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COVID Coagulopathy

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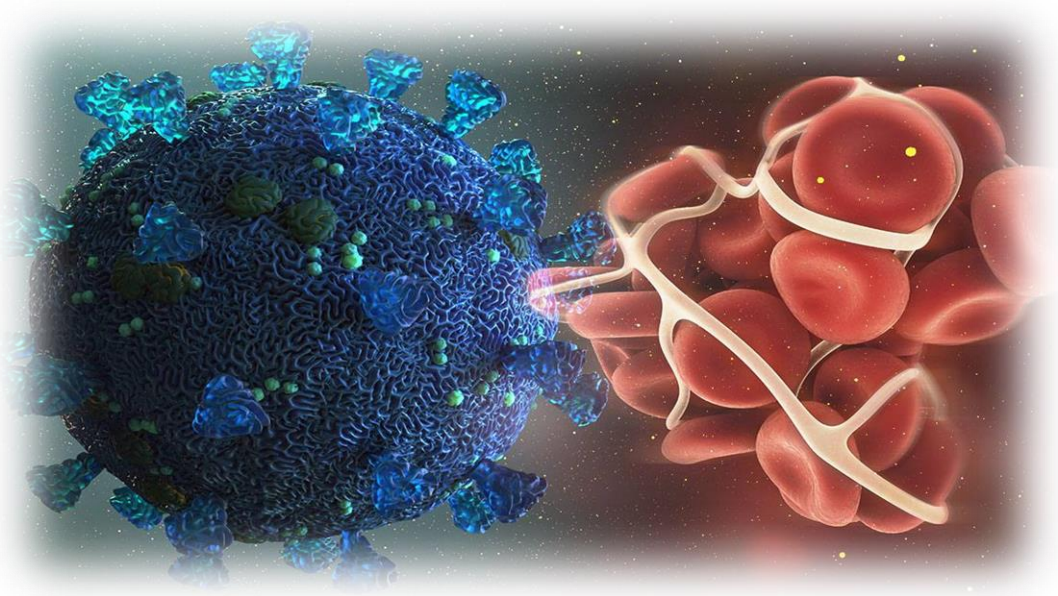

Introduction

The new coronavirus-induced severe acute respiratory syndrome (COVID-19) outbreak was first reported in December 2019. Three months later, the Director-General of the World Health Organization, declared the COVID-19 a global pandemic. Accumulated evidence reveals that a coagulation disorder is often seen in COVID-19, and the incidence is higher in severe cases(1). Because the information in relation to COVID-19 coagulopathy is still limited, it is necessary to summate information from infections caused by similar RNA viruses that frequently cause coagulopathy such as Ebola virus (filovirus), Lassa virus (arenavirus), and Dengue fever virus (flavivirus)(2). In these viral hemorrhagic fevers, uncontrolled virus replication and inflammatory responses are thought to promote vascular damage and coagulopathy (3) , with 30% to 50% of cases showing hemorrhagic symptoms in Ebola virus infection (4) .On the contrary, although coronavirus belongs to the enveloped, single-stranded RNA virus family, it does not cause hemorrhagic complications. For example, the coronavirus that caused severe acute respiratory syndrome (SARS) in 2002 (SARS-CoV-1) were reported to be associated with thrombocytopenia (55%), thrombocytosis (49%), and prolonged activated partial thromboplastin time (aPTT) (63%), but the incidence of bleeding was not high (5),(6). It was also reported that 20.5% of patients had deep vein thrombosis, and 11.4% showed clinical evidence of pulmonary embolism with SARS-CoV-1 infection (7). SARS-CoV-2, the causal virus of COVID-19, is a sister clade to the SARS-CoV-1 and may have similar potential to induce thrombotic complications (8). In this respect, Chinese experts noted that in severe cases, patients can develop acute respiratory distress syndrome (ARDS), with coagulation predominant-type coagulopathy (9). Tang et al (10) reported that 71.4% of nonsurviving COVID-19 patients fulfilled the criteria of disseminated intravascular coagulation (DIC), whereas only 0.6% of the survivors met the criteria. Of note, the derangement of coagulation and fibrinolysis in the pulmonary circulation and bronchoalveolar space are likely to be important factors in the pathogenesis of ARDS in COVID-19. The purpose of this review is to postulate the pathophysiology and clinical implications of this new coronavirus-associated coagulation disorder.

The COVID-19 pandemic has become an urgent issue in every country. Based on recent reports, the most severely ill patients present with coagulopathy, and

disseminated intravascular coagulation (DIC)-like massive intravascular clot formation is frequently seen in this cohort. Therefore, coagulation tests may be considered useful to discriminate severe cases of COVID-19. The clinical presentation of COVID-19-associated coagulopathy is organ dysfunction primarily, whereas hemorrhagic events are less frequent. Changes in hemostatic biomarkers represented by increase in D-dimer and fibrin/fibrinogen degradation products indicate the essence of coagulopathy is massive fibrin formation. In comparison with bacterial-sepsis-associated coagulopathy/DIC, prolongation of prothrombin time, and activated partial thromboplastin time, and decrease in antithrombin activity is less frequent and thrombocytopenia is relatively uncommon in COVID-19. The mechanisms of the coagulopathy are not fully elucidated, however. It is speculated that the dysregulated immune responses orchestrated by inflammatory cytokines, lymphocyte cell death, hypoxia, and endothelial damage are involved. Bleeding tendency is uncommon, but the incidence of thrombosis in COVID-19 and the adequacy of current recommendations regarding standard venous thromboembolic dosing are uncertain.

Incidence of coagulopathy in COVID

Venous thromboembolism **(VTE)** is a common hospital-acquired condition, occurring in medical and surgical intensive care unit (ICU) patients at rates historically ranging from 6.6% to 30% (11). Modern thromboprophylaxis has effectively reduced the risk of VTE development in the ICU patient population to 5% to 15%. However, the initial reports of critically ill patients with COVID-19 in Wuhan, China, demonstrated a VTE rate of 25%, greater than expected in a population with a baseline low incidence of both VTE and thromboprophylaxis usage. Similarities were quickly found across multiple other patient populations. The incidence of VTE in critically ill Dutch patients with COVID-19 was 31% and was 32% in Swiss patients (12). An autopsy study of 12 consecutive patients from Hamburg, Germany, found previously unsuspected deep vein thrombosis in 7 of the 12 patients (58%), with pulmonary embolism (PE) considered the direct cause of death for 4 patients (13).

Pulmonary infection has been established as a risk factor for VTE in multiple studies (14). A mild elevation in VTE risk continues for ≤1 year after recovery from the initial infection. Data are lacking regarding the VTE risk from other coronavirus

pneumonias. The SARS pandemic in 2003 was associated with a 23% to 33% risk of VTE in the critically ill; however, no findings of an association between VTE and Middle East respiratory syndrome were found in a review of the reported data. In contrast, the exaggerated risk described in the early studies of patients with COVID-19 more closely approximated the severe coagulopathy associated with the 2009 H1N1 viral pneumonia pandemic. In that pandemic, the VTE incidence was estimated at 37% among ICU patients. The remarkable similarities between the COVID-19 and 2009 H1N1 pandemics extend to a high incidence of breakthrough VTE, defined as the occurrence of VTE despite aggressive thromboprophylaxis or therapeutic anticoagulation.

In 150 patients infected with SARS-CoV-2 who had developed adult respiratory distress syndrome (ARDS) in France, 64 (42.7%) thrombotic complications were reported. The thrombotic complications included PE in 16.7%, continuous renal replacement therapy circuit clotting in 28 of 29 patients, and ECMO circuit clotting in 3 of 12 patients receiving ECMO support, although all had receiving thromboprophylaxis (70% a prophylactic dose and 30% a therapeutic dose)(15). Another report of 107 ICU patients with COVID-19 pneumonia confirmed the presence of PE in 22 (21%) despite prophylactic dose anticoagulant therapy for 20 patients and a therapeutic dose for 2 patients. In a cohort of French critically ill patients, the incidence of VTE was 100% for those treated with prophylactic anticoagulation and 56% for those who had received therapeutic anticoagulation (16). In a single-center study from Amsterdam of 198 hospitalized patients with COVID-19 (all of whom had received thromboprophylaxis), the cumulative VTE incidence at 7, 14, and 21 days was 16%, 33%, and 42%, respectively. The cumulative incidence of VTE was greater in the ICU patients (n = 75; 26%, 47%, and 59%) than in the non-ICU patients (n = 123; 5.8%, 9.2%, and 9.2%) at 7, 14, and 21 days, respectively. However, none of the 19 patients (0%) who had continued therapeutic anticoagulation therapy for other indications had developed VTE compared with 39 of 179 of the remaining patients (22%; Fisher's exact test, P = .03). VTE was associated with death (adjusted hazard ratio, 2.4; 95% confidence interval, 1.02-5.5)(17). In contrast, SARs-CoV-2–associated arterial thrombosis and thromboembolism has occurred at a lower frequency. In a study of three Dutch hospitals evaluating 184 ICU patients with proven COVID-19 pneumonia, arterial events, which included ischemic stroke,

myocardial infarction, or systemic arterial embolism, occurred in 3.7%.10 Of 829 ICU patients with a high prescription of chemical thromboprophylaxis .

Types of coagulpathy

Sepsis-induced coagulopathy (SIC) and disseminated intravascular coagulation (DIC) :

The pathophysiology of bacterial SIC and disseminated intravascular coagulation (DIC) has been extensively studied. Since “inflammation” and “coagulation” are the common keywords in SIC/DIC and CAC, it is helpful to consider prior studies regarding SIC/DIC. The mechanism of procoagulant responses in bacterial sepsis is complex, and various factors, including pathogen-associated molecular patterns (PAMPs) and host-derived damage-associated molecular patterns (DAMPs), are known to trigger the proinflammatory responses and activate systemic coagulation . Since inflammation and coagulation are both essential host defense mechanisms, the responses increase in proportion to disease severity and can potentially injure the host . Host defense mechanisms include proinflammatory cytokines such as interleukin (IL)-1β, IL-6, tumor necrosis factor-α (TNFα), and complement system proteins, all of which can induce coagulopathy . In addition, tissue factor expression on monocytes/macrophages, neutrophil activation, and neutrophil extracellular traps (NETs) produce activation of thrombosis . This thromboinflammatory response, together with extracellular vesicles, causes endothelial damage that further increase thrombin generation . In SIC/DIC, fibrinolysis is often suppressed due to the over-production of plasminogen activator inhibitor-1 (PAI-1), with progressive fibrin clot formation within the tissue microcirculation leading to organ dysfunction (18). To detect this type of coagulation disorder, a decrease in the platelet count and increase in prothrombin time (PT)—the two laboratory parameters used in the SIC score—are the most useful indicators . There is a lack of increase in D-dimer levels with increasing SIC/DIC severity due to suppression of fibrinolysis, also called fibrinolytic shutdown . In COVID-19, the D-dimer level is commonly high and usually greater than five times the upper limit of the normal range. Also, in SIC/DIC, anticoagulant proteins such as antithrombin decrease significantly because of increased vascular permeability and other mechanisms (18).

In the case of CAC, other coagulation biomarker changes are relatively minor and abnormalities seen less frequently . Guan et al reported on over 1000 patients and found a median platelet count of 168 × 109/L in all patients, but only 137.5 × 109/L (median) in the subgroup of patients with severe respiratory disease (all data representing values obtained at hospital admission). They also reported that abnormal D-dimer levels were observed on admission in slightly less than half of the patients. Another report from China also noted that admission platelet counts were lower in non-survivors versus survivors (median values, 122 vs 178 × 109/L, respectively). The median D-dimer value was 2.03 μg/mL in all cases, but even though it was 4.39 μg/mL in non-survivors, the PT was relatively normal (12.6 s) even in the non-survivors (19) . As a result, the incidence of DIC is low in COVID-19 and less than 1% even in severe cases . In another study, Tang et al. reported that 16 out of 183 cases (8.7%) met the DIC criteria of the International Society on Thrombosis and Haemostasis (ISTH), incidences lower than in sepsis where DIC occurs in approximately 30% of cases ; moreover, the possibility of superimposed bacterial sepsis, rather than progressive CIVID-19 per se, for progression to DIC cannot be excluded.

Consumptive coagulopathy is a typical feature in SIC/DIC; however, that type of coagulopathy is usually not seen in COVID-19 in its early phase. IL-1β and IL-6 are known to induce thrombocytosis and hyperfibrinogenemia, and sustained inflammation may stimulate the production of these factors (20). In addition, inflammation and coagulation are localized within the lung in early stages but with disease progression, hypercoagulability becomes systemic and proceeds towards SIC/DIC. The mismatched D-dimer elevation is explained by the upregulation of local fibrinolysis in alveoli by urokinase-type plasminogen activator (u-PA) released from alveolar macrophages . In addition, the direct infection of endothelial cells by the virus (a mechanism that is rather specific for coronaviruses via their cell entry through ACE2 (angiotensin-converting enzyme 2, the receptor for SARS-CoV-2), abundantly expressed on endothelium) leads to a massive release of plasminogen activators (22). With an increase in disease severity, there is a procoagulant shift with the acceleration of fibrin formation produced by increased fibrinogen levels and activated platelets. The suppressed fibrinolysis by PAI-1 release accelerates clot formation in the lung capillaries. While ACE2 helps to mediate anticoagulant properties of the vascular endothelium in the healthy state, binding of SARS-CoV-2 to ACE2 aggravates cell

damage, upregulates tissue factor expression, and downregulates the protein C system . In this situation, with or without secondary complications such as tissue hypoxia and concomitant infection, coagulopathy and thrombotic events readily occur.

Hemophagocytic syndrome (HPS)/hemophagocytic lymphohistiocytosis (HLH):

Hemophagocytic syndrome (HPS) or hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome characterized by the excessive activation of immune cells such as macrophages, natural killer cells, and cytotoxic T cells. Acquired HPS/HLH is due to large amounts of proinflammatory cytokines (TNFα, interferon-γ, IL-1, IL-2, and IL-6) released from activated macrophages and lymphocytes secondary to various triggers including viral infection (23). The diagnosis is based on five criteria (fever, splenomegaly, decreased counts in two cell lines, hypertriglyceridemia and/or hypofibrinogenemia, and hemophagocytosis) . Recently, three additional criteria were introduced that include low/absent natural killer cell-activity, hyperferritinemia, and high soluble interleukin-2 receptor levels. Although there are some similarities between HPS/HLH and CAC such as the development of “cytokine storm” in COVID-19, the clinical and laboratory findings of the typical HPS/HLH are not common in COVID-19 except fever and hyperferritinemia, with ferritin levels in COVID-19 not usually reaching the extreme high levels often seen in HPS/HLH (24) . A recent retrospective, multicenter study of COVID-19 patients reported elevated ferritin levels in non-survivors versus survivors (1297.6 ng/mL vs 614.0 ng/mL, $P < 0.01$) as well as for IL-6 (11.4 ng/mL vs 6.8 ng/mL, $P < 0.0001$) (25) . Treatment of HPS/HLH requires addressing the causal infection plus immunosuppressive treatments with corticosteroids and/or anticancer chemotherapy for refractory disease . In COVID-19, hemophagocytosis on bone marrow biopsy has not been reported ; the use of chemotherapy is not recommended. In contrast to HPS/HLH, severe lung injury and coagulopathy are the dominant characteristics of COVID-19. Direct SARS-CoV-2 infection in the lung epithelial cells followed by the damage to the lung capillary endothelial cells, and subsequent fibrin deposition with upregulated fibrinolysis by u-PA in the alveoli, may contribute to differences between COVID-19 and HPS/HLH . Based on the hypercytokinemia theory, anti-cytokine therapy may have an important role for COVID-19 (26). However, corticosteroids as

are used for HPS/HLH did not improve outcomes in severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) patients and resulted in delayed viral clearance . Although research is ongoing, there is no strong evidence at present to support the use of corticosteroids to treat COVID-19.

Antiphospholipid syndrome (APS) :

Thrombotic stroke, reported even in young patients, is a serious complication in COVID-19, with the clinical significance of the presence of antiphospholipid antibodies unknown . Secondary antiphospholipid syndrome (APS) is an acquired autoimmune thrombophilia defined by the development of arterial and venous thromboses in the presence of antiphospholipid antibodies (27). Antiphospholipid antibodies, i.e., lupus anticoagulant, anticardiolipin, and anti-β2-glycoprotein (GP) I antibodies, induce thrombocytopenia and a prolonged activated partial thromboplastin time (aPTT), and these findings often are the clues to APS. Though lung injury is not common in APS, catastrophic antiphospholipid syndrome (CAPS), a rare but highly fatal variant, can result in multiple organ dysfunction, including acute lung injury (28) , and the involvement of an over-activated complement system is suspected . Whereas the treatment strategy for the preventing thrombosis in APS can include combined antiplatelet and anticoagulant therapy (29) , the benefit of a similar approach of adding antiplatelets to the therapeutic-dose of unfractionated heparin or low molecular weight heparin (LMWH) in COVID-19 patients is unknown and could increase the potential for risk for bleeding; randomized controlled trials are addressing the question in COVID-19 . In addition to anticoagulant therapy, glucocorticoids, and plasma exchange and/or intravenous immunoglobulin, are used to treat CAPS. Convalescent plasma therapy is being developed for COVID-19 (30) , but the use of intravenous immunoglobulins has not been studied.

Escher et al. reported an interesting COVID-19 case admitted to the hospital with altered mental status, followed by respiratory and renal failure. The patient demonstrated elevated anticardiolipin and anti-β2-GP I IgM antibodies concurrent with strikingly elevated levels of von Willebrand factor (VWF) and factor VIII. The patient was initially treated with prophylactic LMWH, but with progressive abnormalities in coagulation markers, anticoagulation was switched to therapeutic-dose unfractionated heparin, with clinical improvement. Although the prognostic and

treatment implications of APS antibodies and greatly elevated VWF in COVID-19 remain unknown and IgM antibodies are usually not pathogenetic in APS, the authors argued that such unusual laboratory profile suggests a possible role for therapeutic-dose anticoagulation.

Thrombotic microangiopathy (TMA)

Thrombotic microangiopathy (TMA) is the clinical entity encompassing thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and secondary TMAs. TMA is characterized by thrombus formation in the microvasculature (mainly arterioles) with laboratory findings of microangiopathic hemolytic anemia (MAHA) and thrombocytopenia . The diffuse microvascular thrombi in multiple organs in autopsy cases of COVID-19 are similar to that of TMA, and the changes of hematologic markers resemble those in mild MAHA represented by decreased hemoglobin, increased lactate dehydrogenase (LDH), increased bilirubin, decreased haptoglobin, and appearance of schistocytosis (31).

❖ Thrombotic thrombocytopenic purpura (TTP) :

TTP is caused by autoantibody-induced depletion or inhibition of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13), a metalloprotease enzyme that cleaves large multimers of VWF. In TTP, platelet/VWF microthrombi are found along with severe thrombocytopenia and MAHA. Although acquired TTP can be triggered by infection, to date, depletion of ADAMTS13 in COVID-19 has not been reported. Rather, increased VWF levels in COVID-19 have been reported. Helms et al. found markedly elevated levels of VWF activity, VWF antigen, and factor VIII level in COVID-19. Further, nearly 90% of investigated patients were positive for lupus anticoagulant, suggesting that COVID-19 shows features resembling those of TTP and APS. It is hypothesized that increased VWF is the result of vascular injury since VWF and factor VIII are stored in Weibel-Palade body in endothelial cells. SARS-CoV-2 infection of the endothelial cells may stimulate the release of these components, with levels increasing independently from ADAMTS13 levels. Dengue virus, an RNA virus similar to coronavirus, is known to stimulate endothelial cells to release VWF (32) , and an association between elevated circulating levels of VWF and stroke has been reported in dengue . TTP features of

thrombocytopenia, fever, decreased consciousness, and renal impairment, all of which can also be seen in COVID-19 (33) , suggest possible overlapping pathophysiology can exist. However, arterial thromboembolism, such as stroke and acute coronary syndrome, and microvascular (arteriolar) thrombosis predominate in TTP, whereas venous thromboembolism predominates, with MAHA not commonly seen in COVID-19.

❖ Hemolytic uremic syndrome (HUS) :

HUS can also be induced secondary to infection and results from the dysregulation of the complement pathway. The typical symptoms of HUS are MAHA, acute kidney injury, and other organ dysfunctions (34) . Gavriilaki et al. (35) claim that COVID-19 resembles more the pathophysiology and phenotype of HUS rather than SIC/DIC. The activated complement activates platelets, induces hemolysis, and finally forms the membrane attack complexes (MAC [C5b-9]) that damage the cellular membranes. Though studies of the complement system in COVID-19 are sparse, MERS-CoV is known to increase the levels of C5a and C5b-9 in the blood and lung tissues in a murine model . Furthermore, Margo et al. delineated the deposition of MAC, C4d, and mannose-binding lectin-associated serine protease (MASP) 2 in the lung microvasculature of COVID-19 patients. They also reported that these findings were consistent with sustained, systemic activation of the alternative and lectin-based complement pathways. Complement system activation may be involved in the endothelial damage in COVID-19, and the effect of anticomplement therapy is currently studied .

Heparin-induced thrombocytopenia (HIT) :

Heparin-induced thrombocytopenia (HIT) is a prothrombotic complication that can occur following treatment with heparin. As VTE prevention using heparins (unfractionated or LMWH) is emerging as the standard care in COVID-19, patients may be at increased risk of developing HIT. This adverse drug reaction is caused by platelet-activating antibodies that recognize multimolecular complexes of platelet factor 4 (PF4) and heparin. Patients frequently experience moderate-to-severe thrombocytopenia manifesting as venous or arterial thrombi (sometimes both simultaneously). Rarely, a syndrome resembling HIT on both clinical and laboratory

grounds—“spontaneous HIT syndrome”—occurs following infection in the absence of heparin therapy (36) , but this has not been reported in COVID-19.
The risk of HIT is tenfold lower for LMWH compared with unfractionated heparin, and thus, LMWH is preferred for thromboprophylaxis in COVID-19 . The 4Ts scoring system, consisting of thrombocytopenia, timing of onset, thrombosis, and other causes of thrombocytopenia, is helpful for clinical diagnosis (37) , but the application could be challenging in patients with COVID-19. Higher baseline platelet counts in COVID-19 could mask clinical appreciation on HIT-related platelet count declines, so clinical vigilance including appropriate laboratory evaluation for HIT antibodies is needed. When HIT is strongly suspected, anticoagulation should be changed, with options including fondaparinux or direct thrombin inhibitors (e.g., argatroban, bivalirudin) (38).

Treatment

Heparin anticoagulation seems to be the obvious response to such a hypercoagulable process. In addition to its antithrombotic effect, heparin may have anti-inflammatory, anti-complement, and direct antiviral effects that may be beneficial in COVID-19. Heparin inhibits neutrophil activation, binds inflammatory cytokines, and reduces endothelial activation. Experimental models have also shown that heparin directly binds to SARS-CoV spike-protein1, which acts as the viral anchor site for SARS-CoV–ACE2 interaction, and thereby blocks cell entry (39). While promising, these effects have yet to be dem- onstrated in clinical practice, and specific data on the management of CAC are extremely limited.
One study of 449 patients with severe COVID- 19 showed no overall mortality difference (29.7% vs 30.3%, P = .910) between patients who did not and those who did receive heparin (94 patients on low-molecular-weight heparin, 5 patients on unfractionated heparin; prophylactic doses). There was, however, a significant difference in mortality rates (32.8% vs 52.4%, P = .017) in the subgroup of patients with a D-dimer more than 6 times the upper limit of normal (> 3 μg/mL). The authors concluded that heparin improves mortality rates in patients with severe COVID-19 and cited a Chinese consen- sus statement as recommending anticoagulation in severe COVID-19. It must be emphasized that this study retrospectively compared heparin prophylaxis vs no prophylaxis. It remains unclear if therapeutic

anticoagulation would provide additional benefit. Thrombolysis in patients that deteriorate despite anticoagulation has also been suggested. A small case series of patients with persistent severe hypoxia and markedly elevated D-dimer showed improvement in oxygenation after low-dose tissue plasminogen acti- vator. Despite initial improvement and no reported adverse effects, the ultimate outcome in this series was poor (40). Given this lack of evidence, the ASH and ISTH currently do not recommend treatment above and beyond standard prophylaxis unless there is an established indication. Both societies strongly recommend DVT prophylaxis in all patients on admission using low-molecular-weight heparin (unfractionated heparin in renal failure, fondaparinux in heparin-induced thrombocytopenia) and stress that prophylaxis should be continued even in the setting of thrombocytopenia (platelet count > 25 × 109/L).

Our current approach is based on POCUS screening for VTE and intensified prophylaxis in high-risk patients (table 1) . We divide patients into 3 categories:

• *Category 1* : D-dimergreater than 3,000 ng/mL FEU and no evi- dence of VTE. Patients in category 1 receive standard DVT prophylaxis and are monitored using serial D-dimer testing.

• *Category 2* : D-dimer greater than 3,000 ng/ mL FEU, POCUS-negative. Patients in category 2 receive intensified DVT prophylaxis.

• *Category 3* : Patients with confirmed thrombosis receive full anticoagulation.

In patients with high clinical suspicion of VTE and no contraindication for anticoagulation, full anticoagulation should be initiated empirically, if POCUS or confirmatory tests are not immediately available.

TABLE 1

	Category 1 D-dimer < 3,000 ng/mL FEU Standard prophylaxis	Category 2 D-dimer > 3,000 ng/mL FEU High-intensity prophylaxis	Category 3 Confirmed VTE
Standard dose	Enoxaparin 40 mg SC q24h	Enoxaparin 40 mg SC q12h	IV Heparin DVT/PE nomogram or Enoxaparin 1 mg/kg SC q12h
Renal failure *AKI definition: Doubling of creatinine in 48h or anuria	**CrCl > 10-30mL/min:** Enoxaparin 30 mg SC q24h	**CrCl < 30 mL/min or AKI:** Enoxaparin 40 mg SC q24h	IV heparin DVT/VTE nomogram
	CrCl < 10 mL/min or AKI*: UFH 5,000 U SC q12h	**CrCl <10 mL/min or AKI*:** UFH 7500 U SC q12h	
	CRRT: 500 U/h through circuit Circuit clotting: IV ACS nomogram	**CRRT:** 500 U/h through circuit Circuit clotting: IV ACS nomogram	
Obesity			
Standard	**> 100 kg:** Enoxaparin 40 mg SC q12h **> 120 kg:** Enoxaparin 60 mg SC q12h	**> 100 kg:** Enoxaparin 60 mg SC q12h **> 120 kg:** Enoxaparin 80 mg SC q12h	IV Heparin DVT/PE nomogram or Enoxaparin 1 mg/kg SC q12h – up to 150 mg Above 150 kg use UFH
Renal failure CrCl < 30mL/min or AKI* *AKI definition: Doubling of creatinine in 48h or anuria	≤ 120 kg: 7,500 U q12h > 120kg: 10,000U q12h	≤ 120 kg: 7,500 U q8h > 120kg: 10,000U q8h	IV heparin DVT/PE nomogram
	CRRT: 500 U/h through circuit Circuit clotting: IV Heparin ACS* nomogram	**CRRT:** 500 U/h through circuit Circuit clotting: IV Heparin ACS* nomogram	
IV Heparin ACS nomogram: initial dose 60-U/kg bolus, 12 U/kg/h - Target aPTT 49 – 67 seconds - Target heparin anti-Xa 0.2 – 0.5 until/ml			

ACS = acute coronary syndrome; AKI = acute kidney injury; aPTT = activated partial thromboplastin time; CrCl = creatinine clearance; CRRT = continuous renal replacement therapy; DVT = deep vein thrombosis; FEU = fibrinogen equivalent units; IV = intravenous; PE = pulmonary embolism; SC = subcutaneously; UFH = unfractionated heparin

■ *CONTINUOUS RENAL REPLACEMENT THERAPY :*

Given the high rate of clotting on dialysis circuits, all patients on continuous renal replacement therapy receive unfractionated heparin at a rate of 500 U/h. If ongoing clotting is observed, we increase systemic heparin to moderate the aPTT target range (acute coronary syndrome nomogram). The target aPPT may be adjusted if clotting continues despite systemic heparin.

■ *DURATION OF ANTICOAGULATION :*

Anticoagulation should be continued for 6 weeks for catheter-associated thrombosis and at least 3 months for VTE. Convalescent patients with persistently ele- vated D-dimer (greater than 2 times the upper limit of normal) may benefit from extended prophylaxis or treatment (41).

Recommendation

Pharmacological thromboprophylaxis should then be considered in all hospitalized COVID-19 patients who are immobilized or severely ill, unless there are contraindications (such as active bleeding or severe thrombocytopenia). Different scales can be used to assess this hospital risk (Padua, Caprini, IMPROVE). The dose should be adjusted according to renal function. Although drug selection should be guided by available institutional protocols, the World Health Organization recommends the use of unfractionated or low molecular weight heparins (LMWHs) and, if contraindicated, mechanical thromboprophylaxis should be considered.
Pharmacological thromboprophylaxis is recommended once a day, since it reduces the risk of missing additional doses and is also associated with less exposure of health personnel for its administration. If LMWH is not available, unfractionated heparin can be considered, keeping in mind that this requires more frequent injections and, therefore, greater exposure of health personnel. Fondaparinux can also be considered, but there is no evidence that this molecule has the same anti-inflammatory properties as heparins. Patients with more severe infections may require higher doses of thromboprophylaxis due to their hypercoagulable state. The use of direct anticoagulants in thromboprophylaxis is not recommended in this context due to the possible drug interactions that may occur with the different drugs and therapies available and under investigation for the treatment of COVID-19 (42).
Some of the nonanticoagulant properties of LMWH include the potential for binding to inflammatory cytokines, inhibition of neutrophil chemotaxis and leukocyte migration, neutralization of positively charged complement factor C5a, and sequestration of acute phase proteins.
Regarding the above, it is suggested that LMWH administered in the early stages of SARS-CoV2 infection can exert a positive effect not only in terms of preventing thrombosis but also reducing systemic and pulmonary inflammation and limiting viral invasion. Other nonanticoagulant actions of heparin include its antiviral role (experimental models), decreased collagen deposits and antiarrhythmic properties (animal models), as well as modulation of endothelial dysfunction, improvement of microvascular dysfunction, and mitigation of pulmonary coagulopathy (43).
In patients who remain completely immobilized, there may be an additional benefit with intermittent pneumatic compression in addition to drug thromboprophylaxis.

This therapy should also be considered if there is severe thrombocytopenia (platelets <25,000 to 50,000 × 10^9/L).

The use of extended ambulatory thromboprophylaxis (from 14 to 45 days) should be considered in patients at high risk of VTE, independent of COVID-19 infection, and that includes reduced mobility, previous thromboembolic events, comorbidities (eg, active cancer) and Elevated D-dimer (>2 times normal value). Thromboprophylaxis for patients who are quarantined for mild COVID-19, but with significant comorbidities, or patients without COVID-19 but who are functionally severely limited by quarantine is not recommended. These patients should be advised to remain active at home (44).

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