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## Review article

# Venous thromboembolism in patients with COVID-19 infection: risk factors, prevention, and management

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## ARTICLE INFO

## ABSTRACT

**Abstract:** Venous thromboembolic complications have emerged as serious sequelae in COVID-19 infections. This article summarizes the most current information regarding pathophysiology, risk factors and hematologic markers, incidence and timing of events, atypical venous thromboembolic complications, prophylaxis recommendations, and therapeutic recommendations. Data will likely to continue to rapidly evolve as more knowledge is gained regarding venous events in COVID-19 patients.

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## 1. Introduction

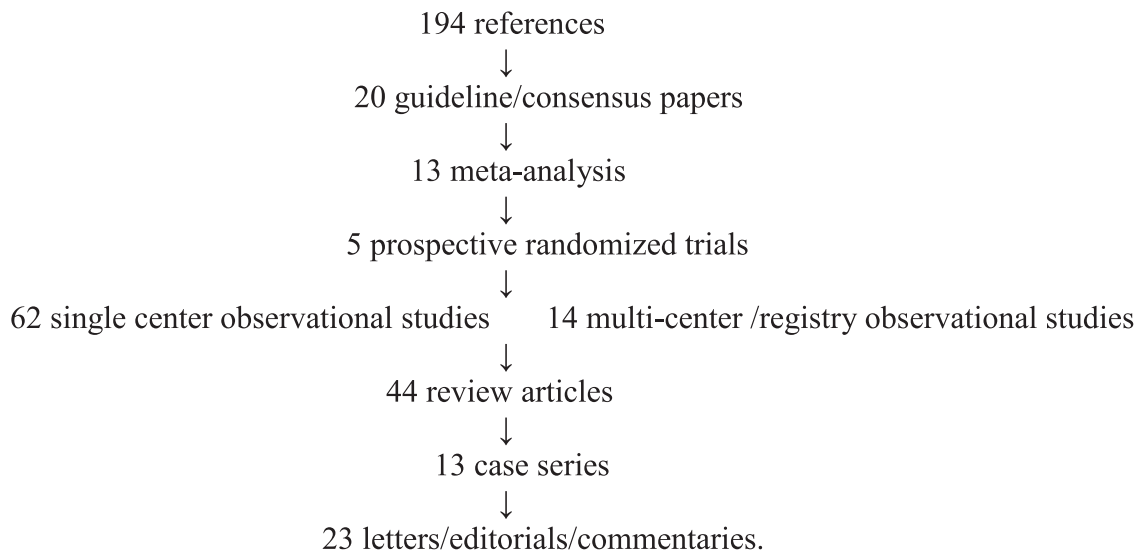
Primary complications associated with the coronavirus disease 2019 (COVID-19) virus have included pneumonia of atypical severity, respiratory failure, shock, and multi-organ dysfunction. In addition, COVID-19 is also associated with hypercoagulability, predisposing patients to arterial and venous thromboembolism. The true incidence of venous thromboembolic events (VTEs) in patients with COVID-19 remains unknown, with studies showing variable rates of 10% to 70%. However, it is becoming clearer that VTEs in patients with COVID-19 are associated with increased morbidity and mortality [1–3]. Parameters for screening, diagnosis, treatment, and outcomes associated with COVID-19 VTEs have rapidly

evolved during the course of the pandemic. This article will provide a comprehensive overview of current data.

We performed a review of the literature using Medline and PubMed. The Medline search was completed using title terms COVID-19 and SARS CoV-2, along with truncated terms *Thrombo*\$, *Hypercoag*\$, and *Coagulat*\$. These were combined with subject terms *coagulopathy*, *anticoagulation*, *thromboembolism*, *thrombophilia*, and *blood coagulation disorders*. Both general and narrower terms within the blood coagulation disorder were incorporated. These results were combined with risk factors. The PubMed search was completed using the terms *COVID-19 coagulopathy*, *venous thrombotic events: pulmonary embolism*, *deep vein thrombosis*, *atypical venous thrombosis*, *pathophysiology*, *incidence*, *risk factors*, *diagnosis*, *clinical management*, *prophylaxis*, *anticoagulation*, and *outcomes*. The review was completed through January 2021 and limited to humans and English language. This mapping strategies yielded 194 references, of which title and abstract (when available) were re-

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**Fig. 1 – Flow chart of references obtained from research strategy for venous thromboembolic events in COVID-19.**

viewed to determine relevance. A summary flow chart is presented in [Figure 1](#). A full review was completed in 101 publications included in this review.

We also reported results from our own study, which evaluated the incidence and outcomes of VTEs in 334 hospitalized patients with COVID-19 in the first COVID-19 peak period. This study was conducted at one of our university-affiliated, tertiary care medical centers during the period March 1 through May 31, 2020 and included all hospitalized patients. The study was approved by the University Institutional Review Board, as well as the medical center in which it was conducted. The electronic medical records of all hospitalized patients with COVID-19 ( $n = 334$ ) were reviewed for demographic characteristics; comorbidities; laboratory results at admission and at time of greatest derangement; diagnostic studies; prophylaxis and anticoagulation; type, initiation, and duration of treatment; need, type, and duration of oxygen supplementation; intensive care unit (ICU) admission and length of stay; need for ventilator support; all complications; VTEs, categorized as arterial thrombosis, stroke, myocardial infarction (MI), deep vein thrombosis (DVT), pulmonary embolism (PE) or combined; time of VTE diagnosis; mortality; and hospital length of stay. The data were analyzed using SPSS software, version 26 (IBM Corp). Univariate analysis was completed using chi-square for categorical variables and independent Student *t*-test for continuous variables. Logistic regression was performed to identify risk for VTEs and mortality. Variables found to be significant by chi-square or those thought to be clinically applicable were included in the models. Significance was set at  $P < .05$ .

## 2. Pathophysiology and etiology

The pathophysiology underlying the hypercoagulability in COVID-19 is incompletely understood, but emerging evidence suggests that the process is inflammatory-mediated and bidirectional [4]. Severe alveolar inflammation leads to inflamma-

tory thrombosis of the pulmonary vasculature and an overall state of hypercoagulability, which in turn induces further inflammation [5–8]. It is increasingly believed that the initial insult leading to hypercoagulability results from dysregulation of the renin-angiotensin system. Typically, angiotensin II (ANGII) binds to angiotensin type I receptor (AT1R) to produce vasoconstriction; angiotensin-converting enzyme 2 (ACE2) counteracts the process by binding with and inactivating ANGII to produce dilatation. ACE2 receptors are abundant in lung, cardiac, renal, and gastrointestinal tissue. The COVID-19 virus has great affinity for ACE2 and attaches to the receptors on the alveolar endothelial membrane via its S spike, triggering an intense proinflammatory response and subsequently a prothrombotic environment [9,10]. Binding of COVID-19 to ACE2 decreases availability of the enzyme and disrupts the cycle by which it degrades ANGII. Effectively, increased levels of ANGII become available to bind with AT1R, which stimulates interleukin-6 (IL-6) release causing inflammation and lung injury [11,12]. Hypercoagulability may ensue because ANGII/AT1R also induces tissue factor and plasminogen activator inhibitor [13,14]. Patients with increased ANGII levels are at higher risk for severe disease; a direct correlation between viral load, lung injury, and ANGII levels has been reported [10]. High levels of other thrombotic and inflammatory markers, such as D-dimer, C-reactive protein (CRP), lactate dehydrogenase, ferritin, and IL-6 have been documented as well [15]. Multiple inflammatory pathways have been implicated in the development of thrombo-inflammation, including cytokines, acute-phase reactants, and inflammatory cell-mediated cellular injury. Elevated levels of IL-6, IL-7, tissue necrosis factor, and chemokines have been reported, which create prothrombotic environments through activation of monocytes, neutrophils, and the endothelium [16,17].

Mononuclear phagocytes have been found to be more prominent in bronchial alveolar fluid of patients with more severe disease and may play a role in the development of thrombotic complications [18]. Activated monocytes stimulate tissue factor expression, which triggers the clotting cascade to

produce thrombin, which subsequently leads to thrombus formation, platelet activation, and further augmentation of inflammatory pathways [12,19].

Elevated levels of neutrophil extracellular traps have been reported with COVID-19, occurring more commonly in hospitalized patients, particularly those requiring mechanical ventilation [20]. It is postulated that abnormal activation of neutrophils and production of NET may contribute to cytokine storm and adverse sequelae of severe disease, such as organ damage, widespread thrombosis, and death [21,22]. Alternatively, Gan et al [23] proposed that ANGII rather than cytokine storm may be responsible for the widespread vascular injury that results from endothelial damage, thrombosis, and vasoconstriction. They further suggest that this might better explain the early hypoxia but sustained lung compliance experienced by patients with COVID.

Infection also produces rigorous activation of the complement system, which plays a vital role in severe COVID, potentially as a principle antecedent to cytokine storm [24,25]. The proinflammatory effects of anaphylatoxins can occur within hours of infection [25] and may contribute to thrombotic microangiopathy and organ dysfunction [17,24]. Ramlall et al [26] also resounded the critical impact of complement on regulation of overall outcomes from infection and were able to identify genetic variants within complement and coagulation regulators that could serve as potential markers of susceptibility [26].

A number of postmortem COVID-19 studies have reported endothelial dysfunction in multiple vascular beds, including endothelial lining of the lungs, and pervasive thrombosis and microangiopathy [27]. Contributing factors include increased production of pulmonary interstitial cytokines, activation of complement components, and direct infection of the endothelium through ACE2 receptors [28]. Elevated levels of von Willebrand factor and factor VII have also been reported in patients with COVID-19, further substantiating endothelial activation [29,30]. Resulting endotheliitis (inflammation of the endothelium in blood vessels) is a major precursor for thrombosis [21].

Early studies have indicated that a large number of patients with COVID-19 meet International Society of Thrombosis and Hemostasis criteria for disseminated intravascular coagulation [31], but lack the clinically associated profile [32,33]. They suggested that abnormal laboratory findings may reflect a more localized coagulopathy that resulted from extensive alveolar inflammation, but remained limited to the pulmonary vasculature [32,33]. Ciceri et al [34] hypothesized that in subgroups predisposed to severe outcomes, the process then extends systemically to the microvasculature of the brain, kidneys, and other organs, causing hypercoagulability and multisystem failure, which they labeled “microvascular COVID-19 lung vessel obstructive inflammatory syndrome.”

### 3. Hematologic markers

The hypercoagulable state in COVID-19 has been associated with several hematological markers, including decreasing

platelet, increased levels of D-dimer, fibrinogen, factor VIII, and von Willebrand factor, with decreased antithrombin, platelets, and thromboelastography results. Table 1 compiles the levels of markers associated with adverse VTE outcomes in COVID-19 [35–51].

D-dimer has been investigated extensively for its potential utility as a prognostic indicator for VTE in patients with COVID-19. Typically, D-dimer  $< 0.5 \mu\text{g/mL}$  is used to rule out VTE. Li et al [40] reported increased risk of VTE (odds ratio [OR] = 14.18) with D-dimer levels  $> 2.07 \mu\text{g/mL}$ , and Al Samkari et al [37] found D-dimer levels between 1.0 and  $2.5 \mu\text{g/mL}$  were associated with increased risk (OR = 3.04), which rose to OR of 6.09 when levels exceeded  $2.5 \mu\text{g/mL}$ . However, Choi et al [35] found that D-dimer levels between 1.0 and  $7.5 \mu\text{g/mL}$  were associated with only a nominal risk of VTE; likelihood ratio (LR) of 1.19, but that the likelihood increased to 4.1 when levels exceeded  $7.5 \mu\text{g/mL}$ .<sup>35</sup> Unfortunately, the clinical functionality of elevated D-dimer levels may be limited. Although a number of studies report high sensitivity among ICU patients; ranging between 85% and 100%, specificity has ranged between 46% and 88.5% [36,39,43]. This is due most likely to the concomitant inflammatory and infectious processes ongoing in patients with COVID-19 causing elevation of levels for most patients.

The association between prothrombin time (PT) and VTE has been less conclusive. Dujardin et al [42] found no significant difference in PT levels between those who did and did not develop VTE, and Al-Samkari et al [37] found a significant difference in peak PT levels between those with and without VTE (16.0 and 14.4, respectively;  $P < .001$ ). Moreover, Klok et al [48] reported that PT  $> 3$  seconds over the normal upper limit were associated with an increased hazard ratio (HR) of 4.1 for VTE. Similarly, the data for activated partial thromboplastin time has been inconsistent. Fibrinogen is another coagulation parameter that can be useful for monitoring VTE risk. Al-Samkari et al [37] reported an OR of 2.22 for VTE among the critically ill when fibrinogen exceeded 7.0. Ierardi et al [49] reported an increased OR of 1.003 for DVT among floor patients.

Consideration should also be given to CRP levels. A number of studies have reported significantly higher CRP levels in those who developed VTE than those who did not, with OR for developing VTE ranging from 1.03 for elevated CRP on admission [50] or in floor patients [49] to 2.71 for elevated CRP among the critically ill [37]. Dujardin et al [42] found a combination of elevated D-dimer  $> 15 \mu\text{g/mL}$  (D-Dimer) with CRP  $> 280 \text{ mg/dL}$  (CRP) had a positive predictive value of 98% for VTE and was the most accurate laboratory marker [42]. The Wuhan model identified decreased fibrinogen, increased D-dimer, and increased increment D-dimer  $\geq 1.5$ -fold combination as having excellent predictive value as well for symptomatic VTE (area under the curve = 0.865; 95% confidence interval [CI], 0.822–0.907; 93% sensitivity, 71% specificity) [40].

According to current data, it would appear prudent that, at minimum, D-dimer, PT/partial thromboplastin time, fibrinogen, platelet levels, CRP, and VTE risk assessment should be completed on admission. Frequency of repeat testing has not yet been determined. However, because ICU patients are at higher risk for VTE, any patient with COVID-19 should be reassessed on transfer.

Table 1 – Hematologic markers for venous thromboembolic events in COVID-19.

Marker	Normal value	First author	Patient population	Abnormal value/marker	Outcomes
D-dimer	0–500 ng/mL	Choi [35]	123 VTEs, New York, NY; 1,739 COVID patients	1,000–7,500	LR = 1.19
		Cui [36]	ICU COVID VTE	>7,500	LR = 4.1
		Al-Samkari [37]	400; 5 institutions VTE; 6%/10.4% in critically ill	>1,500	Sensitivity 85%
				VTE 1,538 (953–3,288)	Specificity 88.5%
				No VTE 891	P = .0002
				VTE 4,001 (2,896–8,821)	Peak P < .0001
				No VTE 1,377	OR = 3.04
				1,001–2,500	OR = 6.79
				>2,500	
		Yu [38]	142 COVID	>2,000	DVT OR = 10.9
		Trigonis [39]	Ventilated ICU COVID DVT	>2,000	Sensitivity 95%
					Specificity 46%
		Li [40]	China: 16 centers; 104 VTEs	D-dimer increment >1.5	OR = 14.18
				2,070 (800–6,570)	OR = 1.33
		610 (290–1,460)			
Helms [41]	ICU/ARDS like	2,270 (1,160–20,000)	>95% elevated		
Dujardin [42]	COVID ICU 127 patients	VTE 2,310 (820–29,200)	0.10		
		No VTE 1,250 (730–3,000)	PPV 53%		
		>2,000	PPV 55%		
		>3,000	PPV 84%		
		>11,000			
Léonard-Lorant [43]	ICU COVID PE	>2,600	Sensitivity 100%		
			Specificity 67%		
Ren [44]	ICU COVID	900 (510–3,100)	No DVT		
		3,530 (1,870–11,640)	Proximal DVT		
		5,310 (1,120–9,780)	Distal DVT		
Santoliquido [45]	COVID floor	4,527	DVT		
		2,050	No DVT		
Cavagna [46]	109 COVID with CTA for PE	11,462 ± 2,528	DVT		
		2,743 ± 568	No DVT		
Motaganahalli [51]	Single-center 71 patients	5,448 ± 2,379	DVT		
		2,644 ± 7,032	No DVT: P = .01		
			Multivariate:		
			↑ D-dimer in DVT: OR = 1.000243		
			(1.000014–1.000472)		
			P = .038		
			NS		
PT	10–12 s	Dujardin [42]	COVID ICU 127 patients	11.3	NS
				11.3	
		Panigada [47]	ICU COVID	1.16	27% >NL range
		Al-Samkari [37]	400; 5 institutions VTE; 6%/10.4% in critically ill	VTE 13.8	NS
				No VTE 13.9	P = .0001 peak
		VTE peak 16			
		No VTE peak 14.4			
Klok [48]	184 ICU COVID 68 VTEs	>3 s above normal upper limit	HR = 4.1		

(continued on next page)

Table 1 (continued)

Marker	Normal value	First author	Patient population	Abnormal value/marker	Outcomes
aPTT	30–45 s	Dujardin [42]	COVID ICU 127 patients	27.7 v 27.4 no VTE	NS
		Al-Samkari [37]	400; 5 institutions VTE;6%/ 10.4% in critically ill	VTE 34.2 No VTE 34.3	NS
Fibrinogen	2–4 g/dL	Panigada [47]	ICU COVID	0.98	17% below low NL
		Klok [48]	184 ICU COVID 68 VTEs	>5 s above normal upper limit	HR = 4.1
		Cui [36]	ICU COVID	39.9 ± 6.4	Higher risk VTE
		Dujardin [42]	COVID ICU 127 patients	7.5 v 7.7 no VTE	NS
CRP	0–5 mg/L	Panigada [47]	ICU COVID	6.8 (2.34–13.44)	93% above NL
		Ierardi [49]	Non-ICU COVID	7.0 v 5.6	Higher in COVID <.001
		Al-Samkari [37]	400; 5 institutions VTE;6%/10.4% VTE ICU	VTE 6.96 No VTE 5.79 VTE 8.28 No VTE 6.62 >7	P = .0045 Peak P = .0001 OR = 2.22 VTE
		Ierardi [49]	Floor COVID	536 (390–691)	DVT OR = 1.003
d-dimer + CRP		Panigada [47]	ICU COVID	16.1 (3.9–34.2)	100% above NL
		Ierardi [49]	Non-ICU COVID	52 (13–115)	DVT OR = 1.004
		Al-Samkari [37]	400; 5 institutions VTE;6%/10.4% in critically ill	VTE 124.7 No VTE 63.3 VTE 277.7 No VTE 130.3 >100	P = .001 Peak <.0001 OR = 2.71 VTE
		Thondapu [50]	Admission value	158.9 v 132.5 no VTE	OR = 1.05 P = .02
vWF antigen	103 (40–165) U/dL	Cavagna [46]	109 COVID with CTA for PE	169 ± 20 92 ± 156	DVT No DVT
		Dujardin [42]	COVID ICU 127 patients	VTE 214 (128–270) No VTE 153 (97–230)	0.035 59%
				PPV >70 >160 >245	71% 93%
Lupus anticoagulant		Dujardin [42]	COVID ICU 127 patients	<1/ < 20 5–9/161–220 >15/ >280	PPV 9% PPV 48% PPV 98%
		Panigada [47]	ICU COVID	529 (210–863)	100% above upper normal
Factor VIII	60%–150%	Helms [41]	ICU with ARDS like COVID	455 (350–521)	16.7% PE
		Helms [41]	ICU with ARDS like COVID	87.7% COVID patients	96.6% on CRRT clot circuit
Wuhan score		Li [40]	104 DVT + COVID	341% ↓Fibrinogen, ↑D-dimer on admit and ↑D-dimer increment > 1.5-fold	AUC 0.865 Sensitivity 93% Specificity 71%

Abbreviations: aPTT, activated partial thromboplastin time; ARDS, acute respiratory distress syndrome; AUC, area under the curve; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CRRT, continuous renal replacement therapy; CTA, computed tomography angiography; DVT, deep vein thrombosis; HR, hazard ratio; ICU, intensive care unit; LR, likelihood ratio; NL, normal limit; NS, not significant; OR, odds ratio; PE, pulmonary embolism; PPV, positive predictive value; PT, prothrombin time; VTE, venous thromboembolic event; vWF, von Willebrand factor.

#### 4. Risk factors

Risks associated with severe COVID disease, development of complications, and increased mortality have been well documented. Zhou et al [52] in a meta-analysis of 34 studies, identified a number of comorbidities, including chronic respiratory disease, hypertension, cardiovascular disease, kidney disease, cerebral vascular disease, malignancy, diabetes, and obesity, which carried increased odds for severe/fatal VTE. Racial disparity in COVID-19 outcomes has also been documented, with African American patients having poorer outcomes than White or Asian patients. The etiology is not entirely clear and multiple factors, such as socioeconomic status, underlying pathophysiology, differences in hemostasis factors, coagulation status, and genetics may be at play [53,54].

Severe COVID is associated with increased risk of VTE, with ORs approximating a 6-fold increase for severe disease as opposed to 3-fold with nonsevere disease [40]. Notably, however, the risk factors for VTE and COVID-19 have indicated that hematologic biomarkers; particularly elevated admission D-dimer, >1.5-fold incremental increase in D-dimer, low admission level fibrinogen, and CRP are more predictive of VTE than comorbid states associated with severe COVID-19 and poorer prognosis [40,42]. A number of studies have reported no significant difference in the incidence of venous thrombosis among patients with cardiovascular disease, kidney disease, cerebral vascular disease, diabetes, or obesity compared with counterparts without disease [38,40,51,55,56]. Interestingly, Xiong et al [55] reported a trend toward lower incidence of VTE among diabetics (OR=0.73; 95% CI, 0.47–1.35) [55]. These findings are perplexing, given the interconnection between COVID-19 pathophysiology and the underlying pathology of these chronic illnesses. Similarly, racial disparity in the prevalence of COVID-19 has been reported, yet the incidence of VTEs across racial groups is comparable [1,56]. Bilaloglu et al [1], in a study of 3,334 consecutive COVID-19 hospitalizations, reported a significantly higher incidence of VTE among Hispanic patients compared with non-Hispanic White patients when “any type” of thrombosis was considered (HR=1.19; 95% CI, 1.15–3.18;  $P=.01$ ). However, significance was lost when evaluation was limited to venous thrombosis (DVT/PE: HR=2.01; 95% CI, 0.81–5.00;  $P=.13$ ). Moreover, they found no significant difference in any type VTE or venous thrombosis between African American patients and non-Hispanic White patients (any VTE: HR=0.93; 95% CI, 0.71–1.23;  $P=.62$  and venous thrombosis: HR=0.97; 95% CI, 0.60–1.55;  $P=.89$ ) [1]. Once again, these findings are puzzling because pre-COVID-19 racial disparity in risk of VTE has been documented, with African American race carrying the highest rate, followed by White then Asians/Pacific Islander [53,57].

A compilation of VTE-specific risks is presented in Table 2. Male sex [50,51,55,58] and ICU admission/need for mechanical ventilation [38,42,58–60] have emerged as prominent factors throughout multiple studies. Increased thrombotic events among ICU patients is not surprising because critically ill patients are prone to hypercoagulability because of immobilization, mechanical ventilation, and nutritional insufficiencies, in addition to indwelling venous and arterial catheters [2]. Age has been reported frequently as well, but results have been in-

consistent. A number of studies have documented increased incidence among older patients [40,55], but others have found the converse [56,58]. Li et al [40] reported older age was an independent predictor of VTE (OR=1.04; 95% CI, 1.03–1.07;  $P=.008$ ), yet Xiong et al [55], in a meta-analysis of 12 studies, indicated trend formation only (mean difference=1.91; 95% CI, 1.58–5.40). Baseline alterations in the renin-angiotensin system might explain the pathogenesis in male and the elderly patients. Cancer has been identified by Li et al [40] as an independent predictor of VTE, presumably due to a pre-existing hypercoagulability. They also found that increased interval from symptom onset until hospital admission was independently associated as well. Increased incidence of VTE among patients with human immunodeficiency virus [38] has also been reported.

Findings of our study of 334 consecutive admissions with COVID-19 echoed results reported in the literature. We found that positive D-dimer on admission (LR=3.21; 95% CI, 1.005–10.25;  $P=.049$ ) and current smoker (LR=3.75; 95% CI, 1.005–10.23;  $P=.018$ ) were independent risks for development of venous and/or arterial thrombosis, and female sex portended lower risk (LR=0.20; 95% CI, 0.06–0.72;  $P=.014$ ). Race was not independently associated with development of venous/arterial thrombosis in COVID-19 admissions. Table 2 compiles the known, suspected risk factors for VTE in COVID-19.

#### 5. Incidence and timing of events in COVID-19-associated coagulopathy and VTE

According to Zhang et al [60], in a meta-analysis of 40 studies that included 7,966 patients hospitalized with COVID-19, the pooled VTE prevalence was 13%; 7% in non-ICU patients and 31% in ICU patients. Screening led to a 3-fold increase in VTE detection. Both PE and DVT were found to occur significantly more often among ICU than non-ICU patients (PE: 37% v 10%;  $P<.0001$  and DVT: 40% v 12%;  $P=.0065$ ) [60].

The temporal relationship between COVID-19 diagnosis, development of associated coagulopathy, and subsequent occurrence of VTE has been explored but not fully elucidated. Li et al [40] reported an independent association between VTE and longer interval from symptom onset to hospital admission. Likewise, a number of studies on hospitalized patients with COVID-19 have reported progressive increases in the cumulative incidence of VTE from days 7 to 21 [36,48,59]. Middeldorp et al [59] noted the incidence of symptomatic VTE was 10% at 7 days, increasing to 21% at 14 days and 25% at 21 days. On further subgroup analysis of ICU patients, they found the 20-day cumulative incidence of VTE was 60%. Collectively, these data suggest that VTEs are less likely to occur as early sequelae of COVID-19, and patients, particularly those with severe disease, can remain at risk for an extended period.

#### 6. COVID-19 severity classification systems

Classification systems have been proposed to stratify severity of COVID-19 disease and risk for adverse sequelae. International Society of Thrombosis and Hemostasis devel-

**Table 2 – Risk factors associated with venous thrombotic events.**

Factor	First author	Study type	n	Significant finding
Severe COVID	Li [40]	Retrospective multicenter (n = 16)	2,779	VTE Nonsevere: OR = 2.79 (95% CI, 1.43–5.60) Severe: OR = 5.94 (95% CI, 3.91–10.09)
Male sex	Thondapu [50] Motaganahalli [51] Xiong [55] Kirshblum [58]	Retrospective single center Retrospective single center Meta-analysis: 12 studies Retrospective single center	138 71 1,083 113	Univariate: OR = 2.64 (95% CI, 1.19–5.84); P = .02 Multivariate: OR = 2.37 (95% CI, 1.01–5.36); P = .048 +DVT: male vs female 68% v 32%; P = .032 RR = 1.10 (95% CI, 0.092–1.33) trend VTE: male v female 41.7% vs 11.1%; P = .039
ICU admission <sup>a</sup> /mechanical ventilation <sup>b</sup>	Yu [38] <sup>a</sup> Dujardin [42] <sup>b</sup> Kirshblum [58] <sup>b</sup> Middeldorp [59] <sup>a</sup> Zhang [60] <sup>a</sup>	Retrospective single center Retrospective single center: ICU Retrospective single center Retrospective single center Meta-analysis: 34 studies	142 127 113 198 7,966	VTE: ICU v non-ICU 90% v 41.3%; P < .000 VTE: with mechanical ventilation v no VTE: with mechanical ventilation 100% v 83.8%; P = .001 VTE with mechanical ventilation v no VTE with mechanical ventilation 60% v 37.5%; P = .049 Cumulative VTE at 21 d: ICU vs non-ICU 59% v 9.2% PE/VTE: ICU vs non-ICU PE: 37% v 10%; P < .001 DVT: 40% v 12%; P = .007
Older age	Li [40] Xiong [55]	Retrospective multicenter (n = 16) Meta-analysis: 12 studies	312 1,083	VTE v no VTE (66 y v 60.5 y): OR = 1.04 (95% CI, 1.03–1.07); P = .008 Mean difference: VTE: 1.91 y (1.58–5.40 y) older: trend
Younger age	Koleilat [56] Kirshblum [58]	Retrospective single center Retrospective single center	135 113	DVT v no DVT 59 y v 64 y; P = .06 trend VTE v no VTE 59.5 y v 67.3 y; P = .024
Cancer	Li [40]	Retrospective multicenter (n = 16)	312	OR = 6.14 (95% CI, 1.29–29.2); P = .021
Interval symptom onset → hospitalization	Li [40]	Retrospective multicenter (n = 16)	312	Interval days: symptoms → hospital VTE v non-VTE 10 d v 5 d OR = 1.12 (95% CI, 1.05–1.20); P = .001
Obesity	Koleilat [56]	Retrospective single center	135	BMI: DVT v no DVT 30.3 v 28.7; P = .07 VTE: HIV <sup>+</sup> v HIV <sup>-</sup> 8.7% v 0%; P = .05

Abbreviations: BMI, body mass index; CI, confidence interval; DVT, deep vein thrombosis; ICU, intensive care unit; OR, odds ratio; PE, pulmonary embolism; RR, relative risk; VTE, venous thromboembolic event.

<sup>a</sup> Articles correlating ICU admission.

<sup>b</sup> Articles correlating need for mechanical ventilation.



**Table 3 – Prophylaxis and venous thromboembolism treatment management.**

First author, date	Location	Study design	COVID-19 prophylaxis	Suspected or proven VTE	Extended therapy
Tang, March 2020 [31]	China	Retrospective review	LMWH (enoxaparin 40–60 mg/d) and UFH (10,000–15,000 U/d) associated with improved survival in patients with sepsis-induced coagulopathy score >4 and D-dimer 6 × normal upper limit	—	—
Thachil, ISTH interim guidelines, March 2020 [61]	International	Consensus-based guidelines	LMWH for all hospitalized patients	—	—
Spyropoulos, May 2020 [83]	International	Guideline based on literature review and expert surveys	Hospitalized non-ICU patients: UFH or LMWH (LMWH preferred) ICU patients: prophylactic to intermediate doses of LMWH (eg, enoxaparin, 40–60 mg) Adjust dose according to BMI, VTE risk scores, and/or biomarkers (eg, D-dimer) Consider multimodal (chemical + mechanical) prophylaxis	Therapeutic LMWH or UFH (prefer LMWH) while in-house, can be converted to DOAC on discharge	Extended prophylaxis (2–6 wk) after discharge with LMWH or DOAC in patients with high VTE risk and low bleeding risk For proven VTE, 3 mo anticoagulation
Barnes, May 2020 [77]	United States	Consensus-based guidelines	Standard dose prophylaxis for all hospitalized Increased dose for critically ill patients (enoxaparin 40 mg subcutaneous twice daily or 0.5 mg/kg subcutaneous twice daily; heparin 7,500 U subcutaneous 3 times daily or low-intensity infusion)	Standard therapeutic dose LMWH or UFH (prefer LMWH)	Extended post-hospital prophylaxis if a patient has ongoing VTE risk factors
Bikdeli, June 2020 [88]	United States	Consensus-based guidelines	All acute hospitalized patients should receive standard prophylaxis unless contraindicated	Standard therapeutic anticoagulation (LMWH or UFH), can be converted to DOAC on discharge	Extended prophylaxis up to 45 d after discharge in patients at high risk for VTE (ie, reduced mobility, comorbidities including cancer, D-dimer >2 × upper normal limit)
Klok, July 2020 184 patients [48]	Italy	Retrospective review	Nadroparin 2,850 IU subcutaneous per day to 5,700 IU subcutaneous twice daily	—	—

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Table 3 (continued)

First author, date	Location	Study design	COVID-19 prophylaxis	Suspected or proven VTE	Extended therapy
Moore, CHEST guidelines, September 2020 [81]	US	Guidelines based on systematic review, expert surveys, and consensus	Acutely ill hospitalized patients Standard prophylactic dose LMWH or fondaparinux over UFH and DOAC Critically ill hospitalized patients Standard prophylactic dose LMWH or UFH over fondaparinux and DOAC Recommend against routine use of mechanical prophylaxis (unless pharmacological prophylaxis is contraindicated)	Acutely ill hospitalized patients Therapeutic weight-based LMWH or UFH; can be converted to DOAC/vitamin K antagonist therapy Critically ill hospitalized patients Therapeutic weight-based LMWH or fondaparinux over UFH Outpatient DOAC or vitamin K antagonist therapy	Consider extended prophylaxis in patients at low risk of bleeding Anticoagulation for at least 3 mo for proximal DVT/PE
Waite, November 2020 [76]	United States	Review article	Standard prophylactic dose LMWH or UFH for all critically ill patients Consider intermediate dosing in high-risk patients	—	—
NIH, February 2021 [63]	United States	Expert panel	Standard VTE prophylaxis for hospitalized patients (Specific agent not specified)	Standard VTE treatment (specific agent not specified)	Recommend against extended prophylaxis unless high VTE risk
Zarychanski, March 2021 [89]	International	Multiplatform international randomized clinical trials (REMAP-CAP, ACTIV-4a and ATTACC)	Standard low-dose or enhanced intermediate-dose prophylaxis over therapeutic anticoagulation in ICU COVID-19 patients	—	—

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Table 3 (continued)

First author, date	Location	Study design	COVID-19 prophylaxis	Suspected or proven VTE	Extended therapy
Condliffe, British Thoracic Society, February 2021 [90]	United Kingdom	Guidelines based on systematic review and expert consensus	Standard low-dose prophylaxis in non-ICU and enhanced intermediate dose prophylaxis in ICU patients	—	Consider extended prophylaxis (4 wk) in patients at low risk of bleeding and high VTE risk
Susen, French Society of Thrombosis & Hemostasis, June 2020 [91]	France	Expert panel consensus	BMI < 30: standard prophylactic dose LMWH (eg, enoxaparin 4,000 IU/d) or fondaparinux (2.5 mg/d) BMI < 30: intermediate dose LMWH (eg, enoxaparin 4,000–6,000 IU twice a day) or UFH 200 IU/kg/d Therapeutic dose LMWH or UFH if on ECMO, catheter thrombosis, dialysis filter thrombosis, or marked inflammatory syndrome and/or hypercoagulability (eg, fibrinogen > 8 g/L and/or D-dimers > 3 µg/mL)	—	—
American Society of Hematology Cuker, February 2021 [87]	United States	Guidelines based on systematic review and expert consensus	Standard prophylactic dose over intermediate or therapeutic dose anticoagulation for VTE prevention in COVID-19-related acute or critical illness	—	—
INSPIRATION trial March 2021 [92]	Iran	Randomized clinical trial	Standard prophylactic dose anticoagulation (enoxaparin 40 mg daily) was similar to intermediate dose (enoxaparin, 1 mg/kg daily) in terms of arterial and venous thrombosis, treatment with ECMO, and 30-d mortality	—	—

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; DOAC, direct oral anticoagulants ECMO, extracorporeal membrane oxygenation; ISTH, International Society of Thrombosis and Hemostasis; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

oped the sepsis-induced coagulopathy score to quantify severity of COVID-19 illness [61]. The scoring system evaluates the following criteria: Sequential Organ Failure Assessment, which reflects the physiologic status of multiple organ systems with scores from 1 for normal to 24 for most deranged; platelet count; and PT/international normalized ratio. A sepsis-induced coagulopathy score of 1 is assigned for results that fall within normal range and 2 for deranged values: platelet count  $<100 \times 10^9/L$ ; PT/international normalized ratio  $<1.4$ , and Sequential Organ Failure Assessment  $\geq 2$ . Total sepsis-induced coagulopathy scores  $\geq 4$  have been used to define severe COVID-19 [62]. Other designations using alternative criteria to identify severe disease have been established. According to the National Health Commission of China, after confirmation of infection by identifying severe acute respiratory syndrome coronavirus 2 RNA, patients meeting any of the following criteria were diagnosed as having severe COVID-19: respiratory rate  $\geq 30$  breaths/min, arterial oxygen saturation  $\leq 93\%$  while at rest, or  $PaO_2/FiO_2 \leq 300$  mm Hg [43,62]. In the United States, the National Institutes of Health has defined severe COVID-19 as those individuals who have been diagnosed with COVID-19 via virologic testing (nucleic acid amplification or antigen test) and meet any of the following criteria: oxygen saturation  $<94\%$  on room air at sea level,  $PaO_2/FiO_2 \leq 300$  mm Hg, respiratory rate  $>30$  breaths/min, or lung infiltrates  $>50\%$  [63].

Most recently, a large National Institutes of Health multiplatform, adaptive-design trial that incorporates 3 global studies/networks (REMAP-CAP, ATTACC, and ACTIV-4A), which evaluated the use of anticoagulation for COVID-19, defined severe state patients as those admitted to an ICU and receiving organ support (ie, high-flow nasal oxygen, receiving noninvasive or invasive mechanical ventilation, or are requiring vasopressor/inotrope) [64].

## 7. Atypical venous thrombosis in COVID-19-associated coagulopathy

Multiple studies have documented atypical VTE events with variable presentations. As such, patients presenting with unusual symptoms and found to have thrombosis should be assessed for COVID-19, even in the absence of respiratory symptoms.

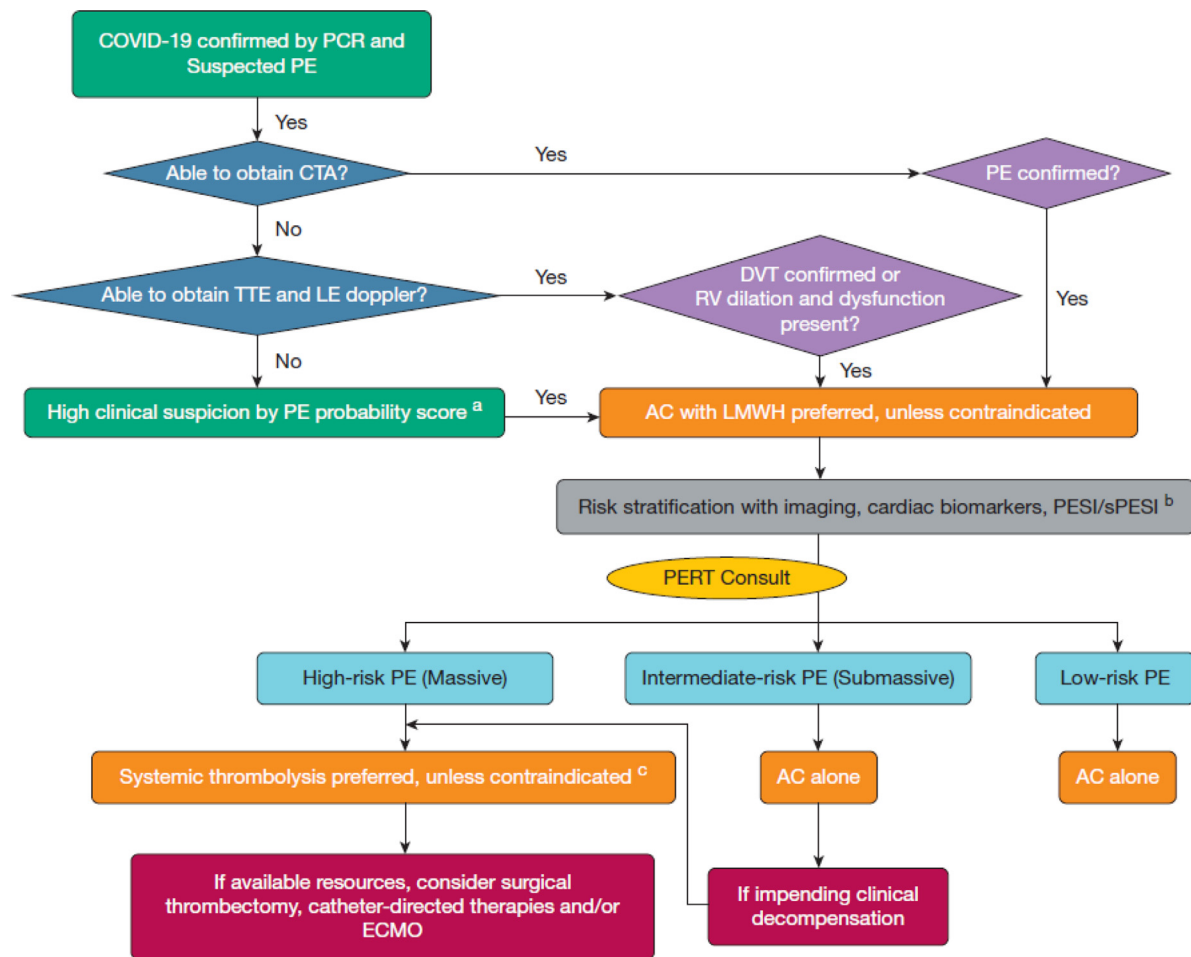
Cerebral venous sinus thrombosis has been documented multiple times in patients with COVID-19. Cerebral venous sinus thrombosis is an uncommon etiology of strokes with an increased incidence among women and younger patients (compared to ischemic strokes). Presenting symptoms range from headache to neurological deficits and seizures [65,66]. Patients can also present with intracranial hemorrhage as a result of the sinus thrombosis [67]. Presence of cerebral venous sinus thrombosis does not appear to be related to the severity of the COVID-19 infection, having been described in patients with mild to severe disease. The timeline is also varied, with some patients having cerebral symptoms as their presenting symptoms for COVID-19 and others developing neurologic symptoms up to 2 weeks after onset of other COVID symptoms.

Colicky abdominal pain in patients with COVID-19 may suggest VTE. Splanchnic vein thrombosis has also been described in COVID-19–positive patients [68]. Most patients diagnosed with splanchnic vein thrombosis presented with colicky abdominal pain that improved with anticoagulation, although presentation with gastrointestinal bleeding has also been described [66,69]. Most commonly, the portal vein [70] is involved, but involvement of other splanchnic veins have been reported [71,72]. Ovarian and renal vein thromboses have also been described in patients presenting with abdominal pain [55–57,73–75].

## 8. Prophylaxis, treatment and management, and outcomes of VTE secondary to COVID-19

Heightened clinical awareness of risk for VTE in patients with COVID-19 in conjunction with serial laboratory monitoring of coagulation and inflammatory factors can lead to timely identification. The threshold to obtain definitive diagnostic studies, such as ultrasonography for DVT and computed tomography angiography or ventilation/perfusion scan for PE, should be low. However, routine screening of all patients with the COVID-19 diagnosis has not been recommended [76] because prevalence of asymptomatic DVT in those with COVID-19 is low. Rather, clinical suspicion should guide imaging decisions [77]. Imaging studies might not be feasible in all cases, particularly those with severe COVID disease. Treatment should not be delayed if there is high clinical suspicion, as this can lead to poorer outcomes. Lippi et al suggested a direct association between COVID-19–associated coagulopathy and poor outcomes [78]. Moreover, the association between VTEs and mortality has been well documented [59,79], with rates reaching 39.1% in those patients with any VTE compared with 26% in those without [79]. In our own study, we found that patients with venous and/or arterial thrombotic events were more likely to require ICU admission (91% v 42%;  $P < .001$ ), require mechanical ventilation (68% v 23%;  $P < .001$ ), have longer hospital stays (30 v 12 days;  $P < .001$ ), have higher incidence of sepsis (55% v 34%;  $P = .048$ ), have more multisystem failure (46% v 15%;  $P < .001$ ), and have higher mortality (55% v 23%;  $P = .001$ ).

The optimal VTE prophylaxis and treatment strategy for patients with COVID-19 remain unclear due to lack of high-quality evidence. Issues yet to be addressed include the optimal agent for prophylaxis, level of intensify of prophylactic medication dosing, and time interval for treatment to continue. Aggressive prophylactic and treatment approaches, especially in critically ill patients have been advocated, yet data to support strategies beyond standard VTE management are still under investigation. Current recommendations suggest that chemical prophylaxis is unnecessary for patients with COVID-19 who are not hospitalized [63,77,80,81]. In contrast, all hospitalized patients with COVID-19 should be treated, at minimum, with a prophylactic dose of either low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) in the absence of any contraindications (eg, bleeding or platelets  $<25,000/\mu L$ ) [61,62]. A potential benefit of heparin medications is their anti-inflammatory properties [82]. LMWH has been advocated over UFH because of decreasing patient interaction with medical staff, and therefore decreased risk of exposure



**Fig. 2 – Algorithm for determining pulmonary embolism (PE) treatment.** AC, anticoagulation; CTA, computed tomography angiography; DVT, deep vein thrombosis; ECMO, extracorporeal membrane oxygenation; LE, lower extremity; LMWH, low-molecular-weight heparin; PESI, Pulmonary Embolism Severity Index; PCR, polymerase chain reaction; PERT, pulmonary embolism response team; sPESI, Simplified Pulmonary Embolism Severity Index; RV, right ventricle; TTE, transthoracic echocardiography.

[81,83]. Prophylaxis recommendations for specific subgroups have also been addressed. LMWH or UFH can be used for pregnant patients with COVID-19 [64,77]. When treating obese patients, dose adjustment based on body mass index will be necessary [63]. Mechanical thromboprophylaxis should be considered if anticoagulation is contraindicated [81,83]. Alternative agents, such as fondaparinux, can be used in patients with history of heparin-induced thrombocytopenia [62,63,84,85].

The role of direct oral anticoagulants (DOACs), such as pixaban, rivaroxaban, edoxaban, and dabigatran, in treatment of VTE in COVID-19 is unclear. Moreover, the potential for significant drug interactions between DOACs and other medications used to treat COVID-19, such as dexamethasone, sarilumab, and tocilizumab, is concerning [64,86]. Moores et al [81] suggested that DOACs can be beneficial in treating outpatient COVID-19 patients who have developed VTE. Use of antiplatelet agents for VTE prevention is also being studied [87].

Determination for standard prophylaxis versus intermediate-level prophylaxis or full therapeutic anticoagulation is unclear. Many strategies have been evaluated.

Cuker et al [87] has provided a detailed review of the various agents along with dosing recommendations. Standard prophylactic dosing levels include enoxaparin 30 to 40 mg daily or twice daily, dependent on body mass index and creatinine clearance, or UFH ranges from 5,000 U twice daily/three times daily to 7,500 U twice daily based on body mass index. Intermediate dosing includes enoxaparin 0.5 mg/kg twice daily or 30 to 60 mg twice daily, dependent on creatinine clearance and body mass index or UFH 7,500 U three times daily. Therapeutic dosing includes enoxaparin 1 mg/kg twice daily or 1.5 mg/kg daily, or UFH dosed to a target activated partial thromboplastin time or anti-Xa levels [87]. A summary of prophylaxis recommendations from multiple current studies is provided in Table 3 [31,48,61,63,76,77,81,83,87–92]. Many institutional protocols have incorporated therapeutic-dose anticoagulation with weight-based dosing in critically ill patients, based on an early observational study by Lemos et al [93] showing decreased ventilatory requirement and improved survival compared to prophylactic dose anticoagulation. However, other studies have shown no difference in outcomes [37]. Importantly, there has been recent concern

about increased mortality with therapeutic anticoagulation [64]. Preliminary data from a multiplatform trial (REMAP-CAP, ATTACC, and ACTIV-4A) suggested that for patients with severe COVID-19 infections (requiring high-flow nasal oxygen, invasive or noninvasive mechanical ventilation, vasopressor therapy, or extracorporeal membrane oxygenation support), empiric therapeutic anticoagulation in the absence of VTE was associated with poorer outcomes, including higher mortality [64]. In contrast, moderately ill patients, that is, those requiring hospitalization but not ICU-level care, were found to have better outcomes with therapeutic compared with prophylactic dose anticoagulation. Final results of these trials are still pending, and the interim data should be interpreted cautiously [64].

Hospitalized patients with COVID-19 remain at increased risk after discharge, especially if nonambulatory, and several studies suggest continued prophylaxis up to 4 weeks for those, with additional risk factors with prophylactic doses of LMWH [64]. Outpatient management of VTE in patients with COVID-19 should include anticoagulation for 3 months, similar to other provoked events [46,85]. Anticoagulants typically include low-molecular-weight heparin or DOAC medications.

Currently, there are more than 100 ongoing clinical studies that assess various VTE issues in COVID-19, including best medications for prophylaxis, dosing levels for prophylaxis, and extended therapy, as well as other issues. A summary of current prospective, randomized studies is provided in Supplementary Table 1. Details can be found at ClinicalTrials.gov. Talasaz et al [94] have provided a thorough review as well.

## 9. Advanced therapies

Interventions such as venous thrombectomy and thrombolysis for severely symptomatic DVT should be weighed against the risk of bleeding and generally reserved for limb salvage purposes. In the absence of severe limb-threatening VTE, invasive interventions should be avoided during the acute phase of the disease.

There is a paucity of data on the use of advanced therapies, such as systemic thrombolysis, catheter-directed therapies, surgical embolectomy, and extracorporeal membrane oxygenation to treat VTE in these patients. The CHEST guidelines recommend systemic thrombolysis only in patients with massive or high-risk PE, especially if confirmed with imaging for routine VTE in non-COVID-19 patients. Thrombolytic therapy can also be considered in select patients without imaging should they have strong predilection to develop hypotension or cardiorespiratory compromise due to PE, that is, progressive worsening tachycardia, decreased systolic blood pressure, worsening hypoxemia, severe right ventricular dysfunction, or signs of shock [81,95]. The risk of bleeding needs to be strongly weighed when considering thrombolytic therapy in these patients. Bleeding risk can be increased in patients critically ill with COVID-19 due to high incidence of disseminated intravascular coagulation, alveolar damage and hemorrhage, and renal dysfunction [96,97]. Studies have shown variable rates of bleeding ranging from 2.7% to 21%, the majority in the group of patients on anticoagulation [20,98]. A meta-analysis including 48 studies reported a pooled incidence of

7.8% (95% CI, 2.6%–15.3%) for bleeding and 3.9% (95% CI, 1.2%–7.9%) for major bleeding in patients with COVID-19 [99]. Given the complexity of these patients, a multidisciplinary team approach in treating them, particularly when advanced therapies are considered, is ideal. Such teams exist in many institutions as a PE response team. Kwok et al [100] reported their experience with PE response teams in New York hospitals during the first phase of COVID-19 and noted increases in PE and activations of the PE response team (26.8% v 64.4%;  $P < .001$ ). Management of these patients was similar to the historical control, with the majority treated with anticoagulation alone (89.5% v 86.4%;  $P = .70$ ). Figure 2 describes an algorithm to diagnose and treat PE in patients with COVID-19 [101].

## Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1053/j.semvascsurg.2021.06.002.

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