Received: 3 June 2020 | Accepted: 19 January 2021

DOI: 10.1111/crj.13330

ORIGINAL ARTICLE

WILEY

A review of venous thromboembolism in COVID-19: A clinical perspective

Savas Ozsu[1] | **Ersin Gunay**[2] | **Stavros V. Konstantinides**[3]

[1]Department of Chest Diseases, Erdem Healthy Group, İstanbul, Turkey

[2]Department of Chest Diseases, Yuksek Ihtisas University School of Medicine, Medical Park Ankara Hospital, Ankara, Turkey

[3]Department of Cardiology, Center for Thrombosis and Hemostasis, Johannes Gutenberg University of Mainz, Langenbeckstr, Germany

Correspondence
Ersin Gunay, Department of Chest Diseases, Yuksek Ihtisas University School of Medicine, Medical Park Ankara Hospital, Ankara, Turkey.
Email: ersingunay@gmail.com

Abstract

Coronavirus disease-19 (COVID-19) started in Wuhan, China in December 2019 and spread to all around the world in a short period of time. Hospitalized patients with COVID-19 mostly could suffer from an abnormal coagulation activation risk with increased venous thrombosis events and a poor clinical course. The reported incidence rates of thrombotic complications in hospitalized COVID-19 patients vary between 2.6 and 85% (both in non-critically ill and critically ill patients). The risk of venous thromboembolism is not known in non-hospitalized patients with COVID-19. There are numerous studies and guidelines for administration of thromboprophylaxis for COVID-19 cases. All hospitalized COVID-19 patients should take pharmacological thromboprophylaxis if there is no contraindication. However, there is no consensus on this issue. In this review, we discussed all these approaches in a critical perspective.

KEYWORDS

anticoagulation, COVID-19, LMWH, mortality, venous thrombosis

1 | INTRODUCTION

Coronavirus disease-19 (COVID-19) started initially in Wuhan, China in December 2019 and spread to all around the world in a short time period. At the end of May 2020, about 5.5 million people fell ill from this outbreak, and more than 350,000 patients died. Recently, in postmortem studies, embolism and microthrombosis formation in the peripheral small pulmonary vessels has been reported in patients diagnosed with COVID-19.[1,2] Although the pathophysiology is not fully defined, excessively increased inflammatory process, hypoxemia, capillary endothelial cell damage, platelet activation, and stasis are accused on pathogenesis of venous thrombosis in patients with COVID-19.[3] Thromboembolic events are common in hospitalized patients (critically ill or non-critically ill patients). In contrast, the risk of thromboembolism is unknown in non-hospitalized patients with COVID-19. Thromprophylaxis or treatment approaches in effected patients (hospitalized or non-hospitalized) are not clear. In this review, we aimed to summarize and criticize the diagnosis and the treatment approaches to venous thrombosis in hospitalized (critically ill or not), non-hospitalized, and discharged COVID-19 patients with current literature and national/international guidelines.

1.1 | Coagulopathy in COVID-19

The endothelial cell dysfunction induced by infectious process results in excess production of thrombin and termination of fibrinolysis, which reveals a hypercoagulable status in patients with infection,[4,5] such as COVID-19. Additionally, decreased oxygen pressure which is present in patients with severe COVID-19 can stimulate thrombosis by means of both increasing blood viscosity, and a hypoxia-inducible transcription factor-dependent signaling pathway.[6]

The increased inflammation secondary to the infections leads to a severe instability of hemostasis typically seen in patients with sepsis. This severe inflammatory state has been described as an acute disseminated intravascular

coagulation (DIC), characterized by decreased thrombocyte count, prolonged prothrombin and activated partial thromboplastin time (PT and aPTT), increased fibrinogen degradation products such as D-dimer as well as low fibrinogen.[7] These characteristic findings in sepsis were also reported in COVID-19. Possibly, COVID-19 shares some pathogenic mechanisms of thromboinflammation with other thrombotic microangiopathies (eg, vascular damage due to inflammatory process, platelets interacting with the vascular endothelium, increased complement and coagulation cascade activity).[8] In a study evaluating anticoagulant profile in COVID-19 patients, decreased level in protein C, protein S, and antithrombin levels were detected in addition to antiphospholipid antibodies.[9] A study conducted by Zaid et al. reported the presence of SARS-CoV-2 RNA in the platelets and high level of platelet-associated cytokine which result in hyperactive platelet function causing thrombosis in patients with COVID-19.[10]

In the previous MERS and SARS outbreaks, only case reports for pulmonary embolism (PE) were reported in the literature.[11] In contrast, during postmortem studies, PE was detected in four of eight laboratory-confirmed SARS patients. It was reported that four patients had PE within the pulmonary arteries and three had deep venous thrombosis.[12] Moreover, histopathological changes similar to SARS have been shown in COVID-19.[1] In a recent autopsy series, Wichmann and colleagues examined 12 SARS-CoV-2-positive patients of whom SARS-CoV-2 RNA was detected by quantitative reverse transcription PCR in the lung of all patients. Autopsy revealed deep venous thrombosis in 7 of 12 patients (58%) in whom venous thromboembolism was not suspected before death and pulmonary embolism in 5 of 12 patients (42%) who were also diagnosed as VTE.[13] In another autopsy findings, microthrombi formation in other organs including lungs, kidneys, brain, and heart revealed that multiple organ systems are at risk of thrombotic complications.[14]

1.2 | Venous thromboembolism (VTE) in COVID-19

There is a close relationship between COVID-19 and VTE. As our knowledge increases, its relationship with VTE is better understood. In the studies reported in the literature, the frequency of VTE in COVID-19 patients varies. In general, VTE is more frequently observed in intensive care patients and in case of critical illness. In contrast, there is a heterogeneity on the use of anticoagulant prophylaxis in the literature.

Klok et al. reported a study including 184 COVID-19 patients treated in the ICU, 25 had confirmed PE and 1 had venous thromboembolism (VTE). They reported that all patients received standard doses of thromboprophylaxis. In this study, 139 (76%) patients were still in the ICU. Therefore, it is not known how many patients developed VTE at follow-up after publication of that paper.[15] In another study evaluating the venous and arterial complication of 388 patients with COVID-19 hospitalized in non-ICU and ICU (16% of patients), despite the use of low molecular weight heparin (LMWH), VTE (4.4%), ischemic stroke (2.5%), and acute myocardial infarction (MI) (1.1%) was reported.[16]

The use of some biomarkers, for example, D-dimer, for the patients with COVID-19 at risk of causing VTE has been demonstrated in several case series and studies. D-Dimer increases in patients diagnosed with COVID-19 and is also associated with poor prognosis. In a study from China in which 191 patients were included, D-Dimer greater than 1 μg/mL on admission was shown to be an independent risk factor for in-hospital death.[17] However, there is no data about the administered anticoagulant therapy dose for patients in this study.

In another study conducted by Cui et al., VTE was detected in 20 (25%) of 81 patients with severe COVID-19 pneumonia, and 8 of those died. D-Dimer was 6.5 times higher in patients with VTE compared to the ones without VTE (6.5 μg/mL vs 0.8 μg/mL).[18]

In contrast, D-Dimer level higher than > 2,500 ng/mL at initial presentation were reported as *predictive of bleeding complications* during hospitalization of patients with COVID-19. It is known that D-Dimer level can also be elevated in some conditions including sepsis, immobilization, and infection. So that elevated D-Dimer level is not recommended as a diagnostic biomarker for VTE in COVID-19 patients.[19]

In a recent retrospective study conducted by Xie et al., computed tomography pulmonary angiography (CTPA) was performed in only 25 patients who were suspected for PE in a total of 1008 patients with COVID-19.[20] They diagnosed PE in 10 patients with COVID-19 pneumonia (40%).

Poissy et al. reported that 22 of 107 (20.6%) confirmed COVID-19 patients followed up in the ICU was diagnosed to have PE with a median time of 6 days (1-18 days) from ICU admission. When they compared these COVID patients with previously followed up 196 ICU patients with same time interval in 2019 (non-COVID-19 patients), they found that the frequency of PE was higher in the COVID-19 group (20.6% vs. 6.1%).[21] They reported that, although all COVID-19 patients with diagnosed PE were receiving prophylactic or therapeutic dosage of antithrombotic treatment (UFH, LMWH, or Vitamin K antagonist), higher obesity prevalence in this patient group may be a factor to develop PE.

It is not known when PE develops in patients with COVID-19. The question is whether the disease develops at the initial phase or during follow-up. However, some cases reported in the literature were found to be diagnosed with PE at the time of admission, during hospitalization, and after discharge from the hospital.[22-24]

In a study comparing 449 patients with COVID-19 and 104 non-COVID-19, the D-Dimer levels were similar between both groups (1.94 μg/mL vs. 2.52 μg/mL).[25]

Following the hospital discharge, Tang et al. reported that 28-day mortality of heparin users were lower than non-users in COVID group with D-Dimer levels > 3.0 μg/mL (40.0% vs. 64.2%, respectively, $P = 0.029$) or sepsis-induced coagulopathy (SIC) score ≥ 4 (32.8% vs. 52.4%, respectively, $P = 0.017$). In the study, no difference in 28-day mortality was found between heparin users and non-users (30.3% vs. 29.7%, respectively, $P = 0.910$).[24] Methodologically, multivariate analysis should be adjusted by using sepsis-induced coagulopathy (SIC) and D-Dimer one-to-one in patients who died and were using heparin.

High mortality rate was found in patients with sepsis who did not use heparin before and in patients with higher SIC scores.[26] When these two studies are compared, the use of heparin after discharge is controversial.

Guan et al. reported that D-dimer was higher than 0.5 mg/L in 260 of 560 COVID-19 patients at admission. Moreover, D-dimer was found to be increased in 43% of non-severe and 60% of severe COVID-19 patients.[27]

1.3 | Diagnosis of VTE in COVID-19

Pulmonary embolism should be suspected in conditions such as pleuritic chest pain, hemoptysis, very high D-Dimer values, worsening dyspnea with severity of pneumonia, VTE signs and symptoms in patients with COVID-19. In addition, pleural effusion, atelectasis, Hampton's sign are important clues for PE in radiological findings.

Current guidelines recommend the use of non-contrast enhanced thorax computed tomography (or high-resolution computed tomography (HRCT) for the diagnosis, severity assessment and follow-up of COVID-19 infection in some extent.[28]

Computed tomography pulmonary angiography should be performed to confirm the diagnosis of VTE in suspected patients. In a recent study, Poyiadji et al.[29] diagnosed 72 of 328 patients (22%) to have PE via CTPA. However, in the case of renal insufficiency and contrast allergy, scintigraphy should be considered. It should be kept in mind that in patients with COVID-19 pneumonia, scintigraphy would have false-positive results. Hence, it will be more appropriate to perform scintigraphy in patients with focal opacity. On scintigraphy, perfusion defects located in sites different from tomographic findings are diagnostic for PE.

Diagnosis of VTE may be more problematic in some patients with respiratory failure (eg, patients with high oxygen requirement or CPAP dependence). When CTPA cannot be performed and scintigraphy is not diagnostic, deep vein ultrasound and colored Doppler ultrasound studies can be considered to assess for deep vein thrombosis. In the study of 82 patients (52 medical wards patients and 30 ICU patients), insidious VTE was investigated using a colored Doppler ultrasound of the upper and lower limbs in Belgium. VTE was diagnosed in 4% of patients in medical wards and 13% of the ones followed up in the ICU.[30]

1.4 | In-hospital thromboprophylaxis

The risk of VTE increases in cases of pneumonia, cancer, and heart failure in hospitalized patients. It is known that TP administration reduce the risk of VTE in these patients.[31,32] Padua Prediction Score, IMPROVE, and Caprini scoring methods consisting of various parameters classify the patients to have high or low risk for VTE.[33-35] None of these scoring methods considers D-Dimer level. One suggested approach for risk stratification in COVID-19 patients within the United Kingdom used D-Dimer thresholds of <1000 ng/mL, 1000–3000 ng/mL, and >3000 ng/mL to identify patients who should receive standard-dose, intermediate-dose, and treatment-dose anticoagulation, respectively.[36] However, this strategy, depending on D-Dimer level, has not been validated.

Helms et al. reported that PE was diagnosed in 25 of (16.7%) 150 COVID-19 patients who were followed in the ICU. Worsening of breath respiration? or significant increase in D-Dimer level were important indications for CTPA in this population. Interestingly, 30% of patients diagnosed with PE were receiving "treatment-dose" heparin on ICU admission.[37] However, in this study, it is not known how many patients developed VTE while under the therapeutic dose anticoagulation. Furthermore, in another study conducted by Middeldorp and colleagues, the incidence of VTE increased from 25% at 7 days to 48% at 14 days in 198 patients with COVID-19.[38] Interestingly, Paranjpe et al. reported that among 2,773 hospitalized COVID-19 patients, only 786 (28%) received systemic anticoagulant treatment during their hospital course. In this population, in-hospital mortality rate was 29.1% for the ones who received anticoagulant treatment, while 62.7% for those who did not. Additionally, in a multivariate proportional hazards model, longer duration of anticoagulant treatment was found to be associated with a reduced risk of mortality.[39] Thus, from our own point of view, all hospitalized patients with COVID-19 should receive pharmacological TP if there are no contraindications, regardless of the D-Dimer level.

The risk of VTE increases during the pregnancy and the postpartum period.[40] Hence, we believe that pregnant patients with COVID-19 may be considered to receive therapeutic dose of anticoagulant therapy in the postpartum period, regardless of the D-Dimer level. However, this approach needs to be investigated with an observational study.

TABLE 1 In-patient and out-patient suggestions of world-wide guidelines for pharmacological thromboprophylaxis for patients with COVID-19[36,47-59]

	Hospitalized patients (In-patient)	Out-patient
World Health Organization (WHO)	• Use pharmacological prophylaxis (low molecular-weight heparin [preferred if available] or heparin 5000 U, subcutaneously twice daily) **in adolescents and adults** without contraindications. • For those with contraindications, use mechanical prophylaxis (intermittent pneumatic compression devices)	
Italian Society on Thrombosis and Haemostasis	• The use of LMWH, UFH, or fondaparinux at doses indicated for prophylaxis of venous thromboembolism (VTE) is **strongly advised** in **all** COVID-19 hospitalised patients	• This should also be maintained at home for ***7-14 days*** after hospital discharge or in the pre-hospital phase, in case of pre-existing or persisting VTE risk factors (i.e., reduced mobility, body mass index (BMI) >30, previous VTE, active cancer, etc.).
International Society of Thrombosis and Haemostasis	• Prophylactic dose low molecular weight heparin (LMWH) which should be considered **in all patients**	
Swiss Society of Hematology	• All hospitalized COVID-19 patients should receive pharmacological thromboprophylaxis	
American Society of Hematology	• Prophylactic dose LMWH is recommended in all patients	• Thromboprophylaxis is **recomended** if risk factors of VTE present at the time of discharge
British Thoracic Society	• D-Dimer thresholds of <1000 ng/mL, 1000-3000 ng/mL and >3000 ng/mL to identify patients who should receive standard-dose, intermediate-dose and treatment-dose anticoagulation	• Extended thromboprophylaxis on discharge can be considered if the patient is considered **at high risk of VTE** (eg past history VTE, cancer, significantly reduced mobility, critical care admission)
Canadian Critical Care Society	• Use pharmacological prophylaxis in critically ill patients	
Chinese Guidelines	• Anticoagulation therapy should be initated for severe COVID-19 patients	
Germany society of thrombosis and Hematology	• Prophylactic dose LMWH is recommended in all patients	
Saudi Ministry of Health Protocole	• LMWH should be considered in all patients (including non-critically ill) requiring hospital admission	
American College of Chest Physician	• Prophylactic dose of LMWH or Fondaparinux (non-critically ill patients) • Prophylactic dose of LMWH (Critically ill patients)	• Extended thromboprophylaxis is not recommended after discharge of patients • Routine thromboprophylaxis is not recommended in nonhospitalized patients
International Society on Thrombosis and Hemostasis	• Prophylactic dose of LMWH (non-critically ill patients) • Prophylactic dose of LMWH, half-therapeutic dose of LMWH (for high risk patients) (Critically ill patients)	• LMWH/Direct oral anticoagulants for up to 30 days can be considered (if high thrombosis risk and low bleeding risk present) (after discharge) • Routine thromboprophylaxis is not recommended in nonhospitalized patients

In a recently published study from France, VTE was diagnosed in 18 (69%) of 28 patients with COVID-19 followed in the ICU. In this study, PE was systematically evaluated in case of respiratory failure by CTPA or trans-esophageal echocardiography when patients were not transportable. All patients had received a therapeutic dose or prophylactic dose anticoagulant. Interestingly, VTE was observed in 10 of 18 (56%) patients receiving full dose anticoagulant treatment. Seven of these 10 patients already had a history of VTE.[41]

Therefore, in the absence of definitive published data to guide the optimal approach to identify patients at increased risk of VTE who may benefit from intermediate or full-dose LMWH, it is not possible to advocate any particular approach and it is suggested that local protocols for risk stratification in COVID-19 patients should be developed. Current data show that TP administration for hospitalized patients with COVID-19 is in an inadequate level.

On the other hand, thrombocytopenia frequently develops in patients with COVID-19 and is associated with poor prognosis.[42] This issue is an important problem during treatment and follow-up of these patients. The mechanisms by which this coronavirus cause thrombocytopenia are unclear. One of the proposed mechanism is that COVID-19 may inhibit hematopoiesis in the bone marrow to produce thrombocytes by binding CD13 receptors and inducing growth inhibition and apoptosis in the bone marrow similar to HCoV-229E.[43] Another mechanism for thrombocytopenia is hemophagocyticlymphohistiocytosis (HLH) secondary to COVID-19 which results in release of large amount of inflammatory cytokines and destroying the large number of blood cells including platelets.[44] Third, COVID-19 may produce autoantibodies and immune complexes, resulting in specific destruction of platelets by the immune system.[45]

Those patients with more than 25.000 platelet counts should receive TP in a controlled manner. Mechanical TP should be preferred in cases with bleeding and severe thrombocytopenia.

High-risk patients (eg, obesity, previous history of VTE, cancer, antiphospholipid syndrome and postpartum period) should receive therapeutic dose TP. If the platelet count is 30-50×10^9/L and fibrinogen is not less than 1.0 g/L, therapeutic anticoagulation should be continued. All other patients do not require therapeutic dose TP, unless VTE is confirmed.

In patients with creatinine clearance <30 mL/min and in obese patients, 5000 U standardized Heparin (s.c.) should be given two or three times a day.

1.5 | Thrombolysis in COVID-19

To our knowledge, there is no comprehensive study in the current literature on thrombolysis treatment for PE in patients with COVID-19, but some case reports. Polat et al. presented a COVID-19 patient with massive PE that was treated with tissue plasminogen activator.[46] Because of the limited number of cases, it is not possible to make a decision for the effectivity of thrombolysis treatment on massive PE due to COVID-19.

1.6 | Thromboprophylaxis following hospital discharge

Incidence of VTE between 0 and 0.6 % has been reported in patients with COVID-19 at 30–42 days following hospital discharge. However, there is no consensus on prophylactic anticoagulant therapy following hospital discharge for COVID-19 patients. Those with D-Dimer levels higher than 3.0 μg/mL alone or sixfold higher than normal should receive TP after discharge (eg, Enoxoparin 1 × 0.4 cc, s.c.). A patient-focused (eg, immobility, obesity, postpartum period) approach should be considered. Based on the above-mentioned high-risk conditions and current risk scores, for the patients who meet guideline requirements for TP, anticoagulant therapy should continue after discharge from the hospital by taking into account of the risk of bleeding. Further studies are warranted by consideration of extended anticoagulation therapies for patients with COVID-19.

Published clinical approaches for pharmacological TP for COVID-19 patients that were suggested in worldwide guidelines and/or experience are summarized in Table 1.[36,47-59]

While the number of patients with COVID-19 increases, in light of newly updated data on patients with COVID-19, we believe that it is prudent to use TP in some patients, especially with the evidence of activation of the coagulation system (eg, increased D-Dimer levels) on admission.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Data Availability Statement

Data are available upon request.

Ethics

The article does not contain the participation of any human being and animal.

Verification

All the authors have seen the manuscript and agree to the content and data. All the authors played a significant role in the paper.

ORCID

Ersin Gunay https://orcid.org/0000-0002-2671-4584

REFERENCES

1. Zhang T, Sun L, Feng RE. Comparison of clinical and pathological features between severe acute respiratory syndrome and coronavirus disease 2019. *ZhonghuaJie He He Hu Xi ZaZhi*. 2020;43:E040. https://doi.org/10.3760/cma.j.cn112147-20200311-00312
2. Luo W, Yu H, Gou J, et al. Clinical pathology of critical patient with novel coronavirus pneumonia (COVID-19). *Preprints*. 2020;2020020407.
3. Jiménez D, García-Sanchez A, Rali P, et al. Incidence of VTE and bleeding among hospitalized patients with coronavirus disease 2019: a systematic review and meta-analysis. *Chest*. 2020;S0012-3692(20):35146-35151. https://doi.org/10.1016/j.chest.2020.11.005

4. Levi M, van der Poll T. Coagulation and sepsis. *Thromb Res*. 2017;149(38-44):13.
5. Schmitt FCF, Manolov V, Morgenstern J, et al. Acute fibrinolysis shutdown occurs early in septic shock and is associated with increased morbidity and mortality: results of an observational pilot study. *Ann Intensive Care*. 2019;9(1):19. 14.
6. Gupta N, Zhao YY, Evans CE. The stimulation of thrombosis by hypoxia. *Thromb Res*. 2019;181:77-83.
7. Taylor FB Jr, Toh CH, Hoots WK, et al. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation On behalf of the Scientific Subcommittee on disseminated intravascular coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH). *Thromb Haemost*. 2001;86:1327-1330.
8. Cattaneo M, Bertinato EM, Birocchi S, et al. Pulmonary embolism or pulmonary thrombosis in COVID-19? is the recommendation to use high-dose heparin for thromboprophylaxis justified? *Thromb Haemost*. 2020;120(8):1230–1232. https://doi.org/10.1055/s-0040-1712097
9. Zhang Y, Cao W, Jiang W et al. Profile of natural anticoagulant, coagulant factor and anti-phospholipid antibody in critically ill COVID-19 patients. *J Thromb Thrombolysis*. 2020;50(3):580-586. https://doi.org/10.1007/s11239-020-02182-9
10. Zaid Y, Puhm F, Allaeys I, et al. Platelets can associate with SARS-Cov-2 RNA and are hyperactivated in COVID-19. *Circ Res*. 2020. 10.1161/CIRCRESAHA.120.317703
11. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. 2020;pii: S2213-2600(20)30076.
12. Chong PY, Chui P, Ling AE, et al. Analysis of deaths during the severe acute respiratory syndrome (SARS) epidemic in Singapore: challenges in determining a SARS diagnosis. *Arch Pathol Lab Med*. 2004;128:195-204.
13. Wichmann D, Sperhake JP, Lütgehetmann M, et al. Autopsy findings and venous thromboembolism in patients with COVID-19 [published online ahead of print, 2020 May 6]. *Ann Intern Med*. 2020;M20-2003. https://doi.org/10.7326/M20-2003
14. Fox SE, Akmatbekov A, Harbert JL, Li G, Quincy Brown J, Vander Heide RS. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. *Lancet Respir Med*. 2020;8(7):681-686.10.1016/S2213-2600(20)30243-5
15. 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 Apr 10. pii: S0049-3848(20)30120-1.
16. Lodigiani C, Iapichino G, Carenzo L, et al. Humanitas COVID-19 task force. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res*. 2020;191:9-14. https://doi.org/10.1016/j.thromres.2020.04.024
17. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020. Mar 28;395(10229):1054-1062.
18. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18(6):1421–1424.
19. Rosovsky RP, Grodzin C, Channick R, et al. Diagnosis and treatment of pulmonary embolism during the coronavirus disease 2019 pandemic: a position paper from the National PERT consortium. *Chest*. 2020 Dec;158(6):2590–2601. https://doi.org/10.1016/j.chest.2020.08.2064
20. Xie Y, Wang X, Yang P, Zhang S. COVID-19 complicated by acute pulmonary embolism. *Radiol: Cardiothoracic Imaging*. 2020;2:e200067.
21. Poissy J, Goutay J, Caplan M, et al. Lille ICU haemostasis COVID-19 group. Pulmonary Embolism in COVID-19 patients: awareness of an increased prevalence. *Circulation*. 2020 Apr 24. https://doi.org/10.1161/CIRCULATIONAHA.120.047430
22. Danzi GB, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: a random association? *Eur Heart J*. 2020;41(19):1858. https://doi.org/10.1093/eurheartj/ehaa254
23. Casey K, Iteen A, Nicolini R, Auten J. COVID-19 pneumonia with hemoptysis: Acute segmental pulmonary emboli associated with novel coronavirus infection. *Am J Emerg Med*. 2020 Apr 8. pii: S0735-6757(20)30239-4. https://doi.org/10.1016/j.ajem.2020.04.011. [Epub ahead of print].
24. Ullah W, Saeed R, Sarwar U, Patel R, Fischman DL. COVID-19 complicated by acute pulmonary embolism and right-sided heart failure. *JACC Case Reports*. 2020. https://doi.org/10.1016/j.jaccas.2020.04.008.
25. Yin S, Huang M, Li D, Tang N. Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2 [online ahead of print]. *J Thromb Thrombolysis*. 2020 Apr 3. https://doi.org/10.1007/s11239-020-02105-8
26. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J ThrombHaemost*. 2020 Mar 27.
27. 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 Feb 28. https://doi.org/10.1056/NEJMoa2002032.
28. 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(1):E216–E222. https://doi.org/10.1148/radiol.2020201629
29. Poyiadji N, Cormier P, Patel PY, et al. Acute pulmonary embolism and covid-19 [published online ahead of print, 2020 May 14]. *Radiology*. 2020;201955. https://doi.org/10.1148/radiol.2020201955
30. Criel M, Falter M, Jaeken J, et al. Venous thromboembolism in SARS-CoV-2 patients: only a problem in ventilated ICU patients, or is there more to it? [published online ahead of print, 2020 May 12]. *Eur Respir J*. 2020;2001201. https://doi.org/10.1183/13993003.01201-2020
31. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: antithrombotic therapy and prevention of thrombosis 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e195S-e226S.
32. Schünemann HJ, Cushman M, Burnett AE. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Adv*. 2018;2(22):3198-3225.
33. Rosenberg D, Eichorn A, Alarcon M, McCullagh L, McGinn T, Spyropoulos AC. External validation of the risk assessment model of the International Medical Prevention Registry on Venous

Thromboembolism (IMPROVE) for medical patients in a tertiary health system. *J Am Heart Assoc*. 2014;3:e001152.
34. Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua PredictionScore. *J ThrombHaemost*. 2010;8:2450-2457.
35. Arcelus JI, Candocia S, Traverso CI, Fabrega F, Caprini JA, Hasty JH. Venous thromboembolism prophylaxis and risk assessment in medical patients. *Semin Thromb Hemost*. 1991;17(Suppl 3):313-318.
36. https://brit-thoracic.org.uk/about-us/covid-19-information-for-the-respiratory-community/
37. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients in severe SARS-CoV-2 infection: a multicenter prospective cohort study. *J Int Care Med*. 2020. https://doi.org/10.1007/s00134-020-06062-x
38. Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venousthromboembolism in hospitalizedpatientswith COVID-19. *J Thromb Haemost*. 2020 May 5. https://doi.org/10.1111/jth.14888.
39. 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 College Cardiol*. May 2020. https://doi.org/10.1016/j.jacc.2020.05.001.
40. James AH, Jamison MG, Brancazio LR, Myers ER. Venous thromboembolism during pregnancy and the postpartum period: incidence, risk factors, and mortality. *Am J ObstetGynecol*. 2006;194:1311-1315.
41. Llitjos JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J Thromb Haemost*. 2020 Apr 22. https://doi.org/10.1111/jth.14869
42. Lippi G, Plebani M, Michael HB. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. *Clin Chim Acta*. 2020 Mar 13. pii: S0009-8981(20)30124-8.
43. Yeager CL, Ashmun RA, Williams RK, et al. Human aminopeptidase N is a receptor for human coronavirus 229E. *Nature*. 1992;357(6377):420-422. https://doi.org/10.1038/357420a0
44. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033-1034. https://doi.org/10.1016/S0140-6736(20)30628-0
45. Xu P, Zhou Q, Xu J. Mechanism of thrombocytopenia in COVID-19 patients. *Ann Hematol*. 2020;1-4.
46. Polat V, Bostancı Gİ. Sudden death due to acute pulmonary embolism in a young woman with COVID-19 [published online ahead of print, 2020 May 11]. *J Thromb Thrombolysis*. 2020;1-3: https://doi.org/10.1007/s11239-020-02132-5
47. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. *J Am Coll Cardiol*. 2020 Apr 15. pii: S0735-1097(20)35008-7. https://doi.org/10.1016/j.jacc.2020.04.031.
48. https://apps.who.int/iris/rest/bitstreams/1272156/retrieve
49. Thachil J, Tang N, Gando S. et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost*. 2020 May;18(5):1023-1026. https://doi.org/10.1111/jth.14810. Epub 2020 Apr 27.
50. http://www.hematology.org/covid-19/covid-19-and-coagulopathy
51. 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 Apr 11;150:w20247. 2020 Apr 6, https://doi.org/10.4414/smw.2020.20247. eCollection.
52. Marietta M, Ageno W, Artoni A, et al. COVID-19 and haemostasis: a position paper from Italian Society on Thrombosis and Haemostasis (SISET). *Blood Transfus*. 2020 Apr 8. https://doi.org/10.2450/2020.0083-20.
53. https://canadiancriticalcare.org/resources/Documents/Clinical%20Care%20COVID-19%20Guidance%20FINAL%20April2%20ENGLISH(1).pdf
54. https://www.sforl.org/wp-content/uploads/2020/03/WUHAN-Experience.pdf
55. www.gth-online.org
56. https://www.moh.gov.sa/Ministry/MediaCenter/Publications/Documents/MOH-therapeutic-protocol-for-COVID-19.pdf ((version 1.7) May 25th, 2020).
57. Moores LK, Tritschler T, Brosnahan S, et al. Prevention, diagnosis and treatment of venous thromboembolism in patients with COVID-19: CHEST Guideline and Expert Panel Report. *Chest*. 2020;158:1143-1163. https://doi.org/10.1016/j.chest.2020.05.559
58. Spyropoulos AC, Levy JH, Ageno W, et al. Subcommittee on perioperative, critical care thrombosis, haemostasis of the scientific, standardization committee of the international society on thrombosis and haemostasis. Scientific and standardization committee communication: clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost*. 2020;18(8):1859-1865. https://doi.org/10.1111/jth.14929
59. Piazza G, Morrow DA. Diagnosis, management, and pathophysiology of arterial and venous thrombosis in COVID-19. *JAMA*. 2020 Dec 22;324(24):2548-2549. https://doi.org/10.1001/jama.2020.23422. PMID: 33226423

How to cite this article: Ozsu S, Gunay E, Konstantinides SV. A review of venous thromboembolism in COVID-19: A clinical perspective. *Clin Respir J*. 2021;15:506–512. https://doi.org/10.1111/crj.13330