Thromboembolism in Covid 19

Dr. Aarti Gupta[1], Dr. Michelle Siew[1], Dr. Balaji Bala Subramaniam[2]

[1](Assistant Professor, Critical Care, RGSSH, India)
[1](Senior Resident, Critical Care, RGSSH, India)
[2](senior Resident, Critical Care, RGSSH,India)

Abstract: Coronavirus disease 2019 (COVID-2019) is caused by a novel coronavirus known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and was identified as a pandemic by the World Health Organization (WHO) on March 11, 2020. Recent observations suggest that respiratory failure in COVID-19 is not driven by the development of the acute respiratory distress syndrome (ARDS) alone, but that (microvascular) thrombotic processes may play a role as well. This may have important consequences for the diagnostic and therapeutic management of these patients. The aim of this study is to understand the pathogenesis of the disease which entails the morbidity, mortality and stagnant life as we know today. proper management and monitoring of thromboembolism in covid has proven to be beneficial in decreasing mortality.
Keywords: SARS-Cov-2, Acute respiratory distress syndrome (ARDS), Microvascular, Thromboembolism.

I.   Introduction

Coronavirus disease 2019 (COVID-2019) is caused by a novel coronavirus known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and was identified as a pandemic by the World Health Organization (WHO) on March 11, 2020 [1]. As of April 12, 2020, more than 1.8 million people were confirmed to have been infected and tested positive for COVID-19, with over 114,000 deaths worldwide [2]. This virus was first identified in the respiratory tract of patients with pneumonia in Wuhan, Hubei China, in December 2019 which was then indicated as a newly identified β-coronavirus (nCoV) [3,4]

SAR-CoV2 is an enveloped, non-segmented, positive sense RNA virus that is included in the sarbecovirus, ortho corona virinae subfamily which is broadly distributed in humans and other mammals [5.6]. As a member of the Nidovirus family, coronavirus infection (SARS-CoV2) can be contracted from animals such as bats, and fellow humans. This virus can enter the human body through its receptors, ACE2 which are found in various organs such as heart, lungs, kidneys, and gastrointestinal tract, thus facilitating viral entry into target cells. The process of CoV entering into the host cell begins through the attachment of the S glycoprotein to the receptor, the ACE2 in the host cells (such as in type II pneumocytes in the lungs) [7]. This attachment occurs in the binding domain of S protein of SARS-CoV-2 receptors which are present at 331 to 524 residues, and can bind strongly to human ACE2 and bat ACE2 [8]. The entry and binding processes are then followed by fusion of the viral membrane and host cell [9].

Generally, the body's immune response to SARS-CoV2 and SARS-CoV is closely similar being mediated by cytokines [10].Excess releasing of pro-inflammatory cytokines such as IFN-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α, TGFβ, and chemokines CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10 from immune effector cells causes hyperinflammation which will eventually lead to ARDS [11'12].High plasma levels of proinflammatory cytokines (interleukin-2, interleukin-7, granulocyte colony-stimulating factor, IP10, MCP1, MIP1A and tumor necrosis factor-α) have been observed in COVID-19 patients admitted to intensive care units. This is consistent with a "cytokine storm" with the secondary development of a hemophagocytic lymphohistiocytosis (**16**, **17**). While many pro-inflammatory cytokines trigger the coagulation system, Zhou and colleagues (**18**) showed that the increase in IL-6 was discrepant with the elevations in D-dimer; IL-6 levels appeared to increase only 13 days after disease onset, whereas D-dimer levels were already 10-fold increased by that time. This observation suggests that the very high D-dimer levels observed in COVID-19 patients are not only secondary to systemic inflammation, but also reflect true thrombotic disease, possibly induced by cellular activation that is triggered by the virus.

During the relatively recent outbreak of SARS-CoV in 2003, which was associated with even higher morbidity and mortality than COVID-19, vascular endothelial damage in both small- and mid-sized pulmonary vessels was noted together with DIC, DVT and PE resulting in pulmonary infarction (**13,14**). A case report of an autopsy described thrombosis in multiple organs in a patient with proven SARS-CoV infection (**15**). Given the similarity between SARS-CoV and SARS-CoV-2, similar thrombotic complications are likely to be present in

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patients with COVID-19. Whether the coagulation cascade is directly activated by the virus or whether this is the result of local or systemic inflammation is not completely understood.

Recent observations suggest that respiratory failure in COVID-19 is not driven by the development of the acute respiratory distress syndrome (ARDS) alone (19), but that (microvascular) thrombotic processes may play a role as well. This may have important consequences for the diagnostic and therapeutic management of these patients. There is a strong association between D-dimer levels, disease progression and chest CT features suggesting venous thrombosis (18). Significant inflammation is present in patients with SARS-CoV-2 infection, based on elevated levels of IL-6, increased CRP and ESR, and elevated fibrinogen at presentation. [27] Given the tropism of the virus for ACE2 receptors, endothelial cell activation and damage with resultant disruption of the natural antithrombotic state is likely. An early report of COVID-19 patients in Wuhan measured proinflammatory cytokines and found elevated plasma concentrations that were higher in ICU patients than non-ICU patients.[28] This inflammation associated with COVID-19 and subsequent activation of coagulation is the probable cause for the elevated Ddimer levels, as increased levels have been associated with many conditions other than thromboembolism, with infection an important etiology.[29,30,31] The finding that D-dimer would track with severity of disease and inflammation is not surprising given the evolving understanding of the interaction between inflammation and activation of coagulation. Some patients appear to have a more pronounced inflammatory response to infection with SARS-CoV2, such as seen with systemic inflammatory response syndrome (SIRS) or cytokine storm, which may explain more dramatic changes in coagulation tests, including significantly elevated Ddimer, especially as the disease progresses. [32] Consistent with vascular endothelial dysfunction with sepsis induced coagulopathy, an endothelialopathy appears to contribute to the pathophysiology of microcirculatory changes in SARS-CoV-2 infections.[33,34] The receptor for viral adhesion is an angiotensin-converting enzyme (ACE) 2 receptor on endothelial cells[35] , with viral replication causing inflammatory cell infiltration, endothelial cell apoptosis, and microvascular prothrombotic effects.43 Recent reports demonstrate viral inclusions within endothelial cells and sequestered mononuclear and polymorphonuclear cellular infiltration, with evidence of endothelial apoptosis in post mortem of SARS-CoV-2 infection.[36] As a result, microcirculatory dysfunction contributes to the clinical sequelae in patients with COVID-19.

Evidence of abnormal coagulation parameters associated with COVID-19 appeared in early reports from China. Baseline characteristics of the first 99 patients hospitalized in Wuhan found that 6% had an elevated aPTT, 5% elevated PT, 36% elevated D-dimer, increased biomarkers of inflammation including interleukin-6 (Il-6), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). [20] Thrombocytopenia occurred in only 12%, however, 5 patients had other coinfections (1-bacterial, 4-fungal), and 4 had septic shock. [20] Additional reports from another Wuhan hospital on the first 138 patients found minimal elevations in PT and normal aPTT.[21] Of the patients requiring ICU admission, 26% had higher D-dimer levels, and 9% had shock. A complete set of clinical laboratory parameters for the hospital course were available for 33 patients who either recovered or died. Characteristics of the 5 non-survivors compared to 28 survivors included rising D-dimer, progressive lymphopenia, and renal dysfunction. D-dimer levels appeared to diverge 5 days after onset of symptoms.[21] In an analysis of 191 patients from 2 of the main Wuhan hospitals, mortality was reported to be 28% (54-patients).[22]Factors associated with mortality included an elevated D-dimer > 1.0 mcg/mL on admission, increased PT, elevations in IL-6, and other biomarkers of inflammation, elevated troponin levels, and co-morbidities including older age, hypertension, diabetes, and coronary artery disease. All 54 non-survivors met the definition of sepsis, and 50% had evidence of coagulopathy defined as a 3-second PT increase or a 5-second increase in aPTT. Half of these patients also had secondary infections, however, DIC was not assessed. In a multivariable logistic regression model of 171 patients with complete data for all variables (53 non-survivors and 118 survivors), a D-dimer level greater than 1.0 mcg/mL at admission was associated with increased mortality with an OR of 18.42 (2.64-128.55, p=0.003).[22] Another early publication evaluated 1099 COVID-19 patients, and excluded individuals who did not require hospitalization. [23]The primary composite outcome of ICU admission, ventilator support, or death occurred in 6.1% (67-patients), with a 1.4% mortality (15-patients). The investigators noted that compromised respiratory status and more severe disease on admission were associated with worse outcomes. Of the 173 patients who were classified with severe pneumonia at admission, based on the American Thoracic Society criteria, 24.9%(43/173) experienced a primary outcome event compared to 3.6% in the non-severe group.[24] D-dimer was dichotomized as either less than or greater than 0.5 mg/liter, with more patients with severe disease experiencing a primary outcome having D-dimer values>0.5 mg/liter. [24]

A more complete assessment of coagulation parameters, including D-dimer, PT, aPTT, fibrinogen, and antithrombin, in 183 COVID-19 positive patients was analyzed by survivor status from admission through 14 days. [25] At the time of publication, 78 (42.6%) patients had been discharged, and 21 (11.5%) patients had died while the rest 84 (45.9%) were still hospitalized. A total of 15 of 21 non-survivors were diagnosed with overt DIC according to ISTH criteria, with median onset at 4 days (1-12 days) after admission, while only 1 of the 78

discharged patients had evidence of DIC. Over their hospitalization, non-survivors had evidence of progressive DIC with decreased fibrinogen, increased D-dimer, and increased PT, occurring 10 days after admission, although information regarding evidence of sepsis was not provided. Although antithrombin levels decreased late in the hospitalization for non-survivors, levels were not below normal in the majority.[25] In an analysis of 449 patients classified as having severe COVID-19 (defined as respiratory rate>30 breaths/min, room air oxygen saturation < 93%, Pa02/Fi02< 300 mmHg), 99 patients (22%) received prophylactic VTE anticoagulation for at least 7 days, with 94 patients treated with enoxaparin 40-60 mg/day, and 5 treated with unfractionated heparin (UFH) 10,000-15000 U/day.[26] Of the 449 patients, 22% (n=97) had an ISTH SIC score of > 4, and 29.8% (134) patients died at time of reporting. Although no difference in 28-day mortality was seen between heparin and non-heparin treated patients overall, stratification by SIC score identified lower mortality in patients treated with heparin when SIC score was > 4 (40.0% vs. 64.2%, p=0.029) compared with SIC score < 4 (29.0% vs 22.6%, p=0.419). A 20% reduction in mortality was observed when patients with D-dimer exceeding 3.0 mcg/ml were treated with prophylactic doses of heparin. (32.8% vs 52.4%, p=0.017) Even using the SIC score, only 21.6% of severe cases met SIC criteria. However, patients with D-dimer > 6 x ULN did comprise a higher proportion of severe cases, (161/446, 35.9%). [26] The aim of this study is to understand the pathogenesis of the disease which entails the morbidity, mortality and stagnant life as we know today. The abovementioned studies have shown that proper management and monitoring of thromboembolism in covid has proven to be beneficial in decreasing mortality. There are numerous researches going on to understand the structure, pathogenesis and epidemiology of covid 19 virus in a hope to find an absolute treatment.

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