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The thromboembolism in COVID-19: the unsolved problem.

Running title: Thromboembolism in COVID-19

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ABSTRACT:

INTRODUCTION: The recent Sars-Cov-2 pandemic (COVID-19) has led to growing research to explain the poor clinical prognosis in some patients.

EVIDENCE ACQUISITION: While early observational studies highlighted the role of the virus in lung failure, in a second moment thrombosis emerged as a possible explanation of the worse clinical course in some patients. Despite initial difficulties in management of such patients, the constant increase of literature in the field is to date clarifying some questions from clinicians. However, several other questions need answer.

EVIDENCE SYNTHESIS: A novel disease (Covid-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was responsible for thousands of hospitalizations for severe acute respiratory syndrome, with several cases of thrombotic complications due to excessive inflammation, platelet activation, endothelial dysfunction, and stasis. Covid-19 and hospitalizations for Covid-19 may carry several potential risk factors for thrombosis. Severe coagulation abnormalities may occur in almost all of the severe and critical ill COVID-19 cases.

CONCLUSIONS: Despite a strong pathophysiological rationale, the evidences in literature are not enough to recommend an aggressive antithrombotic therapy in COVID-19. However, it is our opinion that an early use, even at home at the beginning of the disease, could improve the clinical course.

Key words: coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Thromboembolism; Thrombosis, Low Molecular Weight Heparin.

TEXT

Introduction

Venous thromboembolism (VTE) in hospitalized patients with acute infectious disease is a well know condition which occurs with a moderate to high risk [1, 2, 3].When hospitalization for an infection is required, a VTE occurrence rate of 15.5% is estimated [4] and, in general, even without hospitalization, there is an increased VTE risk [5]. In subjects with pneumonia due to *S. Pneumoniae* or flu virus VTE occurrence was even higher [6,7]. Thromboprophylaxis in critically ill patients with acute infections is currently therefore recommended [8].

Late in December 2019, first cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and coronavirus disease in humans (COVID-19) were reported from Wuhan, China [9];

late on May 2020, more than 6 million cases and 369,000 deaths have been reported worldwide[10]. A novel disease (Covid-19) was responsible for thousands of hospitalizations for severe acute respiratory syndrome, with several cases of thrombotic complications due to excessive inflammation, platelet activation, endothelial dysfunction, and stasis.

Cardiovascular and metabolic diseases, including hypertension and diabetes, have been associated with more severe presentations and/or adverse prognosis in Covid-19 *[11]*.

Covid-19 and hospitalizations for Covid-19 may carry several potential risk factors for thrombosis: activation of inflammatory cascade, immobilization, respiratory failure, mechanical ventilation and use of central venous catheters [12,13]. There is some evidence that anticoagulant therapy with low molecular weight heparins (LMWH) appears to be associated with a better prognosis in patients with COVID-19 [14]. When the clinical course of Covid-19 infection shows a sudden clinical deterioration, acute thromboembolism has recently been proposed as a central mechanism accounting for apparently unexpected clinical worsening [15] **(Tab. 1)**.

On the base of such observations, we sought to perform a systematic review on current evidence available on thrombotic and thrombo-embolic complications and anticoagulant therapy in primary and secondary prevention of thrombotic complications in case of Covid-19.

Methods

We performed a systematic research using Embase and PubMed, inserting the keywords and mesh terms relative to the new coronavirus and to VTE: 'COVID-19', 'SARS', 'MERS', 'coronavirus', '2019 n-CoV', venous thromboembolism', 'pulmonary embolism', 'deep vein thrombosis', 'thromboembolism', 'thrombosis'. Boolean operators 'AND', 'OR', 'NOT' were used where appropriate. We found 133 articles of interest but only 20 were selected, providing the most representative information. Inclusion criteria were: a) publication between January and May 2020, b) epidemiological relevance, and c) clinical impact. We excluded publications that: a) were not directly focused on thrombosis, b) were published early during the pandemic, and c) provided information overlap with larger studies or more recent articles. The use of a combination of the inclusion criteria provided the most recent information.

Evidence Acquisition

Thrombotic complications in Covid-19

Despite Covid-19 was initially identified as a predominantly respiratory disease, given the occurrence of severe clinical case of respiratory distress, there is increasing evidence of an association between Covid-19 and thromboembolism. [16, 17, 18]

Patients with cardiovascular disease and COVID-19 have worse clinical course among all other COVID-19 patients and this risk is probably linked to the increased thromboembolic risk [19].

Several cases of arterial [20,26] and venous thrombosis [27,32] on small and large vessels have been reported; Massive coronary thrombosis [33], coronary stent thrombosis [34], acute myocardial infarction with extensive thrombus burden and cardiogenic shock has been reported [35] and failed fibrinolytic therapy [36].

Unfortunately, many patients receiving antithrombotic therapy for thrombotic disease may develop COVID-19, this could influence the choice, dosing, and laboratory monitoring of antithrombotic therapy.

Thromboembolism in Covid-19

Cui et al. found in a retrospective study an incidence of 25% of thromboembolism in a small cohort of 81 patients with pneumonia due to Covid-19, increasing the amount of evidence about the role of thromboembolism [37]. However, severe coagulation abnormalities may occur in almost all of the severe and critical ill COVID-19 cases [38]. SARS-CoV-2 is associated with a high prevalence of coagulopathy with a systemic coagulation defect that leads to large vessel thrombosis and major thromboembolic complications, including pulmonary embolism [39].
The etiology of the procoagulant responses seems multifactorial and complex and it might be the result of specific interactions between host defense system and the coagulation system [39].

Giannis D et al highlighted the role of coagulopathy during this infection [40] and Kollias et al. [14…41] showed that in COVID-19 patients the disseminated intravascular coagulation may be linked to a pro-thrombotic state, with a major benefit deriving from anticoagulation.
In a case report by Casey et al. a segmental pulmonary thrombosis was found in a patient without other VTE risk factor, suggesting a major role of the pro-thrombotic state [42]. La Vignera et al. analyzed the possible role of other factors [43]. They started from early observations that the virus' spike protein favors the downregulation of angiotension converting enzyme (ACE2) leading to penetration in epithelial cells and in myocardium. According to the previous evidences of a possible role of Vitamin D in cardiac diseases [44], they hypothesized a possible involvement of the Vitamin D deficiency in the clinical course.

Markedly elevated levels of D-dimer with normal fibrinogen levels are the hallmark laboratory findings and correlate with severity of illness and risk of thrombosis[45]. In particular, in the initial phase of this infection, D-dimer and fibrinogen levels are increased, while activated partial prothrombin time, prothrombin time, and platelet counts are often relatively normal. In case of increased D-dimer levels three times the upper limit of normal may trigger screening for venous thromboembolism [39]. Increased D-dimer concentrations of more than 1.0 μg/ml predict the risk of venous thromboembolism [46].
According to these evidences we had reported a case report characterized by the different clinical course between husband and wife, at the same time diagnosed with COVID-19. Despite previous several cardiovascular diseases and ICD implantation, the wife had an excellent clinical course during hospitalization. Instead, her husband suffering only from arterial hypertension needed intubation. One significant difference has been found; the wife was already in treatment with Edoxaban because of paroxysmal atrial fibrillation. We believe that chronic anticoagulant use had possibly a protective role against the pro-thrombotic state in COVID-19.

The use and the efficacy of either parenteral or oral anticoagulant therapy is still controversial. Tang et al. early during the pandemic described a better clinical course for patients assuming anticoagulants [14]. They found that 28-day mortality of heparin users was lower in patients with sepsis-induced coagulopathy (SIC) score>4 or D-dimer > 3 ug/ml, raising the issue of possible benefit from anticoagulant therapy in Covid-19 patients. A case series by Wang et al. a better clinical course was associated to patients with ARDS by Covid-19 receiving tissue plasminogen activator [47].

In the last months, the use of LMWH has grown, especially for critically ill patients [48] and currently several trials are ongoing to test the best dose. However, should be remembered that even LMWH, as any other drug to date, is not infallible [49-53], so we believe that as many strategies are investigated and available the easier is finding a solution for each patient.
Concomitant VTE management, a potential cause of unexplained deaths, frequently reported in COVID-19 cases, is still challenging due to the complexity between antithrombotic therapy and coagulation disorders. [**38]**

In this way the most recent consensus statement by Zahi et al. provided an important and useful guidance for clinicians before the publication of guidelines [38]. They recommend that in COVID-19 patients "suspected for VTE", in the case that "relevant examinations fail to be conducted due to restricted conditions", LMWH should be started at a full curative dose if no otherwise contraindicated. Another important suggestion by these authors is the use of unfractionated heparin in critically ill patients with severe kidney failure with creatinine clearance rate <30 ml/min.

In all hospitalized patients, thromboprophylaxis using low-molecular-weight heparin is currently recommended. Furthermore, Julie Helms et al [18] demonstrated despite anticoagulation, a high number of patients with ARDS secondary to COVID-19 developed life-threatening thrombotic complications. So, they suggested, that higher anticoagulation targets than in usual critically ill patients should therefore probably be suggested.

The inflammatory host immune response

Severe cases of COVID-19, caused by the SARS-CoV-2, are frequently characterized by increased inflammation, thrombotic state, and intravascular coagulopathy with relevant interactions between the different systems [54]

In acute respiratory distress syndrome (ARDS), the increase in proinflammatory cytokines within the lung leads to recruitment of leukocytes, which may propagate the inflammatory response and so the deposition of fibrin in lung parenchyma is coming. These fibrin deposits are due to the dysregulation of the coagulation and fibrinolytic systems [55]

Tissue factor (TF) exposed on alveolar endothelial cells and on the leukocytes promoting fibrin deposition, while significantly elevated levels of plasminogen activator inhibitor 1 (PAI-1) creating a hypofibrinolytic state. [55]

The virus invades cells through the angiotensin-converting enzyme 2 receptor. However, COVID-19-associated tissue injury is not primarily mediated by viral infection, but rather is a result of the inflammatory host immune response, which may lead cytokine activaction and increased inflammation that affect lung parenchymal cells and endothelial cells, resulting in thrombotic events and intravascular coagulation [56]. The complement system, also known as complement cascade, is a part of the immune system that enhances

the ability of antibodies and phagocytic cells to clear microbes and damaged cells from an organism, promoting inflammation, and attacking the pathogen's cell membrane. A crosstalk between complement and the coagulation system exists [57]. Preliminary data providing evidence of complement activation in patients with COVID-19 were reported [58]. It might be the first response of the host immune system to SARS-CoV-2 infection [56]; However, there is growing evidence that excessive activation of complement induced by SARS-CoV-2 in the lungs and other organs may play a pivot role in acute and chronic inflammation, endothelial dysfunction, thrombus formation and intravascular coagulation, and ultimately multiple organ failure and death.

Endothelial dysfunction

In healthy vessels, the endothelium releases the vasodilators and antithrombotic factors, nitric oxide. Whereas in injured vessels, nitric oxide is impaired contributing hypertension and thrombus formation. The "endothelial dysfunction" is a deterioration of endothelium-dependent vasodilatation; it also includes the abnormalities between endothelium and leukocytes, thrombocytes and regulatory molecules resulting in impaired endothelium function [59]. Its correct operation is essential for cardiovascular control. It plays an important role in pathogenesis of many cardiovascular diseases such as atherosclerosis, systemic and pulmonary hypertension, cardiomyopathies and vasculitides.

It is the final common pathway for diabetes/insulin resistance, hypertension, and dyslipidemia. All of these factors are effectively able to promote the original source of heart failure[60]. The inflammatory state, increased oxidative stress, altered nitric oxide bioavailability, and insulin resistance, are key factors of endothelial dysfunction [61,62]. Covid-19 accelerates endothelial dysfunction and nitric oxide deficiency. A hallmark of endothelial dysfunction and thrombotic events is suppressed endothelial nitric oxide synthase (eNOS) with concomitant nitric oxide deficiency [63]. The chronic impairment of systemic endothelial function in patients with cardiovascular and metabolic disorders may be aggravated by the adverse effects of SARS-CoV-2. In these patients, other negative influences over the endothelium are due to proinflammatory cytokines, which promote endothelial cellular apoptosis and lead to lung microvascular dysfunction, alveolar edema and hypoxia. Moreover, proinflammatory cytokines increase the expression of adhesion molecules, resulting in endothelial activation, procoagulant and

proadhesive changes, worsening microvascular flow and, consequently, tissue perfusion [64].

Restoring nitric oxide, independent of eNOS, may contribute to pulmonary vasodilatation and may be a potential treatment for SARS-CoV-2. NO interferes with the interaction between coronavirus viral S-protein and its host receptor, ACE-2.

Evidence synthesis

A novel disease (Covid-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was responsible for thousands of hospitalizations for severe acute respiratory syndrome, with several cases of thrombotic complications due to excessive inflammation, platelet activation, endothelial dysfunction, and stasis. Covid-19 and hospitalizations for Covid-19 may carry several potential risk factors for thrombosis. Severe coagulation abnormalities may occur in almost all of the severe and critical ill COVID-19 cases. According to all these evidences and to the experience of Rotzinger et al. [65] we believe that Chest CT should be performed in all the patients with COVID-19 for at least two reasons: a) subclinical course could be better outlined and b) in patients with severe course and high D-Dimer the CT pulmonary angiography is the most powerful tool to detect pulmonary embolism, providing proper anticoagulation.

There is increasing evidence of an association between Covid-19 and thromboembolism. In the last months, the use of LMWH has grown, especially for critically ill patients and currently several trials are ongoing to test the best dose. In COVID-19 patients “suspected for VTE”, in the case that “relevant examinations fail to be conducted due to restricted conditions”, LMWH should be started at a full curative dose if no otherwise contraindicated. The use of unfractionated heparin in critically ill patients with severe kidney failure with creatinine clearance rate <30 ml/min. In all hospitalized patients, thromboprophylaxis using low-molecular-weight heparin is currently recommended. Prophylaxis treatment of COVID-19 patients with LMWH is important to limit coagulopathy. However, to degrade pre-existing fibrin in the lung it is essential to promote local fibrinolysis.

D-dimer level-guided aggressive thromboprophylaxis regimens using higher doses of heparin should be evaluated in prospective studies.

Although angiotensin-converting enzyme 2 serves as the portal for infection [11] (Kevin Clerkin Circ 2020) no increased risk of in-hospital death was found to be associated with the use of ACE inhibitors or the use of ARBs [66]. The relationship of cardiovascular disease and drug therapy with in-hospital death among hospitalized patients with Covid-19 admitted between December 20, 2019, and March 15, 2020 was evaluated using an observational database from 169 hospitals in Asia, Europe, and North America[66].

Conclusions

Despite a strong pathophysiological rationale, the evidences in literature are not enough to recommend an aggressive antithrombotic therapy in COVID-19. However, it is our opinion that an early use, even at home at the beginning of the disease, could improve the clinical course. Currently several questions need answer, in particular: a) the proper dose of LMWH for each patient (eg. anticoagulation vs thromboprophilaxis); b) the possible protective role of DOAC; c) how much impact has a massive use of Chest CT instead of Chest X-Ray; d) role of hormonal and metabolic factors. Probably answers to these questions will be soon available.

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Conflicts of interest.

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TABLES

Table I.— **Tab.1. COVID-19 and thromboembolism: new insights**

POTENTIAL RISK FACTORS FOR THROMBOSIS	EVIDENCE OF PRO-THROMBOTIC STATE	THE INFLAMMATORY HOST IMMUNE RESPONSE	Endothelial dysfunction (ED)
Activation of inflammatory cascade	Concomitant pulmonary embolism	Cytokine activaction and increased inflammation affect lung parenchymal cells and endothelial cells	Covid-19 accelerates ED and nitric oxide deficiency
Immobilization	Anticoagulant therapy associated with a better prognosis	Proinflammatory cytokines increase the expression of adhesion molecules, resulting in endothelial activation, procoagulant and proadhesive changes	A hallmark of ED and thrombotic events is suppressed endothelial nitric oxide synthase (eNOS) with concomitant nitric oxide (NO) deficiency
Respiratory failure	Better clinical course in patients receiving tissue plasminogen activator	Recruitment of leukocytes propagate the inflammatory response	NO is impaired contributing hypertension and thrombus formation
Mechanical ventilation	Presence of a segmental pulmonary thrombosis without other VTE risk factors	Proinflammatory cytokines promote endothelial apoptosis and lung microvascular dysfunction, alveolar edema and hypoxia	NO interferes with the interaction between coronavirus viral S-protein and its host receptor, ACE-2
Use of central venous catheters		Deposition of fibrin in lung parenchyma	SARS-CoV-2 Cell entry is blocked by a clinically proven protease inhibitor
		Complement activation in Covid-19	
		Excessive activation of complement may play a pivot role in inflammation, endothelial dysfunction, thrombus formation and intravascular coagulation.	

Table note: *VTE: Venous thromboembolism; ED:* Endothelial dysfunction; NO: nitric oxide eNOS: endothelial nitric oxide synthase**.**

TITLES OF FIGURES

Figure 1. Absolute and percentage literature contribution sorted by month. The major contribution was provided by articles published in April 2020.