



Coagulation disorders and thromboembolic disease in COVID-19: review of current evidence in search of a better approach

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Abstract: The new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been an unprecedented global health problem, causing more than 20 million infections and more than 900,000 deaths (September 2020). The SARS-CoV-2 infection, known as COVID-19, has various clinical presentations, from asymptomatic or mild catarrhal processes to severe pneumonia that rapidly progresses to acute respiratory distress syndrome (ARDS) and multiple organ failure. In the last few months, much scientific literature has been devoted to descriptions of different aspects of the coagulation disorders and arterial and venous thrombotic complications associated with COVID-19, particularly venous thromboembolism (VTE). These studies have revealed that SARS-CoV-2 could lead to a prothrombotic state reflecting the high cumulative incidence of associated thrombotic events, particularly in patients admitted to intensive care units (ICUs). As regards the coagulopathy observed in association with SARS-CoV-2 infection, the mechanisms that activate coagulation have been hypothesized as being linked to immune responses, through the release of pro-inflammatory mediators that interact with platelets, stimulate the expression of tissue factor, induce an upregulation of plasminogen activator inhibitor-1, suppress the fibrinolytic system and lead to endothelial dysfunction, triggering thrombogenesis. D-dimer elevation has been recognized as a useful biomarker of poor prognosis, although the best cut-off point for predicting VTE in COVID-19 patients has still not been clarified. This review will try to update all the available scientific information on this important topic with enormous clinical and therapeutic implications.

Keywords: Pulmonary embolism (PE); coronavirus disease 2019 (COVID-19); D-dimer; thrombosis; inflammation

Submitted Sep 24, 2020. Accepted for publication Dec 18, 2020.

doi: 10.21037/jtd-20-3062

View this article at: <http://dx.doi.org/10.21037/jtd-20-3062>

Introduction

In December 2019, the Chinese authorities reported atypical pneumonia clusters of unknown etiology in Wuhan. On 7 January 2020, a novel coronavirus from the *Coronaviridae* family, the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was confirmed

as being responsible for the outbreak of these respiratory infections and then named coronavirus disease 2019 (COVID-19) (1-3).

COVID-19 has been an unprecedented global health problem, causing more than 25 million infections and more than 900,000 deaths [Centres for Disease Control and Prevention (CDC), World Health Organization

(WHO); September 2020]. SARS-CoV-2 seems to enter cells by endocytosis, through the binding of virus envelope glycoprotein to the angiotensin-converting enzyme-2 receptor found in the cells of upper airways, lungs, heart and gastrointestinal tract, as well as in the blood vessels (4). SARS-CoV-2 infection has various clinical presentations, from asymptomatic or mild catarrhal processes to severe pneumonia that rapidly progresses to acute respiratory distress syndrome (ARDS) and multiple organ failure (1). Preliminary reports have suggested that COVID-19 infection can produce coagulation disorders, mainly in more severe forms of presentation, and predispose to thrombotic events and both arterial and venous thrombosis (2,3,5-10). Furthermore, COVID-19 has commonly been associated with coagulopathy in most of the deceased patients. The data derived from all these publications on COVID-19-associated coagulopathy and thrombotic risk have generated doubts and controversy about the best strategy for the thromboprophylaxis, diagnosis and anticoagulant therapy of venous thromboembolism (VTE), as reflected in the variability of the recommendations published by different expert groups.

Therefore, this manuscript summarizes the current published literature regarding the key aspects of coagulation disorders and VTE risk in COVID-19, mainly focusing on pulmonary embolism (PE), and it addresses clinical issues in order to improve our approach to the prophylaxis, diagnosis and management of VTE in COVID-19 patients. We present the following article/case in accordance with the PRISMA reporting checklist (available at <http://dx.doi.org/10.21037/jtd-20-3062>).

Coagulation disorders associated with COVID-19

Various studies have suggested that SARS-CoV-2 induces coagulation disorders, which are associated with poorer outcomes. The most common pattern of coagulopathy is characterized by increased levels of fibrinogen and D-dimer, a slight rise in the prothrombin time (PT) and the activated partial thromboplastin time (aPTT), and a mild thrombocytopenia (2-9,11-14). Of all these factors, the D-dimer is the one most consistently associated with COVID-19. The very first series of hospitalized patients in China already presented elevated levels of D-dimer (≥ 0.5 mg/L) in 46% of the cases (2). One study has shown that COVID-19 patients present elevated levels of D-dimer, significantly higher than those found in healthy controls (15). Even more importantly, early studies identified

a greater frequency of elevated D-dimer in patients with more severe forms of presentation of COVID-19 (60% vs. 43%; $P=0.002$) (2,15,16). Moreover, a comparison of the D-dimer values at admission of the more severely ill patients who would require treatment in an intensive care unit (ICU) and those of the remaining COVID-19 patients confirmed that these values were higher in the former case (3,4). Along the same lines, Tang *et al.* found a relationship between mortality from COVID-19 and D-dimer values in a retrospective study, with these values being almost 3.5 times higher in deceased patients (2.1 vs. 0.6 mg/L; $P=0.001$) (7). Similarly, Zhou *et al.* published the data from a retrospective series of 191 patients hospitalized for COVID-19 in Wuhan (137 survivors, 54 non-survivors) and also found higher D-dimer values on admission in the group of deceased patients than in that of the survivors (5.2 vs. 0.6 mg/L; $P<0.001$), with a cut-off point of 1.0 mg/L an independent risk factor for mortality [multivariable analysis presented odds ratio (OR) 18.4; 95% confidence interval (CI): 2.6–128.6; $P=0.0033$] (8). A meta-analysis of 553 COVID-19 patients (22% admitted to the ICU) established a D-dimer cut-off point of 3.0 mg/L to identify severely ill patients (9). This correlation between the severity of the disease and the D-dimer values was also reported in another meta-analysis that found significantly higher D-dimer values in patients with ARDS compared to non-ARDS patients ($P<0.001$); moreover, within the group of ARDS patients itself, those who died presented higher D-dimer values than the survivors ($P<0.001$) (16).

Another significant marker of coagulation related to the prognosis is the PT. Higher PT values have been associated with both the need for ICU management and greater mortality (3,7,8).

In short, COVID-19 patients present coagulation disorders that are mainly defined by an elevated D-dimer, and this finding has proved to be associated with more severe forms of presentation, including ARDS and the need for an ICU, as well as a higher mortality rate.

Pathophysiology of COVID-19-associated coagulopathy

Both the relationship between inflammation and haemostasis and the activation of the coagulation cascade in infections are well known, and basically explained by the pathophysiology of the immune-thrombotic response in situations involving sepsis (*Figure 1*) (17). Sepsis is thus characterized by a pro-coagulant, pro-inflammatory and

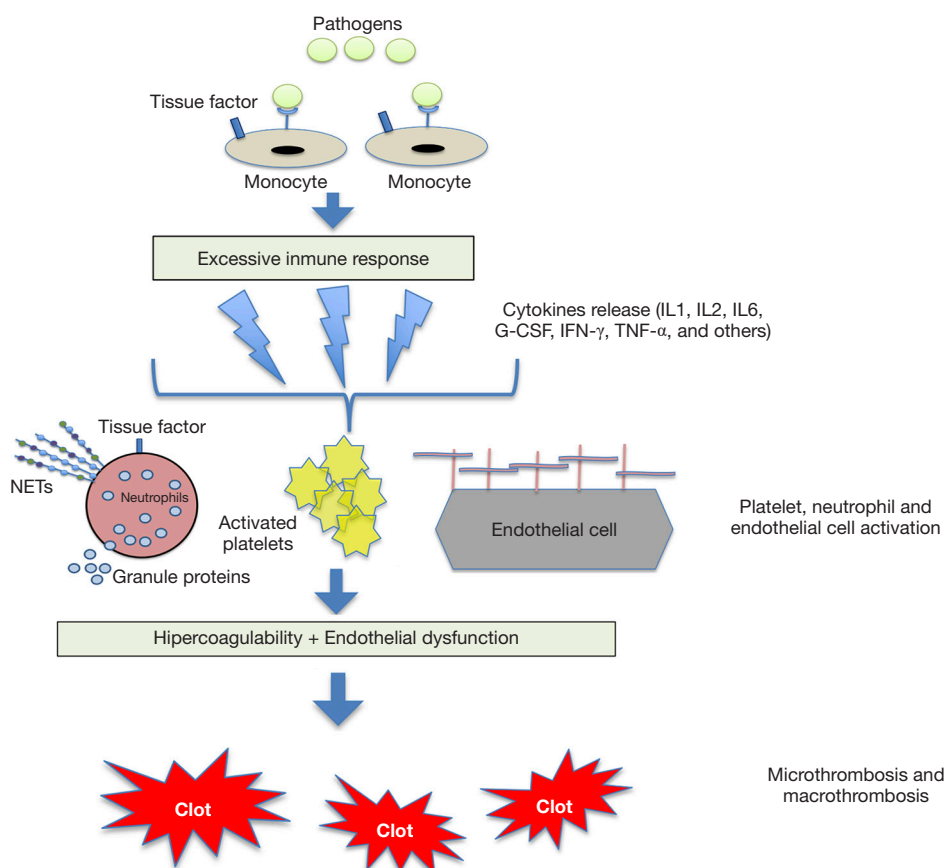


Figure 1 Pathophysiology of coagulation activation in sepsis. The pathogens and its components stimulate the monocytes via specific receptors situated on the surface of their cells. The activated monocytes produce a hyperimmune response with the release of various cytokines and other inflammatory mediators that activate platelets, neutrophils and endothelial cells. A state of hypercoagulability and endothelial damage that modifies the properties of the endothelium from an anticoagulant to a procoagulant state through the interruption of the glycocalyx and the expression of the von Willebrand factor (VWF). Neutrophils, in their turn, express tissue factor and release granulated proteins and other procoagulant mediators, such as neutrophil extracellular traps (NETs) comprised of procoagulant DNA, histones and other molecular patterns associated with cellular damage. All the above leads to the development of micro- and macrothrombotic phenomena. Adapted from ref (17) [with permission of Sociedad Española de Neumología y Cirugía Torácica (SEPAR) copyright]. G-CSF, granulocyte colony-stimulating factor; TNF, tumor necrosis factor; IFN, interferon; IL, interleukin; NETs, neutrophil extracellular traps.

anti-fibrinolytic state that involves many cell strains (such as monocytes, macrophages, neutrophils and the vascular endothelium). Pathogens bind to specific receptors of cells with innate immunity, triggering the release of various cytokines and other inflammatory biomarkers. Cytokines such as IL-6 and IL-8 act by activating the platelets and modifying the properties of the endothelium from an anti-coagulant to a pro-coagulant state by interrupting the glycocalyx and activating clotting factors (e.g., von Willebrand factor). Furthermore, the neutrophils express

tissue factor, trigger and initiate coagulative extrinsic cascades and release thrombotic mediators [e.g., neutrophil extracellular traps (NETs)] that enhance platelet activation (18-23).

The indiscriminate activation of this pathophysiological mechanism gives rise to the picture known as disseminated intravascular coagulation (DIC), which is characterized by the presence of thrombocytopenia, the consumption of coagulation factors and high levels of fibrin degradation products like D-dimer (18-20).

The mechanisms that activate coagulation in COVID-19 have not been fully clarified but they appear to be more closely related to the inflammatory response than the specific virulent properties of the germ (11). It has been shown, for example, that patients with severe SARS-CoV-2 infection present an excessive inflammatory response, with lymphopenia and high levels of ferritin, D-dimer and various cytokines (11,12). In fact, interleukin (IL)-6 plays a fundamental role in the activation of the extrinsic coagulation route (18). Accordingly, it has been postulated that this hyper-inflammatory response in COVID-19 patients, known as a cytokine storm, activates the coagulation cascade. The vascular endothelium seems to play a crucial role in this pathophysiological hypothesis of immuno-thrombosis or thrombo-inflammation, and data from studies in more severe patients support the existence of a link between inflammation and the pro-coagulant state (13). Finally, in contrast to the pattern observed in the classic DIC that occurs in sepsis, the thrombocytopenia associated with COVID-19 is mild and there is only a limited consumption of coagulation factors (11,12,23).

In short, the most severe forms of COVID-19 infection give rise to an immune hyper-response that is associated with coagulation disorders.

Pathophysiology of acute VTE in COVID-19 infection

The thrombotic risk entailed in COVID-19 infection is an emerging problem that has been tackled by numerous publications. VTE is a consequence of the interaction of different pro-thrombotic risk factors related to both the patient and the environment. COVID-19 patients often present risk factors for VTE, such as greater age and obesity, as well as hospitalization for an acute illness (24,25). However, any explanation of a greater thrombotic risk due to COVID-19 itself would suppose that it acts on the main etiopathogenic mechanisms known in VTE: hypercoagulability, endothelial dysfunction and venous stasis—Virchow's triad of the primary inducers of thrombus formation. The pathophysiological mechanisms underlying the association between COVID-19 and thromboembolic complications are still not completely understood, but they seem to involve inflammation, blood hypercoagulability, hypoxia, immobility and DIC, all of which could predispose to the development of thromboembolic complications (2,3,8,24,26-30).

As regards hypercoagulability, we have already seen that coagulation disorders (mainly elevated D-dimer) suggest the existence of a pro-coagulant state in COVID-19 patients, particularly those who are critically ill. Thrombosis is the final stage of inflammation. Therefore, hypercoagulability and the risk of thrombosis could be linked to local and systemic inflammation more than to direct damage from the virus itself (26).

Hypoxia is another factor that could be involved in the coagulopathy associated with COVID-19. It is characteristic of cases of severe pneumonia, and its role in the states of hypercoagulation and thrombosis has been extensively studied (31-33). The cellular response to hypoxia results in the activation of transcriptional factors such as activator protein-1 (AP-1), early growth response protein 1 (Egr-1) and hypoxia-inducible factors (HIF). The most fully investigated of these is HIF-1. Hypoxia leads to the activation of the transcription factor HIF-1, which is responsible for activating a series of proteins involved in the maintenance of vascular homeostasis (34), such as nuclear factor (NF)- κ B, vascular endothelial growth factor (VEGF) and erythropoietin (EPO). These proteins enhance a pro-coagulant state, as has been widely reported in cancer patients (35). Moreover, NF- κ B factor mediates the expression of genes encoding for inflammatory cytokines, tumor necrosis factor, chemokines, adhesion molecules and pro-coagulant factors, including the plasminogen activator inhibitor (PAI)-1 and tissue factor pathway inhibitor (36).

As regards the pathophysiology of endothelial dysfunction in COVID-19, pro-thrombotic changes in endothelial cells are the result of the inflammatory environment (*Figure 1*). Endothelial dysfunction causes the expression of chemo-attractants and adhesion molecules needed to activate monocytes and macrophages, thereby producing tissue factor. Tissue factor then triggers coagulative extrinsic cascades (16,31).

Some authors have suggested that infection by SARS-CoV-2 facilitates the induction of endotheliitis in the pulmonary vascular bed as a result of the rapid replication of the virus. This replication causes massive apoptosis of endothelial cells and triggers a loss of anti-coagulant function in the vascular lumen (26).

Lastly, venous stasis in COVID-19 patients is mainly justified by reduced mobility due to the illness.

In short, SARS-CoV-2 infection could provoke VTE through the three classic mechanistic pathways of Virchow's triad: hypercoagulability, endothelial dysfunction and venous stasis. The evidence that is currently available

suggests that inflammation could be the key factor in the pathophysiology of VTE in COVID-19 patients. Accordingly, the most seriously ill patients develop an inflammatory state that could encourage the development of thrombosis.

Microthrombosis in COVID-19 patients

COVID-19 patients often pass quickly to a situation of ARDS and multiple organ failure (2). The pathophysiology of ARDS in severe cases of SARS-CoV-2 infection has largely been attributed to a hyper-immune host response. Most of the series of necropsies conducted on patients who died from COVID-19 have shown signs of diffuse alveolar damage with atypical pneumocytes, as well as signs of diffuse microthrombosis on a peripheral level (4,37,38). These findings could explain the severe hypoxemia characteristic of SDRA in COVID-19 patients, the result of the ventilation-perfusion disorder and loss of the hypoxic vasoconstriction reflex; they would also support the hypothesis proposed by some authors that severe forms of COVID-19 are linked to endothelial dysfunction and microvascular thrombosis. Accordingly, the concept of MicroCLOTS (microvascular COVID-19 lung vessels obstructive thrombo-inflammatory syndrome) has been put forward as a pathophysiological hypothesis for the atypical SDRA associated with COVID-19 (39).

However, although this phenomenon of microthrombosis is characteristic of ARDS from COVID-19, it is not exclusive to it, as it is also frequently found in the intermediate evolutionary and proliferative phases of acute alveolar damage of any etiology, along with hyperplasia, atypia and mitosis of type II pneumocytes (40).

As regards acute coronary syndrome (ACS) in COVID-19 patients, plaque rupture has previously been reported in patients with viral disease and explained by vascular or plaque inflammation (41,42). On the one hand, none of the currently available data indicate any greater risk of thrombotic ACS; on the other hand, higher troponin levels in COVID-19 (a biomarker of myocardial injury) have been associated with greater severity (43,44).

Risk of acute VTE in COVID-19 patients

Seventeen studies have been published to date on the incidence of VTE in COVID-19 patients (Table 1) (45-60,62). Most of these works have included patients admitted to an ICU and were receiving thromboprophylaxis

(Figure 2).

Those studies that included patients admitted to a hospital ward who underwent an imaging test for suspected VTE presented an incidence of PE and/or deep venous thrombosis (DVT) below 5% (53,55). This rate of symptomatic VTE is not any higher than those obtained in early studies of patients without COVID-19 who were hospitalized for medical causes (63,64).

Critically ill patients have a high risk of developing VTE, with incidences ranging from 13 to 30% with no anti-thrombotic prophylaxis (65,66) and from 6% to 16% with thromboprophylaxis (67). Similarly, COVID-19 patients in an ICU present a high risk of VTE. Middeldorp *et al.* studied 198 patients with COVID-19, 74 (37%) of whom had been admitted to an ICU. The accumulated incidence of VTE at 14 days was higher in those patients in an ICU (48%; 95% CI: 33-61%) than in those in a hospital ward (10%; 95% CI: 3-24%) (53). One study that analyzed the results of all the computerized tomographies of pulmonary arteries performed on COVID-19 patients due to clinical suspicion of PE or an elevation in D-dimer found an accumulated incidence of PE of 24%. The incidence was significantly higher in patients in an ICU (50%; 95% CI: 30-70%) than in those in a hospital ward (18%; 95% CI: 12-27%) (58).

The prevalence of VTE in other studies that included critically ill COVID-19 patients varied from 9% to 54%, depending on methodological differences and the use of thromboprophylaxis and systematic screening for VTE (45,48,49,51,52,54,56,57,62). In one study by Cui *et al.* (45), the patients did not receive thromboprophylaxis and the prevalence of VTE was 25%. However, the highest incidence of VTE (54%) was found in a study by Llitjos *et al.*, even though up to 69% of the patients had received full doses of anti-coagulants. These results can be partially explained by the disease's severity in the cohort, the state of hypercoagulability and the performance of systematic screening for DVT in the lower limbs via sonography (54).

A French prospective study compared the incidence of thrombotic events in COVID-19 patients in an ICU (n=150) with non-COVID-19 patients in an ICU (n=150). By using propensity analysis, the authors found that patients with ARDS due to COVID-19 presented a higher risk of thrombotic events than the non-COVID-19 control group (12% vs. 5%; OR 2.6; 95% CI: 1.1-6.1%) (53).

The incidence rates of VTE in patients hospitalized for COVID-19 are therefore similar to those published in series investigating other diseases. Although COVID-19

Table 1 Frequency of VTE in patients with COVID-19 and related risk factors

First author, journal (reference)	Study design and country of its population	N, % males	Mean age	Patients in ICU (%)	Criteria for inclusion	Use of thromboprophylaxis	Indication for VTE imaging study	Rate of VTE	Risk factors related to VTE
Cui <i>et al.</i> , <i>J Thromb Haemost</i> (45)	Retrospective single-centre, China	81, 46%	60 yrs	100%	COVID-19 pneumonia, admission to ICU	No use of thromboprophylaxis	Not specified	25%, all as DVT	Aged, lymphopenia, prolonged aPTT, DD
Maatman <i>et al.</i> , <i>Crit Care Med</i> (46)	Retrospective, multi-centre, USA	109, 57%	61 yrs	100%	Confirmed COVID-19 pneumonia requiring ICU	All patients received thromboprophylaxis: enoxaparin 40 mg daily, enoxaparin 30 mg b/d or UFH 5,000 IU subcutaneous heparin every 8 h	Clinical suspicion	28%	Values at admission: Platelet count, aspartate aminotransferase lactate dehydrogenase, DD and troponin
Al-Samkari <i>et al.</i> , <i>Blood</i> (47)	Retrospective, multi-centre, USA	400, 57%	62 yrs	36%	Confirmed COVID-19 requiring hospitalization	97% received thromboprophylaxis: standard dose: 88.5%; intermediate- or full-dose: 8.8%	Not specified	4.8%	DD, fibrinogen, C-reactive protein, ferritin, and procalcitonin
Klok <i>et al.</i> , <i>Thromb Res</i> (48)	Retrospective, multi-centre, Netherlands	184, 76%	64 yrs	100%	COVID-19 pneumonia, admission to ICU	All patients with TP at standard dose with Nadroparin (regime varied according to centre)	Clinical suspicion (according to criteria of the clinician responsible)	15%. Accumulated incidence 7 days of 27% (95% CI: 17–37%)	Age, coagulopathy (PT >3 seconds and/or aPTT >5 seconds)
Klok <i>et al.</i> , <i>Thromb Res</i> (49)	Retrospective, multi-centre, Netherlands	184, 76%	64 yrs	100%	COVID-19 pneumonia, admission to ICU	All patients with TP at standard dose with Nadroparin (regime varied according to centre)	Clinical suspicion	37%. Accumulated incidence 14 days of 49% (95% CI: 41–57%)	Long-term anticoagulation was a protective factor
Alonso-Fernández <i>et al.</i> , <i>PLoS One</i> (50)	Prospective, single-centre, Spain	30, 63%	64 yrs	38%	Hospitalized for COVID-19 pneumonia and DD >1,000 ng/mL	Enoxaparin 40 mg daily: 27 (90%)	Elevated DD (>1,000 ng/ml)	15%	Age, DD, platelet count, C-reactive protein
Helms <i>et al.</i> , <i>Intensive Care Medicine</i> , preprint version (51)	Study of prospective cohort of consecutive patients, multi-centre, France	150, 81%	63 yrs	100%	COVID-19 pneumonia, admission to ICU	LMWH: prophylactic dose: 105 (70%); therapeutic dose: 45 (30%)	Clinical suspicion or rapid rise in DD	18%	Not studied
Longchamp <i>et al.</i> , <i>Res Pract Thromb Haemost</i> (52)	Retrospective, single-centre, France	25, 64%	68 yrs	100%	COVID-19 pneumonia, admission to ICU	24/25 (96%) patients were prescribed TP: UFH or enoxaparin at standard prophylactic dose	Lower-limb CCUS was systematically performed in all patients between days 5 and 10 after admission to the ICU. CTPA performed for clinical suspicion	32%	Not studied
Middeldorp <i>et al.</i> , <i>J Thromb Haemost</i> , version preprint (53)	Retrospective study of cohort of consecutive patients, single-centre, Netherlands	198, 66%	61 yrs	37%	Hospitalized for probable or confirmed COVID-19	All with nadroparin: <100 kg: 2,850/12 h; ≥100 kg: 5,700/12 h	CTPA for clinical suspicion; CCUS by randomized selection	17%. Accumulated incidence 14 days of 34%	UCI
Litjós <i>et al.</i> , <i>J Thromb Haemost</i> (54)	Retrospective study of cohort of consecutive patients, multi-centre, France	26, 77%	68 yrs	100%	COVID-19, admission to ICU	Heparin: prophylactic dose: 18 (69%); therapeutic dose: 8 (31%)	CCUS in all patients (day 1-3 and day 7). Study for PE if there is clinical suspicion	54%	Anticoagulation at prophylactic vs. therapeutic doses
Lodigiani <i>et al.</i> , <i>Thromb Res</i> (55)	Retrospective study of cohort of consecutive patients, single-centre, Italy	388, 68%	66 yrs	16%	Hospitalized for confirmed COVID-19	TP in all patients in ICU and in 75% of those in a hospital ward	Clinical suspicion or rapid rise in DD	7.7%. Accumulated incidence 21%	Not studied
Thomas <i>et al.</i> , <i>Thromb Res</i> (56)	Retrospective, single-centre, United Kingdom	63, 69%	59 yrs	100%	COVID-19, admission to ICU	All with Dalteparin adjusted to weight and renal function	Clinical suspicion	9.5%. Accumulated incidence 27%	Not studied
Poissy <i>et al.</i> , <i>Circulation</i> (57)	Retrospective, single-centre, France	107, unspecified	Unspecified	100%	COVID-19, admission to ICU	Antithrombotic prophylaxis with LMWH or UFH, with no specified dose or percentage of use in the complete cohort	Clinical suspicion due to respiratory and/or acute hemodynamic deterioration	20.6%. Accumulated incidence at 15 days of 20.4%	DD, activity of factor VIII, levels of VWF
Bompard <i>et al.</i> , <i>Eur Respir J</i> (58)	Retrospective, multi-centre, France	135, 70%	64 yrs	18%	COVID-19 with pneumonia, with CTPA performed	TP with enoxaparin 40 mg/d in all hospitalized patients (53% of total)	Clinical suspicion and/or elevated DD	24%	DD, ICU, MV

Table 1 (continued)

Table 1 (continued)

First author, journal (reference)	Study design and country of its population	N, % males	Mean age	Patients in ICU (%)	Criteria for inclusion	Use of thromboprophylaxis	Indication for VTE imaging study	Rate of VTE	Risk factors related to VTE
Demelos <i>et al.</i> , <i>Thromb Res</i> (59)	Prospective observational, single-centre, Spain	156, 65%	68 yrs	10%	Hospitalized for COVID-19 ≥2 days, >18 years, DD >1,000 ng/mL	TP with enoxaparin 40 mg/d or bemiparin 3,500 UI/d in 153 patients (98%)	CCUS in all patients	15%. All as DVT: 1 proximal DVT proximal and 22 distal DVT	DD
Poyiadi <i>et al.</i> , <i>Radiology</i> (60)	Retrospective observational, multi-centre, USA	328, 46%	61 yrs	25% ICU	Confirmed COVID-19 (PCR of nasopharyngeal swab) and adequate CTPA	Not studied	CTPA in all patients	22%	BMI >30 kg/m ² , DD ×6 times ULN, history
Mouhat <i>et al.</i> , <i>Eur Respir J</i> (61)	Retrospective, observational, single-centre, France	162, 67%	66 yrs	42% ICU	Hospitalized for COVID-19 and CTPA performed for severe disease (SpO ₂ <94% in room air or BR >29/min)	Anticoagulants in 87% (preventive dose in 74%, therapeutic doses in 13%): LMWH in 85%; UFH in 8%; oral anticoagulant: 7%	All included patients underwent a CTPA for clinical signs of severe disease.	27%	DD >2,590 ng/mL. Lack of any anticoagulant therapy

aPTT, activated partial thromboplastin time; BMI, body mass index; CCUS, compression Doppler ultrasound; BR, breathing rate; COVID-19, coronavirus disease 2019; CTPA, computed tomography pulmonary angiogram; DD, D-dimer; DVT, deep venous thrombosis; ICU, intensive care unit; LMWH, low molecular weight heparin; MV, mechanical ventilation; PE, pulmonary embolism; PT, prothrombin time; RCP, polymerase chain reaction; SpO₂, oxygen saturation; TP, thromboprophylaxis; UFH, unfractionated heparin; ULN, upper limit of normal; USA, United States of America; VTE, venous thromboembolism; VWF, von Willebrand factor.

COVID-19 INFECTION											
Admitted in ICU			Not admitted in ICU			Prophylactic treatment			No Prophylactic Treatment*		
8	Number of studies	7	13	Number of studies	2						
745 (25-184)	Patients (sum)	1,636 (30-400)	1,900 (25-388)	Patients (sum)	481 (81-400)						
66 (59-68)	Age (mean and range)	63.7 (61-68)	64.3 (59-68)	Age (mean and Range)	61 (60-62)						
67% (46-81)	Males (mean % and range)	62% (46-70)	68.5% (57-81)	Males (mean % and range)	51.5% (46-57)						
28% (9.5-54)	INCIDENCE OF VTE (mean % and range)	15.1% (4.8-24)	23.4% (7.7-37)	INCIDENCE OF VTE (mean and range)	14.9% (4.8-25)						

* Only 2 studies without pharmacological thromboprophylaxis

Figure 2 Rates of VTE in patients with COVID-19 infection according to admission to ICU or not (right) or use of pharmacological thromboprophylaxis or not (left). VTE, venous thromboembolism; COVID-19, coronavirus disease 2019; ICU, intensive care unit.

patients in an ICU did present an increased risk of VTE, it is not completely clear whether this is greater than the risk to patients who are critically ill with other diseases (65-67).

VTE prophylaxis in COVID-19 patients

The prevalence of VTE in patients hospitalized for acute diseases is approximately 10-20%, and consequently the guidelines for clinical practice recommend the use of pharmacological thromboprophylaxis in those patients with a high thrombotic risk, as identified by means of well validated scales [e.g., Caprini score, Padua model, IMPROVE (International Medical Prevention Registry on Venous Thromboembolism)] (24,68-72). The use of prophylactic anticoagulation has been shown to reduce the risk of VTE in acutely ill hospitalized patients, including those hospitalized for infections (e.g., pneumonia). Similarly, VTE risk stratification and in-hospital pharmacological VTE prophylaxis should be applicable for hospitalized COVID-19 patients (71-75). However, some publications have reported that anticoagulant therapy at prophylactic doses may be inadequate for controlling the increased risk of VTE in patients hospitalized for COVID-19 (76).

The authors of a study including 1,026 patients hospitalized for COVID-19 evaluated the baseline thrombotic risk by means of the Padua prediction model and they found that up to 40% of the patients presented a high risk of VTE (Padua score >4) (77). Moreover, in a

work of Tang *et al.*, a cohort of 449 patients hospitalized for severe COVID-19 showed that the use of heparin at a prophylactic dosage for at least 7 days was associated with reduced mortality in a subgroup of patients with criteria for sepsis-induced coagulopathy (sepsis-induced coagulopathy score ≥ 4) or with very elevated D-dimer (>3 mg/L) (78).

Table 2 summarizes the main recommendations of international organizations and scientific societies for thromboprophylaxis in COVID-19 patients (79-85). On the basis of the evidence currently available, the various consensual documents that have been published propose the early use of VTE prophylaxis, unless there are contraindications, in COVID-19 patients requiring admission to a hospital and, more especially, an ICU. Some authors and scientific societies have proposed the use of intermediate- or full-dose parenteral anticoagulation for the routine care of ICU COVID-19 patients, even if VTE has not been confirmed, according to the (as yet undemonstrated) hypothesis of a potential benefit in the prevention of microvascular thrombosis (48,78,83,85). Besides, it has been proposed that anticoagulants could help to reduce not only procoagulant effects in inflammatory conditions but could also reduce proinflammatory stimuli via reduced expression of cytokines and chemokines (86).

One study of critically ill (non-COVID) patients with sepsis found that prophylactic anticoagulation at a standard dose fails in 12% of patients. It also observed a beneficial effect from the use of high doses of LMWH on gas

Table 2 Guidelines and recommendations for thromboprophylaxis in COVID-19 patients

Organization/scientific society	COVID-19 patients	Recommendations of thromboprophylaxis
World Health Organization (WHO) (75)	Severe, acute respiratory infection	LMWH (preferably); unfractionated heparin 5,000 UI/12 h; intermittent pneumatic compression if pharmacological anticoagulation is contraindicated
International Society on Thrombosis and Haemostasia (ISTH) (74)	Out-patient mild disease	Encouragement of greater mobility; individualized stratification of the thrombotic and hemorrhagic risk
	Hospitalized moderate or severe disease with no DIC	Individualized stratification of the thrombotic and hemorrhagic risk; prophylactic doses of LMWH (preferably) or UFH; mechanical thromboprophylaxis (intermittent pneumatic compression) if pharmacological anticoagulation is contraindicated; therapeutic anticoagulation or intermediate doses not recommended in the absence of confirmed VTE
	Hospitalized moderate or severe disease with DIC	Every patient must receive prophylactic anticoagulation unless there are contraindications (active bleeding and platelet count $<25 \times 10^9/L$); therapeutic anticoagulation or intermediate doses not recommended in the absence of confirmed VTE; pharmacological thromboprophylaxis considered at discharge for up to 45 days
American Sociedad Americana de Hematología (ASH) (76)	Hospitalized	All patients must receive pharmacological thromboprophylaxis with LMWH or Fondaparinux (preferable to UFH to reduce contact), unless there is a major risk of hemorrhage; fondaparinux in cases of heparin-induced thrombocytopenia; mechanical thromboprophylaxis if pharmacological anticoagulation is contraindicated; anticoagulation at therapeutic doses not recommended in the absence of confirmed VTE
Sociedad Española de Hemostasia y Trombosis (SETH) (79)	Infection without major risk factors for thrombosis	LMWH with adjustment of dose to weight and kidney function
		Creatinine clearance $>30 \text{ mL/min}$
		Enoxaparin
		<80 kg: 40 mg/24 h; 80–100 kg: 60 mg/24 h; >100 kg: 40 mg/12 h
		Tinzaparin
		<60 kg: 3,500 UI/24 h; >60 kg: 4,500 UI/24 h
		Bemiparin
		3500 UI/24 h
		Nadroparin
		0.3 mL/24 h
		Dalteparin
		5,000 UI/24 h
		Fondaparinux if there is allergy to heparin or heparin-induced thrombocytopenia
		Creatinine clearance $>50 \text{ mL/min}$
		Creatinine clearance <50 and $>20 \text{ mL/min}$
Creatinine clearance $<20 \text{ mL/min}$		
Infection with major risk factors for thrombosis	LMWH with adjustment of dose to kidney function	
	Creatinine clearance $>30 \text{ mL/min}$	
	Enoxaparin	
	1 mg/kg/24 h	
	Tinzaparin	
	75 UI/kg/24 h	
	Bemiparin	
	5,000 UI/24 h	
	Nadroparin	
	<70 kg: 0.4 mL/24 h; >70 kg: 0.6 mL/24 h	
	Dalteparin	
	5,000 UI/24 h	
	Fondaparinux if there is allergy to heparin or heparin-induced thrombocytopenia:	
	Creatinine clearance $>50 \text{ mL/min}$	
	Creatinine clearance <50 and $>20 \text{ mL/min}$	
Creatinine clearance $<20 \text{ mL/min}$		
Thrombosis UK (77)	Hospitalized	Evaluation of thrombotic risk in all the patients (NICE/ ASH). LMWH, unless contraindicated, if there is immobilization and criteria of severity: Creatinine clearance >30 : LMWH or Fondaparinux s.c. Creatinine clearance <30 : UFH 5000 UI s.c. or low dose of LMWH. All patients with complete immobilization are recommended intermittent pneumatic compression, as well as pharmacological thromboprophylaxis. Mechanical thromboprophylaxis exclusively if platelets $<30,000$ or bleeding
Working Group on Cardiovascular Thrombosis of the Sociedad Española de Cardiología (77)	Hospitalized	All hospitalized patients must receive LMWH; adjustment of the dose is recommended in BMI >35 and after evaluating the hemorrhagic risk and the platelet count. In patients with criteria of severity and high thrombotic risk, LMWH is recommended at intermediate/extended or therapeutic doses, following an evaluation of the hemorrhagic risk. Prolongation of LMWH at prophylactic doses for 7–10 days after the hospital discharge
British Thorax Society (BTS) (80)	Low risk	Weight-adjusted prophylactic dose (e.g., 70 kg with creatinine clearance $>30 \text{ mL/min}$: Dalteparin 5,000 UI/day, enoxaparin 40 mg/day)
	High risk	LMWH at intermediate doses (e.g., 70 kg with creatinine clearance $>30 \text{ mL/min}$: Dalteparin 5,000 UI/12h, enoxaparin 40 mg/12h)

COVID-19, coronavirus disease 2019; BMI, body mass index; DIC, disseminated intravascular coagulation; LMWH, low molecular weight heparin; NICE, National Institute for Health and Care Excellence; UFH, unfractionated heparin; VTE, venous thromboembolism.

exchange ($\text{PaO}_2/\text{FiO}_2$) in a subgroup of patients with ARDS who received high doses of LMWH (87). The existing data are still very limited, however, and the optimal anticoagulant dose in patients with severe COVID-19 remains unknown, and so further prospective investigation is required.

Similarly, further research needs to be conducted on the use of weight-adjusted thromboprophylaxis in COVID-19 patients, as there have been no studies on this topic to date. Its use has probably been justified by the fact that overweight patients were underrepresented in the pivotal clinical trials (63–65,88,89) and in the data obtained in a systematic review of obese patients who underwent bariatric surgery, which showed a (not statistically significant) trend towards a reduction in VTE events in individuals who received weight-adjusted thromboprophylaxis (0.5% *vs.* 2.0%), without any increase in the risk of hemorrhage (1.6% *vs.* 2.3%) (90).

Another point of controversy is the use of extended thromboprophylaxis after hospitalization in COVID-19 patients (91). Studies of extended thromboprophylaxis in patients with acute diseases have not demonstrated any net beneficial effect, and the current guidelines for clinical practice only recommend its use during a patient's hospitalization (61,92). In the case of COVID-19 patients, although there is no still evidence about the risk of post-discharge VTE and major bleeding rates in COVID-19, some experts have suggested the possibility of individualizing the use of extended VTE prophylaxis (for a month, or even 45 days) considering the net benefit between risk factors for VTE (e.g., reduced mobility, obesity, previous VTE, active cancer, etc.) and low risk of hemorrhage (24,93).

At the moment, there is evidence available on the role of thromboprophylaxis in a patient who presents concomitant mild COVID-19 and significant comorbidities but has not been hospitalized. The consensus document by Bickdeli *et al.* on patients confined with mild COVID-19 without requiring hospital admission recommends encouraging mobility and considering individualized pharmacological prophylaxis in those with a high risk of VTE and a low risk of hemorrhage (27).

Mechanical prophylaxis with intermittent pneumatic compression should only be used in immobilized patients if pharmacological prophylaxis is contraindicated (94).

Furthermore, it must be remembered that the main complication associated with anticoagulant treatment is bleeding. A recent multicentre retrospective study has assessed the rate of bleeding in 400 patients hospitalized

for COVID-19 (144 critically ill), all receiving standard-dose prophylactic anticoagulation. The authors found that the overall and major bleeding rates were 5% (95% CI, 2.9–7.3%) and 2% (95% CI, 1.0–4.2%), respectively, almost all in critically ill patients (47).

In any case, there are no reliable data at present on the real rate of thrombotic and hemorrhagic events in COVID-19 patients, and neither do we know the efficacy and safety of the various strategies used for thromboprophylaxis, or the risk profiles involved. We therefore need results from well-designed clinical studies that would show the benefits of different strategies of anticoagulants in COVID-19 patients (clinicaltrials.org), although this could vary according to patients' specific individual characteristics (e.g., thrombotic risk factors, disease severity) (Table 3).

Diagnosis of acute VTE in COVID-19 patients

VTE is diagnosed via well-validated algorithms that combine scales of clinical probability (e.g., Wells, Geneva, YEARS), D-dimer results and imaging tests (29). A normal D-dimer value rules out a diagnosis of VTE in patients with a low or intermediate clinical suspicion. An imaging test is required to confirm the diagnosis in patients with a high clinical probability (due to the low negative predictive value of D-dimer in this subgroup) or a positive D-dimer value (due to the low specificity of D-dimer for the diagnosis of VTE) (24,93).

However, as mentioned above, an elevated D-dimer level is a common finding in COVID-19 patients (2–4,6,7,14) and the classic cut-off point (0.5 mg/L) excludes very few patients from the need for a confirmatory imaging test, computed tomography pulmonary angiogram (CTPA) and/or lower-limb ultrasound (in the case of clinical suspicion of PE and/or DVT, respectively). Moreover, bedside cardiac ultrasound could be worth considering in patients with hemodynamic instability, to assess for signs of right ventricular dysfunction and, in exceptional cases, the presence of a clot in transit (24,95). Given the lack of specificity of the respiratory symptoms in COVID-19 patients (particularly the most seriously ill), experts have recommended a high degree of clinical suspicion, particularly when there is any deterioration on a respiratory (e.g., hypoxemia disproportionate to lung involvement) or hemodynamic level (acute unexplained right ventricular dysfunction) (25,96).

Furthermore, it must be borne in mind the risk of

Table 3 Future challenges for the study of thrombotic risk in COVID-19 patients

Variable	Challenges
Pathophysiology	To assess which elements of coagulation and other biomarkers (mainly inflammatory biomarkers) are associated with the development of VTE, as well as factors that modulate this association To find the best biomarkers for predicting the development of VTE complications
Epidemiology	To prospectively determine the real incidence of VTE in population-based studies, in out-patient vs. hospitalized patients, and according to the severity of COVID-19 Follow-up studies of international registers of COVID-19 patients to evaluate their risk of VTE To determine the risk of VTE in pregnant COVID-19 patients
Prevention of VTE	To determine the optimal risk stratification for consideration of VTE prophylaxis To assess the efficacy and safety of different anticoagulant doses (prophylactic doses and others) to find the optimal anti-thrombotic strategy, preferably through RCT To assess the efficacy and safety of antiplatelet agents for VTE prevention, preferably through RCT To determine whether the impact of clinical, analytical and/or imaging characteristics should be considered to indicate the dose and time of thromboprophylaxis, preferably through RCT (e.g., weight-adjusted prophylactic dosing) To assess the efficacy and safety of extended (post-discharge) thromboprophylaxis, preferably through RCT To assess the impact of pharmacological thromboprophylaxis in pregnant COVID-19 patients, and during the postpartum period
Diagnosis of VTE	To determine the most appropriate diagnostic algorithm of incident thrombotic events for patients with suspected VTE and COVID-19 infection To prospectively assess the efficacy of classical predictor scores to identify VTE among COVID-19 patients (e.g., Well score, Geneva score) To develop and validate a novel specific score to predict VTE among hospitalized COVID-19 patients
Treatment of VTE	To assess the efficacy and safety of anticoagulant therapy through RCT To assess the utility of reperfusion treatments (e.g., systemic thrombolysis, surgical embolectomy) in patients with concomitant COVID-19 and acute PE with hemodynamic instability To assess the potential drug-drug interactions between anticoagulants and routine COVID-19 therapies
Outcomes of VTE	To assess the impact of acute VTE in outcomes of COVID-19 patients (e.g., survival, post-COVID-19 syndrome) To assess the risk of persistent symptoms of exercise intolerance and dyspnea (post-PE syndrome including CTED and CTEPH) during the follow-up (>3 months of anticoagulant therapy) in COVID-19 patients with concomitant PE vs. without concomitant PE To evaluate the risk of recurrent VTE after stopping anticoagulation

COVID-19, coronavirus disease 2019; CTED, chronic thromboembolic disease; CTEPH, chronic thromboembolic pulmonary hypertension; PE, pulmonary embolism; RCT, randomized clinical trials; VTE, venous thromboembolism.

transmitting infection to health care workers who perform these imaging tests or other patients, with the added difficulty that some patients could be required to be in a prone position for severe ARDS.

One recent retrospective study on 162 patients hospitalized for COVID-19 pneumonia with clinical signs of severity who underwent CTPA in order to rule out PE analyzed the predictive value of D-dimer for the diagnosis of PE. A

D-dimer cut-off value of 2.59 mg/L was identified as the best for predicting the occurrence of PE (AUC: 0.88, $P < 0.001$, sensitivity 83.3%, specificity 83.8%) and it was associated with a 17-fold increase in the adjusted risk of PE (62).

Treatment of acute VTE in COVID-19 patients

Therapeutic anticoagulation is currently the treatment of

choice for confirmed VTE (24) although, as mentioned above, there is insufficient scientific evidence to support the use of full-dose anticoagulation in COVID-19 patients. The choice of agents and dosage for the treatment of incident acute VTE in hospitalized COVID-19 patients should be based on current guidelines, but the pharmacological interactions between some COVID-19 therapies and oral anticoagulants [both vitamin K antagonists (VKA) and direct oral anticoagulants (DOAC)], and the difficulties involved in performing regular out-patient controls of the activity of VKAs render LMWHs in monotherapy the anticoagulant treatment of choice, at least during the first weeks after the thrombotic episode (72). Parenteral anticoagulation has the advantages that it can be withdrawn temporally, does not need to be monitored and has not demonstrated any drug-drug interactions with routine COVID-19 therapies. Furthermore, a daily dosing regimen of LMWH could have the benefit over unfractionated heparin of reducing health care workers' risk of exposure (27,97). Using oral anticoagulation with DOACs also may offer some potential advantages, such as easier out-patient management, reduced contact between health care workers and patients and a lack of any need for monitoring (24,27).

One topic of particular interest is the option of therapeutic anticoagulant management for patients with a diagnosis of incidental acute PE with isolated sub-segmental filling defects in the CTPA. Some recent publications have shown that the incidental acute PE found in COVID-19 patients is characterized radiologically by an overall thrombotic load that is low (as assessed by the Qanadli index), less extensive and predominantly peripheral (more frequently involving only sub-segmental branches), so this issue acquires a special significance in the handling of these patients (98,99). The current guidelines, mostly based on expert opinions due to limited data, indicate that the clinical relevance of the CTPA diagnosis of sub-segmental PE remains unknown, although anticoagulant treatment is recommended in cases of single sub-segmental PE in a hospitalized patient and/or multiple sub-segmental PE (29).

Invasive treatment for acute VTE in COVID-19 patients (e.g., catheter-directed therapies, surgical embolectomy) must be restricted to situations backed by more evidence, due to the risk of contagion to both other patients and health care workers, and the prevailing guidelines must be followed. For example, the placement of an inferior vena cava filter is an adequate treatment for VTE in a setting with absolute contraindications (24).

As regards those patients hospitalized for COVID-19

who received previous oral anticoagulant treatment (atrial fibrillation, valvulopathy, VTE, etc.), a change to HBPM at therapeutic doses is recommended, to avoid any pharmacological interactions with the drugs used to treat COVID-19 and facilitate the hospital management of patients who are potentially seriously ill or vulnerable. This change is proposed until the clinical picture is resolved and/or the pharmacological interaction has finished, bearing in mind the half-life of the drugs involved (84).

Future challenges

The issue of COVID-19 infection and coagulation disorders/ thrombotic risk is one of the most important aspects that need more extensive and higher-quality data if the management of COVID-19 patients is to be improved. The data currently available is still very limited, and there are gaps in our knowledge that require further research. The challenge now is to adequately fill these gaps. *Table 3* shows some of the studies that will be required for this purpose in the future.

All these issues provide opportunities for improving the management of these patients and for answering questions that are having such an enormous clinical impact. Close collaboration will be required between VTE and COVID-19 working groups.

Conclusions

The research now emerging highlights the complex interactions between COVID-19 infection and thrombotic disease. COVID-19 infection induces a pro-thrombotic state, secondary to the organism's hyper-inflammatory response and to hypoxia, which can predispose to an increased incidence of venous thrombotic events, particularly in the most severely ill patients. The results presented in recent scientific publications on the coagulopathy associated with COVID-19 and the risk of thrombotic events have triggered debate and controversy about the optimal strategy for the prophylaxis, diagnosis and anti-thrombotic treatment of VTE, as reflected by the divergences in the recommendations published by various scientific organizations and societies. It is still not clear whether the failure rate of pharmacological thromboprophylaxis is higher in critically ill COVID-19 patients than in others who are critically ill from other diseases; this doubt has led some authors to recommend the use of thromboprophylaxis at intermediate doses

or therapeutic anticoagulation in this patient profile, although we would need to have results from the clinical trials current underway to endorse these proposals. The diagnosis of VTE in COVID-19 patients presents certain difficulties and traits that must be taken into account, such as the risk of contagion of other patients and of health care workers and the overlap of respiratory symptoms that can be explained by both respiratory infection and the presence of acute PE. While we await the definition of the diagnostic algorithm for VTE most suited to patients hospitalized for COVID-19, it seems reasonable to maintain a high degree of clinical suspicion of PE and/or DVT in these patients, in order to determine the optimal antithrombotic treatment. The treatment of incidental VTE in patients with pneumonia due to SARS-CoV-2 should follow the recommendations proposed by the scientific societies, taking into account the benefits to these patients of parenteral anticoagulant treatment, at least during their hospital stay.

To conclude, there is a critical need for rigorous, well-powered studies that will determine the optimal algorithm for the diagnosis of incident VTE in COVID-19 patients and the impact of anticoagulants and antiplatelet agents on the primary and secondary prevention of VTE in these patients. Future studies could benefit from the careful identification of subgroups most likely to present thrombotic complications, as well as from larger sample sizes and the incorporation of predictive scores.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at <http://dx.doi.org/10.21037/jtd-20-3062>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jtd-20-3062>). All authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: García-Ortega A, de la Rosa D, Oscullo G, Castillo-Villegas D, López-Reyes R, Martínez-García MÁ. Coagulation disorders and thromboembolic disease in COVID-19: review of current evidence in search of a better approach. *J Thorac Dis* 2021;13(2):1239-1255. doi: 10.21037/jtd-20-3062