Review Article

COVID-19 Associated Coagulopathy: Inflammation and Coagulation Linkage

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Abstract

The severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) infection, which causes coronavirus disease (COVID-19), has become a worldwide pandemic since emerging in December 2019. The severity of the disease ranges from asymptomatic carriers to severe manifestations, such as acute respiratory distress syndrome (ARDS) and multiorgan failure. The proposed etiology for severe disease and death were micro- and macro-vascular thromboses, which are major components of COVID-19 associated coagulopathy (CAC). CAC is associated with cytokine storm, causing inflammation, endothelial injury, and subsequent thrombosis. Heparin is useful in this circumstance because of many proposed mechanisms. Multiple studies have reported the benefit of heparin in decreasing mortality in critically ill patients. However, the optimal dose and duration are yet to be determined.

Keywords: COVID-19 associated coagulopathy (CAC), Vascular thrombosis, Cytokine storm, Endotheliopathy

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), or Coronavirus disease 2019 (COVID-19), has become a worldwide pandemic. Over 2.5 million deaths have been attributed to COVID-19. Since upper respiratory tract infection is a common presentation of SARS-CoV-2, severely infected patients who present with pneumonia that is complicated by acute respiratory distress syndrome (ARDS) are at high-risk of mortality. Interestingly, the common features of ARDS such as diffuse alveolar damage, hyaline membranes, inflammation and type II pneumocyte hyperplasia are not prominent in the autopsy evidence.[1] On the contrary, there were macro- and microvascular thromboses with platelet-fibrin micro-thrombi in major organs including lungs, indicating that vascular thrombosis plays a crucial role in the pathogenesis of severely infected COVID-19 patients.[1-3] The incidence of thrombotic events in hospitalized COVID-19 patients is around 10 - 40%, even though pharmacologic thromboprophylaxis, mostly heparin, is applied.[4-8] In several recent studies the mortality rate among critically ill patients is still high at around 20%.[7, 8] The unique characteristic of SARS-CoV-2 pathogenesis involving vascular thrombosis is different from other respiratory viruses, even within the same species of SARS virus which emerged in the year 2002. This mystery challenges all physicians to discover whether heparin, known to be the fundamental treatment of blood clots, has particular mechanisms in the treatment of SARS-CoV-2.

Thrombo-inflammation as a pathogenesis

The unique characteristic of this most recent SARS-CoV-2 strain is that even though it is similar to the SARS-CoV virus that emerged in the year of 2002 - 2003, its spike protein is different. The spike protein is primed by transmembrane protease serine 2 (TMPRSS2) and interacts with cellular heparan sulfate (HS) then enters the host cells via cellular angiotensin converting enzyme (ACE2) receptors.[9] These ACE2 receptors are present in various organs, especially the lung endothelium[10] where the virus attaches, causing the ACE2 receptors to be internalized. This leads to angiotensin II upregulation and downregulation of angiotensin 1 - 7, which contribute to vasoconstriction, inflammation and increased vascular permeability.[11]

This viral entry mechanism involves increased activity of heparanase (HPSE) enzyme, the enzyme that normally degrades cellular heparan sulfate (HS), which is thought to play an important role in the maintenance of normal endothelial function.[12, 13] The increase in HPSE activity contributes endothelium activation and subsequently aggravates an inflammatory response by various mechanisms.[12] In normally functioning endothelium, the ACE 2 receptor is internalized after viral entry and can limit further infection and systemic symptoms. However, in the case of severe COVID-19 patients, the activated endothelium that occurs after viral entry can cause more severe symptoms by increasing the expression of ACE2 receptors on activated endothelium, which allows more viral entry that induces profound inflammatory responses via production of cytokines and chemokines. The cytokine and chemokine storm produced by innate and adaptive immunity as a process of infection control causes further endothelial dysfunction.[11, 14] Another mechanism of inflammation occurs when activated endothelium upregulates various ligands such as P-selectin, E-selectin, intercellular adhesion molecule 1 (ICAM-1), and ACE2 on the surface, thus aggravating migration, adhesion, and extravasation of immune cells including platelets and neutrophils. SARS-CoV-2 also stimulates extracellular neutrophils traps (NETs),[2] which containsintracellular components such as DNA, histones and proteins derived from intracellular granules released by activated neutrophils. This process of NETosis, helps control infection but may cause vascular complication. All of these processes consequently cause endothelial dysfunction, increased permeability, enhanced coagulopathy and finally lead to micro- and macrovascular thrombosis.

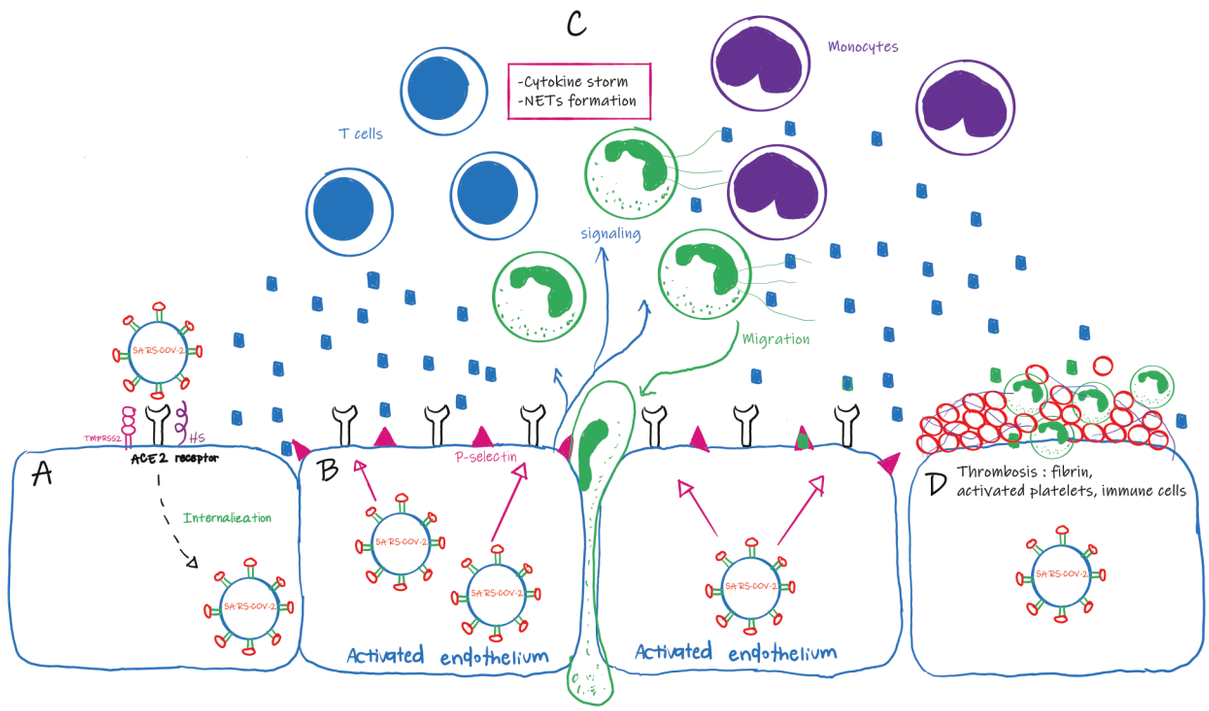

Figure 1 Thrombo-inflammation pathogenesis in COVID-19 patients: **A**. SARS-CoV-2 enters host cells via ACE2 receptor, primed by TMPRSS2 and interact with HS. **B**. Activated endothelium upregulates more ACE2 receptor allowing more viral entry, and numerous ligands, causing neutrophil migration, increased permeability. **C**+**D**. The cytokine storm and NETs formation produced by innate and adaptive immunity as a process of infection control causes further endothelial dysfunction, and subsequent vascular thrombosis.

COVID-19 associated coagulopathy (CAC) laboratory parameters

There are several laboratory parameters suggesting systemic coagulopathy in severe COVID-19 patients, such as elevation of prothrombin time [PT], activated partial thromboplastin time [aPTT], fibrin degradation product [FDP] and d-dimer level, which are similar to sepsis induced disseminated intravascular coagulopathy (DIC), but has less consumption of platelets and coagulation proteins in COVID-19 associated coagulopathy (CAC). Thrombocytopenia is less prominent. Likewise, PT and aPTT are minimally affected; however, significantly elevated PT is observed in non-survivals compared to survivals.[15-17] Factor VIII and fibrinogen are also elevated.

In critically ill patients, CAC turns to florid DIC when PT and aPTT become elevated, accompanied with decreasing levels of platelets and fibrinogen. These increased prothrombotic markers are correlated with increasing levels of proinflammatory markers, such as interleukin-6 (IL-6), c-reactive protein (CRP), lactate dehydrogenase (LDH), and ferritin, supporting the pathogenesis of thrombo-inflammation. The abnormal prothrombotic markers, especially high-level d-dimer, are related to a more severe clinical course, and poor survival prognosis in SARS-CoV-2 infection.[17-20] Other risk factors, in addition to elevated levels of prothrombotic markers, that are associated with increased mortality are advanced age and sequential organ failure assessment (SOFA) score.[18,21] According to evidence from China, sepsis induced coagulopathy score (SICS), developed by International Society of Thrombosis and Hemostasis (ISTH), that includes 4 parameters of SOFA score with PT and platelet count, might be an effective parameter for defining prognosis in early COVID-19 infected patients before they begin to have overt DIC. Importantly, SICS may guide physicians whether patients need more intensive care or higher intensity of anticoagulant.[21-23]

Table 1 comparing laboratory parameters between covid-19 associated coagulopathy (CAC) and disseminate intravascular anticoagulant (DIC)

	CAC	DIC
Platelet	normal	decreased
PT	increased/normal	increased
aPTT	increased/normal	increased
D-dimer	increased (markedly)	increased
Fibrinogen	increased	decreased

Role of heparin: the benefit beyond anticoagulant effect

The combination of thrombosis and cytokine storm plays a crucial role in pathogenesis of severe COVID-19 patients. Heparin, which has both anticoagulant and anti-inflammatory properties, has been suggested as potentially beneficial in treating COVID-19. The mechanism of anticoagulant of heparin is involved with indirect thrombin inhibition by enhancing the potential of antithrombin in inhibition of thrombin and factor Xa. The anti-inflammatory property occurs either by direct binding of heparin to its ligand, P-selectin on activated endothelium, preventing leukocytes recruitment to the sites of inflammation,[24, 25] or by neutralizing inflammatory cytokines that were produced by the immune system in response to COVID-19 infection.

Furthermore, many specific mechanisms of heparin in the treatment of COVID-19 infection were proposed. The first mechanisms were thought to be involved with viral entry inhibition by competitive binding of heparin with SARS CoV-2 spike protein. This process inhibits the binding of the virus to cellular heparan sulfate (HS) on endothelial cells, interrupting the viral entry mechanism. Another mechanism that plays a role in the reduction of COVID-19 infection severity is heparanase (HPSE) inhibition. The later process helps maintain normal endothelial function by preventing HS degradation according to the HPSE enzyme.[12]

In addition to the in-vitro studies that confirm the effects of heparin in treating COVID-19, there are also many clinical studies supporting the use of heparin. An early study from Wuhan revealed better survival outcomes from heparin use in severely ill COVID-19 patients with sepsis-induced coagulopathy (SIC) score ≥ 4 or D-dimer value greater than 6 times the upper limit normal or > 3.0 μg/mL.[22] Although the 28-day mortality of all patients in this study was comparable between heparin and non-heparin users; heparin prophylaxis is recommended by many guidelines as a mainstay of COVID-19 treatment.[26, 27] In fact, the incidence of thrombotic events in critically ill COVID-19 patients admitted in intensive care units (ICU) is around 30 - 50%, even when standard thromboprophylaxis is applied.[4-7, 18] This leads to another question about what the optimal dose of heparin is. A recent pool analysis by Patell, et al. which collected data from 35 observational studies, supports the use of heparin in reducing venous thromboembolism (VTE) rate among COVID-19 patients compared with the no anticoagulant group; however, statistically significant difference of VTE rate was not demonstrated among different intensity of heparin.[7] Data from Mount Sinai suggests that a higher dose of heparin is beneficial for in-hospital survival of severe COVID-19 patients who need mechanical ventilators. Their mortality rate was 29.1% and their median survival was 21 days, compared to a mortality rate of 62.7% and median survival of 9 days in the group including prophylactic dose or no anticoagulant.[28] Data from the University of Southern California (USC) also shows in-hospital survival benefit when comparing an escalated therapeutic dose to a prophylactic dose of heparin in COVID-19 admitted patients. In this study, the patients who received a higher anticoagulant dose had a more severe clinical course than the patients who received prophylactic dose anticoagulant, supporting the use of heparin dose escalation in the more severe patient group.[29] However, bleeding events seem to be higher in patients who received intermediate or therapeutic dose anticoagulant.[7, 29] This makes the higher heparin dose still a matter of uncertainty which should be individualized. Ongoing randomized controlled trials may resolve this question in the future.

Discussion

The role of extended anticoagulant use after discharging also lacks evidence. A study in the UK found that the incidence of post discharge VTE in COVID-19 patients was not different from other hospitalized patients with acute medical illnesses.[30] The role of post-discharge thromboprophylaxis is still unclear.

In summary, the pathophysiology of SARS-CoV-2 infection, or COVID-19, is mainly associated with inflammation induced coagulopathy, and subsequent thrombosis. The use of heparin counteracting its pathogenesis, is one of the crucial treatments that shows survival benefits in severely ill patients who have respiratory compromised conditions and high levels of inflammatory markers. The appropriate heparin dose needs to be validated to confirm whether its benefit outweighs its adverse effects.

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