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Venous and Arterial Thrombosis in COVID-19 Era; Risk and Management

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ABSTRACT

Since its discovery in December 2019, SARS-CoV-2 has resulted in more than 23 million infected cases worldwide with more than 800.000 deaths with a mortality rate of about 3.47%. The respiratory system seems to be the primary target system for SARS-CoV-2, and infected patients may develop acute lung injury and Adult respiratory distress syndrome (ARDS). However, severe COVID-19 is a multi-systemic disease associated with a hypercoagulable state affecting the microvascular, venous, and arterial system. Severe COVID-19 infection is characterized by coagulation derangement and hyperinflammatory state that may lead to overt disseminated intravascular coagulopathy (DIC), a status termed Covid-19 Induced Coagulopathy (CIC). This can result in multi-organ involvement with microvascular, arterial, and venous thrombosis. In this article, we review the incidence of thrombosis in severe covid-19 patients, the mechanisms of Covid-19 induced thrombosis, and recommendations regarding anticoagulation in hospitalized Covid-19 patients.

Key Words: COVID19, Incidence, Arterial, Venous, Thrombosis, Management

INTRODUCTION

Since its discovery in December 2019, SARS-CoV-2 has resulted in more than 23 million infected cases worldwide with more than 800.000 deaths with a mortality rate of about 3.47%.[1] The respiratory system seems to be the primary target system for SARS-CoV-2, and infected patients may develop acute lung injury and Adult respiratory distress syndrome (ARDS). However, severe COVID-19 is a multi-systemic disease associated with a hypercoagulable state affecting the microvascular, venous, and arterial system.[2,3]

Hospitalized COVID-19 patients appear to have a high incidence of venous thromboembolism (VTE) compared to other critically ill patients with other severe medical conditions like sepsis or septic shock.[4,5] COVID-19 associated coagulopathy affects arterial, venous, as well as microvascular systems. In a meta-analysis by Porfidiaa et al. in May 2020, the overall incidence of VTE was around26%, including pulmonary embolism (PE) with or without deep venous thrombosis (DVT) in 12% and DVT alone in 14%. In another meta-analysis by Chi Zhang et al., the incidence of VTE was 25% (the incidence of PE 19% and the incidence of DVT 7%), with 35% in severe COVID-19 patients and 6% in non-severe cases.[6]

Klok et al. reported a cohort of 184 patients admitted to the ICU with proven COVID-19 pneumonia and assessed for the Netherlands' thrombotic events. He found a thrombotic incidence of 31%: 27%venousand 3, 7% arterial thrombotic events.PE was the most typical thrombotic complication occurring in 81% of the reported cases. Thrombotic complications were higher in older age and patients having prolonged prothrombin time>3 s and or extended activated partial thromboplastin time>5 s.[17]

There was a higher incidence of Arterialthrombosis among severe Covid-19 hospitalized patients, with an average acute ischemic stroke rate between 3%and 5%.[7,8]

MECHANISM OF COVID-19 INDUCED COAGULOPATHY

Angiotensin-converting enzyme 2 (ACE-2) receptors in alveolar cells arethe portal of entry of SARS-COV-2. Infected cells release inflammatory mediators as danger-associated molecular patterns (DAMPs), which signal the release of

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pro-inflammatory cytokines and chemokines.[10] ACE-2 receptors were also found in endothelial cells. The activated damaged endothelium up-regulates the release of VWF (von Willebrand factor) and endothelin-1, which is a potent vasoconstrictor. The release of those inflammatory mediators with sub-endothelial collagen exposure leads to the recruitment of leukocytes and platelets and complement activation, leading to platelet aggregation and thrombus formation.[11]

The hypoxic environment aids in thrombus formation by releasing HIFs (hypoxia-inducible factors) that lead to up-regulation of endothelial TF expression. So far, D-dimer, which is a fibrin degradation product and a marker of coagulation activation, seems to be a strong prognostic marker of high mortality in patients with COVID-19.[11] Laboratory findings in severe caseswithCovid-19 showed prolonged PT, high CRP, lymphocytopenia, leucopenia, mild thrombocytopenia, high D-dimers and low fibrinogen.[2,3]

Endothelial injury, low flow circulation and hypercoagulability are all present in COVID-19 infections. In terms of endothelial injury, there is clear evidence that the SARS-CoV-2 virus invades endothelial cells leading to cell injury.[12] Other sources of endothelial injury may include intravascular catheters, acute phase reactants, and other inflammatory mediators.[13] On the other hand, blood flow stasis due to immobilization during intensive care unit hospitalizations is an additional risk factor for VTE. In terms of hypercoagulability, many changes in circulating prothrombotic factors have been observed in COVID -19 patients that include loss of the protective endothelium with its glycocalyx layer, low levels of tPA, and the inhibition of the clot-lysing system that lead to a prothrombotic state; this can be augmented by platelet dysfunction, complement activation, and systemic immune reactions.[13]

Acute coronary syndrome and myocardial injury are common complications of severe COVID-19 clinical course and were found in up to 20% of COVID-19 hospitalizations with an adverse impact on mortality. [9] The underlying cause of myocardial injury is suggested to be due to direct damage of myocardial tissue by SARS-CoV-2. In addition to macrovascular complications, SARS-COV2 also causes microvascular thrombosis. Patients who died with severe ARDS were found to have pulmonary microvascular thrombosis in autopsies.[14] Although this pulmonary thrombosis was found in MERS-COV infection and SARS-COV1 infection; this feature appears more prominent in severeSARS-CoV-2 infection. The lung histology from patients withCOVID-19 demonstrates a 9-fold increase in the prevalence of alveolar-capillary microthrombi compared with patients having other types of influenza. In this regard, autopsy findings have shown that, in addition to the usual features of diffuse alveolar damage found in ARDS, microthrombi was found in about 100% of cases in an autopsy[14] Indeed, considering other reported thrombotic events, the emerging microvascular thrombotic complications is a strong indication of interaction between the SARS-CoV-2 and coagulation.[14]

MANAGEMENT OF THROMBOSIS IN COVID-19 PATIENTS

Evidence suggests that low molecular weight heparin treatment may be associated with lower mortality in COVID-19 patients with an elevated-dimer and/or elevated sepsis-induced coagulopathy score.[15] In addition to its main action that inhibits coagulation by binding the antithrombin, which accelerates the inhibition of FXa or thrombin, heparin appears to have pleiotropic effects which provide special advantages in viral infection context, including antiinflammatory effects by their ability to bind to the inflammatory molecule, such as HMGB-1and pro-inflammatory cytokines.[15]

Based on currently limited evidence, there is a suggestion for the use of anticoagulants for a hospitalized patient with COVID-19 infection.[16] Lin et al. investigate the role of therapeutic anticoagulant inpatient with raised inflammatory markers and D-dimer on day 7 and 14, Given the risk of sepsis-induced coagulopathy (SIC), the authors suggest anticoagulation for COVID-19 patients with increased D-Dimer levels four times above the normal limit, using a dose of 100 IU/kg of LMWH twice a day, for at least 3–5 days.[18]

Tang et al. investigated 449 patients with severe COVID-19; 99of them received LMWH for seven days or longer.[15] D-dimer, prothrombin time, age, and low platelet count were positively correlated with 28-day mortality. But in a subgroup of patients with increased SIC score ≥4 or D-dimer >6-fold of the upper limit of normal, patients treated with heparin had lower 28-day mortality than those who were not treated with heparin (40.0% vs. 64.2%, P = .029), (32.8% vs. 52.4%, P = .017) respectively. The study suggested that anticoagulant therapy with low molecular weight heparin may be associated with a better prognosis in severe COVID-19 patients meeting criteria or with markedly elevated D-dimer.[17] Based on previous studies Oxford University Press, on behalf of the European Society of Cardiology, published a recent algorithm/protocol for the management of coagulopathy in COVID-19 patients which recommended that

- All hospitalized patients with covid-19 should receive anticoagulant according to the risk of thrombosis and D-dimer level.
- If a patient is at a high risk of thrombosis or D-dimer level more than or equal to 3mcg/ml, the patient should receive enoxaparin 1mg/kg twice a day.
- Low-risk patients with D-dimer between 0.5 -3 mcg/

ml should receive enoxaparin 40 mg twice a day.
- Low-risk patients with d dimer less than 0.5 mcg/ml should receive 40 mg once daily enoxaparin.
- For high-risk patient admitted to ICU should receive heparin infusion with target aPTT 60-85 seconds.[16]

DISCUSSION

Since the discovery of COVID19, there were many reports of venous, arterial and microcirculatory thromboembolic complications with higher incidence among critically ill patients.[4,6] The incidence ranging from 20% to 31% in various reports.[6,17] Pulmonary embolism is the most frequent reported thrombotic complications in critically ill patients with COVID 19 pneumonia.[17] Elderly patients with prolonged prothrombin time >3s and activated partial thromboplastin time>5 s were at higher risk of thromboembolic complications.[17]

Angiotensin-converting enzyme 2 (ACE-2) receptors in alveolar cells, proinflamtory cytokines and chemokines have a major role in the pathophysiology of thrombus formations.[10] Indeed, the damaged endothelium increase the release VWF (von Willebrand factor) and endothelin-1 which augment vasoconstrictions, together with inflammatory mediators leads to platelet aggregation and clot formation.[10,11] The triad of endothelial injury, low flow circulation and hypercoagulability are all present in COVID -19 infections.[12] COVID 19 causes both macrovascular and microvascular thrombosis as shown in the pulmonary autopsies of severe ARDS cases. The lung histology from patients withCOVID-19 demonstrates a 9-fold increase in the prevalence of alveolar-capillary microthrombi compared with patients having other types of influenza.[14]

Treatment with low molecular weight heparin has been suggested to lower mortality in COVID-19 patients.[15] Besides its major action of coagulation inhibition, it has anti-inflammatory action by its ability to bind to the inflammatory molecule, such as HMGB-1and pro-inflammatory cytokines.[15]

Based on current evidence, there is a suggestion for the use of anticoagulants for a hospitalized patient with COVID-19 infection.[16]

CONCLUSIONS

Severe COVID-19 disease is associated with features of disseminated intravascular coagulation (DIC) and hypercoagulable state, which can manifest as venous thromboembolism (VTE), arterial ischemia, and/or micro thrombosis. Data on anticoagulation at present based mainly on observational studies, but high-risk patients may benefit from an intensified prophylactic regimen.

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