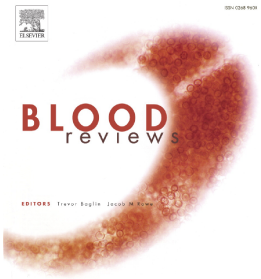

Coagulation and anticoagulation in COVID-19

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Coagulation and Anticoagulation in COVID-19

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Abstract

COVID-19 has become a pandemic in the United States and worldwide. COVID-19-induced coagulopathy (CIC) is commonly encountered at presentation manifested by considerable elevation of D-dimer and fibrin split products but with modest or no change in activated partial thromboplastin time and prothrombin time. CIC is a complex process that is distinctly different from conventional sepsis-induced coagulopathy. The cytokine storm induced by COVID-19 infection appears to be more severe in COVID-19, resulting in development of extensive micro- and macrovascular thrombosis and organ failure. Unlike conventional sepsis, anticoagulation plays a key role in the treatment of COVID-19, however without practice guidelines tailored to these patients. We propose a scoring system for COVID-19-coagulopathy (CIC Scoring) and stratification of patients for the purpose of anticoagulation therapy based on risk categories. The proposed scoring system and therapeutic guidelines are likely to undergo revisions in the future as new data become available in this evolving field.

Keywords: Coagulopathy, coagulation, anticoagulation, thrombosis, COVID-19 induced coagulopathy, COVID-19.

1 Introduction

Human coronavirus is a common pathogen of the respiratory system. It has club-shaped glycoprotein spikes on its envelope giving it the crown appearance, hence the name. While the majority of coronavirus strains induce mild upper respiratory infections, SARS-CoV and MERS-CoV can cause severe respiratory syndromes with an estimated mortality of 10% and 35%, respectively [1-3]. SARS-CoV2, also known as COVID-19 coronavirus is a novel single-stranded RNA virion that was first reported in Wuhan, China and has been spreading exponentially, resulting in thousands of deaths worldwide [4-6]. While COVID-19 infection has a higher predilection to follow a severe and sometimes fatal course, particularly in older individuals with comorbidities [4], more than 50% of patients including those severely ill do not have significant comorbidities [7, 8]. The exact mortality rate of COVID-19 infection has not been accurately estimated possibly due to under-diagnosis as many patients with mild symptoms do not seek medical attention and because many patients are still undergoing treatment. Nonetheless, the overall mortality is believed to range between 2.3 and 12.8% [6, 9]. As of April 23, 2020, the global mortality based on confirmed cases is estimated at 7%. In China, where the pandemic originated and is convalescing, the overall mortality is estimated at 5.5% [6].

COVID-19 infection is associated with multiple cellular and biochemical abnormalities. Leukocytosis, leukopenia, neutrophilia, hypoalbuminemia, hyperglycemia and elevated liver enzymes, lactic dehydrogenase (LDH), C-reactive protein (CRP), ferritin, creatinine kinase, troponin and myoglobin levels can occur [4, 10]. Red blood cell count and platelet count are usually preserved until late in the disease course. Procalcitonin level is typically normal in the majority of the patients [4, 7, 8, 10]. Lymphopenia, a characteristic feature of COVID-19, is reported in 63% of patients and believed to be due to consumption of the immune cells and inhibition of the body cellular immunity, a similar theoretical mechanism described with SARS-CoV infection [4, 11, 12]. Lymphopenia appears to correlate with a more severe disease course

in which 76% of non-survivors and 26% of survivors have a lymphocyte count of <0.8 × 10^9/L [8, 13]. Therefore, the presence and degree of lymphocyte decline is considered a reliable indicator of the severity of the disease [10, 14]. Additionally, neutrophil-to-lymphocyte ratio is considered an independent predictor of mortality [15] with a higher ratio associated with increased risk of venous thromboembolism (VTE) [16]. LDH is an exceptionally sensitive marker for COVID-19 infection and independently correlates with its severity. In addition, LDH correlates positively with inflammatory markers and markers of liver and cardiac injury and negatively with lymphocyte count, which collectively reflect the disease severity. More importantly, unlike troponin level, LDH strongly and positively correlates with the pneumonia severity index and computed tomography abnormalities and can be useful in early detection and monitoring of disease progression, particularly in relation to lung function [13, 15].

While all coagulation parameters can be affected by COVID-19, there is considerable variability in the extent of these alterations and their correlation to disease severity and mortality [10, 17]. These parameters include activated partial thromboplastin time (aPTT), prothrombin time (PT), fibrinogen, fibrin split products (FSP), D-dimer and platelet count. In addition, disseminated intravascular coagulation (DIC) and macrovascular thrombosis can occur in patients with severe COVID-19, which lead to substantial morbidity and mortality [10]. In this report, we review the effect of COVID-19 on coagulation parameters individually, discuss their relationship to COVID-19 severity, disease progression and mortality, review select coagulopathy syndromes and propose a scoring system and therapeutic algorithm for the management of COVID-19-induced coagulopathy (CIC). COVID-19-related literature cited in this paper is updated as of May 10, 2020.

2 Coagulation Parameters and COVID-19

2.1 Activated partial thromboplastin time (aPTT)

APTT is frequently elevated in DIC, particularly in its severe form. aPTT alone is not an independent predictor of DIC and is not included in the International Society on Thrombosis and Hemostasis (ISTH) criteria for diagnosing overt DIC [18, 19]. Unlike conventional sepsis, aPTT is often normal in patients with COVID-19 infection and only 6% of the patients develop prolongation of aPTT [4]. The average duration of aPTT appears to be similar in COVID-19 critically ill and non-critically ill patients, with no significant correlation to disease severity or mortality [10, 17]. Therefore, aPTT does not appear to be a reliable indicator of disease progression in COVID-19.

2.2 Prothrombin time (PT)

PT is frequently elevated in DIC and is included in the ISTH criteria for diagnosing overt DIC [18, 19]. Unlike conventional sepsis, PT is normal or near-normal in most COVID-19 patients with only 5% who have prolonged PT [4]. However, PT is significantly more prolonged in critically ill and fatal COVID-19 cases [8, 10]. On average, PT is 1.9 seconds longer in fatal COVID-19 cases compared to non-fatal cases. Additionally, approximately 48% of fatal cases develop marked and progressive prolongation of PT by more than 6 seconds later in the disease course [17] . Therefore, trending PT can augment clinical evaluation in monitoring the disease course, particularly in severe cases. Progressive prolongation of PT is considered an ominous sign and a predictor of mortality.

2.3 Fibrinogen

Fibrinogen is the most specific test for diagnosis of DIC (100%) but with poor sensitivity (22%) [20]. Fibrinogen is frequently elevated in patients with sepsis but can be low in severe cases of DIC. It is also part of the ISTH criteria for diagnosing overt DIC [18, 19]. Fibrinogen is elevated in most patients with COVID-19 with a median level of 4.55 g/L. However, the degree of elevation has not consistently shown to correlate with mortality, but strongly correlates with

interleukin (IL)-6 level [17, 21]. Nonetheless, progressive decrease in fibrinogen level is strongly associated with mortality where approximately 29% of fatal cases develop fibrinogen <1g/L, but this tends to occur very late in the disease course [17]. As a result, fibrinogen does not appear useful in detecting early signs of progression in COVID-19.

2.4 Platelet count

Thrombocytopenia is common in critically ill patients and often signifies clinical decompensation, organ dysfunction and progression to DIC [22]. Thrombocytopenia is a very sensitive marker for DIC and typically presents in 97% of DIC patients. It is part of the ISTH criteria for diagnosing overt DIC [18, 19]. However, in COVID-19, platelet count is often normal or mildly reduced in COVID-19 and thrombocytopenia is encountered in only 12-36% of patients with only 5% with a platelet count of <100x 10^9/L [4, 7, 10, 17]. Despite being uncommon, severe thrombocytopenia correlates with disease progression as more than 55% of fatal COVID-19 patients have a platelet count of <100x 10^9/L. In a meta-analysis of 1,779 patients with COVID-19 infection, patients with severe COVID-19 infection had a lower platelet count by 31x 10^9/L compared with those who had mild disease. Moreover, thrombocytopenia is associated with more than a five-fold higher risk of developing severe disease and death [8, 23-25]. Therefore, worsening thrombocytopenia often reflects clinical deterioration and probable development of DIC, which is a pre-terminal event in COVID-19 [17]. Additionally, development of severe thrombocytopenia should prompt an investigative work-up for alternative causes. Development of secondary infections is encountered in 50% of critically ill COVID-19 patients, particularly those requiring mechanical ventilation [8, 25]. Moreover, thrombocytopenia induced by drugs such as heparin should be considered. A recent study by Liu et al reported the presence of the anti-heparin-PF4 antibody in most critically ill COVID-19 patients. The presence of this antibody appears to correlate with progressive thrombocytopenia and severity of illness [26]. However, confirmatory testing for heparin-induced thrombocytopenia (HIT) was not

performed in this study, which raises concern that the possibility of these findings may simply be due to immune dysregulation in this highly immunogenic disease and not a true reflection of HIT. Nonetheless, HIT should be considered in patients with intermediate or high probability as determined by the standard 4T scoring system [27]. In the absence of a plausible explanation for progressive thrombocytopenia, COVID-19 progression should be suspected, which should prompt modification of clinical management, including introduction of therapeutic interventions to alter the disease course.

2.5 Fibrin split products (FSP)

FSP is a heterogeneous group that provides a measure of fibrinolysis with 100% sensitivity and 67% specificity for DIC [20, 28]. FSP is part of the ISTH criteria for diagnosing overt DIC [18, 19], and is typically preceded by elevation of D-dimer, which is considered a more sensitive marker for coagulopathy early in the disease possess [20, 28]. FSP is typically normal in most patients with mild or early COVID-19 and significantly higher in fatal cases (4 µg/mL for survivors vs 7.6 µg/mL in non-survivors. In addition, FSP is considered prognostic as progressive elevation of FSP level inversely correlates with survival [17].

2.6 D-Dimer

Quantitative D-dimer is a useful tool for the diagnosis and prediction of recurrence of VTE [29, 30]. It is also a sensitive early marker of DIC but with low specificity [20]. In COVID-19, D-dimer is elevated in 36% of cases with an average level of 0.9 mg/L [4, 7]. A higher D-dimer level is frequently encountered in critically ill patients compared to milder cases (mean level of 2.4 vs 0.5mg/L) and inversely correlates with survival [7, 10, 31]. As compared to COVID-19 survivors where 24% of patients have D-dimer >1mg/L, Zhou et al showed that 81% of non-survivors have D-dimer >1mg/L. In addition, a steady and progressive increase of D-dimer is

commonly seen in COVID-19 non-survivors compared to survivors where D-dimer remains stable or improves [8]. Similarly, Tang et al. showed that more than 85% of COVID-19 non-survivors have D-dimer >3mg/L [17]. Therefore, D-dimer appears to be highly prognostic in COVID-19 and correlates with a more aggressive course and mortality. It may also have value in identifying those who could potentially benefit from anticoagulation therapy [17, 31].

3 Mechanism of coagulopathy in COVID-19

COVID-19 pneumonia appears to have distinguishing features compared to conventional pneumonia. It is evident that COVID-19 patients develop dysregulated uncontrolled host response, that results in excessive release of many inflammatory cytokines and chemokines such as TNF-α, IL-1, IL-6 and IL-8 [12]. The release of these molecules induces macrophage activation syndrome-like picture, which triggers the endothelial cells, macrophages and neutrophils to express tissue factor within the lungs, which in turn initiates and further augments pulmonary coagulopathy and microvascular thrombosis [32]. IL-6 is a key cytokine that is markedly elevated in severe COVID-19 infection and is a key activator of coagulopathy by inducing tissue factor expression and increasing production of fibrinogen and platelets [21, 33-35]. Median IL-6 level in patients with sepsis due to community acquired pneumonia requiring mechanical ventilation is 65.6 pg/mL [36]. In COVID-19 patients requiring mechanical ventilation, median IL-6 is reported to be at 121-218pg/mL [21, 37]. This significant difference in IL-6 level in critically ill patients is likely directly induced by COVID-19 infection, which may explain the significant difference in the pattern of coagulopathy in these patients. In addition, there is cumulative evidence implicating endotheliitis in COVID-19 pathogenesis. A recent postmortem series showed evidence of a direct multi-organ infection of the endothelial cells with COVID-19 with an associated diffuse inflammation. Apoptosis and pyroptosis were suggested as possible mediators of endothelial injury in these patients [38]. Notably, this inflammatory endothelial cascade can directly result in microvascular dysfunction and occlusion but can also

induce hypercoagulable state, resulting in microvascular thrombosis. Moreover, hypoxia, a frequent feature of severe COVID-19 is a prominent stimulant of thrombosis via expression of hypoxia-inducible transcription factors, which in turn target several genes that regulate thrombosis [39]. Moreover, a preclinical model showed that SARS-CoV results in disruption of the fine balance between plasmin and the urokinase pathway, resulting in fibrin accumulation [40]. Dysregulation of the urokinase pathway is likely in part responsible for the coagulopathy encountered in COVID-19, which is more magnified than that seen in conventional sepsis. Together, these events result in extensive microvascular thrombosis within the lungs, an entity referred to as diffuse pulmonary intravascular coagulopathy (PIC). The elevation of D-dimer and FSP in COVID-19 patients reflect the immunothrombosis induced by PIC [32].

4 Differentiating COVID-19-induced coagulopathy (CIC)

The ISTH defines DIC as an acquired syndrome that induces intravascular activation of coagulation causing damage to the microvasculature and eventually results in organ dysfunction [18, 41, 42]. DIC is encountered in 30-50% in patients with severe sepsis [22, 43] resulting in thrombosis, bleeding and organ dysfunction [17, 22]. DIC can be latent or overt. Latent DIC is often subtle and results from an imbalance between the activation and inhibition of the coagulation system. Overt DIC results from a significant dysregulation of the coagulation system, resulting in disseminated microvascular thrombosis and consumptive coagulopathy [22, 41, 42]. While the majority of COVID-19 patients do not develop DIC, it was reported in 71.4% of fatal cases with a median time from admission to development of DIC of 4 days [8, 17]. Therefore, development of DIC in COVID-19 patients is an ominous and late sign that should prompt utilization of all possible medical interventions to reverse the underlying process.

While severe CIC can mimic conventional sepsis-induced coagulopathy in its late stages, several key differences are observed (table 1). Thrombocytopenia that is typically

prominent in conventional sepsis occurring in 22–58% of patients [43], is either absent or very mild in most patients with COVID-19. Moreover, consumption of coagulation factors appears very modest in most COVID-19 patients as manifested by normal or mild prolongation of PT and aPTT and the low prevalence of hypofibrinogenemia compared to conventional sepsis. This may explain the rarity of bleeding in patients with COVID-19 [31]. On the other hand, the elevation in D-dimer is frequent in COVID-19 and appears to be out of proportion to changes in other coagulation parameters, reflecting a marked increase in thrombin generation and fibrinolysis. However, it is possible that this process is limited to certain organs such as the lungs and/or kidneys as disseminated activation of coagulation is not typically seen in COVID-19. In addition, absence of a characteristic finding in DIC, i.e. red blood cell schistocytes, in CIC suggests a more limited process. This was also suggested in a recent series of autopsies showing restricted microvascular thrombosis of the pulmonary small vessels, raising a concern for restricted thrombotic microangiopathy [44]. However, the mechanism through which the CIC remains restricted to certain organs is unknown.

5. Macrovascular thrombosis in COVID-19

It is increasingly evident that COVID-19 is a hypercoagulable disorder. Several observatory reports suggest a higher incidence of VTE in COVID-19 patients [45-48], likely due to excessive inflammation, coagulopathy, immobilization, and at later stages, DIC. While thrombotic events in early observatory reports may have been provoked by immobilization and underuse of pharmacological thromboprophylaxis, several authors reported thrombosis at presentation or despite use of thromboprophylaxis, implying a direct association between COVID-19 and thrombosis [46-48]. Several cohort studies documented a high incidence of VTE in patients with COVID-19 admitted to the intensive care unit (ICU) (table 2). Xu et al, Middeldorp et al and Lodigiani et al also reported VTE risk in ward patients and confirmed it to be much lower than that in critically ill patients. However, this risk of thrombosis remains

significantly high in ward patients as reported by two of these studies (3.3-6.4%) despite the use of thromboprophylaxis[16, 49]. Additionally, there is a wide variability in the reported VTE incidence in ICU patients between different studies, which could be reflective of the disparity in the use of VTE diagnostic and screening modalities and the type and dose of VTE thromboprophylaxis agents used. Under-diagnosis could have occurred as well, due to the inherent inconsistency in clinical practice between practitioners as diagnostic VTE work-up in most studies was chiefly initiated based on clinical suspicion. In the study by Lodigiani et al, VTE was investigated in only 10% of patients [50]. Additionally, Ciu et al reported deep vein thrombosis (DVT) risk of 25% but pulmonary embolism (PE) risk was not reported. Moreover, Ciu et al reported the use of some kind of VTE screening but without providing information about the frequency of screening and the screening modality used [51]. Xu et al reported performing compression ultrasound on all ICU patients and those at high risk for VTE or with high-dimer with occasional use of computed tomography angiography of the chest when possible [49]. However, detailed information about the frequency of use of VTE screening was not provided. In the study reported by Middeldorp et al, routine VTE screening with compression ultrasound was performed every 5 days in the ICU and every 10 days in the wards. The authors reported an incidence of thrombosis at 20.1%, of which 13% were detected clinically and 7.1% found incidentally or by screening. All events detected incidentally or by screening were in the ICU[16]. It is not known whether these thrombotic events detected on routine screening would carry similar clinical implications as in symptomatic events. However, it is plausible to suspect that these events detected incidentally or by screening pose a significantly high risk of propagation and embolization in the critically ill COVID-19 patients. In non-COVID-19 hypercoagulable patients such as those with malignancy, incidentally-found VTE has shown to have similar adverse outcomes to symptomatic VTE [52]. Therefore, VTE therapy is likely beneficial in COVID-19-associated thrombosis even in the absence of symptoms. Additionally, routine VTE screening may be of value and deserves further research, particularly in critically ill

patients. Universal implantation of VTE screening in COVID-19 requires further prospective confirmation in clinical trials.

There is significant variability in the use of pharmacologic thromboprophylaxis between studies. Prophylactic anticoagulation is not employed as a standard of care in China. The high incidence of DVT in the Chinese studies could be related to a prolonged hospital stay due to the severity of illness in the absence of VTE prophylaxis. Ciu et al did not employ VTE prophylaxis and Xu et al employed thromboprophylaxis only in patients with high risk of VTE as determined by a Padua score of above 4. However, all 4 patients who developed VTE in the Xu et al study were already receiving prophylaxis anticoagulation [49]. Klok et al and Middeldorp et al reported high thrombotic risk despite the use of nadroparin with VTE incidence of 31-47% in ICU patients [16, 53]. It is of note that the dose was variable between the patients, which makes it difficult to assure that patients received adequate prophylaxis. Additionally, enoxaparin is possibly more efficacious than nadroparin in thromboprophylaxis [54], however, this difference is quite small and unlikely to explain this remarkably high thrombotic events in this patient population. Of interest, in the Middeldorp et al study, none of the 19 patients who were already on therapeutic-dose anticoagulation at admission for another indication developed thrombosis. Additionally, an exploratory analysis showed a possible association between the development of VTE and higher mortality [16]. Helms et al also reported a considerably high incidence of thrombosis (18%) in COVID-19 patients admitted to the ICU [55]. This figure is lower than what is described by other studies, probably due to the use of more effective VTE prophylaxis, as 30% of patients received therapeutic-dose anticoagulation. In the Italian study by Lodigiani et al, the thrombosis incidence is reported at 7.7% in the total population and 16.7% in ICU patients, which is lower than what is reported by other studies possibly due to the use of more effective thromboprophylaxis. Unfortunately, detailed information about the prophylactic regimens used was not reported by the authors. Interestingly, 50% of the events in this study occurred within 24

hours of admission and 56% were not receiving anticoagulation when they occurred. In contrast, the reported incidence of VTE in ICU patients without COVID-19 infection, is approximately 2.1% [55]. Collectively, the reported studies to date suggest a likely association between COVID-19 and development of thrombosis. It is noteworthy that the majority of thrombotic events occurred in ICU patients despite the use of prophylactic anticoagulation. This may indicate that standard prophylaxis used for hospitalized patients may be inadequate in COVID-19 patients, particularly those who are critically ill.

Several predictors of VTE have been identified. Ciu et al noted that older age, higher D-dimer, lower lymphocyte count and longer aPTT were associated with a higher DVT risk, but D-dimer was the strongest predictor of DVT [51]. Klok et al reported that older age and coagulopathy, defined as spontaneous prolongation of the PT longer than 3 seconds or aPTT longer than 5 seconds were independent predictors of thrombosis. Unfortunately, the predictive value of D-dimer was not reported [53]. Middeldorp et al noted that higher white blood cells, neutrophil to lymphocyte ratio and D-dimer were associated with higher risk for venous thromboembolism[16].

In addition to native vessel VTE, thrombosis of foreign devices has also been documented in patients with COVID-19. Among patients receiving continuous renal replacement therapy (CRRT), the incidence of circuit thrombosis is reported at 96.6% with a median circuit lifespan of 1.5 hours, which is much shorter than the manufacturer recommended lifespan of 3 days [55]. In addition, centrifugal pump thrombotic occlusion of the extracorporeal membrane oxygenation (ECMO) is reported more frequently in COVID-19 patients. Helms et al reported centrifugal pump thrombosis in two of the three patients receiving ECMO. Moreover, inferior vena cava (IVC) filters are not recommended in COVID-19 patients due to the risk of filter thrombosis. In fact, they are often not necessary given the low bleeding risk in this patient

population [55]. IVC and central venous catheter thrombosis has been reported in COVID-19 patients [50]. However, their exact incidence has not been reported.

In addition to venous thrombosis, COVID-19 infection appears to be associated with a high risk of arterial events [53, 55]. A significantly high incidence of stroke (6.3%) was reported, particularly in critically ill patients. Interestingly, approximately two-thirds of these case are diagnosed at presentation [50]. It is noteworthy that diagnosing stroke in ventilated and sedated patients can be challenging and therefore, daily interruption of sedation may be helpful to allow for neurologic assessment. Acute coronary syndrome and myocardial infarction have also been reported in up to 2.1% of ICU patients [50]. Although elevation of myocardial injury markers is commonly encountered in COVID-19 without macrovascular compromise [8], there are postmortem pathologic reports confirming the presence of myocardial infarction in some COVID-19 patients, likely due to coronary arterial thrombotic events [38]. Diagnosing myocardial infarction in COVID-19 patients presents a challenging dilemma due to the difficulty in distinguishing patients with myocardial infarction from those with elevated myocardial injury markers without infarction. This may require relying on electrocardiogram and imaging studies rather than biochemical markers to establish the diagnosis. In addition, concurrent venous and arterial thrombosis and occasionally mesenteric ischemia have rarely been reported in COVID-19 patients [38, 55].

As in non-COVID-patients, D-dimer is an effective tool in predicting the development of thrombosis in COVID-19 [51, 56]. By using different cut-off levels, the sensitivity, specificity, predictive values (positive predictive value, PPV or negative predictive value, NPV) varies. With a cut-off of 1mg/L, the PPV is 54.8% and NPV is 94%. When the cut-off level is 3mg/L, the PPV is 87.5% and NPV is 90.8% [51].This remarkably elevated PPV is crucial when therapeutic interventions such as anticoagulation are employed based on the test value to avoid unnecessary exposure to the anticoagulants.

6. Microvascular thrombosis in COVID-19

In addition to macrovascular thrombosis, COVID-19 patients are thought to be at an increased risk for microvascular thrombosis, likely due to the release of procoagulant cytokines such as IL-6 [12, 21, 37]. It is noticeable from our experience and others that many patients with severe respiratory failure maintain good lung compliance with well-preserved lung mechanics despite severe hypoxemia and pronounced prolonged dependence on mechanical ventilation [8, 57]. Despite the absence of DIC, D-dimer and FSP are often markedly elevated in severe COVID-19 reflecting a high level of fibrin formation and degradation. This constellation of findings is suggestive of pulmonary microvascular thrombosis. Early autopsy reports on COVID-19 patients reported non-specific findings including extensive inflammatory infiltrates, diffuse alveolar damage, pulmonary fibrosis, large atypical pneumocytes, edema and hyaline membranes formation [58-61]. However, more recent and comprehensive reports show small vessels hyperplasia, wall thickening, vascular hyaline thrombosis and focal pulmonary hemorrhage, possibly due to venous congestion [58, 62]. This endothelial injury and fibrin thrombosis were also reported in the glomerular capillaries [38, 63]. A more recent postmortem series from New Orleans thoroughly examined the cardiopulmonary system of four COVID-19 victims and revealed pulmonary consolidation with patchy areas of hemorrhage with small, firm thrombi identified in the peripheral lung parenchyma. Microscopically, there was interstitial lymphocytic infiltrate surrounding thrombosed small vessels (containing fibrin and platelets admixed with inflammatory cells) with significant associated hemorrhage. Alveolar capillaries and small vessels were thickened and contain fibrin thrombi . Pulmonary-restricted thrombotic microangiopathy was raised as a potential cause of death in these patients. Intense complement activation was proposed as an inducer of microvascular thrombosis due to deposition of the terminal complement complex C5b-9, C4d and MASP2 in the lungs [57].

Platelets appear to play an important role in the pathogenesis of COVID-19. Postmortem reports noted the presence of a significant number of platelets and megakaryocytes within the alveolar capillaries , raising the possibility of extramedullary platelet production. This interpretation may also explain the relatively higher platelet count in COVID-19 compared to conventional sepsis and raises the possibility of pulmonary megakaryocytic activation resulting in platelet aggregation and formation platelet-fibrin thrombosis. Interestingly, megakaryocytic response has been documented previously in viral infections such as H1N1 influenza and SARS-CoV by overexpressing interferon-induced transmembrane protein 3, which stimulates platelet production [44, 64]. Evidence also suggests that SARS-CoV directly infects megakaryocytes, which may influence platelet count and function [44, 65]. The effect of COVID-19 on megakaryocytes remains unknown but it is possible that the release of cytokines (mainly IL-6) in these patients enhances megakaryocytic proliferation, differentiation and activation through increasing the production of thrombopoietin [66, 67], and may be linked to the low incidence of significant thrombocytopenia in COVID-19 patients.

7. COVID-19 and thrombophilia

While patients with COVID-19 are at higher risk for thrombosis, the mechanism through which thrombosis occurs is yet to be precisely verified. There is some proposition that COVID-19 infection may induce thrombophilias such as antiphospholipid antibody (APLA) syndrome. A recent report from China described three patients with cerebral infarctions and positive serology for anti-cardiolipin IgA and IgG and beta-2 glycoprotein IgA and IgG [68]. The diagnosis of APLA syndrome requires persistence of the antibody over 12 weeks, which was not confirmed in these patients. All three patients were elderly with multiple cerebrovascular risk factors such as hypertension, diabetes, coronary heart disease and malignancy; thus at risk for stroke due to these risk factors. Therefore, the association between COVID-19 and APLA appears to be limited. Notable, a positive lupus anticoagulant is reported in 45% of COVID-19 patients and up

to 88% of those admitted to the ICU [55, 69]. A modest deficiency of factor XII was also reported in some patients [70], which may be associated with an increased thrombotic risk [71]. In our COVID-19 experience, we identified 1 patient with positive anti-cardiolipin IgA, beta-2 glycoprotein IgA and lupus anticoagulant without thrombosis and 7 additional patients with positive lupus anticoagulant, one with recurrent thrombosis of the continuous renal replacement therapy (CRRT) circuit (unpublished data) and one with pulmonary embolism. All patients had a markedly elevated fibrinogen level (623-1,332 mg/dL), severe lymphopenia (0-0.32 × 10^9/L) and prolonged PT (14.4-39.7 sec) and aPTT (36.5-133.2 sec). Seven of these patients required mechanical ventilations and six patients had D-dimer of >3 mg/L. Five of these patients succumbed to their disease without thrombosis. Surprisingly, only one patient had a pre-existing autoimmune disease, specifically immune thrombocytopenia purpura. All patients received anticoagulation at variable doses. Interestingly, a repeat lupus anticoagulant testing on the patient who developed thrombosis of the CRRT circuit became negative 7 days later, which may suggest a transient hypercoagulable process. Collectively, these unique abnormalities in COVID-19 may be explained, hypothetically, by immune dysregulation and endothelial damage induced by COVID-19. Yet, although these findings may be partly responsible for the increased risk of thrombosis in COVID-19 patients, they are not the sole responsible factors. In our recent experience, we encountered 11 patients with COVID-19-associated thrombosis (4 DVTs, 6 PEs and 1 stroke), who underwent at least partial testing for APLA syndrome (unpublished data). Among these patients, only one patient was found to be positive for lupus anticoagulant. This observation suggests the presence of other alternative contributing factors for thrombosis in COVID-19 apart of APLA.

8. Therapeutic Implications

8.1 Role of anticoagulation

Given the increased risk of macrovascular and microvascular thrombosis in patients with COVID-19, anticoagulation was suggested as a mitigating option. In addition, the anti-inflammatory effect of heparins can be advantageous in this highly inflammatory condition [72-74]. Moreover, there is some proposition that anticoagulation may block or slow progression to DIC [21]. While anticoagulation is controversial in conventional sepsis [72, 75], COVID-19 sepsis is a distinct entity as reflected by the difference in coagulation parameters. Therefore, anticoagulation appears to have a significant role in COVID-19 treatment (table 3). A recent Chinese study by Tang et al described 449 patients with severe COVID-19 infection and reported reduced mortality with anticoagulation in patients with high-D-dimer and/or a high sepsis-induced coagulopathy (SIC) score [31, 76]. By using different increasing D-dimer cutoffs, the 28-day mortality improved steadily in patients who received anticoagulation, compared to those who did not receive anticoagulation, beginning when D-dimer exceeded twice the upper limits of normal (ULN) and reaching statistical significance when D-dimer was above 6x ULN. The 28-day mortality reductions with D-dimer above the 6x ULN and 8x ULN D-dimer were 19.6% and 21.5%, respectively. In addition, patients with a SIC score of 4 or higher had 24.2% improvement in 28-day mortality with the use of anticoagulation. It is worth noting that the majority of patients received prophylactic-dose enoxaparin in this study [51]. Notably, the mortality benefit observed in COVID-19 patients with the use of anticoagulation was not observed in non-COVID-19 patients, further illustrating the fundamental difference between COVID-19 and conventional sepsis [77]. Another recent study from New York examined the effect of therapeutic-dose anticoagulation in unselected 2,773 hospitalized patients with COVID-19 [78]. The study reported modest improvement of median survival with the use of anticoagulation. However, this benefit appears to be significantly higher in mechanically ventilated patients with a 33.6% reduction of mortality. Inpatient mortality in mechanically ventilated patients was 29.1% and 62.7% for patients who received and did not receive anticoagulation, respectively. The median days of anticoagulation was 3 days and a longer

course of anticoagulation correlated with improved survival [78]. Notably, D-dimer and SIC were neither reported in this study nor used as decision factors to prompt the use of anticoagulation. In this study, it is likely that sicker patients were more likely to receive anticoagulation as manifested by higher mechanically ventilated patients in the anticoagulation group. Prospective clinical trials are ongoing to confirm the survival benefit of anticoagulation in patients with COVID-19.

The optimal dose of anticoagulation remains unknown. While the mortality benefit in the Chinese study reported by Tang et al was achieved with a prophylactic-dose anticoagulation, primarily enoxaparin, this approach is unlikely to be adequate. First, there is a significant difference in the mean weight between the United States and China. The mean weight of American men and women is 90.9kg and 87kg, respectively and of Chinese men and women is 70.5kg and 59.4kg, respectively [79]. This difference may influence the efficacy of the weight-based anticoagulation in high-risk American patients. Second, the considerably high incidence of macrovascular thrombosis (16-47%) in critically ill COVID-19 patients despite the use of anticoagulation suggests inadequate dosing (table 2) [16, 52, 53, 55, 57]. Moreover, Paranjpe et al showed reduced inpatient mortality in COVID-19 patients with the use of therapeutic-dose rather than prophylactic dose anticoagulation [55]. It is also documented that the risk of developing DVT rises as D-dimer increases with PPV of developing VTE approaching 88% in patients with D-dimer above 3g/L. A gradual decline in D-dimer level was noted with the use of anticoagulation, suggesting response to therapy and highlighting the importance of D-dimer as a predictive marker of such response [51]. At a molecular level, Ranucci et al showed that increasing the anticoagulation dose beyond standard prophylactic LMWH and combining it with anti-platelet therapy decreases fibrinogen level, D-dimer level and also reduces fibrinogen and platelet contribution to clot strength [21]. Together, these observations suggest the need for higher dosing than what is typically used for hospitalized non-COVID-19 patients. Several

randomized clinical trials investigating the optimal dosing of anticoagulation in COVID-19 are underway.

While direct oral anticoagulants are feasible and convenient for outpatient management of COVID-19 patients, caution should be exercised due to the existing interactions with several agents used to treat COVID-19 [80]. In hospitalized patients, the use of heparins, particularly LMWH is favored. LMWH is convenient and requires limited exposure of healthcare staff to COVID-19 patients

8.2 Proposed CIC scoring system

While the ISTH DIC score is helpful in detecting overt DIC in septic patients [42], its value in CIC is likely limited. DIC is a late and often pre-terminal event in COVID-19. In addition, the effect of COVID-19 on the values of key variables as reflected in the ISTH DIC score (PT, fibrinogen and platelet count) is modest. Moreover, organ dysfunction, a common finding in COVID-19 is not accounted for in the ISTH DIC scoring system. More importantly, D-dimer, a key marker in COVID-19, is not part of the ISTH DIC scoring system. Therefore, there is a clear need to modify the ISTH DIC scoring system to incorporate COVID-19-specific variables. Similarly, the Caprini scoring system, a score mostly suited to assess the benefit of chemoprophylaxis in surgical patients, fails to incorporate the coagulopathic prognostic features of COVID-19 [81]. SIC is a validated scoring system in patients with conventional sepsis. To calculate SIC, computation of sequential organ failure assessment (SOFA) should be performed first, which includes assessment of the lung, liver and kidney function (excluding assessment of hematologic and neurologic systems) [82]. Then, the SOFA total score (up to 2 points) is combined with scores of platelet count (up to 2 points) and PT (up to 2 points) to yield a final score (up to 6 points) [76]. In COVID-19, SIC is a key predictor of mortality and response to anticoagulation [31]. As previously discussed in section 5, organ dysfunction is known to be at least partly induced by microvascular thrombosis and potentially predictive of response to

anticoagulation. Thus, it is not surprising that patients with high SIC (≥4) who received anticoagulation had higher survival compared to those who did not receive anticoagulation [31]. However, the SIC scoring system does not include D-dimer, the most important and distinctive laboratory finding in CIC and key predictor of response to anticoagulation [31, 83]. Therefore, there remains a need for a comprehensive COVID-19-specific scoring system for assessment of CIC and to help in stratifying COVID-19 patients for anticoagulation.

To establish a COVID-19-specific scoring system, we combined the SIC and SOFA scores in a single table and applied an appropriately weighted score to each item. Notably, PT and platelet count (included in the SIC score) are established predictors of mortality and a surrogate of disease severity in COVID-19 [17]. As they both represent a higher SIC score thus higher benefit of anticoagulation [31], they were combined given a weight of 40% of the total score. It is notable that their original combined weight is 67% in the SIC scoring system, which was lowered to allow for the addition of D-dimer. As D-dimer also strongly correlates with mortality, risk of thrombosis and response to anticoagulation, it was added to the scoring system (table 4). Due to its importance, it was given a weight of 40% of the total score with progressively higher points granted as D-dimer increases, based on the established linear correlation between D-dimer level and the magnitude of benefit from anticoagulation [31], which formed the base of this selection. Finally, organ dysfunction as measured by SOFA was given a weight of 20% (up to 4 points). In the SIC scoring system, SOFA weight was 33%. This weight was lowered due to the known interaction between organ dysfunction and elevation of D-dimer (organ dysfunction will likely be partly measured by D-dimer). Therefore, the new CIC scoring system will add D-dimer to the pre-existing SIC score (platelet count, PT, SOFA) with a maximum possible score of 20. Then, we constructed an algorithm to triage patients to various intensity of anticoagulation based on their risk (figure 1). A CIC of 8 corresponds roughly with the mortality benefits of anticoagulation therapy reported by Tang et al. The patients were

stratified into three risk categories with therapeutic-dose and prophylactic-dose anticoagulation recommended for high-risk and intermediate risk groups, respectively (table 5). A slightly more intensive prophylactic dose was proposed to address the hypercoagulability of COVID-19. Although patients with intermediate risk may potentially benefit from therapeutic-dose anticoagulation, the available data remain limited in this population to warrant its unselected use. This proposed scoring system and triaging algorithm are a preliminary interim effort to establish a COVID-19-specific system based on the currently available published and practice evidence and yet to be validated. Therefore, it should be used with caution as it is not yet validated. We are certain that this effort likely needs optimization and prospective validation as additional data become available through randomized clinical trials.

The risk of thrombosis in patients with COVID-19 appears to last for several weeks resulting in re-hospitalization and could potentially contribute to the sudden deaths encountered in some of these patients [53]. Therefore, continuation of anticoagulation after hospital discharge in those with increased VTE risk is recommended with the appropriate dosing tailored based on the risk category and VTE risk factors (figure 1). While a 4-week course is suggested for high-risk patients, which allows time for the infection to resolve, the optimal necessary anticoagulation course is yet to be determined.

8.3 Replacement of coagulation factors

The current available data suggest that COVID-19 patients are at low risk for major bleeding (≤3%) even when anticoagulation is administered [51, 55, 78]. Therefore, prophylactic replacement of coagulation factors and platelets is not recommended, in the absence of bleeding, to avoid increasing the thrombotic risk. Similar to non-COVID-19 patients, replacement of coagulation factors and platelets with fresh frozen plasma (FFP), cryoprecipitate, prothrombin complex concentrate (PCC) and platelet transfusion should be individualized to

meet the clinical and procedural needs of the patients [84]. High-level evidence to guide factor replacement remains limited, which makes these decisions predominantly driven by clinical judgment and consensus of experts. In the absence of bleeding, platelet transfusion can be reserved for patients with platelet count <10 x 10^9/L given the low risk of bleeding when platelet count is above this threshold [85]. FFP and/or 4-factor PCC can be used in bleeding patients to achieve homeostasis. An initial dose of 15 ml/kg of FFP is typically used. Close monitoring of hemodynamics should be exercised in patients receiving FFP to avoid volume overload, which can worsen respiratory failure, particularly in patients with already compromised respiratory function due to COVID-19. Factor replacement with 4-factor PCC has the advantage of having smaller volume, which minimizes the risk for volume overload. The suggested initial dose varies based on the degree of coagulopathy ranging between 25 and 50 units/kg. Cryoprecipitate and purified fibrinogen concentrates are reserved for bleeding patients with a fibrinogen level of less than 1.5 g/dl [84]. The response to blood and factor replacement should be closely monitored to assess the need for additional replacement as guided by the presence of clinical bleeding and laboratory parameters. While a COVID-19-specific monitoring guideline is lacking, we suggest monitoring of blood counts, inflammatory markers and coagulation values as for non-COVID-19 coagulopathy (figure 1) [18]. Implementing such a procedure may assist in early detection of the disease progression, which may prompt initiation of additional interventions that may impact the overall outcome of COVID-19.

8.4 Other potential therapeutic options

In the absence of high-level evidence, management of COVID-19 has been predominantly driven by small studies and observatory reports. Given the importance of platelet activation and contribution of platelets to clot formations [21, 44], and the observed increase in

the number of pulmonary megakaryocytes in pulmonary microvasculature, platelet aggregation was proposed as a potential contributing factor to thrombosis and organ dysfunction [44]. Therefore, the use of anti-platelet therapy such aspirin is reasonable. Dipyridamole, another anti-platelet agent, was found *in vitro* to suppress COVID-19 replication. *In vivo*, dipyridamole significantly improved platelet and lymphocyte counts and decreased D-dimer levels in a study of 12 patients with COVID-19 [86]. Prospective studies are needed to confirm the clinical benefit. While dipyridamole may have a role in management of CIC, prospective studies are needed to confirm the benefit. Chloroquine and hydroxychloroquine combined with azithromycin may reduce viral loads and shorten viremia in patients with severe COVID-19, but the observed benefit has been inconsistent [87-90]. The effect of these agents on CIC has not been reported. Tocilizumab, a recombinant humanized antibody that binds IL-6 receptor, is proposed as a potential therapy. As IL-6 is has potent prothrombotic properties, it is plausible to predict that this type of therapy may improve CIC. While several studies suggested potential benefits from the use of tocilizumab in decreasing oxygen requirement, radiologic improvement, lymphocyte recovery and decrease in CRP [91, 92], its effect on CIC remains unknown. Finally, the use of convalescent plasma and immunomodulatory agents such as steroids and intravenous immunoglobulin have shown some promise in management of COVID-19 infection [93, 94], but with unknown effect on CIC. It is noteworthy that concurrent use of anticoagulation and cytokine-reducing agents such as steroids and tocilizumab may be particularly effective as release of cytokines principally IL-6 induces microvascular thrombosis, therefore dual blockage of this pathway may have significant benefit to those with COVID-19. However, this theoretical advantage requires further confirmation in clinical trials.

9. Future Considerations

It is now evident that anticoagulation plays a key role in the management of COVID-19 infection but an optimal anticoagulation agent and dose remain uncertain.

Randomized clinical trials are needed to identify the magnitude of anticoagulation benefit and specify the most effective agent and appropriate dosing. Moreover, the CIC scoring system presented in section 8 will require prospective validation and possibly revision as new data become available. It is possible that patients with a CIC who score less than 8 may benefit from therapeutic-dose anticoagulation. This benefit is best examined prospectively in the setting of clinical trials. In addition, preliminary studies suggest a promising role for anti-platelet therapy in the management of COVID-19. However, it is unclear whether adding aspirin to anticoagulation therapy will result in additional benefit. Also, it is unknown whether the use of other anti-platelet agents such as clopidogrel or dipyridamole alone or in combination with aspirin is advantageous. As more agents are being used for treatment of COVID-19, it is critical to evaluate the effect of such therapies on CIC, particularly D-dimer, which is an effective predictor of survival. Furthermore, it is possible that there is a synergistic or additive effect between therapies discussed above and therefore, certain combinations of anticoagulants and anti-COVID-19 therapy may be beneficial, particularly when microvascular thrombosis and pulmonary inflammation are targeted simultaneously. Clinical trials are ultimately needed to address these questions. Ideally, an international effort should be coordinated to facilitate multi-center research with rapid turn-around time to systemically address this rapidly-spreading pandemic.

Practice Points

- CIC is a distinct entity from sepsis-induced coagulopathy with characteristic marked elevation of D-dimer and fibrin split products but has minimal effect on prothrombin and partial thromboplastin times.
- In COVID-19, D-dimer strongly correlates with survival and is an effective predictor of response to anticoagulation.
- COVID-19 infection is associated with high incidence of micro- and macrovascular thrombosis.
- Unlike conventional sepsis, the use of anticoagulation is associated with improved survival in COVID-19 but prophylactic dosing is inadequate in high-risk patients.
- The proposed CIC scoring system may be helpful in triaging patients to various risk categories for the purpose of anticoagulation.

Research Agenda

- Impact of various COVID-19 treatment agents on CIC
- Prospective validation of the proposed CIC scoring system
- Optimal anticoagulation agent and dose in COVID-19
- Impact of anti-platelet therapy on survival in COVID-19

Author contribution

Tarik Hadid, MD, MPH, MS: conceptualization, literature review, writing-original draft, draft editing, figure and table construction, revision, submission.

Zyad Kafri, MD, MS: visualization, literature review, draft editing, revision.

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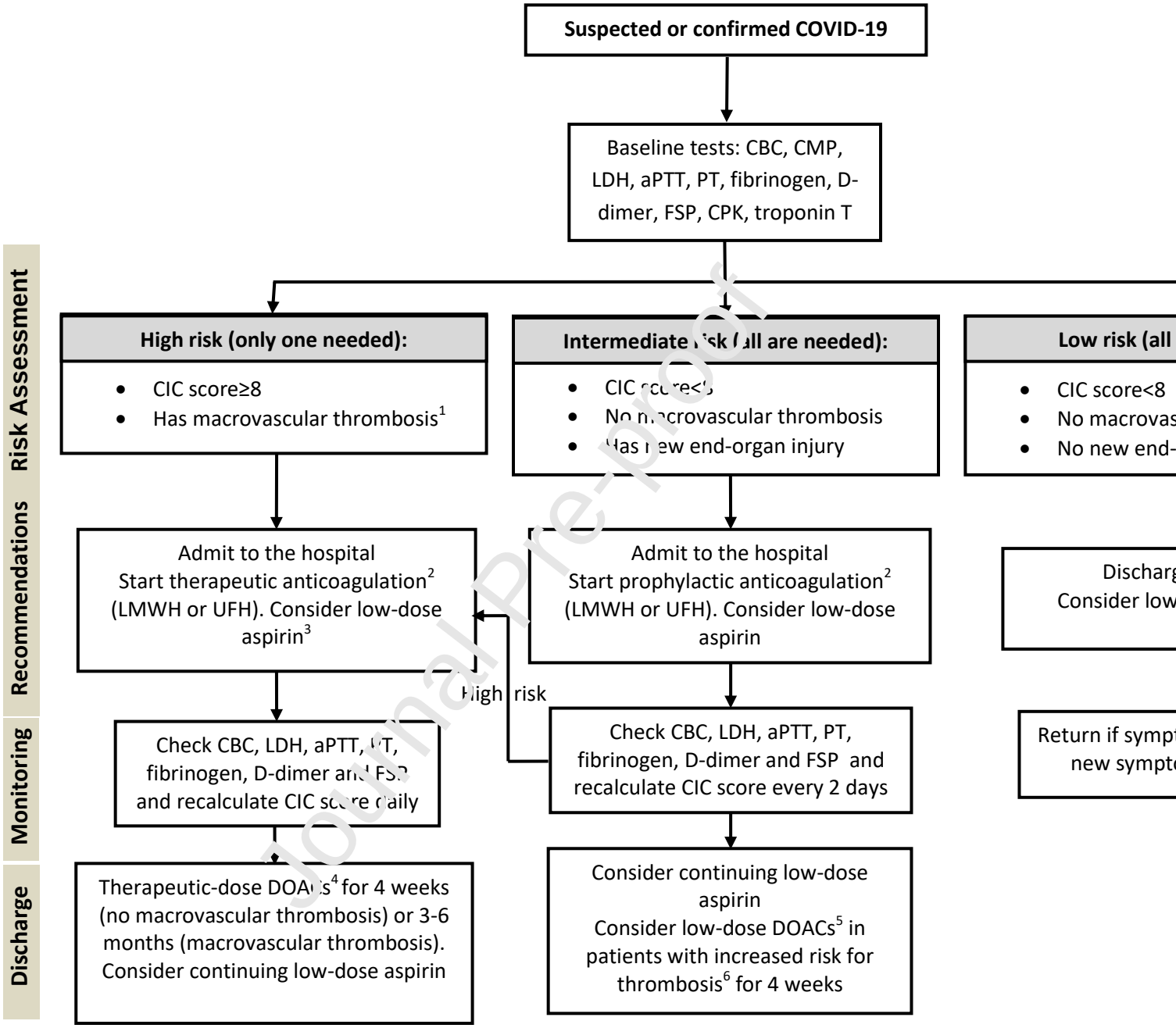
Figure legend

Figure 1: A proposed algorithm to triage COVID-19 for the purpose of anticoagulation.



Abbreviations: CBC: complete blood count, CMP: comprehensive metabolic panel, LDH: lactic dehydrogenase, aPTT: activated partial thromboplas
fibrin split products, CPK: creatine phosphokinase, CIC: COVID-19-induced coagulopathy score, LMWH: low molecular weight heparin, UFH: unfrac
anticoagulants

[1]consider testing for antiphospholipid antibodies; [2] enoxaparin is preferred. See table 3, [3]example of low-dose aspirin is 81mg daily, [4] examples of
5mg twice a day, rivaroxaban 20mg once a day, [5]examples of low-dose DOACs: apixaban 2.5mg twice a day, rivaroxaban 10mg once a day, [6]examp
for thrombosis: history of thrombosis, active cancer, known thrombophilia, immobility, recent major operation.

Disclaimer: This algorithm should be used with caution as it was not validated.

Highlights

- COVID-19-induced coagulopathy (CIC) is a distinct entity from sepsis-induced coagulopathy as it manifests by considerable elevation of D-dimer and fibrin split products but has no or mild effect on prothrombin and activated partial thromboplastin times.

- The cytokine storm is more severe in COVID-19 compared to conventional sepsis and results in organ-restricted intravascular coagulopathy, which induces immunothrombosis and organ dysfunction.

- COVID-19 infection is associated with high risk of micro- and macrovascular thrombosis and high incidence of anticoagulation failure.

- Unlike conventional sepsis, anticoagulation plays a key role in management of COVID-19 infection with a positive impact on survival.

- The proposed CIC scoring system may be helpful in triaging patients to various risk categories for the purpose of anticoagulation.

Table 1. Difference in coagulation parameters between COVID-19 and conventional sepsis

Variable	COVID-19 Sepsis	Conventional Sepsis
aPTT	N/↑	↑↑/↑↑↑
PT	N/↑	↑↑/↑↑↑
Fibrinogen	↑↑↑/↑↑/↓	↑↑↑/↑↑/↓
Thrombocytopenia	N/↓	↓↓/↓↓↓
FSP	↑/↑↑	↑↑/↑↑↑
D-Dimer	↑↑/↑↑↑	↑/↑↑
Schistocytes on peripheral blood smear	Not present	Frequent

Abbreviations: aPTT: activated partial thromboplastin time, PT: prothrombin time, FSP: fibrin split products, N: normal, ↑:mild increase, ↑↑: moderate increase, ↑↑↑, marked increase, ↓:mild decrease, ↓↓: moderate decrease, ↓↓↓: marked decrease.

Table 2. Summary of studies estimating macrovascular thrombosis risk in COVID-19

Authors	Country	N	Setting	Prophylactic Anticoagulation (%)	VTE Incidence (%)
Xu et al [51]	China	123	Ward	Prophylactic LMWH* UFH*	Total: (<1) DVT: (<1) PE: NR
		15	ICU	Prophylactic LMWH* UFH*	Total: (20) DVT: (20) PE: NR
Ciu et al [50]	China	81	ICU	None	Total: (25) DVT: (25) PE: NR
Klok et al [55]	Netherlands	184	ICU	Nadroparin 2,850-5700 IU once/twice a day (100)	Total : (31) VTE: (24) DVT: (3.7) CVA: (3.7)
Helms et al [53]	France	150	ICU	Enoxaparin 4,000 IU once a day or UFH 5–8 U/kg/h (70) Therapeutic-dose anticoagulation** (30)	Total: (18) DVT: (2) PE: (16.7) CVA: (1.3) ECMO thrombosis: (1.3) CRRT thrombosis: (18)
Middeldorp et al [16]	Netherlands	123	Ward	Nadroparin 2,850-5700 IU once/twice a day (84) Therapeutic-dose anticoagulation** (9.6)	Total: (3.3) DVT: (1.6) PE: (1.6)
		75	ICU		Total: (47) PE: (15) DVT: (32)
Lodigiani et al [49]	Italy	327	Ward	Prophylactic LMWH*** (41) Intermediate-dose LMWH*** (21) Therapeutic-dose LMWH*** (23)	Total: (6.4) PE: (2.5) DVT: (1.6) CVA: (1.9) ACS/MI: (1)
		61	ICU	Prophylactic LMWH*** (97) Therapeutic-dose LMWH*** (3)	Total: (16.7) PE: (4.2) DVT: (8.3) CVA: (6.3) ACS/MI: (2.1)

* exact dosing, type of LMWH and percentage who those received therapy were not reported, ** the type and dosing of anticoagulation were not reported, *** the exact type and dosing of LMWH were not reported
Abbreviations: VTE: venous thromboembolism, ICU: intensive care unit, LMWH: low-molecular weight heparin, UFH: unfractionated heparin, DVT: deep vein thrombosis, PE: pulmonary embolism, NR: not reported, CVA: cerebrovascular accident, IU: international

unit, U/kg/h: unit/kilogram/hour, ECMO: extracorporeal membrane oxygenation, CRRT: continuous renal replacement therapy, ACS/MI: acute coronary syndrome/myocardial infarction,

Table 3. Summary of studies evaluating role of anticoagulation in COVID-19

Authors	Country	N	Anticoagulation	Group/subgroup	Outcome
Tang et al [31]	China	449	Enoxaparin 40-60mg/day (95%) UFH (10,000-15,000 U/day (5%)	Unselected	28-day mortality: 30.3% for AC vs 29.7% for no AC (p=0.91
				SIC score≥4	28-day mortality: 40% for AC vs 64.2% for no AC (p=0.029)
				D-dimer>6 ULN	28-day mortality: 32.8% for AC vs 52.4% for no AC (p=0.017)
				D-dimer>8 ULN	28-day mortality: 33.3% for AC vs 54.8% for no AC (p=0.011)
Paranjpe et al [78]	United States	2,773	NR	Unselected	In-hospital mortality: 22.5% (median=21days) for AC vs 22.8% (median=14days) for no AC (p=NR)
		395	NR	Mechanically ventilated	In-hospital mortality: 29.1% (median=21days) for AC vs 62.7% (median=9 days) for no AC (p=NR)

Abbreviations: UFH: unfractionated heparin, U/day: Unit/day, AC: anticoagulation, SIC: sepsis-induced coagulopathy, NR: not reported.

Table 4: A proposed CIC Scoring System

	Item	2 points		4 points		CIC Score
SIC Score	**Platelet Count (x 10^9/L)**	100-150		<100		Max=4
	INR	1.2-1.4		>1.4		Max=4
	SOFA items	0.25 point	0.5 point	0.75 point	1 point	
SOFA Score	**PaO2/FiO2 (mmHg)**	301-400	201-300	101-200 with respiratory support	≤ 100 with respiratory support	Max = 1
	Hypotension (mmHg) or vassorprssor use (µg/kg/min) Dobutamine dopamine epinephrine norepinephrine	MAP <70 - - -	any <5 - -	- 5-14 ≤0.1 ≤0.1	- > 15 >0.1 >0.1	Max = 1
	Bilirubin (mg/dL)	1.2-1.9	2.0-5.9	6-11.9	>12	Max =1
	Creatinine (mg/dL) or urine output (mL/day)	1.2-1.9 -	2.0-3.4 -	3.5-4.9 200-499	>5 <200	Max = 1
D-dimer	**D-dimer (mg/L)** x ULN	2 points	4 points	6points	8 points	
		>1 &≤ 2	>2 & ≤4	>4 & ≤6	>6	Max = 8
Total CIC Score						Max = 20

Abbreviations: SIC: Sepsis-induced coagulopathy, CIC: COVID-19-induced coagulopathy, INR: international normalization ratio, SOFA: sequential organ failure assessment, MAP: mean arterial pressure, ULN: upper limit of normal

Disclaimer: This scoring system should be used with caution as it was not validated

Table 5. Therapeutic and prophylactic-dose anticoagulation

Clinical Condition	Therapeutic-dose		Prophylactic-dose	
	Enoxaparin	**UFH**	**Enoxaparin**	**UFH**
Standard-dose	1mg/kg SC every 12 hrs	80 units/kg bolus + 18 units/kg/hr infusion**	40mg SC every 12 hrs	7,500 units SC every 8 hrs
Renal Adjustment CrCl 10-29 mL/min CrCl <10 mL/min	1 mg/kg SC every 24 hrs Avoid use	80 units/kg bolus + 18 units/kg/hr infusion**	30 mg SC every 12 hrs Avoid use	7,500 units SC every 8 hours
Overweight (>150kg)	1mg/kg SC every 12 hrs*	80 units/kg bolus + 18 units/kg/hr infusion**	40 mg SC every 12 hrs	7,500 units SC every 8 hours
Underweight (<50kg)	1mg/kg SC every 12 hrs*	80 units/kg bolus + 18 units/kg/hr infusion**	40 mg SC every 24 hrs	5,000 units SC every 8 hours

* Monitor anti-Xa level, ** Monitor anti-Xa level if baseline activated partial thromboplastin time is prolonged

Abbreviations: UFH: unfractionated heparin, SC: subcutaneously, hrs: hours, CrCl: creatinine clearance