

# Coagulation Dysfunction on COVID-19 With Diabetes Mellitus: an Overview

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## Abstract

COVID-19 is a severe acute respiratory syndrome caused by the SARS-CoV-2 virus. People with comorbidities such as Diabetes Mellitus are at higher risk of developing severe illness and even death. COVID-19 is not only dominated by respiratory manifestations but also by coagulation disorders found in severe COVID-19 patients. This is described by the significant increase in D-dimer levels in severe COVID-19 patients, which results in a high risk of mortality. According to the World Health Organization (WHO), 70% of global deaths are caused by non-communicable diseases. Some COVID-19 complications are non-communicable diseases, such as Diabetes Mellitus and coagulopathy.

In patients with Type 2 Diabetes Mellitus and COVID-19, there is a significant increase in hypercoagulability compared to non-diabetic patients. Diabetes Mellitus type 2 patients with COVID-19 are also more prone to hypercoagulability and complications compared to non-diabetic patients with COVID-19. Research has shown that the virus can induce the activation of coagulation factors, hypercoagulability, inflammatory response, and the production of cytokines in COVID-19 patients. The increased levels of D-dimer and fibrinogen suggest the occurrence of hypercoagulability. The presence of diabetes mellitus increases the risk and severity of COVID-19 disease and can affect the disfunction of various organs, including the lungs.

Keywords: COVID-19, Diabetes Mellitus, Coagulation

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## 1. Introduction

Coronavirus is a large family of viruses that can cause diseases in humans and animals. In humans, these diseases usually relate to respiratory infections, ranging from the common cold to more severe conditions such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS), which can be transmitted to other people. The new coronavirus, discovered in Wuhan, China, in December 2019, has been named SARS-CoV-2 and causes a respiratory infection known as COVID-19. Epidemiologically, the prevalence of Coronavirus Disease 2019 (COVID-19) has increased very rapidly worldwide. According to World Health Organization, (2020) COVID-19 was declared a global pandemic on March 9, 2020.

The cause of COVID-19 is SARS-CoV-2. In confirmed COVID-19 patients who undergo hemostasis tests, there is a prolongation of Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT), with the most significant finding being an increase in D-dimer levels in patients with severe symptoms (Yunus et al., 2022). In this case the significant increase in D-dimer levels in severe COVID-19 patients can result in a high risk of mortality.

In patients with Type 2 Diabetes Mellitus and COVID-19, there is a significant increase in

hypercoagulability compared to non-diabetic patients. Diabetes Mellitus type 2 patients with COVID-19 are also more prone to hypercoagulability and complications compared to non-diabetic patients In which stated by Minuljo et al., (2020) 42,9% patient died because of COVID-19 with Diabetes Mellitus with the average D-dimer was found to be 3937.4 ng/mL.

In this review, we summarize results of key studies, and discuss the current understanding of coagulation dysfunction in COVID-19 patients with. Diabetes Mellitus.

## **2. Coagulation Dysfunction on COVID-19 With Diabetes Mellitus**

### **2.1. Definition of Coagulation Dysfunction on COVID-19 With Diabetes Mellitus**

COVID-19 is caused by the SARS-CoV-2 virus. In confirmed COVID-19 patients, hemostasis tests show prolongation of Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT), with the most significant finding being an increase in D-dimer in patients with severe symptoms.

The relationship between the increase in Acute Respiratory Distress Syndrome (ARDS) and coagulation disorders is a known complication. Severe COVID-19 patients will show reduced levels of fibrinogen, which can be used to monitor patient conditions. Due to this, COVID-19 patients with severe symptoms need regular monitoring of PT and D-dimer levels for appropriate and timely treatment. Severe COVID-19 patients, thrombocytopenia was found to be low compared to patients with Disseminated intravascular coagulation (DIC). Thrombocytopenia is associated with a higher risk of developing diseases and death in COVID-19 patients. In severe COVID-19 patients with heavy symptoms, a decrease in thrombopoietin and fibrinogen levels is also observed.

The presence of Diabetes Mellitus further influences the magnitude of inflammatory and coagulation dysfunction in COVID-19. COVID-19 Diabetes Mellitus patients are more susceptible to coagulation dysfunction and inflammation when compared to non-COVID-19 Diabetes Mellitus patients (Varikasuvu et al., 2020).

### **2.2. Epidemiology of Coagulation Dysfunction on COVID-19 With Diabetes Mellitus**

Epidemiologically, the prevalence of Coronavirus Disease-2019 (COVID-19) is increasing very rapidly throughout the world. The COVID-19 disease was declared a global pandemic on March 9, 2020 (WHO, 2020). The first case of COVID-19 was discovered in December 2019 in Wuhan, China. Not long, within a few weeks this virus spread to all parts of China and within a month it spread to other countries. As of June 21, 2022, COVID-19 has been found in 216 countries, the number of people positively infected with the corona virus in the world has reached 544,761,091. Meanwhile, 6,341,655 people died. The United States is the country with the most COVID-19 cases with a total of 88,053,819 cases, followed by India with 43,320,845 cases, and followed by Brazil with 31,756,118 cases. The first COVID-19 cases in Indonesia were confirmed on March 2, 2020, totaling 2 people. As of June 21, 2022, of the 230 countries affected by the corona virus pandemic, Indonesia was in 19th place with 6,069,255 cases and 156,695 people died

(WHO,2022).

Meanwhile according to research by Jin et al., (2020) The prevalence of coagulopathy in Chinese COVID-19 inpatients is high which has the average D-dimer value of COVID-19 patients is 0.67  $\mu\text{g/mL}$  (95% confidence interval [CI]: 0.56–0.78), and 29.3% (95% CI: 20.1–38.5%) of patients showed elevated D-dimer values. Pathophysiology of Coagulation Dysfunction on COVID-19 With Diabetes Mellitus

The coagulation mechanism in COVID-19 is not yet fully understood, but it is believed to be related to several parts of DIC/bacteria-induced septic coagulopathy. The production of proinflammatory cytokines, increased damage related to molecular patterns, cell death mechanisms, and vascular endothelial damage are the main causes of coagulation dysfunction during severe infection. Patients with confirmed COVID-19 experience increased levels of fibrin, prolonged Prothrombin Time, and Activated Partial Thromboplastin Time, but not as severe as DIC. Proinflammatory cytokines and chemokines such as IL-1 $\beta$ , monocyte chemoattractant protein-1 (MCP-1), and tumor necrosis factor (TNF)- $\alpha$  are involved in COVID-19. (Yunus et al., 2022)

Immune will activate Tissue Factor in macrophages/monocytes and blood vessel endothelial cells. The coagulation cascade is initiated by Tissue Factor on the cell surface. In COVID-19 infection, coagulopathy is characterized by thrombocytopenia, increased fibrinogen, fibrin deposition and prolonged PT and aPTT. Thrombus formation in the microvasculature is related to organ dysfunction and tissue ischemia. Although bleeding and thrombosis in coagulopathy coexist, the dominant symptoms will differ depending on the virus that causes it. (Iba et al., 2022)

### 2.3. Symptoms of Coagulation Dysfunction on COVID-19 With Diabetes Mellitus

COVID-19 can cause abnormal blood clotting, which can lead to various complications. People infected with COVID-19 develop tiny blood clots that cause reddish or purple areas on the body, People who already have damage to the blood vessels from diabetes or high blood pressure may be at higher risk of developing blood clots due to COVID-19. The signs and symptoms of a blood clot in your leg or arm can include swelling, pain or tenderness not caused by injury, skin that is warm to the touch, and redness or discoloration of the skin. (Chen et al., 2022)

### 2.4. Diagnosis of Coagulation Dysfunction on COVID-19 With Diabetes Mellitus

D-dimer examination is useful for detecting abnormal blood clot formation or thrombotic events (indirect) and for assessing clot lysis or fibrinolytic processes (direct). The results of D-dimer levels have high sensitivity and negative predictive value for these two conditions. The indications for D-dimer examination are disseminated intravascular coagulation (DIC), deep vein thrombosis (DVT), pulmonary embolism (PE), venous and arterial thrombosis (VT and AT), anticoagulant and thrombolytic therapy, and as an additional parameter in coronary heart disease. The principle of D-dimer examination is by using monoclonal antibodies that recognize epitopes on the D-dimer fragment. There are several examination methods, including Enzyme-

Linked Immunosorbent Assay (ELISA), Latex Agglutination (LA), and Whole Blood Agglutination (WBA). The ELISA method is recommended as the gold standard examination. The results of the quantitative D-dimer examination are expressed in  $\mu\text{g/L}$  units. A D-dimer cutoff value with the latex agglutination method is 500  $\mu\text{g/L}$ . An elevated D-dimer level indicates a high level of fibrin degradation products, which means there is clot formation and breakdown in the body. A normal D-dimer level can be used to rule out differential diagnoses of blood clotting disorders as the cause of existing clinical symptoms. (Widjaja, 2010)

### 2.5. Complications of Coagulation Dysfunction on COVID-19 With Diabetes Mellitus

Coagulopathy will cause increased D-dimer and increased fibrinogen and then endothelial cells (EC) will be activated. The same thing also happens to platelets, leukocytes and monocytes which are also activated, resulting in macrothrombosis and microthrombosis. Macrothrombosis is thromboembolism in veins and arteries which will result in pulmonary embolism, while microthrombosis is a disease characterized by multiple organ dysfunction syndrome and microangiopathy which will result in Acute Respiratory Distress Syndrome (ARDS).

### 3. Conclusion

Diabetes mellitus patients who experience COVID-19 have a higher risk of death than COVID-19 sufferers who do not have a history of comorbidities. In COVID-19 patients, many other disorders are also found, such as cytokine storms and hs-CRP (High Sensitive C-Reactive Protein). This can cause hyperinflammation in the body. With this happening, the hyperinflammation that occurs can result in coagulopathy. Coagulopathy will cause increased D-dimer and increased fibrinogen and then endothelial cells (EC) will be activated. The same thing also happens to platelets, leukocytes and monocytes which are also activated, resulting in macrothrombosis and microthrombosis. Macrothrombosis is thromboembolism in veins and arteries which will result in pulmonary embolism, while microthrombosis is a disease characterized by multiple organ dysfunction syndrome and microangiopathy which will result in Acute Respiratory Distress Syndrome (ARDS). Apart from that, other comorbid diseases can worsen COVID-19, namely hypertension, obesity, malignancy, chronic lung disease, chronic liver disease, hepatitis B infection, and others. Sociodemographic factors are also one of the risk factors besides comorbidities that can increase the severity of COVID-19 disease, such as age, gender, education, and occupation. These things can increase the risk factors for mortality in COVID-19 patients.

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