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The Role of Fibrin Monomer Compared to D-dimer and CRP in Determining COVID-19 Severity

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ABSTRACT

Fibrin Monomer (FM), as a product of thrombin activity in cleaving fibrinogen, can be used as an early marker of thrombotic events in COVID-19 patients. D-dimer is a commonly used marker of hemostasis as a product of plasmin activity in cleaving polymeric fibrin. D-dimer is often used to help decide whether to initiate anticoagulant administration. This study aims to know whether FM can be used as a marker for thrombotic events such as D-dimer in COVID-19 patients; CRP levels were also examined to determine how inflammation affected the two hemostatic indicators. A total of 93 patients were confirmed with COVID-19 by PCR. The median (min–max) FM in the severe stage was 4.53 (2.26–58.20) μg/mL, whereas, in the mild-moderate stage, it was 4.21 (2.19 – 32.35) μg/mL. There are significant differences in median D-dimer levels in severe stages to mild-moderate, respectively 0.46 (0.14–7.58) and 0.7890, and ages. The level of FM that can be used to differentiate the severe stage is ≥ 4.46 μg/mL (sensitivity 56.3%, specificity 58.0%) as in the D-dimer level is ≥ 0.58 μg/mL (sensitivity 75.0%, specificity 65.2%). There is a moderate positive correlation between fibrin monomer and D-dimer, a weak positive correlation between D-dimer and CRP, and no correlation between FM and CRP. This study concludes that the FM median level is higher in severe COVID-19 than in D-dimer. Fibrin monomer levels have a positive correlation with D-dimer. Fibrin Monomer levels are not affected by CRP.

Keywords: Fibrin monomer, D-dimer, CRP, COVID-19

INTRODUCTION

Coagulation issues in COVID-19 patients are thrombotic events, also known as COVID-19-Associated Hemostatic Abnormalities (CAHA).[1] D-dimer, as a fibrin-related product, has been frequently studied in COVID-19. High levels are associated with increased mortality, but its role in predicting thrombotic events is still unclear. Fibrin Monomer (FM) is a promising marker for detecting thrombotic events earlier than other fibrin-related products.

Combining several hemostatic markers as recommended by ISTH for diagnosing DIC (increased PT, decreased platelet count, increased fibrin-related markers, and decreased fibrinogen) may be applicable in predicting hypercoagulopathy in COVID-19. The ISTH recommendation states increasing "fibrin-related markers" could be D-dimer, FM, or Fibrin Degradation Products (FDP).[2] It is necessary to understand where these markers take roles in hemostasis when comparing hemostatic parameters, especially fibrin-related markers such as D-dimer, FM, prothrombin fragment 1.2, and thrombin antithrombin complexes. Prothrombin fragment 1.2 and thrombin antithrombin complexes indicate fibrin generation catalyzed by thrombin. Fibrin monomer formation does not depend on fibrinolysis. Meanwhile, D-dimer is the degradation of fibrin complexes by plasmin. In several FM evaluation reports on COVID-19, it is stated that the combination of FM with D-dimer could be more helpful in determining anticoagulant therapy.

Fibrin degradation is formed by the action of 3 enzymes, namely thrombin, FXIIIa, and plasmin. First, thrombin as a serine protease enzyme will activate fibrinogen to become a fibrin monomer; then thrombin also activates FXIII to become FXIIIa. Second, FXIIIa will catalyze the formation of covalently bonded fibrin to crosslinked fibrin. Third, plasmin, as a fibrinolysis enzyme, will break down crosslinked fibrin into fibrin degradation products and D-dimers.[3]

The most consistent marker in COVID-19 patients when examining a thrombotic event is an increase in

D-dimer. D-dimers in the circulation indicate the cleavage of fibrin polymers by plasmin and correlate with excessive thrombus formation. Evidence of hypercoagulability in COVID-19 patients is still under observation using thromboelastography analysis. The International Society on Thrombosis and Hemostasis has proposed markers to detect coagulopathy in COVID-19 patients. These markers are D-dimer, PT, platelet count, and fibrinogen. These markers can help decide whether patients need hospitalization and also help monitor the administration of antithrombotic drugs.[1] However, it is necessary to consider whether there is a role for FM as a potential to predict thrombotic events and hypercoagulable processes relatively earlier than other hemostatic markers in COVID-19 patients. An inflammatory marker represented by CRP was used to see whether inflammatory markers had a role in increasing FM and D-dimer levels.

METHODS

This study was cross-sectional; all consecutive patients with RT PCR-confirmed COVID-19 who were hospitalized were included. Fibrin monomer and D-dimer examinations were carried out simultaneously according to the clinical needs assessed by the doctor. The plasma citrate was used to determine levels of D-dimer and FM, and serum was used to determine C-Reactive Protein (CRP) levels. D-dimer and FM measurements were conducted using reagent STA-Liatests® FM and hemostasis analyzer STA Compact Max3 from Stago. CRP measurements were conducted using reagen and immunology analyzer Cobas e311 from Roche Diagnostics.

The Ethics Committee of the Faculty of Medicine, Yarsi University, has approved this study, ethical approval number 285/KEP-UY/BIA/VII/2021.

Extracted data was analyzed with Statistical Package for the Social Sciences (SPSS) version 25. The D-dimer, FM, and CRP levels between two or more subgroups were analyzed with either Mann-Whitney or Kruskal-Wallis. The correlation was conducted with Pearson. The cut-off was conducted by ROC analysis. Youden's index is calculated by the formula YI = sensitivity + specificity - 1 for each coordinate point of the ROC curve to determine the cut-off value and maximum sensitivity and specificity.[4]

RESULTS AND DISCUSSIONS

The study population included 59 (63.4%) male and 34 (36.6%) female (Table 1). A total of 93 patients were diagnosed with COVID-19 with PCR tests. There were 83.4% male patients, most of them were over 40 years old, and 19.3% of patients had severe COVID-19. The FM level in severe patients seemed higher than in mild-moderate patients; respectively, the median (min-max) was 4.53 (2.26–58.20) and 4.21 (2.19–32.35). Although there was no significant difference between the two groups, this study did have data on patients with very high FM levels in the severe group.

The D-dimer levels in severe patients were significantly higher than in mild-moderate patients; respectively, the median (min-max) were 0.78 (0.18–2.7) and 0.46 (0.14–2.7). The D-dimer levels in the age category were significant, based on the post hoc test. Ages>60 had higher D-dimer levels compared with age ≤40 years and age 40 - ≤60.

The CRP levels vary widely according to age category and severity category because each patient has a different underlying disease and inflammatory response. In our laboratory, clinically, the normal level of FM was <5.2 µg/mL, D-dimer <0.5 µg/mL, and CRP <5mg/L.

Table 1. The profile of FM, D-dimer, and CRP level

Characteristics	n=93 (%)	FM (µg/mL) Median (Min-Max)	p-value	D-dimer (µg/mL) Median (Min-Max)	p-value	CRP (mg/L) Median (Min-Max)	p-value
Gender							
Male	59 (63.4)	4.21 (2.19-58.20)	0.943	0.59 (0.18-7.58)	0.180	7.70 (0.4–78.0)	0.986
Female	34 (36.6)	4.65 (2.19-22.07)		0.45 (0.14-4.34)		6.80 (1.0–77.9)	
Age							
≤40 y.o	31 (33.3)	4.21 (2.19–32.35)	0.443	0.46 (0.18–1.83)	**0.014**	6.80 (1.0–72.0)	0.078
40 -60 y.o	42 (45.2)	4.21 (2.19–58.20)		0.48 (0.14–7.58)		12.90 (0.4–78.0)	
>60 y.o	20 (21.5)	4.5 (2.55-30.15)		0.75 (0.21–3.55)		4.0 (0.6–28.6)	
COVID-19 severity							
Mild-moderate	75 (80.7)	4.21 (2.19–32.35)	0.579	0.46 (0.14–7.58)	**0.002**	7.7 (0.8–77.9)	0.745
Severe	18 (19.3)	4.53 (2.26–58.20)		0.78 (0.18–2.7)		5.15 (0.4–78.0)	

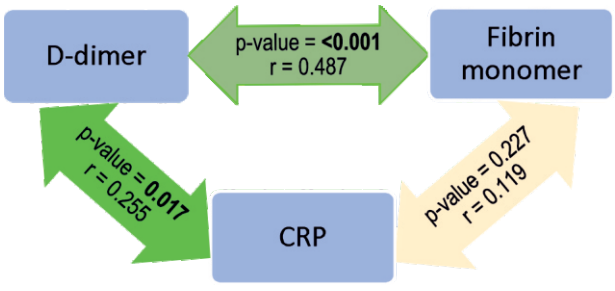

Figure 1. Correlation between D-dimer, FM, and CRP

Note: Pearson's correlation with normalized data, n=93. Dark green line: moderate positive correlation, light green line: weak positive correlation, yellow line: no significant correlation

Pearson's correlation shows a significant positive moderate correlation between FM and D-dimer levels. There was also a significant positive weak correlation between D-dimer and CRP levels. There was no significant correlation between FM and CRP levels (Figure 1).

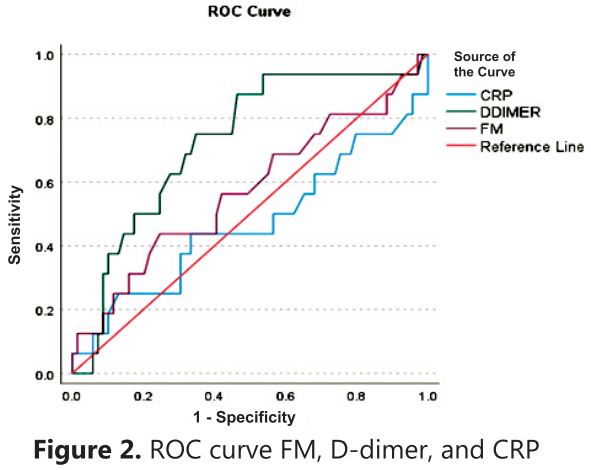

Figure 2. ROC curve FM, D-dimer, and CRP

The Area Under Curve (AUC) value of FM levels in patients with severe COVID-19 was 0.572 (95% CI=40.4%-73.90%), with a cut-off value of ≥ 4.46 µg/mL (sensitivity of 56.3% and a specificity of 58.0%). The AUC value of D-dimer levels in patients with severe COVID-19 was 0.726 (95% IC=59.1%-86.0%); using the Yougen index chart, the recommended cut-off value was ≥ 0.58 µg/mL (sensitivity of 75.0% and specificity 65.2%). The AUC value of CRP level in patients with severe COVID-19 was 0.468 (below 0.5) (Figure 2).

Hypercoagulability is often found in COVID-19 patients, especially those with severe clinical stages. This condition indicates a poor prognosis, including death. Increased coagulation cascade activation and excessive thrombin production in COVID-19 patients occur due to hyperinflammation. This process will cause the production of fibrin monomers to increase. Fibrin monomer is a product of thrombin-induced cleavage of fibrinogen; if thrombin production increases, FM also increases.

In this study, the median FM levels in mild-moderate stages were 4.21 (2.19-32.35), while in severe stages, they were 4.53 (2.26-58.20). Gordon *et al.*, in their study of 341 COVID-19 patients who were examined for FM and D-dimer on day 2 of admission, found a moderate correlation between FM and D-dimer, and 58% of FM levels were below 5 µg/mL.[5]

This study found the cut-off value to predict severe outcome for FM was 4.46 µg/mL with a sensitivity of 56.3% and a specificity of 58.0%, as for D-dimer the cut-off was 0.58 µg/mL with a sensitivity of 75.0% and a specificity of 65.2%. Another study found the optimal cut-off to predict thrombotic event for FM was 5.7 µg/mL with 67% sensitivity and 77% specificity, and for D-dimer was 3.3 µg/mL with 75% sensitivity and 71% specificity.[5]

This study showed no increase in FM levels in patients with severe COVID-19. However, some of these study subjects had relatively high levels of FM. These findings are in line with other studies. Sridharan *et al.* found that FM levels were elevated in only 18.5% of COVID-19 patients with elevated D-dimers.[6] Hardy *et al.* found that in 83% of COVID-19 patients who were treated in the ICU, FM levels tended to be lower than normal values; this was in contrast to D-dimer levels, which tended to be higher, implying that the level of FM in COVID-19 patients was not superior to D-dimers in predicting thrombotic events.[5,7] D-dimer levels have been proposed in multiple publications as a valuable marker for poor outcomes in COVID-19 patients.[7,8] Moosavi *et al.* showed that FM was also significantly elevated in patients with COVID-19 with poor outcomes, the median and range was 25 (7-150) µg/mL.[8]

The finding that the FM level is often low can be helpful if it can determine when FM increases in clinical conditions such as COVID-19 infection. After reaching the peak, FM levels decreased rapidly, and FM peak levels were transient, which immediately increased during intravascular fibrin formation. The explanation was that FM has a shorter half-life, about 2.3 hours, and its production is less dependent on fibrinolysis than D-dimer.[9] Therefore, it gives the impression that FM can also be used as a biomarker in detecting hypercoagulation earlier than other coagulation biomarkers, such as D-dimer in COVID-19 infection.

The finding of elevated D-dimer levels is very common in COVID-19; however, the incidence of

systemic coagulopathy is relatively infrequent. Thrombotic events occur more frequently than bleeding events in COVID-19 patients. Elevated D-dimer levels are associated with lung injury, and this reflects the presence of extravascular fibrin deposits.[5,10] Lung autopsy examination of COVID-19 patients showed widespread thrombosis and microangiopathy in pulmonary vessels. Furthermore, in COVID-19 patients, microthrombi in the alveolar-capillary were found ten times more often than in influenza patients with acute respiratory distress syndrome.[11]

D-dimer has a lower molecular weight than FM and could come from extravascular deposits such as the lungs and other organs. D-dimer levels are more dependent on the degree of alveolar inflammation and damage correlating with disease severity rather than intravascular fibrin formation. High D-dimer levels are also associated with the extent of lung injury, reflecting the occurrence of extravascular fibrin deposits. This phenomenon refutes the theory that intravascular fibrin formation is the leading site of D-dimer formation. In contrast, FM reflects the intravascular process. Fibrin monomer consists of two fibrin molecules in a soluble complex with a molecular weight of one thousand kDa that circulates in the blood more commonly from the blood vessel.[12]

Fibrinopeptide A and FM are proteolysis products of fibrinogen, which are thrombin-induced. Thrombin (a proteolytic enzyme) is a very specific serine protease that occurs after activating its zymogen (prothrombin). A fibrin monomer is produced in thrombin-induced fibrinogen proteolysis, which occurs before the formation of polymeric fibrin, which happens early in the process before plasmin acts. Fibrin monomer levels reflect thrombin activity and can be detected earlier than D-dimer.[13]

The most important result of this study is the finding that there are significant correlations between FM and D-dimer and higher FM levels in severe COVID-19. Thrombin is a proteolytic enzyme of the serine protease group, which is highly specific after activation of its zymogen; prothrombin will break down fibrinopeptide A and B from fibrinogen molecules into FM; this process occurs before the formation of crosslinked fibrin, while D-dimer is formed after formation of crosslinked fibrin by factor XIII and plasmin (fibrinolysis of crosslinked fibrin).[13,14]

Hyperfibrinolysis occurs in 97% of COVID-19 patients. Increased fibrinolytic activity by plasmin causes an increase in FDP. An increase in FDP was reported in all COVID-19 deaths. The rise of fibrin and FDP occurs during intravascular clotting.[15]

Fibrin monomer seems promising to predict thrombotic events, although this parameter has not been widely used in clinical implementation.[5] A meta-analysis study by Nugroho found that higher FDP on admission was associated with poor outcomes.[15] The non-survivors had higher FM levels than the survivors of early-stage disease of COVID-19. One of the implementations of using FM in non-COVID-19 was in post-operative day one patients with hypercoagulability; it was found that FM was more sensitive for predicting thrombotic events than D-dimer and other fibrin-related markers.

C-reactive protein has been used to predict respiratory distress with thrombotic complications.[8] In this study, the cut-off value of CRP to differentiate between mild and moderate stages of COVID-19 was 46 mg/L; other studies also put a threshold of CRP to predict mortality.[16] C-reactive protein plays a role in guiding clinicians to decide treatment, monitor therapy, and plan further treatment in COVID-19 patients. As an easy and available test, CRP becomes a potential parameter to evaluate in COVID-19 patients.

C-reactive protein examination is a valuable marker of the systemic inflammatory response in COVID-19. C-reactive protein levels rise 4-6 hours after stimulus and peak in 36-50 hours with a half-life of 19 hours. C-reactive protein levels can also change during chronic inflammation. The normal value for CRP levels by consensus is <5mg/L. C-reactive protein levels may generally be elevated due to mild to severe inflammation and bacterial and viral infections. According to the Diagnosis and Treatment Program of 2019 New Coronavirus Pneumonia, the CRP biomarker is reported to be associated with the severity of COVID-19. This finding is in line with other research stating that the CRP biomarker was found to increase in the early phase of infection in patients with severe COVID-19.[17]

C-reactive protein molecules are produced by the interaction of SARS-CoV-2 with Angiotensin I Converting Enzyme 2 (ACE2). It can be a marker of the acute phase inflammation associated with the prognosis and severity of COVID-19. The human CRP gene is located at 1q23.2. Synthesis occurs in hepatocytes as a response to the increase of inflammatory cytokines, especially IL-6 and IL-1.[18] The binding of CRP with the Fc receptor on the cell surface will cause the release of proinflammatory cytokines. High CRP levels are associated with increased mortality.[18]

Roles of CRP in SARS-CoV-2 infections start from the viral S protein, which binds ACE2 and forms a complex in the cell. The cellular complex decreases ACE2 and increases the activity of angiotensin II and ADAM-17 on the cell surface. Angiotensin II will bind to its receptor and induce the production of proinflammatory cytokines, Reactive Oxygen Species (ROS), fibrosis, vasoconstriction, and CRP, and increase the activity of ADAM-17. C-reactive protein is known as a molecule that can cause damage in SARS-CoV-2 infection. Once CRP binds to the Fc receptor, it induces a deleterious effect mediated by complement activation, which induces apoptosis. C-reactive protein and cytokine production can cause cytokine storm.

The pathogenesis of inducing coagulopathy in COVID-19 has not yet been explained. It is presumably similar to coagulopathy in sepsis/DIC. One of the signs of coagulation disorder is a significant increase in D-dimer and FDP, in addition to prolonged PT and thrombocytopenia.[19,20]

The main receptors of the SARS-CoV-2 are respiratory epithelial cells, lymphocytes, and vascular endothelial cells, which are sources of increased production of proinflammatory cytokines, destructive molecules, stimulation of cell death, and endothelial damage, which become the leading causes of coagulation problems. In addition, it is also influenced by the role of proinflammatory cytokines and chemokines such as TNF-α, IL-1β, and monocyte chemoattractant protein-1. An increase in these substances will recruit immune cells to infected tissue and cause damage to the host's defenses.[19,20] This explains ARDS, shock, and coagulopathy in severe-stage COVID-19.

Typically, the pulmonary alveolar spaces of the lungs provide a favorable environment for fibrinolysis. In ARDS, the fibrinolytic system can be depressed due to increased plasma and serum PAI-1. Plasmin, as a fibrinolytic substance, can cleave many proteins besides fibrinogen, such as misfolded and necrotic proteins, increasing D-dimer. An increase in D-dimer in all stages of CAHA indicates a functional fibrinolysis mechanism. However, in stage 3 of CAHA, the fibrinolytic system fails to resolve excess fibrin and necrotic materials. Experts believe that the increase in D-dimer is a result, not a cause, of disease progression. This outcome is due to the overwhelming failure of the hosts' fibrin and necrotic tissue in the lungs due to decreased plasmin-plasminogen activity.[1]

It is known that in COVID-19 patients, endothelial dysfunction often occurs. A reciprocal relationship exists between platelets, endothelium, and the immune system. The mechanism of endothelial dysfunction can be grouped into direct damage due to viral infection, increased ROS, hypercoagulability, and hyperinflammation.[20] Endothelial is one of the cells that have ACE2 receptors. The endothelium infected with COVID-19 undergoes cytopathic changes. Infection of the endothelium can lead to endothelialopathy (characterized by increased von Willebrand factor/VWF) or endothelium. Both increased thrombin production and decreased fibrinolysis result in hypercoagulability.[21,22]

This study's limitation was its cross-sectional design; there are variations in the timing of FM measurement relative to acute events, the cut-off values, and the levels of FM and D-dimer are influenced by the anticoagulant regimen in ward therapy.

CONCLUSION AND SUGESTIONS

Fibrin monomer levels seem promising as a candidate biomarker for early warning of ongoing thrombotic events. Further study is needed to set a starting time or repetition time and cut-off value, and it is necessary to consider examining this marker earlier in the disease process.

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