Review Article

Anticoagulants in Covid-19 Therapy: An Evidence-Based Review

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ABSTRACT

The novel coronavirus disease 2019 (COVID-19) which is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has affected humans globally and has led to significant morbidity and mortality. The virus is believed to be transferred from bats and most commonly affects the respiratory system, lungs as the primary site of infection. The patients can have a varied presentation from being asymptomatic to develop acute lung injury worsening to respiratory failure and even multiorgan failure leading to death. The novel nature of the virus is the reason for the absence of prior immunity and has ended up in a huge surge of cases globally. The clinical presentation of COVID-19 has been evolving as the number of cases increasing and hence the plan of treatment also keeps on modifying. The classical symptoms include fever, dry cough, tiredness, and sometimes can also have nasal congestion, headache, conjunctivitis, sore throat, diarrhoea rash on the skin, anosmia, hyposmia, ageusia, and dysgeusia. COVID-19 has also been seen to be associated with coagulopathy because of a prothrombotic state in the venous and arterial circulations which can be due to SARS-CoV-2 induced inflammation, dysregulation of the coagulation cascade, platelet activation and endothelial dysfunction. The presentation can mimic the patients with disseminated intravascular coagulopathy and the initial stage mostly presents with an elevation of D-dimer and fibrin degradation products. Primary screening of the coagulation profile is suggested along with the estimation of D-dimer and fibrinogen levels to assist in early recognition of the high-risk patients and also predict prognosis. Early diagnosis and intervention with anti-coagulants can improve prognosis and associated complications. This article reviews the epidemiology, pathogenesis, presentation, and management of the abnormal coagulation findings related to COVID-19.

Keywords: COVID-19; Coronavirus; Coagulation findings; SARS-CoV-2; Anti-coagulants; Heparin.

INTRODUCTION

The novel coronavirus disease 2019 (COVID-19) has led to a radical increase in worldwide morbidity and mortality. It is caused by novel Coronavirus (nCoV) which is thought to be classically found in bats and birds and was transmitted to humans.[1] Bat was found to be the most suspected animal among all because of 96% genomic nucleotide sequence similarity of the bat Coronavirus(CoV) to nCoV.[2] Suggestions have also been made about pangolins being a possible intermediate host of nCoV after finding about 85.5-92.4% CoV genomic similarity between pangolin CoV and nCoV.[3] However, none of these theories have been proven to date.[4] Early cases started coming in December 2019 from Wuhan, Hubei Province, China with patients presenting as cases of pneumonia with an unknown etiology.[5] Thereafter, with the isolation of the pathogen from the lower respiratory tract, it was named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[6] Soon it began to spread from Wuhan to other countries also following which the World Health Organisation (WHO) declared it as an emergency and later on 11th March 2020 it was declared as a pandemic.[5,6,7] According to WHO, presently an overall 4,218,212 cases and 290,242 deaths have been confirmed.[8] The worst-hit areas have been Europe, the USA, Eastern Mediterranean in addition to this further spread has occurred in Western Pacific, South-East Asia, and the African region.[8]

The clinical features of COVID-19 have a wide array of presentations and differ in individuals with certain people having an asymptomatic state to others having a state of acute respiratory distress syndrome.[9] The clinical features are typically mild in nature and appear steadily. General symptoms include fever, dry cough, and tiredness. The less frequent symptoms affecting certain patients include aches and pain, nasal congestion, headache, conjunctivitis, sore throat, diarrhoea, loss of taste or smell, or a rash on skin or discoloration of fingers or toes.[10] Laboratory findings include lymphopenia, elevation in lactate dehydrogenase and inflammatory markers such as C-reactive protein, D-dimer, ferritin, and interleukin - 6.[2,11] Computed tomography (CT) scans show bilateral pulmonary parenchymal ground-glass opacity with pulmonary consolidation and presence of nodules having a bilateral diffuse distribution with a rounded morphology with peripheral lung distribution.[12,13] Certain unusual findings were also reported to be associated with COVID-19 such as anosmia, hyposmia, ageusia, dysgeusia along with certain dermatological, auditory, and coagulation findings.[14,15] This review describes the pathogenesis, presentation, and management of the abnormal coagulation findings related to COVID-19.

Structure of Novel Coronavirus SARS-COV-2

The genome of SARS-CoV-2 encodes a large non-structural protein that is further proteolytically cleaved to generate 15/16 proteins, 4 structural proteins, and 5 accessory

proteins.[16,17] These four structural proteins are composed of spike (S) surface glycoprotein, the membrane (M) protein, the envelope (E) protein, and the nucleocapsid (N) protein which is required for SARS-CoV-2 assembly and infection.[18]

The novel coronavirus can be transmitted among humans through respiratory droplets.[19] Though, there are other routes of transmission like though direct and indirect contact with mucous membranes of eyes, nose, and mouth.[19, 20, 21]

Infection and Pathogenesis of COVID-19

SARS-CoV-2, a single-stranded RNA coronavirus enters the human cells majorly by attaching with the angiotensin-converting enzyme-2 (ACE-2) which is vastly present in the alveolar cells, cardiac myocytes, vascular endothelium, and other cells.[22] As a part of innate immunity, infection by bacterial, viral, or fungal pathogens initiates complex systemic inflammatory responses.[23] Activation of the host defense systems results in the commencement of coagulation and thrombin generation via humoral and cellular amplification pathways which are termed as thromboinflammation or immunothrombosis.[23,24,25] Polyphosphates that are formed from microorganisms trigger the activation of platelets, mast cells, and factor XII in the pathway of coagulation and is also culpable for other downstream roles in increasing the procoagulant reaction of the intrinsic coagulation pathway.[26] In addition to this, the complement system is also responsible for the activation of the coagulation factors hence enhancing the procoagulant state.[27] Activation of neutrophils by microbial or inflammatory stimuli tends to release neutrophil extracellular traps (NETs) which are basically made up of DNA, histones, and antimicrobial proteins.[28] These NETs which are present in thrombi activates the intrinsic pathway and also promote the extrinsic pathway by degrading the tissue factor pathway inhibitor hence enhancing the production of thrombin.[28,29] The inflammatory effect of cytokines tends to activate the endothelial cells and additional endothelial injury leads to a resultant prothrombotic environment.[28,30] An inflammatory response to infection also results in the reduction of the levels of circulating serine protease inhibitors which include antithrombin, C1 esterase inhibitor and protein C hence increasing prothrombotic state again.[31]

Similar kind of coagulopathy and coagulatory changes have also been found the patients of COVID-19 and has been termed as COVID-19 associated coagulopathy (CAC).[32]

COVID-19 and Coagulopathy: Evidence as Reported

COVID-19 associated coagulopathy, in its early stage, reflects the test abnormalities however it does not fulfill the usual description of a clinical coagulopathy in which there is a loss of ability to clot resulting in bleeding.[32] Among the hemostatic abnormalities, the most constant finding found in patients suffering from COVID-19 is mild thrombocytopenia and increased D-dimer levels, which are connected with a higher risk of requiring mechanical ventilation, intensive care unit admission, or death.[33,34] Early on, the reports about the atypical coagulation parameters in patients with COVID-19 came from China. Chen N et al in his study of 99 hospitalized COVID-19 patients found that 6% had increased elevated activated partial thromboplastin time (aPTT), 5% had increased prothrombin time (PT), 36% had elevated D-dimer levels, increased levels of the biomarkers of inflammation which include interleukin-6 (IL-6), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP).[35] Thrombocytopenia was found in only 12% however, 5 patients had other co-infections (1-bacterial, 4-fungal), and 4 were in septic shock.[35] It is been seen that correlation between the severity of disease and inflammation can be found by tracking the D- dimer levels and it points towards the fact about the interaction between inflammation and activation of coagulation.[32] An analysis by Zhou F et al of 191 patients from two Wuhan hospitals showed mortality in 28% (n=54) of the total patients.[11] The factors found associated with mortality were an elevated D-dimer which was >1.0 µg/ml during the time of admission, increased levels of PT, IL-6, troponin levels, and other biomarkers of inflammation.[11] Each of the 54 nonsurvivors among these, met the sepsis definition criteria and of these, about 50% showed evidence of coagulopathy.[11] Tang N et al in an analysis conducted on 183 COVID-19 patients based on survivor status from the time of admission till 14 days stated that 78 (42.6%) patients had been discharged and 21 (11.5%) patients had died while the rest 84 (45.9%) were still hospitalized.[36] Among the 21 nonsurvivors, 15 were diagnosed with evident disseminated intravascular coagulation (DIC) based on the International Society on Thrombosis and Haemostasis (ISTH) criteria with a median onset of 4 days (1-12 days) after admission.[36] Meanwhile, only 1 out of the 78 discharged patients showed evidence of DIC. The nonsurvivors over their course of hospitalization also showed evidence of progressive DIC with decreased levels of fibrinogen, increased levels of D-dimer, and increased PT during the 10 days of admission.[36] An early report about COVID 19 patients from Wuhan by Huang C et al showed much higher levels of proinflammatory cytokines in the critical patients admitted in an intensive care unit (ICU) as compared to non-ICU patients.[37] An admission report by Ranucci M et al on 16 COVID-19 patients suffering from acute respiratory distress syndrome (ARDS) who were on mechanical ventilation showed increased levels of IL-6 in correlation with increased levels of fibrinogen thereby signifying and confirming the link between inflammation and procoagulant changes.[38] Inconsistency with vascular endothelial dysfunction with sepsis-induced coagulopathy, endotheliopathy also takes part in the pathophysiology of the microcirculatory changes in SARS-CoV-2 infections.[30,39] Post mortem reports of SARS-CoV-2 infected patients by Varga Z et al demonstrated the presence of viral inclusions within the endothelial cells and sequestrated mononuclear and polymorphonuclear cellular infiltration with possible proof of endothelial apoptosis.[40] So it can be said that

microcirculatory dysfunction also plays a role in the clinical sequelae in patients with COVID-19. In addition to these, nutritional deficiencies and liver dysfunction can further worsen the scenario by a decrease in the production of coagulation factors.[41] A study by Wang T et al from China which was conducted using the Padua model showed that 40% of the total hospitalized patients suffering from COVID-19 were at high risk of venous thromboembolism (VTE).[42]

Recommendations to Prevent Coagulopathy

Based on the evidence and scenario, it seems that all the hospitalized and acutely ill patients should undergo the risk stratification for early diagnosis and treatment of VTE in these patients. The coagulation testing should be performed on admission in all hospitalized patients with newly confirmed or presumptive COVID-19 infection which should include D-dimer, PT, aPTT, fibrinogen, and platelet count which can detect the prognosis early in the course of the disease.[36]

According to the current recommendations by the International Society on Thrombosis and Haemostasis, all patients be it critical or non-critical requiring hospital admission for COVID-19 infection should receive a prophylactic dose of low molecular weight heparin (LMWH) unless and until it is contraindicated in cases with active bleeding and platelet count of <25 x 10^9/l.[43] The American Society of Hematology (ASH) recommends that all hospitalized patients with COVID-19 must receive pharmacologic thromboprophylaxis with LMWH or fondaparinux unless and until it is contraindicated or unavailable.[44] If the pharmacologic thromboprophylaxis is contraindicated or unavailable then in such a case use of mechanical thromboprophylaxis is advised.[44] The ASH, still does not recommends empirical therapeutic intensity anticoagulation in seriously ill COVID-19 patients (i.e. in absence of confirmed VTE).[44]

A study conducted by Tang N et al on 449 severe COVID-19 patients stated that about 99 patients received prophylactic VTE anticoagulation for 7 days with 94 being treated with enoxaparin 40-60 mg/day and rest 5 were treated with unfractionated heparin 10,000-15,000 U/day.[45] Of the 449 patients, 22% (n=97) had an ISTH sepsis-induced coagulopathy score (SIC) score of >4, and 29.8% (n=134) patients died at the time of reporting. There was no difference seen in the 28-day mortality between heparin and non-heparin treated patients but stratification by SIC score identified lower mortality in patients treated with heparin, the SIC score being >4 (40.0% vs 64.2%, p=0.029) compared with the SIC score <4 (29.0% vs 22.6%, p=0.419).[45] In addition, a 20% reduction in mortality was observed after patients with D-dimer levels >3.0µ/ml were treated with prophylactic doses of heparin (32.8% vs 52.4%, p=0.017).[45] The preliminary step for the management of DIC is to identify and treat the underlying condition and if found bacterial superinfections they should be treated aggressively. Providing LMWH prophylaxis may decrease thrombin generation and modify the course of DIC. These early results from a study conducted the Tang N et al suggest favorable response in support of LMWH prophylaxis in COVID-19 patients.[45]

CONCLUSION

The current pandemic of COVID-19 has shown a varied presentation and the signs are symptoms that have been evolving with time. The SARS-CoV-2 infection has also presented with dysregulation of the coagulation cascade leading to thromboinflammation and thrombosis. It can present with VTE and even in severe cases can lead to DIC. The coagulation profile should be screened and if required, the therapy with anticoagulants should be started early in the treatment as per the standard guidelines to prevent the complications of the disease.

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