

Thrombotic complications in severe COVID-19: focus on venous thromboembolism, thromboprophylaxis and anticoagulation

Complicaciones trombóticas en COVID-19 grave: enfoque en tromboembolia venosa, tromboprofilaxis y anticoagulación

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Abstract

Severe coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and predisposes to thrombotic complications. In this review, we address the close relationship between venous thromboembolism and COVID-19, providing practical aspects on epidemiology, risk factors, and thromboprophylaxis, as well as potential options of anticoagulation. The scientific data on COVID-19 is scarce; however, day by day we continue to learn, being aware of the evolving and dynamic changes in this emerging infectious and immunothrombotic disease.

Keywords: Anticoagulation. COVID-19. Venous thromboembolism. Thromboprophylaxis. Thrombosis.

Resumen

La enfermedad grave por coronavirus 2019 (COVID-19) está causada por el Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) y predispone a complicaciones trombóticas. En esta revisión se aborda de manera práctica la estrecha relación entre la tromboembolia venosa y la COVID-19, enfatizando aspectos epidemiológicos, factores de riesgo y tromboprofilaxis, así como potenciales opciones de anticoagulación. Actualmente la evidencia científica es muy escasa, pero día a día seguimos aprendiendo, estando atentos a cambios novedosos y dinámicos en esta enfermedad infecciosa e inmunotrombótica emergente.

Palabras clave: Anticoagulación. COVID-19. Tromboembolia venosa. Tromboprofilaxis. Trombosis.

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Introduction

Severe coronavirus disease 2019 (COVID-19) is defined as a respiratory viral disease caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), which on January 30, 2020, was declared by the World Health Organization as a public health emergency of international concern¹, and in March 11, as an emerging global pandemic². Patients with risk factors such as preexisting cardiovascular and cerebrovascular disease, hypertension and diabetes mellitus, among others, are more likely to experience respiratory complications, multiple organ failure and death^{3,4}. The importance of assessing the risk of thrombosis and the need for thromboprophylaxis becomes evident in the course of the evolution of this disease, with the fact that we are still lacking sufficient clinical evidence to escalate from a prophylactic dose to a full anticoagulation dose standing out, as well as that neither do we have recommendations for extended thromboprophylaxis in this group of patients⁵.

The purpose of this review is to address, in a practical manner, the narrow relationship between venous thromboembolism (VTE) and COVID-19, with an emphasis on epidemiological aspects, risk factors, thromboprophylaxis and anticoagulation.

Method

A thorough and focused search for thrombotic complications in COVID-19 patients was carried out through the MEDLINE and PubMed platforms. The following keywords were used: "COVID-19", "coronavirus disease 2019", "venous thromboembolism", "epidemiology", "anticoagulation", "heparins", "thrombosis", "thromboembolic disease" and "thromboprophylaxis". The date of the last recorded search was July 25, 2020.

What are the pro-thrombotic and hemostatic alterations in COVID-19?

SARS-CoV-2 causes a marked systemic inflammation, characterized by an elevation of pro-inflammatory cytokines such as tumor necrosis factor alpha and interleukins 1 and 6, which activates platelets, leukocytes and vascular endothelium, which in turn promotes tissue factor activation and, therefore, extrinsic coagulation pathway activation, triggering a higher production of both systemic and local thrombin in the

lungs of patients with severe pneumonia, which results in tissue damage and microangiopathic pathology, thus making the patient more prone to disseminated intravascular coagulation (DIC) and thrombosis⁶. In a retrospective review of 183 COVID-19 patients, those who died had higher values of D-dimer and fibrin breakdown products, longer prothrombin time, and longer activated partial thromboplastin time at presentation in comparison with those who managed to survive. Among the patients who died, 71.4% met the International Society on Thrombosis and Haemostasis diagnostic criteria for overt disseminated intravascular coagulation (≥ 5 points), in comparison with 0.6% of those who survived^{7,8}. In another retrospective cohort of 201 patients, 84 developed acute respiratory distress syndrome (ARDS) and had a significantly longer prothrombin time (11.7 vs. 10.6 seconds, $p < 0.001$) and higher D-dimer values (1.16 vs. 0.52 $\mu\text{g/mL}$, $p < 0.001$) at the time of presentation, in comparison with those who did not develop ARDS. Of the 84 patients with ARDS, 52.8% (44) died and had significantly higher D-dimer values (3.95 $\mu\text{g/mL}$ [1.15-10.96]) than those who survived (0.49 $\mu\text{g/mL}$ [0.31-1.18]); $p = 0.001$ ⁹. This disease clearly confers high risk of thrombosis, which is why using an antithrombotic strategy that helps prevent adverse results and a fatal outcome in these patients is crucial¹⁰.

What is the incidence of venous thromboembolism in COVID-19?

In a prospective cohort of 150 critically ill COVID-19 patients admitted to the intensive care unit (ICU) for acute hypoxemic respiratory failure at two tertiary care hospitals in France, a high prevalence of thrombotic complications was observed, with pulmonary thromboembolism (PTE) in 25 (16.7%) of them despite prophylactic or therapeutic anticoagulation (truncular in nine cases, lobar in eight, segmental in five and sub-segmental in three cases)¹¹. Another study reported an incidence of VTE of 25% in 81 critically ill COVID-19 patients, out of whom eight died from high-risk VTE. Interestingly, the researchers observed that D-dimer values $> 1,500 \text{ ng/mL}$ represented a good prognostic index for VTE identification¹². It should be emphasized that, in this study, no patient did initially receive thromboprophylaxis. Klok et al.¹³ evaluated the incidence of thromboembolic events at three tertiary care hospitals in The Netherlands, where they analyzed 184 patients with severe COVID-19 admitted to

Table 1. Thromboprophylaxis and anticoagulation strategies in patients with severe pneumonic COVID-19*

Anticoagulant	Prophylactic dose	Intermediate dose	Therapeutic dose
Enoxaparin Weight-optimized	< 80 kg: 40 mg SC Q24H 80-99 kg: 60 mg SC Q24H ≥ 100 kg: 80 mg SC Q24H Reduce to 50% with Cr clearance < 30 mL/min	1 mg/kg/day Anti-Xa levels 0.3-0.6 IU	1 mg/kg Q12H 1.5 mg/kg Q24H Anti-Xa levels 0.5-1.0 IU
Nadroparin Weight-optimized With Cr clearance > 50 mL/min	≤ 70 kg: 3800 IU SC Q24H > 70 kg: 5700 IU SC Q24H Reduce by 25-33% with Cr clearance ≥ 30 and < 50 mL/min	NA	< 50 kg: 3800 IU Q12H 50-59 kg: 4750 IU Q12H 60-69 kg: 5700 IU Q12H 70-79 kg: 6650 IU Q12H 80-89 kg: 7600 IU Q12H ≥ 90 kg: 8550 IU Q12H Reduce by 25-33% with Cr clearance ≥ 30 and < 50 mL/min
Dalteparin Weight-optimized With Cr clearance > 30 mL/min	< 49 kg: 2500 IU SC Q24H 50-99 kg: 5000 IU SC Q24H 100-139 kg: 7500 IU SC Q24H 140-180 kg: 5000 IU SC Q12H	NA	200 IU/kg (maximum 25,000 IU/24 h)
Fondaparinux†	2.5 mg Q24H (Cr clearance > 30 mL/min)	NA	< 50 kg: 5 mg SC Q24H 50-100 kg: 7.5 mg SC mg Q24H > 100 kg: 10 mg SC Q24H
Unfractionated heparin	5000 IU Q8-12H	NA	80 U/kg or 5000 U IV bolus followed by continuous infusion of 18 U/kg/h or 1300 U/h adjusted to anti-Xa activity of 0.4-0.8 IU

IV: intravenous; SC: subcutaneous; NA: not applicable.

*Thromboprophylaxis or anticoagulation strategy contraindicated if < 25,000 platelets, active bleeding or high bleeding risk (IMPROVE > 7)¹⁷⁻¹⁹.

†Use fondaparinux in case of previous thrombotic events due to heparin-induced thrombocytopenia.

the ICU; all patients received appropriate thromboprophylaxis. Total cumulative incidence of thrombotic events was 16.8% (31), with acute PTE being more common in 25 (13.5%) of them (segmental PTE in 18 cases and sub-segmental PTE in 7). There were two cases of upper extremity thrombosis secondary to catheter use, one case of lower extremity proximal deep vein thrombosis and three patients had an ischemic stroke¹³.

What are the risk factors for venous thromboembolism in the patient with severe COVID-19?

Risk factors for VTE in patients with severe COVID-19 are the same as those of patients admitted to the ICU for other causes: prolonged immobilization, mechanical ventilation, central venous catheter, use of inotropic drugs, dehydration, cardiovascular risk factors such as ischemic heart disease, previous stroke, diabetes, hypertension, obesity, cancer, peripheral arterial disease or history of VTE, among others¹⁴. However, having severe COVID-19 confers even higher risk; Virchow's triad criteria (venous

stasis, endothelial dysfunction and hypercoagulability) are perfectly met in these patients¹⁵. Assessing the risk of VTE in every patient admitted to the hospital is a quality parameter of in-hospital care for hospital certification. It is imperative to assess the risk of VTE and administer pharmacological thromboprophylaxis to every patient with COVID-19, and even more so if they have been admitted to the ICU, unless there is some absolute contraindication for it (e.g., severe thrombocytopenia with < 25,000 cells/mm³ or suspected active bleeding). Today, a wide variety of clinical tools are available to stratify thromboembolic and hemorrhagic risk in hospitalized patients (PADUA, CAPRINI, IMPROVE, IMPROVE DD)¹⁶⁻¹⁹.

What are the recommendations for the use of thromboprophylaxis and anticoagulation in severe COVID-19?

So far, the evidence on thromboembolism in COVID-19 does not warrant a change in current directions for thromboprophylaxis in hospitalized patients, and neither has experience on extended thromboprophylaxis been reported in patients with severe COVID-19

Table 2. Recommendations for thromboprophylaxis and anticoagulation regimen in special situations

Special situation*	Hospitalized patient for severe COVID-19			High clinical suspicion or confirmed diagnosis of VTE or PTE
	Anticoagulant	Standard dose	Intermediate dose	Therapeutic dose
Kidney failure	Enoxaparin			
	Cr clearance: > 30 mL/min 20-30 mL/min < 20 mL/min	40 mg SC Q24H 30 mg SC Q24H UFH 5000 U Q8 or 12H	NA	Individualize case, particularly if there is acute progressive renal function impairment, change to UFH
Obesity	BMI > 40-49	40 mg SC Q12H	NA	Individualize each case
	BMI > 50	60 mg SC Q12H		
Pregnancy and puerperium	< 50 kg	20 mg SC Q24H	40 mg SC Q12H	1 mg/kg Q12H or 1.5 mg/kg Q24H
	51-90 kg	40 mg SC Q24H		
	91-130 kg	60 mg SC Q24H		
	> 130 kg	80 mg SC Q24H		
	Dalteparin	5000 IU SC Q24H	7500 IU SC Q24H	200 IU/kg Q24H or 100 IU/kg Q12H
	Tinzaparin	4500 IU SC Q24H	NA	175 IU/kg Q24H
Current anticoagulation with DOAC	Nadroparin	2850 IU SC Q24H	NA	NA
	Switch to LMWH or UFH at therapeutic doses at hospital admission			NA

BMI: body mass index; Cr: creatinine; DOAC: direct oral anticoagulants; DVT: deep vein thrombosis; LMWH: low molecular weight heparin; NA: not applicable; PTE: pulmonary thromboembolism; SC: subcutaneous; UFH: unfractionated heparin.

*Implies that there is no consensus or limited solid scientific evidence on the management of thromboprophylaxis and anticoagulation in these subgroups of patients^{23,26,27}.

Table 3. Clinical trials of intermediate-dose thromboprophylaxis vs. anticoagulation in patients with COVID-19²⁸

Clinical trial	ClinicalTrials.gov registration no.	Phase	Antithrombotic	Dose	Initiation date	End of recruitment	N
COVI-DOSE*	NCT04373707	4	LMWH	Weight-adjusted prophylactic dose vs. low prophylactic dose	May 13, 2020	October 2020	602
X-covid 19†	NCT04366960	3	LMWH	40 mg Q24H vs. 40 mg Q12H	May 14, 2020	November 2020	2712
Anticoagulation Strategies in COVID-19	NCT04359277	3	LMWH UFH	Anticoagulation vs. thromboprophylaxis	April 21, 2020	April 21, 2021	1000
ATTACC‡	NCT04372589	3	LMWH UFH	Anticoagulation vs. thromboprophylaxis	May 20, 2020	January 2021	3000

LMWH: low molecular weight heparin; UFH: unfractionated heparin.

*LMWH weight-adjusted vs. fixed low doses for the prevention of venous thromboembolism in COVID-19 patients.

†Comparison of two enoxaparin doses for thromboprophylaxis in hospitalized patients with COVID-19.

‡Antithrombotic therapy to decrease COVID-19 complications.

that manage to survive the disease. However, the Italian Society on Thrombosis and Haemostasis²⁰ recommends considering extended thromboprophylaxis after discharge in COVID-19 patients at higher risk of VTE. The choice of the thromboprophylaxis or anticoagulation regimen may vary depending on clinical characteristics of each patient and the protocol established by each medical society or healthcare institution²¹⁻²³. The

Anticoagulation Forum and *Chest* have published specific recommendations regarding the thromboprophylaxis regimen that could be used in COVID-19, including the most seriously ill patients admitted to the ICU^{24,25}. Table 1 shows a proposal for VTE risk evaluation in patients with severe COVID-19, recommendations regarding thromboprophylaxis strategies and a therapeutic anticoagulation regimen in case of high clinical

suspicion or objective confirmation of VTE. Table 2 shows some of the thromboprophylactic strategies for special clinical scenarios^{26,27}.

Future perspectives and conclusions

The experience accumulated so far demonstrates that patients with COVID-19 are at very high risk of thrombosis, which confers them a poorer prognosis and higher morbidity and mortality. Strategies with different anticoagulation regimens, both thromboprophylactic and therapeutic, deserve to be studied in depth by new clinical trials, emphasizing which subgroup of patients are ideal candidates for extended thromboprophylaxis, as well as assessing the hemorrhagic risks posed by these preventive and therapeutic strategies in the area of thrombosis and anticoagulation.

Several clinical trials are currently underway, which will provide us with guidelines to follow with regard to thromboprophylaxis or anticoagulation doses for patients with COVID-19 (Table 3)²⁸; for the time being, medical actions should be in accordance with available scientific evidence.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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