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Coagulopathy in Covid-19

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INTRODUCTION

Infections are often accompanied by activation of the blood coagulation system. These abnormalities range from subtle activation of haemostasis that can only be detected by sensitive markers for coagulation factor activation to somewhat more stronger hemostatic activation that may be detected by small decrease in platelet count and sub-clinical prolongation of global clotting times, to fulminant disseminated intravascular coagulation [DIC] characterized by simultaneous widespread microvascular thrombosis and profuse bleeding from various sites. There is ample evidence that activation of coagulation in concert with inflammatory activation can result in microvascular thrombosis and thereby contributes to multiple organ failure in patients with severe infections. Indeed, infection-associated coagulopathy has shown to be and independent predictor of organ failure in patients with sepsis [1,2].

COVID-19-associated Coagulopathy and Thrombosis

An infection-related derangement of coagulation is very relevant in COVID-19. Many patients with severe COVID-19 infections present with coagulation abnormalities that mimic other systemic coagulopathies associated with severe infections, such as DIC or thrombotic microangiopathy, but have distinct features. The occurrence of coagulopathy in COVID-19 infected patients is associated with higher risk of death. Furthermore, the relevance of COVID-19-coagulation abnormalities is becoming increasingly clear as a substantial proportion of patients with severe infection develop venous and arterial thromboembolic complications. There seem to be a remarkable high incidence of venous thromboembolism [VTE] in patients with COVID-19. The incidence ranges from 3-37% for deep venous thrombosis [DVT] and 7-35% for pulmonary embolism [PE]. There is some debate whether that high incidence of VTE is similar to that seen in critically ill patients with severe systemic inflammatory state and multiple organ dysfunctions or whether a frequently occurring coagulopathy in COVID-19 increases the risk. Rate of arterial thrombotic events are between 2.8-3.8%. Large vessel wall arterial thrombosis would support wide-scale endotheliopathy involving medium and large arteries [3-6].

Mechanism of COVID-19-asociated Coagulopathy

Inflammation likely plays a central role in interplay with thrombosis now referred to as thromboinflammation or immune thrombosis. A variety of relevant mechanisms contributing to the derangement of coagulation in COVID-19-infected patients have been elucidated. Initiation and propagation of coagulation with concurrent impairment of physiological anticoagulant pathways and a deficit of endogenous fibrinolysis, all as a result of systemic inflammatory activation are resulting in platelet activation and fibrin deposition. In addition neutrophil extracellular traps [NETs] composed of denaturated DNA, histones and proteolytic enzymes, may play a crucial role in the development of thrombus deposition. Infection and inflammation-induced endothelial perturbation and injury may cause platelet-vessel wall interactions resulting in thrombotic microangiopathy in the vasculature. In the most severely affected COVID-19 patients, an exaggerated immune response is observed in the form of a cytokine storm, characterized by increased levels of pro-inflammatory cytokines, such as TNF-α and interleukins 1 and 6 also leading to activation of coagulation. Clinically these patients develop multi-organ dysfunction and have a very high mortality risk [6-10].

COVID-19-associated Endotheliopathy

An important feature of the COVID-19 associated coagulopathy is the microcirculatory endothelial damage in pulmonary circulation and other vascular beds. Therefore, COVID-19 can be considered as the consequence of an endothelial dysfunction and as an endothelial disease [11,12]. Since SARS-COv-2 directly infects the vascular endothelial cell causing cellular damage and apoptosis, the antithrombotic properties of the endothelium are remarkably decreased. Both alveolar damage and microcirculatory disturbances associated with thrombus formation contribute to respiratory dysfunction. At autopsy, findings reported include clot formation in pulmonary arterioles with diffuse alveolar damage and hyaline membranes. In addition, accumulation of inflammatory cells and viral inclusions occur within the vascular endothelium of the heart, small bowel and kidneys. The major features of COVID-19 associated coagulopathy are endothelitis, intussusceptive angiogenesis and diffuse microangiopathy with microvascular thrombosis [13,14]. Indeed, as reported recently the over inflammation with endothelial dysfunction, coagulopathy and disseminated intravascular coagulation lead to worse prognostic outcome in COVID-19 patients [12].

Regarding cardiovascular risk factors associated with endothelial dysfunction, patients with hypertension and those with specific ABO blood groups could evidence poor prognosis by higher rate of hospital and ICU admissions and deaths. Also in this case, the expression of ACE2 and the prothrombotic status seem to be linked to worse prognosis [15,16]. Finally, a high risk population of patients is mainly represented by patients with diabetes and in those with hyperglucemia to hospital admission. Increased concentrations of pro inflammatory cytokines may have a pivotal role in the mechanisms underlying this association, again suggesting a link between endothelial dysfunction and coagulopathy in COVID-19 [17].

Metabolic abnormalities, oxidative stress, chemokines, cytokines and by products of damage associated molecular patterns [DAMPs] also cause endothelial cell injury. As noted previously, pro inflammatory cytokines elicit endothelial cells a change from their homeostatic functions to those that can contribute to thrombosis and local tissue injury. The deranged balance in the prothrombotic/antitrombotic properties of the endothelium predispose to thrombosis not only in the pulmonary circulation but also in peripheral veins and arteries [macrothrombosis] including organs such as myocardium, kidneys and veins, causing DVT and PE [11].

Laboratory Features of COVID-19-associated Coagulopathy

COVID-19 presents with dramatic derangement of coagulation. It is relatively mild at the onset and more severe in patients admitted to intensive care unit [ICU] elevated D-dimer [DD] is the most important feature. Some studies have shown that DD levels are associated with progression to acute respiratory distress syndrome and death. While prothrombin time [PT] is slightly prolonged or [near] normal, activated partial thromboplastin time [APTT] is normal or even shortened. High fibrinogen and factor VIII are other characteristic features of the COVID-19 coagulopathy and their values parallel the disease severity. Low platelet count is uncommon, antithrombin is low [or normal] and protein C is normal or increased. The above features are difficult to reconcile with the coagulopathy associated with DIC. Von Willebrand factor is elevated and parallels the disease severity [3,4,18].

Thrombocytopenia has been observed in 18-36% of hospitalized patients, but is usually not severe. It is multifactorial in etiology, including cytokine storm, possible direct cytopathic effect on marrow, immune-mediated clearance of platelets due to anti-platelet antibodies and platelet activation and consumption [3,4].

Elevated D-dimer at admission is a predictor for both severity of COVID-19 and mortality. In series of more than 1,000 COVID-19 cases from 30 chines provinces, 69.4% of patients who met the composite end point of admission to the ICU, need for mechanical ventilation or death had an elevated D-dimer >500ng/mL compared with 44.2% of those who did not [10]. These results have also been confirmed in a recent met analysis [18]. It is important to note that the elevations in these hospitalized patients are not accurate predictor of subsequent VTE.

To summarize, COVID-19-associated coagulopathy is characterized by elevated D- dimer, hyperfibrinogenemia, lack of severe thrombocytopenia, and typically normal PT and APTT. Overall, the balance of coagulation tips towards hyper coagulability and endothelial dysfunction, leading to the high risk of thrombotic complications, partially explaining the fact that thromboprophylaxis may reduce their incidence, although not completely.

Prevention of VTE in Hospitalized Patients with COVID-19

Unique characteristics of VTE in hospitalized and critically ill COVID-19 patients include the high incidence of VTE [and especially pulmonary embolism], the finding of *in situ* pulmonary embolism associated with micro thrombi that suggest a thrombotic microangiopathic process in addition to classic macro vascular disease, and most importantly from a clinical perspective, the unusually high rate of VTE that has been reported despite standard thromboprophylaxis, preferably with low molecular weight heparin. There have been a number of guidance statements focusing on management of VTE in

these patients [19-21]. Ongoing randomized trial that address key clinical questions, especially more intense thromboprophylactic strategies and novel antithrombotic approaches, have the potential to reduce the morbidity and mortality from VTE in hospitalized and critically ill COVID-19 patients.

In summary, COVID-19 is associated with a high incidence of thrombotic complications. Autopsy findings reinforce the importance of coagulopathy and venous and arterial thrombi as potential immediate cause of death in these patients. Anticoagulant interventions may mitigate the risk of thrombosis and mortality.

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