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REVIEW ARTICLE

An Evidence-based Protocol for Minimizing Thromboembolic Events in SARS-CoV-2 Infection

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Coronavirus Disease 2019 (COVID-19) is complicated by significant coagulopathy, that manifests in the form of both pulmonary artery microthromboses and systemic venous thromboembolism (VTE) leading to excess mortality. Dysregulated innate immune response in the lung due to viral-entry mediated angiotensin-I-converting enzyme 2 (ACE2) receptor downregulation causes endothelial injury in the pulmonary vasculature, inflammatory cytokine release, increased thrombin generation and impaired fibrinolysis. The inflammatory disease process, immobilization with prolonged hospital stay, hypoxia due to extensive lung injury and pre-existing comorbidities can contribute to thromboembolic episodes (TE). The observed risk for TE in COVID-19 is high despite anticoagulation, particularly in intensive care unit (ICU) patients. A high level of clinical suspicion, lower threshold for diagnostic imaging and aggressive early and extended thromboprophylaxis is indicated. The available evidence on the optimal strategies to prevent, diagnose, and treat VTE in patients with COVID-19 is heterogenous, but rapidly evolving. We propose an evidence-based, risk-stratified protocol in approaching the risk of TE episodes in COVID-19 patients. © 2020 IMSS. Published by Elsevier Inc.

Introduction

Patients with Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) infection present with a variety of clinical phenotypes ranging from asymptomatic infection to profound multiple-organ dysfunction syndrome and death. Early reports suggested that coagulation disturbance was a prominent feature of severe disease (1,2). There is now increasing evidence that the combination of increased thromboembolic (TE) events and extensive microvascular thrombosis in the pulmonary circulation and elsewhere in the body may be one of the key drivers of clinical deterioration and death (3).

A variety of reasons including endothelial dysfunction, severe hypoxemia, inflammation, along with more

mundane factors such as immobilization and central venous catheter use have been implicated in the pathophysiology of coronavirus disease related coagulopathy (CRC) (4). This short review presents current understanding of the pathophysiology of CRC and discusses its implications for the evaluation and management of coagulation abnormalities in patients with SARS-CoV-2. The search strategy and the databases searched for this narrative review are tabulated in Table 1. We have also presented the level of evidence currently available for the management of Coronavirus Disease 2019 (COVID-19) patients, with respect to the biochemical investigations, imaging, thromboprophylaxis and treatment for inpatient management and extended thromboprophylaxis for outpatient management (Oxford system for grading level of evidence) (5).

Pathophysiology of Covid-19 Related Coagulopathy

SARS-CoV-2 uses its ‘spike’ surface glycoprotein (peplomer) to gain access to host cells using the human angiotensin-I-converting enzyme 2 (ACE2) receptor.

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Table 1. Search strategy used for writing this review (last date of search July 15th 2020)

Database	Key words	Items found
MEDLINE	(['COVID'] OR 'SARS-CoV-2' [MeSH Terms] OR 'Coronavirus' [Title/Abstract]) AND (['thrombosis'] OR 'thromboembolic' [MeSH Terms] OR 'anticoagulant' OR 'anticoagulation' [Title/Abstract] OR anti-coag [MeSH Terms] AND [2020/07/15 date of publication])	230
EMBASE	(['COVID']/exp OR 'SARS-CoV-2' OR 'Coronavirus': ab, ti) AND (['thrombosis']/exp OR 'thromboembolic' OR 'thromb*': ab, ti) AND (['anticoagulant']/exp OR 'anti-coag*': ab, ti) AND [embase]/lim AND [01/12/2019-15/07/2020]/py)	133
PubMed	All fields; Search term: (COVID* OR SARS CoV-2 OR Coronavirus OR COVID-19) AND (Thrombosis* OR thromboembolic OR thrombo*) AND (embolic* OR anticoagulant OR anticoagulation OR anticoag* OR anti-coag*). Date limit used until July 15, 2020. No other limits.	544
Cochrane Library	#1 MeSH descriptor: COVID-19 explode all trees #2 SARS-CoV-2 #3 thrombosis #4 thromboembolic #5 MeSH descriptor: [thrombo] explode all trees #6 anticoagulant #7 anti-coagulant #8 MeSH descriptor: [anticoag/anti-coag] explode all trees #9 #1 and #5 and #8	33
CINAHL	#1 COVID #2 SARS-CoV-2 #3 Coronavirus #4 OR 1-3 #5 thromboembolic #6 thrombosis #7 thromb* #8 OR 5-7 #9 anticoagulant #10 anti-coagulant #11 anticoag* OR anti-coag* #12 OR 9-12 #13 4 AND 8 AND 12	41
Google Scholar	Search terms: COVID, SARS-CoV-2, coronavirus, thrombosis, thromboembolic, thrombo-embolic, anticoagulation, anti-coagulation	33

A search strategy was conducted in line with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines. An electronic search of Medline, EMBASE, PubMed, Cochrane Library, CINAHL and Google scholar was conducted between the dates December 1 2019 until July 15 2020. Bibliographies of relevant studies and the "related articles" link in PubMed were used to identify additional studies. References of retrieved articles were also examined manually for further studies.

ACE2 is a peptidase, highly expressed in type 2 pneumocytes and has a role in protecting lungs from acute injury (6). Viral binding dysregulates lung protective pathways by causing a reduction in the ACE2 receptors and creating an imbalance in renin-angiotensin-aldosterone system (RAAS) eventually leading to diffuse alveolar damage (7). Increased thromboembolic events have been reported in previous iterations of the coronavirus epidemic such as SARS (8). However, the incidence and severity of these events in the current COVID-19 pandemic is unprecedented. Multiple pathways have been proposed to explain this generalized prothrombotic tendency (9). A schematic representation of COVID-19 related coagulopathy leading to TE complications is described in Figure 1.

Endothelial Injury

In humans, the ACE2 receptor mRNA is expressed in virtually all organs including heart, blood vessels, small

intestine, kidney and testis (10). Immunohistochemistry studies have shown ACE2 receptors to be present not only in the endothelium of all veins and arteries, but also in the smooth muscle cells of the muscularis mucosae and the muscularis propria (11). This explains their role in maintaining blood pressure and how their dysregulation can lead to systemic endotheliitis and multiorgan damage. In health, the endothelium prevents blood clotting by providing an antithrombotic surface which also promotes fibrinolysis. Endothelial cell damage secondary to viral binding to its ACE2 receptors promotes acute inflammation and development of a thrombotic endovascular surface (12).

ACE-2 Receptor Downregulation and Inflammatory Cytokines

Down regulation of ACE-2 receptors after viral infection is now a well-recognized phenomenon in SARS-CoV-2

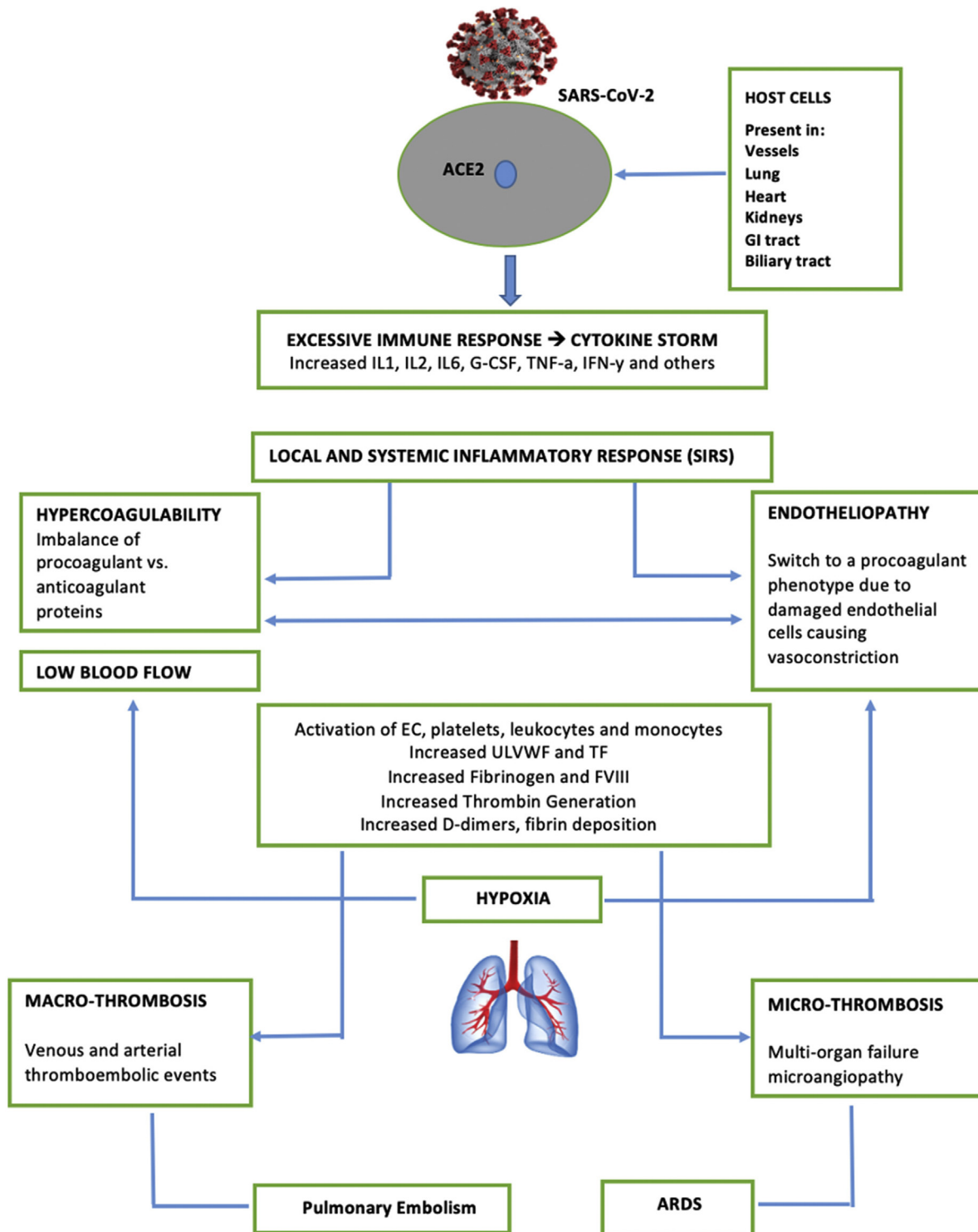


Figure 1. Schematic representation of the pathogenesis of COVID-19 related coagulopathy.

infection. Immune response in COVID-19 is dysregulated due to this ‘down-regulation’ with resulting increased Angiotensin II levels. Higher Angiotensin II levels promote endothelial apoptosis and vasoconstriction leading to

regional hypoxia and progression of inflammation (13). Inflammatory cytokines, together with endothelial injury, up-regulate tissue factor expression and drive the prothrombotic state (14).

Role of Hypoxia and Other Factors

Pulmonary microvascular thrombi developing in an environment of profound peri-vascular inflammation can lead to regional hypoxia (15). Hypoxia stimulates further thrombosis through a hypoxia-inducible transcription factor-dependent signaling pathway (16). Increased blood viscosity and dehydration leads to stasis which along with endothelial injury and a hypercoagulable state completes the well-known Virchow’s triad placing these patients at high risk for thrombotic events (17). Additional precipitants in these patients are the practice of prone ventilation, which by itself is pro-thrombotic as it puts all four limbs in position lower to the heart and extensive usage of central venous catheters which initiate endothelial injury.

Relevance in Clinical Management

Venous thrombosis has been reported in around 20% of all COVID-19 patients, with the rates of venous thromboembolism (VTE) correlating with the severity of the COVID-19 (18). Patients admitted to intensive care unit (ICU) are the high-risk group with rates as high as 50–70% (Table 2) (19–25). Majority have involved the pulmonary circulation supporting the hypothesis of local derangement of anti-thrombotic mechanisms in addition to a generalized pro-thrombotic tendency (19). It is unclear how many of these

pulmonary VTE events are embolic in origin from deep venous thrombosis (DVT) and how many are inflammatory thromboses originating in peripheral pulmonary arterioles and progressing into the main arteries. Data on incidence of VTE in non-ICU patients is limited but the incidence appears to be higher than the usual incidence in hospitalized patients (Table 2) (19–25). Reports of COVID-19 patients with mild symptoms being managed at home presenting emergently with acute pulmonary embolism (PE) suggests that there is no direct correlation between severity of chest symptoms and development of VTE complications (4).

There are also several reports of extra-pulmonary venous thrombosis including cerebral venous thrombosis and mesenteric venous thrombosis (26–28). Increased incidence of arterial thrombotic events has been reported in COVID-19 and can involve a variety of vessels with different flow and pressure dynamics, including cerebral circulation, coronary arteries, peripheral vessels and mesenteric arteries (29,30). The fact that some of these patients present with relatively mild chest symptoms, again suggests that the extra-pulmonary thrombotic events may not always be linked to clinical severity alone.

Interestingly, there is increasing evidence that standard VTE prophylaxis does not protect patients against VTE episodes in COVID-19. Patients have developed PE despite being on prophylactic and even therapeutic anticoagulation

Table 2. Management of COVID-19 thrombosis in ICU and non-ICU patients in the literature

Intensive care unit (ICU) patients					
Author	Country	Number of patients	VTE rates	Anticoagulation status	Comments
Klok FA et al. (19)	Netherlands	184	VTE-27% PE-14%	All on prophylactic dose	75% were male
Helms J et al. (20)	France	150	VTE-43% (Increased vascular line thrombosis noted in 28 out of 29 ECMO patients)	70% prophylactic dose 30% therapeutic dose	Higher rate of VTE in COVID ARDS compared to non-COVID ARDS (12 vs. 2%)
Middeldorp S et al. (21)	Netherlands	74	VTE-39%	Prophylactic dose for every one	Sequential testing done for DVT on day 1, 7, 21
Cui S et al. (22)	China	81	VTE-25%	Not described	If 1.5 µg/mL was used as the D-dimer cut-off value to predicting VTE, the sensitivity was 85.0%, the specificity was 88.5%, and the negative predictive value (NPV) was 94.7%.
Llitjos JF et al. (23)	France	26	VTE-69%	Majority were receiving therapeutic dose	Recommend VTE screening for all severe patients
Non-Intensive care unit (non-ICU) patients					
Lodigiani C et al. (24)	Italy	314	VTE-64%	41% prophylactic dose 21% Intermediate dose 23% therapeutic dose	Half of VTEs occurred within 24 h of admission
Artifoni M et al. (25)	Iran	71	VTE-21%	All were receiving prophylactic dose	Only two were symptomatic
Middeldorp S et al. (21)	Netherlands	124	VTE-20%	All were receiving prophylactic dose	All hospitalized patients were evaluated for DVT on day 7,14,21.

(Table 2) (19–25). These patients may potentially warrant significantly higher doses of anticoagulants and the use of unconventional methods such as thromboelastogram (TEG) to assess coagulation status to titrate anticoagulant dosing (31). The relative ineffectiveness of standard heparin congeners in preventing VTE in this setting also supports the important role of inflammation in the pathogenesis of VTE in COVID. The protective role of high dose steroids in COVID-19 may be to an extent related to the reduction of inflammatory endotheliitis and reduction in frequency of both minor and major VTE events.

Laboratory Evidence for Dysregulation of Coagulation in COVID

Derangement of several coagulation and TEG parameters is seen in COVID-19 patients even without any history of TE events (Table 3) (2,17,32–35). CRC has some similarity in laboratory findings to disseminated intravascular coagulation (DIC) such as a marked increase in D-dimer levels and in some cases, mild thrombocytopenia. However typical findings in COVID-19 also include high fibrinogen and high factor VIII activity, ruling out significant consumption of coagulation factors (36). While DIC can occur in critically ill COVID-19 patients, this is likely to be a part of the spectrum of terminal multi-organ dysfunction and is unrelated to CRC (37).

Evaluation of Patients for COVID-19 Related Coagulopathy

Inpatients (Level of Evidence 4)

All patients admitted with COVID-19 infection should undergo a full blood count and coagulation studies including prothrombin time (PT), activated partial thromboplastin time (aPTT), Fibrinogen and D-Dimer levels at admission (38–41). Repeat testing is reasonable on a daily basis though frequency can be modified based on initial results, trend in values and the patient's clinical condition.

Imaging (Level of Evidence 2a)

Routine imaging to rule out DVT or PE in asymptomatic cases is not currently recommended, as it can expose health care workers to risk of infection. There is currently no evidence that routine imaging for DVT in asymptomatic patients improves outcomes (42). A normal D-dimer by and large is sufficient to exclude the diagnosis of PE but an increased D-dimer in this setting is not specific for VTE (43). In patients with suspected PE, computed tomography with pulmonary angiography (CTPA) is the preferred test to confirm or exclude the diagnosis (44). A bedside ECHO may be the only feasible option in case of logistic difficulties in transferring a sick ICU patient for CTPA. If DVT is suspected, a bedside compression ultrasound scan may be performed if it is likely to guide further management (45).

Outpatients (Level of Evidence 4)

Coagulation testing for asymptomatic or mild symptomatic patients may be considered in the presence of other risk factors for VTE such as chronic inflammatory conditions, diabetes and obesity. Patients who have elevated inflammatory markers such as C-reactive protein (CRP) or D-dimer on initial assessment should also be considered for coagulation testing, as these patients represent a more severe phenotype. There is no role for routine imaging studies in asymptomatic patients (37,46).

Management of COVID-19 Related Coagulopathy

An evidence-based algorithm for the management of COVID-19 patients based on disease severity is depicted in Figure 2. Low-molecular weight heparin (LMWH) is known to reduce the risk of VTE and may have additional anti-inflammatory properties (47). LMWH has been shown to improve survival in ICU patients but not in non-ICU patients (48). There is a report of improved survival in those who receive pharmacological prophylaxis, when compared to those with no prophylaxis, especially in those with a high

Table 3. Laboratory parameters related to coagulation in patients with SARS-CoV-2 infection

Laboratory tests	
Prothrombin Time	Normal or slightly prolonged
Platelets	Normal or increased
Fibrinogen	Increased
D-Dimer	Increased
Factor VIII activity	Increased
Von Willebrand Factor	Greatly increased
ATIII and protein S	Small decrease
Protein C	Small increase
Thromboelastogram (TEG) findings	
Reaction time (R)	Shortened, consistent with increased early thrombin burst
Clot formation time (K)	Shortened, consistent with increased fibrin generation
Maximum amplitude (MA)	Increased, consistent with greater clot strength
Clot lysis@ 30 minutes (LY30)	Reduced, consistent with reduced fibrinolysis

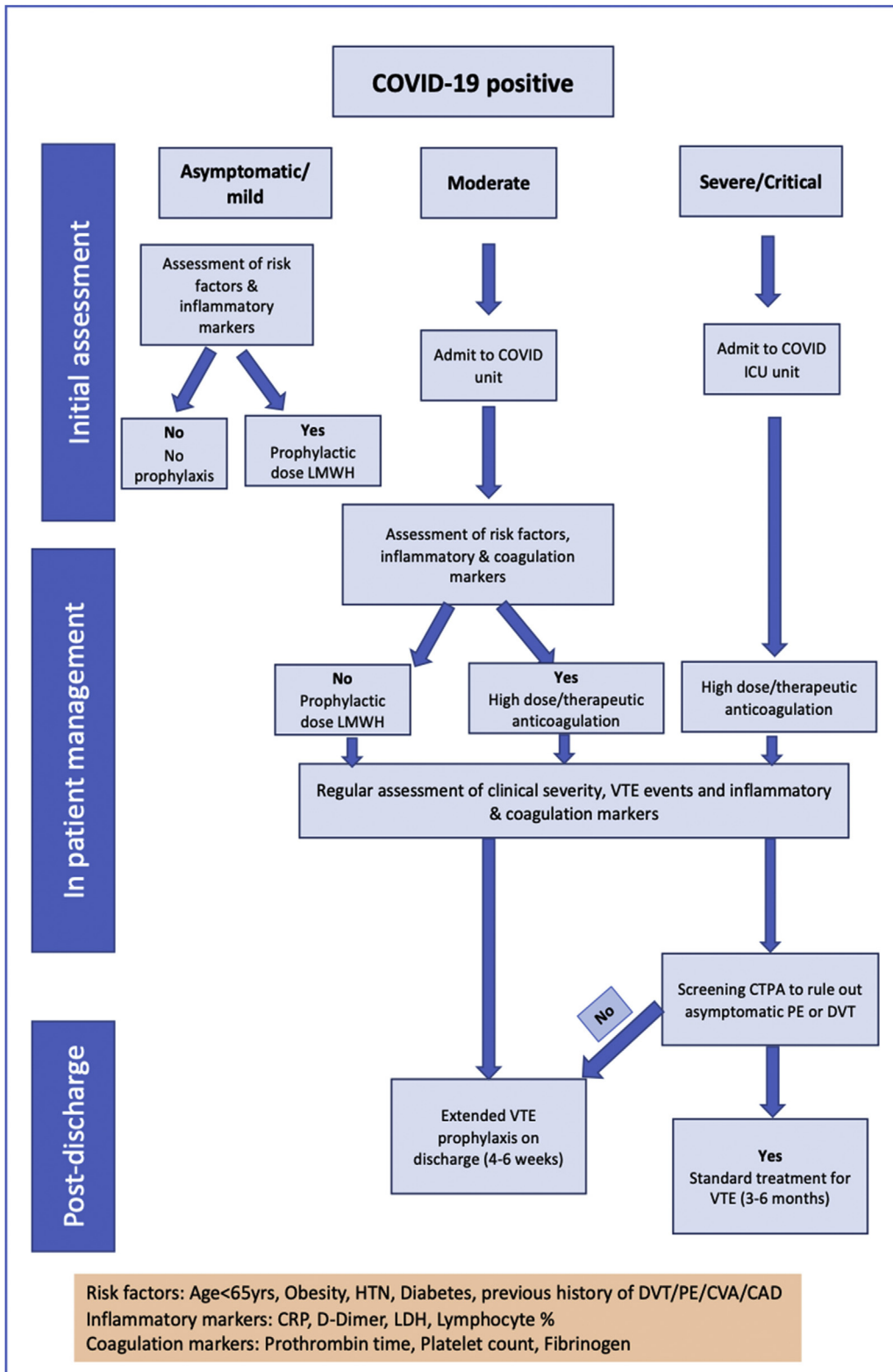


Figure 2. An evidence-based algorithm for the management of COVID-19 related coagulopathy based on disease severity.

D-dimer (six times) upper limit of normal and for subsets with high sepsis-induced coagulopathy score (35). However, prophylactic and even therapeutic anticoagulation does not appear to completely alleviate the risk of VTE in COVID and this should always be combined with adequate fluid resuscitation and agents to reduce inflammation.

There is a report of heparin resistance in COVID-19 patients, with requirement of very high doses to achieve a therapeutic aPTT or anti-factor Xa activity (49). The reason for heparin resistance in this setting is unclear and for patients with a falsely prolonged aPTT at baseline due to lupus anticoagulant, the aPTT may be unreliable, and anti-factor Xa activity should be monitored to guide dosing. TEG monitoring may be a useful technique in these settings to assess the coagulation status and guide anticoagulant therapy (31).

Management in the Outpatient Setting (Level of Evidence 4)

Outpatient thromboprophylaxis may be appropriate for selected individuals with COVID-19 who are not admitted to the hospital, especially those with other thrombotic risk factors such as prior VTE or recent surgery, trauma, or immobilization, based on clinical judgment. Prophylaxis may also be indicated for outpatients in the presence of high inflammatory markers, with view of reports of acute PE in such patients (4,50).

Management in the Inpatient Setting

Prophylactic Therapy (Level of Evidence 2a)

Standard VTE prophylaxis is appropriate in all hospitalized medical, surgical, and obstetric patients with COVID-19, unless there is a contraindication to anticoagulation (e.g. active bleeding or serious bleeding in the prior 24–48 h). An alternative agent such as Fondaparinux should be used if heparin or its derivatives cannot be used as in patients with past history of heparin-induced thrombocytopenia (HIT) (51).

High Dose VTE Prophylaxis (Level of Evidence 2b)

Despite the lack of high-quality evidence, the risk of major VTE in patients with COVID-19 infection is high enough for some experts to suggest more aggressive thromboprophylaxis dosing or even empiric therapeutic-dose anticoagulation for VTE prevention (Table 2) (19–25). While the reported risk of bleeding complications in COVID patients is low, the potential bleeding risk must be balanced with the benefit of aggressive thromboprophylaxis in these patients (52). Well recognised risk factors of increased VTE risk such as obesity, elderly age, cancer, and past history of

VTE may warrant consideration during the decision-making process.

Full Dose/Therapeutic Anticoagulation (Level of Evidence 2b)

Therapeutic-dose (full-dose) anticoagulation (e.g. enoxaparin 1 mg/kg every 12 h) may be considered in the following settings, unless there is a contraindication to anticoagulation.

- Documented or presumed VTE
- Clotting of intravascular access devices—clotting of intravascular lines or extracorporeal circuits despite prophylactic anticoagulants
- Critically ill patients in view of the reported high incidence of VTE events whilst on standard thromboprophylaxis

Role of Anti-platelet Agents (Level of Evidence 5)

While aspirin is being used along with standard VTE prophylaxis in some centers, there is currently no robust evidence to support use of aspirin or clopidogrel for VTE prophylaxis for medically ill patients or on outpatient basis (53).

Role of Fibrinolytic Agents (Level of Evidence 4)

The indication that fibrin deposits occur prior to symptoms of the disease suggests that targeting the fibrinolytic system to promote fibrin resolution, could limit severity and improve pulmonary function. A case series described administration of tissue plasminogen activator (tPA) to three critically ill individuals with ARDS associated with COVID-19 (54). One individual had transient improvement in laboratory parameters but ultimately died. The other two had improvement in laboratory parameters though final clinical outcomes were not known. Its current role in management of severe COVID-19 patients outside the setting of major thromboembolic event such as a PE or stroke, is unclear.

Mechanical Methods of Thromboprophylaxis (Level of Evidence 2b)

Mechanical methods should be used in addition to pharmacological agents for patients admitted to the ICU due to their very high risk of DVT. However, the risk of infection transmission for the healthcare workers involved in putting the thrombo-embolic deterrent (TED) stockings and managing them for COVID patients cannot be underestimated. Isolated mechanical methods should only be considered in patients at high risk of bleeding or in whom anticoagulation is contraindicated. In such circumstances, transition to a pharmacologic agent should be considered as soon as the bleeding risk becomes acceptably low or has been reversed (55).

Extended Thromboprophylaxis Following Discharge (Level of Evidence 2a)

In view of the high incidence of VTE in patients needing ICU admission, our unit protocol is to perform a CTPA for all patients with severe illness prior to discharge. Individuals with documented VTE whether symptomatic or incidentally detected will require a minimum of three months of anticoagulation (56). Individuals with COVID-19 who have not had a VTE may also warrant post-discharge prophylactic anticoagulation. Recommendation from societies is to apply criteria similar to those used in Medically Ill Patient Assessment of Rivaroxaban versus Placebo in Reducing Post-discharge Venous Thromboembolism Risk (MARINER) trial (57). Most hospitalized patients with COVID-19 would probably meet these criteria. However, bleeding risk also needs to be incorporated into decision-making. Our protocol is to recommend post-discharge anticoagulation prophylaxis for all patients with moderate or severe illness for 6 weeks, if not contraindicated. Oral agents such as rivaroxaban are recommended to minimize the need for frequent blood tests which requires repeated contact with health care services.

Conclusion

Covid-19 related coagulopathy is a major contributor to the overall burden of COVID related morbidity and mortality. Multiple factors are involved in the development of a pro-coagulant milieu in the lungs and the rest of the body. More than half of all critically ill COVID patients will develop DVT or PE and currently used prophylactic measures appear to provide only partial protection. Most patients with COVID-19 infection, irrespective of severity should be considered for VTE prophylaxis, while higher dose prophylaxis or therapeutic anticoagulation may be indicated in subsets of patients. Close monitoring is necessary to identify and treat VTE episodes early and these hospitalized patients should receive extended prophylaxis against VTE events in the early post-discharge period.

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References

1. Guan WJ, Ni ZY, Hu Y, et al. China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020;382:1708–1720.
2. Tang N, Li D, Wang X, et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 2020;18:844–847.
3. Hunt B, Retter A, McClintock C, et al. Practical Guidance for the Prevention of Thrombosis and Management of Coagulopathy and Disseminated Intravascular Coagulation of Patients Infected with COVID-19. Available at: <https://b-s-h.org.uk/media/18171/th-and-covid-25-march-2020-final.pdf>. Accessed July 15, 2020.
4. Gervaise A, Bouzad C, Peroux E, et al. Acute pulmonary embolism in non-hospitalized COVID-19 patients referred to CTPA by emergency department. *Eur Radiol* 2020;30:6170–6177.
5. The Oxford 2011 Levels of Evidence. OCEBM Levels of Evidence Working Group. Available at: <http://www.cebm.net/index.aspx?o=5653>. Accessed July 15, 2020.
6. Imai Y, Kuba K, Rao S, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature* 2005;436:112–116.
7. Zhang H, Penninger JM, Li Y, et al. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: Molecular mechanisms and potential therapeutic target. *Intensive Care Med* 2020;46:586–590.
8. Xiang-hua Y, Le-min W, Ai-bin L, et al. Severe Acute Respiratory Syndrome and Venous Thromboembolism in Multiple Organs. *Am J Respir Crit Care Med* 2010;182:436.
9. Marchandot B, Sattler L, Jesel L, et al. COVID-19 Related Coagulopathy: A Distinct Entity? *J Clin Med* 2020;9:1651.
10. Chen L, Li X, Chen M, et al. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. *Cardiovasc Res* 2020;116:1097–1100.
11. Hamming I, Timens W, Bulthuis M, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004;203:631–637.
12. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020;395:1417–1418.
13. Sardu C, Gambardella J, Morelli MB, et al. Hypertension, Thrombosis, Kidney Failure, and Diabetes: Is COVID-19 an Endothelial Disease? A Comprehensive Evaluation of Clinical and Basic Evidence. *J Clin Med* 2020;9:1417.
14. Lillcrap D. Disseminated intravascular coagulation in patients with 2019-nCoV pneumonia. *J Thromb Haemost* 2020;18:786–787.
15. Marongiu F, Grandone E, Barcellona D. Pulmonary thrombosis in 2019-nCoV pneumonia? *J Thromb Haemost* 2020;18:1511.
16. Gupta N, Zhao YY, Evans CE, et al. The stimulation of thrombosis by hypoxia. *Thromb Res* 2019;181:77–83.
17. Ranucci M, Ballotta A, Di Dedda U, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. *J Thromb Haemost* 2020;18:1747–1751.
18. Potere N, Valeriani E, Candeloro M, et al. Acute complications and mortality in hospitalized patients with coronavirus disease 2019: a systematic review and meta-analysis. *Critical Care* 2020;24:389.
19. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* 2020;191:145.
20. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med* 2020;46:1089–2098.
21. Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost* 2020;18.
22. Cui S, Chen S, Li X, et al. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost* 2020;18:1421.
23. Litjens JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J Thromb Haemost* 2020;18:1743–1746.
24. Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res* 2020;191:9.
25. Artifoni M, Danic G, Gautier G, et al. Systematic assessment of venous thromboembolism in COVID-19 patients receiving thromboprophylaxis: incidence and role of D-dimer as predictive factors. *J Thromb Thrombolysis* 2020;50:211–216.

26. Borazjani R, Seraj SR, Fallahi MJ, et al. Acute portal vein thrombosis secondary to COVID19: a case report. <https://orcid.org/0000-0002-8562-5637>. Accessed July 15, 2020.
27. Oxley TJ, Mocco J, Majidi S, et al. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. *N Engl J Med* 2020;382:e60.
28. Wichmann D, Sperhake JP, Lutgehetmann M, et al. Autopsy findings and venous thromboembolism in patients with COVID-19. *Ann Intern Med* M20-2003 2020;173.
29. Kashi M, Jacquin A, Dakhil B, et al. Severe arterial thrombosis associated with Covid-19 infection. *Thromb Res* 2020;192:75–77.
30. Perini P, Nabulsi B, Massoni CB, et al. Acute limb ischaemia in two young, non-atherosclerotic patients with COVID-19. *Lancet* 2020;395:1546.
31. Panigada M, Bottino N, Tagliabue P, et al. Hypercoagulability of COVID-19 patients in Intensive Care Unit. A Report of Thromboelastography Findings and other Parameters of Hemostasis. *J Thromb Haemost* 2020;18:1738–1742.
32. Yin S, Huang M, Li D, Tang N. Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. *J Thromb Thrombolysis*, 20201–4. <https://doi.org/10.1007/s11239-020-02105-8>.
33. Fogarty H, Townsend L, Ni Cheallaigh C, et al. COVID19 coagulopathy in Caucasian patients. *Br J Haematol* 2020;189:1044–1049.
34. Amgalan A, Othman M. Exploring possible mechanisms for COVID-19 induced thrombocytopenia: Unanswered questions. *J Thromb Haemost* 2020;18:1514.
35. Tang N, Bai H, Chen X, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost* 2020;18:1094.
36. Connors JM, Levy JH. Thromboinflammation and the hypercoagulability of COVID-19. *J Thromb Haemost* 2020;18:1559–1561.
37. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. *Am J Hematol* 2020;95:834–847.
38. Akima S, McLintock C, Hunt BJ. RE: ISTH interim guidance to recognition and management of coagulopathy in COVID-19. *J Thromb Haemost* 2020;18:2057–2058.
39. ACC. <https://www.acc.org/latest-in-cardiology/articles/2020/04/17/14/42/thrombosis-and-coronavirus-disease-2019-covid-19-faqs-for-current-practice>. Accessed July 15, 2020.
40. Casini A, Alberio L, Angelillo-Scherrer A, et al. Thromboprophylaxis and laboratory monitoring for in-hospital patients with Covid-19 - a Swiss consensus statement by the Working Party Hemostasis. *Swiss Med Wkly* 2020;150:w20247.
41. Coronavirus. <https://www.england.nhs.uk/coronavirus>. Accessed July 15, 2020.
42. Oudkerk M, Büller HR, Kuijpers D, et al. Diagnosis, Prevention, and Treatment of Thromboembolic Complications in COVID-19: Report of the National Institute for Public Health of the Netherlands. *Radiology* 2020;297:E216–E222.
43. Perrier A, Desmarais S, Goehring C, et al. D-dimer Testing for Suspected Pulmonary Embolism in Outpatients. *Am J Respir Crit Care Med* 1997;156:492–496.
44. Kaminetzky M, Moore W, Fansiwala K, et al. Pulmonary Embolism on CTPA in COVID-19 Patients. *Radiology: Cardiothoracic Imaging* 2020;2. <https://doi.org/10.1148/ryct.2020200308>.
45. Kermali M, Khalsa RK, Pillai K, et al. The role of biomarkers in diagnosis of COVID-19 - A systematic review. *Life Sci* 2020;254:117788.
46. Zhou F, Yu T, Ronghui D, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395:1054–1062.
47. Thachil J. The versatile heparin in COVID-19. *J Thromb Haemost* 2020;18:1020–2022.
48. Paranjpe I, Fuster V, Lala A, et al. Association of Treatment Dose Anticoagulation with In-Hospital Survival Among Hospitalized Patients with COVID-19. *J Am Coll Cardiol* 2020;76:122–124.
49. White D, MacDonald S, Bull T, et al. Heparin resistance in COVID-19 patients in the intensive care unit. *J Thromb Thrombolysis* 2020;50:287–291.
50. Aryal MR, Gosain R, Donato A, et al. Venous Thromboembolism in COVID-19: Towards an Ideal Approach to Thromboprophylaxis, Screening, and Treatment. *Curr Cardiol Rep* 2020;22:52.
51. Schindewolf M, Steindl J, Beyer-Westendorf JB, et al. Fondaparinux for Management of Heparin-Induced Thrombocytopenia. Available at: http://www.onlinejacc.org/content/70/21/2636?_ga=2.212718736.50781243.1594576423-1748705103.1592075610. Accessed July 15, 2020.
52. Cohen AT, Spiro TE, Büller HR, et al. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. *N Engl J Med* 2013;368:513–523.
53. Watson R, Johnson D, Dharia R, et al. Doherty Anti-coagulant and anti-platelet therapy in the COVID-19 patient: a best practices quality initiative across a large health system. *Hospital practice* 2020;48:169–179.
54. Wang J, Hajizadeh N, Moore EE, et al. Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): A case series. *J Thromb Haemost* 2020;18:1752–1755.
55. Tal S, Spectre G, Kornowski R, et al. Venous Thromboembolism Complicated with COVID-19: What Do We Know So Far? *Acta Haematol* 2020;143:417–424.
56. Moores L, Tritschler T, Brosnahan S, et al. Prevention, Diagnosis, and Treatment of VTE in Patients With COVID-19. *CHEST Guideline and Expert Panel Report* 2020;158:1143–1163.
57. Spyropoulos AC, Ageno W, Albers GW, et al. Rivaroxaban for Thromboprophylaxis after Hospitalization for Medical Illness. *N Engl J Med* 2018;379:1118–1127.