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Review Article

Clinical Experience, Pathophysiology, and Considerations in the Prophylaxis and Treatment of Hypercoagulopathy of COVID-19: A Review Study

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What's Known

- Since the emergence of the COVID-19 pandemic, an increasing number of reports and studies have tried to warn the medical community about the thrombotic complications of CVOID-19. It is suggested that the hyperinflammatory response and endothelial injury, especially in patients with severe disease, lead to a hypercoagulable state.

What's New

- COVID-19 increases the risk of thrombotic complication via induction of a hypercoagulable state.
- In the absence of contraindications, thromboprophylaxis with at least standard-dose low-molecular-weight heparin is recommended by major societies for all severely or critically ill hospitalized patients.
- Antiplatelets should not be used to prevent thrombotic complications.
- Hypercoagulopathy may temporarily continue after the acute phase of the illness; thromboprophylaxis extension may be considered in patients who were critically ill.

Abstract

Since the emergence of the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) pandemic, an increasing number of reports and studies have tried to warn the medical community about the thrombotic complications of coronavirus disease 2019 (COVID-19). It is suggested that the hyperinflammatory response and endothelial injury, especially in patients with severe disease, lead to a hypercoagulable state. Sudden deaths occurring in some patients also point to fulminant arrhythmias and massive pulmonary embolism (PE). Several expert panels have published recommendations regarding the prophylaxis and treatment of such complications. Nonetheless, there are limited high-quality studies for evidence-based decision-making, and most of these recommendations have arisen from descriptive studies, and optimal anticoagulant agents and dosages are yet to be designated. The coagulopathy persists after the acute phase of the illness, and some panels recommend the continuation of deep vein thrombosis prophylaxis for several days after regaining the normal daily activities by the patient. Here, we review the incidence and possible mechanisms of thrombotic complications, and present a summary of the considerations for the prophylaxis and treatment of such complications in the adult population.

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Introduction

In late December 2019, cases of a presumably novel viral pneumonia emerged from Wuhan city in Hubei Province, China, which immediately spread to other countries and caused numerous cases of acute respiratory failure and massive consumption of healthcare resources. Soon a novel member of the *Coronaviridae* family, later called "severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2)", was identified as the etiology of this outbreak, and the disease from the virus was generally termed "COVID-19". Later, on March 11th, World Health Organization declared the COVID-19 outbreak as a pandemic. SARS-CoV-2, a single-stranded RNA virus, contains spike proteins on its envelope, that attach to a complex of host cell membrane proteins, in which angiotensin-converting enzyme 2 (ACE2) and transmembrane protease, serine 2 (TMPRSS-2)

are the major cell entry elements.[1] ACE2 is highly expressed in type II pneumocytes and enterocytes, followed by the proximal tubules of renal nephrons, vascular endothelia, brain, the cholangiocytes of the liver, and the bone marrow. Almost all tissues express this protein.[2] As mentioned above, endothelial cells express ACE2 and may protect against viral invasion. The probability of endothelial inflammation gives rise to the hypothesis that diffuse thrombosis and ischemia in the microvascular bed of organs may be implicated in the rapid deterioration of some patients.[3-5] Moreover, significantly higher viral RNA titers have been identified in the kidneys, livers, and hearts of more than 40% of deceased patients.[6] Still, despite the vast expression of ACE2 in the human body, the cytokine release syndrome (CRS) is the number one suspected mechanism for multiorgan failure in patients with severe disease, not the direct invasion of organs by the virus itself.[7, 8] Whether the multiorgan failure is because of CRS or diffuse ischemia, or both, is unclear. However, it is speculated that through similar signaling pathways, viral invasion, and CRS both lead to endothelial injury, and the release of coagulation factors, eventually leading to a hypercoagulable state.[9] Another finding that suggests fulminant cardiovascular events is the occurrence of sudden deteriorations and deaths among patients.[10] To date, the optimum dosage of low-molecular-weight heparin (LMWH) for thromboprophylaxis purposes in patients with COVID-19 has not been designated, and many experts call for high-quality clinical trials. There is an increase in the incidence of thrombotic complications even among patients receiving standard-dose thromboprophylaxis.[11, 12] In this study, we review the evidence regarding thrombotic complications and their probable pathophysiology and present the current recommendations for the prophylaxis and treatment of such complications. We do realize that these recommendations are mostly expert opinions and maybe revised by upcoming high-quality studies.

A Rapid Review of the Clinical Experience and Observations

There has been a surge in thrombotic complications affecting both intensive care unit (ICU) and non-ICU COVID-19 inpatients.[13, 14] A postmortem study of 12 inpatients demonstrated the presence of deep vein thrombosis (DVT) in 58%, and PE as the direct cause of death in 25% of patients.[6] There are numerous reports of unexpected thrombotic complications, some of which are summarized in table 1.

In a Dutch study on 184 patients in the ICU, despite a minimum standard-dose thromboprophylaxis, 31% of the study population had at least one thrombotic complication, with DVT/PE accounting for the majority of the cases (81%), followed by an ischemic stroke. In that study, older age and coagulopathy (defined as

Table 1: Summary of interesting reports on the thromboembolic complications of patients with COVID-19

Authors	Demographics	Risk Factor(s)	Complication(s)	Management and Outcome
Martinelli and others[15]	A 17-year-old Italian woman	Pregnancy (29th week of gestation) and obesity	PE and *Staphylococcus aureus* septicemia	Survival and emergent delivery of the fetus via caesarian section, followed by anticoagulation
Giacomelli and others[16]	A 67-year-old Italian man	Abdominal aortic prosthetic graft six years earlier	Thrombosis of the aortic graft	Death
Baldacini and others[17]	A 62-year-old Italian woman	Undiagnosed acute promyelocytic leukemia	Recurrent CVAs and DIC	Death
Le Berre and others[18]	A 71-year-old French man	Prominently elevated D-dimer levels	DVT, PE, and aortic thrombosis	Survival and conservative management with enoxaparin
Ullah and others[19]	A 59-year-old American woman	Hypertension, diabetes, and elevated D-dimer levels	PE and right ventricular failure	Survival and conservative management with enoxaparin
de Barry and others[20]	A 79-year-old French woman	None	Thrombosis in the superior mesenteric artery and vein	Death
Oxley and others[21]	A series of 5 American patients younger than 50 years old	Two patients had no risk factors, one had hyperlipidemia and hypertension, and two had diabetes (one of these two patients also had a prior stroke)	CVA	One patient was admitted to the ICU and four patients were discharged. Endovascular intervention, antiplatelets, and anticoagulants

CVA: Cerebrovascular accident; DIC: Disseminated intravascular coagulation; DVT: Deep vein thrombosis; PE: Pulmonary embolism

a prolongation of the prothrombin time [PT]>3 s or a prolongation of the partial thromboplastin time [PTT]>5 s) were independent risk factors for thrombotic complications.[22] In a follow-up study on the same patients, it was revealed that thrombotic complications occurred more commonly than was previously assumed (in 49% of all the patients). These complications were predictors of all-cause mortality. Patients already on chronic anticoagulation therapy had lower rates of such complications, and therapeutic anticoagulation was not associated with higher mortality rates. Finally, the study recommended strict thromboprophylaxis and the determination of the optimal dose of anticoagulants in future studies.[14] Although immobilization is a well-known risk factor for the development of DVT/PE, in an Italian descriptive study on 388 patients, 50% of the study population were diagnosed with these complications, which presented within 24 hours of hospital admission. Moreover, cerebrovascular accidents (2.5%), acute coronary syndromes (1.1%) and overt disseminated intravascular coagulation (DIC) (2.2%) were more common among the patients. Based on this study, provisions should be taken for the early diagnosis of such complications, as the prophylaxis dose of LMWH is not sufficient for the treatment of pre-existing PE.[23] In a study conducted on 63 patients in a teaching hospital in the United Kingdom, the prolongation of ICU stay was associated with an increased risk of thrombotic events. At the end of the study, because of the high rates of thrombotic complications, the DVT prophylaxis protocol at the ICU was intensified to twice the conventional dose.[24]

In a Chinese study on 183 patients, the majority of the study population (71.4%), who succumbed to the disease, fulfilled the criteria for DIC by the fourth day of admission and had significantly higher levels of D-dimer and fibrin-degradation products with prolonged PT and PTT than the survivors.[25] In a study on 88 inpatients, higher levels of D-dimer (≥5 μg/mL) were related to the severity of the disease and the risk of DVT development.[26] An investigation demonstrated that higher D-dimer levels at the time of initial presentation predicted the need for ICU admission.[27]

In a neurological study on 212 patients, those with severe disease were commonly complicated by a decrease in consciousness (14.8%), cerebrovascular accidents (5.7%), and muscular injury.[28] In a report on 221 patients, the incidence of cerebrovascular accidents was as following: 5% ischemic stroke, 0.5% intracerebral hemorrhage, and 0.5% venous sinus thrombosis. Risk factors in these patients were older age, a history of diabetes, hypertension, ischemic heart disease, a previous history of cerebrovascular disease, and the presence of renal or hepatic injury.[29]

In a cohort study on 416 patients, myocardial injury, as indicated by an elevation in cardiac troponin (19.7% of all the patients), was associated with a mortality rate of 51.2%.[30] Additionally, in 187 patients from Wuhan, those with both an underlying cardiovascular disease and an elevated troponin level had a mortality rate of 69.4%, in contrast to those without cardiovascular disease or myocardial injury, who had a mortality rate of 7.6%.[31]

Increasing cases of limb ischemia have been reported as well; it has not, however, been confirmed whether limb ischemia is a complication of shock and vasopressor administration, heparin-induced thrombocytopenia, DIC, emboli from probable valvular vegetation in the heart (as many ICU patients require central lines and are prone to sepsis and endocarditis), or just coagulopathy of COVID-19.[32] In a study on 20 patients with acute limb ischemia, 90% of the patients were male, and all were elderly. Additionally, these patients had a higher mortality rate than did their counterparts in other studies. After revascularization, a continuous infusion of heparin resulted in better survival and a lesser need for reinterventions.[33]

Risk Factors for Venous Thromboembolism in ICU Patients

DVT of the lower limbs is not an uncommon phenomenon in ICU patients complicating 5-15% of patients receiving thromboprophylaxis.[34] Risk factors for the development of DVT in the ICU, regardless of COVID-19, include immobilization, genetic factors (e.g., Factor V Leiden), older age, obesity, smoking, pregnancy, cancer, drugs (e.g., combined oral contraceptives, tamoxifen, and thalidomide), a history of previous DVT, renal failure and nephrotic syndrome, heart failure, chronic liver disease, stroke, spinal injury, sepsis, platelet transfusion, vasopressor infusion, longer ICU stay, central lines, and longer duration of mechanical ventilation.[35-37]

Patients with acute respiratory distress syndrome often need higher pressure supports. Continuous positive airway pressure and central venous catheters may cause stasis in the draining veins of the upper limbs in ICU patients and has been implicated in the thrombotic complication of the upper limbs.[38-41]

For patients with COVID-19 admitted to the ICU, D-dimer levels are important predictors of the evolution of venous thromboembolism

(VTE). A study on 81 patients with a severe disease showed that D-dimer levels of 1.5 µg/mL or greater predicted DVT with a sensitivity of 85%, a specificity of 88.5%, and a negative predictive value of 94.7%.[42] DVT should be ruled out in patients with substantially high levels of D-dimer.[43]

Pathophysiology of Thrombotic Complications in COVID-19

Pathological studies on patients with COVID-19 provide evidence of the prominent role of thrombosis in the severity of the disease. Thrombosis in the pulmonary and extra-pulmonary microvasculature bed of a deceased patient was reported.[44] Biopsies from five severely ill patients reported inflammatory septal capillary injury with fibrin clots in the capillary beds. Interestingly, the deposition of complement components and mannose-binding lectin-associated serine protease 2 both in the pulmonary and cutaneous microvasculature was reported, which is in favor of the activation of the complement pathways. Besides, the co-localization of viral spike glycoproteins and complement components in the interalveolar septa and the cutaneous microvasculature was observed.[45] These findings suggest a central role for inflammatory endothelial injury in the pathophysiology of COVID-19. In addition, hypoxemia in patients suffering from acute respiratory distress syndrome (ARDS) activates the circulating neutrophils, which manifests itself by an increase in reactive oxygen species generation and protease degranulation, which leads to a hyperinflammatory state.[46] Based on a recent review, the involvement of ACE2 and the renin-angiotensin-aldosterone system, in general, may lead to impaired fibrinolysis and lung injury.[47] Overshoot in the inflammatory response modulates the hemostatic balance toward thrombosis. Hence, the major effects can be summarized as the inhibition of fibrinolysis by the upregulation of plasminogen activator inhibitor-1, and the suppression of the protein C pathway, which has three major functions, namely the inhibition of thrombosis in the microvasculature, the inhibition of neutrophil-endothelial adhesion and extravasation, and the inhibition of the release of pro-inflammatory mediators such as tissue necrosis factor-α.[48] Remarkably, although the protein C pathway downregulates the pro-inflammatory mediators in neutral conditions, it is suppressed in hyperinflammation. Thus, the release of cytokines is unchecked and a vicious cycle is formed.[49] Coagulation and platelet activation enhances the release of pro-inflammatory cytokines and augments this vicious cycle.[50] As was discussed, CRS leads to a cycle of hypercoagulation and intensified inflammation. A sustained elevation in the level of interleukin-1 (IL-1) and IL-6 is a sign of CRS evolution. The blockade of IL-6 by a monoclonal antibody, tocilizumab, has been studied; it could be effective in the termination of this cycle and alleviate its detrimental effects.[51, 52] In a study on 63 patients with severe disease, treatment with tocilizumab resulted in reduced D-dimer levels.[53] This can be proof that controlling the hyperinflammatory state may reduce thrombotic complications. Although in almost all studies, patients receiving tocilizumab had more severe disease, they had a lower mortality rate than patients who did not receive tocilizumab.[54] In a randomized clinical trial on the efficacy of dexamethasone, patients under mechanical ventilation benefited the most and had a reduced mortality rate.[55]

COVID-19 frequently induces a chain of cytokine responses, leading to a DIC-like condition in favor of hypercoagulopathy. Nevertheless, there are differences between this condition and the previously defined DIC, as fibrinogen and factor VIII (FVIII) levels are elevated in the former, probably in response to IL-6.[37] No COVID-19–related bleeding diathesis has been reported so far. In a study on 24 ICU patients, thromboelastography (TEG) parameters were commonly deranged as decreased R and K values and increased K angle and MA. Moreover, D-dimer and fibrinogen levels were elevated.[56] Another study on ICU patients via TEG demonstrated increased maximum clot firmness in all patients.[57] Thus, a hypercoagulable state rather than DIC is suspected to be implicated in thrombotic complications. In a TEG analysis of 44 ICU patients, 57% had no lysis of clot in 30 minutes. This finding was a strong predictor of DVT development (area under the receiver operating characteristics curve [AUC]=0.742). Additionally, D-dimer levels of 2.6 µg/mL or greater predicted acute kidney injury and the need for hemodialysis (AUC=0.779).[58] A rotational thromboelastometry (ROTEM) analysis of 40 ICU patients showed a persisting hypercoagulable state in a considerable portion of patients characterized by a shortened clot formation time in INTEM in 40% and EXTEM in 50%, as well as increased maximum clot firmness in INTEM in 50%, EXTEM in 70%, and FIBTEM in 72.5%.[41] There were similar findings in another study on ICU patients.[59] As no consumption of clotting factors is seen, it appears that the hypothesis of COVID-19 hypercoagulopathy, and not DIC, is true. Furthermore, FVIII and von Willebrand factor

levels were increased in these studies, which is in the same line with findings from another study, suggesting the inflammatory response of endothelia.[9]

Based on previous observations, patients with pre-existing atherosclerosis of arteries are at high risk of the acute rupture of atheroma and acute coronary syndromes during viral illnesses and inflammatory states.[60, 61] The innate arm of the immune system reacts by the detection of pathogens through pattern recognition receptors, an important part of which are toll-like receptors (TLRs). TLRs are increasingly known to detect viral patterns. All of these receptors possess strictly conserved intracellular domains similar to that of the IL-1 receptor, all giving a start to a similar inflammatory cascade and leading to activation of NF-κB and interferon release. Some TLRs such as types 3, 7, 8, and 9 are only present in the endocytic compartments to prohibit them from reacting to similar but friendly patterns.[62] Single-stranded RNAs with particular patterns are recognized by TLR 7 and 8.[63] The activation of TLR7 in platelets causes platelet-neutrophil adhesion and transient thrombocytopenia in some viral infections, but it is not associated with thrombosis.[64] Currently, there is no evidence for the direct implication of TLRs in the thrombotic events of CVOID-19. In fact, loss of function-variations in the TLR7 gene has been associated with more severe illness.[65]

Previous studies have shown that a transient appearance of antiphospholipid antibodies is a common finding in viral infections and does not mandate anticoagulation therapy.[66, 67] In an investigation, a 72-year-old previously healthy man was reported to have rapid deterioration toward ARDS and acute kidney injury mandating hemodialysis. A tremendous rise in the levels of D-dimer, Von Willebrand factor, and FVIII was noticed, which the authors related to endothelial injury and the release of the two latter factors. With the appearance of anticardiolipin and anti-β2-glycoprotein immunoglobulin M (IgM), a high-titer infusion of unfractionated heparin (UFH) at therapeutic doses was commenced, and improvements in clinical condition and laboratory findings were achieved.[9] Antiphospholipid antibodies, including anticardiolipin and anti-β2-glycoprotein IgG and IgM, were detected in three Chinese patients who had acute limb ischemia and CVAs in multiple vascular territories. These patients also had high levels of D-dimer and fibrin-degradation product titers with prolonged PT and PTT.[68] In a French study on 56 patients, 45% of the study population were tested positive for lupus anticoagulants, and 10% were positive for anticardiolipin or anti-β2-glycoprotein IgG and IgM.[69] Additionally, a study investigated the reason for a falsely prolonged activated partial thromboplastin time (aPTT) among 35 patients, and revealed that 91% of the patients were positive for antiphospholipid antibodies. Interestingly, there was a rise in levels of FVIII, shortening aPTT. The authors posited a tendency toward thrombosis in such patients, despite the prolonged aPTT and advised not to recognize this issue as a contraindication to administration of thromboprophylaxis.[70]

Current Considerations in Prophylaxis and Treatment

The latest guideline from the American College of Chest Physicians, regarding the prevention of DVT/PE in critically ill patients, recommends evaluation of the risk of thrombosis versus bleeding before the administration of pharmaceutical thromboprophylaxis.[71] The Padua Prediction Score has been widely used with the aid of calculators since 2010 for the assessment of DVT risk in hospitalized patients; patients with a score of 4 or higher benefit from prophylaxis.[72] The IMPROVE Prediction Score was proposed as a tool for assessing the risk of major hemorrhage due to anticoagulation. A study showed that the combined use of these two prediction scores might attenuate health expenditures without increasing the rate of DVT/PE.[73] There are no high-quality studies to assess the clinical effects of the use of these two methods for patients with COVID-19. In clinical decision-making, a prolonged aPTT, which is a common finding among patients, should not be considered a sign of bleeding tendency, and should not prohibit clinicians from thromboprophylaxis.[70, 74] Statins are known for their immunomodulatory properties and are shown to reduce the oxidative stress in endothelia.[75, 76] Because of evidence of efficacy in patients with severe influenza, statins have been given as add-on adjuvants in COVID-19. Preliminary results from a meta-analysis showed that statins might decrease severe or fatal disease by 30%.[77] The International Society of Thrombosis and Hemostasis (ISTH) has published a guideline regarding the management of DIC in patients with COVID-19. The guideline recommends that the levels of D-dimer, PT, PTT, and if possible fibrinogen, as well as the platelet count, be checked for all patients at the time of admission and during hospitalization. In addition, if these parameters worsen, a more aggressive approach (checking coagulation parameters once or twice daily), ICU care, and correction of any derangements, especially in bleeding patients, are warranted.

Furthermore, thromboprophylaxis is mandated for all inpatients without contraindications.[74]

Based on the recommendations from a French expert panel, for outpatient care, standard-dose thromboprophylaxis with LMWH is recommended for patients with significant immobilization and at least one of the following: age over 70, body mass index of over 30 kg/m^2, a history of DVT, active cancer, and major surgery within the preceding 30 days. The duration of prophylaxis is generally between 7 and 14 days. If the patient is not ambulant after this time, the continuation of treatment should be discussed individually. Still, risk stratification for bleeding should be performed before the administration of LMWH for the risk-benefit assessment of anticoagulation.[78]

Based on recommendations from the ISTH and the American Society of Hematology, all inpatients should receive thromboprophylaxis with enoxaparin or fondaparinux, unless a patient has contraindications (active bleeding or platelet count < 25000/mL), which necessitate mechanical prophylaxis. Patients with a history of heparin-induced thrombocytopenia should receive fondaparinux.[74, 79]

The CHEST Guideline and Expert Panel Report suggests the application of thromboprophylaxis with the standard dose of LMWH in all acutely ill hospitalized and critically ill patients without contraindications. LMWH is recommended over UFH and direct-acting oral anticoagulants. Antiplatelets are not to be used for thromboprophylaxis. Extended thromboprophylaxis after discharge may be considered in light of additional evidence of the ongoing risk of VTE.[80] Based on an Italian expert consensus, anticoagulation should be continued for 7 to 14 days after discharge.[43]

Prone positioning of selective patients with ARDS results in significantly improved oxygenation and survival.[81, 82] This method also may be effective in the reduction of DVT due to the alleviation of pressure stasis on the lower limb veins. Better oxygenation may also reduce the inflammatory response due to hypoxemia.[46]

In patients with suspected PE (sudden onset of tachycardia, hypotension, respiratory compromise, or failure in improvement despite clearing lungs), it may be reasonable to save computed tomography pulmonary angiography (CTPA) as the second choice in patients at high risk of contrast-induced nephropathy, and if this modality is associated with a significant delay in treatment. In such circumstances, the first steps could be electrocardiography (right ventricular strain patterns), recheck of D-dimer levels, ultrasound, Doppler evaluations of the lower limbs for DVT, transthoracic echocardiography, and measurements of cardiac stress markers such as N-terminal-pro-B type natriuretic peptide.[83] These methods are easily accessed and can be done at the point of care, without the need for patient movement, which can be associated with recurrent PE and requires portable ventilators, which are not easily available in many low-income countries. A Chinese study on 700 patients demonstrated that acute kidney injury (in 5.1% of the total sample) occurred within several days in patients with baseline chronic kidney disease, and at least a week later in patients with normal baseline renal function. Many patients had proteinuria (43.9%) and hematuria (26.7%) on the first day of admission.[84] Because it has been shown that 50% of patients with DVT/PE are diagnosed in the first 24 hours of admission,[23] it has been proposed that a lower threshold be established for obtaining CTPA at the time of admission.[85] Proximal DVT or PE is recommended to be treated with LMWH or infusion of UFH. Again, LMWH is preferred to avoid the unnecessary exposure of the staff. Apixaban or rivaroxaban can also be used as the initial anticoagulant. However, the administration of dabigatran, edoxaban, or warfarin should follow the initial parenteral anticoagulation, and a certain period of overlap in the latter. In the presence of recurrent VTE, switching the anticoagulant to LMWH is recommended, and if the patient is already on LMWH, the dosage should be increased by 25% to 30%. The duration of therapy is at least three months. For patients with suspected massive PE (systolic blood pressure<90 mm Hg or a drop>40 mm Hg for at least 15 min) or deteriorating hemodynamics, the use of systemic fibrinolysis is recommended.[80] Treatment of massive PE using fibrinolytic therapy is a clinical challenge in patients with DIC or thrombocytopenia. The close monitoring of coagulation parameters, and the aggressive correction of derangements are essential in such patients. For DIC patients with a bleeding phenotype, catheter-directed therapy with lower doses of fibrinolytic should be considered the first choice.[86, 87]

For patients with COVID-19 complicated by CVA, the current expert panel recommendations are similar to those for patients without COVID-19, except for additional care regarding contrast studies and in the administration of fibrinolytic drugs.[88]

The recommendations of the American College of Cardiology concerning the management of acute coronary syndromes in the COVID-19 era underscore the recognition of patients suspected of concomitant COVID-19 infection and providing

healthcare workers with personal protective equipment. Recommendations in indications and timing for percutaneous coronary interventions and fibrinolytic therapy are not different for these patients.[89] A report on an asymptomatic COVID-19 patient with anterior ST-elevation myocardial infarction who failed to respond to fibrinolytic therapy and underwent coronary angioplasty with two subsequent episodes of stent thrombosis shortly after the procedure, predicted a higher failure rate in this population and recommended the administration of glycoprotein IIb/IIIa inhibitors and new generation P2Y12 inhibitors (i.e., ticagrelor and prasugrel) for all patients.[90]

A thorough examination of peripheral arteries and checking for evidence of DVT should be a part of the routine examination of patients with COVID-19.[91] The revascularization of ischemic limbs in hypercoagulable patients has less satisfying results, and based on the results from a previous study,[33] we recommend a continuous infusion of heparin as soon as possible after revascularization interventions. Of course, this method requires generous hemostasis and careful anastomosis during surgical interventions. Moreover, close postoperative monitoring for probable failure in revascularization is important for early diagnosis of ischemia and limb salvage. Measuring and charting the ankle-brachial index may be helpful for this purpose. Additionally, since these patients are liable to exposure to higher dosages of contrast agents, along with cytokine storm induced by COVID-19 itself, shock, and pre-existing conditions (e.g., diabetes mellitus, chronic kidney disease, and heart failure), acute kidney injury might ensue more commonly.[92] Vigorous hydration before and after endovascular interventions (or CTPA), and the selection of non-ion and hypo- or iso-osmolar contrast media with lower-volume injections might help prevent this complication.[93] Prophylaxis with N-acetylcysteine and high-dose atorvastatin for high-risk patients during coronary artery interventions might have a protective effect.[94] Nonetheless, N-acetylcysteine alone was not effective in high-risk patients in a previous investigation.[95] These studies were done before the pandemic; some small studies now recommend the use of N-acetylcysteine for the prevention of cytokine storm, which is implicated in multiorgan failure in COVID-19 infection.[96, 97]

Because of the hypercoagulable state, for women receiving menopausal hormone replacement, it is generally suggested that for the period of illness based on the severity of the disease, treatment be discontinued or at least substituted with transdermal hormones in milder cases without other risk factors. All perimenopausal women using oral combined contraceptives are encouraged to discontinue these medications for the time of illness. For patients with a mild disease in need of oral contraception, it is suggested that it be substituted with progestogen-only contraception. All women under these treatments should receive thromboprophylaxis with LMWH, except women with a mild disease taking oral combined contraceptives. Women already on progestogen-only contraception do not require thromboprophylaxis or changes in the treatment.[98] The levels of D-dimer, PT, aPTT, and fibrinogen, as well as the platelet count, should be routinely checked and followed in all pregnant women with COVID-19.[99]

Discussion

Almost all researchers and experts agree on the higher incidence of thrombotic complications in patients with COVID-19. In a pathological study, in addition to diffuse alveolar injury, thrombotic occlusion in the microvasculature of lungs and extra-pulmonary organs was reported.[44] Moreover, in a large study presenting data on 1066 patients in China, those with severe disease or poor outcomes had higher levels of D-dimer.[100] A series of 27 patients empirically receiving tailored doses of UFH or LMWH reported improvements in oxygenation (the PaO_2/FiO_2 ratio) within 72 hours, suggesting that some part of the respiratory failure may be due to PE or micro thrombosis in the pulmonary vasculature.[101] In a series of three patients with ARDS, the empirical administration of the tissue plasminogen activator resulted in the improvement of oxygenation.[102] Postmortem pathological studies have revealed the presence of thrombosis in the vasculature of most deceased patients. Most panels recommend lower thresholds for the administration of thromboprophylaxis, and higher-than-standard doses have also been recommended. Moreover, it has been proposed that heparin may possess additional anti-inflammatory effects.[103] The hyperinflammatory state leads to endothelial damage, which is believed to be the cornerstone of multiorgan failure in patients with severe disease.[104] In agreement with the pathophysiology of hypercoagulopathy, any treatment that diminishes the hyperinflammatory state and endotheliitis may reduce thromboembolic complications. A decrease in the level of D-dimer after the administration of tocilizumab in a previous study could be an example of this hypothesis.[53] All societies recommend LMWH

over UFH; controversies, however, persist over the dosage. As discussed above, a prolonged aPTT solely should not preclude the application of thromboprophylaxis in hospitalized patients. Until the optimum dose for prophylactic LMWH is defined in studies, TEG or ROTEM can be used for the determination of coagulopathy in critically ill patients.

Conclusion

Numerous studies are reporting increased thrombotic complications in patients with COVID-19. The hyperinflammatory state in COVID-19 leads to endothelial injury and a hypercoagulable state with subsequent thrombotic complications. We reviewed the risk factors and probable pathophysiology of such complications and briefly presented the clinical recommendations concerning prophylaxis and treatment. However, it is noteworthy that these recommendations have not arisen from high-quality studies, and they may be revised with emerging clinical trials and high-quality studies. The optimal dose for thromboprophylaxis has yet to be determined. Still, based on some clinical experiences and expert recommendations, higher dosages are required for the prevention of VTE in patients with severe COVID-19. At present, major societies recommend the standard dose for prophylaxis. The hypercoagulopathy also persists after the acute phase of the disease, and some panels recommend continuing enoxaparin for 7 to 14 days after patients regain their normal daily activities. Thus far, there has been no evidence suggesting a role for platelet activation in these complications. Hence, in alliance with the current recommendations, we suggest strict thromboprophylaxis with heparins, especially LMWH, for all immobilized patients in the absence of contraindications.

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