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Coagulopathy and COVID-19

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Abstract:

Caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), coronavirus disease 2019 (COVID-19) is a potentially fatal disease as a global public health issue. Several mechanisms may be involved in mortality. One of these is coagulopathy and disseminated intravascular coagulation caused by SARS-CoV-2. When patients have coagulation disorders, treatment becomes more challenging and mortality rate increases accordingly. The aim of this article is to review the potential mechanisms of coagulopathy in COVID-19 in light of literature data.

Keywords:

COVID-19, coagulopathy, disseminated intravascular coagulation

Introduction

The pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome- coronavirus-2 (SARS-CoV-2) has become an important threat across the entire world. One of the important factors related to mortality is hypercoagulation, the potential mechanisms of which will be discussed in this article. As reported by recent studies, a severe COVID-19 infection is usually complicated with coagulopathy, and disseminated intravascular coagulation (DIC) may present in many cases died.[1-3] Due to evidence on viral infection and respiratory dysfunction, most of the severe COVID-19 patients meet the Third International Consensus Definitions (Sepsis-3).[4] In addition, the risk of venous thromboembolism (VTE) is increased for severe COVID-19 patients who are on prolonged bed rest and possibly hormone therapy. Due to these reasons, some experts have suggested an active use of anticoagulants (like heparin) for severe COVID-19 patients.[5] The International Society of Thrombosis and Haemostasis (ISTH) has recommended a new category of sepsis-associated DIC, called sepsis-induced coagulopathy (SIC), which describes a former stage.[6] It has been verified that patients meeting the diagnostic criteria of SIC benefited from anticoagulant therapy.[7] Severe COVID-19 patients often have coagulation disorder, and available data indicate that a high D-dimer level is a common laboratory abnormality and associated with mortality.[1,3] When patients have coagulation disorders, treatment becomes more challenging and mortality rate increases accordingly.

The study by Zhang *et al*. reported the clinical data of seven patients with COVID-19 and severe ischemia. The results of the study suggest that hypercoagulable state of critical COVID-19 patients requires immediate care, and extremity ischemia is associated

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with poor prognosis.[8] Clinical experience is still limited regarding how to manage such patients. For these patients, anticoagulation therapy may delay worsening of the disease and save some time for the treatment of primary disease. All seven patients in the said study had elevated myocardial injury markers and significant extremity ischemia, which suggested the presence of *in vivo* overt microcirculatory disorders. Multiple microthrombi were supported by the significantly elevated D-dimer, fibrinogen degradation products, etc., in patients in case of ischemia. When considered together with other laboratory parameters such as elevated fibrinogen, this suggested a tendency to hypercoagulability for this patient group.[8]

A retrospective study published by The Journal of the American Medical Association (JAMA) demonstrated a significant difference in D-dimer levels of 138 patients between those with and without the need of intensive care unit (ICU) (414 vs. 166 mg/L).[9] Reports from Wuhan Tongji Hospital further indicate that elevated D-dimer and fibrinogen degradation products are associated with mortality outcomes (2.12 vs. 0.61 μg/ml).[1]

An important elevation in D-dimer is believed to be linked with the formation of multiple microthrombi in the body. Recently published postmortem findings demonstrated vascular congestion and alveolar septal edema, mononuclear and lymphocyte infiltration, thrombus in veinlets and capillaries, vascular endothelial and intimal injury in cardiovascular system, and microthrombus in hepatic portal region, which suggests that COVID-19 may result in thrombus within multiple organs.[9-11]

All foregoing findings suggest that COVID-19 is likely to cause multiple microthrombi by intensively activating the coagulation system and exacerbating organ ischemia. There is limited research on hypercoagulable state due to COVID-19. The experience is mostly based on research on SARS, Middle East respiratory syndrome, and influenza viruses.

Hypercoagulability Mechanisms

Disseminated intravascular coagulation induced by viral infection and inflammatory storm (cytokine storm)

The SARS-CoV-2 protein infects human cells through angiotensin-converting enzyme 2 (ACE2). ACE2 is found in alveolar epithelial cells, endothelial cells of large and small arteries, small intestinal epithelial cells, immune system tissues, etc.[12] SARS-CoV-2 may attack directly vascular endothelial cells and activate the coagulation system upon vascular endothelial injury. SARS-CoV-2 may activate the innate immune system in order to clear the virus after it enters the body. However, excessive activation may lead to a cytokine storm, damage microvascular system, and activate coagulation system as it inhibits fibrinolysis and anticoagulation systems. Interleukin-6 is an important factor during the cytokine storm induced by SARS-CoV-2, which stimulates the liver to produce more thrombopoietin and fibrinogen.[13]

Antiphospholipid Syndrome Induced by Viral Infection

Antiphospholipid syndrome (APS) is a series of endothelial damage, thrombocyte activation, and thrombosis mediated by antiphospholipid antibodies, and it may manifest itself as catastrophic APS (CAPS) in some patients. CAPS and DIC have several overlapping clinical findings, which makes differential diagnosis difficult. APS manifests itself mostly with a tendency to hypercoagulability; the function of abnormal coagulation is not evident, and an extensive hypocoagulation phase is rare. Identification is based on measuring antiphospholipid antibodies. The literature has reported that viral infections such as hepatitis C virus, human immunodeficiency virus, parvovirus B19, and influenza viruses may cause CAPS.[14] A case report of 2013 demonstrated that the H1N1 virus was induced by CAPS, and the extremity ischemia was very similar to those in that study.[15] The mechanism of APS due to infection may be linked with molecular simulation. The structure of viral protein is similar to the structure of the body's own protein, which induces the production of autoantibodies.[8]

Other Factors

Other factors may occur during CoV infection, such as ischemia–hypoxia–reperfusion injury and medication-related hypercoagulable state. In a severe COVID-19 case, hypoxia does not only increase blood viscosity, but also induce thrombosis through a hypoxia-inducible transcription factor-dependent signaling pathway.[16] Recent reports indicated occlusion and microthrombosis formation in pulmonary veinlets of critical COVID-19 patients.[17] Therefore, an early initiation of anticoagulant therapy was recommended for severe COVID-19 in China.[5]

The study by Tang *et al*. compared 28-day mortality between cases receiving and not receiving heparin, and mortality was found lower with heparin use (in patients with SIC score ≥4 or D-dimer >3.0 μg/ml) than those without heparin use. Heparin therapy was reported to be linked with a better prognosis in severe COVID-19 patients with coagulopathy.[18] Another potential factor is stasis caused by immobility, in other words, related to hospitalization. Hospital-associated VTE includes the development of VTE during hospital

Table 1: Treatment of coagulopathy in coronavirus disease 2019 patients

Thrombosis prophylaxis in patients with D-dimer <1000 ng/ml
CrCl >: 30 ml/min
BMI <40 kg/m^2: Enoxaparin 40 mg/day
BMI >40/kg/m^2: Enoxaparin 40 mg 2×1 SC
CrCl <30 ml/min
Standard heparin 5000 U SC 2×1 or 3×1 or a reduced dose of low-molecular-weight heparin is recommended
Patients with D-dimer >1000 ng/ml or severe disease
Enoxaparin: 0.5 mg/kg q12 h SC
CrCl <30 ml/min: Standard heparin 5000 U SC 2×1 or 3×1 or a reduced dose of low-molecular-weight heparin is recommended

CrCl: Creatinine clearance, BMI: Body mass index

stay and up to 90 days of discharge. Patients infected with COVID-19 are at increased risk of hospital-associated VTE, especially when they are immobilized in the ICU. So then, elevated D-dimer and fibrinogen degradation products of hospitalized patients due to COVID-19 may be associated with poor prognosis.[19]

Because a decreased platelet count and a prolonged prothrombin time (PT) are associated with increased mortality, and hypofibrinogenemia is not common in sepsis, ISTH has verified the benefit of this simple score as they developed SIC criteria to guide anticoagulant therapy.[7]

In conclusion, elevated D-dimer and fibrinogen degradation products are associated with poor prognosis. According to the available data, coagulopathy should be monitored, and monitoring of platelets, PT and activated partial thromboplastin time, fibrinogen, and D-dimer.. All COVID-19 patients should be administered thrombosis prophylaxis, and antiplatelet drugs should be given to patients considered appropriate by the physician [Table 1].[20]

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Conflicts of interest
There are no conflicts of interest.

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