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Review

COVID-19: Potential role of prophylactic anticoagulation in preventing thrombotic events and mortality. Narrative review

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ABSTRACT

The COVID-19 pandemic and the limited therapeutic arsenal available strain daily clinical practice. Guidelines have recently recommended routine anticoagulation of hospitalized COVID-19 patients. However, apart from the expert panels' experience, the provenance of this recommendation is not clear, due to the scarce published evidence. We provide a narrative review with the objective of unraveling the rationale for this practice.

First, we analyze the biochemical, histopathological and clinical evidence for a pro-thrombotic profile in COVID-19 patients. Then, we present the clinical data from previous studies and discuss to what extent they aid in clinical decision-making.

We conclude that, in the absence of randomized controlled trials, which are of utmost importance, prophylactic-dose anticoagulation should be offered to critically ill patients hospitalized for COVID-19 pneumonia, particularly those with high d-dimer levels, since they are the population most likely to benefit from it.

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1. INTRODUCTION

In November 2019 in Wuhan, capital city of Hubei, China, the first cluster of pneumonia caused by the novel coronavirus -later named SARS-CoV-2- was described [1]. A unique pro-inflammatory and pro-coagulant profile was identified [2-6], which is presumed to be caused by an increase in interleukins and a dysregulation of inflammatory markers, and to develop in a minority of patients into a state called cytokine storm (CS) which evolves to respiratory distress syndrome (COVID-19 SARS) around day 10-14 of symptoms [7], even with scarce systemic evidence of sepsis.

These patients usually present with risk factors and represent the majority of hospitalized patients [8-10].

Here we aim to review the available and growing evidence that supports prophylactic anticoagulation in hospitalized patients with COVID-19 pneumonia, from the molecular basis to the scarce clinical evidence.

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2. PATHOPHYSIOLOGY

SARS-CoV-2 enters the endothelium through the angiotensin conversion enzyme receptor, which may derive in its tropism for certain organs, thus determining the spectrum of clinical manifestations. Afterwards, it triggers a cascade of inflammatory mediators that not only can derive in cell death but also lead to NF-kB transcription, macrophage recruitment, activation of T-cells and cytokine production. Particularly within the lungs, this sequence may evolve into diffuse alveolar damage, macro as well as microthrombi and hyaline membrane syndrome [7].

This partly explains the characteristic findings of lymphocyte activation and destruction -which derives in lymphopenia with particular T-cell depletion- high lactic dehydrogenase (LDH), high ferritin and d-dimer with mild thrombocytopenia and mild transaminasemia.

In COVID-19 SARS, biochemical markers for thrombosis appear to behave differently from conventional sepsis. The prothrombin time and the activated partial thromboplastin time that are usually prolonged in conventional sepsis, are commonly preserved in COVID-19. Similarly, while thrombocytopenia is the most sensitive marker in conventional sepsis' disseminated intravascular coagulation (DIC), only mild thrombocytopenia is frequently found in COVID-19, unless critically ill - supposedly due to the effect of thromboplastin activation secondary to lung damage [11].

Fibrinogen serum levels, the most specific marker of DIC, are frequently raised in COVID-19 patients, while lower levels predict mortality. D-dimer is described as frequently elevated in COVID-19 in some reports, disproportionately to the levels found in conventional sepsis. Moreover, higher incidences of thrombotic events and mortality have been reported with elevations of serum d-dimer levels at admission (Table 1) [6, 12-19]. However, even while other authors report higher levels in conventional sepsis, the main difference may reside in its elevation in the absence of overt sepsis or DIC [20, 21].

Literature describing thrombosis in COVID-19 patients range from descriptions of venous thromboembolic disease (VTE) and lung microthrombi to arterial thrombosis. However, when faced with the latter, the medical community confronts the uncertainty raised by the fact that arterial wall shear stress, among other factors, may determine the development of such thrombosis, independently from coagulation abnormalities. In particular, in the case of the central nervous system, it has been hypothesized that SAMHD1, a dNTP hydrolase upregulated by viral infections that could play a pro-viral role in COVID-19 -as well as in other viral infections- through NFκB activation inhibition and suppression of the IFN-I induction pathway, may be the link to neurological symptoms. Moreover, SAMDH1 mutations have been reported to alter immunoregulation and cerebrovascular homeostasis and to be associated with cerebrovascular events in patients with Aicardi-Goutieres syndrome and various inflammatory vasculopathies of the brain [22], thereby raising the question about its role in COVID-19-associated strokes.

3. THROMBOTIC MANIFESTATIONS

One of the first reports of COVID-19-associated thrombosis was a case series of 11 randomly selected autopsies [23]. The majority of patients had comorbidities - mainly diabetes and hypertension- with a mean age of 80.5 years. Almost every patient had high LDH, CRP-hs, D-dimer and lymphopenia. While edema (10/11) and hyaline membranes (10/11) were among the main lung findings, pulmonary artery thrombosis was present in all patients. Particularly, the thrombi found compromised the whole arteries' diameter, which is not compatible with emboli.

Meanwhile, a German study presented 12 patients with an age range of 52-87 years. While all patients presented comorbidities, 5 were deemed unfit for mechanical ventilation and/or cardiac resuscitation. When those patients were excluded, almost all patients had a major thrombotic event documented, considered the primary cause of death (5/7) [24].

A larger German study reported 80 autopsies from patients with COVID-19. Only 17 of these patients died in ICUs, which raises the question about the criteria employed for non-resuscitation/non-intubation. In 8 patients a fatal fulminant pulmonary artery embolism developed, and 9 additional cases were found to have peripheral pulmonary artery embolisms. Fifteen others had evidence of thrombi in the deep lower extremity veins. However, this incidence of thrombotic events cannot be extrapolated. Previous studies suggested a high incidence of these events in patients under mechanical respiratory support, which raises the hypothesis that these events develop late in the course of hospitalization [25].

Table 1. Summarized data for mortality, DVT and VTE incidence, and odds ratio of mortality and any thrombotic event across different d-dimer levels at admission

Variable	Ref	D-dimer levels at admission (ug/mL)									
		<0.25	**0.25-0.5**	**0.5-1.0**	**1.0-1.5**	**1.5-2.0**	**2.0-2.5**	**2.5-3.0**	**3.0-4.0**	**4.0-5.0**	**>5.0**
Mortality (%)	**[12] (a)**	9.7%	32.7%	36,9%	42.5%	44.5%	48.8%	52.4%	54.8%	9.7%	
	[13] (b)	4,00%		17.3%		18.6%			60,00%		
Mortality (OR)	**[14] (c)**	Ref. value (no deaths under 0.5)			2.21 (0.12-38.61)#		10.17 (1.10-94.38)				
	[6] (d)	Ref. value		2.14 (0.21-21.39) #	20.04 (5.52-61.56)						
	[15] (e)	Ref. value	1.58 (1.21 -2.1)	2.26 (1.66-3.1)	2.37 (1.58-3.6)		3.93 (2.6-6.0)				
DVT (%)	**[16] (f)**	No data			3.8%	10.5%	25.8%				
	[17] (g)	15.4%		16.7%	62.1%						
VTE or Mortality (%)	**[18] (h)**	11.4%					29.9%		55.7%		
Any thrombosis (OR)	**[19] (i)**	Ref. value	1.17 (0.85-1.60)	1.92 (1.40-2.64)			2.82 (1.87-4.27)			**5.0-10.0**	**>10**
										5.55 (3.57-8.62)	7.9 (4.69-10.71)

 # Difference not statistically significant. (a)Retrospective study, n=449; 28-day mortality in patients with no anticoagulation [12]. (b)Retrospective analysis, n=483 [13]. (c)Case control study, n=248; data from multivariate analysis [14]. (d)Retrospective multicenter cohort, n=191; data from multivariate analysis [6]. (e)Prospective cohort study, n=5279; data from multivariate analysis [15]. (f)Prospective observational study, n=156; screening for asymptomatic DVT incidence in non-ICU hospitalized patients on thromboprophylaxis [16]. (g)Cross-sectional survey, n=159; screening for DVT in hospitalized patients [17]. (h)Retrospective cohort study, n=9407; combined endpoint of in-hospital VTE or mortality, only 10.4% of patients not on anticoagulation [18]. (i)Retrospective cohort, n=3334; hospitalized patients, symptomatic venous or arterial thrombotic events, data from multivariate analysis [19]. DVT: Deep vein thrombosis; VTE: Venous thromboembolic disease.

Previous studies showed a high presence of microthrombi in COVID-19 patients' autopsies [26], while others argued that it may be a feature of SARS- not exclusive of COVID-19 [27]. This may be implicated in the torpid development of disease courses. However, a recent study, with a translational histopathological perspective [28], showed that platelet-rich microthrombi found in these patients' autopsies were formed by neutrophil-platelet complexes and that the relationship between these complexes and total leukocyte count increased with severity. It also showed a tendency towards a high platelet activity, particularly in the lungs, with peripheric hypoactivity.

From a clinical perspective, various studies assessed the incidence of thrombotic events in COVID-19 patients with heterogeneous methodologies.

A prospective study from Wuhan conducted consecutive lower extremities doppler ultrasonographies to assess the presence of deep vein thrombosis (DVT) in hospitalized patients with COVID-19 pneumonia with at least 3 days of hospital stay. There were a high proportion of patients already bedridden at admission, with a late admission date from symptom onset compared to previous studies. 46.5% developed a DVT, symptomatic or not, while only 35% were receiving prophylactic anticoagulation. These patients had a higher mortality risk, but were also older, more bedridden and presented with more severe disease status, worse levels of biochemical markers and lower oxygenation index [17].

Another study included 184 patients with proven COVID-19 pneumonia admitted to ICUs -of which 76% remained at the end of the study. All patients received at least standard doses of thromboprophylaxis, but the cumulative incidence of the composite outcome of TVP/PE and arterial thrombosis was 31% (95% CI 20-41%), with PE constituting the most frequent thrombotic complication (81%, n=25). The median time from ICU admission to thrombosis development was 7 days (around day 21 from hospital admission) [29].

Retrospectively analyzed data from 199 hospitalized patients, with DVT screening performed in some patients, showed a cumulative incidence of 20% (DVT 13%; PE 6.6%), with a higher incidence in ICU patients (47 vs

3.3%), with all patients at least on prophylactic anticoagulation [30].

A multicentric retrospective study was conducted later on in the pandemic course in the New York City Health System's hospitals. It included 3334 patients and found an incidence of the composite outcome of DVT/PE and arterial thrombosis of 16%, also with the majority of patients at least on prophylactic anticoagulation. ICU patients (829) presented with a higher incidence of thrombotic events (29.4 vs 11.5%) with 52 patients (6.2%) developing a PE. While ICU patients that did not develop a thrombotic event had similar initial d-dimer levels, the maximum d-dimer level significantly differed from that of general ward patients, with wide confidence intervals that overlapped with those of patients with thrombosis, which may be explained by unnoticed events. The composite outcome was also associated with mortality in this series [19].

To assess the hypothesis that COVID-19 SARS has an increased risk of thrombosis when compared to conventional SARS, a propensity-score matched study was conducted comparing retrospectively a cohort of COVID-19 patients from a French tertiary hospital to a historical cohort of non-COVID-19 SARS. After population matching, only 222 patients remained (77 COVID-19 patients), of which the composite outcome of any thrombotic event was reached in only 16 patients. Therefore, while the patients with COVID-19 SARS had significantly more events (n=9, 11.7% vs n=7, 4.8%; p=0.04) at the expense of PE (n=9), the confidence of these results is diminished by the low number of events [21].

This study also found that 87.7% of the COVID-19 patients tested had detectable levels of lupus anticoagulant. While this could be related to an aged population, it also correlated to disease severity.

4. THERAPEUTIC INTERVENTIONS

Regarding the amount of evidence about the role of thrombosis in COVID-19 patients, especially in the hospitalized and severely ill, few strategies have been proposed, with a limited number of studies published -none of them prospectively controlled randomized trials. However, we may expect a huge number of those in the forthcoming months, as the avalanche of papers about COVID-19 hits. Whether this will clarify the role of interventions in the prevention of thrombosis in these patients is another matter.

Due to the apparent importance of microthrombi in the progression of COVID-19 SARS -despite the fact that it is not clear whether this finding is exclusive of COVID-19- aspirin was proposed since, secondary to endothelial dysfunction, platelet aggregation is supposed to play a key role.

However, only one study has assessed the role of aspirin in COVID-19. This retrospective study extracted data from the CRUSH COVID registry from the US. Such registry included adult patients with COVID-19 pneumonia confirmed by PCR, excluding those deemed not fit for ICU admission and those that were already ventilated at admission, since this was the primary outcome assessed. The study group included those patients that received aspirin during their hospital stay -provided that the primary outcome developed after the first 48 hours of treatment- and those that were receiving it at home for chronic conditions. The aspirin group was significantly older and with more comorbidities, as expected. But the unexpected finding was that this group, with a significantly higher proportion of frailer patients, was in a substantially better state at admission, with a higher proportion of patients at room air and a three times lower amount of patients requiring intubation at admission. A significant remark is that 75.5% in the aspirin group was already taking aspirin at home, so that the proportion of patients in which there was an actual intervention is underrepresented. Another remark is that even though the results were balanced through a Cox-regression, since the primary outcome occurred more frequently at admission in the no-intervention group, this imbalance could not be corrected [31].

They found no difference in major bleeding or overt thrombosis and found a significant difference in the primary outcome of mechanical ventilation favoring the aspirin-treated group in the unadjusted analysis. After adjusting, the benefit of aspirin use on the risk of mechanical ventilation remained significant (aHR 0.56; 95% CI 0.37-0.85, p=0.007) and also reduced the risk of ICU admission -in approximately the same magnitude- and in-hospital mortality (aHR 0.53; 95% CI 0.31-0.90, p=0.02). In the subgroup of patients that did not require mechanical ventilation at admission, the benefit on the risk of the primary outcome and ICU admission was almost reduced to non-significance. Although under-powered, the sensitivity analysis conducted on the timing of aspirin use showed that in those receiving aspirin only in the 7 days prior to hospitalization, the rate of ICU admission did not significantly differ from those not treated.

Therefore, one could conclude from this study that maybe those patients that received aspirin at admission, benefitted from its administration. However, irremediable

asymmetries at admission, inconclusive results, the retrospective nature and the faulty methodology do not permit certainty about the results and therefore do not aid in clinical decision making.

In an attempt to prevent clinically significant thrombosis, few authors studied retrospectively the impact of -the nowadays ubiquitous practice of- anticoagulation.

One of the first retrospective studies included 2075 Spanish COVID-19 patients. It found that even when the group of heparin-treated patients was sicker and older, after adjustments, anticoagulation was associated with a decreased risk of in-hospital mortality (OR 0.42 95% CI 0.25-0.55; p<0.001). Similar to these findings, a retrospective study from the Mount Sinai Health System of New York reported that among 2773 COVID-19 patients, those that received systemic dose anticoagulation, even when they were sicker and more prone to end up intubated, were significantly less likely to die after adjustments in a Cox regression (in-hospital mortality 29.1% vs 62.7%; median survival – in days- 21 vs 9) [32].

Among the most cited publications about anticoagulation in COVID-19 patients, that of Tang et al (2020) stands out. It was conducted at the onset of the Chinese epidemic, when anticoagulating these patients were not a regular practice. It included 449 patients with a male-to-female ratio of 1.5 and a median age of 65.1 years. 99 patients (22%) were treated with heparin (mainly low-molecular-weight heparin) for at least 7 days. They found 29.8% 28-day mortality, without differences between subgroups, while one would have expected a higher mortality rate in the heparin-treated group, due to baseline severity. In the multivariate analysis -which included underlying diseases and biochemical markers but not clinical presentation- heparin was not significantly associated with mortality risk. However, when stratified according to d-dimer levels, heparin may have prevented the swift increase in mortality shown in the non-treated population when d-dimer levels increased (with d-dimer >8 ULN, 28-day mortality 54.8% vs 33.3%; OR 0.412 95% IC 0.207-0.917; p=0.011) [12].

A retrospective cohort included 3625 patients who tested positive for COVID-19 from one of three medical centers in the Bronx. In these centers a protocol suggested the decision on anticoagulation based on baseline d-dimer levels. Despite the protocol in place, some patients (12.3% with d-dimer <3ug/mL and 5.5% with d-dimer >3ug/dL) did not receive anticoagulation and served as controls to evaluate the impact of anticoagulation on in-hospital mortality. Patients with d-dimer <3ug/mL predominantly received thromboprophylaxis, while those with d-dimer >3ug/dL received therapeutic dose anticoagulation -enoxaparin was the preferred therapeutic regimen for prophylaxis and apixaban for therapeutic anticoagulation. In the multivariate analysis, apixaban and enoxaparin -without differences between prophylaxis and therapeutic dose- were significantly associated with decreased mortality (OR 0.46 95% CI 0.30-0.71 for apixaban prophylaxis and OR 0.49 95% CI 0.32-0.73 for enoxaparin). In an analysis stratified by d-dimer levels, both apixaban and enoxaparin prophylaxis were associated to a mortality reduction in the groups of d-dimer 1 to <3ug/dL and >10ug/dL, with the greater clinical impact on the latter [33].

The best evidence available about anticoagulation in COVID-19 comes from a propensity-score matched retrospective study with an inverse probability of treatment weighting (IPTW), conducted on the Mount Sinai Health System of New York population of COVID-19 patients. Data was recovered through electronic health records and a total of 4389 PCR-positive COVID-19 patients were included to assess the primary endpoint of in-hospital mortality and the secondary endpoints of intubation and major bleeding. 1530 patients received no anticoagulation, 900 patients received treatment-dose anticoagulation and 1959 prophylactic-dose. There was a marked asymmetry at inclusion, with more comorbidities, worse general status and worse biochemical parameters in the anticoagulated group -particularly when treatment-dose was administered. Only a minority of patients was previously anticoagulated due to comorbidities and no patients had evidence of thrombosis at inclusion. There was a 24.4% cumulative incidence of in-hospital mortality, with similar incidence across groups (no anticoagulation 25.6%, prophylactic-dose anticoagulation 21.6% and treatment-dose anticoagulation 28.6%) in the unadjusted analysis. After propensity-score matching, anticoagulation, whether at treatment or prophylactic-dose, significantly reduced in-hospital mortality risk compared to no anticoagulation (HR 0.69 95% CI 0.51-0.94; HR 0.72 95% CI 0.58-0.89, respectively). While prophylactic-dose anticoagulation did not increase the incidence of major bleeding events, a 3% risk was observed with treatment-dose anticoagulation. Only low-molecular-weight heparin and new oral anticoagulants were adequately represented [34].

A recently published phase II trial (HESACOVID) showed that patients treated with therapeutic anticoagulation significantly increased PaO2/FiO2 ratios at day 7 and 14, while the group on prophylactic anticoagulation did not, and showed comparatively a higher median of ventilator-free days and a higher cumulative incidence of liberation from mechanical ventilation (HR 4, 95% CI 1.04-15.1,

p=0.031), albeit the small sample [35].

More recently, a retrospective cohort of 4297 COVID-19 patients with propensity score matching through IPTW was published, using electronic health records from the US Department of Veterans Affairs. This population was composed mainly of men (93.4%) with a median age of 68 years. Apart from that, this health system is characterized by a population with a higher prevalence of chronic health conditions and risk behaviours. 3627 (84.4%) received prophylactic anticoagulation within 24 hours of hospital admission (subcutaneous heparin n=1094, 30.2%; enoxaparin n=2506, 69.1%). These patients had less comorbidity but had a worse clinical condition at admission. After weighting, prophylactic anticoagulation was associated with a reduction in 30-day mortality (HR 0.73 95% CI 0.66-0.81), which represented 22 patients needed to be treated to avoid one death. It also reduced the secondary endpoints of in-hospital mortality and requirement to initiate therapeutic anticoagulation [36].

On January 22, 2021, the US NIH released a preliminary report that stated that based on the interim results of more than 1000 moderately ill patients from three multinational clinical trials, therapeutic anticoagulation in general wards may reduce the requirement of vital organ support [37].

5. DISCUSSION

COVID-19 brings forth the challenges of a new unknown disease. Nevertheless, the medical community is the one that has to rise up to the challenge and provide answers to the public, the patients and the patients' families' demands. The core demand is to determine the best way forward, a path that leads to a decreased mortality in a pandemic that affects millions worldwide.

The evidence about a prothrombotic biochemical state, the histopathological reports of thrombosis -many of which were unsuspected previous to the patients' deaths and subsequent autopsies- and the increased incidence of venous and arterial thrombosis in this population, give utmost importance to the topic of anticoagulation. However, it is extremely difficult to determine whether anticoagulation increases survival, while there is still a lack of randomized controlled trials.

Nevertheless, until such studies are available, the mounting pathophysiological evidence along with findings from retrospective studies is of unsurmounting importance. While retrospective findings bring little certainty to the medical community, due to selection bias and unmeasured confounders, propensity-score matching is among the best available tools. The utilization of such methodology in the Mount Sinai study is therefore a certain advantage. Another advantage is that the endpoint assessed was in-hospital mortality, reducing uncertainties derived from softer endpoints or doubts about the clinical importance of asymptomatic thrombosis and the possibility of under-diagnosis.

However, this methodology is still subjected to unmeasured confounders, if those are not recognized when the study is designed. Particularly, most biases would derive from the inclusion of sicker patients among those anticoagulated, which would decrease the probability of finding a mortality benefit rather than augment it. Finally, the mortality benefits observed, due to their magnitude, are unlikely to be derived from biases or chance.

We remark that performing prospectively controlled randomized trials that assess anticoagulation and therapeutics that impact on the development of microthrombi is of utmost importance and that not performing them would be an irreparable mistake. Meanwhile, it is the authors´ opinion that prophylactic-dose anticoagulation should be offered to critically ill hospitalized COVID-19 patients, particularly those with high d-dimer levels, since they are the population most likely to benefit from it.

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