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Review Article

COVID-19-Related Hypercoagulability as a Long-term Complication in SARS-CoV-2: Lessons from SARS and MERS

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) leads to a various clinical and laboratory finding in affected patients. Similar to the previous outbreak, patients with SARS-CoV-2 showed elevated levels of D-dimer, thrombocytopenia, prolonged prothrombin time, and the activated partial thromboplastin time. Meanwhile, two lethal coagulation disorders of disseminated intravascular coagulation and pulmonary embolism have already been reported in patients with SARS-CoV-2. Although further cohort studies are needed to document long-term complications, considering the similar pathogenicity of SARS-CoV and SARS-CoV-2, the same chronic cardiovascular impairments could be expected.

Keywords: Severe Acute Respiratory Syndrome Coronavirus 2; Disseminated Intravascular Coagulation; Pulmonary Embolism; COVID-19

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Introduction

Novel coronavirus disease (COVID-19) is a newly discovered respiratory infection, caused by the new beta coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). Its outbreak was first identified in late December 2019 in Wuhan, China, and the number of patients is still continuing to grow (2). The virus has the ability of human-to-human transmission; so, airborne precautions are recommended to prevent further spread. Most of the COVID-19 patients presented with fever, dry cough, fatigue, myalgia, and dyspnea. Less common symptoms include headache, dizziness, insomnia, and intestinal complications (3). There is still a scarcity of data available about the disease manifestation, complications, diagnosis, and management (4).

According to a study by Guan et al., the typical laboratory findings in patients with COVID-19 include lymphocytopenia, leukopenia, thrombocytopenia, higher neutrophil counts, and elevated D-dimer (5). Tang et al. have reported various coagulation parameters in the cohort of 138 confirmed cases of COVID-19 among patients who

survived and died from the disease infection. They have found that the prothrombin time (PT) and the activated partial thromboplastin time (aPTT) were relatively longer in non-survivors and proposed a relation between these parameters and poor prognosis in patients infected with SARS-CoV-2 (6). Herein, we shortly describe the recent findings about the relationship between the coagulation indices in the blood of patients with COVID-19 infection and the disease prognosis.

Coagulation Parameters in Coronavirus Infections

The COVID-19 pandemic is the third outbreak of beta coronaviruses since 2003, in which the outbreak of severe acute respiratory syndrome (SARS) occurred. The second one was the Middle East Respiratory syndrome (MERS) in 2012. In patients suffering from severe COVID-19, PT and D-dimer levels were significantly higher than the normal levels, supporting that disseminated intravascular coagulation (DIC) may be prevalent in COVID-19 patients. Nevertheless, there was no critical variation in platelets count and activated partial thromboplastin time (APPT) between severe and mild forms of the disease (7).

Similar to COVID-19, SARS patients showed elevated levels of D-dimer, thrombocytopenia, and prolonged PT and aPTT (8). Another study showed that in the first two weeks of infection with SARS, 63% of patients had provisional rises of the APTT, while PT was normal in the majority of patients. There was no evidence of elevated D-dimers. DIC was seen in 2.5% of the patients, while the mortality rate was high in this group (9). In the outbreak of MERS, a study showed that 36% of patients had thrombocytopenia (10). Also, resembling COVID-19, DIC was a common finding in the non-survivors of MERS (11). Although the available data for MERS is limited, compared with the SARS and COVID-19, the thrombotic manifestations of the MERS are very similar to the others. As described before, the clinical phenotypes of these three viral respiratory syndromes are very similar in terms of coagulation issues. Therefore, lessons can be learned from previous experiences in this topic.

Hematologic Issues in COVID-19

Two possibly lethal coagulation disorders have been reported along with COVID-19 so far; DIC and pulmonary embolism (PE). Recently, Tang *et al.* noticed that 71% of died COVID-19 patients (the so-called non-survivors) matched the criteria of DIC, according to "International Society on Thrombosis and Hemostasis" diagnostic guidance. Strikingly, only one survivor was confirmed to have DIC (6), which makes it pragmatic to conclude that DIC worsens the prognosis of COVID-19 patients. In another recent study, according to computed tomography (CT) pulmonary angiography, the rate of PE in COVID-19 patients who were admitted to intensive care unit (ICU) was twice higher than the rate of PE in the control group with a similar severity score at the entrance in ICU (20% vs. 6%) (12). The prevalence of PE in COVID-19 patients admitted to ICU was 23% in another study, which is a relatively high prevalence. Also, patients with PE were more likely to need mechanical ventilation and critical care (13). The rate of PE in COVID-19 patients was even higher, compared with patients with influenza because of respiratory failure (7.5%). The rationale behind this is still unclear. However, it seems that higher levels of D-dimer, factor VIII activity, and von Willebrand factor (VWF) lead to a greater risk of PE in these patients. Therefore, CT pulmonary angiography could be recommended for such patients with COVID-19 upon admission, while PE is a lethal but potentially treatable condition (12).

Several concurrent mechanisms play a role in the pathogenesis of DIC. Excess fibrin formation caused by tissue factor-mediated thrombin generation and simultaneous impairment of physiological anticoagulant pathways, along with a deficit of endogenous fibrinolysis, contributes to the formation of DIC. Some inflammatory mediators, like tumor necrosis factor (TNF)-α, interleukin-1 (IL-1), and IL-6, can trigger the process. Neutrophil extracellular traps (NETs) may also promote coagulation (14). SARS-CoV-2 induces a systemic inflammatory reaction in the organs, causing a sudden release of pro-inflammatory cytokines (15, 16). This inflammatory system-wide reaction damages the microvascular system and makes it highly potential to form disseminated clots (17, 18). Moreover, viral infections lead to an imbalance between anti- and pro-coagulant factors in the blood by increasing pro-coagulant factors

(19). In such infections, platelets become activated and stimulate white blood cell (WBC) activation and clot formation in the site of antigen recognition, thus confining the infection (20). This can explain the thrombocytopenia and elevated D-dimer in the blood of COVID-19 patients.

DIC is not a primary condition, but is usually associated with underlying diseases. These underlying conditions must be taken into account in visiting patients with COVID-19. Although the primary treatment targets the underlying condition supportive treatments can be administered for patients with severe coagulopathies and other conditions like liver failure and renal dysfunction. The complexity of treating DIC patients is to lessen the risk of bleeding or thrombotic complications with timely and effective interventions. As low levels of platelet and coagulation factors can lead to bleeding, plasma and platelet substitution therapy along with prothrombin concentrates or other coagulation factor concentrates should be administered for patients with life-threatening hemorrhages. In the case of COVID-19-associated coagulation therapy, a recent study showed a markedly better prognosis in patients upon receiving low molecular weight heparin (LMWH) as an anticoagulant therapy (21-23). Also, in the case of PE, heparin could be beneficial in the prevention of thrombotic emboli, but the appropriate dosage is controversial (12).

Potential Long-term Coagulopathies

Since the start of the COVID-19 outbreak, studies have focused on the etiology, diagnosis, and therapeutic solutions, underestimating the costs of possible long-term complications. Once a large number of people are affected, and the acute phase is controlled, long-term outcomes will be a matter of debate.

As it is too early to speculate about possible long-term outcomes in COVID-19 survivors; data could be extracted from experiences in the previous SARS-CoV outbreaks. A study on 25 recovered SARS patients, 12 years after recovery, indicated a lower quality of life, compared with controls. An examination demonstrated that SARS-CoV survivors were more prone to tumors, inflammation, and some metabolic disorders. According to the survey, 60% had glucose metabolism alterations, 68% had lipid metabolism disorders and hyperlipidemia, and 44% experienced cardiovascular disorders (24). Although the association is currently being discussed, there is an assumption that COVID-19 survivors might suffer from the same chronic complications in the long-term. Considering the similar pathogenicity of SARS-CoV and SARS-CoV-2, the same chronic cardiovascular impairments could be expected (25).

Several case reports in the literature determined coagulation dysfunction as a major cause of death during the acute phase of COVID-19. Hyper-inflammation can cause microvascular damage, leading to thrombotic events and coagulopathies. Also, previous studies showed an association between high D-dimer levels and high abnormal coagulation activity. Other complications, such as hemodynamic changes, might play a contributory role in predisposing patients to thrombosis, as well as ischemia (26). In line with the fact that these complications might result in a progressive state, hospitalization might increase the possible risk of cardiovascular disease (27).

Conclusion

A high risk of developing cardiovascular complications, particularly coagulopathies in long term, is expected after COVID-19. So, a comprehensive cohort study investigating possible long-term cardiovascular complications and proper follow-up seems inevitable. As the number of COVID-19 patients is still increasing and thrombotic issues are a big part of COVID-19 complications, future planning for such long-term and debilitating complications must be taken into account.

Conflict of interests

The authors have no conflict of interest

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