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IM - REVIEW

COVID-19, coagulopathy and venous thromboembolism: more questions than answers

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Abstract

The acute respiratory illnesses caused by severe acquired respiratory syndrome corona Virus-2 (SARS-CoV-2) is a global health emergency, involving more than 8.6 million people worldwide with more than 450,000 deaths. Among the clinical manifestations of COVID-19, the disease that results from SARS-CoV-2 infection in humans, a prominent feature is a pro-thrombotic derangement of the hemostatic system, possibly representing a peculiar clinicopathologic manifestation of viral sepsis. The severity of the derangement of coagulation parameters in COVID-19 patients has been associated with a poor prognosis, and the use of low molecular weight heparin (LMWH) at doses registered for prevention of venous thromboembolism (VTE) has been endorsed by the World Health Organization and by Several Scientific societies. However, some relevant issues on the relationships between COVID-19, coagulopathy and VTE have yet to be fully elucidated. This review is particularly focused on four clinical questions: What is the incidence of VTE in COVID-19 patients? How do we frame the COVID-19 associated coagulopathy? Which role, if any, do antiphospolipid antibodies have? How do we tackle COVID-19 coagulopathy? In the complex scenario of an overwhelming pandemic, most everyday clinical decisions have to be taken without delay, although not yet supported by a sound scientific evidence. This review discusses the most recent findings of basic and clinical research about the COVID-associated coagulopathy, to foster a more thorough knowledge of the mechanisms underlying this compelling disease.

Keywords COVID-19 · Coagulopathy · D-dimer · Unfractionated heparin · Low molecular weight heparin · Venous thromboembolism · Antiphospholipid antibodies · Disseminated intravascular coagulation · Sepsis-induced coagulopathy

Introduction

In December 2019, a cluster of acute respiratory illnesses caused by severe acquired respiratory syndrome corona virus-2 (SARS-CoV-2) virus occurred in Wuhan, Hubei Province, China. The disease has rapidly spread from Wuhan to many other countries, soon becoming a global health emergency. Indeed, at the time of this writing, more than 8.6 million cases of COVID19 have been reported worldwide with more than 450,000 deaths [1].

Although most patients have mild manifestations and good prognosis after infection, some of them develop severe symptoms and die from multiple organ complications [2–4]. The pathogenesis of COVID-19, the disease that results from SARS-CoV-2 infection in humans, remains unclear, but it is very likely that the most severe manifestations of this disease may be linked to host–pathogen interaction immune mechanisms [5, 6]. In critically ill COVID-19 patients, indeed, massive cytokine storms (including IL-6, TNF-α, and other inflammatory biomarkers), as well as increments of circulating neutrophils and monocyte activation, are typically observed together with low T lymphocyte counts and functional exhaustion of effector T cell responses [5, 6]. Such ineffective and detrimental expansions of innate/humoral responses, alongside T cell suppression, are reminiscent of classical features of sepsis, which is currently defined as a life-threatening organ dysfunction induced by dysregulated host response to infection, being characterized not only by systemic inflammatory response syndrome

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(SIRS) with related endothelial and organ damage, but also by impairment of adaptive T cell immunity [5, 6]. Moreover, the derangement of the hemostatic system observed in end-stage COVID-19 could well fit with the idea that severe COVID-19 possibly represents a peculiar clinicopathologic form of viral sepsis, displaying a prominent prothrombotic feature instead of the hemorrhagic one observed in other viral diseases, such as Lassa, Marburg and Ebola hemorrhagic fevers [7].

From a clinical perspective, the extent of the derangement of coagulation parameters in patients affected by severe COVID-19 pneumonia has been found to be associated with a poor prognosis [8, 9]. In these patients, low molecular weight heparin (LMWH) or unfractionated heparin (UFH) at doses registered for prevention of venous thromboembolism (VTE) seemed to be associated with a lower risk of death [10] and is currently recommended by the World Health Organization [11] and by several scientific societies [12–18] (Table 1).

However, some relevant issues on the relationships between COVID-19, coagulopathy and VTE have yet to be fully elucidated.

What is the incidence of VTE in COVID-19 patients?

Data on this issue are puzzling, as the reported incidence of VTE in COVID-19 patients ranges from 0% to about 8% in general wards [19–22], and from 16 to 35% in the ICU setting, often despite adequate LMWH prophylaxis [21–28].

An even higher rate of VTE, up to 58%, has been reported in consecutive autopsies performed in COVID-19 patients in whom VTE was not suspected before death [29] (Table 2).

Several reasons may account for this discrepancy: just a few studies systematically screened patients for VTE, and imaging in suspected cases is challenging in the setting of a striking pandemic, with overcrowded hospital wards, given the risk of transmitting infection to other patients or health-care workers and the technical problems in performing investigation for pulmonary embolism (PE) in critically ill patients in prone position.

On this ground, it is conceivable that a non-negligible portion of PE episodes remains undiagnosed, because of these technical constraints. However, deep vein thrombosis (DVT) is rarely found in these patients [24], raising the question whether the occlusions observed in the pulmonary vascular bed of COVID-19 patients result from embolization of a DVT or from a localized thrombotic microangiopathy [19].

The question is not trivial, as the pathophysiological mechanism triggering the pulmonary vascular disease in COVID-19 could impact on the treatment.

Indeed, whereas high doses of UFH or LMWH are the mainstay of treatment in case of established pulmonary embolism from peripheral vein thrombosis, the same treatment would be ineffective, or even dangerous because of the bleeding risk, in the hypothesis that a thrombotic microangiopathy would be mainly responsible for the pulmonary vascular occlusion observed in COVID-19 patients in the absence of a proven DVT [19].

On these grounds, a better knowledge of the pathogenesis of COVID-19 coagulopathy is urgently needed to provide more precisely targeted treatments to this disease.

How do we frame the COVID-19-associated coagulopathy, that is, DIC, SIC, CAC or PIC?

Despite a rapidly growing amount of literature on this topic [7, 30–35], the pathophysiological mechanisms underlying the derangement of the hemostatic system induced by SARS-Cov2 have not been fully elucidated yet. Indeed, no evidence of an intrinsic procoagulant effect exerted by the SARS-CoV-2 virus is so far available. Therefore, the most reasonable hypothesis is that the virus activates the coagulation cascade by eliciting a large-scale inflammatory response, similar to that observed in other forms of sepsis. Several studies have already demonstrated the tight interconnection between thrombosis and inflammation, two processes mutually reinforcing each other [36, 37]. Both coagulation factors and platelets are directly implicated in the modulation of the host immune response, displaying proinflammatory functions independent of their hemostatic effects [38–40]. Moreover, the cytokines storm stimulates the expression of tissue factor on monocytes/macrophages and vascular endothelial cells, on whose surfaces the coagulation cascade is initiated. The thrombus formation at the microvascular level contributes to tissue ischemia and organ dysfunction [41].

A remarkable inflammatory response can be observed in COVID-19 patients, attested by a significant increase in fibrinogen, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), interleukin-6 (IL-6) and ferritin levels [42, 43]. Moreover, the increase of IL-6 levels has been found to correlate with that of fibrinogen, confirming the link between inflammation and procoagulant changes [44].

The hypercoagulable state of COVID-19 patients has been assessed mainly by viscoelastic methods [44–46] or by an increase in D-dimer levels, whose extent correlates with the risk of death [8, 47, 48]. This finding is not surprising, as increased D-dimer levels have already been demonstrated to be associated with a poorer outcome in other cohorts of septic patients [49].

However, the exact role of D-Dimer test in the context of COVID-19 coagulopathy deserves some further comments.

Table 1 Main recommendations endorsed by International institutions or scientific societies on antithrombotic therapies in COVID-19

Institution [ref]	Setting	Recommendation
WHO [11]	VTE prophylaxis	Recommended with LMWH [preferred] OD or UFH 5000 IU sc BID or TID in adolescents and adults without contraindications
ISTH [12]	VTE prophylaxis in all hospitalized pts.	Recommended with LMWH at prophylactic dose unless contraindicated *(i.e., active bleeding, plt* $< 25 \times 10^9$*/L; monitoring advised in severe renal impairment; abnormal PT or APTT is not a contraindication)*
SISET [13]	VTE prophylaxis in all hospitalized pts.	Strongly recommended with LMWH, UFH, or fondaparinux at doses indicated for VTE prophylaxis *Intermediate-dose LMWH* (i.e., enoxaparin 4,000 IU BID) *can be considered on an individual basis* in patients with multiple risk factors for VTE (i.e., BMI > 30, previous VTE, active cancer, etc.). Therapeutic doses of UFH or LMWH not supported by evidence outside of proven VTE
	VTE prophylaxis after hospital discharge	Suggested at home for 7–14 days after hospital discharge or in the pre-hospital phase, in case of pre-existing or persisting VTE risk factors
Swiss Society of Hematology [14]	VTE prophylaxis in all hospitalized pts.	Recommended according to a risk stratification score, unless contraindicated, with LMWH if CrCl > 30 ml/min according to the prescribing information; consider an increased dose in overweight patients (> 100 kg). If CrCl < 30 ml/min, UFH SC BID or TID or IV
	ICU pts.	Intermediate or therapeutic dosing of LMWH or UHF should be considered, according to the bleeding risk, in pts. with a large increase in D-dimers, severe inflammation, or signs of hepatic or renal dysfunction or imminent respiratory failure
Prevention and Treatment of VTE associated with COVID-19 Infection Consensus Statement Group [15]	VTE prophylaxis in severe or critically ill pts.	Strongly recommended with LMWH in pts. at low or moderate risk of bleeding and with no contraindication
	VTE prophylaxis in mild and moderate pts.	Recommended with LMWH in pts. assessed to have a high or moderate risk of VTE (PADUA or IMPROVE RAM), in the absence of contraindication
	VTE prophylaxis after hospital discharge	Consider prolonged outpatient VTE prophylaxis with LMWH in pts with persistent risk factors for VTE
	VTE treatment	Curative anticoagulant parenteral treatment with LMWH recommended in pts. *suspected* for VTE, in absence of contraindication
ASH [16]	VTE prophylaxis in all hospitalized pts.	Recommended with LMWH or fondaparinux unless the risk of bleeding is judged to exceed the risk of thrombosis
	VTE prophylaxis after hospital discharge	Consider extended thromboprophylaxis after discharge using a regulatory-approved regimen (DOAC up to 40 days)

Table 1 (continued)

Institution [ref]	Setting	Recommendation
Anticoagulation Forum [17]	VTE prophylaxis in non-critically ill hospitalized pts.	Recommended with LMWH standard doses, regardless of VTE risk assessment score
	VTE prophylaxis in ICU pts.	Recommended with increased doses of heparin (e.g., enoxaparin 40 mg SC BID, enoxaparin 0.5 mg/kg SC BID, UFH 7500 IU SC TID or low-intensity IV
	VTE prophylaxis after discharge	Not routinely recommended; consider on a case-by-case basis
CHEST Guidelines [18]	VTE prophylaxis in acutely ill hospitalized pts.	Recommended with LMWH or fondaparinux at standard doses over intermediate or full treatment dosing or over DOAC
	VTE prophylaxis in critically ill hospitalized pts.	Recommended with LMWH of UFH over fondaparinux or DOAC Suggested current standard dose over intermediate or full treatment dosing
	VTE prophylaxis after hospital discharge	Recommended inpatients prophylaxis only over inpatient plus extended prophylaxis after hospital discharge

WHO World Health Organization, *VTE* venous thromboembolism, *OD* once daily, *SC* subcutaneously, *BID* twice daily, *TID* three times daily, *IV* intravenously, *ISTH* International Society on Thrombosis and Hemostasis, *pts* patients, *SISET* Italian Society on Thrombosis and Hemostasis, *LMWH* low molecular weight heparin, *UFH* unfractionated heparin, *CrCl* Creatinine clearance, *PT* prothrombin time, *APTT* activated partial thromboplastin time, *CrCL* creatinine clearance, *ICU* intensive care unit, *ASH* American Society of Hematology, *DOAC* direct oral anticoagulants

Table 2 Incidence of venous and arterial thromboembolism in hospitalized COVID-19 patients

Author [ref]	Setting	Generalized VTE screening	VTE incidence
Cattaneo [19]	64 GW pts on LMWH prophylaxis	yes	0% DVT
Zhang [20]	143 GW pts. (37% on LMWH prophylaxis)	yes	16% proximal DVT, 30% distal DVT (one ward) 8.8% DVT (all the hospital)
Lodigiani [21]	314 GW pts (75% on LMWH prophylaxis) 48 ICU pts (100% on LMWH prophylaxis)	yes	GW: PE 2.5%, 1% DVT (including UEDVT), 1.9% stroke ICU: PE 4.2%, 4.1% isolated DVT (including UEDVT), 6.3% stroke
Middeldorp [22]	123 GW pts (standard LMWH prophylaxis) 75 ICU pts (doubled LMWH prophylaxis)	Yes (28% GW)	GW: PE 6.6%, 13% DVT (including UEDVT) ICU: PE 15%, 32% DVT (including UEDVT)
Thomas [23]	63 ICU pts (standard LMWH prophylaxis)	no	8% PE, 1.5% DVT (including UEDVT)
Klok [24]	184 ICU pts on LMWH prophylaxis	no	35% PE, 1.6% DVT (including UEDVT) **3.8% ATE**
Poissy [25]	107 ICU pts (100% on VTE prophylaxis)	no	20.6% PE
Cui [26]	81 ICU pts NOT on LMWH prophylaxis	yes	25% DVT
Llitjos [27]	26 ICU pts (31% LMWH prophylactic, 69% therapeutic)	yes	23% PE VTE significantly higher in pts. on prophylactic vs therapeutic anticoagulation (100% vs. 56%)
Helms [28]	150 ICU pts (70% LMWH prophylactic, 30% therapeutic)	no	16.7% PE 2.6% ATE
Whichmann [29]	12 consecutive AUTOPSIES on COVID-19-positive pts	–	Unsuspected DVT in 7 of 12 patients (58%) PE direct cause of death in 4 patients

GW general ward; pts: patients, *LMWH* low molecular weight heparin, *DVT* deep vein thrombosis, *ICU* intensive care Unit, *UEDVT* upper extremity deep vein thrombosis, *VTE* venous thromboembolism, *ATE* arterial thromboembolic events, *PE* pulmonary embolism

A recent review of nearly 20 papers reporting original data on D-dimer levels in COVID-19 showed some relevant bias, as most publications neither identified whether D-dimer values were reported as D-dimer units (DDU) or fibrinogen equivalent units (FEU) (~ 2 × differences), nor report on normal cutoff values [50]. These methodological flaws greatly reduce the usefulness of this parameter on a clinical decision setting.

Moreover, the reliability of D-dimer test as prognostic factor in septic patients has already been questioned by Semeraro and colleagues in a paper published before the onset of COVID-19 pandemic [51]. The The authors found that the D-dimer levels poorly correlate with the risk of death in a population of septic patients admitted to ICU. On the other hand, they showed that D-dimer corrected for thrombin and plasmin generation (DD_{corr}) more properly reflects the tilting of coagulation–fibrinolysis balance, displaying a high prognostic value in septic patients [51]. Notably, the authors found the highest mortality in patients with low DD_{corr} levels, which reflect the fibrinolytic shutdown associated with late and more severe phases of sepsis. The mechanisms behind fibrinolysis suppression are multiple and include PAI-1 elevation, TAFI activation, and release of nuclear products such as histones and DNA.

This finding warrants particular attention in the context of COVID-19 coagulopathy, as it has been reported that fibrinolysis shutdown, assessed by elevated D-dimer levels and complete failure of clot lysis at 30 min on thromboelastography, predicts thromboembolic events and need for hemodialysis in critically ill COVID-19 patients [52]. Of note, in this population of 44 COVID-19 admitted to ICU, the median ISTH disseminated intravascular coagulation (DIC) score was 0 (0-2), with no patients having a score higher than 4 [52].

Consistent with this finding, other reports showed that COVID-19 patients do not typically develop overt systemic DIC, unless in the late stages of the disease, as demonstrated by the consistent observation that platelet count and fibrinogen concentration are not significantly reduced in these subjects, despite a marked increase in D-dimer concentrations [7, 8].

Moreover, only 21.6% of subjects in a cohort of critically ill COVID-19 patients have been found to meet the criteria for an infection-induced organ dysfunction and coagulopathy according to the sepsis-induced coagulopathy (SIC) score of the International Society on Thrombosis and Haemostasis [7, 53].

These findings suggest that the linear progression from SIC to DIC usually seen in septic patients does not necessarily occur in the process of SARS-Cov2 infection, which seems to be rather associated with a peculiar form of coagulopathy, termed by some authors as "COVID-19-associated coagulopathy" (CAC) [54]. CAC displays clinical and laboratory features distinct from either DIC or SIC, such as the lack of consumption of platelets and coagulation factors, first of all fibrinogen, the very low incidence of bleeding, and the main involvement of the pulmonary microcirculation, determining a localized microangiopathy, named by other authors as pulmonary intravascular coagulopathy (PIC) [55]. (Table 4).

This peculiar involvement of pulmonary microvascular bed during the course of SARS-CoV2 infection fits well with the reported high rate of acute respiratory distress syndrome (ARDS) in COVID-19 patients (about 40% of cases) [9]. Of note, ARDS itself has been identified as a hemostatic disease occurring as a result of endotheliopathy in critically ill patients. Generalized endotheliopathy in turn activates in a vicious circle the inflammatory and microthrombotic pathway, which promotes consumptive thrombocytopenia, TTP-like syndrome, and hypoxic multi-organ failure [56].

How do we gather these puzzling data on a unified clinicopathological picture, helpful to improve the management of CAC?

1. Although the mechanism underlying CAC has not been fully elucidated, it is conceivable that the major role in its development is played by the activation of the thromboinflammation pathway induced by a "cytokines storm" elicited by SARS-CoV2 infection.
2. As in other forms of sepsis, endothelial dysfunction leading to widespread microthrombosis, mainly localized in the pulmonary vascular bed, is observed in COVID-19 patients. In this regard, it has been demonstrated that SARS-CoV-2 uses angiotensin-converting enzyme (ACE) 2 receptor to facilitate viral entry into target cells [56, 57]. Thye ACE2 system is a critical protective pathway against heart failure, myocardial infarction and hypertension, and against lung disease and diabetes mellitus [58]. In experimental models of lung disease, catalytically active ACE2 alleviates pulmonary injury and vascular damage and prevents pulmonary hypertension, decreases lung fibrosis and arterial remodeling, and improves right ventricular performance [58]. ACE2 is highly expressed on alveolar epithelial type II cells (AECII), which can serve as a reservoir for viral invasion, and also in endothelial cells. SARS-CoV-2 infection can induce endothelial cell injury in several organs, because of direct viral involvement, of the host inflammatory response and of the induction of apoptosis and pyroptosis [59, 60]. COVID-19-endotheliitis could explain the systemic impaired microcirculatory function in different vascular beds and the clinical sequelae in patients affected by this disease [61].
3. Thrombotic microangiopathy, induced by an enhanced platelet–vessel wall interaction, mainly induced by the release of (ultralarge) von Willebrand factor (VWF) mul-

timers as a result of inflammation-induced endothelial cell perturbations, is thought to be a major component of the SIC [62]. The level of (ultralarge) VWF multimers in patients with sepsis has been shown to be inversely correlated with the plasma level of ADAMTS-13, and several studies have confirmed the association between low ADAMTS-13 levels and sepsis severity. Of note, very recently Bazzan and colleagues reported significantly reduced ADAMTS-13 levels in a cohort of COVID-19 patients [63]. Moreover, they found that ADAMTS-13 levels lower than 30% were significantly associated with a higher mortality, suggesting that low ADAMTS-13 associated with high plasma VWF levels can have a role in the strong prothrombotic tendency observed in COVID-19 patients [63].

Taken together, these findings suggest that the pathogenesis of CAC, although multifactorial, is mainly localized at a microvascular level, with a late involvement of venous and arterial vessels. Such a pathophysiological picture raises some questions about the effectiveness of fully antithrombotic doses of anticoagulants to effectively tackle this disease, as later discussed.

Which role, if any, do antiphospholipid antibodies have?

Among the coagulation abnormalities found in COVID-19 patients, some reports of positivity for antiphospholipid antibodies (APL) are of particular interest [64–66] (Table 3).

However, these findings are worth discussing.

Table 3 Antiphospholipid antibodies in COVID-19 patients

Author [ref]	Setting	Relevant issues
Zhang [64]	3 ICU pts with stroke	aCL and aβGPI IgA → the significance of these tests remains controversial and their implementation is not recommended LAC not assessed
Harzallah [65]	56 hospitalized pts	45% LAC positive aCL or aβ2GPI detected in only 5/50 pts (10%, 3 associated to LAC) using IgG and IgM detection
Bowles [66]	216 hospitalized pts 44 with prolonged APTT	34/31 (91%) with prolonged APTT were LAC positive 2 VTE No aCL or aβ2GPI reported
Abdel-Wahab [69]	Systematic review on aPL in viral infections	aCL = 13–63% LAC = 2% aβ2GPI = 2–9% Statistically significant increased risk of TE observed only in pts with HCV and positive aPL

ICU intensive care unit, *aCL* anticardiolipin antibodies, *aβGPI* anti-beta2 Glicoprotein I antibodies, *LAC* lupus anticoagulant, *APTT* activated partial thromboplastin time, *VTE* venous thromboembolism, *HCV* hepatitis C virus, *aPL* antiphospholipid antibodies

Table 4 Main laboratory and clinical features of DIC, SIC and CAC

	OVERT DIC	SIC	CAC
Laboratory features			
Platelet count	↓↓↓	↓↓	↔
APTT ratio	↑↑↑	↑	↔
PT ratio/INR	↑↑↑	↑↑	↔
Fibrinogen levels	↓↓↓	↓↓	↑↑↑
D-dimer levels	↑↑	↑↑	↑↑↑
Clinical features			
Bleeding	Common, often serious	Sometimes present	Very rare
Microthrombosis	Present in initial phases, then coagulation factors consumption prevails	Present, leading to hypoxic organ dysfunction	Very pronounced, mainly in the pulmonary microcirculation
Organ involvement	Multi-organ failure	Multi-organ failure: respiratory, cardiovascular, hepatic, renal	Mainly pulmonary

DIC disseminated intravascular coagulation, *SIC* sepsis-induced coagulopathy, *CAC* coronavirus-associated coagulopathy, *APTT* activated partial thromboplastin time

The tests for assessing APL are slippery ones, because their results are affected by several pre-, post- and analytical factors, including methodical problems due to the heterogeneity of the autoimmune antibodies, inadequate standardization of assays, differences in local working conditions, difficulties in correct interpretation of the results, lack of large prospective evaluation studies, lack of a link between antibody potency and clinical effect [67].

Notably, only the paper from Harzallah and colleagues reported the results of lupus anticoagulant (LA), anticardiolipin (aCL) and anti-beta2 glycoprotein I (aGPI) IgG and IgM tests [65], whereas current guidelines recommend performing all three tests to diagnose antiphospholipid syndrome (APS) [68].

The same guideline recommends confirming the positivity of APL on two or more occasions, at least 12 weeks apart [68], but the results of this further control, if performed, are not reported by the authors [64–66].

Moreover, the significance of positivity for aCL and aGPI IgA, reported by Zhang and colleagues, is controversial, and the implementation of these assays is not currently recommended [64].

We should recall that APL positivity has been frequently observed during viral infections, but the association with thrombotic phenomenon on this setting is unclear, depending on the aCL and aGPI titers, especially in hepatitis B and C virus infections [69]. Of note, Bowles and colleagues did not report the results of aCL and aGPI tests [66], whereas Zhang and Harzallah did not report the titers of these assays [64, 65].

Moreover, a recently published paper from Galeano-Valle and colleagues found only 2 (8.3%) cases with ACA IgM and aGPI I IgM weakly positive in a cohort of 24 COVID-19 patients with proven VTE [70].

In conclusion, we believe that there is no convincing evidence that aPL plays a relevant role in the hypercoagulable tendency of COVID-19 patients.

Therefore, we suggest that physicians should be very careful before adopting a more aggressive antithrombotic approach in COVID-19 patients only based on aPL positivity, given the many technical aspects that reduce the usefulness of these tests in such a specific setting.

How do we tackle COVID-19 coagulopathy?

First reports from the front of Wuhan showed that the use of LMWH or UFH at prophylactic doses reduced 28-day mortality in COVID-19 patients with severe pneumonia and either an SIC score ≥ 4 (mortality rate 40.0% vs 64.2%, $p = 0.029$), or D-dimer levels > 6-fold the upper limit of normal (mortality rate 32.8% vs 52.4%, $p = 0.017$) [10].

This finding prompted clinicians to look at the "good old heparin", UFH or LMWH, as the panacea for the treatment of COVID-19, because of its already well-known anticoagulant and anti-inflammatory properties [71, 72].

Indeed, LMWH has been shown to protect glycocalyx from shedding and to display immunomodulatory properties [73]. Moreover, in vitro and in vivo experimental studies have shown that human coronaviruses utilize heparin sulfate proteoglycans for attachment to target cells [74], suggesting a potential role for heparin in the therapeutic armamentarium against COVID-19.

Fondaparinux has been also proposed as a treatment for COVID-19 [75], because of its anti-inflammatory and antiviral properties [76, 77]. Fondaparinux can be an attractive drug in this setting, as it is not associated with heparin-induced thrombocytopenia, a fearful side effect of heparin treatment reported in a non-negligible part of COVID-19 patients, which is associated with a worse prognosis [78].

It is conceivable that doses of LMWH higher than those in use for the prevention of VTE in acutely ill medical patients are able to display a more intense anti-inflammatory activity, lowering cytokines storm and improving the clinical course of the disease.

However, no good evidence is available on the efficacy and safety of high dose of LMWH in COVID-19 patients, and many issues remain to be addressed, regarding the proper timing and the proper dosages and administration schemes of anticoagulant drugs.

The issue of the safety of heparin deserves close attention, as Tang and colleagues found a non-significant trend toward a negative effect of the treatment with LMWH in patients with the less severe degree of coagulopathy, as assessed by an SIC score < 4 or D-dimer levels < 6-fold the upper limit of normal [10].

As recently pointed out by Landi and De Servi, one-size-fits-all strategy cannot be applied to COVID-19 patients, and an individualized approach carefully balancing thrombotic and hemorrhagic risk should guide the complex management of these patients [79].

As shown in Table 1, a puzzling discrepancy exists on the doses of heparin suggested in different clinical settings, and no evidence-based recommendations can be issued.

This lack of knowledge prompted several researchers to design clinical trials, most of which randomized, comparing efficacy and safety of different doses of UFH or LMWH (mainly prophylactic vs therapeutic) in COVID-19 patients (Table 5).

From a public health's perspective, these trials failed to recruit because of a massive drop of subjects infected by SARS-Cov2.

However, in the worst case scenario of a further outbreak of the pandemic, these already existing protocols could allow to rapidly obtain a stronger evidence about the best

Table 5 Ongoing trials assessing LMWH or UFH for the treatment of COVID-19 patients

NCT trial number	Study design	Population (all in-hospital)	Intervention	Comparator	Primary Outcome
NCT04401293	Randomized, open label	308 pts with coagulopathy and requiring supplemental oxygen	LMWH at full anticoagulant dose	Prophylactic/intermediate dose enoxaparin	Composite outcome of ATE, VTE and all-cause mortality at 30 days
NCT04344756	Randomized, open label	808 GW and ICU pts	LMWH tinzaparin 175 IU/kg/24 h for 14 days or UFH at full anticoagulant dose	Prophylactic LMWH	Group 1: Survival without ventilation at 14 days (VNI or mechanical ventilation) Group 2: ventilator free survival at 28 days
NCT04345848	Randomized, open label	200 GW and ICU pts	LMWH OR UFH at full anticoagulant dose	Prophylactic LMWH or UFH	Composite outcome of ATE, VTE, DIC and and all-cause mortality at 30 days
NCT04373707	Randomized, open label	602 GW and ICU pts	LMWH at intermediate dose (i.e., 70 IU/kg bid)	Prophylactic LMWH	VTE at: 28 days
NCT04372589	Randomized, open label	300 GW pts	LMWH OR UFH at full anticoagulant dose	Prophylactic LMWH or UFH	Intubation and mortality at 30 days
NCT04367831	Randomized, open label	100 ICU pts	LMWH at intermediate dose (enoxaparin 1 mg/kg SC daily)	Prophylactic LMWH or UFH	Symptomatic VTE or ATE in ICU at 14 days
NCT04377997	Randomized, open label	300 GW and ICU pts with D-dimer > 1500 ng/ml	LMWH or UFH at full anticoagulant dose	Prophylactic LMWH or UFH	Efficacy: composite endpoint of death, cardiac arrest, symptomatic VTE or ATE, AMI, or hemodynamic shock. Safety: major bleeding (ISTH)
NCT04359212	Observational prospective, cohort	90 GW and ICU pts	Prophylactic LMWH of fondaparinux	–	Symptomatic VTE or ATE at 14 days
NCT04409834	Randomized, open label	750 ICU pts	Prophylactic LMWH or UFH + clopidogrel LMWH or UFH at full anticoagulant dose ± clopidogrel	Prophylactic LMWH or UFH	Composite of death due to VTE or ATE, symptomatic VTE or ATE, AMI, stroke, asymptomatic VTE
NCT04394377	Randomized, open label	600 GW and ICU pts with D-dimer > 3 times ULN	Rivaroxaban, LMWH or UFH at full anticoagulant dose	Prophylactic LMWH or UFH	Composite of mortality, number of days alive, number of days in the hospital and number of days with oxygen therapy at the end of 30 days
NCT04362085	Randomized, open label	462 GW patients with D-dimer ≥ 2X ULN	LMWH OR UFH at full anticoagulant dose	Prophylactic LMWH, UFH or fondaparinux	Composite of ICU admission, non-invasive positive pressure ventilation, invasive mechanical ventilation, or all-cause death at 28 days
NCT04366960	Randomized, open label	2712 GW pts.	Enoxaparin 4000 IU BID	Enoxaparin 4000 IU OD	VTE detected by imaging at 30 days

Table 5 (continued)

NCT trial number	Study design	Population (all in-hospital)	Intervention	Comparator	Primary Outcome
NCT04408235	Randomized, open label	300 GW pts with severe pneumonia and coagulopathy	LMWH at intermediate dose (i.e., 70 IU/kg BID)	Enoxaparin 4000 IU OD	Efficacy: composite outcome of ATE, VTE, death and escalation of ventilation and all-cause mortality during hospital stay Safety: major bleeding (ISTH) during hospital stay
NCT04359277	Randomized, open label	1000 GW and ICU pts with D-dimer > 500 ng/ml	LMWH OR UFH at full anticoagulant dose	Prophylactic LMWH or UFH	All-cause mortality at 1 year VTE, ATE, AMI, cardiac arrest hemodynamic shock at 21 days
NCT04412304	Observational, retrospective	166 ICU pts	Three different doses of tinzaparin (prophylactic, intermediate, fully anticoagulant)	-	Days alive from ICU-admission at 28 days
NCT04393805	Observational, retrospective	877 GW and ICU pts	LMWH prophylactic	–	Bleeding Thrombosis Mortaliy
NCT04406389	Randomized, open label	186 GW and ICU pts.	Therapeutic dose: LMWH 1.0 mg/kg BID, UFH according to APTT; fondaparinux 5-10 mg OD according to body weight	Intermediate prophylactic dose: LMWH 0.5 mg/kg BID; UFH 7500 IU TID; fondaparinux 2.5 mg OD	All- cause mortality at 30 days

pts patients, *LMWH* low molecular weight heparin, *UFH* unfractionated heparin, *GW* general ward, *ICU* intensive care unit, *ATE* arterial thromboembolism, *VTE* venous thromboembolism, *SC*: subcutaneously, *ULN* upper limit of normal, *bid* BID; twice daily, *TID* three times daily, *OD* once daily

Available on-line at: https://clinicaltrials.gov; last accessed June 22, 2020

management strategies to improve the outcome of COVID-19 patients.

Conclusions

The COVID-19 pandemic has disrupted many aspects of human life, forcing us to admit that medical knowledge is finite, and that the usual pathway to improve it can be too slow in the devasting scenario of an awfully fast spreading disease.

The CAC reliably illustrates this epistemological problem. The difficult journey toward a better understanding of the coagulation derangement observed in COVID-19 patients has just started, and many questions on this issue still remain unanswered.

It is therefore conceivable that physicians involved in the first-line management of COVID-19 patients are tempted to adopt conceptual shortcuts to rapidly deal with the everyday clinical problems, without waiting for an evidence which is feared to arrive too late for the patients' needs.

On this ground, the scientific community should spare no effort to ensure a faster, but always methodologically sound, process to improve medical knowledge, starting as usual from pathophysiology and cautiously moving toward a stronger evidence provided by properly designed randomized controlled trials.

Perhaps it can be a "long and winding road", but certainly it is worth traveling.

Compliance with ethical standards

Conflict of interest The Authors declare no potential conflicts of interest.

Statement of human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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