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Venous thromboembolism in patients with COVID-19. A prevalent and a preventable complication of the pandemic

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ABSTRACT

Coronavirus disease 2019 or most commonly known as COVID-19 is a trending global infectious disease which a few months ago was affirmed as a global health emergency or a pandemic by the WHO Emergency Committee. The common symptoms manifested in this pandemic disease are high grade fever, cough, fatigue, shortness of breath and flu like symptom which can evolve into severe respiratory disorders such as pneumonia, acute respiratory distress syndrome (ARDS) and/or end-organ failure. Factors that contribute to the severity or high mortality rate in COVID-19 include old age, comorbidities like hypertension, diabetes, hyperlipidaemia, neutrophilia, and organ and coagulation dysfunction. Disseminated intravascular coagulation and other various coagulopathies including Venous thromboembolism have known to become a major contributing factor to high mortality rate. Venous thromboembolism is a disease which is a combination of deep vein thrombosis and pulmonary embolism. Prophylactic anticoagulation in patients prone to or with a pre-existing history of venous thromboembolism is associated with decreased mortality in severe COVID-19 pneumonia. This review article focuses upon COVID-19 and increased incidence of venous thromboembolism in patients infected by COVID-19 along with the role it has in high mortality rate in COVID-19 patients.

1. Introduction

Coronavirus disease 2019(COVID-19) is a trending global health emergency or a pandemic caused by severe acute respiratory syndrome coronavirus2(SARS-COV-2) This infectious disease was first detected in December 2019 in Wuhan, China and has now become an ongoing global health emergency.[1]Currently, more than 108 million cases of infection and 2.38 million deaths have been reported world wide.SARS-CoV-2 belongs to the family Coronaviridae and order Nidovirales. The family comprises two sub-families, Coronavirinae and Torovirinae. The members of the subfamily Coronavirinae are further subdivided into four genera, which are as follows:(a)Alphacoronavirus, which encompasses the human coronavirus(HCoV)-229E and HCoV-NL63; (b)Betacoronavirus, which includes HCoV-OC43,severe acute respiratory syndrome human coronavirus (SARS-HCoV), HCoV-HKU1, and Middle Eastern respiratory syndrome coronavirus (MERS-CoV); (c) Gammacoronavirus, which includes viruses of whales and birds, and(d)Deltacoronavirus, which includes viruses isolated from pigs and birds.SARS-CoV-2 is a member of the genus Betacoronavirus along with two extremely pathogenic viruses, SARS-CoV and MERS-CoV.SARS-CoV-2 contains an enveloped and positive-sense single-stranded RNA(+ssRNA).[2]The symptoms manifested in this disease include high-grade fever, cough, fatigue, body aches, shortness of breath and flu-like symptoms, etc., which may progress to severe respiratory disorders such as viral pneumonia, acute respiratory distress syndrome (ARDS), respiratory failure and/or end-organ failure.[2–5] Other known comorbidities such as hypertension, hyperlipidemia, diabetes, and pre-existing ischemic heart disease and respiratory disorders increase the propensity of fatality in COVID-19 in addition to lifestyle factors such as smoking and alcohol intake.[6–7] The disease is mainly transmitted between individuals via close contact, most often through droplet infection occurring while coughing, sneezing, and speaking. Rarely, people may contract the infection by touching a contaminated surface and then touching their face.[7–8] Infected patients are more prone to be contagious or spread the disease during the first three days after the onset of symptoms, even though contagion is possible before symptoms appear; asymptomatic patients can spread the disease as well.[8] A study conducted by Liet al. showed that human-to-human transmission had occurred among close contacts since the middle of December 2, 019.[9] The current standard method for diagnosis is the real-time reverse transcriptase polymerase chain reaction (rRT-PCR), the sample for which is obtained from a nasopharyngeal swab.[10] Chest computed tomography (CT) imaging has

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proven to be helpful in diagnosis in individuals in whom there is a high suspicion of infection based on symptoms and risk factors; however, guidelines do not recommend the use of CT imaging as a routine screening modality.[5,11,12,13] Laboratory findings in the early stages of the disease include lymphocytopenia,[14] elevated CRP, neutrophilia, mild thrombocytopenia, prolonged prothrombin time, and increased levels of D-dimer and fibrinogen. Low levels of fibrinogen are seen in severe cases of COVID-19.[15–17] Venous thromboembolism (VTE), a common cardiovascular and respiratory complication seen among hospitalized patients, is one of the well-known sequelae of the illness. COVID-19 patients who require hospitalization are usually elderly and immobile and display signs of coagulopathy.[18] Hence, it is likely that increased rates of VTE are seen among these COVID-19 patients. Currently, the incidence of VTE is 25% in patients admitted to the intensive care unit for COVID-19, even under anticoagulant treatment at prophylactic doses.[19,20]

2. VTE in patients with COVID-19

Numerous current studies propose the presence of hypercoagulable states, predominantly VTE, in patients presenting with COVID–19. VTE is a name given to a group of coagulation disorders, which comprise deep vein thrombosis and pulmonary embolism (PE). Deep vein thrombosis is a phenomenon of the formation of blood clots in the deep veins of the lower limbs, but may also occur in other parts of the body.[21,22] Venous thrombosis consists of the so-called Virchow's triad, which comprises irregular blood flow, blood coagulation disorders, and vessel wall abnormalities. The symptoms of VTE include erythema, pain, and edema.[23,24] Patients with COVID-19, particularly those with severe disease, have a predisposition to develop coagulation disorders. Coagulation disorders among COVID-19 patients are associated with an increased risk of a fatal outcome.[25–27] In viral infections such as SARS-COV-2 infection, the human body, as part of the innate immunity reaction, induces a complex systemic inflammatory response.[2] Initiation of this host defence mechanism results in activation of the coagulation pathway and generation of thrombin as an important communication factor between the humoral and cellular amplification pathways, an expression known as thromboinflammation or immunothrombosis.[28,29] Coagulation in COVID-19 patients is triggered by the inflammatory response through several procoagulant pathways. The microorganisms also produce polyphosphates, which in turn stimulate platelets, mast cells, and factor XII (FXII) in the contact pathway of coagulation, and manifest other mechanisms involved in intensifying the procoagulant reaction of intrinsic coagulation. Activation of coagulation factors can also occur via the complement pathway mechanisms.[28] This results in the release of enormous inflammation boosting cytokines that act on the liver, thereby stimulating it into the production of clotting factors;[30,31,3] for example, fibrinogen levels in critically ill COVID-19 patients were found to be 10–14 g/L compared to the normal value of 2–4 g/L in healthy individuals and a value of 5–6 g/L in pregnant women.[30] A study conducted by Tang et al. established elevated levels of fibrinogen and D-dimer and prolonged PT in infected patients.[32,33] In another study conducted by Ranucci among 16 COVID-19 patients with ARDS requiring mechanical ventilation, it was verified that elevated IL-6 levels were associated with elevated fibrinogen levels, thereby establishing the linkage between inflammation and procoagulant changes.[34] Substantial inflammation in patients with SARS-CoV-2 infection, shown by elevated levels of IL-6, increased C-reactive protein and erythrocyte sedimentation rate, and elevated levels of fibrinogen at the time of presentation to hospital have been reported.[35] Endothelial cell activation and damage resulting from the disruption of the natural anti-thrombotic state are likely due to the affinity of the virus for ACE-2 receptors. Plasma concentrations of pro-inflammatory cytokines were higher in ICU than in non-ICU COVID-19 patients in Wuhan based on an early report.[3,28] The subsequent activation of coagulation along with the inflammation occurring due to COVID-19 is the probable cause for the elevated D-dimer levels.[28] The infection induces dysfunction of endothelial cells because excess thrombin generation and fibrinolysis shutdown occur, which indicates the presence of a hypercoagulable state in patients with COVID-19. Moreover, in severe COVID-19, hypoxia due to respiratory complications initiates thrombosis by increasing blood viscosity and via a hypoxia-inducible transcription factor-dependent signalling pathway.[33] About a quarter of patients not on any thromboprophylaxis have developed VTE, of which 40 have died.[36,37] The majority of these patients were found to have elevated levels of D-dimer$>$ 1.5 μg/mL, thereby predicting VTE with a sensitivity of 85% and specificity of 88.5% and a negative predictive value of 97.4%. This raises the question of the significance of the measurement of D-dimer levels in COVID-19 patients.[37,38]

Patients with a history of ischemic heart disease or injury who contract COVID-19 have been shown to be increasingly predisposed to the development of coagulation disorders when compared to those without any cardiac involvement. These patients, who might have high Troponin-T levels, might present with increased prothrombin time ($P = 0.005$), activated partial thromboplastin time (APTT) ($P = 0.003$), and D-dimer ($P < 0.001$).[39]

Another notable thromboembolic event occurring in COVID-19 patients is PE. However, the pathophysiology of PE is different in COVID-19 patients. The thrombi, instead of migrating from other parts of the body to the lungs, are formed in the pulmonary vessels themselves owing to local inflammatory processes.[40] It is clear that the activation of the coagulation pathway could perhaps occur by the contact system and the kallikrein/kinin system (KKS).[41] Since the kallikrein/kinin system is dysregulated by binding of SARS-CoV-2 to ACE-2 receptors in type II pneumocytes of the lungs, this could be the probable mechanism of the association between COVID-19 and the occurrence of thrombosis in pulmonary vessels.[42] Even though PE is thought to be a comparatively late complication of severe COVID-19, it is important to determine whether the perceived median period of 7 days to the onset of thrombotic events is actually the median period after the first onset of COVID-19 symptoms.[43]

3. Management of VTE in COVID-19 patients

In any acute and severe infection, there is a risk of VTE; hence, prophylactic anti-thrombotic therapy at regular dosages is vital. Use of low molecular weight heparins (LMWH) or unfractionated heparin (UFH) is preferable to using direct oral anticoagulants (DOACs). This is due to possible drug interactions with co-administered antiviral drugs such as anti-HIV protease inhibitors like ritonavir or antibacterial medications such as azithromycin. These drugs might interfere with CYP3A4 and/or P-gp pathways and could possibly increase the risk of bleeding or decrease the anti-thrombotic effects of DOACs.[44,45] Generally, in the absence of the need to alter the dose of LMWH when there is concomitant thrombocytopenia, in general, an optimal balance between thrombotic complications and the risk of bleeding should be attempted.[46] Initial outcomes also indicate a possible positive effect of LMWH in the prevention of VTE and its complications among patients with very severe COVID–19.

COVID-19 patients can quickly progress to a stage of severe or life-threatening disease, resulting in a series of complications such as renal failure, respiratory failure, or liver dysfunction, which may in turn affect both the risk of VTE and the bleeding status of the patient. Thus, careful evaluation of VTE and bleeding risks is vital.[4,47,48] In a study in China conducted by Wang et al. on behalf of the National Clinical Research Centre for Respiratory Disease, together with the National Health Commission of the People's Republic of China, data were collected from 1099 laboratory-confirmed COVID-19 patients in 31 provincial administrative regions throughout the country. After the exclusion of 73 patients, from among the 1026 patients selected, 407 patients were considered to beat high risk on the basis of Padua prediction score. Anticoagulation medications were used as the mainstay therapeutic option for VTE prophylaxis in these patients; nonetheless, COVID-19 patients who were highly prone

to developing VTE in this study were also found to be highly prone to bleeding complications. In these patients, the duration and dosage of anticoagulant medications should be adjusted depending upon their status, and mechanical compression techniques, such as the use of elastic compression stockings or intermittent pneumatic compression, were preferred.[48]

In a retrospective analysis study by Tang et al. conducted at the Tongji Hospital of Wuhan, China, it was stated that 22% of severely affected COVID-19 patients in the study had reduced rates of mortality with few mild bleeding complications when treated mainly with heparin, Low molecular weight heparin like enoxaparin at thromboprophylactic dose of 40–60 mg/day and a few patients received UFH (10 000–15 000 U/d) for at least 7days. Some studies have reported occlusion and microthrombi formation in small pulmonary vessels among critical COVID-19 patients. Therefore, improved outcomes from early application of anticoagulant therapy in patients with severe COVID-19 was reported in China.[33]

In patients at risk of developing thrombosis, it is crucial that precaution is taken not to miss the occasional occurrence of PE. The treatment strategy in stable patients is different from that in unstable patients. The preferred treatment modality among unstable patients is reperfusion therapy, which is carried out via thrombolysis and UFH.[36] However, most COVID-19 patients exhibit an absolute or relative resistance to thrombolysis, which could be due to accompanying complications such as coagulation disorders, thrombocytopenia or a history of recent invasive procedure, pericarditis, and old age of >75 years.[5,18,49] Furthermore, invasive diagnostic or interventional procedures, such as insertion of central-line catheters, pericardiocentesis, chest tube insertion, or ECMO, which might be indicated in patients who have received thrombolysis, could not be performed due to the risks posed by thrombolysis. Although it is challenging to discriminate between the two clinical pictures, one should be aware that if hemodynamic imbalance is due to infectious disease and not due to VTE, then thrombolysis is not the preferred choice of treatment. One of the diagnostic clues for PE as a cause of hemodynamic instability is impaired RV function. RV failure related to PE may also respond to a fluid replacement or to vasopressors, both of which may already be administered to some COVID-19 patients. No cases of thrombolytic therapy for PE in COVID-19 patients have been published so far. However, thrombolysis was used off-label for ARDS.[50,51]

In countries such as the Netherlands, a considerable number of patients are still being treated using Vitamin-K antagonists for situations such as concomitant the presence of mechanical heart valves, elderly patients with a history of atrial fibrillation, but with good renal functional status with monitoring of their INR levels.[52]

The anticoagulation regimen among patients with stable PE generally involves the use of LMWH or DOACs. Among patients associated with intermediate- or high-risk PE, UFH can also be considered ideal owing to its short half-life and the potential advantage of the option of use of protamine sulfate as an antidote in case the patient needs an urgent procedure or suffers from bleeding. However, UFH administration would necessitate cautious monitoring, which we might want to avoid in a highly contagious disease such as COVID-19. Therefore, in COVID-19patients, LMWH may be preferred. For other various causes, in order to reduce the contact between nurses and COVID-19 patients some establishments might favour DOACs.[36,53] Inferior vena cava filters should be considered in certain patients with acute PE and absolute contraindication to anticoagulation, or in cases of recurrence despite proper anticoagulant treatment.[54]

Regarding the initiation of treatment, the current European Society of Cardiology PE guidelines[54] highlight the need for initiation of anticoagulation treatment in all suspected high-or intermediate-risk patients for PE without any holdup, while diagnostic workup to confirm the diagnosis is in progress. Keeping in mind the likelihood of delay in the confirmation of the diagnosis following safe guarding of the medical team, decontamination of the equipment, and the difficulties occurring in the due course of transfer of hemodynamically unstable or intubated patients out of the ICU, these recommendations by the European Society of Cardiology are also mostly relevant among COVID-19 patients.

4. Conclusion

VTE is one of the most common and preventable causes of death among hospitalized patients. Among COVID-19 patients, VTE presents a unique challenge to an already unique, unprecedented illness. First, the diagnosis has to be assumed in spite of the presence of varied differential diagnoses and causes of respiratory disorders and hemodynamic decline such as ARDS, secondary bacterial infection, and heart failure. Afterwards, if the diagnosis is confirmed, one needs to contemplate starting full-dose anticoagulation and the risk associated with the diagnostic workup.

As anticipated during a pandemic breakout, there is currently a lack of data describing the true features and incidence of VTE among COVID-19 -positive patients. At present, only few studies are available describing an incidence of 27% for VTE in COVID-19 patients hospitalized in the ICU receiving prophylactic anticoagulation and 25% for DVT in COVID-19 patients hospitalized in the ICU, along with a few case reports. Further data and evidence regarding the disease will surely be available in the immediate future. COVID-19 as of now still stands as a major, lengthy, complex, and at times fatal threat. However, during hospital admission, numerous complications might ensue, which could impact the outcome of the disease in these patients. Such is the case with VTE, particularly due to the risk of under diagnosis, under-treatment, and possible progression to PE. Hence, the significance of understanding the tangible burden of VTE in these patients and the appropriate treatment strategies throughout these exceptional situations cannot be over-estimated. A proper authorized management protocol for COVID-19 is not yet available, but VTE is a well-established clinical disorder, with possibly avertable and curable consequences. Further studies are required to obtain a stronger insight into the efficacy of modes of treatment, and a model needs to be formulated to ensure their implementation and achieve better results in the management of VTE in COVID-19 patients.

V. Conflict of interest

The authors have no conflict of interest.

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