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Hemostatic system and COVID-19 crosstalk: A review of the available evidence

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Abstract

Since the discovery of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its resultant coronavirus disease 2019 (COVID-19) pandemic, respiratory manifestations have been the mainstay of clinical diagnosis, laboratory evaluations, and radiological investigations. As time passed, other pathological aspects of SARS-CoV-2 have been revealed. Various hemostatic abnormalities have been reported since the rise of the pandemic, which was sometimes superficial, transient, or fatal. Mild thrombocytopenia, thrombocytosis, venous, arterial thromboembolism, and disseminated intravascular coagulation are among the

many hemostatic events associated with COVID-19. Venous thromboembolism necessitating therapeutic doses of anticoagulants is more frequently seen in severe cases of COVID-19, especially in patients admitted to intensive care units. Hemorrhagic complications rarely arise in COVID-19 patients either due to a hemostatic imbalance resulting from severe disease or as a complication of over anticoagulation. Although the pathogenesis of coagulation disturbance in SARS-CoV-2 infection is not yet understood, professional societies recommend prophylactic antithrombotic therapy in severe cases, especially in the presence of abnormal coagulation indices. The review article discusses the various available evidence on coagulation disorders, management strategies, outcomes, and prognosis associated with COVID-19 coagulopathy, which raises awareness about the importance of anticoagulation therapy for COVID-19 patients to guard against possible thromboembolic events.

Key Words: SARS-CoV-2; COVID-19; Thrombosis; Pulmonary embolism; Disseminated intravascular coagulation

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Core Tip: The pathogenesis of hypercoagulable state and thrombosis related to coronavirus disease 2019 (COVID-19) is unclear. Evidence on endothelial cell injury by direct infection of severe acute respiratory syndrome coronavirus 2 is increasing. Histologic and immunohistochemistry examination of lung autopsies and/or the skin of patients who have died of severe COVID-19 has shown microvascular injury and thrombosis, consistent with intensive and generalized activation of both alternative and lectin-based pathways of complement.

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INTRODUCTION

One of the frequently encountered complications of systemic infections is activation of the coagulation cascade, which can present with a broad spectrum of clinical manifestations varying from subclinical activation, which is expressed by elevated laboratory markers for thrombin and fibrin products, to disseminated intravascular coagulation (DIC) and resultant formation of microvascular thrombi in various body tissues and organs[1]. Inflammation affects all phases of blood coagulation, which in turn, leads to both thrombotic as well as hemorrhagic complications[2]. Various viral infections, such as the human immunodeficiency virus, Dengue virus, and Ebola virus, occur by activation of the coagulation cascade[3-5]. Either direct or indirect activation of endothelial cells by viral infection can affect the balance between the coagulation and fibrinolytic systems[6,7]. The clinical presentation of this altered coagulation appears in hemorrhage, thrombosis, or both. An exaggerated response may even lead to DIC with the formation of microvascular thrombi in various organs[8]. Tissue factor (TF) expression is increased in herpes simplex virus and Dengue virus-infected endothelial cells[9].

The Ebola virus induces TF expression in circulating blood cells, especially macrophages, a condition known as Ebola hemorrhagic fever[4,9]. Stimulation by the poly I:C toll-like receptor 3 (TLR3) agonist induces activation of many proinflammatory cytokines as an antiviral chemokine, which is a selective chemoattractant for both activated type 1 T lymphocytes and natural killer cells. Thus, poly I:C increases TF expression in cultured endothelial cells and activates the coagulation system in mice [4]. On the other hand, inhibition of the TF/factor VIIa (FVIIa) complex was shown to decrease the cytokine storm and mortality in a rhesus monkey model of Ebola hemorrhagic fever[10]. Other hematological disorders that frequently occur with viral infections are hemolytic uremic syndrome, idiopathic thrombocytopenic purpura, and thrombotic thrombocytopenic purpura[7]. However, it is not clear why some viruses cause hemorrhage while others are associated with thrombosis as cytomegalovirus or both complications such as varicella-zoster virus[10,11].

Viral respiratory tract infections carry a higher risk for deep venous thrombosis and possibly pulmonary embolism (PE)[12]. Influenza A virus is associated with DIC and 18 pulmonary microembolism[13,14]. In the influenza A virus subtype H1N1, both thrombotic and hemorrhagic complications have been reported such as deep vein thrombosis (DVT), PE, and pulmonary hemorrhage with

hemoptysis, hematemesis, petechial rash, and one case of disseminated petechial brain hemorrhage[15]. Another example of viral infection associated with coagulopathy is H5N1, the highly pathogenic avian influenza that results in DIC, pulmonary hemorrhage, and thrombocytopenia in many cases[16]. The outbreak of severe acute respiratory syndrome (SARS) has been associated with significant morbidity and mortality caused by a broad spectrum of clinical presentation, *e.g.*, DIC, deep venous thrombosis, and pulmonary thromboembolic disorders resulting in pulmonary infarction, due to activated coagulation and vascular endothelial damage in both small and mid-sized pulmonary vessels[17].

Due to the ambiguity of the pathogenesis of the hypercoagulable state related to coronavirus disease 2019 (COVID-19) and the evidence of endothelial cell injury by direct infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, histologic and immunohistochemistry examination of lung autopsies and/or skin of patients who died of severe COVID-19 showed microvascular injury and thrombosis. This review discusses the evidence of coagulation disorders, management strategies, outcome, and prognosis associated with COVID-19 coagulopathy to guard against possible thromboembolic events.

DATA FROM SARS-COV-1 AND MIDDLE EAST RESPIRATORY SYNDROME

SARS-CoV or SARS-CoV-1 emerged in China in 2003 and spread to another 26 countries and is associated with thrombotic complications and hematologic disorders. Histopathological examination of pulmonary vasculature has revealed fibrin thrombi in pulmonary, bronchial, and small lung veins. Many studies of postmortem autopsies identified PE, DVT, and widespread multi-organ infarcts due to thrombi associated with polyangiitis and microcirculation disturbance as ischemic stroke (IS). SARS-CoV-1 causes placental circulation dysfunction through fibrin deposition, avascular and fibrotic villi formation, and prothrombotic tendency resulting in many intrauterine fetal complications such as oligohydramnios, intrauterine growth delay, and small fetal size[18,19]. Laboratory parameters of SARS-CoV-1-infected patients show prolonged prothrombin time (PT), prolonged activated partial thromboplastin time (especially over the first 2 wk), elevated D-dimer, and worsening thrombocytopenia. Increased thrombopoietin level has been reported in SARS-CoV-1 patients in the convalescent phase compared to normal controls with a concomitant increase in platelet count. Anticardiolipin antibodies have been detected in patients with post-SARS osteonecrosis and those with positive lupus anticoagulant tests in children[20,21]. *In vitro* studies have revealed that some genes have procoagulant effects when expressed in SARS-CoV-1-infected mononuclear cells. TLR9 and thromboxane A synthase genes are the targets of the SARS-CoV-1, where the TLR9 receptor is expressed in platelets to increase platelet activation, degranulation, and aggregation while increased thromboxane production promotes vasoconstriction, platelet aggregation, and endothelial dysfunction[22-24]. Upregulation of the five genes is associated with changes in the coagulation pathway in human hepatoma cells. These genes are: (1) The TF pathway inhibitor 2, which usually inactivates the tissue factor-VIIa complex and thrombin generation, and upon upregulation, it counteracts the mechanism that inhibits overt coagulation cascade activation in response to inflammation; (2) Early growth response 1; (3) Plasminogen activator inhibitor 1, which causes inhibition of fibrinolysis and promotes fibrin deposition during inflammatory states; (4) Phospholipid scramblase 1; and (5) Thrombospondin 1[25-27]. Urokinase pathway dysregulation is involved in the pathogenesis of SARS-CoV-1-related coagulation disorders leading to fatal disease in mice. The nucleocapsid protein of SARS-CoV-1 is one of the determinants of the prothrombotic state caused by SARS-CoV-1 as it induces the human fibrinogen-like protein-2 prothrombinase gene with activation of the C/EBP- α transcription factor[28-31]. The Middle East respiratory syndrome (MERS-CoV) that occurred in Saudi Arabia in 2012 is also associated with thrombotic complications and hematologic manifestations. Histopathologic examination of MERS-CoV-infected patients revealed microthrombi on day 4 of infection in the pulmonary vessels associated with parenchymal consolidation, alveolar edema, and cellular infiltrates. Thrombocytopenia was identified in the 1st week of laboratory-confirmed MERS-CoV cases with relatively lower platelet count in MERS-CoV patients than negative controls. DIC was one of the major complications reported in fatal MERS-CoV infections[32-34].

PATHOGENESIS OF COVID-19-RELATED THROMBOSIS

The pathogenesis of hypercoagulable state and thrombosis related to COVID-19 is unclear. Evidence on endothelial cell injury by direct infection of the SARS-CoV-2 virus is increasing. Histologic and immunohistochemistry examination of lung autopsies and/or skin of patients who died of severe COVID-19 showed microvascular injury and thrombosis, consistent with intensive and generalized activation of both alternative and lectin-based pathways of complement[35]. Subsequent activation of the clotting pathway, causing fibrin deposition, might also be implicated[36]. The hypercoagulable state due to profound derangement of hemostasis is another contributor to venous thromboembolism (VTE), PE, and/or DVT of the lower limbs, which has been observed in patients with COVID-19. There is

controversy about the pattern of hypercoagulability associated with COVID-19. Viral, bacterial, or fungal infection elicits a complex systemic inflammatory response as a part of innate immunity. Activation of the host defense mechanism induces subsequent coagulation and thrombin formation as a critical interaction between humoral and cellular mechanisms, a term called thromboinflammation or immunothrombosis[37]. Severe inflammation in patients with COVID-19, proved by elevated levels of interleukin 6 (IL-6), increased erythrocyte sedimentation rate, increased C-reactive protein (CRP), and elevated fibrinogen at presentation[38], results in subsequent activation of coagulation and may cause elevation of D-dimer levels[39]. Some experts have postulated that the predominant hypercoagulability in patients with COVID-19 suggests a unique hypercoagulable multifactorial state termed thromboinflammation or COVID-19-associated coagulopathy (CAC), which seems to be inconsistent with DIC, even though DIC has been reported in severely ill patients[40,41]. Other potential pathogenesis for coagulation abnormalities in patients with COVID-19 includes antiphospholipid antibodies, anticardiolipin and anti- β 2-glycoprotein I immunoglobulin G (IgG) and IgA[42]. Another explanation for coagulation abnormalities in the presence of lupus anticoagulant has been observed in a high percentage (88%-91%) of COVID-19 patients[43,44].

Although COVID-19 pathogenesis is associated with pulmonary intravascular coagulopathy (PIC) and thrombosis, it differs from sepsis-associated DIC. The first explanation of the pathogenesis of PIC and thrombosis in COVID-19 was directed to binding of SARS-CoV-2 to angiotensin converting enzyme-2 receptors that are located on type II pneumocytes (and possibly on vascular endothelial cells). This binding results in lysis of the cells immediately causing activation of the endothelium and procoagulant activity with the activation of fibrin deposits and accumulation in pulmonary microcapillary venous vessels, finally ending in PIC and thrombosis[45]. The second opinion is that the immune-mediated mechanism results in marked microvascular thrombosis and hemorrhage linked to extensive alveolar and interstitial inflammation, sharing features with macrophage activation syndrome in terms of lung-restricted vascular immunopathology associated with COVID-19[46].

In this context, infection with COVID-19 presumably induces a process of immune system hyperactivation known as immunothrombosis, in which activated neutrophils and monocytes interact with platelets and the coagulation cascade, leading to intravascular clot formation in small and larger vessels. It is presumed that the exaggerated immunothrombosis that occurs within lung microvessels is the main driver of COVID-19 manifestations[47,48].

Endothelial dysfunction is thought to be the most striking pathophysiological event in COVID-19 that infects vascular endothelial cells leading to cellular damage and apoptosis, decreasing the antithrombotic activity of the normal endothelium[49-51].

Similar to other respiratory infections, leukocyte recruitment to the lungs, a higher percentage of macrophages and neutrophils together with higher levels of proinflammatory cytokines (*e.g.*, IL-6, IL-8, and IL-1 β) and chemokines (*e.g.*, CCL2, CCL3, CCL4, and CCL7) found in the bronchoalveolar fluid are major contributors to inflammatory responses in COVID-19 infection[52].

Until recently, the association between COVID-19 and VTE, including PE and DVT, has been published as case reports. The prevalence of VTE in COVID-19 patients appears to be higher than that reported for patients admitted to intensive care units (ICUs) for other disease conditions[53]. Diagnosis of VTE was 12.7% in COVID-19 patients, as shown in a meta-analysis of multiple studies including 1783 ICU patients[54]. Patients with COVID-19 had some laboratory abnormalities, including a marked increase in D-dimer and, in some cases, mild thrombocytopenia, similar to DIC. However, other coagulation parameters in COVID-19, including high fibrinogen and high factor VIII activity, suggest that coagulation factors' consumption is not evident are inconsistent with DIC. Studies based on biochemical markers such as a marked increase of fibrin degradation products (FDP) (*e.g.*, D-dimer), prolonged PT/activated partial thromboplastin time (aPTT), and low platelet counts were compatible with the state of DIC. However, prolonged PT/aPTT is not confirmed in some studies[55]. Other studies using thromboelastography (TEG), a method of testing the efficiency of blood coagulation, together with biochemical parameters, demonstrated that results observed in patients with COVID-19 are not compatible with DIC[55]. In this context, careful monitoring of PT, platelet count, and D-dimer concentrations may help predict the clinical improvement and the expected complications.

EPIDEMIOLOGY AND CLINICAL PRESENTATION OF THROMBOTIC EVENTS IN COVID-19

Despite the plethora of publications regarding SARS-CoV-2, there are no available solid epidemiologic data on the actual prevalence and incidence of hemostatic derangements among patients. Most available data to date are retrospective observational data and can be classified as case series from a single-center experience that cannot be considered a true reflection of the prevalence and incidence of hemostatic derangements associated with SARS-CoV-2. However, there is some light at the end of the tunnel as the World Health Organization registry has several ongoing prospective studies aimed towards accurately determining the incidence. For example, a French study located in Centre Hospitalier Universitaire de Nice, started February 28, 2020[56], aims to screen prospectively any cardiovascular complication in

COVID-19 patients including PE, DVT, and VTE. Another study initiated in Shandong Provincial Hospital[57], where patients are recruited with novel coronavirus pneumonia (NCP), aims to calculate the rates of venous thrombosis among those patients and determine the risk factors. The Centre Hospitalier Universitaire de Nîmes registered in April 2020 is conducting a more dedicated study[58] to analyze coagulopathy. They observed any abnormality resulting from sepsis, including coagulopathy and DIC, and excluded all factors that would alter or influence outcomes such as pregnancy and lactation, anticoagulants, or antiplatelet therapy before recruitment or those with hypercoagulable states. In a study on 81 ICU hospitalized patients with NCP in Wuhan, 25% (20/81) had VTE with a significant increase in their D-dimer levels[59]. Dutch published data from three hospitals (184 patients) found that the cumulative incidence of thrombotic complications was 31%, most commonly PE (in 25 patients), VTE in 27%, and arterial thrombosis in 2.7% of all thrombotic events, despite receiving standard thromboprophylaxis[60]. In Italy, 22.2% of 54 ICU-admitted patients developed VTE despite prophylactic low molecular weight heparin (LMWH)[61].

Thrombocytopenia is one of the earliest observations in COVID-19 patients. A meta-analysis of nine studies suggested that thrombocytopenia was significantly associated with the severity of COVID-19, with more platelets found in non-survivors. Alhazzani *et al*[62] presented the data of 1099 patients from 522 hospitals and found that 36.2% of those patients had thrombocytopenia, which was even more evident in more severe cases (57.7%) *vs* 31.6% in non-severe cases[62]. However, in another case study performed on 150 COVID-19 patients in ICU, PE was reported in 43% of cases, besides extracorporeal circuit clotting, which was detected in 28 of 29 patients on renal dialysis. This research compared a group of patients with COVID-19 related acute respiratory distress syndrome (ARDS) *vs* non-COVID-19 ones and demonstrated a higher incidence of thrombotic events among COVID-19 patients[43]. In another series of 107 ICU-admitted COVID-19 cases, PE was found in 22% of cases despite receiving prophylactic anticoagulation[61]. VTE was noted in 39% of COVID-19 ICU cases in a case series composed of 74 patients, yet it was demonstrated in 25% of severe COVID-19 pneumonia patients in an earlier case series done on a cohort of 81 patients[59,63].

In a screening study done on 26 COVID-19 severely infected patients using Doppler lower limb ultrasound, VTE was detected in around 69% of patients; besides, bilateral DVT was demonstrated in 38% of cases though they were all on prophylactic anticoagulation therapy[64].

One of the earliest alarming laboratory findings observed in COVID-19 patients requiring hospitalization was marked elevation of the D-dimer. Elevated D-dimer levels are correlated with disease intensity and with high levels of proinflammatory cytokines, suggesting a possible relation between hypercoagulability and inflammation[65].

Different arterial thrombotic events have also been described in COVID-19 patients, and at the top of the list are ischemic central nervous system events. In a study performed in New York, 5 COVID-19 patients demonstrated large vessel occlusion and IS, astonishingly all these patients were young (under 50 years)[66]. Moreover, IS was noticed in 3.7% of patients in another case series composed of 184 COVID-19 patients[60]. Acute limb ischemia is the second most common arterial thrombotic event observed in COVID-19 patients. A recent study demonstrated acute lower limb arterial thrombosis in 20 COVID-19 patients; most were men with an average age above 75 years[67]. Another study reported acute lower limb ischemia in 4 patients, but they were young and did not suffer comorbidities[68]. Myocardial infarction was also described in COVID-19 patients and was reported in 2 Chinese studies [69,70]. **Figure 1** demonstrates the hemostatic system and COVID-19 interplay, possible complications, organs affected and outcomes.

LABORATORY ABNORMALITIES AND DIAGNOSTIC WORKUP

COVID-19 patients may have many hemostatic abnormalities (which may result in a hypercoagulable state as illustrated in **Table 1**[71-74]), so appropriate evaluation is mandatory for the correct diagnosis and management of COVID-19-associated thrombosis. Thromboinflammation or CAC is the predominant coagulation abnormality in COVID-19 patients, which will lead to a hypercoagulable state; it seems to be distinct from DIC, although DIC has been reported in severely affected patients[75]. A unique coagulopathy and procoagulant endothelial phenotype associated with a proinflammatory state with COVID-19 infection have a prominent effect on elevation of fibrinogen and D-dimer/fibrin(ogen) degradation products, which in turn results in systemic hypercoagulation and frequent venous thromboembolic events[76].

It is well known that the high level of D-dimer in COVID-19 is triggered by excessive clots and hypoxemia, which is likely reflecting pulmonary vascular bed thrombosis and fibrinolysis and correlates significantly with mortality. In many retrospective studies conducted in COVID-19 pneumonia patients, elevated baseline D-dimer levels are observed with inflammation. However, they cannot be accurately correlated with VTE score, which could help determine whether this is possible anticoagulation is needed or not based on levels of D-dimer[76,77].

The most common hemostatic abnormalities with COVID-19 include mild thrombocytopenia[78]; as reported in the literature, the incidence of thrombocytopenia ranges between 5%–41.7% of COVID-19

Table 1 The various hematological parameters in significant relation to coronavirus disease 2019 and their mechanisms

Hematological parameter	Significant relation to COVID-19	Mechanism
High RDW (greater than 14.5%)	Increase in mortality risk (from 11% to 31%)[86]	Not completely understood however reports suggested elevated RDW was attributed to affection of RBC production kinetics[86]
Leucopenia or lymphopenia (ALC $1.0 \times 10^9/L$)	Observed in most of COVID cases especially hospitalized patients and associated with poor prognosis[86]	(1) Defective immune response; and (2) Drug induced as with steroids[87]
Normal or increased platelet count	Found in some cases of COVID-19	May be caused by the large amounts of platelets produced in response to increased thrombopoietin formation from liver stimulation and megakaryocytes in the lung[88]
Prolonged PT and aPTT, elevations of D dimer, fibrinogen and FDP and decreased levels of antithrombin III	Direct relationship was observed between severity of COVID and affection of coagulation profile, Overt DIC (ISTH score of 5 and higher) is seen more frequently in non-survivors[89]	aPTT prolongation is caused by increased Factor VIII level and Factor XII deficiency secondary to the presence of factor XII inhibitors. Von Willebrand factor is quantitatively increased. LA is positive in 91% of those with prolonged aPTT. The presence of both LA and Factor XII deficiency are not associated with bleeding tendency

ALC: Absolute lymphocyte count; aPTT: Activated partial thromboplastin time; COVID-19: Coronavirus disease 2019; DIC: disseminated intravascular coagulation; ISTH: International Society on Thrombosis and Hemostasis; LA: Lupus anticoagulant; PT: Prothrombin time; RBC: Red blood cell; RDW: Red cell distribution width.

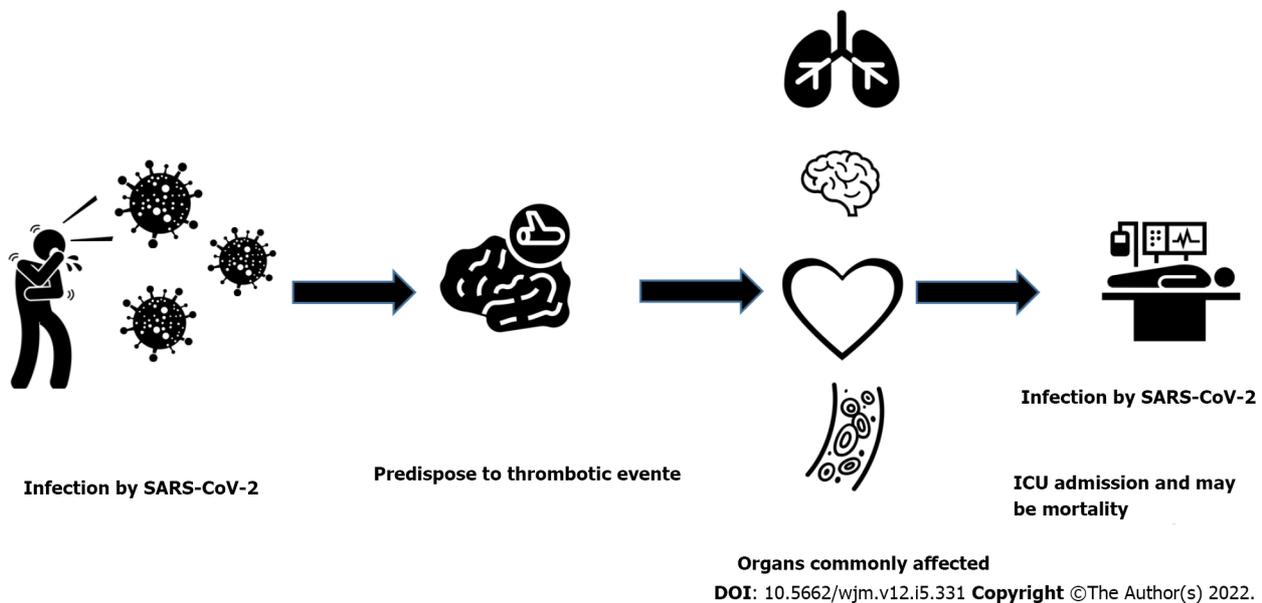


Figure 1 Hemostatic system and coronavirus disease 2019. All icons above are from <http://thenounproject.com>. ICU: Intensive care unit; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

infected patients, and it varies according to the disease severity. Moreover, rebound thrombocytosis was also reported in some cases[79,80]. Several mechanisms of COVID-19-associated thrombocytopenia have been reported, such as direct viral-platelet interaction activation, platelet autoantibody formation, subsequent platelet clearance, splenic/hepatic sequestration, and/or marrow/megakaryocyte suppression owing to inflammatory response, direct viral infection, or reduced thrombopoietin level [81].

One study suggested that patients with COVID-19 have higher platelet counts than patients with other coronavirus infections[82] and elevation of D-dimer[83], which were related to increased risk of requiring mechanical ventilation, and death[65]. However, high D-dimer levels are common in acutely ill individuals with various infectious and inflammatory diseases. Disease severity is variably related to PT prolongation[84], thrombin time[85] and shortened aPTT[86]. The retrospective analysis of 99 COVID-19 patients conducted by Wuhan Jinyintan Hospital showed that 36% of patients had elevated D-dimer, 16% showed a reduced aPTT, 6% showed an extended aPTT, 30% showed a shortened PT, and 30% showed an extended PT[87]. In a large meta-analysis of 7613 COVID-19 patients, it was found that in severe infection and non-survivors, the platelet count was lower, indicating that platelet counts may be a predictor of COVID-19 mortality[88,89]. COVID-19-associated thrombocytopenia primarily affects clot formation kinetics and clot strength on Quantra viscoelastic analysis; however, the details of *in vivo* fibrinolysis in COVID-19 have not yet been thoroughly investigated[89].

A retrospective analysis of the routine coagulation parameters of 183 patients with COVID-19 revealed that plasma FDP and D-dimer in non-survivors were significantly above those in survivors; PT and aPTT were also significantly prolonged[39]. A retrospective analysis of 138 COVID-19 patients confirmed that D-dimers increased after admission[90]. Previous studies have shown that elevated D-dimer is an independent risk factor for ARDS and mortality in COVID-19 patients[91].

COVID-19 infection has a significantly elevated vWF level together with increased FVIII clotting activity; this likely reflects the combined effect of the more significant release of Weibel-Palade bodies from endothelial cells and the acute-phase reaction. Meanwhile, ADAMTS13 activity was found to be mildly to moderately reduced in COVID-19 patients[75,92,93]. Fibrinogen level is increased to 5.0–7.0 g/dL on average for COVID-19-infected patients, CRP is also increased as an acute-phase reactant associated with elevated IL-6[94,95]. Meanwhile, antithrombin is consumed during coagulation, and the mild antithrombin deficiency occurs in COVID-19 infection whereas protein C has not been decreased in any of the patients assessed[96]. Mildly prolonged aPTT clotting times have been reported in some COVID-19 patients, indicating a prothrombotic state[96].

In a series of 24 intubated patients with severe COVID-19 pneumonia, PT and aPTT were either normal or slightly prolonged, platelet counts were normal or increased (mean, 348000/mL), fibrinogen increased (mean, 680 mg/dL; range 234 to 1344), D-dimer increased (mean, 4877 ng/mL; range, 1197 to 16954), factor VIII activity increased (mean, 297 units/dL), vWF antigen significantly increased (mean, 529; range 210 to 863), *per* endothelial injury. A slight decline in antithrombin and free protein S, with a slight increase in protein C, were also reported. Regarding TEG, there was shortening in reaction time (R) in 50% of patients and in clot formation time (K) in 83% of patients. There was an increase in maximum amplitude in 83% of patients, and also a reduction in clot lysis (LY30) in 100% of patients. Other studies have reported similar hypercoagulable states, including very high D-dimer, vWF antigen and activity, and factor VIII activity[43,97]. Two studies showed a high rate of lupus anticoagulant in patients with prolonged aPTT [50 of 57 tested individuals (88%) and 31 of 34 tested individuals (91%)] [42]. Another study reported 3 cases with severe COVID-19 and cerebral infarction, one with bilateral limb ischemia, within the setting of elevated antiphospholipid antibodies. Whether antiphospholipid antibodies play a significant role in the pathophysiology of thrombosis related to COVID-19 requires further investigation[41]. DIC manifests as coagulation failure and an intermediate phase within the development of multiple organ failure, which is common in many critically ill patients[98]. Tang *et al*[25] recently assessed 183 patients with COVID-19, of whom 21 (11.5%) died. The primary common differences between those who died and survivors were the increased levels of D-dimer and FDPs (an approximate 3.5- and approximately 1.9-fold increase, respectively) and PT prolongation (by 14%, $P < 0.001$), 71% of these patients who died fulfilled the International Society on Thrombosis and Hemostasis (ISTH) criteria for DIC compared with only 0.6% among survivors[40,99]. The COVID-19-related hypercoagulable state has been described as a DIC-like state, especially because many affected individuals are acutely ill and meet the criteria for probable DIC in the ISTH scoring system[99]. However, the main clinical finding in COVID-19 is thrombosis, whereas the main finding in acute decompensated DIC is bleeding. COVID-19 has similar laboratory findings of DIC, including elevated D-dimer and thrombocytopenia in some patients. However, in COVID-19, there is high fibrinogen and high factor VIII activity which are not found in DIC[40,99]. According to the recommendations from ISTH, the American Society of Hematology (ASH), and also the American College of Cardiology, routine testing for inpatients should include complete blood count, coagulation studies (PT and aPTT), fibrinogen, and D-dimer, and it will be repeated according to the clinical situation[100]. According to the American Society of Hematology recommendations regarding the diagnosis of PE, a normal D-dimer is sufficient to exclude the diagnosis of PE. In patients with suspected PE because of unexplained hypotension, tachycardia, worsening respiratory status, or other risk factors for thrombosis, computed tomography with pulmonary angiography (CTPA) is the preferred test. Ventilation/perfusion (V/Q) scan is an alternative if CTPA cannot be performed or is inconclusive, although the V/Q scan is also unhelpful in individuals with significant pulmonary involvement from COVID-19[101]. To date, whether these hemostatic changes are characteristic for SARS-CoV-2 or are an element of cytokine storm, as observed in other viral diseases, is unknown[102,103].

Regarding COVID-19 induced coagulopathy, we conclude that it meets the criteria of sepsis-induced coagulopathy (SIC), defined as a reduced platelet count, increased INR, and higher organ dysfunction score[40,104]. Table 2 shows the various laboratory parameters altered in SARS-CoV-2 and their implications in COVID-19 severity[105,106].

MANAGEMENT STRATEGIES

The cumulative incidence of COVID-19-associated VTE risk has raised concerns. Table 3 shows the frequency of venous thromboembolic complications in COVID-19 patients in different studies[64,107,108].

Many international societies and ministries of health have to publish their interim guidance to overcome this challenging situation[49,65,109-111]

Table 2 Various laboratory parameters that are altered in severe acute respiratory syndrome coronavirus 2 and their implications in coronavirus disease 2019 severity

Clinical index	Alterations with COVID-19 severity	Ref.
Neutrophil-to-lymphocyte ratio	Increased	[84,122-124,131,134-136]
CRP	Increased	[122,124,125,128,129,131,134-136,137-144]
Platelets	Decreased	[78,83,122,126,129,131-133,136,145,146]
Lymphocytes	Decreased	[78,128,129,131,134-136,147,148]
D-dimer	Increased	[55,83,84,127,128,131,137,144-146,149-152]
Ferritin	Increased	[91,94,128,129,131,134,135,137-139,144,153-155]
Procalcitonin	Increased	[83,84,128,144,156-158]
Lactate dehydrogenase	Increased	[106,129-131,152,159-173]
Albumin	Decreased	[111,116,128,129,136,148,174-186]

COVID-19: Coronavirus disease 2019; CRP: C-reactive protein.

Table 3 Frequency of venous thromboembolic complications in coronavirus disease 2019 patients

Ref.	Proportion	Cumulative incidence	Median follow-up	Patients
Cui <i>et al</i> [59]	20/81 (25%)	NR	NR	ICU patients
Klok <i>et al</i> [60]	68/184 (37%)	57% or 49% adjusted for competing risk of death	14 d	ICU patients only.19 PE were limited to subsegmental arteries.65/68 venous events were PE (95.6%)
Poissy <i>et al</i> [61]	VTE 22.2% of 54 ICU admitted			
Helms <i>et al</i> [44]	27/150 (18%)	NR	NR	ICU patients with ARDS 25/27 events were PE (92.5%)
Poissy <i>et al</i> [61]	PE only 22/107 (20.6%)	20.4% calculated at ICU day 15	6 d	ICU only
Middeldorp <i>et al</i> [63]	Venous thromboembolism 39% of COVID-19 ICU cases 74 patients			
Llitjos <i>et al</i> [64]	DVT: 18/26 (69%); PE: 6/26 (23%)	NR	NR	ICU patients. Systematic ultrasound screening
Léonard-Lorant <i>et al</i> [183]	PE only 32/106 (30%)	NR	NR	24/32 (75%) PE-positive patients were in the ICU
Grillet <i>et al</i> [184]	PE only 23/100 (23%)	NR	NR	Ward: 6/61 (9.8%); ICU: 17/39 (43.6%)
Middeldorp <i>et al</i> [63]	33/198 (17%)	15% at 7 d; 34% at 14 d	5 d	Ward: 4/123 (3.3%); ICU: 35/75 (47%); 11 (5.4%) clots detected on screening 11/33 events were PE (33%)
Lodigiani <i>et al</i> [185]	16/362 (4.4%)	21% (time not reported)	10 d	ICU 4/48(8.3%); Ward 12/314 (3.8%)
Thomas <i>et al</i> [186]	6/63 (9%)	27%	8 d	ICU patients
Cattaneo <i>et al</i> [108]	DVT only 0/388 (0%)	NR	NR	Non-ICU Ward 64 patients had screening ultrasound. All negative

DVT: Deep vein thrombosis; ICU: Intensive care unit; NR: Not reported; PE: Pulmonary embolism.

Although the general adoption of many societies[112] of the interim guidance of the ISTH[110], some institutions may vary in their management strategy of thromboembolic complications and would encourage enrollment in clinical trials to determine the best approach[113,114]. The ISTH recommends that all inpatients (ICU, medical non-ICU, and perioperative surgical and obstetric patients with COVID-19) receive prophylactic anticoagulation unless contraindicated after careful stratification with a DIC score. The low prophylactic dose molecular weight (LMW) heparin is preferred [e.g., enoxaparin in a dose of 40 mg to 60 mg once daily for patients with creatinine clearance (CrCl) > 30 mL/min, and 30

mg once daily for patients with CrCl 15 to 30 mL/min]. Dalteparin, nadroparin, and tinzaparin are also recommended. In a retrospective study of 449 patients with severe COVID-19, 99 patients who received enoxaparin in prophylactic doses showed a better prognosis concerning mortality, especially those with high SIC score and markedly elevated D-dimer[115]. Moreover, LMWH could have anti-inflammatory properties that would help in COVID-19 patients where proinflammatory cytokines are markedly elevated[116]. The high incidence (43%) of VTE reported in a multicenter prospective study of ICU patients, mainly PE, despite being on a regular prophylactic dose of LMWH[43], prompted many experts to suggest higher doses and call for more aggressive anticoagulation with intermediate-dose or even therapeutic dose anticoagulation for thromboprophylaxis. For patients with CrCl < 15 mL/min or renal replacement therapy, unfractionated heparin can be used. Doses should be modified according to weight and pregnancy conditions. Full-dose anticoagulation is indicated in those with documented VTE like DVT or PE in the same way as those without COVID-19 infection.

Not all patients have access to confirmatory tests for VTE in real life. The empirical initiation on full-dose anticoagulation can be justified by the local consultation of expertise in hemostasis and thrombosis and clinical evaluation of individual patients. Sudden respiratory status deterioration in a previously stable intubated patient not explained by a cardiac cause indicates a high suspicion of PE. Moreover, those with highly elevated fibrinogen and/or D-dimer and otherwise unexplained respiratory failure, superficial thrombophlebitis, retiform purpura, recurrent clotting of arterial lines, or central venous catheters despite prophylactic anticoagulation are highly indicated for full-dose anticoagulation. The dose dilemma for critically ill ICU COVID-19 patients is still not resolved. Whether the regular prophylactic, intermediate, or therapeutic dose would better treat disease morbidity and mortality needs future clinical trials to improve our practice. This strategy is supported by the American Society of Hematology, which recommends against empiric full-dose anticoagulation because of the increased risk of bleeding in the same setting of VTE with this approach[55]. Tissue plasminogen activator (tPA) is suitable for use in its known indications, *e.g.*, massive limb DVT, extensive PE, acute cerebrovascular stroke, and acute myocardial infarction. TPA use was described in a case series of three advanced COVID-19 patients with ARDS that improved their respiratory status and laboratory parameters[117]. Of note, all patients with proven VTE must be maintained on anticoagulation for at least 3 mo after discharge. Immobility, old age, recent surgery, and other risk factors for thrombosis should be considered before deciding thromboprophylaxis in outpatients with COVID-19 with close observation. Patients undergoing clinical trials for COVID-19 new therapeutic options should be closely monitored for possible drug-drug interactions with thromboprophylaxis treatment. The British Thoracic Society recommends therapeutic LMWH for inpatients with COVID-19 disease who are managed on general wards and require supplemental oxygen.

In contrast, the patients with no evidence of VTE or other indication for therapeutic anticoagulation who require high-flow oxygen, CPAP, NIV for severe ventilatory failure, or invasive ventilation should receive less than therapeutic dosing[118]. Meanwhile, The Italian Society of Thrombosis and Hemostasis strongly recommends prophylactic anticoagulation with LMWH, UFH, or fondaparinux for the entire hospital stay for 7–14 d more after hospital discharge[119]. Furthermore, the American College of Chest Physicians and Global COVID-19 Thrombosis Collaborative Group recommends standard dose anticoagulation for inpatients with COVID-19 disease and ICU/Critical Care patients; meanwhile, SIGN and NICE NG-191 exerts intermediate-dose/ standard dose anticoagulation for those patients[120–122].

Much International and National guidance regarding VTE thromboprophylaxis has been published; however, more extensive studies are required to investigate the potential therapeutic approach. Most of the international guidelines and recommendations (ISTH-IG, ACF, CDC, and ASH) adopt stopping anticoagulation in patients who developed bleeding or severely thrombocytopenic; furthermore, they also do not recommend a particular platelet count threshold[123]. Furthermore, the expert panel reports by CHEST/AIPPD/AABIP stated that empiric use of therapeutic anticoagulation regimens in ICU patients with COVID-19 is not beneficial and may be harmful, while its use in hospitalized, noncritically ill patients with COVID-19 remains uncertain[123].

OUTCOME AND PROGNOSIS

The catastrophic event of unopposed coagulopathy and DIC is a strong predictor of mortality in patients with COVID-19. On a laboratory basis, a significant elevation in D-dimer and INR with a decrease in fibrinogen level was also observed in non-survivors at days 10–14, and this was considered a poor prognostic sign[55]. For this reason, continuous and close monitoring of their levels is essential to determine prognosis and outcome, D-dimer level above 1 µg/mL was a strong and independent risk factor for death in this population[124]. In an observational study, a mean D-dimer level of 2.12 mg/L was observed in patients who did not survive compared to a concentration of 0.61 mg/L in survivors [55]. Another study revealed that patients admitted to ICU had significantly higher median D-dimer concentrations than patients who did not receive ICU care[84]. A third study reported that D-dimer on admission greater than 1 mg/L resulted in an 18-times increased risk of death[125]. These data provided strong evidence that D-dimer could be used as an excellent prognostic sign[125]. A retrospective study

that included 449 patients admitted to the hospital with severe COVID-19 infection showed that the use of prophylactic heparin was associated with a lower mortality rate than in patients who did not receive prophylactic heparin[115]. The available data about coagulopathy in COVID-19 patients suggest that regular monitoring of PT, platelet count, and D-dimer concentrations could predict prognosis and expected complications. Accordingly, there is justifying evidence supporting using a prophylactic dose of LMWH to prevent VTE in critically ill COVID-19 patients[126].

COVID-19 AND BLEEDING

Indeed SARS-CoV-2 is not as pathogenic as other RNA viruses (Ebola and hemorrhagic fever viruses) in causing severe hemorrhagic manifestations[127]. Owing to the abnormal coagulation cascade and subsequent high risk of thrombosis necessitating pharmacologic VTE prophylaxis, especially in severe COVID-19, the risk of bleeding with COVID-19 due to over anticoagulation, SIC, or DIC is inevitable. Although there are few reported data about clinically-overt bleeding in the setting of COVID-19, close observation for the occurrence of bleeding or thrombosis is mandatory for all COVID-19 patients who develop SIC or DIC[128]. In the absence of overt bleeding, the correction of coagulopathy is not mandatory in most COVID-19 patients. It is recommended to monitor full blood count, coagulation profile, and/or TEG and Rotational Thromboelastometry are all needed in cases of minor bleeding. However, in cases of significant bleeding as observed with a decrease in systolic blood pressure to less than 90 mmHg and/or increase of heart rate more than 110 beats *per* minute, management should be started immediately with FFP (15-25 mg/kg if PT/INR or aPTT ratios are greater than 1.5), platelet transfusion (for platelet count < 50 × 10⁹/L), fibrinogen replacement (when fibrinogen level is < 1.5 g/L).

Additionally, prothrombin complex concentrate will be given if FFP transfusion is not feasible and/or tranexamic acid (in a dose of 1 g over 10 ml) followed by a further dose (of 1 gm) if bleeding persists or restarts in the following 24 h provided that the patient does not have any evidence of DIC and followed by repeated monitoring with coagulation screens[129]. In a unique observation from Thailand on 41 COVID-19 infected patients initially presented with bleeding and petechiae, no specific additional treatment for this hemorrhagic problem was needed, and fortunately, no deaths occurred. This study and other studies may be of great value to raise awareness about the hemorrhagic presentation associated with COVID-19. Therefore, investigation and follow-up for possible hemorrhagic problems induced by COVID-19 are highly recommended[130]. A retrospective study comparing the risk of thrombosis *vs* the risk of bleeding in COVID-19 patients showed that critically ill patients had an increased incidence of bleeding (26.7%). This was a complicated situation in the setting of VTE prophylaxis and could be explained by dysregulated hemostasis in severe COVID-19. However, in noncritically ill COVID-19 patients, the prediction risk of VTE and major bleeding was minor. Based on that, critically ill COVID-19 patients are predisposed to both high risk of thrombosis and bleeding, so prevention strategies should be individualized according to the assessment of thrombosis *vs* bleeding risk[131]. Another study reported two cases of a significant hemorrhagic complication in severe COVID-19 patients presented by spontaneous abdominal, internal bleeding. Patients had bilateral interstitial pneumonia, and there were no other apparent predisposing factors for bleeding. Patients were managed with interventional radiology, with no mortalities recorded. These imbalances (or disruption) in platelet production and disorders of the coagulation system induced by SARS-CoV-2 need to be further clarified in extensive prospective studies[132]. Only a few published data about COVID-19 infection with known bleeding disorder patients are available. A case report of mild COVID-19 in a known hemophilia-A patient reported no evidence of bleeding linked to COVID-19 infection, and the patient recovered completely with only home isolation, antiviral agents, empirical antibiotics, and supportive therapies. Indeed, mild COVID-19 is not known to increase the risk of bleeding, even in patients with known bleeding disorders[133]. Transfusion therapy should be restricted for those with active bleeding, requiring an invasive procedure, or at otherwise high risk for bleeding complications and accordingly to be managed similar to those in ISTH guidelines for DIC[134].

CONCLUSION

In conclusion, and based on all the previously discussed data, we should highlight the importance of using empirical therapeutic anticoagulation for COVID-19 patients to guard against possible thromboembolic events with close observation for the occurrence of bleeding.

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