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Coagulopathy: A Vicious Indicator of COVID-19

Shreya Pawar*, Nitin Bhola

Department of oral and maxillofacial surgery, Sharad Pawar dental college and hospital, Datta Meghe Institute of medical sciences, Wardha – 442 004, Maharashtra, India

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ABSTRACT

COVID-19 is routinely associated with coagulopathy and complications associated with thrombosis. However, the difference between the coagulopathy, which is associated with COVID-19 and the coagulopathy, which is due to different causes, is that the "COVID-19 associated coagulopathy" shows raised levels of D-Dimer and that of fibrinogen. However, it shows quite some abnormalities in the levels of prothrombin time and also in the platelet count. "Venous thromboembolism" and arterial thrombosis is frequently seen in COVID-19 associated coagulopathy as opposed to "disseminated intravascular coagulopathy". Patients suffering from COVID-19 have many have multiple factors in common for thromboembolism which is associated with "Adult respiratory distress syndrome" from different etiologies like generalized inflammation and being unambulatory. "Cytokine storm" is the hallmark of COVID-19 associated coagulopathy which is distinguished by high levels of IL-6,1, tumour necrosis factor and other cytokines. The clinical features of COVID-19 associated coagulopathy overlap that of some syndromes like antiphospholipid syndrome and thrombotic microangiopathy. Studies have shown that patients diagnosed with disseminated intravascular coagulation have a poor prognosis compared to the one's that don't get diagnosed with DIC. The advancement of the condition from coagulopathy in the vasculature of the lungs to DIC in patients who have tested positive for COVID-19 shows that the patient's dysfunction associated with coagulation has evolved from local to generalized state. Investigating the coagulopathies will help in understanding the mechanism of COVID-19 associated coagulopathy.

*Corresponding Author

Name: Shreya Pawar
Phone: 7021590292
Email: shreyap2412@gmail.com

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INTRODUCTION

The novel coronavirus infection which is caused due to "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)", has significantly contributed to the increase in mortality rate worldwide. The patients infected with "SARS-CoV-2" either present with no symptoms or with symptoms ranging from a mild cold to severe breathlessness (Brandon *et al.*, 2020). The virus was first recognized in Wuhan, China, where it killed around 3000 people at the beginning of March, after which a global pandemic was triggered. Most of the critically unwell patients present with dyspnoea or more progressive disorders like multi-organ failure. Most of the patients present with respiratory distress, after which the condition advances to more systemic disease and finally progresses to multiple organ dysfunction. One such feature which suggests a poor prognosis is a coagulopathy.

Pathophysiology

"COVID-19 associated coagulopathy" has multiple factors, and patients suffering from COVID-19 have many of the typical risk factors for venous thromboembolism seen in "adult respiratory distress syndrome" from other causes, such as immobility, systemic inflammation. Cytokine storm is the hallmark of COVID-19, which is characterized by hyped-up values of TNF interleukin 1, Interleukin-6 and some cytokines (Hardy *et al.*, 2020). Thrombosis is aggravated by inflammation activated by the tissue factor-factor VIIa pathway along with the other inflammatory cells and by the alteration in the natural anticoagulant pathways. Massive inflammation in combination with evidence of thrombosed pulmonary vessels has been noted in "adult respiratory distress syndrome" with different causes. Serum proteomic profiling of patients with "severe acute respiratory syndrome (SARS)" identified an "N-terminal fragment of complement C3C-alpha", which is a part of the complement pathway and has proven to be a sensitive biomarker of early "SARS". "Complement inhibition" has been suggested as a treatment for COVID-19, but clinical data are not yet available (Iba *et al.*, 2020). The supposed mechanism which is exclusive to COVID-19 of thrombosis of the microvasculature is the virus's affection for angiotensin-converting enzyme 2, manifested on epithelial type II cells of the alveolus along with other extrapulmonary tissues like the endothelial cells. Activation of the cells of the endothelium is a distinctive characteristical mechanism of COVID-19-mediated injury to the microvasculature and the sequelae that subsequently leads to multiple organ failure.

There is an 87.7% rate for positivity for "lupus anticoagulant" in patients with COVID-19 reported by Helms et al., which supports the idea that injury to the cells of endothelium is the explanatory mechanism of multiple organ failure in association with coagulopathy (Klok *et al.*, 2020). The "two-hit" model of thrombosis, which is linked with "antiphospholipid syndrome", states that after the injury to the cells of the endothelium, which is the first hit, the "antiphospholipid antibodies" cause the formation of thrombus, which is the second hit. Further investigation warranted due to the activation of the contact system caused by an increase in permeability of the vascular and microangiopathy caused due to thrombosis.

Platelets in COVID-19-Associated Thrombosis

Platelets play a dual role by protecting or by promoting a response that is immune-mediated towards the pathogens (Becker, 2020). Platelets get bound to a number of microorganisms by interacting directly, which is mediated by "Fc receptors" or indirectly through "plasma protein bridges". Just like agonist-activation, the binding of microorganisms can provoke liberation of "platelet microbial" proteins and peptides like platelet factor 4, normal T cell and fibrinopeptide B. Platelets play a massive role in the evacuation of the viral load. Interactions of the platelets with the leukocytes generate recruitment and infiltration of tissue which is essential for clearance of the pathogenicity. In terminally unwell patients, thrombocytopenia is associated with multiple organ failure and subsequent death. It is accompanied by a decline in the number of platelet count, even in the absence of thrombocytopenia which leads to a worse outcome. An exclusive characteristic of COVID-19 infection is the occurrence of extramedullary megakaryocytes that make platelets.

Site of Origin of Coagulopathy in COVID 19

COVID-19 manifests as cough, cold, fever, rhinorrhoea, loss of taste and anosmia in the majority of patients as an "upper respiratory tract disease".In patients with progressive clinical features show involvement of the lower respiratory tract. The typical features that including the ground-glass pattern, bilateral patchy infiltrates in CT findings of the chest in association with biopsy findings create a vital question about the lungs as a chief cause of COVID-19 associated coagulopathy (Becker, 2020). Epithelial cells secrete mucin, lactoferri, nitric oxide and defensin as a defense mechanism. They secrete other factors along with platelet-activating factor-like IL-1β, (TNF)-alpha and granulocyte-macrophage colony-stimulating factor in employing inflammatory cells. The respiratory tree is lined by the inflammatory cells and the mediators of inflammation, after which the pathogens get phagocytosed and secrete chemokines and cytokines and other mediators of inflammation**.** The parenchyma of the airway tract and the lungs is infiltrated with lymphocytes. Immunity is provided by the T-cells, which is mediated by the cells and the synthesis of antibodies, whereas B cells provide immunity by human responses. Migration of the neutrophils takes place at the interstitial spaces and into the alveolus from the capillaries where they are appointed at the infected or the inflamed site. Viral infections stimulate the immune system, which is innate in nature through the toll-like receptors that identify patterns formed by the molecules. Helper- T cells produce IF-γ.During the infection, the lungs hold some significant functions like preservation of generalized homeostasis, and it regulates the responses of regulation. The negative feedback loop is initiated

by the activation by factors like interleukins which prevents the formation of inflammatory responses in association with the cytokines. Furthermore, Depression of the inflammatory signals is caused due to neural-immune interactions. Observation with the lethal infections related to COVID 19 is the inability to manage the intensity of the inflammation. Platelets are released in a dynamic fashion as the megakaryocytes circulate through the microcirculation of the lungs. The megakaryocytes of the lungs originate from the bone marrow. They contribute very substantially to the pulmonary synthesis, which is anchored within the vasculature of the lungs. Restoration of the stores of the bone marrow is carried out by megakaryocytes which are present in the lungs and the blood cells forming progenitor cells. Inflammation, infection, dysfunction of the lungs and cardiovascular embarrassment caused an increase in the density of megakaryocytes of the lungs. Pulmonary thrombopoiesis is observed in patients with "Adult respiratory distress syndrome" and injury to the lungs. Activation of the platelets contributes to furthermore harm. The systemic condition of the patient determines the accessible proof proposes that ~ 90% of unblemished megakaryocytes of aspiratory beginning stay in the microcirculation of the lungs; in any case, an expanded extent can leave and enter the blood vessel course within sight of lung contamination and irritation. Platelet creation from megakaryocytes in the fringe flow can happen. Fox et al. recognized a high thickness of captured neutrophils in the lungs of Covid-19 decedents, which may mirror a favorable to fiery and prothrombotic fabricating plant that delivers the conditions fundamental and suitable for Covid-19-related coagulopathy in an inadequately controlled state. The solid cytokine reaction is seen in basically sick Covid-19 patients, just as likenesses to optional HLH or macrophage initiation disorder, recommend that medications focusing on at least one pathogenic cytokines in the lungs may have both nearby and fundamental advantages. IL1 canakinumab, IL6 tocilizumab, (TNF)- infliximab, and lanzilumab are a portion of the treatment targets.

Coagulation Markers

The increase in D-dimers has been one of the most common laboratory findings in COVID-19 patients who needed hospitalisation. A D-Dimer with a normal value of less than 0.50 is considered normal. A positive D-Dimer has a value of 0.50 or higher. E xcessive coagulation activation and hyperfibrinolysis are signs of elevated D-dimer levels (Iba *et al.*, 2020). As a result, D-dimer is often used to detect active thrombus, despite its poor specificity. D-dimer levels steadily decreased after anticoagulant treatment, indicating that D-dimer does not only predict thrombosis but also control anticoagulant effectiveness. Patients with significantly elevated D-dimers should be admitted to the hospital even though they have no other severe symptoms, as this clearly indicates increased thrombin production. The prothrombin time (PT) and platelet count are two other diagnostic tests that are usually performed on sick patients.

Monitoring Coagulation Markers

Identification of worsening coagulopathy is made by monitoring the hemostatic markers (Thachil *et al.*, 2020). Monitoring D-Dimer, prothrombin time, Activated partial prothrombin time, serum fibrinogen is recommended by Simon et al.

Management of Coagulopathy

The most widely recommended management is the administration of a prophylactic dose of low molecular weight heparin or unfractioned heparin in the absence of any contraindication. Along with the antithrombotic properties, heparin also possesses anti-inflammatory and anti-viral properties. In case of worsening of parameters, more aggressive care is warranted, use of experimental therapy is considered along with support from blood products. If the markers are stable in addition to the clinical condition, stepping down of the treatment is considered (Klok *et al.*, 2020).

CONCLUSION

The death rate due to COVID-19 is increasing exponentially. The probable rationale for it is the increased frequency of thrombosis in patients suffering from the disease. Raised levels of D-dimer suggests the presence of hyperfibrinolytic activities. COVID-19 associated coagulopathy is multifactorial and has many aspects to it which are unique from the coagulopathies which result due to other etiologies. This multifactorial dysfunction is a major cause for morbidity in the current scenario, which is dominated by the SARS-CoV-2 and is yet to be understood and studied further for its befitting management.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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