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A Narrative Review on Evaluation of Hypercoagulability State in Severe Covid-19 Patients with Background Risk Factors

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ABSTRACT

Coronavirus disease (COVID-19) can induce coagulopathy at the base of sepsis-induced coagulopathy (SIC), which is an important cause of death in these patients. Cytokine storm causes imbalance in coagulation and fibrinolytic system. A combination of hypercoagulability state, decrease or inhibition of fibrinolysis and endotheliopathy causes thromboembolic events. Underlying diseases such as diabetes and hypertension with a high rate of mortality in COVID-19 and some conditions like aging and obesity are the main disorders with hemostatic disturbance and increase of coagulopathy. Therefore, it seems that the combination of COVID-19 infection and these risk factors increase the risk of thromboembolic complications all together.

Keywords: COVID-19, DIC, Coagulopathy, SarsCovid, Blood coagulation disorder

Introduction

Novel coronavirus disease (COVID-19) is an emerging coronavirus with severe respiratory involvement that first appeared in Wuhan, China, and then spread around the world **(1, 2)**. Up to now, more than 31 million people have been diagnosed with the virus, about one million of whom have died **(3)**. COVID-19 binds to angiotensin-converting enzyme 2 (ACE2) receptor on cell surface via the S protein **(4)**, and it can cause acute respiratory distress syndrome (ARDS). A common finding about sepsis-induced ARDS is that it is caused by extensive thrombosis **(5)**. Increased coagulation in very severe COVID-19 patients has been reported in various articles. Based on the existing evidence, increasing coagulation is one of the most common manifestations of COVID-19 and plays an important role in patient mortality **(6)**. Although this is rare for other coronavirus infections, it has been reported in severe influenza. In order to be able to differentiate between critically ill COVID-19 patients who need more care, even before the clinical symptoms worsen, we realized the patients' conditions, took the necessary care, and conducted several studies to differentiation of these conditions helps to find test to show coagulation disorders.

Materials and Methods

An extensive search was performed on Medline, Scopus, Web of Science, PubMed, and Google Scholar databases for the studies reporting coagulopathy, blood coagulation, disseminated intravascular coagulation (DIC), COVID-19, and SARS COVID published from 20 February 2020 to 29 May 2020. Two independent researchers performed the screening and extracted the related studies for final inclusion. No standardized protocol for the literature search was defined. We did not register the systematic review protocol because we anticipated very limited evidence available on the topic and due to the urgency of the matter.

Discussion

Hemostatic Imbalance

Patients with viral infections may develop sepsis-induced multiple organ failure (MOF). Sepsis is one of the most common and important causes of DIC. Progress to DIC occurs when monocytes and endothelial cells are activated by the release of cytokines, expressed by tissue factor and Von Willebrand factor secretion. Free thrombin in circulation can activate platelets and stimulate fibrinolysis **(7)**. Infectious diseases have been identified as an activator of inflammatory and coagulation responses in critically ill patients **(8)**. In 2017, the International Society on Thrombosis and Hemostasis (ISTH) provided criteria for defining sepsis induced coagulopathy (SIC) and overt DIC **(9-11)**. Coagulation disorders with SIC are less severe and occur at the beginning of the course of the disease and become DIC if the patient does not recover **(8-10, 12)**. In patients with COVID-19, it is called COVID-19 associated coagulopathy. In the early stages of the disease, coagulation test disorders occur but are not associated with bleeding in these patients **(13)**. COVID-19 patients have shown an increase in coagulation, which is associated with increased prothrombin time (PT), elevated levels of D-dimer and fibrinogen, and normal partial thromboplastin time (PTT). Persistent inflammatory response in critically ill patients (cytokine storm) acts as an important stimulus for coagulation cascade. Specific cytokines, including IL-6, can activate coagulation system and suppress the fibrinolytic system. Pulmonary and peripheral endothelial damage due to a direct viral attack may be an important factor in increasing coagulability **(14)**. The increase in D-dimer is due to an imbalance in the thrombotic and fibrinolysis systems **(15)**. Hypoxemia due to COVID-19 respiratory disease causes vasoconstriction and decreased blood flow, followed by endothelial damage **(16-19)**. Hypoxemia alters the endothelial phenotype by changing its normal state, which has anti-inflammatory and anticoagulant properties, in increasing coagulation and inflammation. This effect is caused by changing factors such as EGR 1 (early growth response cell 1) and HIF1 (hypoxia-inducible factor 1) **(18)**. Inflammatory cytokines based on endothelial damage causes increased secretion of large multimers of VWF (LMVWF) and then follows increasing of tissue factor (TF) **(18, 20-22)**. The presence of circulating monocytes, neutrophils, platelets, and micro particles attached to the activated endothelium causes a localized TF and neutrophil extracellular traps (NET), followed by activated coagulation with the TF/VII pathway, and then an increase in thrombin **(23)**. Increases in factors V, VIII, and fibrinogen are induced and the level of coagulation inhibitors such as anti-thrombin and protein C, S are decreased or normalized **(18, 21)**. The increased thrombin appears to play a major role in the development of venous macro thrombosis, while an increase in ULVWF plays a major role in the occurrence of arterial macro thrombosis **(24)**. In addition, studies have shown that the cause of ARDS in patients with COVID-19 is endothelial damage in the field of changings of micro-vascular in the pulmonary and alveolar vessels due to the connection of platelet/ULVWF-rich strings to endothelial and localized micro thrombosis **(18, 25)**. The reason for the increase in ULVWF is the effect of IL6 on reducing ADAMTS13 activity (26) and cytokinemia appears to play an important role in creating ADAMTS13 inhibitors **(27)**. In a study, Zhang observed that angiotensin-converting enzyme 2 (ACE2) receptors on monocytes are increased **(22)**. Based on the results obtained from flow cytometry, the present study found that the number of classic monocytes decreased in COVID-19 patients, but the number of non-classic and intermediate monocytes in these patients increased. It has also been suggested that monocyte series monitored with flow cytometry can be helpful in determining prognosis and treating patients with COVID-19 **(22)**, and can increase ACE 2 receptors in patients with COVID-19 and SARS **(28-31)**. D-dimer above 1mcg/mL at admission increases the risk of death by 18 times **(32)**. Coagulopathy is seen in 60% of patients with severe COVID-19 pneumonia **(21, 33)**. Twenty-five percent of patients with severe COVID-19 had lower limb thrombosis, in which the age was higher, the absolute lymphocyte count was lower, and PTT and D-dimer were increased. With a sensitivity of 76.9% and a specificity of 94.9%, the D-dimer above 3000 ng/mL can be a criterion for diagnosing deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE) **(34)**. PT, PTT, and thrombocytopenia was seen in 5%, 6%, and 12% of patients, respectively **(35)**. Plasminogen activator inhibitor-1 (PAI-1) is a serine proteinase inhibitor that is secreted by endothelial cells, vascular smooth muscle cells, and hepatocytes **(36)**. In plasma, PAI-1 induces clot formation, which can lead to heart attacks and strokes **(37)**. Another disorder affecting coagulation in patients with COVID-19 is an increase in PAI-1 **(38-40)**. This increase is due to two mechanisms: the first is the stimulant effect of angiotensin 2 on the release of PAI-1 from adipocytes by the type 1 angiotensin 2 receptor, and the second is the ACE-mediated bradykinin that causes vasodilation and release of PAI-1 from endothelial cells **(26, 39)**. The study also found that PAI-1 could be a strong factor in predicting the progression of acute lung damage caused by ARDS, with high levels of PAI-1 antigen (>640 ng/mL) predicting 100% mortality **(41)**. In one study, PT and PTT tests were normal in all patients at the time of hospitalization, but D-dimer and fibrinogen tests increased significantly at baseline. In this study, patients with more coagulation disorders had a worse prognosis and higher fibrinogen and C-reactive protein (CRP) level. Furthermore, an increase in PT and D-dimer on the fourth day of hospitalization was associated with a worse prognosis. Finally, it was concluded that patients with coagulation disorders and underlying disease are associated with worse prognosis and higher mortality **(2)**. The study by Tang found that

patients who died had lower levels of anti-thrombin and fibrinogen at the time of death. Also, 71% of patients who died had a DIC (according to the ISTH criteria) on the fourth day of hospitalization (21). In another study, the most common underlying diseases were hypertension, diabetes, heart, liver, and obstructive pulmonary diseases (1). In a study by Dawei *et al.*, the patients admitted to the intensive care unit (ICU) were older and had more underlying co-morbidities, including hypertension and diabetes, cardiovascular disease, and brain disease, respectively (42). In another study, 32% of the patients had underlying diseases, 20% had diabetes, 15% had hypertension, and 15% had cardiovascular disease with a mean age of 49 years (43).

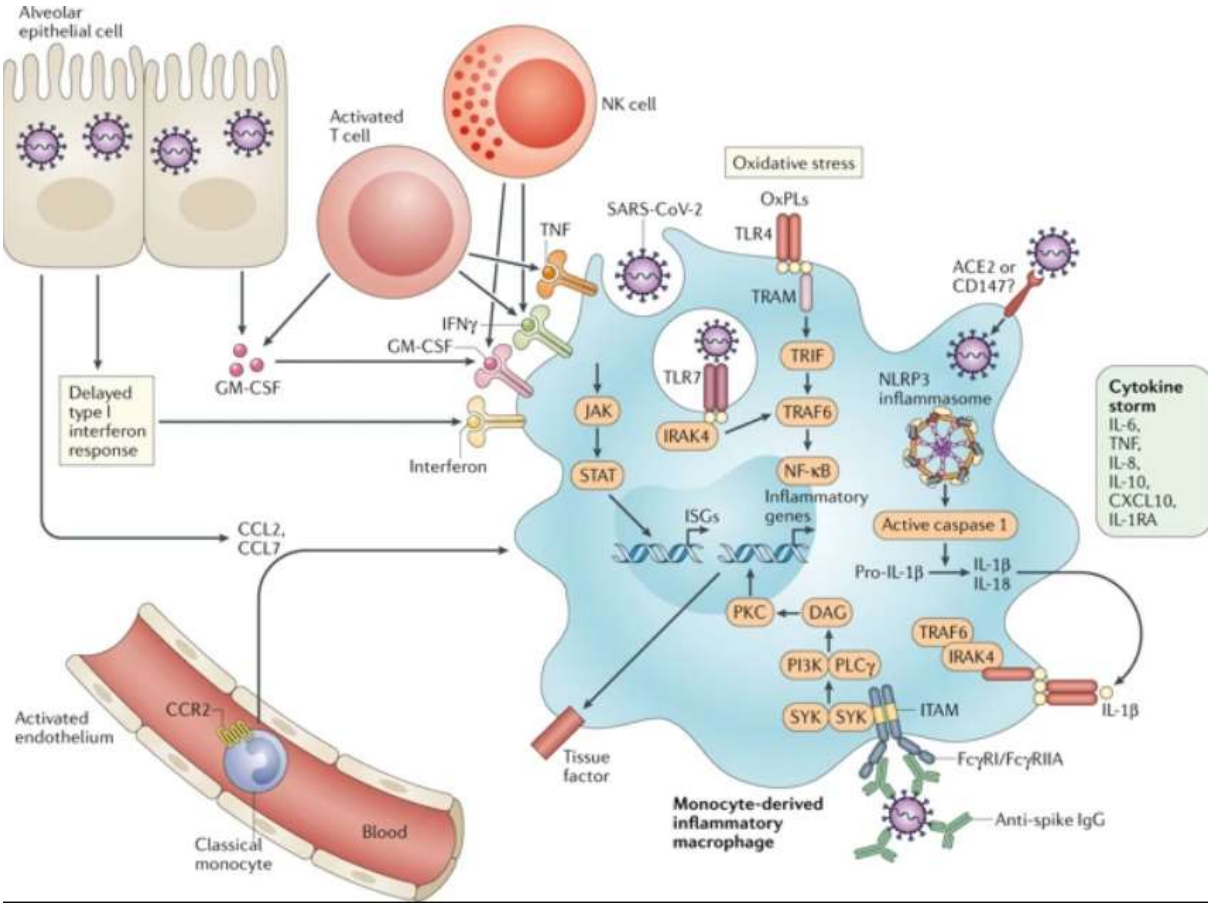

Figure 1. Activated monocyte-derived macrophages contribute to the COVID-19 cytokine storm by releasing massive amounts of pro-inflammatory cytokines. CCL, CC-chemokine ligand; CXCL10, CXC-chemokine ligand 10; ISG, interferon-stimulated gene; ITAM, immunoreceptor (67)

Background Risk Factors

Diabetes

Diabetes, as a hypercoagulable state, can both disrupt fibrinolysis pathways and impair endothelial function and platelets (44). Plasma levels of various coagulation factors, including fibrinogen and factors V, VII, VIII, X, XI, XII, and Kallikrein and von Willebrand increase in diabetes, while protein C decreases. Moreover, PAI-1 is increased in diabetic patients (45). The study by Paul showed that diabetes increases the risk of thromboembolic disease in young patients without comorbidities (46). In a study by Peng *et al.* on patients with type 1 Diabetes, it was found that during eight years of follow-up, after eliminating the effect of factors such as dyslipidemia, hypertension, fracture, obesity, and surgery, the risk of venous thromboembolism in the patients was five times more than non-diabetic patients (47). In another study, COVID-19 patients were divided into diabetic and non-diabetic groups. Diabetic patients had more severe lung involvement in computerized tomography (CT) scans and increased coagulation activity. Levels of IL6, CRP, ferritin, and D-dimer were higher, indicating that the cytokine storm was more severe in these patients; also, it was concluded that diabetic patients with COVID-19 would have more severe disease and worse prognosis (14).

Coronary Artery Disease

High blood serum cholesterol, which is associated with an increased risk of cardiovascular events, can increase high fibrinogen in the patients (48). Patients with fibrinogen levels above 3.5 g/l and cholesterol above 6.2 mmol/l have been shown to be six times

more likely to have a heart attack (49). In patients without cardiovascular disease, D-dimer levels appear to be associated with the prognosis of patients with COVID-19, but this relationship is clearly not present in patients with heart disease (50).

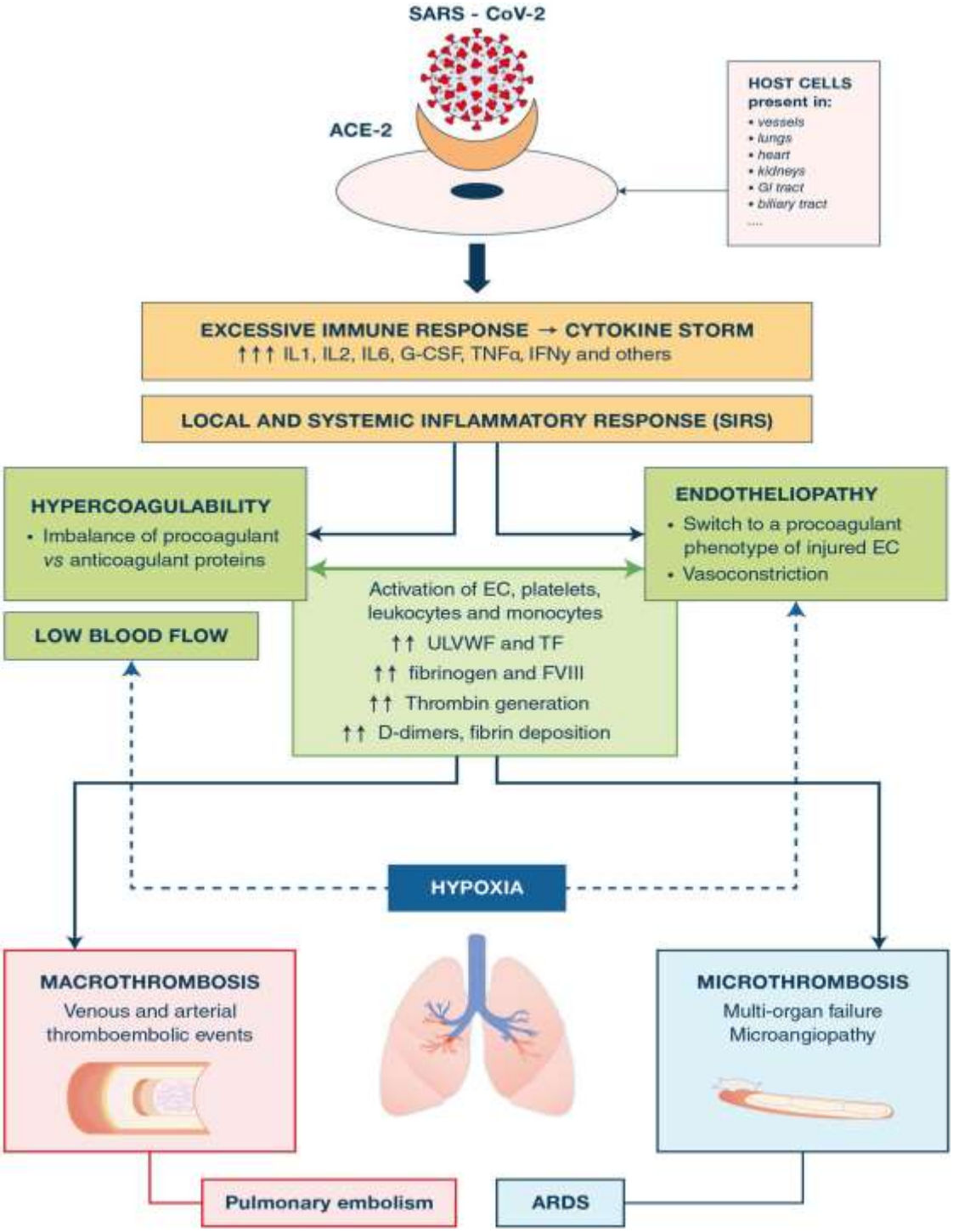

Figure 2. Pathophysiology for thrombosis in critically ill patients with COVID-19. The figure summarizes the steps of the thrombotic pathophysiological sequence that consecutively includes the aggression of the host cells by the SARS-CoV-2, the excessive immune response-induced cytokine storm, the local and systemic inflammatory response responsible for an endotheliopathy and a hypercoagulability state, leading to both systemic and macro- and micro-thrombosis. The exact pathophysiological mechanisms leading to severe pulmonary vascular dysfunction and ARDS have not been elucidated. *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *ACE-2* angiotensin-converting enzyme 2, *GI* gastrointestinal, *IL* interleukin, *G-CSF* granulocyte colony stimulating factor, *TNF* tumor necrosis factor, *IFN* interferon, *SIRS* systemic inflammatory response syndrome, *EC* endothelial cells, *TF* tissue factor, *ULVWF* ultralarge von Willebrand factor multimers, *FVIII* factor VIII, *ARDS* acute respiratory distress syndrome (68)

Hypertension

Although in patients with hypertension, highpressure blood contact with the vessel wall occurs, in contrast, thrombotic events are more common than bleeding **(51)**. Causes of homeostasis disturbance in patients with hypertension include end organ damage, like microalbuminuria, which indicates endothelial damage due to von Willebrand increase **(52)**. It is interesting that the duration and severity of hypertension have an increasing effect on von WillBrand and coagulation factors **(51, 53, 54)**. PAI-1 could be one of the causes of hypertension **(55)**. Briefly, studies show that increasing plasma PAI-1 significantly rises the risk of high blood pressure among American Indians independent of many known risk factors **(56)**. In the patients with hypertension, endothelial dysfunction, platelet hyperactivity disorder, and fibrinolysis disorder occur, all of which destroy the balance of homeostasis and cause hypercoagulable state and thrombotic complications **(57, 58)**.

Aging

Aging causes vascular and homeostasis changes that affect platelets, coagulation, fibrinolysis and endotheliopathy. Age-related sclerotic changes increase the risk of thrombotic complications **(59)**. Increased coagulation in the elderly may still be another cause of thrombotic tendency. Aging is associated with increased plasma levels of several coagulation factors (e.g. factor VII, factor VIII, and fibrinogen) and platelet activity **(60)**. The fibrinolytic system is disrupted over age. The long-term increases in euglobulin lysis time (ELT) duration and PAI-1 are impaired as well **(61-63)**.

Cancer

Malignancy is a thrombogenic disease some causes of which are increase in TF, fibrinogen, and PAI-1 **(64)**. In epidemiological studies conducted during the COVID-19 pandemic among a variety of risk factors and in prospective studies, the percentages of involved patients with cancer were lower than other underlying diseases **(65)**. However, the incidence of COVID-19 in these patients is higher than the normal population **(66)**.

Conclusion

It seems that important causes are involved in the occurrence of COVID-19 coagulation disorders. In general, a combination of factors influencing the increase in coagulation activity, inhibition of fibrinolysis due to increased PAI-1, the presence of microparticles, the role of monocytes, and endotheliopathy are the causes of this event. On the other hand, the most important underlying diseases with poor prognosis (including diabetes, hypertension, obesity, aging, and coronary artery disease) are among other causes of increased coagulation. Therefore, it seems that a combination of these underlying problems and the addition of disorders in critically ill COVID-19 patients is a good justification for increasing mortality in this patients. Also, the reasons for the lower incidence of COVID-19 in cancer patients in comparison to patients with other underlying diseases needs to be further investigated. Finally, it is recommended that future studies examine hemostatic system in underlying comorbidity and evaluate their changes with COVID-19 infection.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of Interest

Authors declared no conflict of interest.

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