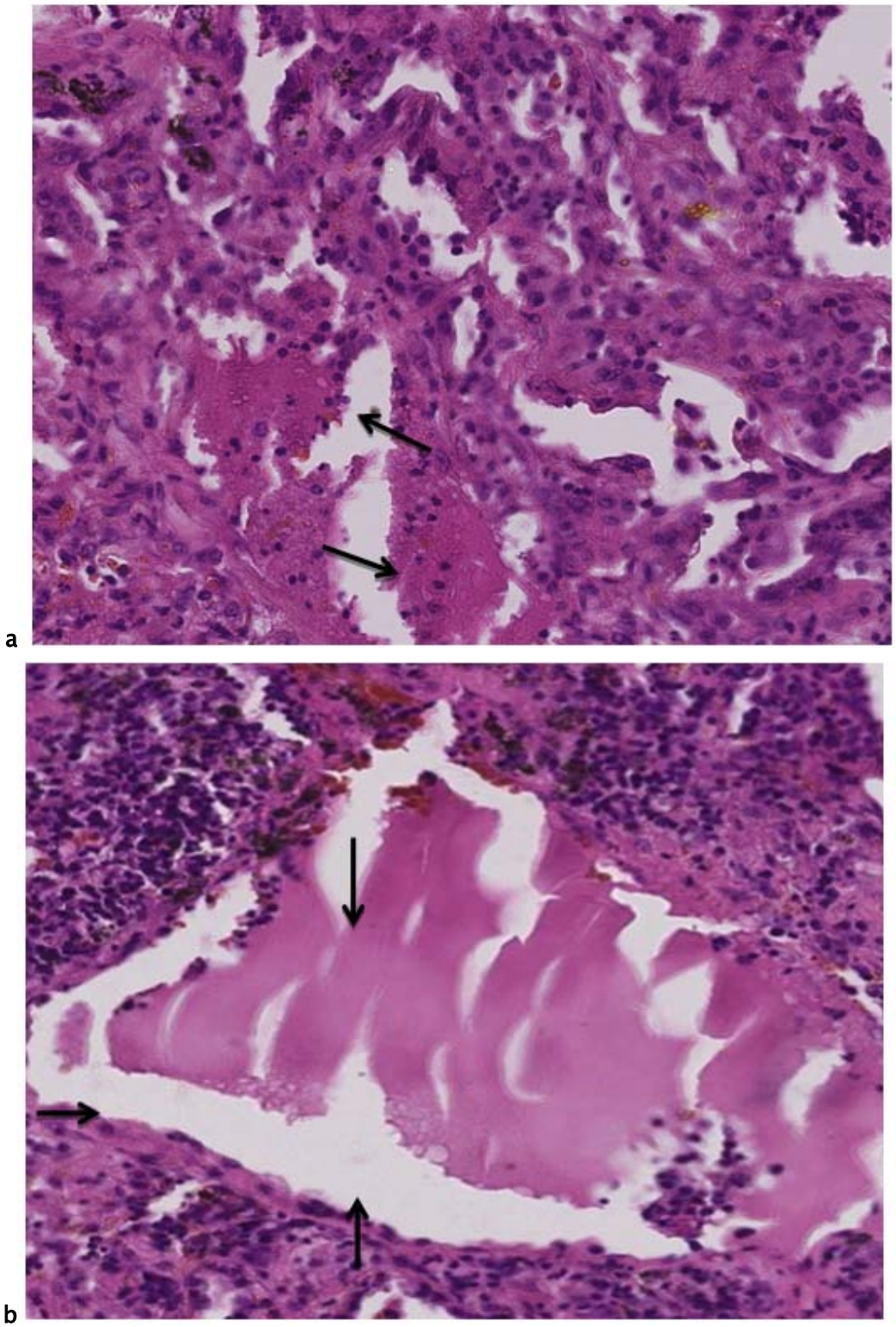

Figure 12: Exudate filling the alveolar cavity (a: x10magnification; b: x40magnification)

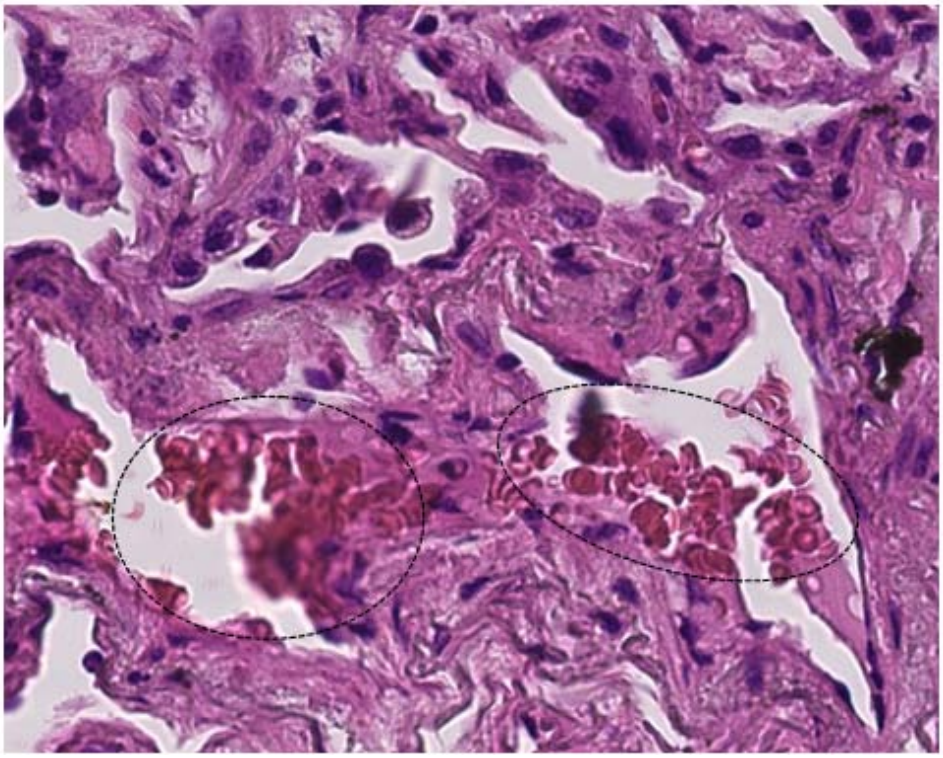

Figure 13: Alveolar haemorrhage (x20 magnification)

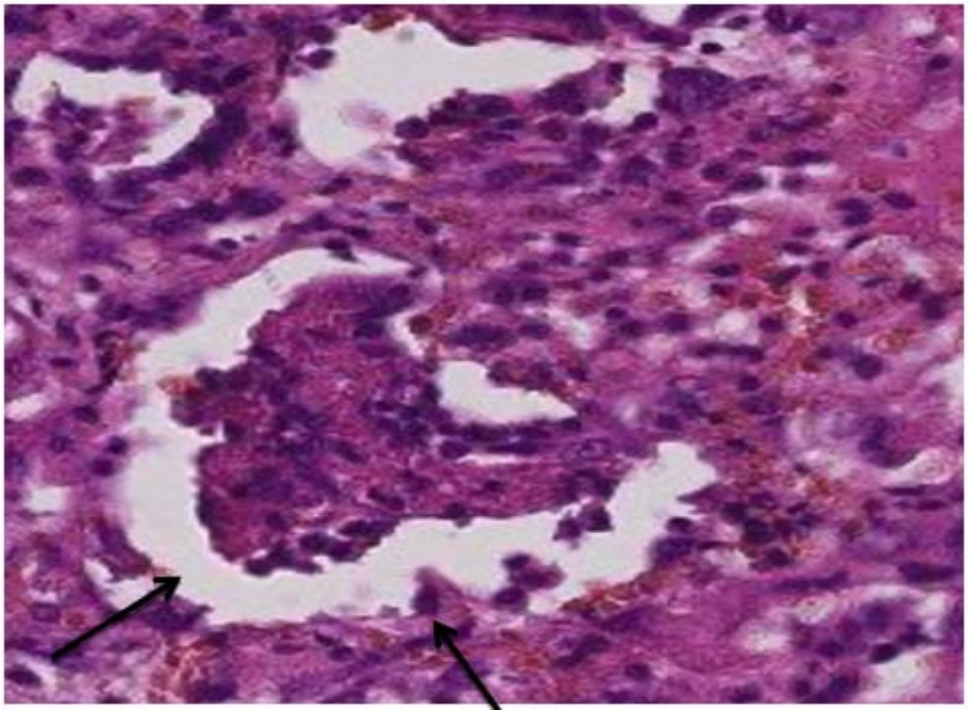

Figure 14: Intra-alveolar fibrin deposit (x40 magnification)

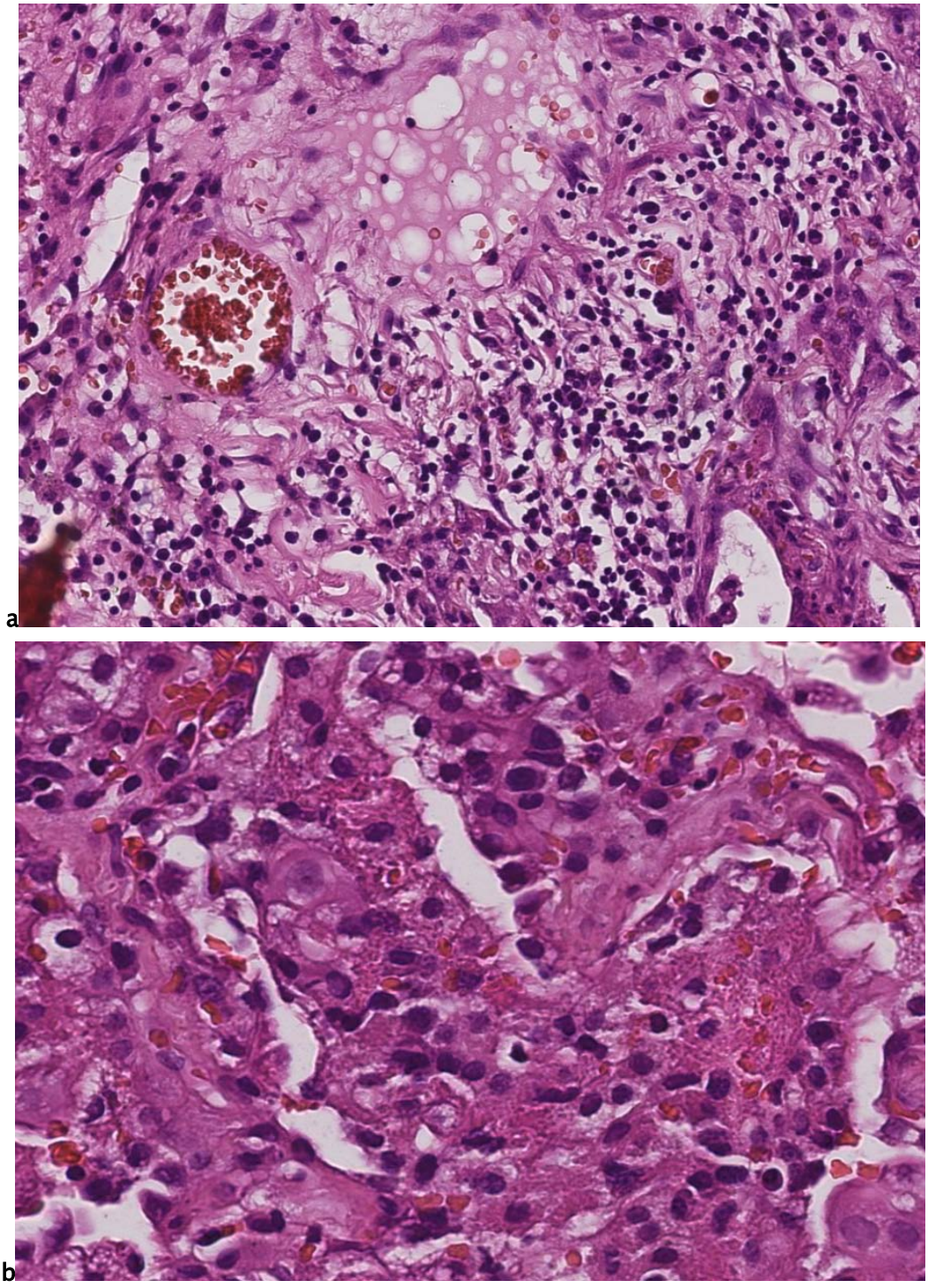

Figure 15: Intense polymorphic inflammation (a: x20 magnification, b: x40 magnification)

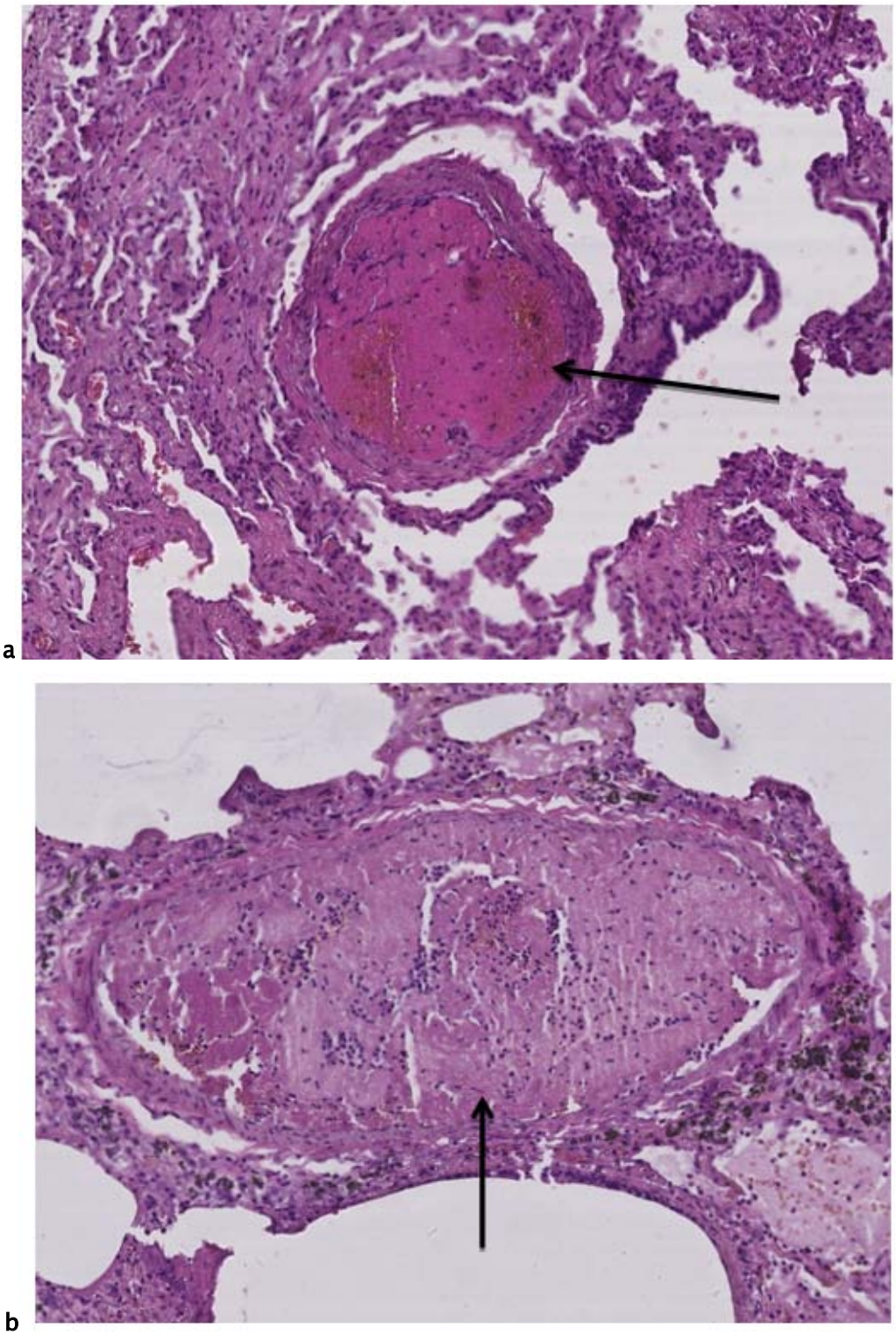

Figure 16: Prominent microthrombi (a, b : x20 magnification)

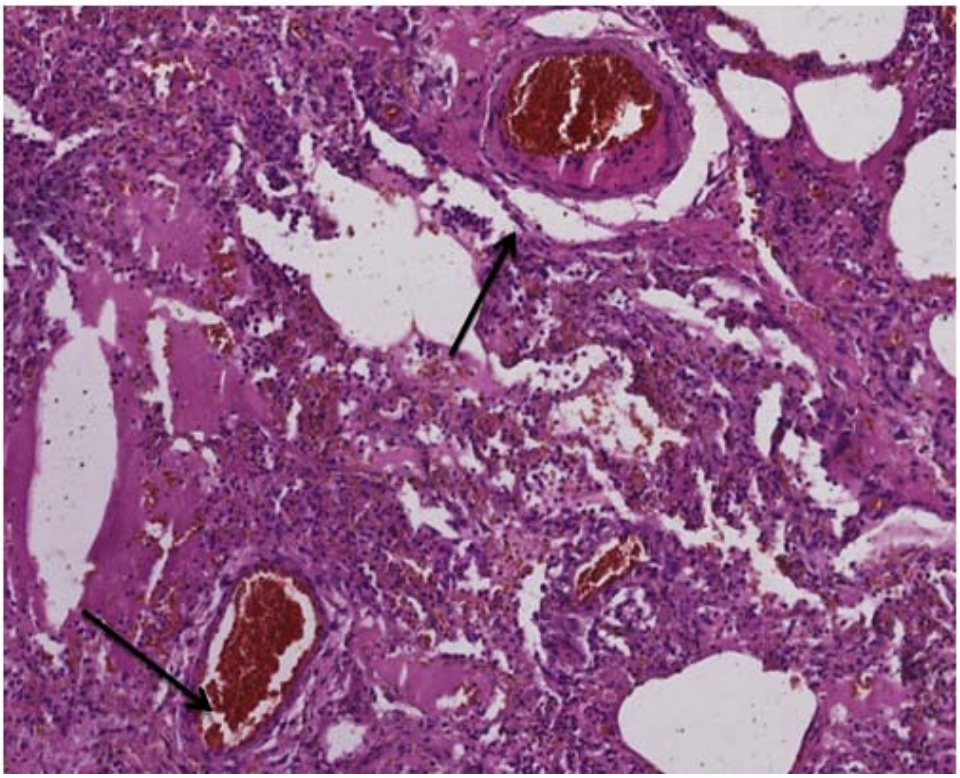

Figure 17: Vascular congestion (x 20 magnification)

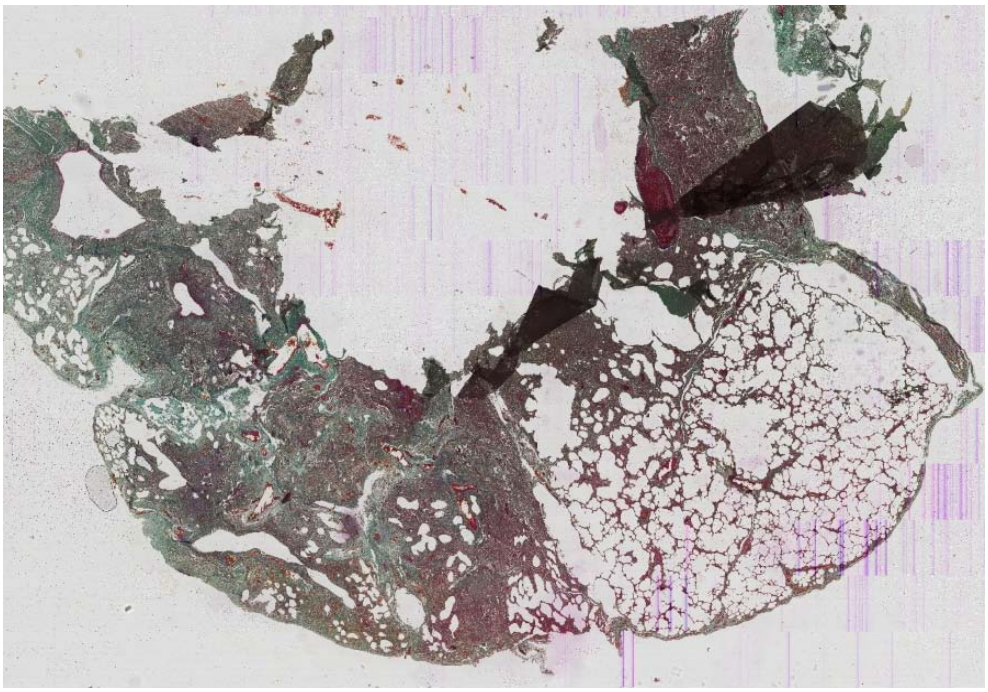

Figure 18: Trichome Masson Coloration showing no pulmonary fibrosis.

Table II : Histological features of lung biopsy patients.

	Case 1	Case 2	Case 3
Alveoli	Variable size Collapsed +++	Variable size Collapsed +++ Enlarged +	Enlarged +++ Collapsed +
Inter-alveoli wall	Thickened +++	Thickened +++	Thickened ++ Dystrophic +
Type II pneumocyte	➢ Hyperplasic +++ ➢ Atypical ➢ Multinucleated ➢ Enlarged	➢ Hyperplasic +++ ➢ Atypical ➢ Multinucleated ➢ Enlarged	➢ Discontinuous ➢ Hyperplasic ++
Alveolar Cavity : **• Hyaline Membrane** **• Exudate** **• Alveolar haemorrhage**	 + + + + + + + +	 + + + + + + 0	 + + ++ +
Interstitial Tissue : **• Inflammatory infiltrate**	➢ Diffused ➢ Minimal ➢ Lymphocyte +++ ➢ Eosinophilic polynuclear ++	➢ Diffused ➢ Minimal ➢ Lymphocyte +++ ➢ Eosinophilic polynuclear ++ ➢ Neutrophil polynuclear ++ ➢ Multinucleated giant cells +	➢ Diffused ➢ Minimal ➢ Lymphocyte + ➢ Plasmocyte ++ ➢ Macrophage + ➢ Fibroblast ++
Microthrombi	+ + +	+ + +	+ +
Vascular congestion	+ + +	+ + +	+ + +
Consolidation	45%	55%	60%
Alveolar Fibrosis *(Masson Trichome staining)*	Negative	Negative	Negative
Co-infection *(Periodic Acid Schiff staining)*	Negative	Negative	Negative

DISCUSSION

I. A historic glance at ARDS

In their ground-breaking paper of 1967, Ashbaugh et al. (4) were the first to describe the syndrome that would become one of the distinctive sub-fields of intensive care medicine, namely ARDS. The 12 patients' observations outlined a hypoxemic respiratory failure with patchy bilateral alveolar infiltrates. It also contains a description of the course of the disease, possible causes, and risk factors, pathological findings, loss of surfactant activity, the effectiveness of Positive End-Expiratory Pressure (PEEP) at improving oxygenation, and the conflicting effect of corticosteroids, inotropes, and diuretics. It is noteworthy to mention that, necropsy revealed hyaline membrane and diffuse interstitial inflammation without any sign of micro-thrombi.

In 1994, in the effort to clarify and standardize the concept of Acute Lung Injury (ALI) and ARDS the American-European Consensus Committee was formed (11). ALI was defined as an acute syndrome of inflammation and increased pulmonary permeability that is associated with a constellation of radio-clinical abnormalities, which included ARDS as a severe subgroup. Although both categories demonstrate bilateral infiltrates seen on frontal chest radiograph, the gas exchange impairment in ALI was characterized by $Pa_{O2}/Fi_{O2} \leq 300$ mm Hg (regardless of PEEP level), whereas ARDS was reduced to PaO2/FiO2 ≤ 200 mm Hg, Therefore, all patients exhibiting ARDS have ALI, but not all patients with ALI have ARDS. The Committee also focused on compartmentalizing risk factors into direct and indirect injuries that induce defects of surfactant balance as well as a ventilation-perfusion mismatch. On one hand, direct insults were portrayed in aspiration, diffuse pulmonary infection; near-drowning, toxic inhalation, and lung contusion, on the other hand, indirect injuries were outlined in sepsis syndrome, hyper-transfusion for emergency resuscitation, and cardiopulmonary bypass.

After 18 years of extensive ARDS research, fundamental concerns have been raised regarding the explicit onset time frame, the sensitivity of PaO2/FIO2 to different ventilator settings (PEEP mainly), interpretation variability of the chest radiograph, and difficulties ruling out hydrostatic oedema.

Table III. The AECC Definition —Limitations and Methods to Address These in the Berlin Definition(9)

	AECC definition	AECC limitations	Berlin definition modifications
Timing	Acute onset	No exact timeframe	Acute time onset specified
ALI category	All patients with $Pa_{O2}/Fi_{O2} \leq 300$ mm Hg	Misinterpret as Pa_{O2}/Fi_{O2} =201-300 mm Hg leading to	3 mutually exclusive severity subgroups of ARDS ALI term was removed
Oxygenation	$Pa_{O2}/Fi_{O2} \leq 300$ mm Hg (regardless of PEEP)	Inconsistency of Pa_{O2}/Fi_{O2} ratio due to the effect of PEEP	Minimal PEEP level added across subgroups
Chest radiograph	Bilateral infiltrates observed on frontal image	Wide interpretation variability	Image abnormalities explicitly clarified
Risk Factors	None	Not formally included in the definition	Included When none is identified, need to objectively rule out hydrostatic oedema
Abbreviations: AECC; American European Consensus Conference, ALI; Acute Lung Injury, ARDS; Acute Respiratory Distress Syndrome, Fi_{O2}; Fraction of inspired oxygen, $Pa_{O2;}$ arterial partial pressure of oxygen, PEEP; Positive End-Expiratory Pressure.			

Considering that the lack of a standardized terminology hindered clinical research, the Berlin definition was introduced in 2012 to add clarity and uniformity to the notion of ARDS (9). All changes were made with the understanding that syndrome definitions must meet three criteria: practicality, reliability, and validity.

The following update was fundamental because the AECC's definition of ALI as broad-spectrum was withdrawn. The task force suggested 3 mutually exclusive categories of ARDS based on the degree of hypoxemia: mild (200 mm Hg<PaO2/FIO2<300 mm Hg with PEEP or CPAP ≥5 cm H2O), moderate (100 mm Hg<PaO2/FIO2<200 mmHg with PEEP ≥5 cm H2O), and severe (PaO2/ FIO2<100 mmHg with PEEP ≥5 cm H2O).

It is crucial to note that, the onset must occur within one week of recognized clinical abnormalities or the beginning of new or worsening respiratory symptoms. The panel retained bilateral opacities on the chest radiograph consistent with pulmonary oedema as defining criterion, which could not be completely explained by cardiac failure or fluid overload. Moreover,

diffuse alveolar damage was perceived to be the hallmark of the acute phase of ARDS, although not pathognomonic of the disease (12).

Positive end-expiratory pressure can markedly affect PaO2/FIO2; therefore, a minimum level of PEEP (5 cm H2O), which can be delivered noninvasively in mild ARDS, was included in the draft definition of ARDS. A minimum PEEP level of 10 cm H2O was proposed and empirically evaluated for the severe ARDS category It is unlikely, for example, that the requirement for a minimal level of PEEP would explain the significant variation in incidence figures.

Although their approach brought uniformity to the definition, it presented a serious challenge in low-income countries. This signifies that ARDS could not be identified especially in settings with scarce resources, considering the requirement of arterial blood gas measurements and chest radiographs. It is reasonable to assume that material shortage challenges diagnosing patients with ARDS, but also prevents physicians from having providing timely adequate medical care.

Moreover, an alternative Kigali definition has been proposed to further simplify the identification of ARDS in settings with scarce access to mechanical ventilation and supplemental oxygen and to adapt its feasibility (13). Furthermore, it was recommended to use Sp_{O2}/Fi_{O2} rather than Pa_{O2}/ Fi_{O2} in defining the hypoxemia cut-off and severity of ARDS: $Sp_{O2}/Fi_{O2} \leq 315$ (with a requirement of SpO2 $<$ 97%). It also went further to replace chest radiograph with lung ultrasound, considering that recent studies validated the utility of lung ultrasound in detecting alveolar filling and consolidation accurately in ARDS(14) (15). As a result, the combination of pulmonary ultrasonography evaluation with SpO2/FiO2 measurement provides a relatively sensitive approach for identifying individuals who fulfil standard ARDS oxygenation and imaging criteria (16). It is important to mention that; minimal PEEP requirement was called into question and eventually discarded as a criterion, as a recent paper illustrated the variability of hypoxemia with different PEEP levels and suggests that hypoxemia at lower PEEP levels may be more predictive of death (17).

Table IV. Kigali modification proposal (13).

	Berlin criteria	Kigali modification
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Oxygenation	$Pa_{O2}/Fi_{O2} \leq 300$ mmHg	$Sp_{O2}/Fi_{O2} \leq 315$
PEEP requirement	Minimum 5cm H_2O PEEP required by invasive mechanical ventilation (non-invasive accepted for mild ARDS	No PEEP requirement
Chest imaging	Bilateral opacities not fully explained by effusion, lobar /lung collapse, or nodules by chest radiograph or CT scans	Bilateral opacities not fully explained by effusion, lobar /lung collapse, or nodules by lung ultrasound
Origin of oedema	Respiratory failure is not fully explained by cardiac failure nor fluid overload (if no risk is present, need echocardiography to exclude hydrostatic oedema)	Respiratory failure is not fully explained by cardiac failure nor fluid overload (if no risk is present, need echocardiography to exclude hydrostatic oedema)
Abbreviations: PEEP; Positive End-Expiratory Pressure, FiO2; Fraction of inspired oxygen, PaO2; arterial partial pressure of oxygen, SpO2; peripheral capillary oxygen saturation.		

II. C-ARDS

In the early months of 2020, the world witnessed an outbreak of the severe respiratory syndrome coronavirus (SARS-Cov-2), which caused a tremendous flood of coronavirus-related pneumonia. In most cases, coronavirus disease 2019(COVID-19) is rapidly resolved, whereas 26% require intensive care unit admission (18). Clinical manifestations of COVID-19 vary from mild pneumonia (dry cough, fever, fatigue...) to progressive Acute Respiratory Distress Syndrome (ARDS).

Since the beginning of the pandemic, many attempts have been made to understand C-ARDS pathophysiology, and therefore aroused global controversy among clinicians and researchers.

The pivotal question revolved around if acute respiratory failure due to COVID-19 falls into the definition of ARDS, but also reasons behind severe blood-gas exchange deterioration (PaO2/FiO2 ratio) compared to non-C-ARDS (19).

Xu Li and Xiaochun Ma (20) claimed that C-ARDS does not fulfil the criteria of a typical ARDS, and argued that the clinical manifestation did not correspond to the severity of the laboratory and radiological images, as well as the time of ARDS onset exceeded 1 week (median was 8-12 days).

Nevertheless, in his cutting edge observation; Gattinoni et al. stated that despite matching the Berlin criteria, C-ARDS exhibits singular features of associating severe hypoxemia with well-maintained respiratory mechanics (21).

Moreover, a fundamental distinction revealed C-ARDS phenotypes; Type 1 (H) with near-normal pulmonary compliance with isolated viral pneumonia and Type 2 (L) with decreased pulmonary compliance (22). In the same report, it has been suggested that Type L, as an early phenotype, is characterized by profound hypoxemia with relatively high compliance (> 50 ml/cmH2O) paired with high gas volume, thus a minimal percentage of non-aerated tissue and high venous admixture. Whereas in 20-30% of cases, patients present Type H aligned with low respiratory compliance (< 40 mL/ cm H20), but high lung weight due to lung diffuse oedema and inflammation. Interestingly, it was affirmed that C-ARDS patients reached, over the course of hospitalisation, a higher value of extravascular lung water index compared to non-C-ARDS which reflects the volume of inflammatory fluid and tissue accumulated during lung injury (19).

On these distinctive grounds, a crucial question rose: How does COVID-19 damage the lungs to cause a rapidly progressive onset of profound hypoxemia? We conducted this Open-Lung-Biopsy in mechanically ventilated patients to identify the pathophysiology of C-ARDS and deduct potential therapeutic targets to eventually allow clinicians to tailor therapy to individuals, making treatment more effective.

III. Pathogenesis

To our knowledge, this is the first report addressing the pulmonary lesions in C-ARDS. In all samples, a diffuse pattern of exudative and early proliferative phases of diffuse alveolar damage was observed. It is noteworthy to mention that, in our report hyperplasic Type 2 pneumocyte with an atypical appearance suggested viral cytopathic changes, thus a direct attack on the lung alveoli. The most striking pattern to emerge from this data was the prominent thrombi in alveolar microvascular beds.

These results correlate favourably with Ackerman et al.(23), and further supports the distinctive angiocentric features of COVID-19. Moreover, the lungs from patients with COVID-19 in the same study had widespread vascular thrombosis with microangiopathy and occlusion of alveolar capillaries. Two hospitals in northern Italy analysed lung tissue samples from 38 patients who succumbed to COVID-19, and demonstrated consistent diffuse alveolar damage, which was observed in all cases, included capillary congestion, interstitial and intra-alveolar oedema, dilated alveolar ducts and collapsed alveoli, hyaline membranes composed of serum proteins and condensed fibrin, and loss of pneumocytes (24). More recent papers highlight the presence of platelet-fibrin thrombi in small arterial vessels as predominant findings in lungs (24-29).

Significant new vessel growth through a mechanism of intussusceptive angiogenesis was noted, and it was hypothesized that a greater degree of endothelialitis and thrombosis in the lungs from patients with COVID-19 may contribute to the relative frequency of angiogenesis (23). Interestingly, it was demonstrated, using Ki67 immunostaining, that vascular endothelium proliferation was frequent and responsible for low perfusion in severe cases of COVID-19 (25).

Other viral respiratory infections have already created substantial public health concerns and led to alarming outbreaks, such as Severe Acute Respiratory Syndrome (SARS), H1N1, and Middle East Respiratory Syndrome-Related Coronavirus (MERS) in 2003, 2009, and 2012 respectively. Table V portrays a pulmonary pathological comparison between different viral pathogens that were responsible for fatal ARDS.

Table V : Distinctive pathologic features in a panel of viruses responsible for ARDS.

Characteristics	SARS	Swine Flu	MERS	COVID-19
Status	First reported in Asia in February. 2003, 8000 people infected, 774 deaths	First reported in Mexico in April 2009 with 201,200 deaths (26)	First reported in Saudi Arabia in September 2012. 2519 people infected, 866 deaths	First reported in Wuhan, China in December 2019. As of 23 October 2021 , 4,955,403 deaths. (27)
Causative virus	SARS-CoV	A/H1N1	MERS-CoV	SARS-CoV-2
Macroscopy	Edematous lungs with increased gross weight and multiple areas of congestion, enlargement of lymph nodes in the pulmonary hila	Edematous lungs with extensive haemorrhagic appearance with an aspect of red hepatisation (28)	Edematous lungs with increased gross weight and multiple areas of congestion	Edematous lungs with increased gross weights, multiple areas of congestion, and pulmonary embolism (29)
Microscopy	Bronchial epithelial denudation, loss of cilia, squamous metaplasia, acute diffuse alveolar damage, and in the late phase acute fibrinous and organizing pneumonia	Acute phase of diffuse alveolar damage, with end-stage organizing pulmonary fibrosis and occasional microthrombi (30)	Exudative diffuse alveolar damage with hyaline membranes, pulmonary oedema, type II pneumocyte hyperplasia, interstitial lymphocytosis, multinucleate syncytial cells cast formation	Diffuse alveolar damage, severe capillary congestion, interstitial mononuclear cell infiltrates, and multinucleated syncytial cells with atypical enlarged pneumocytes, and consistent microthrombosis(31)

IV. Cytokine Storm

For these inpatients, the illness severity spectrum includes not just pneumonia, pulmonary oedema, but also ARDS, which is a cause of death in 70% of fatal COVID-19 cases and is characterised by aggressive inflammatory responses of the host response (32), as exhibited in our case series.

When viral elements of Sars-CoV-2 penetrate lungs, the virus uses angiotensin-converting enzyme II (ACE 2) as host entry through epithelial and endothelial cells, leading to an increased serum level of angiotensin II (Ang II) due to the scarcity of ACE 2 surface expression (33) (34). It is noteworthy to mention that, Ang II appear to function as a vasoconstrictor but also as a pro-inflammatory cytokine via Ang II type 1 receptor (AT1R) (35). Moreover, this AT1R transduces intracellular signalling via complex enzyme and growth factors in order to activate interleukin 6 (IL-6) (36). This chemotaxis cascade of chemokines are known to recruit and migration of leukocytes (macrophages, neutrophils, and T cells) and plasma protein to the inflammation site, where they could eliminate the virus, but simultaneously destruct alveolar epithelial wall, capillary permeability and induce multi-organ failure and ultimately death. This hypothesis is reinforced with our pathological findings of widespread inflammatory infiltrates in the interstitial tissue.

Thus, during extensive lung inflammation in ARDS Ang II-AT1R signalling can generate an IL-6-mediated positive feedback loop, a process known as the IL-6 amplifier resulting in an excessive inflammatory reaction (Fig. 19). The "cytokine storm" is caused by a rapid spike in circulation levels of several pro-inflammatory cytokines such as IL-6, IL-1, TNF-, and interferon (37).

More recent evidence highlights that, when COVID-19 survivors and non-survivors are evaluated, serum level of IL-6 is directly correlated to disease mortality, among the high inflammatory mediators (38) (39). Cytokine storm has been found in a variety of viral diseases, including influenza H5N1 virus, influenza H1N1 virus, and two coronaviruses closely related to COVID-19, SARS-CoV and MERS-CoV (37).

Cytokine storm is a life-threatening complication with a high death rate that necessitates critical care admission and timely-appropriate treatment.

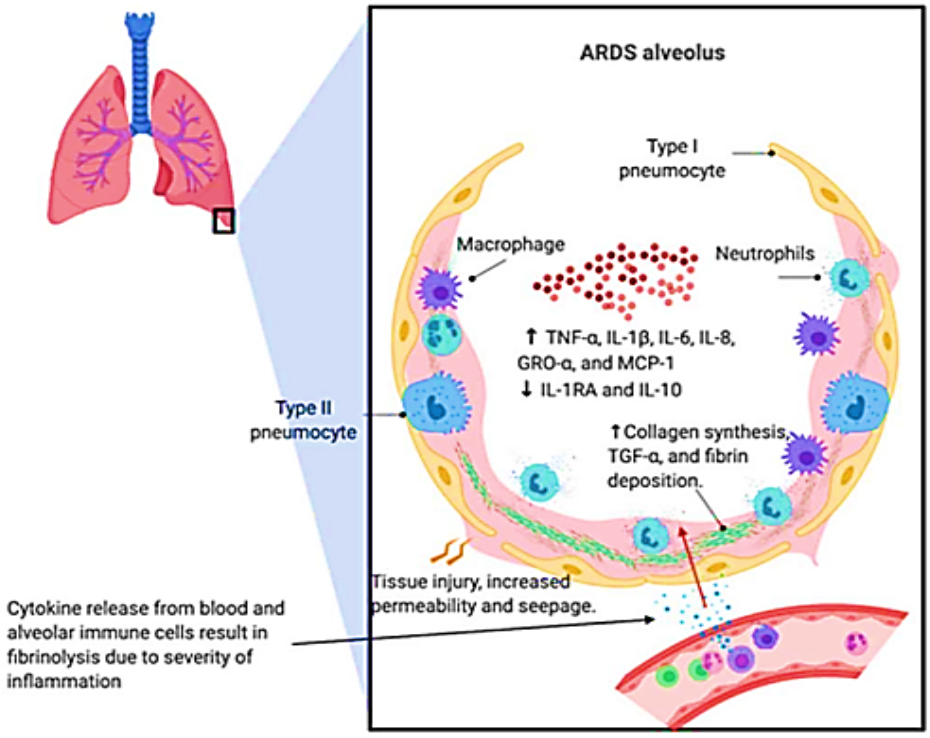

Figure 19: The role of cytokine inducing C-ARDS (40).

V. Immunothrombosis

The presence of SARS-CoV-2 viral elements within the pulmonary and peripheral endothelial cells and the accumulation of inflammatory cells may generate a prothrombotic state by strongly activating endothelial coagulation cascade (41). Moreover, roughly 72% of COVID-19 non-survivors demonstrated evidence of hypercoagulability (42). In addition, accumulating evidence point out that C-ARDS patients may have higher levels of coagulation cascade activation and lower anticoagulant and fibrinolytic system activity than those with ARDS caused by other disorders or illnesses (43) (44). In contrast, ebola, dengue, and other haemorrhagic viruses, which may similarly induce endothelium damage, have been linked to enhanced anticoagulant effects and fatal haemorrhage (45) (46).

Normally, the glycocalyx is fundamental to epithelial and endothelial barrier function under homeostatic conditions and confers an anticoagulant and anti-adhesive surface, however, its shedding is allied with endothelial barrier rupture, and also contribute to increased vascular permeability, leukocyte recruitment and micro-clots in capillaries (47).

It is noteworthy to mention that, endothelial dysfunction is a key component of a variety of disorders, and it also serves as the common denominator for all COVID-19 comorbidities, including hypertension, diabetes, and obesity, all of which are substantial contributors to COVID-19-related mortality (48). On the other hand, endothelial impairment is linked to a low anti-aggregatory prostacyclin production from the endothelial cells and an increased pro-aggregatory thromboxane synthesis from activated platelets (49).

Von Willebrand factor (VWF) levels are significantly elevated in COVID-19 patients (529 U/dL compared to 100 U/dL, normal) further supporting the hypothesis of SARS-CoV-2 induced endothelial dysfunction or damage (50).

VWF is a circulating adhesive glycoprotein released by endothelial cells and platelets, and its levels are raised in disorders such as vasculitis, inflammation, ageing (51), and diabetes (52), all of which are linked to endothelial dysfunction. Furthermore, VWF stimulates platelets, causing them to cluster together (53), functions as a carrier for coagulation factor VIII, and promotes blood coagulation (54).

VWF also has a role in the vasculature system, modulating angiogenesis and vascular permeability.

Interestingly, high inflammation mediated by cytokine, mainly IL-6, (55) regulates coagulation by activating C-reactive protein (CRP), which promotes tissue factor exposure on monocytes and alveolar macrophages (56) and stimulates thrombin production and fibrin deposition.

It is reasonable to assume that the sequestration of endothelial cells-platelet-leukocyte aggregation on the walls of a smaller vessel (Fig. 20) , and the subsequent development of immunothrombosis would be sufficient to cause microthromb in the alveolar-capillary circulation (57) (49), thus a loss of microvascular perfusion in the lungs and other organs

eventually, and in some circumstances the development of disseminated intravascular coagulation (Fig. 21).

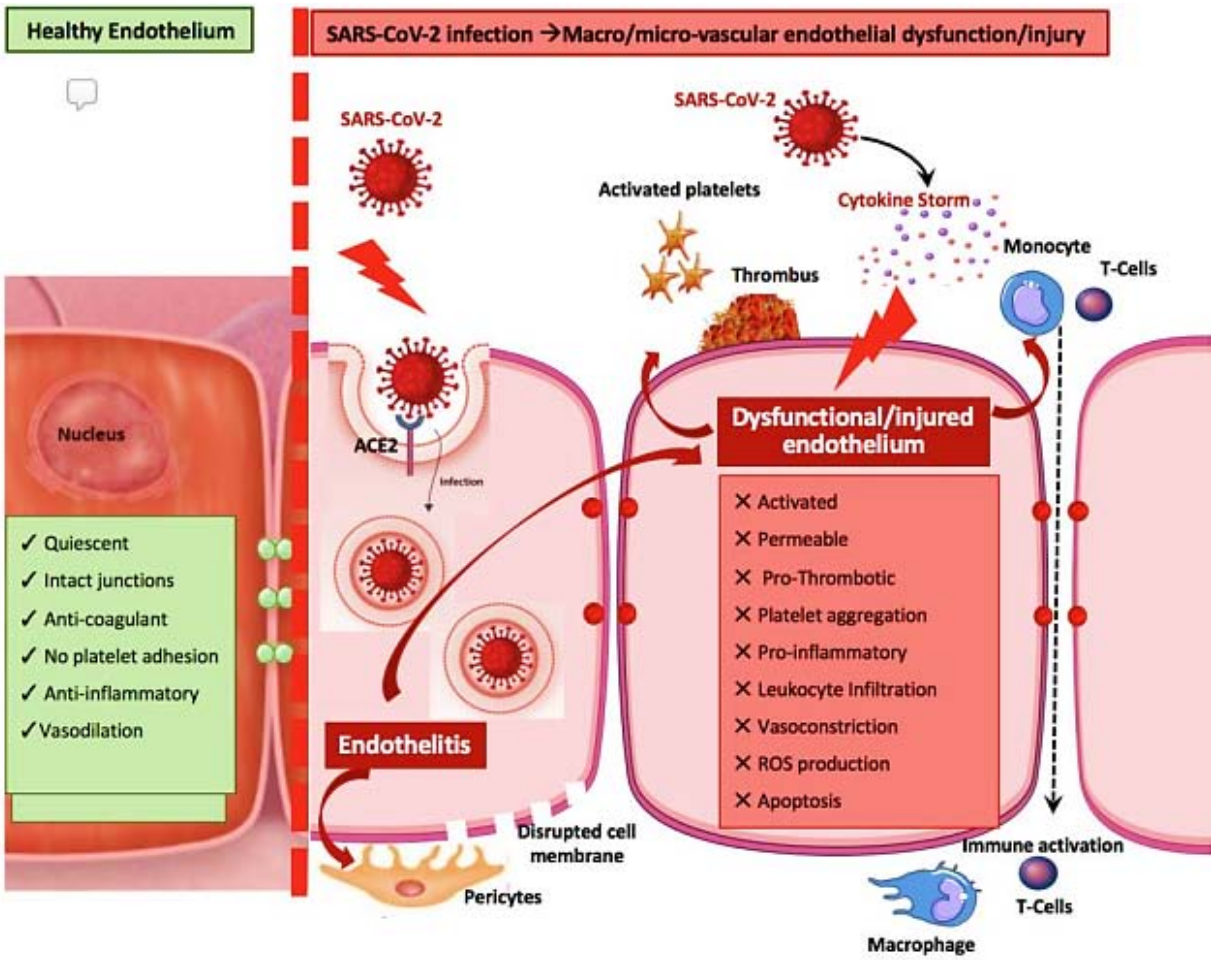

Figure 20: SARS-CoV-2 induced vascular damage (49)

Hypoxia might be, at the same time, the outcome of vascular occlusion and also an accelerator of thrombus formation and progressively exhaust the fibrinolytic activity of the endothelium, acting as a positive loop of reciprocal induction (58).

Additionally, it was noted that mechanical ventilation itself can cause local and systemic inflammatory activation and a hypercoagulable state (59).

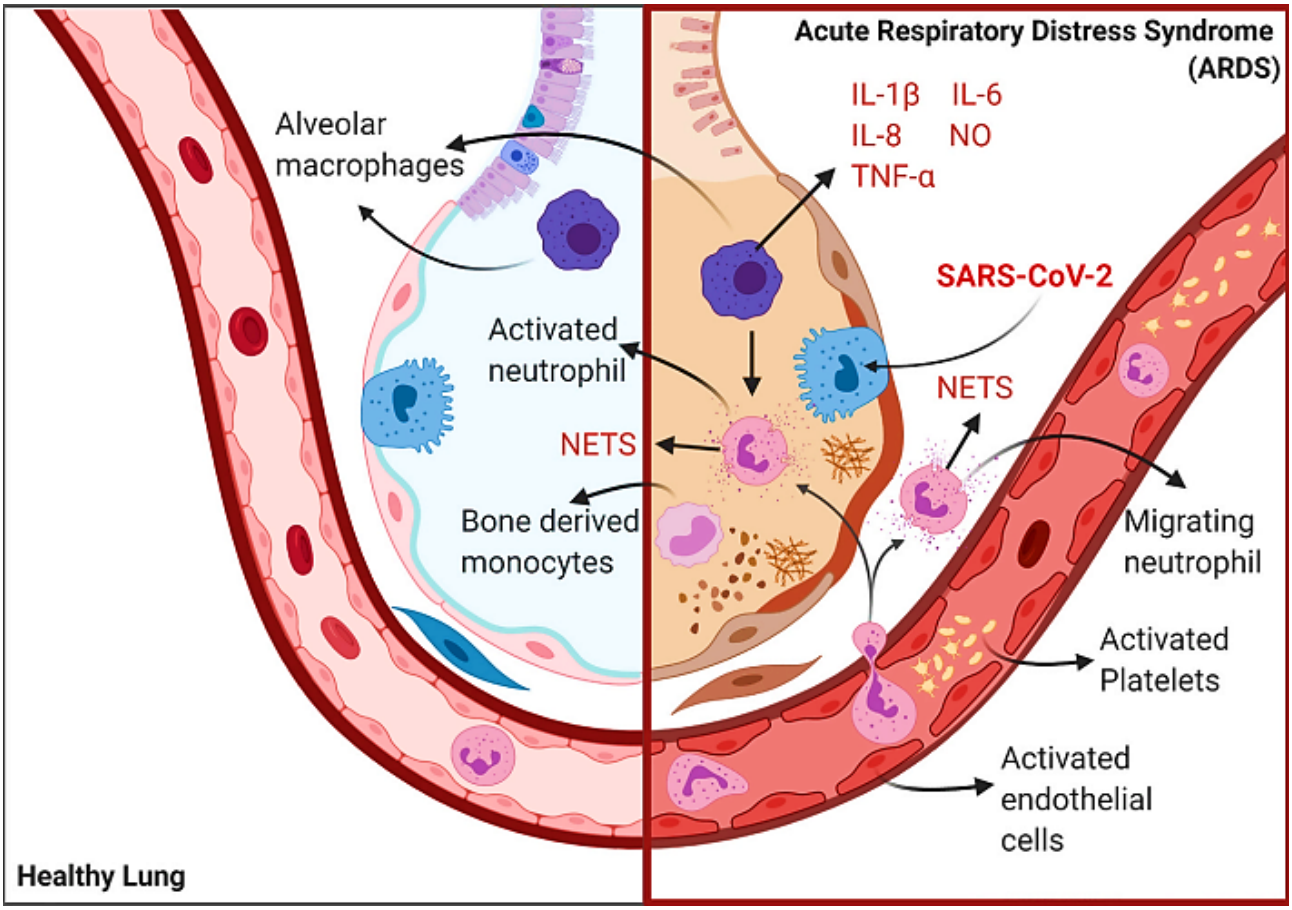

Figure 21: The pathophysiology of COVID-19 ARDS (60)

Our patients demonstrated elevated levels of D-dimer and it only progressed over time. A meta-analysis of 16 studies found that D-dimer levels were significantly higher in COVID-19 patients compared to healthy controls, in COVID-19 patients with severe disease or a composite end-point compared to non-severe disease, in ARDS patients compared to non-ARDS patients, and in deceased ARDS patients compared to ARDS patients who survived (61).

Ciceri et al. have proposed MicroCLOTS (microvascular COVID-19 lung vessels obstructive thrombo-inflammatory syndrome) as a new name for the severe pulmonary disorder related to COVID-19 (62). They hypothesise that, in predisposed individuals, alveolar viral damage is followed by an inflammatory reaction and by microvascular pulmonary thrombosis.

VI. Co-infection

In our samples, bacterial and fungal cultures were negative, in contrast with the recent finding of bacterial abscesses in 4 patients among 38 who succumbed to COVID-19, with a single fungal abscess in one, and were presumed to be formed after hospital admission (24). SARS-CoV-2 RT PCR was positive in two of our patients, whereas other respiratory pathogens were not present in lung tissue.

Other studies focused on the examination of broncho-alveolar lavages within 24h of tracheal intubation, and interestingly early co-infection was demonstrated in 13 patients out of 47 (63). Three bacterial species accounted for≥90% of all identified bacteria: *Staphylococcus aureus* (all methicillin-sensitive), *Haemophilus influenza*, and *Streptococcus pneumonia.*

Extreme caution must be taken interpreting these results, as co-infection with other pathogens cannot be ruled out since it could be present in another pulmonary parenchyma that is not included in the biopsy fragment. It also appears to be difficult to distinguish between morbid infection and tissue colonization.

It would be reasonable to hypothesize, that patients with C-ARDS may be considered as easy prey for secondary infection due to their immune-compromised state, portrayed in lymphopenia in particular.

VII. Therapeutic implications

1. Anticoagulants

Heparin is a polysaccharide that was first extracted from mammalian animal tissue in 1916 (64), its reliance on anti-thrombin to inhibit blood clot formation renders the medicine an indirect antithrombotic agent, and the lack of intrinsic fibrinolytic action inhibits thrombi disintegration after they have formed (65) (66). In addition, heparin is a well-tolerated anticoagulant drug that has been used efficiently for more than 80 years and has few relatively

manageable side effects since it is a natural product (67). Moreover, heparin belongs to a distinct class of medications with effective antidotes, making its use in practice safe.

Besides, heparins also present an interesting immune-modulatory activity: it was found that a non-anticoagulant fraction of enoxaparin was reported as a partial inhibitor of IL-6 and IL-8 release (68). Furthermore, several studies have demonstrated the anti-inflammatory properties of heparin (69) (70), which may be helpful to manage this disease, but also provide endothelium protection.

Our patients showed coagulation abnormalities and received a therapeutic dose of LMWH after their admission to the ICU. Of note, there are several possible explanations for the inefficacy of LMWH administered in our patients. On the one hand, perhaps an asymptomatic pulmonary embolism was already present before the hospitalization of our hypercoagulable patients, considering their advanced age and their cardiovascular comorbidities but also the delay between the symptom onset and their hospitalization.

In line with, a recent major randomized clinical trial that included 1098 patients; proved that in critically ill patients with COVID-19 an initial strategy of therapeutic-dose anticoagulation with heparin did not result in a greater probability of survival to hospital discharge, or a greater number of free organ-support days than did usual-care pharmacologic thrombo-prophylaxis (71).

In another study, severe COVID-19 patients admitted to the ICU were categorised into one of the four groups (fixed-dose, increasing amount, decreasing dose, multiple changes in quantities). As result, no significant difference in dose of anticoagulants between survivors and non-survivors was found and showed no impact in 28-day survival among four strategies of dose modification (72).

In a multicentre randomised clinical trial including COVID-19 unstable patients with elevated D-dimer concentration, a 30-day course of therapeutic anticoagulation (rivaroxaban at 20 mg daily or enoxaparin 1 mg/kg twice daily) did not result in better clinical outcomes, when compared with in-hospital prophylactic anticoagulation with heparin (73). On the contrary, therapeutic anticoagulation led to a higher incidence of bleeding than did in-hospital prophylactic anticoagulation.

It seems plausible that, for anticoagulation to be **efficient** it should be **timely-appropriate**, in parallel with the micro-thrombi formation and elevated D-dimer, before shifting to a clinical unstable status. In contrast with previous studies mentioned above, a large randomized clinical trial In non-critically ill patients with Covid-19 demonstrated that an initial prescription of therapeutic-dose anticoagulation with LMWH improved the probability of survival to hospital discharge with reduced use of organ support, as compared with usual-care thrombo-prophylaxis (74). Moreover, therapeutic-dose anticoagulation was beneficial regardless of the patient's baseline d-dimer level.

Another anticoagulation approach was suggested, using nebulised unfractionated heparin reaching directly the lung micro-environment. In addition to its anti-viral (75) (76), anti-inflammatory (77) (78) and mucolytic effects (79) nebulised unfractionated heparin targets pulmonary fibrin deposition and inflammation, as well as local administration to the lungs, offers higher doses and enhances local performance, minimises the danger of systemic haemorrhage, and is more beneficial than intravenous treatment (80) (81). It is noteworthy to mention that, pulmonary bleeding did not result from the use of nebulised unfractionated heparin in other respiratory settings (82).

2. Corticosteroids

From another angle, our findings would seem to support the role of corticosteroid therapy. They are steroid hormones that are produced as a result of cholesterol metabolism. It is well known that glucocorticoids reduce endothelial leakage by decreasing capillary permeability and lowering leukocyte migration to the inflammation site, while effectively stopping the inflammatory cascade. It is fundamental to state that; dexamethasone is associated with decreased capillaries permeability, in addition to reduced neutrophil and lymphocyte migration into the inflammatory sites (Fig. 22) (64).

Concerning C-ARDS, it was reported in a single-blind, randomised controlled clinical trial involving 68 severe COVID-19 patients that injecting 250 mg/day of methylprednisolone for 3 days, during the early pulmonary phase lead to a substantial death risk decrease as well as amelioration of ventilation and inflammatory markers (83). Moreover, it was outlined that a high-dose (1000 or 500 mg/day), short-term (3 days) methylprednisolone intravenously enabled extubation of the patients within seven days (84).

The World Health Organization (WHO) have conflicting views concerning the use of corticosteroids in COVID-19 and does not recommend their use in routine practice unless under clinical trial conditions (85). However, it is pragmatic to consider a powerful anti-inflammatory medication, such as dexamethasone therapy, that is required to address the excessive inflammation. Dexamethasone may disrupt the development of the host's natural immunity and abrogate antiviral response, such as in the early stages of the disease, resulting in a delayed viral clearance (64).

The RECOVERY trial investigated the efficacy of dexamethasone in 2104 hospitalized patients (Vs. 4321 standard-care) that received 6 mg once daily for up to 10 days and concluded to reduced 28-day mortality than usual care in patients who were receiving invasive mechanical ventilation or non-invasive ventilation (86). Furthermore, 20 mg of dexamethasone intravenously daily for 5 days, followed by 10 mg of dexamethasone daily for 5 days or until ICU discharge led to a significant increase of survival and free of mechanical ventilation days, in a randomized trial of 299 adults with moderate or severe C-ARDS (87).

It seems reasonable to say that, glucocorticoids use has a clear benefit in the early onset of hypoxemia correlated with inflammatory diffuse alveolar damage, although it might slow viral RNA clearance and increase in antibiotic use and infections without a prolonged hospital stay or increased mortality (88).

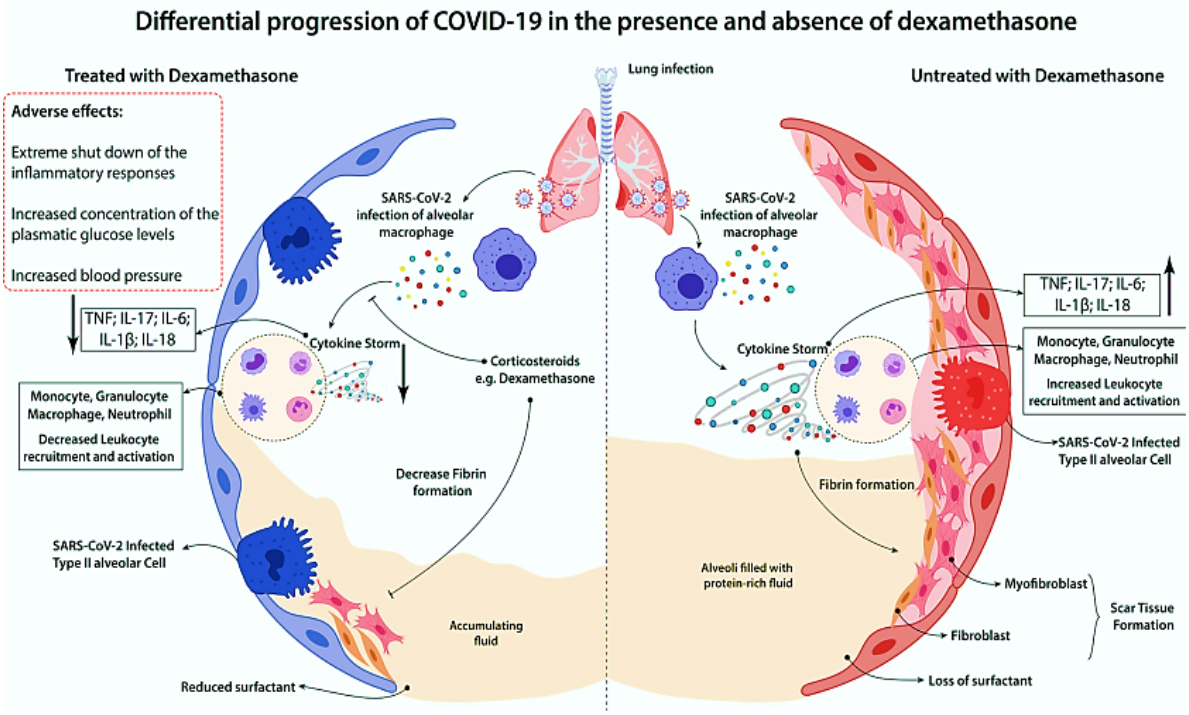

Figure 22: Differential progression of COVID-19 in the presence and absence of dexamethasone. (64)

3. Ventilation management

A key aspect of care should be addressed in ventilation management, not all cases of C-ARDS are considered similar. COVID-19 provides us with a crucial lesson: the broad spectrum of C-ARDS may necessitate alternative ventilatory settings, depending on how they influence lung characteristics: What is a protective tactic in one circumstance may turn out to be a potentially lethal strategy in another (89). Gattinoni et al. conceptualised the L and H type but also differentiated between the distinctive ventilation treatment in his cutting-edge papers (90) (91), as follows (Fig. 23) :

- Initially, we should aim to improve hypoxemia through an increase in FiO2.
- Several non-invasive alternatives are designed for Type L patients with persistent dyspnea (high-flow nasal cannula, continuous positive airway pressure, or non-invasive ventilation), assuming that they do not make excessive inspiratory efforts.

- If the respiratory drive is not lowered by oxygen delivery and non-invasive support, however, consistently high spontaneous inspiratory attempts increase tissue stresses while also increasing pulmonary transvascular pressures, vascular flows, and fluid leaks.
- Risk of lung injury increases during the transition from the Type L to the Type H phenotype, which could be determined with the magnitude of inspiratory pleural pressures swings.
- Therefore, early intubation, effective sedation, and/or paralysis should be done as soon as possible to break the process.
- Once intubated and deeply sedated, the Type L patients, if hypercapnic, can be ventilated with volumes greater than 6 ml/kg (up to 8-9 ml/kg), as the high compliance results in tolerable strain without the risk of ventilation-induced-lung-injury (VILI).
- Targeting lower PEEP (8-10 cm H2O) is appropriate since lungs have low recruitablity; higher levels will decrease pulmonary compliance and can impact right heart function.
- Prone position may be used as a rescue manoeuvre not to aerate collapsed alveoli, but only to facilitate the redistribution of pulmonary blood flow.
- The type H phenotype progressively develops with the increase of lung oedema and infiltrates. Of note, complete respiratory mechanics assessment performed 4-6 days later in 15 patients suggested that initial status may change more frequently from poorly recruitable to highly recruitable than the reverse (92).
- In this advanced state, it is advisable to apply a more conventional lung-protective strategy: higher PEEP (15 cm H2O), lower tidal volume (6 mL/kg), and prone positioning while minimizing oxygen consumption.

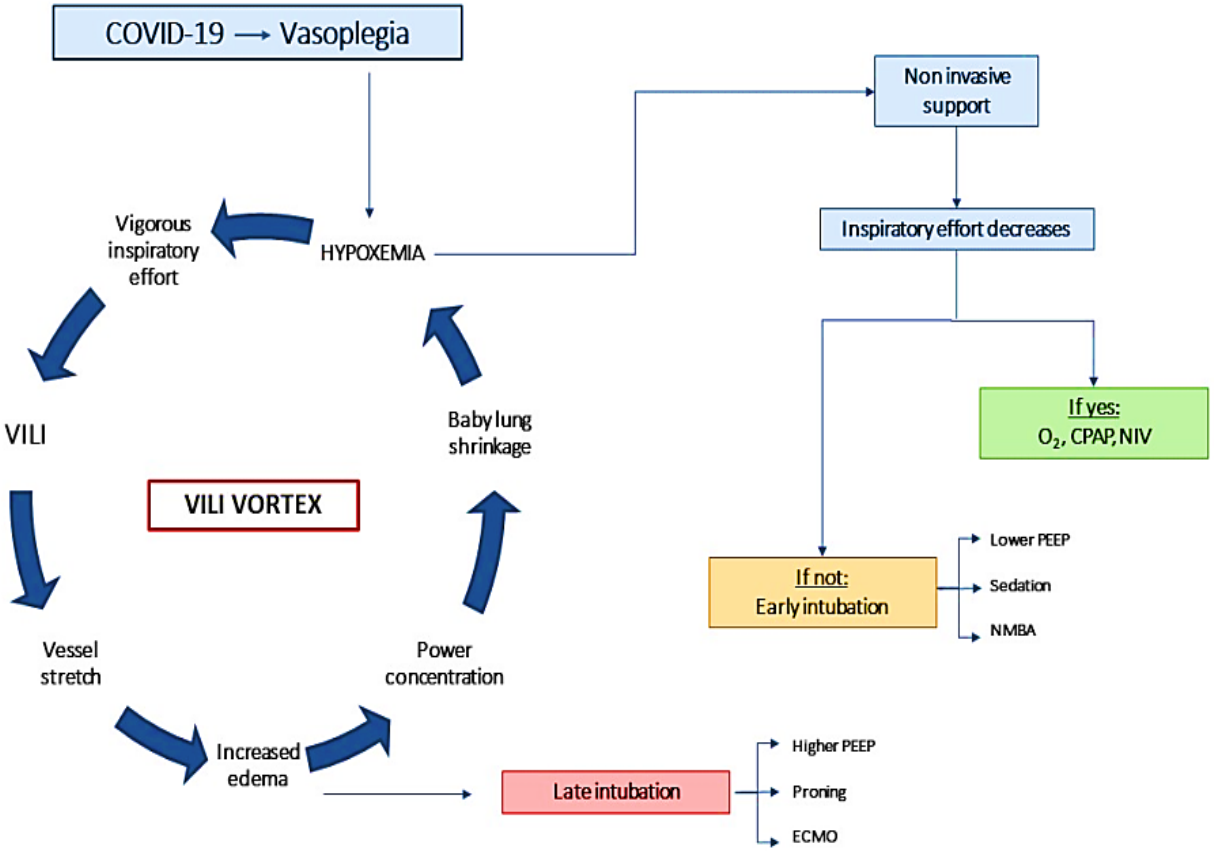

Figure 23: Drivers and Interrupters of Progressive Lung Injury in COVID-19 Infection (93).

VIII. Limitations

The present study has several limitations; we did not investigate the samples using immune-histochemical staining for additional insights, due to lack of materials. No autopsy was performed to determine the presence of pulmonary embolism in the main vessels.

Despite the sample size, we believe our preliminary work could be a starting point to further provide concrete and substantial answers regarding the mechanism and pathogenesis of severe hypoxemia in C-ARDS and its management.

IX. Strength points

It's noteworthy to mention that our novel work contains some strength points:

- It was a prospective study carried out during the first wave of COVID-19 pandemic that tremendously improved our comprehension of the pathophysiology and also influenced our clinical management.
- To the best of our knowledge, this is the first study in the world and in Morocco to address the pathology in C-ARDS patients.
- It was specifically during the first 24h of intubation to avoid Ventilation induced Lung Injury bias
- Our work was published (94) in Biomed Research International Journal with an impact factor value of 2.5 and 3 other publications have already cited our study including the Lancet Respiratory Journal.

CONCLUSION

The evidence from this study allows us to not only hypothesize that SARS-CoV-2 directly attacks lung alveoli leading to diffuse alveolar damage and more particularly plurifocal fibrin microthrombi in the peripheral vasculature beds, but also elucidate the mechanism behind VA/Q mismatch in severe C-ARDS hypoxemia.

Immunothrombosis may be implicated in the dead space effect through compromising pulmonary perfusion in the early stages, followed by cytokine storm that tends to cause diffuse alveolar damage which is solely responsible for the shunt effect.

Additionally, this research points out the crucial benefit of an early therapeutic dose of LMWH anticoagulant therapy (enoxaparin 1mg/kg twice daily) and corticosteroids in particular dexamethasone (6 mg once daily), in improving survival and lowering C-ARDS mortality.

Despite sample size, we believe that our preliminary report provides a shred of evidence and insight concerning the pathophysiology of C-ARDS. It goes without saying, that further investigation should be conducted in order to determine pertinently C-ARDS hypoxemia mechanisms and the proper ventilation and therapeutic management.

ANNEX

Fiche d'exploitation

IP :……

I. Identité :

- Nom et prénom : …….. Sexe : □ F □M
- Âge : ….. Origine : □ Urbain □ Semi Urbain □ Rural □ Non connu

II. Antécédents :

1. Personnels : □Oui □Non

1.1. Médicaux :

□HTA □Coronaropathie □Asthme □BPCO □Diabète
□Insuffisance rénale C □VIH □Hémopathie maligne
□Néoplasie □Cirrhose □Tabac □Alcool
□Maladie auto-immune □Immunosuppresseurs/CTC □
Autre, Précisez……..
Traitement actuel : ……

1.2. Chirurgicaux : □Oui □Non Précisez :…….

2. Familiaux : □Oui □Non Précisez :…….

III. Symptomatologie

Début de symptômes : ……

□Fièvre	□Toux	□Frissons	□Dyspnée, Si oui, Stade :……
□Fatigue	□Céphalées	□Diarrhée	□Vomissements
□Myalgies	□Hémoptysie	□Crachat	□Douleurs abdominales

IV. Examen physique:

- **Fonction respiratoire :**
  - FR= cpm □Cyanose, au niveau de……
    □ SLR □ SpO2= % Ausculation PP =
- **Fonction circulatoire**
  - FC= bpm, PA= mmHg TRC 3s
    □ Marbrure, au niveau de ……
    □Pâleur □Sueurs Auscultation cardiaque=

- Diurese= L/24h mL/Kg/24h

- **Fonction neurologique**
  - GCS= /15 □ Déficit moteur, type..... Dextro= g/L
  - □ Déficit sensitif, type..... □ Convulsions,type.....
  - Les pupilles= □ symétrique □ isocore : □ réactive

V. Bilan paraclinique :

1. Radiologique :

- ECG : .....
- ETT : .....
- Radio Thorax : Opacité : □Alvéolaire □Interstitielle □Mixte
  □Unilatérale □Bilatérale
  Pleurésie : □Oui □Non
- TDM Thoracique : □Verre dépoli □Condensation bilatérale
  □ Crazy paving □Autre, Préciser :.....
  Etendue : □<25 □25-50 □50-75 □>75
  Classification CORADS : □1 □2 □3 □4 □5 □6
- Autre : .....

2. Biologique :

- PCR virologique: (Tableau joint)
- Hémoculture : □Oui □Non
  Résultats :.....
  .....
- ECBU : □Oui □Non
  Résultats :.....
  .....
- Paramètres biologiques:
- Bilan immunologique:

VI. Traitement :

- **Analgésie-Sédation**
  □ Fentanyl 100µ/h □ Midazolam 3mg/h
  Récoronium=.....

- **Antibiothérapie- Antiparasitaire-Antiviral**
  - □ Chroloquine 500mgx2/jr OU Plaquenil 200x3/jr
  - □ Azithromycine 250mg/jr
  - □ Ceftriaxone 2g/jr
  - □ Moxifloxacine 400mg/jr
  - □ Lopinavir-Ritonavir
  - □ Favipiravir

- **Anticoagulation**
  - □ Enoxaparine 100 UI/kg x2/jr en SC OU ……

- **Autre**
  - □ Oméprazole 40mg/jr
  - □ Paracetamol 500mg/6h
  - □ Methylprednisolone 1mg/kg
  - □ Vitamine C 1g x 2/ jr par SNG
  - □ Sulfate de Zinc 1cp 220mg/jr

- **Ventilation**

  VNI : □Oui □Non Vent. Invasive : □Oui, (tableau) □Non

- **Drogues et autres**

  Noradré :□Oui □Non Dobutamine □Oui □Non Hémodialyse : □Oui □Non

VII. Resultat de la biopsie :

1) **Analyse anatomopathologique :**……
2) **Analyse microbiologique :** ……

VIII. Evolution

□Sepsis □Choc septique Gravité : CURB-65 :…… SOFA :……

□Insuffisance cardiaque □Insuffisance rénale □Pneumopathie nosocomiale

□Embolie pulmonaire □CIVD □Troubles de rythme

Durée de VNI : ……J

Durée de ventilation mécanique : ……J

Durée d'hospitalisation :……J □Survivant □Décédé, cause : ……

ABSTRACT

Abstract

Difficulties have risen while managing Acute Respiratory Distress Syndrome (ARDS) caused by COVID-19, although it meets the Berlin definition. Severe hypoxemia with near-normal compliance was noted along with coagulopathy. Understanding the precise pathophysiology of this atypical ARDS will assist researchers and physicians in improving their therapeutic approach.

Previous work is limited to post-mortem studies, while our report addresses patients under protective lung mechanical ventilation. An open-lung minithoracotomy was performed in 3 patients who developed ARDS related to COVID-19 and were admitted to the intensive care unit to carry out a pathological and microbiological analysis on lung tissue biopsy.

Diffused alveolar damage with hyaline membranes was found, as well as plurifocal fibrin microthrombi and vascular congestion in all patients' specimens. Microbiological cultures were negative, whereas qualitative Reversed Transcriptase Polymerase Chain Reaction (RT-PCR) detected SARS-CoV-2 in the pulmonary parenchyma and pleural fluid in two patients.

COVID-19 causes progressive ARDS with onset of severe hypoxemia, underlying a dual mechanism: shunt effect through diffused alveolar damage and dead space effect through thrombotic injuries in microvascular beds. It seems reasonable to manage this ventilation-perfusion ratio mismatch using a high dose of anticoagulant combined with glucocorticoids.

It's noteworthy to mention that our work was published on 10th December 2020, in "**Biomed Research International**" Journal with an impact factor value of **2.5** and 3 other publications have already cited our study including the **Lancet Respiratory** Journal.

Resumé

Des difficultés sont apparues lors de la gestion du syndrome de détresse respiratoire aiguë (SDRA) causé par la COVID-19, bien qu'il réponde à la définition de Berlin. Une hypoxémie sévère avec une compliance quasi normale a été constatée ainsi qu'une coagulopathie. La compréhension de la physiopathologie précise de ce SDRA atypique aidera les chercheurs et les médecins à améliorer leur approche thérapeutique.

Les travaux antérieurs se limitent à des études post-mortem, tandis que notre rapport porte sur des patients sous ventilation mécanique . Une biopsie à mini-thoracotomie a été réalisée chez 3 patients qui ont développé un SDRA lié au COVID-19 et ont été admis dans l'unité de soins intensifs pour effectuer une analyse pathologique et microbiologique du tissu pulmonaire.

Des dommages alvéolaires diffuses avec des membranes hyalines ont été trouvées, ainsi que des microthrombi de fibrines plurifocales et une congestion vasculaire dans les échantillons de tous les patients. Les cultures microbiologiques se sont révélées négatives, tandis que l'amplification en chaîne par polymérase à transcriptase inverse (RT-PCR) qualitative a détecté le SARS-CoV-2 dans le parenchyme pulmonaire et le liquide pleural de deux patients.

La COVID-19 provoque un SDRA progressif avec installation d'une hypoxémie sévère, à travers un double mécanisme : effet de shunt par des lésions alvéolaires diffuses et effet espace mort par des lésions thrombotiques dans les lits microvasculaires. Il semble raisonnable de gérer cette inadéquation du rapport ventilation-perfusion en utilisant une forte dose d'anticoagulant associée à des glucocorticoïdes.

Il est important à noter que notre travail a été publié le 10 décembre 2020 dans le Journal « **Biomed Research International** » avec une valeur de facteur d'impact de **2,5** ainsi que, 3 autres publications ont déjà cité notre étude, dont le **Lancet Respiratory** Journal.

ملخص

ازدادت الصعوبات خلال ادارة جائحة كوفيد-19المرتبطة بمتلازمة الضائقة التنفسية الحادة الناجمة عن التعفن الفيروسي سارس-كوف-2 , على الرغم من سهولة تشخيص المرض وفق تعريف برلين لعام 2012 , لوحظ تناقض كبير من حيث الخطورة بين الحالة السريرية للمرضى و النقص الحاد لنسبة تشبع الأنسجة بالأكسجين.

أمام تفاقم الوضعية الوبائية و عدم نجاعة التوصيات العلمية- نسبيا آنذاك- لعلاج هاته المتلازمة غير النمطية و غير المألوفة في أقسام الانعاش.

ارتأى الفريق الطبي فهم كيفية تأثير فيروس كورونا-19 المستجد على النسيج الرئوي بغية تحسين النهج العلاجي. اقتصرت الدراسات السابقة على التشريح المرضي لعينات الأنسجة الرئوية للمرضى المتوفين, بينما استهدف هذا البحث العلمي اخد عينات تلاث مرضى خاضعين للتنفس الاصطناعي بعد تدهور حالتهم الصحية الحرجة , و ذلك عن طريق عملية جراحية محدودة مع مراعاة الشروط الوقائية لتفادي العدوى.

كشفت النتائج على انتشار تلف الحويصلات الرئوية مع توضع أغشية الهيالين , و كذلك احتقان و تخثر الأوعية الدموية في جميع عينات المرضى. الى جانب ذلك, لم يتم العثور على تعفن بكتيري , و لا فيروسي و لا طفيلي , في حين تفاعل البوليميراز التسلسلي المعكوس للسارس كوف-2 كان ايجابيا عند مريضين.

يتسبب مرض كوفيد-19 في الاصابة بمتلازمة الضائقة التنفسية الحادة مع ظهور نقص تدريجي في نسبة الأكسجين الدموي الحاد , و يرجع ذلك لآليتين **shunt effect:** من خلال انتشار الاضرار السنخية الى جانب **dead space effect** بواسطة تجلط الدم المجهري في شعيرات الدموية الرئوية. يبدو منطقيا في هذا الاطار استخدام جرعة عالية من مضادات التخثر بالاضافة الى ڤلوكوكورتيكويد.

من الجدير بالذكر أن عملنا نُشر في 10 ديسمبر 2020 ، في مجلة " **Biomed Research International**" مع قيمة عامل التأثير **2.5** وقد استشهدت 3 منشورات أخرى بالفعل بدراستنا بما في ذلك مجلة **Lancet Respiratory Journal**.

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قسم الطبيب

أقْسِم بِالله العَظِيم

أن أراقبَ الله في مِهْنَتِي.

وأن أصُونَ حياة الإنسان في كآفّةِ أطوَارهَا في كل الظروف والأحَوال باذلة وسْعِي في انقاذها مِن الهَلاكِ والمرَضِ والألَم والقَلَق.

وأن أحفَظَ لِلنَاسِ كرَامَتهُم، وأسْتر عَوْرَتهُم، وأكتمَ سِرَّهُمْ.

وأن أكونَ عَلى الدوَام من وسائِل رحمة الله، باذلة رِعَايَتي الطبية للقريب والبعيد، للصالح والطالح، والصديق والعدو.

وأن أثابر على طلب العلم، وأسَخِّرَه لِنَفْعِ الإنْسَان لا لأذَاه.

وأن أُوَقّرَ مَن عَلَّمَني، وأُعَلّمَ مَن يَصْغرَني، وأكون أخـًا لِكُلِّ زَميلٍ في المِهنَةِ الطِّبِّيَة مُتعَاونِينَ عَلى البرِّ والتقوى.

وأن تكون حياتي مِصْدَاق إيمَاني في سِرّي وَعَلانيَتي، نَقِيَّة مِمّا يُشينهَا تجَاهَ الله وَرَسُولِهِ وَالمؤمِنين.

والله على ما أقول شهيدا

كليـــــــة الـطـب
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FACULTÉ DE MÉDECINE
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UNIVERSITÉ CADI AYYAD

سنة 2021 أطروحة رقم 219

ما تعلمنا عينة الرئة المفتوحة عن متلازمة الضائقة التنفسية الحادة في مرضى كوفيد-19 : الآليات، علم التشريح والأثار العلاجية.

الأطروحة

قدمت ونوقشت علانية يوم **2021/12/08**

من طرف

السيدة ياسمين أبو الرضى

المزدادة في 30 غشت 1996 بمراكش

لنيل شهادة الدكتوراه في الطب

الكلمات الأساسية:

متلازمة الضائقة التنفسية الحادة - عينة الرئة - تجلط الدم المجهري - الأضرار السنخية المنتشرة

اللجنة

السيد	م. عبد الناصر السمكاوي أستاذ في الإنعاش والتخدير	الرئيس
السيدة	ح. الرايس أستاذة في التشريح المرضي	المشرف
السيد	ح. الرباحي أستاذ مبرز في الإنعاش والتخدير	المشرف
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