Clinics in Oncology

Review Article
Published: 05 Aug, 2020

SARS-CoV-2 Associated Thrombotic Coagulopathy

Ajaz Bulbul[1,2,3] and Karl Koessler-Streiker[4]*

[1]Department of Hematology and Oncology, Artesia General Hospital, Mexico

[2]Department of Hematology and Oncology, Texas Tech University Health Sciences Center School of Medicine, USA

[3]Department of Internal Medicine, The University of New Mexico, Mexico

[4]Burrell College of Osteopathic Medicine, Mexico

Abstract

The most common patterns of hematological complications in a critically affected COVID-19 patient are a subject of great interest currently. As more data comes to fray, we are beginning to understand the underpinnings of the myriad hematological effects of COVID-19 associated multiorgan affects. The hematological issues concerning COVID-19 include thrombosis (COVID Associated Coagulopathy: CAC), PIC (Pulmonary Intravascular Coagulopathy)/DIC, thrombocytopenia and leucopenia (lymphocytopenia). COVID-19 patients like all critically ill have variety of potential risk factors driving coagulopathy, including systemic infection, immobilization, mechanical respiratory ventilation, central catheterization [1]. It is this interplay of risk factors that makes management of COVID-19 associated coagulopathy complicated to understand and manage.

Keywords: SARS-CoV-2; COVID-19; Coagulopathy

Introduction

Ever since Severe Acute Respiratory distress Syndrome-Associated Coronavirus-2 (SARS-CoV-2) emerged in the Wuhan province of China, it has quickly spread to become a pandemic as of March 11th, 2020 [2]. The Coronavirus Disease 2019 (COVID-19) illness caused by SARS-CoV-2 can have an overwhelming effect on immune response mechanism by causing a cytokine release phenomenon. This primarily causes ARDS and in effect an under-recognized, hyper-inflammatory syndrome which is usually characterized by a fulminant hypercytokinemia leading to multiorgan failure in the worse end of the spectrum to a milder cytokine effect of unremitting fever, fatigue and constitutional symptoms [3,4]. A syndrome similar to systemic secondary HLH known previously to be triggered by viral infections possibly plays a role in causing a systemic hyperinflammation [5]. This effect may be the underpinning of the hematological manifestations of COVID-19 led by high Interleukin (IL)-2, IL-6, macrophage inflammatory protein 1-α, TNF (Tumor Necrosis Factor)-α among others [6]. In data collected from China about 40% of patients were retrospectively deemed high risk for VTE, an estimated 11% of these high-risk patients would go on to develop VTE without prophylaxis and about the same percentage of patients were deemed high risk for bleeding based on age, INR, hepatic failure, renal failure, active GI ulcer and platelet $<50 \times 10^9$/L [7].

Clearly, signs and symptoms of SARS-CoV-2 vary widely, from asymptomatic disease to ARDS and multiorgan failure. Worsening of disease is commonly associated with hematological manifestations including thrombotic and bleeding coagulopathies and unfortunately death in some cases [6,8].

There is no clear practical guidance regarding coagulopathies associated with COVID-19 that can be applied universally across healthcare resource settings. International Society on Thrombosis and Hemostasis have published an interim guidance statement on the management of coagulopathy in COVID-19 patients until more is known about its incidence and how to manage it [9].

COVID-19-Associated Coagulopathy (CAC): Thrombosis

The spectrum of coagulopathy in SARS-COV-2

Thrombosis seems to be the most common pattern of coagulopathy that has been observed in COVID-19 patients requiring hospitalization. The pattern of coagulopathy can be considered a continuum commonly seen in other adult patient admitted for sepsis/SIRS. This continuum can range from mild elevations in laboratory indicators to acute phase reaction like ESR, CRP, fibrinogen, Ferritin, D-dimer, mild thrombocytopenia (~100×10^9/L) to marked abnormalities in PT, PTT,

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Correspondence:
Ajaz Bulbul, Department of Hematology and Oncology, New Mexico Hematology and Oncology Associates, Artesia General Hospital, Mexico, E-mail: ajazbulbul@gmail.com

Received Date: *01 Jul 2020*
Accepted Date: *24 Jul 2020*
Published Date: *05 Aug 2020*

Citation:
Bulbul A, Koessler-Streiker K. SARS-CoV-2 Associated Thrombotic Coagulopathy. Clin Oncol. 2020; 5: 1726.

Table 1: Adapted from Thachil et al. [9].

Recommendations	
Establish baseline (Admit if)	D-Dimer (3 fold increase) Platelet Count (<100 × 10^9/L) Prothrombin-time (prolonged) Fibrinogen (<2.0 g/L)
Prophylaxis	LMWH
Maintain	Platelets >20 × 10^9/L Fibrinogen above 2.0 g/L
If bleeding	Follow ISTH guidelines, maintaining: Platelets >50 × 10^9/L) Fibrinogen >2.0 g/L PT ration <1.5

thrombocytopenia, and lymphocytopenia which is seen in up to 40% of patients. It can also progress as a syndrome of sequential organ failure with evidence of diffuse thrombosis and cytokine culminating in ARDS on an organ level and significant consumptive coagulopathy similar to Disseminated Intravascular Coagulopathy (DIC) [10].

The pattern of DIC in COVID-19 may differ from sepsis or trauma by a somewhat limited elevation of aPTT and a higher PT elevation. In a yet normally functioning liver COVID leads to a significant factor VIII elevation blunting the effect on aPTT [11].

Bleeding is less common in COVID-19 than thrombosis [6,8,12]. Some patients with fulminant COVID-19 infection and high IL-6 cytokine levels can develop a coagulopathy meeting criteria for DIC (as per ISTH criteria see Table 1) with fulminant activation of coagulation and consumption of coagulation factors [13,14]. This is reflected by moderate to severe thrombocytopenia (platelet count <50 × 10^9/L), prolongation of the PT and aPTT, marked elevation of D-dimer and decreased fibrinogen (<1.0 g/L). Fibrinogen has been noted to drop dramatically over 3 days [15].

Study on Wuhan COVID-19 patients suggested that 71% of non-survivors from COVID-19 infection met the ISTH criteria for DIC compared to 0.4% of survivors [11]. Elevated D-dimer at admission and 3 to 4 fold increase in D-dimer were associated with high mortality and more frequent ICU stays [10,11,16].

Incidence of thrombosis

Although the exact incidence is unclear, small case reports suggest a higher rate of Venous Thromboembolism (VTE) in COVID-19 patients [17,18]. In a recent Dutch study of 184 COVID-19 ICU patients, 13% had pulmonary embolism, 1 had DVT and 2 had catheter-related thrombosis [19]. The caveat in this study is that these were critically ill patients. Traditionally the incidence of thrombosis in Dutch registry studies have been higher compared to other studies, besides variation in rates may reflect differences in ICU admission criteria [20]. Another study suggested COVID-19 thrombosis incidence of VTE among critically ill patients at 20% [12]. Epidemiological studies have also shown VTE to be 3 to 4 fold lower in Chinese compared to Caucasian populations, Hispanics with lower perveance compared to Caucasians and higher incidence in African-American population [21,22]. Since thrombotic risk is influenced by race there is an intriguing suggestion that the patterns of mortality and pulmonary thrombosis may partly be influenced by racial susceptibility. These data however cannot be extrapolated to non-ICU COVID cases since there are no large current COVID-19 outpatient or non-ICU VTE studies.

Pathophysiology

The precise mechanism for VTE is not yet fully established but is understood to be multifactorial. A generalized Systemic Inflammatory Response (SIRS) and direct endothelial damage and thrombin generation from viral injury/ACE2 binding seem to be likely culprits [15,23,24].

Autopsies on Wuhan COVID-19 patients have reported finding microthrombi embedded in pulmonary vasculature [25], which was thought to contribute to local V/Q mismatch and pulmonary edema. More studies have since come out supporting these observations suggesting an atypical ARDS with well-preserved lung mechanics despite hypoxemia and thrombotic microvascular injury in alveolar capillaries [26]. An underlying immune mediated diffuse pulmonary interstitial inflammation in COVID-19 may involve a syndrome akin to Macrophage activation syndrome that triggers extensive pulmonary hemophagocytosis and thrombosis and or intrapulmonary micro-hemorrhage [27]. The underlying mechanisms have not been proven and further data suggests that these microthrombi may well be cellular debris from vascular endothelial damage [24]. It has been postulated that it is the cleavage of the SARS-CoV Spike protein which promulgates infectivity and sepsis. This is likely caused by factor Xa and factor IIa (Thrombin) [28]. When thrombin is activated, it cleaves fibrinogen; this leads to stable fibrin polymerization and eventually cross linking with factor XIII which stabilizes the clot [29]. It is this cross linking obstructive microvascular/macrovascular fibrin clot that leads to activation of the fibrinolytic system through plasmin and t-PA which leads to dissolution of the cross-linked fibrin fibers into smaller D-dimers. Therefore, the D-dimer reflects the activation of thrombin and indirectly activation of coagulation cascade and recent presence of fibrin [30]. In a normally functioning liver D-dimer is cleared; however impending liver failure of worsening hepatic function will lead to rise to D-dimers usually at the pace seen in critical COVID-19 infection which usually indicated poor prognosis as discussed [11,13,24].

Another underlying mechanism comes from the observations of extensive multiorgan deposits of complement complex C5b-9, C4d, and MASP2 from over activation of both the alternative and lectin-based pathways [26].

It is this concern that has led to the hypothesis that anticoagulation may even inhibit SARS-CoV-2 replication [31]. Anticoagulation and antiplatelet agents may be useful to inhibit activity but require further investigation prior to being used therapeutically. The current use of low dose ASA should be restricted to outpatient extended anticoagulation in patients post discharge considered high risk of VTE [31].

Recommendations

Diagnostics

The recommendations for diagnostic testing vary widely based on institutional practices. There are no universal guidelines but for all inpatient COVID-19 patients we can consider obtaining baseline D-dimer, aPT/aPTT, fibrinogen, ferritin, troponin, and CBC with differential. IL-6 can be drawn at presentation awaiting return if severely ill and considering IL-6 antibody use [32]. Lupus Anticoagulant, Beta-2 glycoprotein, Anticardiolipin antibody should be consider if thrombocytopenia or VTE is noted on admission due to risk for associated Antiphospholipid syndrome (APL) [13]. Trending D-dimer, fibrinogen daily if baseline values are >1000 ng/mL suggests high risk for mortality in addition to age, comorbidities. There is data to suggest that D-dimer levels on admission were higher

in patients needing critical care support [6,10,12,17]. In one study (median D-dimer level 2400 ng/mL than those patients who did not require it (median D-dimer 0.5 ng/nL, p=0.0042) [6]. In a subgroup analysis that compared patients by survival it was noted that lower platelet count correlated with mortality. Thrombocytopenia was also associated with over five-fold increased risk of severe COVID-19 illness (OR, 5.1; 95% CI, 1.8 to 14.6). This suggests thrombocytopenia at presentation may be prognosticator [33]. Case reports of ITP based on temporal sequence suggests that immune mechanism may be at play with thrombocytopenia related to COVID-19 [4,34,35].

Multi-organ failure is more likely in patients with sepsis if they develop coagulopathy and inhibiting thrombin generation may have benefit in reducing mortality [9,36,37]. This is what makes monitoring PT, D-dimer, platelet count and fibrinogen helpful in prognostication. There is consensus in considering a more aggressive approach if these criteria worsen with experimental therapies and blood product support [8,9,11]. It is already well-established that older individuals and those who have co-morbidities (both groups tend to have higher D-dimer) are more likely to die from COVID-19 infection [16].

Prognosis

Higher D-dimer and FDP levels track with multi-organ dysfunction syndrome and poorer prognosis [1,10]. Typically, the median time to developing DIC is around day 4 in 71.4% patients who did not survive the infection compared to 0.6% who survived. There is a significant increase in D-dimer levels, and PT with a decrease in fibrinogen levels in non-survivors at 14 days [8,11].

LMWH has been shown to have anti-inflammatory properties which may be an added benefit in COVID infection where proinflammatory cytokines are markedly raised [6,9,16].

Management

All patients admitted for COVID-19 (including non-critically ill) should receive standard prophylactic anticoagulation with LMWH provided there are no contraindications like active bleeding, platelet count <30,000, low fibrinogen (50 to 100 mg/dl) (Figure 1). Monitoring is advised in patients with associated renal impairment (CrCl<30 ml/min); abnormally prolonged PT or APTT on their own are not absolute contraindication to prophylactic anticoagulation [6,9,16]. The LMWH dose should be 40 mg subq daily If CrCl>30 mL/min. However, with a CrCl<30 ml/min consider using UFH (5,000 units q 8 h; 7,500 units for >150 kg).

In patients who develop or have a recent history of HIT or HITT within the last 90 days consider a non-heparin alternative for thromboprophylaxis and line flush (5 ml of 4% sodium citrate) or fondaparinux 2.5 mg subq 24 h for prophylaxis [38,39]. It is unclear, whether in cases where anticoagulation is contra indicated whether mechanical prophylaxis e.g., Intermittent Pneumatic Compression (IPC) devices provide adequate protection. There is no direct evidence in COVID cases but IPC should be considered given previous evidence of reducing VTE in moderate to low risk cases [40,41].

Patients who are already on DOAC's (Direct oral anticoagulant) or warfarin as an outpatient (e.g. for atrial fibrillation, h/o VTE, prosthetic valves) should be switched to therapeutic dose of LMWH (preferred over UFH to decrease blood draws to monitor PTT) due to possible interactions with COVID 19 treatments) [9]. However, we do need to consider higher risk of mechanical prosthetic valve thrombosis in such situations and consideration should be given to cardiology consultation and considering Vitamin K antagonist aiming target INR of 2.5 to 3 [42].

For patients with an established acute DVT or PE or on therapeutic anticoagulation prior to hospitalization consideration should be given to conversion to LMWH to minimize blood draws and repeated contact by nursing during admission. LMWH is preferred, to minimize blood draws and has superior efficacy [33].

Consideration to UFH should be made only in cases where its short half-life is considered crucial to management (e.g. Scheduled procedure predicted). These patients can be monitored with anti-Xa levels (do not follow aPTT, since it can prolong commonly in severe COVID-19 and can be unreliable to manage therapeutic levels).

There is no clear evidence currently to suggest using treatment dose anticoagulation without the presence of VTE. Randomized controlled trial addressing this question is underway (NCT04345848, NCT04338932). There is however consensus to initiate therapeutic dose anticoagulation in COVID-19 patients with documented DVT/PE. Using t-PA for anticoagulation is not recommended currently [8,9]. Recently however a French guidance document recommends using therapeutic-dose anticoagulation for patients with increased fibrinogen >8 g/L or D-dimer >3.0 µg/mL [43]. The evidence of using D-Dimer in predicting thrombosis and failure of anticoagulation is based on cases of idiopathic thrombosis and not studied well in acute settings [44,45]. There are currently ongoing studies evaluating the role of intermediate or full therapeutic anticoagulation for critically ill COVID-19 (NCT04345848, NCT04338932).

Given the limitations of imaging available during the COVID crises a venous Doppler, if possible, should be performed bedside for asymmetric limb pain or edema. Treatment dose anticoagulation should be started. If patient is unable to get US due to concern of staff exposure to COVID-19, and clinical suspicion for DVT is high, consideration can be given to full dose anticoagulation (unless contraindicated) over obtaining any diagnostics testing.

Pulmonary embolism should be considered in case where with imaging findings not consistent with worsening COVID-19 PNA, ARDS and with a (3 to 4 fold rise; >1000 ng/ml baseline) and rapid worsening of oxygen saturation, BP, tachycardia possibly with unexplained right heart strain pattern on a bedside echocardiogram [46,47].

For COVID-19 patients with active bleeding due to consumptive coagulopathy currently there is limited data available regarding bleeding issues in the setting of COVID-19. If bleeding does develop, principles of septic coagulopathy management based on ISTH guidelines with respect to blood product replacement should be followed [8].

Use of blood products

The overall concept of CAC management is that treatment of the underlying COVID-19 and/or associated bacterial infection condition is paramount. Given limited proven therapies of benefit in COVID-19, supportive care with blood products needs to be individualized and reserved only for clinical reasons and not merely to correct lab values. Aggressive plasma or blood based therapy has not been shown to improve survival and ISTH guidelines may be followed [8,10].

Given limited Blood product resources available and widespread

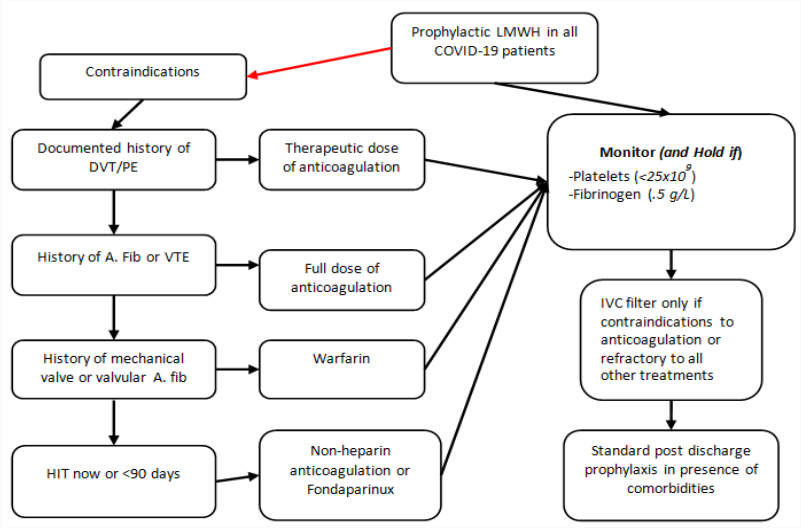

Figure 1: Anticoagulation decision making flow diagram in COVID-associated coagulopathy.

shortages blood or platelet transfusions should be reserved for those with active bleeding or for those, requiring an invasive procedure. No clear thresholds are known for COVID-19 and "safe" cut-off for hematological parameters should be used for transfusions [48]. Platelets <20-25 × 10^9/L [49], Hb <7 gm/dl [50] and the thresholds below are for guidance only.

In patients with CAC/DIC who are not bleeding, there is no current evidence to suggest that correction of laboratory parameters with blood products improves survival or shortens ICU stays [24]; while restrictive transfusion strategies have been shown to reduce inpatient mortality [50]. There is ample evidence that aggressive replacement of blood products may worsen disseminated thrombosis and further deplete scarce blood products [51]. In a patient with CAC/DIC who is actively bleeding, transfuse platelets (one adult dose) if the platelet count is less than 50 × 10^9/L, give plasma (4 units) if the INR is above 1.8 and order fibrinogen concentrate (4 grams) or cryoprecipitate (10 units) if the fibrinogen level is less than 1.5 g/L. For patients with severe coagulopathy and bleeding due to liver dysfunction, consider 4F-PCC instead of plasma as volume status appears to be a significant factor associated with respiratory compromise. The hemostatic effectiveness of Tranexamic Acid (TXA) is unknown in this setting and is not recommended in COVID-19.

Prophylactic anticoagulation is acceptable in all admitted COVID-19 patients unless actively bleeding or consider high bleeding risk. In cases of active bleeding deemed medically significant therapeutic dose anticoagulation with Low Molecular Weight Heparin (LMWH), Unfractionated Heparin (UFH) or (Direct oral anticoagulants) DOAC's are not recommended or necessary unless evidence of VTE or atrial fibrillation is documented and then it should be treated as such.

Medication interactions

Given that COVID-19 is a risk factor for CAC and DIC there is growing consensus that laboratory parameters should be monitored to track progression and help/guide management [10,11,25]. Close daily monitoring of dropping platelet counts, increase in ++PT/+aPTT, D-dimer (>6 ULN), and fibrinogen (<100) suggests worsening of COVID-19 infection and predicts a more aggressive clinical course. It is under these scenarios that therapies pending approvals like Remdesivir and experimental or promising therapies like Convalescent Plasma, Hydroxychloroquine, Lopinavir or IL-6 pathway inhibitors like Tocilizumab or Sarilumab may be considered.

Some of these novel drug options for COVID-19 affect the cytochrome P450 and affect drug levels. Remdesivir is not known to affect anticoagulant drug levels. Patients on warfarin would need an increased dose if used concurrently with Sarilumab which can increase P450 enzyme activity and should also be avoided with rivaroxaban (Xarelto®) or Apixaban (Eliquis®). Lopinavir/ritonavir also increases drug concentrations of apixaban and rivaroxaban and decrease the active metabolite of and clopidogrel and prasugrel (COVID-19 drug interactions webpage at (http://covid19-druginteractions.org/).

Cardiac patients on anticoagulants

In patients already on anticoagulation for VTE or atrial fibrillation, therapeutic doses of anticoagulant therapy should continue, and individual case-based assessment would be needed to balance risk of thrombosis and bleeding. There is consensus to hold anticoagulation if patient is at high risk of bleeding due to low platelet counts (30 to 50 × 10^9/L) or low fibrinogen (<1.0 g/L) [24].

Patients on warfarin who are unable to get INR monitoring during isolation may be candidates for DOAC's while keeping in view the interactions with some novel COVID-19 treatments (http://covid19-druginteractions.org/).

Cardiac risk patients that form a majority of critically ill COVID-19 admissions with atrial fibrillation due to valvular abnormality, mechanical heart valves, ventricular assist devices should continue treatment with warfarin therapy given that data for preventing thrombosis is superior with warfarin than LMWH and DOAC's should be avoided in these settings and cardiology consultation may be considered for these patients [52,53].

Summary of CAC (Thrombosis) Management

Prophylactic dose LMWH is currently recommended for all COVID-19 admitted patients despite abnormal coagulation tests in the absence of active bleeding. It should be held only if platelet counts are less than 25 × 10^9/L, or fibrinogen less than 0.5 g/L. Abnormal PT or aPTT is not a contraindication for pharmacological thromboprophylaxis.

Mechanical thromboprophylaxis should be used when pharmacological thromboprophylaxis is contraindicated. Data regarding use of IVC filters is limited and currently not recommended due to risk of worsening filter thrombosis [24]. Only in cases of PE refractory to anticoagulation or an absolute contraindication should placement of an IVC filter be considered. Anticoagulation will need to remain a critical part of management and be resumed soon after filter placement [54].

Prophylactic LMWH or UFH may be of benefit in those patients with severe COVID-19 and D-dimer baseline levels (>6x ULN) and/or 1000 ng/ml and 3 to 4-fold rise levels >6 times the upper limit of normal. Consider LMWH in preference to UFH [11].

Initiate prophylactic anticoagulation therapy for all COVID-19 patients unless otherwise contraindicated:

- If CrCl>30: Lovenox 40 mg SC daily
- If CrCl< 30 or AKI: Heparin 5000 units SC TID
- Hold if Platelets <30,000 or bleeding, fibrinogen <50 to 100. Consider using TEDs and SCDs

If the patient is on (DOACs) or warfarin for Afib or VTE, switch to full dose anticoagulation (LMWH or UFH, as indicated based on renal function or clinical scenario). Mechanical value and valvular A. fibrillation may continue to use warfarin given higher valvular thrombosis risk with DOAC's. Review medication interactions with P450 and antiviral drugs used in COVID-19 t-PA is not recommended due to unknown efficacy and bleeding risks in COVID related CAC.

Post-discharge thromboprophylaxis

Patients hospitalized for acute medical condition and presumably COVID-19 cases are at increased risk for VTE for up to 90 days post discharge. Extended thromboprophylaxis should be considered in the presence of co-morbidities such as active cancer, and elevated D-dimer >2 times ULN at discharge, hypercoagulable hereditary disorder. It is reasonable to use for VTE prophylaxis in low-risk patients after orthopedic surgery and could be considered for COVID-19 VTE prophylaxis if criteria for post-discharge thromboprophylaxis are met after at least five days of inpatient anticoagulation [55]. Consideration can be given to use Rivaroxaban 10 mg daily for 31 to 39 days [56].

Arterial Thrombosis

COVID-19 may predispose to arterial thromboembolic events in addition to venous thrombi presumably due to excessive inflammation, hypoxia, immobilization [1,10,16].

Klok et al. [19] evaluated composite outcome of Venous Thromboembolism (VTE) and arterial thrombosis in COVID-19 patients admitted to the ICU. The cumulative incidence of the composite outcome was 31% confirmed by CT Angiogram and/or Doppler ultrasonography confirmed VTE in 27% and arterial thrombotic events in 3.7% [19].

There is precedence of arterial thrombosis increased risk of MI/STEMI during the SARS epidemic. Plaque instability caused by inflammation and cytokine storm may have played a role in plaque instability [57,58]. In influenza, increase incidence of Acute MI was found compared to control [59].

Mechanisms for thrombosis seen have included rupture of preexisting high risk plaques [60], platelet aggregation over inflamed atherosclerotic plaques noted in animal models, proliferation of smooth muscles, and fibrin deposition in atherosclerotic plaques [61].

Data is evolving in regards to the risk of arterial thrombosis in COVID-19. An international registry for ACS has been developed (https://www.facs.org/quality-programs/covid19-registry).

So far in COVID-19 both ST-segment elevation and NSTEMI have been described in case reports. Presentations can be variable but a high prevalence of non-obstructive disease has been seen along with a poor prognosis [62]. Myocardial injury in patients with COVID-19 could be due to plaque rupture, cytokine storm, hypoxic injury, coronary spasm, microthrombi, or direct endothelial or vascular injury with signs of acute myopericarditis noted in a case [63,64]. Cerebral infarcts and limb ischemia have also been noted in association with APL antibodies [13]. Expectedly, older patients with cardiovascular risk factors are more likely to develop CVD [62,64]. A single center retrospective study reported 11 cases (5%) of acute ischemic stroke among 221 patients infected with COVID-19 with an increased inflammatory response and hyper coagulable state reflected in this cohort reflected by an elevation in CRP (51.1 *vs.* 12.1 mg/L, $p<0.01$) and D-dimer (6.9 *vs.* 0.5 mg/L, $p<0.001$) [65].

Recent evidence of case reports suggest arterial and venous hyper coagulability with APL antibodies that have been noted in COVID-19 [13]. It's known to cause thrombocytopenia [66] and associated thrombosis. It is possible that presence of Lupus anticoagulant, and/or APL antibodies is a risk factor for thrombotic events in COVID-19 and a related cause of thrombocytopenia [13,66]. It is difficult to differentiate whether thrombocytopenia and associated arterial thrombosis in COVID-19 are associated with HIT, HITT and TTP as seen in other acute illnesses. The incidence of these is unclear in COVID, and testing for these should be considered in appropriate situations.

Conclusion

It becomes apparent then that there is constant interplay between thrombosis and bleeding risk in COVID-19 patients. The dose, duration and mechanical compressions may be warranted in appropriate situations and risk of bleeding should be considered at all times in those with known bleeding risk factors.

Assessing for changes associated with coagulopathy regularly is essential and as the data evolves our understanding will evolve with it. It is possible that the pathogenesis of coagulopathy differ in COVID-19 patients from critically ill ICU patients. During early hospital course those with a more severe inflammatory response (D-dimer, CRP, IL-6) to the viral infection demonstrate increased risk for thrombosis.

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