Advances in the relationship between coronavirus infection and coagulation function

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To the Editor: It is reported that the patients with coronavirus disease 2019 (COVID-19) infection who were admitted to the intensive care unit (ICU) had longer prothrombin time and higher plasma D-dimer levels compared to those who were not admitted to the ICU. This indicates that these patients had a higher risk of thromboembolism. In addition, plasma tumor necrosis factor-α (TNF-α) levels in ICU patients were significantly higher than those in non-ICU patients, and plasma TNF-α levels, interleukin (IL)-1 levels and IL-8 levels in all infected patients were higher than normal.[1] The high expression of these inflammatory cytokines indicates that there is an inflammatory response in infected patients, and the inflammatory response is more obvious in severe patients. The findings of thrombus formation and high levels of inflammatory cytokines in COVID-19 patients are consistent with those in severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) patients. Since 2019 novel coronavirus (2019-nCoV), SARS-CoV, and MERS-CoV are all coronaviruses, and their genomic sequences are similar,[2] it can be considered that the thrombogenesis process of COVID-19 patients is similar to that of patients infected with other coronaviruses, as inflammatory factors cause hypercoagulability and lead to thromboembolism. In fact, opposite findings have been reported that there are no significant differences in prothrombin time, accompanied by or regardless of that in D-dimer levels between ICU and non-ICU patients.[3,4] We consider this discrepancy as a result of the limited quantity of subjects, and thus believe that a larger sample size is needed for this study. Whether the significant difference is absent or present, it is of significance for clinicians to obtain a clear basic understanding of the relationship between coronavirus and coagulation function as well as the influence of inflammatory factors on this process to make clinical judgement, provide early preventive anti-coagulation therapy for COVID-19 patients and eventually reduce the risk of thromboembolism.

Normal coagulation processes include platelet thrombosis, fibrin formation, and fibrinolysis. When the blood vessel wall is damaged and the subcutaneous tissue in the blood vessel comes into contact with the blood, the coagulation process starts. The platelet membrane protein and the collagen at the damaged vessel bind simultaneously to vascular hemophilia factor (VWF). By this bridging effect, platelets adhere to the damaged tissue. The platelets bound to the damaged tissues undergo morphological changes at the same time. This change is conducive to the aggregation of more platelets and more stable adhesion to the damaged vascular sites. These binding platelets activate prothrombin conversion to thrombin, which promotes activation of the clotting system, resulting in the formation of fibrin, which further stabilizes the formation of thromboembolus.

The patients with a coronavirus infection show hypercoagulability. This suggests that coronavirus infection can lead to hypercoagulability. Unfortunately, the specific mechanism is still unclear. However, coronaviruses may cause hypercoagulability through complex pathophysiological processes and have pro-coagulant effects throughout the coagulation process. Within the patients with SARS-CoV, the total VWF level and binding VWF level were increased, while the platelet level in blood circulation decreased, suggesting that coronavirus infection promoted the process of platelet thrombosis, thereby activating the subsequent coagulation cascade. In addition, as noted above, patients with a coronavirus infection have elevated levels of inflammatory cytokines, which have been shown to promote the clotting process in a number of ways. Studies have confirmed that the inflammatory factors can directly promote the generation of the tissue factors and reduce the activity of tissue factor pathway inhibitor, which results in an increased level of tissue factor. In addition, inflammatory factors reduce the level of thromboregulatory protein, which directly inhibits the synthesis, activation, and function of protein C, while increasing the consumption of protein C, finally leading to the activation of the coagulation

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cascade. In addition, the inflammatory factors can increase the formation of plasminogen activator inhibitor-1 (PAI-1), and the inhibition of protein C also reduces the lysis of PAI-1, which collectively causes a rise of PAI-1 levels and the inhibition of fibrinolysis, thus promoting the coagulation process and even the formation of microthrombi. When the coagulation system is stimulated, it can be utilized in turn by specific viruses for their infection. It is conjectured that 2019-nCoV can also proliferate and spread by virtue of the disordered clotting function. Moreover, coronavirus can be wrapped by fibrin from the coagulation system for ease of escaping from immunological recognition, leading to the proliferation as well as a prolonged course of the disease.

Current evidence shows that infection and cytokine storms triggered by 2019-nCoV can cause clotting disorders through various mechanisms, which may increase the risk of thromboembolism. This finding suggests that it is good practice to assess the risk of thrombosis in the diagnosis and treatment of patients with coronavirus infection. According to the Padua risk prediction score, those high-risk patients with scores ≥4, combined with a low risk of bleeding, should be given preventive anti-coagulant therapy and relevant examinations to prevent the occurrence of thromboembolism. Anti-coagulation treatment should be maintained throughout the whole therapeutic process. Novel opinions and suggestions are likewise needed regarding the relationship between COVID-19 and the coagulation system, especially those different from septic clotting disorders caused by other infections. Furthermore, glucocorticoids should be required to suppress inflammation so as to improve the hypercoagulation state. Severe COVID-19 patients need to go off glucocorticoid when cytokine storms are inhibited, because glucocorticoids can equally inhibit the normal immune system and promote the activation of the coagulation system.[5] The pathophysiological mechanism of coronavirus-induced thromboembolism needs to be further studied to provide a biological basis and to amend the SOP of clinical anti-coagulation therapy.

Conflicts of interest

None.

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