Coagulation System Abnormalities in Patients With COVID-19 Infection

COVID-19 Enfeksiyonu Olan Hastalarda Koagülasyon Sistemi Bozuklukları

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ABSTRACT

COVID-19 infection caused by Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) in China led to a pandemic all over the world. Although mortality rate between 4.3% to 14.6%, studies have shown that coagulation dysfunction is a major cause of death in patients with severe COVID-19 infection. The majority of the severely ill patients have underlying disease (i.e. diabetes, cardiovascular disease, hypertension) and initially present with respiratory insufficiency but some of them progress to systemic disease causing multiple organ dysfunction. This manuscript reviews coagulation system abnormalities in patients with COVID-19 infection.

Key Words: COVID-19, Disseminated Intravascular Coagulation, Sepsis

ÖZ

Çin'de Şiddetli Akut Solunum Yetmezliği Sendromu-Coronavirus-2'nin (SARS-CoV-2) neden olduğu COVID-19 enfeksiyonu tüm dünya çapında bir pandemiye yol açmıştır. Ölüm oranı %4.3-14.6 arasında değişmekle birlikte, çalışmalar koagülasyon disfonksiyonunun ağır COVID-19 enfeksiyonu olan hastalarda önemli bir ölüm nedeni olduğunu ortaya koymuştur. Ağır hastaların çoğunda altta yatan bir hastalık (diyabet, kardiyovasküler hastalık, hipertansiyon) vardır ve başlangıçta solunum yetmezliği ortaya çıkar, ancak bazıları çoklu organ disfonksiyonuna neden olan sistemik hastalığa ilerler. Bu yazıda COVID-19 enfeksiyonu olan hastalardaki koagülasyon sistemi bozuklukları tartışılmaktadır.

Anahtar Kelimeler: COVID-19, Dissemine intravasküler koagülasyon, Sepsis

INTRODUCTION

COVID-19 infection caused by Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) was first described in December 2019 in Wuhan, China (1). After that, the disease has become a worldwide threat with estimated mortality rates ranging from 4.3% to 14.6% (1,2). Although the mortality is predominantly related to the acute respiratory distress syndrome, COVID-19 associated coagulopathy was also reported in several studies (3-5). Because of SARS-CoV-2 has been detected in various cells in the body, high number of proinflammatory cytokines to be released, promoting a systemic inflammatory response syndrome (SIRS), accelerating cell death in the lungs, liver, heart, kidneys and the adrenal parenchymal organs, which can ultimately lead to multiple organ dysfunction syndrome (MODS) (6). As inflammatory reactions occur in the all organs of the body, the microvascular system is damaged, leading to abnormal activation of the coagulation system, which pathologically manifests as generalized small vessel vasculitis and extensive microthrombosis (3-5). This manuscript reviews coagulation abnormalities in patients with COVID-19 infection.

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Inflammation and Coagulation

SARS-CoV-2 targets respiratory epithelium and it enters host cells through the angiotensin converting enzyme 2 (ACE2) receptor (1,2). This viral invasion initiates complex systemic inflammatory response as a part of innate immunity. Microorganisms and their components bind to the pattern-recognizing receptors on host defense cells inducing proinflammatory cytokines and coagulation. Coagulation is activated by the inflammatory response through several mechanisms. Products of microorganisms, polyphosphates, activates platelets and FXII that triggers the intrinsic coagulation pathway. Activation of complement system also activates coagulation. Additionally, neutrophil extracellular traps (NETs) composed of components of cell-free DNA and histones activate the contact pathway of the coagulation. Finally, the proinflammatory cytokines activate the vascular endothelial cells and as a consequence of prothrombotic effects, endothelial injury occurs (7). These cytokines promote release of ultralarge vonWillebrand factor (vWF) multimers, production of tissue factor (TF) and factor VII (FVII) leading to increased thrombin generation, and decrease levels of endogenous anticoagulants such as tissue factor pathway inhibitor (TFPI), antithrombin, and activated protein C. The interaction between endothelial cells, platelets, macrophages, neutrophils, the complement system and the coagulation system results in a hypercoagulable state with increased levels of procoagulants, decreased levels of anticoagulants, and depressed fibrinolysis. If the activation of coagulation system cannot be taken under control, can lead to sepsis-induced disseminated intravascular coagulation (DIC). Sepsis-induced DIC (SIC) is characterized by an infection and systemic activation of coagulation, which can cause organ dysfunction as a result of interactions between coagulation and inflammation. Coagulation abnormalities associated with SIC are less severe and occur earlier in patients with sepsis than DIC. If the underlying etiology of sepsis is not resolve, the changes continue with SIC progressing to DIC. The International Society of Thrombosis and Haemostasis (ISTH) has developed diagnostic criteria for DIC and SIC score (8).

Initial reports from China during COVID-19 outbreak have disclosed that the severely ill patients had met both DIC and SIC criteria (1,9-11). Chen et al.(1) analyzed the characteristics of the first 99 patients hospitalized in Wuhan, and reported 5% of the patients had an elevated prothrombin time (PT), 6% had elevated activated partial thromboplastin time (aPTT), and 36% had elevated D-dimer. Wang et al. (9) also analyzed 138 patients with COVID-19 infection and reported 38 of them had transferred to the intensive care unit. When non-survivors compared with the survivors, showed higher D-dimer levels (2.12µg/ml vs. 0.61 µg/ml) and progressive lymphopenia (9). Another study included 191 patients has reported to the mortality rate of 28% and elevated D-dimer, PT, interleukin-6, and troponin levels were associated with mortality. Multivariate analysis showed that a D-dimer level higher than 1.0 mcg/

mL on admission had predicted mortality (OR 18.42 [CI 2.64-128.55], p=0.003) (10). In the largest analysis of clinical cases in China, which included 1099 patients, it was noted that D-dimer was ≥0.5 mg/L in 46.4% of the patients, and it was higher in those with severe disease compared to non-severe group (11).

Tang et. al (3) analyzed the coagulation parameters of the 183 patients with COVID-19 positivity. Totally, 15 (71.4%) of the 21 patients who did not survive, and 0.6% of the survivors met criteria of DIC according to ISTH with median 4 days after admission. On admission, the non-survivors had significantly higher D-dimer and fibrin degradation product (FDP) levels, and longer PT compared to survivors. By the late hospitalization, non-survivors had findings of progressive DIC with decreased fibrinogen and antithrombin III levels, this suggested that coagulation parameters during the course of the disease significantly associated with prognosis (3). Ranucci et al. (12) noted elevated IL-6 levels on admission in 16 COVID-19 patients with acute respiratory distress syndrome (ARDS) requiring mechanical ventilation. They reported that increased interleukin-6 (IL-6) levels correlated with increased fibrinogen levels, demonstrating the link between inflammation and procoagulant changes (12). All of the results of these studies revealed that during the early phase of COVID-19 infection, coagulation abnormalities are seen but do not cause clinical bleeding. As the disease get severe, coagulation abnormalities progress to SIC and then to DIC. Additional factors including medications used and underlying diseases (diabetes, hypertension, and cardiovascular disease) may affect to progress to SIC or DIC. Consequently, coagulation abnormalities occur in COVID-19 infected patients are most likely a result of the excessive inflammatory response (3,13).

A recent post-mortem case series regarding COVID-19 associated lung pathophysiology disclosed that in patients with severe COVID-19 infection, there was diffuse alveolar damage with a mild to moderate mononuclear cell infiltration consisting of CD4+ cell aggregates around thrombosed small vessels, and associated hemorrhage. Another mechanism that may have contributed to death is thrombotic microangiopathy which was restricted to the lungs. This process may involve activation of megakaryocytes, possibly those native to the lung, with platelet aggregation and platelet-rich clot formation, in addition to fibrin deposition. Small vessel thrombus formation in the lung periphery was associated with foci of alveolar hemorrhage in many cases (14). Collectively, all these data suggest that the diffuse pulmonary inflammation observed in COVID-19 is associated with a novel pulmonary-specific vasculopathy which recently termed pulmonary intravascular coagulopathy (PIC) as distinct to DIC. Though the pathophysiology of PIC is scarcely understood, ACE-2 receptor used by SARS-CoV-2 is expressed on both type II pneumocytes and vascular endothelial cells in the lungs, which may suggest the possibility of direct pulmonary endothelial activation and damage (5). A recent report demonstrated viral inclusions within endothelial

cells and sequestered mononuclear and polymorphonuclear cellular infiltration, with evidence of endothelial apoptosis in the lungs (15). In the setting of PIC, it was hypothesized that the refractory ARDS occurred in severe COVID-19 is related to ventilation (V) and perfusion (Q) disequilibrium in the lungs where alveoli and pulmonary microvasculature exist in close anatomical localization (5). Moreover, emerging data showed that severe COVID-19 is also associated with a significant increased risk for developing deep vein thrombosis and pulmonary embolism (16,17).

Management of Coagulopathy

Based on the experience from published literature, serial measurement of PT, PTT, D-dimer, platelet count and fibrinogen can be helpful in determining prognosis in COVID-19 patients requiring hospital admission. Evaluation of endogenous coagulation system with PT and PTT can be used to determine heparin dosage or hypercoaglable state. Prolonged thrombin time (TT) and decreased fibrinogen can suggest hypofibrinogenemia. For the evaluation of fibrinolytic system, D-dimer and FDP are necessary, if they increased indicates the possibility of thrombosis, as deep vein thrombosis, pulmonary embolism, myocardial infarction or cerebral infarction (18,19). If there is worsening of these parameters, more aggressive critical care support is necessary and 'experimental' therapies and blood product support as appropriate should be considered. If these markers are stable or improving together with the patient's clinical condition, it gives a confidence for stepdown of treatment. In case of multi-organ failure in patients with sepsis and coagulopathy, inhibiting thrombin generation may have beneficial in reducing mortality (8). Additionally, ISTH DIC score is recommended to diagnose COVID-19-related coagulation dysfunction, ≥5 points is associated with overt DIC. Unfractionated heparin / low molecular weight heparin (LMWH) are recommended for anticoagulant therapy to severe COVID-19 patients with coagulation dysfunction (17,18). Classic heparin can be preferred for a short half-life, a convenient monitoring process and can be neutralized with protamine (18). LMWH has a longer half-life, a prophylactic dose (4000 U enoxaparin once daily) should be considered in all patients (including non-critically ill) who require hospital admission for COVID-19 infection, in the absence of any contraindications (active bleeding and platelet count less than $25x10^9$ /L; monitoring advised in severe renal impairment; abnormal PT or aPTT is not a contraindication). LMWH is also protect critically ill patients against venous thromboembolism and have anti-inflammatory properties which may be an added benefit in COVID infection (19). Tang et al.(20) reported the benefit of this approach in 449 patients with severe COVID-19; of which 99 (22%) received heparin (94 patients with enoxaparin, and 5 with unfractioned heparin) at prophylactic doses. Although no difference was observed in the 28-day mortality in those received heparin compared to those who did not, but a stratification by SIC score identified lower mortality in patients treated with heparin when

SIC score was >4. A similar reduction of mortality was also noted in those with D-dimer > six-fold of upper limit of normal (32.8% vs 52.4%, P=0.017) (20). Fogarty et al. also analyzed whether there were differences in coagulopathic features in 83 COVID-19 infected Caucasian compared to Chinese patients. Unless contraindicated all of the hospitalized patients with COVID-19 received weight- and renal- appropriate doses of LMWH as thromboprophylaxis. D-dimer levels were above the normal range in 67% of the patients, whereas PT and PTT were normal on admission. However, fibrinogen levels were significantly increased probably due to acute phase reactant. During hospitalization period, none of the patients developed systemic DIC, but progressive increase is seen in D-dimer levels in patients transferred to intensive care unit. They concluded prophylactic LMWH does not significantly impact the progressive increase in D-dimer levels observed in patients with severe COVID-19 (5). However, Klok et al. (21) noted a 31% cumulative incidence of thrombosis in a cohort of 184 ICU patients with COVID-19, despite antithrombotic prophylaxis, and the vast majority of them (81%) were pulmonary emboli. Likewise, Corrado et al. analyzed 388 patients (median age 66 years, 16% requiring intensive care) with COVID-19 and despite thromboprophylaxis, thromboembolic events occurred in a cumulative rate of 21%. Half of the events were observed within 24 h of admission. Venous thromboembolism was shown in 16 (36%), pulmonary embolism was shown in 10 (7.7%), ischemic stroke was 2.5% and acute coronary syndrome was 1.1% of the patients (22). Therefore, when pulmonary embolism is suspected, objective diagnosis with radiologic methods should be performed quickly and appropriate heparin doses given to the patient.

Bleeding is unusual during COVID-19 infection, but even if it develops, blood component support according to ISTH guidelines should be given. Critically ill patients at high-risk of mortality may benefit from treatment strategies to inhibit excessive inflammatory responses, but the success of these therapies may depend on the time course and evolution of the infection. Serine protease inhibitors including antithrombin, C1 esterase inhibitor, and protein C are decreased in the setting of the inflammatory response to infection (8). Fibrinolytic shutdown that also occurs in sepsis is characterized by increased plasminogen activator inhibitor-1 (PAI-1) activity resulting in low D-dimers. Vascular endothelial injury causes further thrombocytopenia, reduction of natural anticoagulants, but also hemostatic activation as the phenotypic expression of thrombotic DIC. Analysis of septic patients who are coagulopathic and receive serine protease inhibitors such as antithrombin or thrombomodulin suggest there may be a survival benefit (23). Wang, et al. (24) reported 3 cases of off-label intravenous administration of tissue plasminogen activator (tPA) for patients with COVID-19 with ARDS and respiratory failure. In all 3 cases demonstrated an initial improvement ranging from a 38% to ~100%, but this response was transient and lost over time in all patients after completion of their tPA infusion (24).

Additionally, in severe COVID-19 patients, the antithrombin III activity should be maintained above 80% (18,19). Another recommendation is viscoelastic tests (thromboelastometry) which used to evaluate the dynamic changes in coagulation function of severe COVID-19 patients, if possible (19). In patients with secondary liver failure, plasma exchange can decrease the dosage of vasoactive drugs, remove inflammatory cytokines, reduce capillary leakage and platelet consumption (25).

In conclusion, hyperinflammation and detrimental immunothrombosis may be central to the pathophysiology of COVID-19. Platelet hyper-reactivity, hypercoagulability, hypofibrinolysis, complement overactivation, in the presence of underlying inflammatory-induced endothelial dysfunction likely lead to a state of COVID-19 induced coagulopathy. The recommendation of the Ministry of Health is close monitoring of the coagulation markers in these patients, and enoxaparin should be given 40 mg a day in patients with D-dimer <1000 ng/mL, and 0.5 mg/kg two times a day in patients with severe disease or D-dimer >1000ng/mL (26). Early initiation of thromboprophlaxis in patients infected with COVID-19 can be life-saving for these patients.

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