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Coronavirus Pandemic

Serum fibrinogen levels and lung fibrosis in COVID-19 patients

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Abstract

Introduction: Coronavirus disease-2019 (COVID-19) has been declared a global pandemic. Along with multi-organ failure, increased fibrinogen occurs in severe disease and is converted to fibrin, which can trigger pulmonary fibrosis. This study aimed to analyse the correlation between serum fibrinogen levels and the occurrence of lung fibrosis in COVID-19 patients using the core biopsy technique.

Methodology: This was a prospective observational study in patients who died during severe COVID-19 treatment in the intensive care unit of a tertiary hospital. Serum fibrinogen levels were measured using a Sysmex Coagulometer based on the Clauss method, which is an automated coagulometric technique. The core biopsy procedure was performed in fibrotic areas identified by radiological imaging. The degree of lung fibrosis according to the Ashcroft scale. Results of fibrinogen levels, fibrosis incidence, and the degree of fibrosis were compared.

Results: There was an increase in fibrinogen with a mean level of 616.14 mg/dL, and 35 of 37 samples were positive for fibrosis. The Ashcroft scale score of 5 was the most common fibrosis degree (37.8%). Fibrosis was found among COVID-19 lung biopsies, and fibrinogen also tends to increase in lung fibrosis based on the Ashcroft score, despite no significant correlation between the serum fibrinogen levels and lung fibrosis degree ($p = 0.716$).

Conclusions: Pulmonary fibrosis was frequently observed in lung biopsy specimens from patients with fatal COVID-19. Serum fibrinogen levels tended to be higher in patients with fibrosis, they were not significantly associated with fibrosis severity as assessed by the Ashcroft scale.

Key words: COVID-19; serum fibrinogen; fibrin; lung fibrosis; Ashcroft scale.

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Introduction

The World Health Organization (WHO) declared COVID-19 a global pandemic in 2020. The Center for Systems Science and Engineering (CSSE) at Johns Hopkins University reported approximately 1400000 cases worldwide, with a mortality rate of 2.3%, and in some countries, it reached 7.2% [1]. Thousands of deaths caused by this disease have put the national health system under pressure [2]. COVID-19 is caused by SARS-CoV-2, an RNA virus belonging to the beta-CoV subclassification [3]. The primary manifestation of SARS-CoV-2 is the respiratory system, although other organs can also be affected [4].

Patients who died were primarily due to multi-organ failure, such as respiratory failure, shock, and acute respiratory distress syndrome (ARDS), with 94%, 81%, and 74% of cases, respectively. Simultaneously with the occurrence of multi-organ failure, there is also an increase in D-dimer and fibrinogen levels and prolongation of thrombin time in severe disease [1,3]. In the coagulation pathway, prothrombin is converted into thrombin, and fibrinogen into fibrin. Excessive fibrin deposits further increase the inflammatory response [5]. Interleukin (IL)-6 is an inflammatory cytokine synthesized in the airway epithelium that increases fibrinogen synthesis in the liver by five times. Therefore, increasing IL-6 levels also indicated an increase in fibrinogen levels [6]. This process can result in restoration of the standard lung structure or cause pulmonary fibrosis with structural distortion and irreversible lung dysfunction [7].

As fibrosis usually occurs due to tissue damage and

is associated with inflammation, collagen staining can confirm the presence of fibrosis. In Masson's trichrome staining, mature collagen produces a blue color [8]. According to Ashcroft *et al*., the fibrosis scale was assessed based on the affected lung [9]. The core biopsy technique takes lung tissue samples within 1 hour of death; another previous study used an autopsy technique [10]. There is limited data on the correlation between serum fibrinogen levels and the occurrence of pulmonary fibrosis in COVID-19 patients using the core biopsy technique, which is the basis for this study.

Methodology

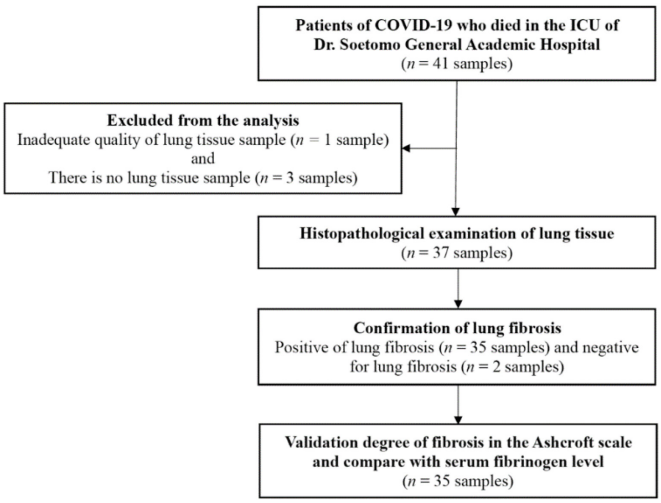
Study design

This was a prospective observational study in patients who died during treatment in the ICU of a tertiary hospital from COVID-19 from July to December 2020. The samples were collected based on consecutive sampling. Participants who fulfilled the inclusion criteria were included in this study until the end of the sampling period (Figure 1). COVID-19 diagnosis was made by history taking, physical examination, and supporting examinations [11,12]. In this study, the patients were admitted to the ICU with severe COVID-19, and all were administered intravenous corticosteroids, which served as a life-saving intervention aimed to improve pulmonary oxygen diffusion.

Ethics approval and consent to participate

The authors certify that they have obtained all signed and written informed consent from the patient's families or guardians. This study was approved by the Ethics Committee on July 6th, 2020, with the number 0022/KEPK/VII/2020.

Figure 1. Flow chart of study sample and selection.



Laboratory examination and core biopsy procedures

Laboratory test was conducted at early admission and subsequently re-evaluated according to the patient's condition. Serum fibrinogen was measured at early admission and re-evaluated upon clinical deterioration. The fibrinogen level was measured using a Sysmex Coagulometer based on the Clauss method, which is an automated coagulometric technique. In this study, all laboratory results were presented according to the latest data before the patients died.

The location of the core biopsy procedure was in a specific fibrotic area based on radiological imaging. Sampling was conducted after obtaining permission from the patient's families or guardians. Patients who died during treatment in the ICU underwent a post-mortem core biopsy performed on the lung within one hour after death to avoid lung tissue damage or unfitness, and were carried out in a negative pressure room. The procedure was performed without ultrasound guidance, so that the patient's last radiographic image was used as a guide in carrying out the core biopsy. The obtained tissue was fixed in formalin for more than 24 hours and examined according to the standards.

Histopathology and Masson's Trichrome staining

The lung tissue samples were placed in a sample pot containing neutral buffered formalin, labelled, and placed in a vacuum container to be sent to the anatomical pathology laboratory to check the suitability of the quality of the lung tissue taken through the core biopsy procedure. Lung fibrosis was observed by staining with Masson's trichrome and then microscopically with a light microscope, and the degree of fibrosis was determined using the Ashcroft scale. The degree of lung fibrosis according to the Ashcroft scale consists of the normal lung (grade 0), minimal fibrous thickening in the alveolar or bronchiolar (grade 1), moderate thickening of the lung wall without causing damage to the lung structure (grade 3), increased fibrosis accompanied by damage to the lung structure and the formation of fibrous bands or small fibrous sections (grade 5), severe distortion of lung structure and extensive fibrous areas; including the presence of "honeycomb" (grade 7) and total fibrous obliteration in the lung fields (grade 8) [9].

Results

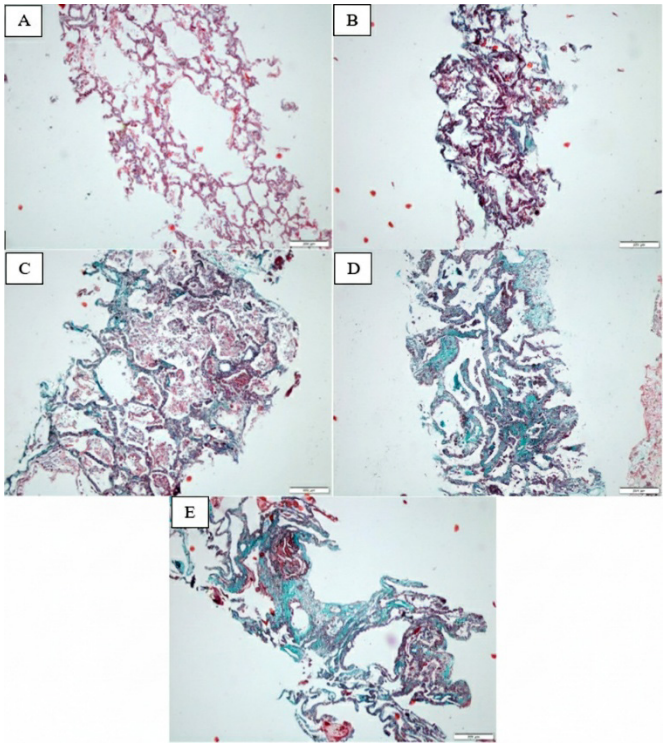
This study involved 37 of the 41 fatal COVID-19 patients under treatment in the ICU. Four samples from 41 research subjects were excluded because there was no lung tissue or the lung tissue was so small that histopathological examination could not be performed.

The mean age of study subjects was 48.86 year; most of them were men (70.3%). The mean length of stay was 10.81 days, and the most common comorbid was diabetes mellitus (75.7%). The mean fibrinogen levels were 616.14 mg/dL, with the highest frequency of abnormal results (fibrosis): 94.6% with a mean value of 637.37 mg/dL, compared to expected results (no fibrosis), 5.4% with a mean value of 244.55 mg/dL.

Table 1. Characteristics and laboratory results of the patients (n = 37).

Characteristics	Results
Sex	
Male	26 (70.3%)
Female	11 (29.7%)
Age (years)	
Mean ± SD	48.86 ± 2.09
Median	49
Minimun	24
Maximum	69
Age (years)	
10-19	0 (0%)
20-59	28 (75.7%)
≥ 60	9 (24.3%)
Length of stay (days)	
Mean ± SD	10.81 ± 0.88
Median	11
Minimun	3
Maximum	21
Comorbids	
Diabetes mellitus	28 (75.7%)
Hypertension	18 (48.6%)
Obesity	11 (29.7%)
Renal failure	3 (8.1%)
Hepatitis	1 (2.7%)
Pulmonary fibrosis	
Positive	35
Negative	2
Last radiological evaluation	
Bilateral pneumonia showing worsening condition	16
Bilateral pneumonia showing improvement	12
Bilateral pneumonia remains unchanged	6
Bilateral pneumonia, right side unchanged, left side improving	1
Bilateral pneumonia with minimal right pleural effusion	1
Heart and lungs show no abnormalities	1
Laboratory Results (Mean ± SD (min-max))	
Hemoglobin (g/dL)	11.23 ± 0.33 (6.5-15.8)
Leukocytes (/uL)	22876.76 ± 2198.10 (4950-63400)
Neutophils %	88.95 ± 1.31 (58.9-95.3)
Limphocytes %	5.86 ± 0.82 (1.6-24.8)
Fibrinogen (mg/dL)	616.14 ± 27.91 (165-920)
Ferritin (mcg/L)	1824.14 ± 239.07 (362-7481)
D-dimer (µg/mL)	6000.00 ± 1363.06 (340-35200)
C-reactive protein (mg/L)	14.78 ± 3.18 (0.7-115.2)
Procalcitonin (ng/mL)	16.20 ± 4.97 (0.01-100)
Neutrophil-lymphocyte ratio (NLR)	27.07 ± 31.50 (2.67-200)
Platelet-lymphocyte ratio (PLR)	330.56 ± 276.98 (17.48-1074.19)
Monocyte-to-lymphocyte ratio (MLR)	1.03 ± 0.97 (0.10-5.92)
Mean serum fibrinogen levels (mg/dL)	
Positive pulmonary fibrosis (n = 35)	637.37
Negative pulmonary fibrosis (n = 2)	244.55

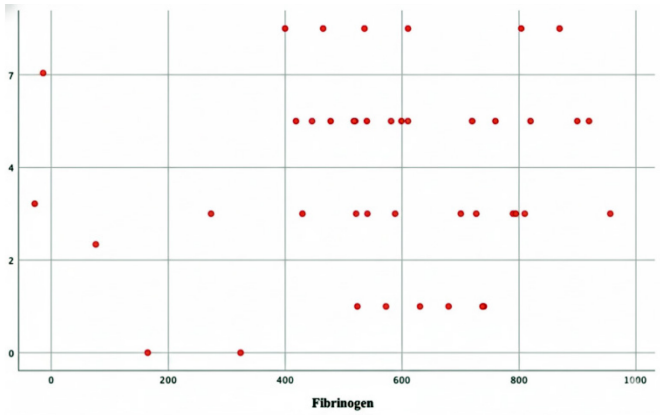
Figure 2. Degree of pulmonary fibrosis according to the Ashcroft scale in the sample. (A) Ashcroft scale 0, (B) Ashcroft scale 1, (C) Ashcroft scale 3, (D) Ashcroft scale 5, (E) Ashcroft scale 7.



These results were presented in Table 1.

In this study, all patients were admitted to the ICU with severe COVID-19 and died due to ARDS. Therefore, the COVID-19 severity for all patients was critical COVID-19 with ARDS. The degree of lung fibrosis using the Ashcroft scale found grade 0 for 5.4%, grade 1 for 16.2%, grade 3 for 24.3%, grade 5 for 37.8%, grade 7 for 16.2%, and grade 8 for 0% (Figure 2). The correlation test for serum fibrinogen levels using the Ashcroft Scale showed insignificant results

Figure 3. Scatter diagram of the correlation between serum fibrinogen levels and the degree of fibrosis according to the Ashcroft Scale. Spearman correlation = 0.062 and $p = 0.716$.



(Spearman correlation = 0.062 and p = 0.716). This result shows that serum fibrinogen levels do not correlate with the degree of pulmonary fibrosis in COVID-19 patients (Figure 3).

Discussion

A total sample of 37 COVID-19 patients (26 men and 11 women) met the inclusion and exclusion criteria. A previous study also reported that the number of male sufferers (56.4%) is more significant than that of females (54.4%). The most significant number of research subjects came from the adult, elderly, and adolescent age groups, at 75.7%, 24.3%, and 0%, respectively. A previous study reported that the highest number of COVID-19 deaths in the world also came from the elderly group who had a history of previous comorbidities [13]. The differences in data obtained in this study could be caused by several factors, one of which is the limitations of the ICU: patients accepted for intensive care have a high life expectancy, such as young age, minimal history of comorbidities, and risk factors.

The average duration of treatment obtained from the data was 10.81 days in the ICU. A previous study reported that the time required for shortness of breath is on the fifth day from onset, and the emergence of complications such as acute lung injury (ALI), ARDS, shock, and kidney failure on days 7-8 of treatment in the hospital [14]. Diabetes mellitus (DM) was the most common comorbidity in this study. In people with DM, there is an increase in blood sugar levels, which can cause an increase in the ability of the virus to infect humans. DM also increases the inflammatory response and worsens immune system function [15].

The severity of systemic inflammation in response to COVID-19 has a mechanism called cytokine storm or macrophage activation syndrome (MAS). Several markers can indicate the presence of an inflammatory response. Hemoglobin-related markers such as bilirubin and ferritin progressively increase as the disease worsens. Freely circulating heme usually injures endothelial cells; therefore, excess ferritin deposits can play a role in remodeling the vascular wall. However, progressive hyperferritinemia will significantly affect the integrity/permeability of the alveolar-capillary/cell membranes; therefore, inflammation, oedema, and lung cell necrosis will ultimately worsen the lung condition [16]. In this study, the average ferritin value was 1824.14 mcg/L, which indicated that the condition of the lungs worsened, causing high mortality in the sample. COVID-19 can simultaneously interact with endothelial cells, iron metabolism, and erythrocytes, causing hypoxia [17].

When tissue injury occurs, the coagulation cascade is active, and prothrombin is converted into thrombin, which plays a role in converting fibrinogen into fibrin. If the lungs are healthy, alveolar hemostatic balance is performed by antithrombotics and profibrinolytics. However, when disorders occur in the lungs, the balance shifts, thereby increasing procoagulant (including fibrinogen) and antifibrinolytic activities. Accumulation of fibrin in the intra-alveolar extravascular hyaline membrane is characteristic of ALI/ARDS [5]. Fibrinogen enters the interalveolar gap owing to increased microvascular permeability and transforms into fibrin in the interalveolar compartment. As the amount of antithrombotics decreases, there is an increase in intra-alveolar procoagulant activity [18]. Excessive fibrin deposits increase the inflammatory response by increasing pulmonary vascular permeability and activating endothelial cells to produce pro-inflammatory mediators [19]. Meanwhile, fibrinogen generally increases with an ongoing acute-phase response [20]. In this study, the average fibrinogen level was 616.14 mg/dL, with the highest frequency of abnormal results (fibrosis), namely 35 samples (94.6%), indicating that samples with ARDS had increased fibrinogen levels.

A study reported that increased plasma levels of fibrin degradation products, including D-dimer, are biomarkers of a worsening prognosis [20]. Coagulation dysfunction, as previously described, is common in COVID-19; therefore, an increase in D-dimer level was detected [21]. This is based on the data obtained if the average D-dimer value of the research sample is 6000.00 μg/mL. This figure is far above the normal range for D-dimer levels. Another marker is C-reactive protein (CRP), which is directly correlated with disease severity and progression [22]. CRP levels are generally elevated; however, procalcitonin values are usually typical. A high procalcitonin level indicates the presence of bacterial co-infection [14]. In this study, the average CRP value was 14.78 mg/L, and the average procalcitonin was 16.20 ng/mL. These data showed that the inflammatory markers in the samples, in the form of ferritin, fibrinogen, D-dimer, and CRP, increased with a mean value above the average value, indicating a hyperinflammatory reaction or what is usually called a cytokine storm [23]. This is also in accordance with a previous study that found an increase in serum ferritin, CRP, and D-dimer levels in COVID-19 patients [15].

There was an increase in fibrinogen with a mean level of 616.14 mg/dL, and 35 of 37 samples were positive for fibrosis. The Ashcroft scale score of 5 was

the most common fibrosis degree (37.8%). Fibrosis was found among COVID-19 lung biopsies, and fibrinogen also tends to increase in lung fibrosis based on the Ashcroft score, despite no significant correlation between the serum fibrinogen levels and lung fibrosis degree ($p = 0.716$). Of the 37 samples, two samples with Ashcroft scale grade 0 had serum fibrinogen levels of 324 and 165 mg/dL, which means they are still within normal limits. This showed that patients who die from COVID-19 do not always experience pulmonary fibrosis. There was no correlation between the serum fibrinogen levels and the degree of pulmonary fibrosis using the Ashcroft scale. The Scatter diagram also shows that no such correlation exists. Thus, according to the Ashcroft scale, higher serum fibrinogen levels are not always accompanied by a high degree of lung fibrosis. These results also showed that high serum fibrinogen levels can be found in mild degrees of fibrosis and vice versa. Serum fibrinogen levels that are not too high can be found in patients with high degrees of fibrosis. Fibrinogen sampling was not a routine examination of blood samples in COVID-19 patients in our hospital; therefore, the serum fibrinogen timeline during the patient's treatment is challenging to evaluate and analyze with other factors that influence the patient's condition.

Current evidence suggests that pulmonary fibrosis is a complication of COVID-19 infection [24]. In normal conditions/intact basement membrane, fibroblast tissue is broken down through a fibrinolytic process or remodeled into the interstitial tissue through epithelial and endothelial proliferation for the repair process. However, because of the significant damage to the basement membrane due to COVID-19, the activity of procoagulants (including fibrinogen) and antifibrinolytics will increase so that fibroblastic activity continues, and tissue progression occurs. Scar tissue formation can be either focal or diffuse, resulting in irregular alveolar structures. Hence, the excessive extracellular matrix deposition is central to pulmonary fibrosis [25,26].

In contrast, in samples with normal or low fibrinogen levels, lung tissue did not show any histopathological features of pulmonary fibrosis [9]. Fibrinogen plays an essential role in the coagulation cascade following tissue injury and acts as a procoagulant, resulting in increased fibrin deposition that affects fibroblastic activity [27,28]. Another previous study showed that all lung tissue from samples from COVID-19 patients who died experienced structural damage and severe inflammation. Fibrin deposits and collagen fibrosis are accompanied by damaged structures over large areas [29]. However, this study did not use a core biopsy but rather an autopsy technique.

Based on the Ashcroft scale, grade 0 indicates typical lung histopathology, while grades 1-8 indicate fibrosis. In this study, 35 samples with the Ashcroft scale varying from 1 to 7, indicating fibrosis in the sample. Two samples with an Ashcroft scale of 0 indicated no fibrosis. Fibrinogen also tends to increase in lung fibrosis based on the Ashcroft score, despite no significant correlation between the serum fibrinogen levels and lung fibrosis degree ($p = 0.716$). Therefore, with every increase in serum fibrinogen levels, the occurrence of pulmonary fibrosis will also be more significant. Samples with positive fibrosis had a mean value of 637.37 mg/dL, whereas samples with negative fibrosis had a mean value of 244.55 mg/dL (Table 1). This result showed that serum fibrinogen levels exceeded the average threshold, and the lung tissue showed a histopathological picture in the form of pulmonary fibrosis.

The limitation of this study is the number of samples, which included 37 cases and an imbalance between positive (n = 35) and negative (n = 2) fibrosis findings, which limited the possibility of performing robust statistical correlation analyses. In addition, this study only evaluated a single laboratory parameter (fibrinogen). Therefore, further studies with larger cohorts and more comprehensive parameters are warranted.

Conclusions

Fibrosis was found among COVID-19 lung biopsies, and fibrinogen also tends to increase in lung fibrosis based on the Aschrocft score, despite no significant correlation being found between fibrinogen levels and the degree of fibrosis. Ashcroft grade 5 was the most frequently found lung fibrosis degree, which found in the study samples (37.8%). These results suggest a possible role of fibrinogen in fibrosis development. Further studies with larger cohorts and more comprehensive parameters are required.

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Conflict of interest
No conflict of interest is declared.

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