Increased D-Dimer in Covid-19 Patients: Article Review

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Abstract. COVID-19, which was first discovered in Wuhan, China in December 2019, has infected more than 200 countries. The virus that causes it is the Severe Acute Respiratory Syndrome Corona Virus 2 or better known as SARS-CoV-2. Symptoms in infected individuals vary widely from asymptomatic to severe ones. Individuals infected with COVID-19 may develop hypercoagulability and thrombosis. D-dimer is a degradation product of fibrin which indicates the formation of thrombin and dilution of fibrin by plasmin. Literature search was done in PubMed and Google Scholar from January 2020 to October 2021. The search method used the Boolean operators to link titles and abstracts with the keywords "D-Dimer" AND "COVID-19". The year of publication was all after 2019. The types of research were not limited, so all sources, meta-analyses, reviews, original articles, and reports, were collected.In COVID-19 patients, D-dimer can be an early marker to improve the management of COVID-19 patients. D-dimer can serve as a marker to determine the severity of lung damage. An increase in D-dimer indicates a degradation of accumulated fibrin in the alveoli and lung parenchyma as a result of lung trauma due to the reaction between the immune system and SARS-Cov-2 in the alveoli or lung parenchyma. The results showed that elevated plasma D-dimer levels were more common in patients with severe COVID-19 cases. The D-dimer is positively correlated with the prognosis of COVID-19. A fourfold increase in D-dimer or greater predicts in-hospital mortality.

Keywords: COVID-19 · D-Dimer · Hypercoagulability

1 Introduction

Since the first case of Coronavirus Disease 2019 (COVID-19) was discovered in Wuhan, China in December 2019, based on the Worldometer report on October 12, 2021, it has now spread to more than 200 countries [1]. The spread of this virus is very fast, going beyond previous estimates, and reaches a global scale that causes a pandemic in the world. The symptoms of each infected person are different from each other, so at the beginning of the attack some sufferers are diagnosed with another disease, making this disease called The Great Imitator of Disease. The patient's conditions can be asymptomatic,

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or with mild-moderate symptoms such as fever, cough, diarrhea, and loss of smell, or even with severe conditions such as difficulty in breathing or requiring a ventilator. The condition of decreased oxygen saturation in some individuals is not realized (happy hypoxia). With varying symptoms, the outcome also varies. After being infected, an individual can recover completely, whether being accompanied by symptoms or not, or still have leftover symptoms or long COVID and even death.

Some people develop hypercoagulability and thrombosis. Inflammation which occurs continuously in an effort to fight the virus that causes COVID-19 affects the walls of blood vessels, thereby increasing the risk of blood clots [2].

2 Method

The literature search was conducted in PubMed and Google Scholar from January 2020 to October 2021. The search method used the Boolean operators to link titles and abstracts with the keywords "D-Dimer" AND "COVID-19". The year of publication was above 2019. The types of research were not limited, so all sources were used, including meta-analyses, reviews, original articles, and reports. The difficulty in analyzing was that the tools and units used in each source were different, but most of them did not explain in detail. The information from these various sources was then analyzed, and conclusions were drawn.

3 Result and Discussion

3.1 COVID-19

The cause of COVID-19 is the corona virus, which is a single-stranded RNA virus. The coronavirus that causes COVID-19 is named SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) which was isolated from a pneumonia patient in Wuhan.

This virus infects epithelial cells in the lung and is able to enter macrophages and dendritic cells which induce the secretion of pro-inflammatory cytokines. SARS-CoV-2 infects alveolar epithelial cells through angiotensin-converting-enzyme 2 (ACE2) which is an Angiotensin 2 antagonist distributed in the cardiovascular system, kidneys, testes, lungs, and intestines [3].

The function of ACE2 is to cleave Angiotensin 2 to form Angiotensin 1–7, which mediates vasodilating, anti-inflammatory, and anti-proliferative protective effects. When the virus binds to the ACE2 receptor on the surface of the alveolar epithelial cells, ACE2 cannot perform its antagonistic function, leading to increased production of Angiotensin 2. This condition causes an inflammatory response, exudation of neutrophils, macrophages, and fibrin, which results in decreased pulmonary ventilation function and oxygenation [4].

The common clinical manifestations found in COVID-19 patients are fever and cough. However, other symptoms vary widely such as diarrhea, anosmia, shortness of breath, and others. The presence of dyspnea or shortness of breath indicates decreased lung function and oxygen deprivation. Viral infections cause inflammation in the body

that can lead to a cytokine storm, thus resulting in systemic immune damage and failure of several vital organs [4]. Although the lungs are the main organs infected with SARS-CoV-2, other organs can also be affected, such as the gastrointestinal system, liver, heart, neurological organ, and kidneys. Recent studies have shown that 20% of COVID-19 patients have abnormal coagulation function [5]. In addition, the incidence of venous thromboembolism (VTE) in severe COVID-19 patients is 25%, and 30% COVID-19 patients are diagnosed with pulmonary embolism. Monocytes and tissue cells are activated upon injury, causing the secretion of cytokines and various tissue factors, thereby leading to hypercoagulation of the blood. These conditions increase the risk of thrombosis and cause ischemia and hypoxia due to embolization of visceral vessels, eventually leading to critical conditions or death [4, 6].

Thrombotic complications and coagulopathy including disseminated intravascular coagulopathy are common in COVID-19, possibly reflecting the activation of the coagulation cascade due to viremia or cytokine storm but probably also caused by superinfection and organ dysfunction. Some sources say the increase in D-dimer occurs due to viremia and cytokine storm syndrome. The increase in pro-inflammatory cytokines (IL-2, IL-6, IL-8, IL-17, TNF-α) is insufficiently controlled by anti-inflammatory factors that overwhelm the coagulation cascade. Hypoxia predisposes COVID-19 patients to thrombosis. This condition often affects elderly patients and patients with comorbidities. Advanced age and common comorbidities such as hypertension, diabetes mellitus, and cardiovascular disease can lead to thrombotic events in patients [7].

3.2 D-Dimer

D-dimer is a fibrin degradation product that indicates thrombin formation and fibrin dissolution by plasmin. D-dimer assays in the laboratory are widely available, relatively inexpensive, and easy to perform [7]. Generally, an increase in D-dimer indicates an activation of coagulation process and fibrinolysis. However, high levels of D-dimer often occur in acutely-ill patients due to various infections and inflammations. Therefore, D-dimer levels are related to disease severity, not as a sign of a disease [2].

D-dimer values increase with age and in pregnancy. D-dimer also rises with the increasing severity of community-acquired pneumonia. An increase in D-dimer reaching 3–4 times the normal value indicates the presence of hypercoagulable blood and dehydration of the patient's body. Therefore, high levels of D-dimer may indicate increased fibrinolysis, thrombotic disease, cytokine storm, tissue damage, or sepsis in the body [7].

Elevated levels indicate that there is a state of secondary hypercoagulation and fibrinolysis in the body, which are so useful for the diagnosis of thrombotic diseases that they are used as biomarkers for thrombotic disorders [7]. Prior to the 2019 COVID-19 pandemic, D-dimer was not considered a useful biomarker for bacterial or viral pneumonia despite some evidence to the contrary. Since the COVID-19 pandemic, D-dimers have been identified as potential indicators for prognosis in COVID-19 patients. A study found that higher D-dimer values at the time of hospital admission significantly associated with the incidence of death in COVID-19 patients [8].

Several studies have been conducted to examine the relationship between baseline D-dimer measurements and disease severity and outcome. The results found that higher

D-dimer values at the time of hospital admission were significantly associated with in-hospital mortality in COVID-19 patients [8]. Autopsies of COVID-19 patients also revealed the presence of a widening fibrin thrombus. Small blood vessels and capillaries, and extensive extracellular fibrin deposition [9].

4 Discussion

Studies have shown that elevated plasma D-dimer levels are a useful early marker to indicate a coagulation disorder associated with mortality in COVID-19 patients [5, 10, 11, 12]. Thus, the D-dimer can predict the mortality of hospitalized COVID-19 patients. Furthermore, a fourfold increase in D-dimer from the normal value can effectively predict in-hospital mortality. Therefore, D-dimer can be an early marker to determine the management of COVID-19 patients [12]. Another study showed that overall dynamic changes in D-dimer levels were positively correlated with the prognosis and severity of COVID-19 patients [13, 14]. D-dimer can predict severe and fatal COVID-19 cases with moderate accuracy. In addition, D-dimer also shows high sensitivity and relatively low specificity for detecting the incidence of deep vein thrombosis related to COVID-19, suggesting that D-dimer can be used to detect deep vein thrombosis patients [15].

The results showed that elevated plasma D-dimer levels were more common in patients with severe COVID-19 cases. Unfortunately, there is no consistent limit value set to predict to date, or no threshold has been found to predict the prognosis of COVID-19 patients [5, 11]. The heterogeneity of the D-dimer examination may be due to different reference standards, which may affect the sensitivity in differentiating between severe and non-severe patients. In addition, the accompanying conditions of each patient are different. Different laboratories use different kits for measurements, and the accuracy and reliability of measurements may vary according to the kit manufacturer. Also, there are variations in reporting units. The analysis conducted on 20 papers on COVID-19 and D-dimer found that most of the papers did not report which manufacturer and reagent kit were used and whether D-dimer values were reported in D-dimer units (DDU) or Fibrinogen equivalent units (FEU). It was also found that nearly half of the studies did not report borderline normal values. This lack of standardization leads to possible bias in the analysis and interpretation of D-dimer values in COVID-19 [7].

The increase in D-dimer and disease severity are indication factors for starting treatment as soon as possible. Anticoagulation, despite the risk of bleeding, can be started after the diagnosis of disseminated intravascular coagulation (DIC) in COVID-19 patients. This condition is a major cause of death. However, the incidence of DIC and severe bleeding is rare in COVID-19 patients [16]. Current recommendations suggest routine use of anticoagulants, especially in patients with higher D-dimer levels [17].

Prophylaxis can be done by giving parenteral heparin preparations. This procedure is preferred in the hospital. Low Molecular Weight Heparin (LMWH) is recommended as the first-line therapy for prophylaxis of venous thromboembolism in hospitalized COVID-19 patients [18]. Administration of anticoagulants can indeed be beneficial for patients with severe COVID-19 [14]. However, its administration should be based on a comprehensive clinical assessment [2].

5 Conclusion

The results show that elevated plasma D-dimer levels are more common in patients with severe COVID-19 cases. The D-dimer is positively correlated with the prognosis of COVID-19. A fourfold increase in D-dimer or greater can predict in-hospital mortality.

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