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REVIEW

Pulmonary Embolism Prophylaxis in Patients With COVID-19: An Emerging Issue

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Severe acute respiratory syndrome (SARS)-CoV-2 virus disease (coronavirus disease 2019; COVID-19) is associated with increased coagulation activity, resulting in an excessive risk of venous thromboembolism (VTE) and poor prognosis. The most common manifestation of VTE is pulmonary embolism (PE), with approximately one in five hospitalised patients being at risk. These reports led to the empirical use of prophylactic anticoagulation, even in the absence of established or clinically suspected disease. This review summarises current aspects and recommendations regarding the use of thromboprophylaxis for PE in patients with COVID-19.

Keywords COVID-19 • Pulmonary embolism • Coagulopathy • Thromboprophylaxis

Introduction

Since December 2019, the world has faced a rapidly expanding pandemic of respiratory tract infections caused by the novel severe acute respiratory syndrome (SARS)-Cov-2 virus, named coronavirus disease 2019 (COVID-19) [1]. After the emergence of SARS and Middle East respiratory syndrome, SARS-Cov-2 is the third coronavirus since 2000 to result in a major global public health crisis. The outbreak was first described in Wuhan, the capital of Hubei province in China, and, to date, >126 million cases have been reported worldwide, including about 2.77 million deaths in >200 countries [2].

The virus gains entry through the mouth, nose, eyes, and lungs. The most common symptoms include fever, cough, headache, anosmia, vomiting, diarrhoea, dyspnoea, and myalgias. It has the potential to induce severe illness such as acute respiratory disease syndrome (ARDS), systemic inflammatory response syndrome, and shock. The clinical spectrum of COVID-19 includes asymptomatic or presymptomatic infection (individuals testing positive for SARS-CoV-2 but without symptoms), mild illness (symptomatic individuals without shortness of breath, dyspnoea, or abnormal chest imaging), moderate illness (individuals with lower respiratory disease and an oxygen saturation of ≥94% on room air at sea level), severe illness (individuals with an oxygen saturations of <94% on room air at sea level; ratio of arterial partial pressure of oxygen to fraction of inspired oxygen <300 mmHg; respiratory rate >30 breaths/minute; or lung infiltrates >50%), and critical illness (individuals with respiratory failure, septic shock, and/or multiple organ dysfunction) [1,2].

Common laboratory abnormalities include lymphopaenia, mild thrombocytopaenia, increased fibrin, fibrin degradation products, fibrinogen, D-dimers, ferritin and interleukin (IL)-6, prolongation of prothrombin time (PT), international normalised ratio (INR) and thrombin time (TT), and shortened activated partial thromboplastin time (aPTT).

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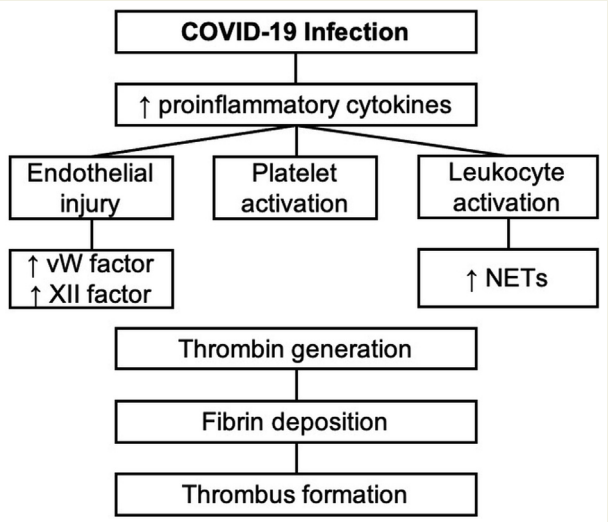

Figure 1 A flowchart of coronavirus disease 2019 (COVID-19) coagulopathy.
Abbreviations: NETs, neutrophil extracellular traps; vW factor, von Willebrand factor.

Abnormal haemostatic results identified a novel acquired syndrome called "COVID-19-associated coagulopathy", which predisposes patients to venous thrombo-embolism (VTE) (Figure 1) [1].

Incidence

The incidence of VTE ranges from 5% to 10% in hospitalised patients; it is much higher in intensive care units (ICUs; up to 30% of patients). The majority of patients have no prior history of VTE; the most common manifestation is pulmonary embolism (PE), with an estimated incidence of 4–23% [3]. All related data, mainly from ICU patients, concluded that PE is diagnosed in critically ill patients irrespective of standard thromboprophylaxis (Table 1) [4–6,9,10].

In a prospective cohort of 150 patients with COVID-19 with hypoxaemic ARDS from four ICUs in France taking prophylactic or empirical treatment dose anticoagulation, 16.7% developed a PE despite therapy. The disease was diagnosed by computed tomography pulmonary angiography (CTPA) in a median time of 5.5 days after admission. This observation represents nearly a six-fold increase in the incidence of PE versus those with ARDS not related to COVID-19 [4].

A study of 184 patients with pneumonia secondary to severe COVID-19 from three ICUs across the Netherlands found that 13.6% suffered from a PE despite systemic thromboprophylaxis. It should be noted that two of the three ICUs initially used lower-than-standard doses of low-molecular-weight heparin (LMWH) and the doses were increased over time. Age and coagulopathy, defined as spontaneous prolongation of PT >3 seconds or aPTT >5 seconds, have been recognised as independent predictors of thrombotic complications [5].

Table 1 Incidence of pulmonary embolism (PE) in intensive care units (ICUs) and general wards.

Study	Country	Patients (n)	PE Incidence (%)	
			ICU	General Ward
Helms et al. [4]	France	150	16.7	–
Klok et al. [5]	The Netherlands	184	13.6	–
Llitjos et al. [6]	France	26	23	–
Poyiadji et al. [7]	USA	328	6	16
Lodigiani et al. [8]	Italy	375	0.6	2.1
Tavazzi et al. [9]	Italy	54	3.7	–
CCF study	France	1,240	–	8.3

Abbreviation: CCF, Critical COVID-19 France.

In a retrospective study of 26 mechanically ventilated patients from two French ICUs treated with either prophylactic or therapeutic anticoagulation, 23% were diagnosed with a PE. Remarkably, all of these patients developed a PE, even though they were on a therapeutic dose of anticoagulation, presumably owing to the higher thrombotic burden [6].

The Critical COVID-19 France trial demonstrated that 103 of 1,240 (8.3%) hospitalised patients with COVID-19 had a confirmed PE by CTPA. Male sex, elevated C-reactive protein (CRP), and a longer delay from the onset of symptoms to hospitalisation increased the risk of PE. However, anticoagulation with a therapeutic dose administrated before admission or a prophylactic dose introduced during hospitalisation reduced the occurrence of a PE [11].

A cohort of 328 patients with COVID-19 in Detroit (MI, USA) revealed that 22% suffered a PE. Obese patients and those with higher D-dimer and CRP levels were more susceptible to developing a PE. Additionally, statin therapy prior to admission was associated with a decreased rate of PE [7].

Two (2) studies from Italy indicated a lower incidence of PE. In a retrospective cohort of 375 patients, 44 underwent VTE imaging tests and 16 were positive. Half of the thromboembolic complications occurred within 24 hours after hospital admission. Ten (10) patients (2.7%) were diagnosed with a PE: two who were in the ICU and eight who were in a general ward [8]. Another study revealed that only two of 54 patients (4%) with COVID-19 who were admitted to the ICU, sedated, mechanically ventilated, and treated with prophylactic LMWH developed a PE [9].

Aetiology

It is not clear yet if these haemostatic derangements are a consequence of severe inflammation or a specific effect of

Table 2 Recommendations regarding in-hospital prophylaxis.

International Societies and Consensus Groups	Recommendations
ISTH	• Thromboprophylaxis with LMWH or UFH in all hospitalised patients, unless contraindicated • Intermediate dose of LMWH in high-risk patients • 50% dose increase in obese patients
Global COVID-19 Thrombosis Collaborative Group	• PE risk stratification in all hospitalised patients • Thromboprophylaxis with LMWH or UFH in hospitalised critically ill patients and those at high risk of PE, unless contraindicated • NOACs could be used in the prehospitalisation period in high risk patients
ESC	• Thromboprophylaxis at standard prophylactic dose in all hospitalised patients, unless contraindicated
WHO	• Thromboprophylaxis with LMWH or UFH in all hospitalised patients, unless contraindicated
CHEST Guideline and Expert Panel Report	• Thromboprophylaxis at standard dose in all hospitalised patients, unless contraindicated • LMWH and fondaparinux over UFH to limit staff exposure
NIH	• Thromboprophylaxis with LMWH or UFH in all hospitalised patients, unless contraindicated
Expert Opinion of the Section on Pulmonary Circulation of PCS	• PE risk stratification in all hospitalised patients • Thromboprophylaxis in hospitalised critically ill patients and those at high risk of PE, unless contraindicated • UFH in patients with CKD stage 4 or 5 • Intermediate LMWH dose at high-risk patients • If HIT is suspected, bivalirudin over fondaparinux should be used • If bivalirudin is unavailable, fondaparinux might be considered
SISET position paper	• Thromboprophylaxis with LMWH, UFH, or fondaparinux in all hospitalised patients, unless contraindicated • Intermediate dose of LMWH in patients with multiple risk factors (BMI >30, previous VTE, active cancer, etc.)
SSH Working Party on Hemostasis	• Thromboprophylaxis in all hospitalised patients, unless contraindicated • In patients with a creatinine clearance >30 mL/min, LMWH should be administered • In patients with a creatinine clearance <30 mL/min, UFH SC two or three times daily or IV should be administered • Increased dose of LMWH or UFH in patients >100 kg • No use of NOACs • Intermediate or therapeutic dose of LMWH or UHF in ICU patients with a large increase in D-dimer, severe inflammation, signs of hepatic or renal dysfunction, or imminent respiratory failure

Abbreviations: ISTH, International Society on Thrombosis and Haemostasis; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; COVID-19, coronavirus-19 disease; PE, pulmonary embolism; NOAC, novel oral anticoagulant; ESC, European Society of Cardiology; WHO, World Health Organization; CHEST, American College of Chest Physicians; NIH, National Institutes of Health; PCS, Polish Cardiac Society; CKD, chronic kidney disease; HIT, heparin-induced thrombocytopaenia; SISET, Italian Society on Thrombosis and Haemostasis; BMI, body mass index; VTE, venous thromboembolism; SSH, Swiss Society of Hematology; SC, subcutaneous; IV, intravenous.

SARS-CoV-2. A hypothesis is that SARS-CoV-2 intervenes in coagulation pathways and that there are alterations to the three components of the Vircow's triad. Endothelial cell inflammation and dysfunction, along with altered blood flow dynamics, platelet activation, high concentrations of von Willebrand factor, and cell-free DNA, histones, and viral RNA trigger factor XI activation, thrombin production, and fibrin modulation [12].

A hypercoagulable state is present in lungs of patients with COVID-19 with ARDS, resulting in the accumulation of fibrin in the lung parenchyma and the development of microthrombi in the pulmonary vasculature. Inflammatory leukocytes such as neutrophils, monocytes, and macrophages are recruited to the pulmonary vasculature and alveolar air space damaging the alveolar–capillary membrane and leading to the exudation of fluid rich in cells and plasma proteins, including coagulation factors and fibrinogen. Local fibrinogen synthesis in lung epithelium is also evident, further amplifying the deposition of fibrin [13].

This hypercoagulable state is combined with a hypofibrinolytic situation in the alveolar space. The principal fibrinolytic inhibitor in the pathogenesis of ARDS, namely plasminogen activator inhibitor 1, is elevated in patients with COVID-19. Plasminogen activator inhibitor 1 is expressed on the surface of macrophages and monocytes, inhibiting the

degradation of fibrin deposits by blocking tissue plasminogen activator and urokinase plasminogen activator [13].

A cytokine storm is generated by an overproduction of early-response pro-inflammatory cytokines such as IL-6, IL-22, IL-7, and C-X-C motif chemokine 10 (CXCL10). This hyperinflammatory situation causes lung injury (microvascular damage and endothelial dysfunction), provoking haemostatic changes and the development of pulmonary thrombi in situ. In addition, thrombus formation might also be secondary to deep veins thrombosis. The first autopsy series described extensive diffuse alveolar damage and thrombi within small peripheral pulmonary vessels. In addition, a microvascular endotheliopathy owing to SARS-CoV-2 binding to the angiotensin-converting enzyme 2 receptor on endothelial cells results in inflammatory cell infiltration, endothelial cell apoptosis, and microvascular prothrombotic effects [12,14–17].

Further, increased antiphospholipid antibodies have been detected in patients with COVID-19, probably contributing to thrombotic events [18]. A retrospective French study of 25 patients with COVID-19-related ARDS verified the high frequency of antiphospholipid antibodies. Eighteen (18) individuals were lupus anticoagulant positive and 13 had double antiphospholipid antibody positivity. Six (6) of them, all antiphospholipid antibody positive, were diagnosed with a massive PE, irrespective of anticoagulation treatment. Fibrinogen levels were increased in 18 patients and D-dimer levels were high in all patients [19].

In-Hospital Prophylaxis

Coronavirus-19 disease itself is associated with a prothrombotic state. Moreover, patients might have several risk factors for PE such as advanced age, obesity, cancer, congestive heart failure, and past history of VTE, along with other ICU-specific factors such as sedation and immobilisation [1].

Currently, there is no consensus on whether a prophylactic or therapeutic dose should be given in the absence of confirmed PE.

According to the Global COVID-19 Thrombosis Collaborative Group and the Polish Cardiac Society (PCS), PE risk stratification should be undertaken in all hospitalised individuals using specific scores such as the modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE VTE), the revised Geneva score, and the Padua score. In the absence of contraindications, the vast majority of patients with COVID-19, including those with respiratory failure or comorbidities such as active cancer or heart failure, and those who are bedridden or require intensive care, qualify for in-hospital PE prophylaxis [1,3,20,21].

Other societies, including the International Society on Thrombosis and Hemostasis (ISTH), the Italian Society on Thrombosis and Hemostasis (SISET), and the Swiss Society of Hematology (SSH), suggest the administration of thromboprophylaxis in all hospitalised patients with COVID-19 unless there are contraindications (i.e., active bleeding and profound thrombocytopaenia) [22–24].

Based on current recommendations, unfractionated heparin (UFH) given intravenously, and LMWH and fondaparinux given subcutaneously, at standard doses are preferred as they have shorter half-lives and fewer interactions with other drugs used for COVID-19 disease (i.e., antivirals) than oral anticoagulants. In addition to their antithrombotic properties, UFH and LMWH have anti-inflammatory and antiviral effects. The PCS, the SISET, and the ISTH recommend an intermediate dose of LMWH in patients with multiple PE risk factors such as a body mass index >30 kg/m^2, previous history of VTE, or active cancer. Additionally, higher-than-standard doses are suggested by the SSH in overweight patients (>100 kg) or those admitted to ICUs with a large increase in D-dimers, severe inflammation, hepatic or renal dysfunction, or imminent respiratory failure [1–3,22–28]. Recommendations from several international societies and consensus groups regarding in-hospital thromboprophylaxis in patients with COVID-19 are summarised in Table 2.

Recent data from Wuhan demonstrated that UFH (10,000–15,000 U daily) or LMWH (40–60 mg enoxaparin daily) at prophylactic doses for at least 7 days are associated with a better prognosis in patients with COVID-19 and coagulopathy. The 28-day mortality rate in more severe cases with a sepsis-induced coagulopathy score $\geq$ 4 (40.0% vs 64.2%) or D-dimer >3 μg/mL (six times the upper limit of normal; 32.8% vs 52.4%) was lower in those on heparin than those not on it [29].

In terms of novel oral anticoagulants (NOACs), drug–drug interactions with investigational therapies for COVID-19, particularly with lopinavir/ritonavir via cytochrome P450 3A4 (CYP3A4) and P-glycoprotein inhibition, should be considered. In addition, concerns remain about the use of NOACs given their renal clearance and the difficultly in administering reversal agents [28].

Nevertheless, a few centres have integrated oral anticoagulants for in-hospital prophylaxis, predominantly in chronically anticoagulated patients. NOACs are preferred over vitamin K antagonists (VKAs) unless they are not indicated. If combined therapy with a CYP3A4 inhibitor is prescribed, patients with COVID-19 should be switched to dabigatran, edoxaban, or betrixaban, as these agents have fewer drug–drug interactions. Novel oral anticoagulants could also prevent thrombo-embolic events in patients at high risk of a PE in the prehospitalisation period [28,30].

In the case of clinical signs suggestive of PE at hospital admission, or clinical deterioration despite in-hospital thromboprophylaxis, it is important to consider imaging assessment for PE. If thrombi are identified, a therapeutic dose of anticoagulation is administered according to existing evidence-based guidelines for patients without COVID-19 [1,2,14,26,31]. A proposed algorithm for the management of hospitalised patients is provided in Figure 2.

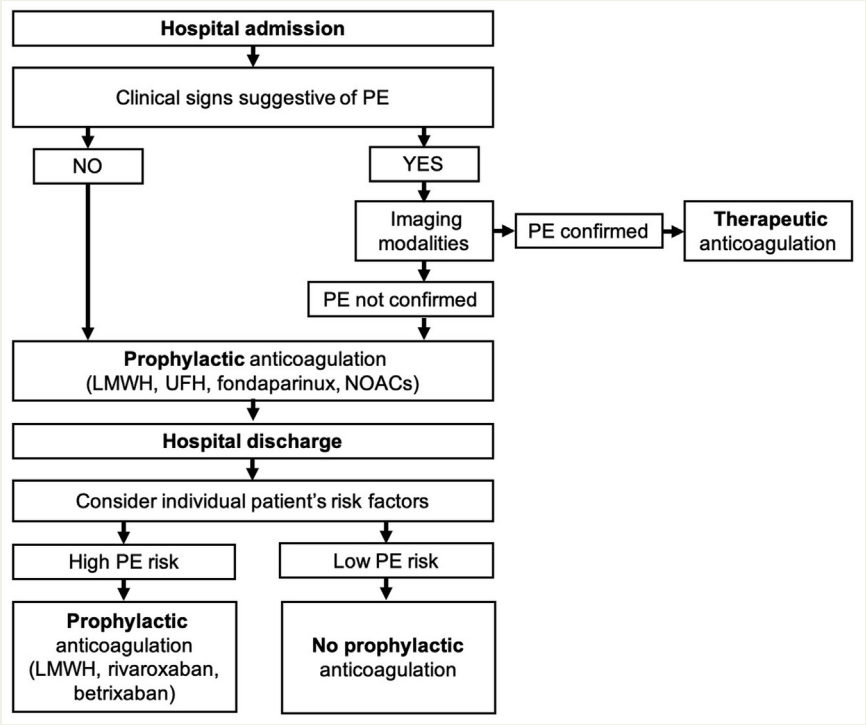

Figure 2 A proposed approach to hospitalised patients with coronavirus disease 2019 (COVID-19).
Abbreviations: LMWH, low-molecular-weight heparin; NOACs, novel oral anticoagulants; PE, pulmonary embolism; UFH, unfractionated heparin.

Postdischarge Prophylaxis

Thus far, it is uncertain whether patients with COVID-19 receiving PE prophylaxis should be anticoagulated after hospitalisation or not. An individualised PE risk stratification should be carried out and thromboprophylaxis could be indicated in patients with a persistently elevated risk. Several criteria that might justify postdischarge prophylaxis include (1) reduced mobility (i.e., patients admitted to the ICU, intubated, sedated, and possibly paralysed for multiple days); (2) comorbidities such as active cancer; (3) modified IMPROVE VTE risk score ≥4 or modified IMPROVE VTE risk score ≥ 2 with D-dimers >2 times the upper limit of normal; (4) age ≥75 years; (5) age >60 years with D-dimers >2 times the upper limit of normal; and (6) age 40–60 years, D-dimers >2 times the upper limit of normal and a previous history of VTE [1,2,14].

Novel oral anticoagulants or LMWH reduce the risk of PE, whereas there is no evidence to indicate the administration of VKAs. Enoxaparin, rivaroxaban and betrixaban are recommended in patients with COVID-19 but for a limited time only. The suggested intake for enoxaparin is 40 mg once daily for 6–14 days, 10 mg once daily for 31–39 days for rivaroxaban, and an initial single dose of 160 mg on day 1, followed by 80 mg once daily for 35–42 days for betrixaban (which is still not available in Europe) [1,2,14,27,32,33].

D-Dimer Monitoring

Daily measurement of D-dimer to guide anticoagulant prophylaxis is not recommended [2]. A single-centre study from Wuhan suggested a D-dimer cut-off value of 1.5 μg/mL for detecting VTE. The sensitivity of this was 85.0%, the specificity 88.5%, and the negative predictive value 94.7%. Nevertheless, the small sample size and the lack of validation were recognised as limitations of the study [34].

D-dimer monitoring might be used as a marker of disease severity and prognosis [2]. A retrospective cohort of 191 patients (137 survivors and 54 non-survivors) identified D-dimer >1 μg/mL at admission as a strong and independent risk factor for in-hospital mortality [35].

Catheter-Directed Therapies and Reperfusion Strategies

The indiscriminate use of interventional therapies amidst a pandemic should be limited to the most critical situations. The placement of an inferior vena cava filter might be considered in cases of recurrent PE, despite optimal therapy. In terms of reperfusion strategies for acute PE, the current guideline recommendations should be followed. Systemic fibrinolysis is indicated in patients with overt haemodynamic instability (i.e., high-risk PE and massive PE), while

catheter-based therapies could be employed in those that are not candidates for systemic fibrinolysis. Last, but not least, in patients with COVID-19 with refractory symptoms or when thrombolysis is contraindicated or has failed, pulmonary embolectomy might be beneficial. This procedure can be successfully performed with or without cardiopulmonary bypass; the bleeding risk is always manageable even under the most challenging circumstances [1,21,36].

Conclusions

In hospitalised patients with COVID-19, PE prophylaxis with parenteral anticoagulant agents over oral ones is recommended predominantly in those with severe disease and in those at high risk of a PE. Extended duration prophylaxis after discharge, especially for patients with ongoing risk factors, should be individualised.

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Conflicts of Interest

There are no conflicts of interest to disclose.

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