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Review Article

Venous Thromboembolism Prevention in COVID-19: A Review of Latest Evidences

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ABSTRACT

COVID-19 has become major public health problems, with new cases and deaths growing around the world. COVID-19 has been reported to associate with a hypercoagulable state, which may lead to venous thromboembolism (VTE) formation. This condition is also associated with worse outcomes in COVID-19 patients. It is, therefore, critical for clinicians to identify this condition and manage accordingly. VTE formation in COVID-19 occurs through several mechanisms, such as inflammatory reaction leading to a hypercoagulable state and vascular dysfunction and direct vascular injury by the virus. The rate of VTE formation was as high as 31% in Intensive Care Unit (ICU) patients and 9.2% in general wards patients. It was also associated with poor prognosis. Thromboprophylaxis with heparin, particularly low molecular weight heparin (LMWH), has been shown to improve these patients' prognosis. A careful individual assessment is required to determine which patients will benefit from this therapy. There are still no sufficient prospective trials to establish guidelines for VTE thromboprophylaxis in COVID-19. The assessment includes laboratory parameters such as PT, platelet count, D-dimer, fibrinogen, and other risk factors incorporated in the PADUA risk assessment model (RAM), versus the risk of bleeding incorporated in IMPROVE bleeding RAM.

1. Introduction

In December 2019, a cluster of acute atypical respiratory disease was found in Wuhan, China, followed by rapid spreading from Wuhan to other areas. It was later found that a pathogen named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) responsible for this disease. This disease, coronavirus disease 2019 (COVID-19), kept growing as the primary health problem worldwide.[1,2] As of 20th June, this disease has infected 8.148.006 worldwide with total deaths of 462.691, while in Indonesia, it has infected 45.029 people with 2.429 dead cases. [3,4]

One of the worse prognostic factors in COVID-19 is hypercoagulability state, which can lead to venous thromboembolism (VTE) formation. According to Zhai et al., severe coagulation abnormalities were found in 20% of COVID patients. The major coagulation disorder was found in almost all patients with the condition of severe COVID-19.[5] Cui et al. showed that VTE was found in 25% of severe COVID-19 patients in ICU, and eventually, 40% of them died.6 Therefore, clinicians should be able to identify this condition and manage it accordingly. In this review, we will discuss the hypercoagulability state and venous thromboembolism (VTE) formation, how to evaluate the risk of VTE formation in COVID-19 patients, and the role of low molecular weight heparin (LMWH) in preventing this condition.

2. COVID-19 Pathophysiology: Its Role on Hypercoagulability State and Thromboembolism Formation

SARS-CoV-2 binds to angiotensin-converting enzyme (ACE) 2 receptors, which are widely expressed in lung epithelial cells, to enter the host cells.[3] Three main components for innate immunity in the airway; dendritic cells (DCs), alveolar macrophages, and epithelial cells, fight against viruses until adaptive immunity is activated. Antigen presentation initiates T cell responses via DCs and macrophages.[2]

The activated immune cells will produce proinflammatory cytokines, including interleukin (IL) 10, IL-6, IL-8, granulocyte-colony stimulating factor (G-CSF), tumor necrosis factor (TNF)-α, and macrophage inflammatory protein (MIP)-1α.[2] These proinflammatory cytokines would up-regulate procoagulant factors and down-regulate the anticoagulant pathway, particularly protein C. This process will result in the activation of coagulation cascade and inhibition of fibrinolytic reaction, thus stimulating thrombosis. [5,7]

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Table 1. Sepsis-induced coagulopathy (SIC) score[27]

Category	Parameter	0 point	1 point	2 point
Prothrombin time	PT-INR	≤1.3	>1.2	>1.4
Coagulation	Platelet count (x10^9/L)	≥150	<150	<100
Total SOFA*	SOFA four items	0	1	≥2

Note, *The total Sequential Organ Failure Assessment (SOFA) is the sum of the four items (respiratory SOFA, cardiovascular SOFA, hepatic SOFA, and renal SOFA; PT-INR, prothrombin time - international normalized ratio

Table 2. SOFA scoring[27]

SOFA Score	Respiratory SOFA PaO2/FiO2 (mmHg)	Cardiovascular SOFA (MAP ± vasopressors)	Hepatic SOFA (Bilirubin mg/dl)	Renal SOFA (Creatinine mg/dl)
0	≥ 400	MAP ≥ 70 mmHg	<1.2	<1.2
+1	< 400	MAP < 70 mmHg	1.2-1.9	1.2-1.9
+2	< 300	Dopamine ≤ 5 µg/kg/min or dobutamine (any dose)	2.0-5.9	2.0-3.5
+3	< 200 and mechanically ventilated	Dopamine > 5 µg/kg/min OR epinephrine ≤ 0.1 µg/kg/min OR norepinephrine ≤ 0.1 µg/kg/min	6.0-11.9	3.5-4.9
+4	< 100 and mechanically ventilated	Dopamine > 15 µg/kg/min OR epinephrine > 0.1 µg/kg/min OR norepinephrine > 0.1 µg/kg/min	>12.0	>5.0

Note, SOFA, Sequential Organ Failure Assessment; MAP, mean arterial pressure

Other than through proinflammatory cytokines, it is also proposed that SARS-CoV-2 directly injures endothelial cells, as endothelial cells also express ACE2.[8] The normal endothelium plays a significant role in inhibiting thrombosis by producing prostaglandin, NO, and ectonucleotidase CD39, which have vasodilatory properties and inhibit platelet aggregation.[7] Hence, the dysfunction of endothelial cells by SARS-CoV-2 will favor thrombosis.

SARS-CoV-2 antigens can also activate platelets through IL-8 production. These activated platelets would activate white blood cells and form a clot to facilitate the pathogen's elimination.[9] Besides, hypoxia caused by severe COVID-19 can cause increased blood viscosity, thus stimulating thrombosis.10 Immobilization in COVID-19 patients also contributes to increasing VTE events.[11]

3. Venous Thromboembolism Formation in COVID-19: the Incidence and Its Prognostic Significance

Klok et al. found that the rate of thrombotic complications in COVID-19 patients in ICU was 31%, consisting of pulmonary embolism, deep vein thrombosis, catheter-related upper extremity thrombosis, and ischemic stroke.[12] Another study suggested that acute pulmonary embolus was found in 23% of patients with severe COVID-19.[13] Furthermore, an autopsy of COVID-19 patients showed microthrombi in lung microvasculature, suggesting that refractory hypoxemia in these patients might be caused by ventilation-perfusion mismatch due to the obstruction of the capillary by these microthrombi. Similar to what happens in the condition of severe sepsis, activation of coagulation cascade by cytokines can cause disseminated intravascular coagulation (DIC), causing multiple organ damage.[14] In a study by Tang et al., DIC was found in 71.4% of nonsurvivors and 0.6% of survivors during their hospital stay.[15] Nonsurvivors were found to have a correlation between progressive DIC with decreased fibrinogen, increased D-dimer, and increased PT, noting a median count DIC 4 days (1-12 days) after admission.[16]

Although ICU patients were found to have a higher risk of VTE, patients on the general ward were also at increased risk. The incidences of VTE in ICU patients were 26% (95% CI, 17-37), 47% (95% CI, 34-58), and 59% (95% CI, 42-72) at 7, 14, and 21 days, respectively; while for the patients in general wards, the incidences were 5.8% (95% CI, 1.4-15), 9.2% (95% CI, 2.6-21), and 9.2% (2.6-21) at 7, 14, and 21 days, respectively.[17]

4. Risk Assessment for Thromboembolism Formation in COVID-19 Patients

In COVID-19, the coagulation disorders seem to be similar to other coagulopathies due to severe infections, such as DIC and sepsis-induced coagulopathy (SIC) SIC, an earlier phase sepsis-associated DIC, can be assessed using a category by The International Society of Thrombosis and Haemostasis (ISTH).[10] The SIC scoring system includes prothrombin time, platelet count, and SOFA score (Table 1 and 2). In a study by Tang et al., it was found that severe COVID-19 patients who meet SIC criteria (≥4) or who have a prominent elevation of D-dimer (6 times upper limit of normal) have a better prognosis if they were treated with anticoagulant therapy (mainly with LMWH).[10]

Other than the SIC scoring, the predictor of thromboembolic formation in COVID-19 is D-dimer, PT, and PTT level. Increased D-dimer levels > 1.5 µg/ml (normal range: 0.0–0.5 µg/ml) can predict VTE with sensitivity 85%, specificity 88.5% and negative predictive value 94.7%.6 Spontaneous prolongation of the PT by more than 3 s or PTT by more than 5 s was also found to be an independent predictor for VTE formation.12

Table 4. IMPROVE bleeding RAM: score ≥ 7 indicates high bleeding risk.[29]

Risk Factor	Points
Critically Ill	4
Inflammatory bowel disease	4
Active cancer (local or distant metastases and with chemotherapy or radiation in the previous 6 months)	3
Previous VTE	3
Reduced mobility (bed rest with bathroom privilage for at least 3 days)	3
Thrombophilic condition (defects of antithrombin, protein C or S, factor V Leiden, G20210A prothrombin mutation, or antiphospholipid syndrome)	3
Recent trauma / surgery (<1 month)	2
Age ≥ 70 years	1
Heart or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection or rheumatologic disorder	1
BMI ≥ 30	1
Ongoing hormonal treatment	1

Note, GFR, glomerular filtration rate; INR, international normalized ratio

A higher score in PADUA risk assessment model (RAM) to predict VTE (Table 3) has been associated with worse outcomes in COVID-19.18 Its direct relationship with thromboembolism formation in COVID-19 has not been studied.

Most patients with severe COVID-19 may have other comorbidities, such as liver dysfunction, that may increase bleeding risk. The predisposing factors of bleeding should be assessed (i.e. using IMPROVE bleeding risk assessment model in table 4) and corrected actively.

5. Preventing Thromboembolism in COVID-19 Patient: When Do We Need It?

While patients with severe COVID-19 in ICU are at obvious increased risk for VTE, those in general wards also have significant risk factors, such as immobilization and infectious disease. Considering that VTE incidence in non-severe COVID-19 was well above 1% even on thromboprophylaxis, anticoagulant thromboprophylaxis has been suggested to be given for all admitted COVID-19 patients by the majority of sources. The ISTH and American Society of Hematology (ASH) guideline advised prophylactic LMWH in all COVID-19 patients who meet the requirement of hospitalization if no contraindication (active bleeding and platelet count < 25 × 109/L).19-21 However, now it is required in individual patient's evaluation, integrating VTE risk factors and bleeding risk factors with clinical judgment. There were still no sufficient prospective trials to establish a guideline for antithrombotic treatment strategy in COVID-19 patients. Assessment of VTE risk could be done from laboratory parameters such as PT, platelet count, D-dimer, and other risk factors incorporated in PADUA risk assessment model (RAM), while the risk of bleeding can be assessed using IMPROVE bleeding RAM.

6. The Role of Low Molecular Weight Heparin in Thromboembolism Prevention: Mechanism and Administration

Heparin works by dramatically enhancing the aggregation of complexes between antithrombin and coagulation factors such as thrombin (IIa), factors Xia, Xa, and IXa, which will disable these coagulation factors. Furthermore, heparin also compromises platelet function.[7]

Low molecular weight heparin (LMWH) preparations have a more significant ability to inhibit factor Xa than inhibit thrombin. It also interacts less with platelets than standard heparin, hence lesser bleeding side effects and less likely to cause heparin-induced thrombocytopenia (HIT). They have higher bioavailability and longer plasma half-life, making once-daily administration feasible. LMWH also has a more predictable dose-response compared to unfractionated heparin (UFH), thus eliminating the need for routine monitoring.[7] Furthermore, LMWH also has anti-inflammatory properties that might be beneficial in COVID-19 by significantly lowering the level of IL-6.[22] The reduction of IL-6 level is expected to lessen the cytokine storm caused by the virus, thus improving the patient's condition.[23]

Table 5. Standard VTE prophylaxis regimens for patients with high VTE risk[28]

Patient population	VTE prophylaxis regimens
Medical patients	Enoxaparin 40 mg SQ every 24 hours (Class I, level B) Or Heparin 5000 units SQ every 8 to 12 hours (Class I, level B)
Renal impairment (CrCl < 30 mL/min) Not on renal replacement therapy	Enoxaparin 30 mg SQ every 24 hours (Class IIa, level B) Or Heparin 5000 units SQ every 8 to 12 hours (Class I, level B)
Extreme obesity patients (BMI > 40 kg/M^2)	Enoxaparin 40 mg SQ every 12 hours (Class IIa, level B)
Low body weight patients (weight < 50 kg)	Enoxaparin 30 mg SQ every 24 hours (Class IIb, level C) Or Heparin 5000 units SQ every 8 to 12 hours (Class I, level B)

Note, VTE, venous thromboembolism; CrCl, creatinine clearance; BMI, body mass index

The current standard dose anticoagulant prophylaxis is recommended (table 5), rather than intermediate or full treatment dosing.[19] The doses of LMWH for prophylaxis are once-daily subcutaneous doses of 4000 to 5000 units or twice-daily subcutaneously doses of 2500 to 3000 units. The dose is reduced in a patient with renal impairment.[24] The drug should be administered for at least 7 to 10 days.[5] However, in cases where the patients have a great increase in D-dimers and severe inflammation, intermediate or therapeutic dosing should be considered, according to the bleeding risk.[4] Ranucci et al. found that VTE formation still existed with 4000 IU b.i.d LMWH as

thromboprophylaxis in severe COVID-19 infection. No VTE formation was found when the dose of LMWH was increased to 6000 IU b.i.d (8000 IU b.i.d if body mass index > 35).[25]

In severe COVID-19 patients, it is recommended to use mechanical prevention for VTE prevention alternatively to the contra-indicated pharmacological thromboprophylaxis due to its high bleeding risk or active bleeding. Intermittent pneumatic compression (IPC) and graduated compression stockings (GCS) are the mechanical prevention that should be given until major bleeding risk factors were removed. Once the bleeding risk decrease, the pharmacological thromboprophylaxis should be initiated as soon as possible.[5]

In patients with severe kidney impairment (CrCl <30 mL/min), The use of unfractionated heparin (UFH) is being recommended.[5] Up to date, there was no research evaluating the use of direct oral anticoagulant (DOAC) for VTE prevention in COVID-19. However, it was known that the use of DOAC in critically ill patients with high VTE risk did not reduce the risk of VTE and associated with increased major bleeding.[26] Another consideration against DOAC use was DOAC and COVID-19 medical treatment interaction, (as some of them are potent inhibitor of CYP3A4). The risk of organ failure and the lack of an effective reversal agent in some centers also taken as considered against DOAC use.[20]

7. Conclusion

Patients with COVID-19 are at increased risk of VTE due to several mechanisms; strong inflammatory reaction leading to hypercoagulability state, vascular injury due to the direct effect of the virus, and inflammatory reaction. Studies have shown that prophylaxis with heparin, particularly LMWH, improved the prognosis of these patients. A rigorous individual patient assessment incorporating VTE risk factors and bleeding risk factors is required. Assessment of VTE risk with laboratory parameters such as PT, platelet count, D-dimer, and other risk factors incorporated in PADUA RAM, versus the risk of bleeding such as incorporated in IMPROVE bleeding RAM, may aid in determining which patients benefit most with thromboprophylaxis strategy.

8. Declarations

4.1. Ethics Approval and Consent to participate
Not applicable.

4.2. Consent for publication
Not applicable.

4.3. Availability of data and materials
Data used in our study were presented in the main text.

4.4. Competing interests
Not applicable.

4.5. Funding source
Not applicable.

4.6. Authors contributions
Idea/concept: MDHQ. Design: MDHQ. Control/supervision: MDHQ. Data collection/processing: MDHQ, HA, NAN. Extraction/Analysis/interpretation: MDHQ, HA, NAN. Literature review: HA, NAN. Writing the article: MDHQ, HA, NAN. Critical review: MDHQ, HA, NAN. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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