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HOT TOPIC

Venous Thromboembolism in COVID-19: Towards an Ideal Approach to Thromboprophylaxis, Screening, and Treatment

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Abstract

Purpose of Review Novel coronavirus disease 2019 (COVID-19) has been associated with an increased risk of arterial and venous thromboembolic (VTE) diseases. However, there is a limited amount of data regarding the prevention and management of VTE in severe hospitalized COVID-19 patients.

Recent Findings In this article, we review currently available clinical data, and mechanisms for COVID-associated coagulopathy, and propose algorithms for screening, prevention (including extended-duration prophylaxis), and treatment of these patients.

Summary Although these recommendations are subject to change given rapidly evolving data, we provide a framework that can guide clinicians in managing thrombotic complications in this challenging condition.

Keywords COVID-19 · Venous thromboembolism · Thromboprophylaxis · Deep vein thrombosis · Pulmonary embolism · Extended prophylaxis

Introduction

Studies have previously shown that both pneumococcal and influenza infections can be associated with increased risks of venous thromboembolism (VTE) [1, 2]. In critically ill influenza A H1N1 patients with acute respiratory distress syndrome (ARDS), empiric systemic anticoagulation was associated with decreased rates of VTE [2]. Similarly, novel coronavirus disease 2019 (COVID-19) has been thought to predispose to both venous and arterial thromboembolic diseases. Prevalence can be as high as 25% in patients that develop ARDS and can lead to higher rates of complications and poor overall prognosis [3].

Given the lack of clear guideline recommendations on the prevention and management of VTE in severe hospitalized COVID-19 patients, we believe that the following clinical questions deserve further study and clarification.

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Is There a Biologic Basis for Increased Risk of VTE in COVID-19?

Increased VTE events in COVID-19 are thought to be due to immobilization, excessive inflammation, and diffuse intravascular coagulation (DIC) [4]. Although not primarily a thrombotic process, inflammation and hypoxia with acute lung injury leads to a profound inflammatory state due to cytokine storm, macrophage, and endothelial activation–related processes associated with a surge in IL-1, IL-6, IL-8, and TNF-alpha which suggest that there are biological evidences for the thrombotic process. Evidence of coagulopathy has been reported, with patients demonstrating often markedly elevated serum levels of D-dimer, lactate dehydrogenase, and total bilirubin with slight prolongation or no changes in partial thromboplastin time (PT) or activated partial thromboplastin time (PTT) [5]. Diffuse microvascular thrombi with possible thrombotic microangiopathy in multiple organs have been reported on autopsy review without viral infiltrates [6]. In addition, the association of COVID-19 with clinically significant coagulopathies, multiple infarcts, and antiphospholipid antibodies has also been described [7]. However, the association between COVID-19 and antiphospholipid syndrome (APS) remains speculative at this point given that the definitive diagnosis of APS requires persistence of IgG antibodies (rather than IgA antibodies as reported) at 12 weeks along with thrombotic events meeting the Sapporo criteria. In patients that harbor rare germline mutations in complement regulatory genes, complement activation can lead to antiphospholipid antibody–induced thrombotic events [8], suggesting a possible role for complement blockade in managing complement-mediated APS [6].

Should We Screen all Hospitalized Severe COVID-19 Patients for VTE?

Although the incidence of VTE seems to be higher in COVID-19 patients, further studies on VTE in these patients are needed. Confirmation of such a relatively high rate of VTE would warrant consideration for screening lower limb ultrasounds and consideration of intermediate to full-dose anticoagulation akin to the approach used in heparin-induced thrombocytopenia without thrombosis. Based on the current evidence, International Society on Thrombosis and Hemostasis (ISTH) recommends measuring D-dimer, PT, PTT, and platelet count in all hospitalized patients with COVID-19 [9]. Rapid deterioration in oxygen saturation or increased dead space ventilation might be better indicators of a new VTE event, rather than relying solely on hematological abnormalities. Given logistical issues resulting from the strict isolation in COVID-19 patients, it is likely that there is a higher threshold to perform diagnostic imaging in these patients. Many critical care units in high-income countries utilize point-of-care ultrasound, which may be utilized for screening purposes. The use of dedicated ultrasound for COVID-19-infected patients may limit the risk of cross-contamination to patients without COVID-19. Elevations in D-dimer are very common in this group and are not specific for VTE events [5].

Klok et al. evaluated the incidence of the composite outcomes of VTE and arterial thrombotic complications in all COVID-19 patients admitted to the intensive care unit (ICU) [4]. A total of 184 consecutive patients with COVID-19 pneumonia admitted to the ICU were evaluated. All patients received at least standard-dose thromboprophylaxis. Among these, only those patients with a clinical suspicion for VTE underwent diagnostic evaluation with further imaging. Confirmed VTE was noted in 27% and arterial thrombotic events in 3.7% of patients. Pulmonary embolism (PE) was the most frequent VTE (81%). Spontaneous prolongation of the PT by more than 3 s or PTT by more than 5 s was an independent predictor of thrombotic complications. Similarly, Tang et al. reported an association between 28-day mortality with D-dimer, PT, age, and platelets on multivariate analyses [10]. This study was limited due to its retrospective design and a much lower rate of thromboprophylaxis compared with Western countries (only a fifth of patients were administered thromboprophylaxis) (Table 1).

What Is the Appropriate VTE Prophylaxis and Treatment for Severe COVID-19 Patients?

Given the high risk of VTE in critically ill COVID-19 patients, appropriate VTE prophylaxis seems to be an important part of managing these patients. Many critically ill patients we considered in our observational studies have high Padua scores and are associated with lower mortality rates when given LMWH or heparin; we suggest that all severely ill COVID-19 patients undergo weight-based thromboprophylaxis. While the use of standard-dose thromboprophylaxis in hospitalized patients is acceptable, the high reported incidence of VTE (25–31%) suggests that higher doses, i.e., enoxaparin 0.5 mg/kg twice daily, may be more appropriate [3, 4]. Given that thrombocytopenia in COVID-19 patients may be less profound than that in other sepsis syndromes [11], prophylactic anticoagulation is likely to be feasible.

Anticoagulation treatment in severe COVID-19 patients seems to be associated with better outcomes [10]; empiric anticoagulation should be strongly considered in patients with high suspicion for VTE but cannot undergo diagnostic imaging, in the absence of contraindications to anticoagulation therapy. Patients with physical findings consistent with superficial or DVT should also undergo therapeutic anticoagulation. Helms et al. found that despite prophylactic anticoagulation, a high number of patients with COVID-19 ARDS developed life-threatening thrombotic complications; hence, higher anticoagulation targets have been suggested (Fig. 1) [12].

A large study of 1087 patients found that nearly 40% had high-risk Padua scores (defined as score of ≥ 4), and that higher

Table 1 Baseline characteristics of included studies

Characteristics	Klok et al.	Cui et al.	Chen et al.	Tang et al.	Wang et al.	Helms et al.
Sample size	184	81	25	449	1026	150
Study design	Multi-center, retrospective study	Single-center retrospective study	Single-center, retrospective study	Retrospective analysis	Multi-center, retrospective study	Multi-center, prospective cohort
Study population	Severely ill COVID-19 patients admitted to the ICU	Severely ill COVID-19 patients admitted to the ICU	Hospitalized COVID-19 patients who underwent CTPA	Hospitalized, severely ill COVID-19 patients	Hospitalized COVID-19 patients	Severely ill, admitted to ICU
Age in years (mean)	64	60	Not reported	65.1 ± 12.0	42 for Padua score < 4 and 52 for score of ≥ 4	63 (median)
Male sex (%)	139 (76%)	37 (46%)	Not reported	268 (60%)	Not reported	122 (81.3)
Prophylaxis for VTE	All patients received at least standard doses of thromboprophylaxis Prophylaxis options: LMWH nadroparin 2850 IU/day > 100 kg = LMWH nadroparin 5700 IU/day Therapeutic anticoagulation: 17 (9.2%) on admission	None	20 pts. treated with LMWH 0.6 mg/kg every 12 h	• 94/99 patients received LMWH (40–60 mg/day) for 7 days or longer	10 (7%) of 140 patients for whom anticoagulation data were available had received anticoagulant drugs during hospitalization (nine received heparin and one received rivaroxaban)	Low molecular weight heparin 4000 UI/day or if contra-indicated, unfractionated heparin at 5–8 U/kg/h 105 (70%) prophylactic dosing 45 (30%) therapeutic dosing

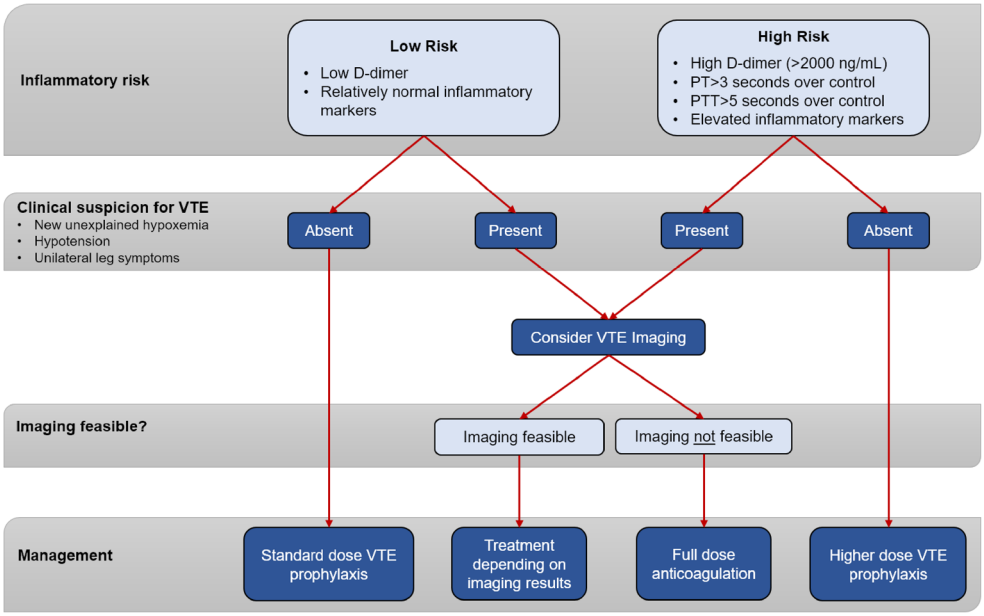

Fig. 1 Proposed algorithm for the evaluation and management of VTE in severe COVID-19 patients. Inflammatory marker refers to C-reactive protein, procalcitonin, ferritin, etc. An example of higher dose VTE prophylaxis includes enoxaparin 0.5 mg/kg twice daily

scores were associated with higher risk of bleeding, admission to ICU, intubation, and death due to COVID-19 or complications such as VTE. The study, however, reported significantly lower rates of VTE prophylaxis (< 7%) [13]. In another retrospective study by Tang et al., the use of low molecular weight heparin (LMWH) treatment was associated with a better 28-day mortality among patients with severe COVID-19 infection and sepsis-induced coagulopathy score ≥ 4, or D-dimer more than 3 μg/mL (6 times upper limit of normal) [10]. In other studies, strongest association for VTE was found with D-dimer cutoff of 1500 ng/mL (sensitivity of 85% and specificity of 89%) [3]. However, as noted above, the majority of patients did not receive thromboprophylaxis implying a potentially severe selection bias.

VTE prophylaxis for COVID-19 patients have been incorporated into different guidelines including the Journal of American College of Cardiology state of the art review [14], Swiss consensus statement [15], and NHS model [16]. American Society of Hematology also offers frequently asked questions on VTE on COVID-19 patients.[16(p19)] Until better evidence emerges, we support the Swiss consensus statement that reads: "In patients in intensive care with a large increase in D-dimers, severe inflammation, or signs of hepatic or renal dysfunction or imminent respiratory failure, intermediate or therapeutic dosing of LMWH or unfractionated heparin should be considered, according to the bleeding risk."

Should We Use Extended VTE Prophylaxis (4–6 Weeks) in Severe COVID-19 Patients?

The risk of VTE among COVID-19 patients that are discharged from the hospital remains unclear with a lack of published data. However, in prior studies, in acutely ill medical patients, extended-duration anticoagulation with rivaroxaban and betrixaban has been shown to reduce the risk of VTE [17]. However, extended anticoagulation may be associated with an increased risk of bleeding [18, 19]. While further studies are needed, extended-duration prophylaxis for 4–6 weeks may be reasonable for some patients such as those with additional risk factors or persistent coagulopathy in the absence of contraindications to anticoagulation therapy.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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