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Hemostatic system and COVID-19 cross talks: a review of the available evidence

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Abstract

Since the discovery of the SARS-CoV-2 virus and its resultant COVID-19 diseases pandemic, respiratory manifestations were the mainstay of clinical diagnosis, laboratory evaluations, and radiological investigations. As time passes, other pathological aspects of SARS-CoV-have been revealed. Various hemostatic abnormalities have been reported since the rise of the pandemic, which was sometimes superficial, transient, and sometimes fatal. Mild thrombocytopenia, thrombocytosis, venous, arterial thromboembolism, and disseminated intravascular coagulation were among 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 can rarely arise in COVID-19 patients either to a hemostatic imbalance resulting from severe disease or as a complication of over anticoagulation. Although the pathogenesis of coagulation disturbances 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 unique issue in this review article is that we will discuss the various available evidence of coagulation disorders, management strategies, Outcomes, and prognosis associated with COVID-19 coagulopathy, which raises the awareness about the importance of anticoagulation therapy for COVID-19 patients to guard against the possible thromboembolic events. Figure 1 demonstrates the Hemostatic system and COVID-19 graphic abstract.

Keywords: 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 COVID-19 is incompletely unclear. The evidence of endothelial cell injury by direct invasion of the SARS-CoV-2 virus is growing up. Histologic and immunohistochemistry examination of lung autopsies and/or skin of patients 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.

INTRODUCTION

One of the frequently encountered complications of systemic infections is the activation of the coagulation cascade which could 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 the resultant formation of microvascular thrombi in various body tissues and organs [1]. Inflammation affects all phases of blood coagulation, which in return will lead to both thrombotic as well as hemorrhagic complications [2]. Various viral infections are accused by activation of the coagulation cascade, such as the Human immunodeficiency virus (HIV), Dengue virus, and Ebola virus [3-4, 5]. Either direct or indirect activation of the endothelial cells by a viral infection can affect the balance between the coagulation and the 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 HSV and Dengue virus-infected endothelial cells [9].

Moreover, the Ebola virus induces expression TF in circulating blood cells, especially macrophages, a condition known as Ebola hemorrhagic fever [4, 9]. The Toll-

like receptor 3 (TLR3) agonist poly I:C stimulation-induced activation of many proinflammatory cytokines as antiviral chemokine, which is a selective chemoattractant for both activated type 1 T lymphocytes and natural killer cells; thus, the TLR3 agonist poly I:C increases TF expression in cultured endothelial cells and activates the coagulation system in mice [10]. On the other hand, inhibition of the TF/factor VIIa (FVIIa) complex decreased the cytokine storm and mortality in a rhesus monkey model of Ebola hemorrhagic fever [11]. Other hematological disorders that are frequently encountered with viral infections are hemolytic uremic syndrome (HUS), idiopathic thrombocytopenic purpura (ITP), and thrombotic thrombocytopenic purpura (TTP) [7]. However, it is not yet clear why some viruses cause hemorrhage while others are associated with thrombosis as cytomegalovirus or both complications such as varicella-zoster virus [12, 13].

Viral respiratory tract infections carry a higher risk for deep venous thrombosis and possibly pulmonary embolism [14]. Influenza A virus has been associated with DIC and18 pulmonary micro-embolism [15, 18]. In H1N1, both thrombotic and hemorrhagic complications were reported, such as DVT, pulmonary embolism, and pulmonary hemorrhage with hemoptysis, hematemesis, petechial rash, and one case of a disseminated petechial brain hemorrhage [16]. Another example of viral infection associated with coagulopathy is H5N1, the highly pathogenic avian influenza that resulted in DIC, pulmonary hemorrhage, and thrombocytopenia in many cases [17]. The outbreak of 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 disasters resulting in pulmonary infarction, due to activated coagulation and vascular endothelial damage in both small and mid-sized pulmonary vessels [19].

Due to the ambiguity of the pathogenesis of hypercoagulable state related to COVID-19 and facing the evidence of endothelial cell injury by direct invasion of the 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 will discuss the evidence of coagulation disorders, management strategies, outcome, and prognosis associated with COVID-19 coagulopathy to guard against the possible thromboembolic events.

Data from SARS-CoV1 and MERS-CoV:

Severe acute respiratory syndrome-related coronavirus virus (SARS-CoV or SARS-CoV-1) emerged in China in 2003 and spread to another 26 countries, and it was also associated with thrombotic complications and hematologic disorders. Histopathological examination of pulmonary vasculature revealed fibrin thrombi in pulmonary, bronchial, and small lung veins. Many studies of postmortem autopsies identified pulmonary embolism, deep vein thrombosis, and widespread multi-organ infarcts due to thrombi associated with polyangiitis and microcirculation disturbance as ischemic strokes. SARS-CoV-1 was also implemented to cause 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 [20, 29]. Laboratory parameters of SARS-CoV-1 infected patients showed prolonged prothrombin time, prolonged activated partial thromboplastin time (especially over the first two weeks), elevated D-dimer, and worsening thrombocytopenia. Increased thrombopoietin level was reported in SARS-CoV-1 patients in the convalescent phase compared to normal controls with a concomitant increase in platelet count. Anticardiolipin antibodies were detected in patients with post-SARS osteonecrosis and those with positive lupus anticoagulant tests in children [30, 32]. In vitro studies revealed that some genes could have a procoagulant effect when expressed in SARS-CoV-1 infected mononuclear cells. Toll-like receptor 9 (TLR9) and Thromboxane synthase (TBXAS) gene 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 [33, 36]. The upregulation of the expression of five genes was associated with changes in the coagulation pathway in human hepatoma cells (Huh7). These genes are (1) the tissue

factor pathway inhibitor 2 (TFPI2), 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 (EGR1), (3) plasminogen activator inhibitor 1 (PAI1/SERPINE1) that causes inhibition of fibrinolysis and promotes fibrin deposition during inflammatory states, (4) the phospholipid scramblase 1 (PLSCR1), and (5) thrombospondin 1 (THBS1) [37, 39]. Urokinase pathway dysregulation was involved in the pathogenesis of SARS-CoV-1 related coagulation disorders with a fatal disease in mice. Nucleocapsid protein of SARS-CoV-1 was one of the determinants of the prothrombotic state caused by SARS-CoV-1 as it induces the human fibrinogen-like protein-2 (HFGL2) prothrombinase gene with activation of the C/EBP-α transcription factor [40, 43]. The Middle East respiratory syndrome (MERS-CoV) that occurred in Saudi Arabia in 2012 was 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 [44]. Thrombocytopenia was identified in the first 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 [45, 47].

Pathogenesis of COVID-19 related thrombosis

The pathogenesis of hypercoagulable state and thrombosis related to COVID-19 is incompletely unclear. The evidence of endothelial cell injury by direct invasion of the SARS-CoV-2 virus grows. 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 [48]. Subsequent activation of the clotting pathway, causing fibrin deposition, might also be implicated [49]. Hypercoagulable state due to profound derangement of hemostasis is another contributor to VTE, pulmonary embolism, and/or deep vein thrombosis of the lower

limbs, observed in patients with Covid-19. There is an enormous 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 [50]. Severe inflammation in patients with COVID-19, proved by elevated levels of IL-6, increased erythrocyte sedimentation rate (ESR), increased C-reactive protein (CRP), and elevated fibrinogen at presentation [51], results in subsequent activation of coagulation and may cause elevation of D-dimer levels [52]. Some experts suggest the predominant hypercoagulability in patients with COVID-19 suggests a unique hypercoagulable multifactorial state termed thromboinflammation or COVID-19-associated coagulopathy (CAC). It seems to be inconsistent with DIC, even though DIC has been reported in severely ill patients [53, 54]. Other potential pathogenesis for coagulation abnormalities in patients with COVID-19 includes antiphospholipid antibodies, anticardiolipin and anti–β2-glycoprotein I immunoglobulin G (IgG) and immunoglobulin A (IgA) [55]. Another explanation for coagulation abnormalities in the presence of lupus anticoagulant was observed in a high percentage (88% - 91%) of COVID-19 patients [56, 57].

Although COVID-19 pathogenesis is associated with pulmonary intravascular coagulopathy (PIC) and thrombosis, it differs from sepsis-associated disseminated intravascular coagulation (DIC). The first explanation of the pathogenesis of PIC and thrombosis in COVID-19 directed to binding of SARS-CoV2 to ACE2 receptors that located on type II pneumocytes and possibly on vascular endothelial cells that 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 [58]. 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 (MAS) in a term of lung-restricted vascular immunopathology associated with COVID-19 [59].

In this context, Infection with COVID-19 is supposed to induce a process of immune system hyperactivation is 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 supposed that the exaggerated immunothrombosis that occurred within lung microvessels is the main drive for the COVID-19 manifestations [60, 61].

Endothelial dysfunction was suggested as 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 [62-64].

Like other respiratory infections, leukocyte recruitment to the lungs, a higher percentage of macrophages and neutrophils together with higher levels of proinflammatory cytokines (such as IL-6, IL-8, and IL-1β) and chemokines (such as CCL2, CCL3, CCL4, and CCL7) that found in the bronchoalveolar fluid is the major contributor to inflammatory responses in COVID-19 infection [65].

Up till recently, the association between COVID-19 and venous thromboembolism (VTE), including pulmonary embolism and deep vein thrombosis, has been published as case reports. The prevalence of VTE in COVID-19 patients appears to be higher compared to that reported for patients admitted to ICUs for other disease conditions [66]. Diagnosis of VTE was 12.7% in COVID-19 patients, as shown in a meta-analysis of multiple studies including 1783 ICU patients [67]. 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 (e.g., D-dimer), prolonged PT/APTT, and low platelet counts were compatible with the state of DIC. However, prolonged PT/APTT is not confirmed in some studies

[68]. 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 [69]. In this context, careful monitoring of prothrombin time, 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, no available solid epidemiologic data about the actual prevalence and incidence of hemostatic derangements among those patients. Most available data till the current time are retrospective observational data and can be classified as case series belonging to single-center experience and 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 WHO registry has several ongoing prospective studies aiming to determine accurately such an errand. For example, a French study located in Centre Hospitalier Universitaire de Nice, started February 28 [70], aims to screen prospectively any cardiovascular complication in COVID-19 patients, including **pulmonary embolism (PE), deep venous thrombosis, and venous thromboembolism (VTE)**. Another study initiated in Shandong Provincial Hospital [71], where they recruit patients with novel coronavirus pneumonia (NCP), aims to calculate the rate of venous thrombosis among those patients and determine the risk factors in such cases cohort. At the same time, Centre Hospitalier Universitaire de Nīmes registered in April 2020 a more dedicated study [72] to analyze coagulopathy. They observe any abnormality resulting from sepsis, including coagulopathy and DIC. They 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% of patients (20/81) had VTE with a significant increase in their D-Dimer levels [73]. Dutch published data from 3 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 [74]. . In Italy, 22.2% of 54 ICU admitted patients developed VTE despite prophylactic low molecular weight heparin (LMWH) [75].

Thrombocytopenia was one of the earliest observations in COVID-19 patients. A meta-analysis of nine studies has suggested that thrombocytopenia was significantly associated with the severity of COVID-19, with more platelet drops found in non-survivors [77]. Guan *et al* presented the data of 1,099 patients from 522 hospitals and found that 36.2% of those patients had thrombocytopenia; it was even more evident in more severe cases (57.7%) *vs* 31.6% in non-severe cases [76]. However, in another case study performed on 150 COVID-19 patients in ICU, pulmonary embolism was reported in 43% of cases, besides extracorporeal circuit clotting, which was detected in 28 out of 29 patients on renal dialysis. This research compared a group of patients with COVID-19 related acute respiratory distress syndrome *vs* non-COVID-19 ones and demonstrated a higher incidence of thrombotic events among COVID-19 patients [56]. In another series of 107 ICU admitted COVID-19 cases, pulmonary embolism was found in 22% of cases despite receiving prophylactic anticoagulation [78]. Venous thromboembolism 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 [73, 79].

In a screening study done on 26 COVID- 19 severely infected patients using Doppler lower limb ultrasound, venous thromboembolism was detected in around 69 % of patients; besides, bilateral DVT was demonstrated in 38% of cases though they were all on prophylactic anticoagulation therapy. [80].

One of the earliest alarming laboratory findings observed in COVID-19 patients requiring hospitalization was the marked elevation of 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 [81].

Different arterial thrombotic events were also described in COVID-19 patients, and on top of the list is the ischemic central nervous system events; in a study

performed in New York, 5 COVID-19 cases demonstrated large vessel occlusion and ischemic stroke, astonishingly all these patients were young (under 50 years) [82]. Moreover, ischemic stroke was noticed in 3.7% of patients in another case series composed of 184 COVID-19 patients [74]. 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 [83]. Another study reported acute lower limb ischemia in 4 patients, but they were young and did not suffer comorbidities [84]. Myocardial infarction was also described in COVID-19 patients and was reported in 2 Chinese studies [85, 86].

Laboratory abnormalities and diagnostic workup:

COVID-19 patients may have lots of hemostatic abnormalities (which may result in a hypercoagulable state as illustrated in table 1 [87-90]), so appropriate evaluation is mandatory for correct diagnosis and management of COVID-19 associated thrombosis. Thromboinflammation or COVID-19-associated coagulopathy is the predominant coagulation abnormalities in COVID-19 patients, which will lead to a hypercoagulable state; it seems to be distinct from DIC, though DIC has been reported in severely affected patients [69]. 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 [91].

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 venous thromboembolism (VTE) score, which could help determine

whether this is possible anticoagulation is needed or not based on levels of D-dimer [92, 93].

The most common hemostatic abnormalities with COVID-19 include mild thrombocytopenia [77]; as reported in the literature, the incidence of thrombocytopenia ranges between 5–41.7% of COVID-19 infected patients, and it varies according to the disease severity. Moreover, rebound thrombocytosis was also reported in some cases [94, 95]. 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 [96].

One study suggested that patients with COVID-19 have higher platelet counts than patients with other coronavirus infections [97] and elevation of D-dimer [98], which were related to increased risk of requiring mechanical ventilation, and death [81]. However, high D-dimer levels are common in acutely ill individuals with various infectious and inflammatory diseases. Disease severity is variably related to prothrombin time (PT) prolongation [99], thrombin time (TT) [100], and shortened activated partial thromboplastin time (aPTT) [101]. The retrospective analysis of 99 COVID-19 patients conducted by Wuhan Jinyintan Hospital showed that 36% of patients had an elevated D-dimer, 16% showed a reduced APTT, 6% showed an extended APTT, 30% showed a shortened PT, and 30% showed an extended PT [102]. In a large meta-analysis of 7,613 COVID-19 patients, it was found that in severe infection and non-survivors, the platelet count was lower; this could raise the attention to have the platelet counts as a predictor of COVID-19 mortality [103, 104]. 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 [105].

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 [52]. A retrospective analysis of 138 COVID-19 patients confirmed that D-dimers increased after admission [106]. Previous studies evidenced elevated D-dimer is an independent risk factor for acute respiratory distress syndrome (ARDS) and mortality in COVID-19 patients [107].

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 mild-to-moderately reduced in COVID-19 patients [108-110]. 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 [111-113]. Meanwhile, antithrombin is known to be consumed during coagulation, and the mild antithrombin deficiency was described in COVID-19 infection while protein C was not decreased in any of the patients assessed [114]. Mildly prolonged aPTT clotting times were reported in some COVID-19 patients implying a prothrombotic state [115].

In a series of 24 intubated patients with severe COVID-19 pneumonia, prothrombin time (PT) and aPTT were either normal or slightly prolonged, platelet counts were normal or increased (mean, 348,000/microL), fibrinogen increased (mean, 680 mg/dL; range 234 to 1344), d-dimer increased (mean, 4877 ng/mL; range, 1197 to 16,954), 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 thromboelastography, there was shortening in reaction time (R), in 50 percent of patients, and in clot formation time (K), in 83 percent, and there was an increase in maximum amplitude (MA), in 83 percent, and also a reduction in clot lysis (LY30), in 100% of patients [53]. Other studies have reported similar hypercoagulable states, including very high D-dimer, VWF antigen and activity, and factor VIII activity [56, 116]. Two studies have found a high rate of lupus anticoagulant in

patients with prolonged aPTT (50 of 57 tested individuals [88 %] and 31 of 34 tested individuals [91 %]) [55]. 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 [54]. Disseminated intravascular coagulation manifests coagulation failure and an intermediate phase within the development of multiple organ failure (MOF), which is common in many critically ill patients [117]. Tang *et al* recently assessed 183 patients with COVID-19; 21 (11.5%) died. The primary common differences between those who died and survivors were the increased levels of D-dimer and fibrin degradation products ([FDPs], ~3.5- and ~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 [52, 118]. 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 International Society on Thrombosis and Haemostasis (ISTH) scoring system [118]. 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 [53]. According to the recommendations from ISTH, the American Society of Hematology (ASH), and also the American College of Cardiology (ACC), routine testing for inpatients should include complete blood count (CBC), coagulation studies (prothrombin time [PT] and activated partial thromboplastin time [aPTT]), fibrinogen, and D-dimer, and it will be repeated according to the clinical situation [119]. 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, CT 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 [120]. Till now, 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 [121, 122].

Regarding COVID-19 induced coagulopathy, we can conclude that it meets the criteria of sepsis-induced coagulopathy (SIC), defined as a reduced platelet count, increased INR, and higher organ dysfunction score [123-124]. Table 2 shows the various laboratory parameters altered in SARS Cov-2 and their implications in COVID-19 severity [125-199].

Management strategies:

The cumulative incidence of COVID-19 associated venous thromboembolism (VTE) risk has urged concern. Table 3 shows the frequency of venous thromboembolic complications in COVID-19 patients in different studies [56, 73-75, 78-80, 200-204].

Many international societies and ministries of health have to publish their interim guidance to overcome this challenging situation [68-70, 78-80, 82-86, 97-102, 105, 107, 116-122, 2004-209].

Although the general adoption of many societies [210] of the interim guidance of the International Society on Thrombosis and Haemostasis (ISTH) [2008], some institutions may vary in their management strategy of thromboembolic complications and would encourage enrollment in clinical trials to determine the best approach [211, 212]. 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 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 sepsis-induced coagulopathy score (SIC) and markedly elevated D-dimer [213]. Moreover, LMWH could have anti-inflammatory properties that would help in COVID-19 patients where proinflammatory cytokines are markedly elevated [214]. 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 [56], prompted many experts to suggest higher doses and call for more aggressive anticoagulation with intermediate-dose or even therapeutic dose anticoagulation for thromboprophylaxis [211]. 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 deep vein thrombosis (DVT) or pulmonary embolism (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 [68]. 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 [215]. Of note, all patients with proven VTE must be maintained on anticoagulation for at least three months 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 [216]. Meanwhile, The Italian Society of Thrombosis and Hemostasis (SISET) strongly recommends prophylactic anticoagulation with LMWH, UFH, or fondaparinux for the entire hospital stay for 7–14 days more after hospital discharge [217]. 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 [218-221].

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 [222]. 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 [223].

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 [224]. 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 [225]. 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 [224]. Another study revealed that patients admitted to ICU had significantly higher median D-dimer concentrations than patients who did not receive ICU care [226]. A third study reported that D-dimer on admission greater than one mg/L resulted in an 18-times increased risk of death [227]. These data provided strong evidence that D-dimer could be used as an excellent prognostic sign [224. 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 [213]. The available data about coagulopathy in COVID-19 patients suggest that regular monitoring of prothrombin time, platelet count, and D-dimer concentrations could predict prognosis and expected complications. Accordingly, there is justifying evidence supporting using a prophylactic dose of low molecular weight heparin (LMWH) to prevent venous thromboembolism in critically ill COVID-19 patients [208].

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 [228]. 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, sepsis-induced coagulopathy, 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 sepsis-induced coagulopathy or DIC [229]. 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 Thromboelastography [TEG] and Rotational Thromboelastometry [ROTEM] 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 (15-25mg/Kg if PT/INR or APTT ratios are greater than 1.5), platelet transfusion (for platelet count < 50x 10^9/L), fibrinogen replacement (when fibrinogen level is <1.5g/L).

Additionally, prothrombin complex concentrate will be given if FFP transfusion is not feasible and/or tranexamic acid (in a dose of 1g over 10 minutes) followed by a further dose (of 1gm) 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 [230, 231]. 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 [232]. 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 [233]. 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 [234]. 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 [235]. 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 [236].

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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