Review

Massimo Franchini*, Giuseppe Marano, Mario Cruciani, Carlo Mengoli, Ilaria Pati, Francesca Masiello, Eva Veropalumbo, Simonetta Pupella, Stefania Vaglio and Giancarlo Maria Liumbruno

COVID-19-associated coagulopathy

Abstract: Coronavirus disease 2019 (COVID-19), a viral respiratory illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been recently recognized as a systemic disorder inducing a pro-thrombotic state. The molecular mechanisms underlying the hypercoagulable state seen in patients with COVID-19 is still incompletely understood, although it presumably involves the close link between inflammatory and hemostatic systems. The laboratory coagulation monitoring of severely ill COVID-19 patients is mandatory to identify those patients at increased thrombotic risk and to modulate thromboprophylaxis accordingly. In this review, we summarize the current understanding on the pathogenesis, epidemiology, clinical and laboratory features and management of coagulopathy associated with COVID-19.

Keywords: anticoagulant therapy; COVID-19; prophylaxis; SARS-CoV-2; thromboembolism; thrombosis.

Introduction

A novel flu-like coronavirus named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), causing Coronavirus Disease 2019 (COVID-19, a severe illness mainly affecting the respiratory tract), has been initially associated with an epidemic focused in Wuhan, China at the end of 2019 [1–3]. From there, SARS-CoV-2 has spread quickly throughout China and to neighboring Asian countries but, immediately after, it infected most countries of the world [4, 5]. On March 11, 2020 the World Health Organization (WHO) declared the rapidly spreading coronavirus outbreak a pandemic and Italy is currently one of the countries with the highest number of cases of SARS-CoV-2 (2,32,000 infected cases with 32,000 deaths updated to 20 May, 2020) [6, 7]. Currently, more than 4,500,000 cases have been diagnosed worldwide and over 300,000 infected people have died (data updated on May 20, 2020) [6]. No vaccine, hyperimmune immunoglobulin or specific antiviral agents for COVID-19 are currently available and several therapeutic modalities, including steroids, chloroquine, antiviral medications (i.e., remdesivir, loparinir/ritonavir), anti-inflammatory agents (i.e., tocilizumab, sarilumab) and the use of hyperimmune convalescent plasma, are being investigated in a number of non-randomized or randomized trials in patients with severe COVID-19 [8–16]. Anticoagulant prophylaxis and treatment play also a key role in the management of COVID-19 patients. Indeed, as soon as the first cases of COVID-19 were described, it became evident that SARS-CoV-2-related symptoms were not confined to the respiratory tract but that the virus was able to trigger multiple systemic inflammatory responses and coagulopathy [17–24]. Thromboembolic complications have been consistently reported in almost all publications involving patients' populations from different countries, regardless of racial origin [25]. This concise review will be dedicated to the coagulation abnormalities occurring in association with COVID-19. In particular, we will summarize the current evidence from the published studies, reviews and expert commentaries, focusing on the pathogenesis, laboratory, clinical, and on practical therapeutic and management aspects.

Search methods

For this review we analyzed the medical literature for published articles on the coagulation aspects of SARS-CoV-2 infection. The Medline and PubMed electronic database

*Corresponding author: Massimo Franchini, MD, Italian National Blood Centre, Rome, Italy; Department of Hematology and Transfusion Medicine, Carlo Poma Hospital, Mantua, Italy, Phone: 0039-0376-201234, Fax: 0039-0376-220144, E-mail: massimo.franchini@asst-mantova.it

Giuseppe Marano, Carlo Mengoli, Ilaria Pati, Francesca Masiello, Eva Veropalumbo, Simonetta Pupella, Stefania Vaglio and Giancarlo Maria Liumbruno: Italian National Blood Centre, Rome, Italy

Mario Cruciani: Italian National Blood Centre, Rome, Italy; Infection Control Committee and Antibiotic Stewardship Programme, AULSS9, Scaligera, Verona, Italy

was searched for publications during the period January 2020–May 2020 using English language as a restriction. The Medical Subject Heading and key words used were: "novel coronavirus disease", "COVID-19", "SARS-CoV-2", "acute respiratory distress syndrome", "coagulopathy", "coagulation", "thrombosis", "deep vein thrombosis", "pulmonary embolism", "venous thromboembolism", "disseminate intravascular coagulation", "anticoagulants", "low molecular weight heparin". We also screened the reference lists of the most relevant review articles for additional studies not captured in our initial literature search.

Pathogenesis and laboratory features of coagulopathy associated with COVID-19

Sars-CoV-2 has a peculiar mechanism of infection, utilizing the angiotensin-converting enzyme 2 (ACE-2) receptors on human cells, including endothelial cells [26]. In particular, the binding to ACE-2 receptors on endothelial cells initiates localized inflammation, endothelial activation, tissue damage and altered cytokine release (tumor necrosis factor [TNF]-α, interleukin [IL-1, IL-2 and IL-6]), which are responsible for the activation of coagulation frequently reported in COVID-19 patients [19, 20]. The suggested underlying molecular mechanism involves a pivotal role for angiotensin-II (AngII), which is metabolized by ACE-2 to the vasodilatory and anti-inflammatory peptide angiotensin [20]. The consumption of ACE-2 by viral entry in the early phases of the infection leads to the interruption of AngII metabolism, with the resulting increase in its plasma concentration. AngII exerts a number of prothrombotic effects, including vasoconstriction, endothelial and platelet activation, and pro-inflammatory-cytokine release [20]. Another pathogenic pathway involves the neutrophil extracellular traps (NETs), which protect against pathogens but also may be implied in thromboinflammation by activating the contact or other prothrombotic pathways resulting in enhanced thrombin generation [19]. NETs are recognized as linking inflammation, coagulation, and thrombosis both locally and systemically in multiple conditions [27]. Finally, dysregulated complement activation has been demonstrated to contribute to coagulopathy, not only by exerting pro-inflammatory effects, but also with a direct pro-thrombotic effect through activation of platelets and endothelial cells, as well as increasing tissue factor and von Willebrand factor expression [28]. In addition to the previous pathogenic mechanisms, the prolonged

immobilization of patients, along with co-morbidities (cancers, diabetes, cardiovascular disorders, inherited thrombophilia) and patients' characteristics (advanced age and obesity) certainly contribute to this hypercoagulable state. A number of coagulation abnormalities are typically found in patients with severe COVID-19 and about 20–55% of COVID-19 patients admitted to hospital have laboratory evidence of coagulopathy [21, 22], the most relevant including an elevation of D-dimer concentration, a decrease of platelet count and fibrinogen concentration and a prolongation of prothrombin time (PT) [21, 29, 30]. In a large study on 1,099 patients with COVID-19 from China, elevated D-dimer levels (>0.5 mg/L) were found in nearly half of the patients (260/560, 46%) [31]. In another observational study in 183 patients with COVID-19 in China, a statistically significant difference in mean D-dimer concentration at admission was found between survivors and non-survivors COVID-19 patients (2.12 mg/L [range 0.77–5.27] in non-survivors vs. 0.61 mg/L [range 0.35–1.29] in survivors, p<0.05) [32]. In another study [2], D-dimer on admission greater than 1 mg/L was associated with an 18-times increased risk of death (95% CI 2.6–128.6; p=0.0033). The correlation between D-dimer levels and COVID-19 severity emerged from another study which found that patients who were admitted to the intensive care unit (ICU) had significantly higher median D-dimer concentrations (2.4 mg/L, IQR 0.6–14.4) than patients who received no ICU care (0.5 mg/L, 0.3–0.8) [33]. Finally, in a prospective cohort study conducted among 5,279 COVID-19 patients admitted to hospital in New York City, D-dimer levels greater than 2.5 mg/L were associated with an approximately fourfold higher odds of critical illness than a normal D-dimer concentration [34]. Regarding thrombocytopenia, studies in COVID-19 patients have reported that only about 5% of them have a platelet count of less than 100×10^9/L [31, 33]. However, a mild thrombocytopenia (platelet count <150×10^9/L) can be found in 70–95% of cases with severe COVID-19. A meta-analysis by Lippi and colleagues [35] identified significantly lower platelet count in patients with severe disease (mean difference: -31×10^9/L, 95% CI: -35 to -29×10^9/L) and thrombocytopenia was associated with fivefold higher odds of having severe disease (OR: 5.13; 95% CI: 1.81–14.58). Notably, a direct correlation between platelet count decrease and mortality for COVID-19 was showed by Yang and colleagues [36] in a study on 1,476 consecutive patients. Among the coagulation parameters, PT is another test that results altered during COVID-19. In the above mentioned Chinese study [32], PT was only mildly prolonged in patients with severe COVID-19 who died vs. survivors (15.5 s [range 14.4–16.3 s] vs. 13.6 s [range 13.0–14.3 s]). Finally, fibrinogen levels in

COVID-19 patients are often increased, due to the acute phase response [22]. However, in the late stage of the disease, fibrinogen levels were significantly lower (<1 g/L) in non-survivors vs. survivors [33], assuming the characteristics of a worse prognostic factor. A significant coagulopathy (increased D-dimer and fibrinogen levels) correlating with COVID-19 severity was observed by Fogarty and colleagues in a study conducted in 83 Caucasian patients [37]. The COVID-associated hypercoagulability was confirmed also by viscoelastic coagulation tests in two different studies conducted in Italy [38, 39]. Similarly, Wright and colleagues found that fibrinolysis shutdown, as evidenced by elevated D-dimer levels and complete failure of clot lysis at 30 min on thromboelastography, predicts thromboembolic events in critically ill patients with COVID-19 [40].

The excess production of pro-inflammatory cytokines, increased levels of damage-associated molecular patterns (DAMPs) and endothelial damage are at the basis of the disseminated intravascular coagulation (DIC) occurring during severe infections and/or sepsis, which is characterized by reduction in coagulation factors levels associated with increased fibrinolysis [19]. Although the COVID-19-associated coagulopathy (thrombocytopenia, D-dimer elevation and prolonged PT) resembles that observed in DIC associated with sepsis, most cases cannot be classified as having DIC according to the score of the International Society on Thrombosis an Haemostasis (ISTH) for the peculiar laboratory features (very high D-dimer levels and mild thrombocytopenia), at least at an early stage of COVID 19 infection [41]. Overt cases of DIC may be observed in later stages of COVID-19 [19].

Clinical features of coagulopathy associated with COVID-19

Pertaining to the clinical features of COVID-19 coagulopathy, both arterial and thrombotic events have been reported [42]. Despite the use of anticoagulant prophylaxis, a high rate of thromboembolic events (7.7% of total; cumulative rate 21%) within 24 h of admission was observed by Lodigiani and colleagues in a single-center study conducted in Italy on 388 consecutive COVID-19 patients [43]. Such events included predominantly venous thromboembolism (VTE, 57%), while arterial thromboembolic episodes (i.e., ischemic stroke and acute coronary syndrome/ myocardial infarction) accounted for the 43% of the total cases [43]. In a recent Dutch paper, symptomatic VTE was diagnosed in 15% (cumulative rate 27%) of 184 patients receiving thromboprophylaxis during intensive care and mainly consisted of pulmonary embolism (PE, 25/28 cases), while only a minority of patients (3.7%) experienced arterial thrombotic events [44]. A recent analysis from a French group showed that the rate of thromboembolic complications in 150 COVID-19 patients with acute respiratory distress syndrome (ARDS) was much higher (11.7%) than what observed in a historical control group of non-COVID-19 ARDS patients (2.1%) despite anticoagulation [45]. Another center in France also found a prevalence of PE of 20.6%, higher than the 6.1% found in a cohort of ICU patients from the same time period the year before [45]. Of the 22 PE that occurred in the first 107 patients admitted to the ICU, 20 occurred while patients were on standard dose VTE prophylaxis [46]. The COVID-19-associated prothrombotic risk was further confirmed by early autopsy reports demonstrating microvascular thrombosis as well as marked inflammatory changes [47].

Management of coagulopathy associated with COVID-19

While heparin thromboprophylaxis has been usually utilized in hospitalized COVID-19 patients according to their thrombotic risk, the experience of ICU revealing the growing need for more attention to thromboembolic complications in severely ill patients has prompted to reconsider a more extensive use of anticoagulation [48–50]. The first evidence of the beneficial effect of heparin come from the Chinese study by Tang and colleagues in a retrospective report on 449 COVID-19 patients [51]. Although no difference on the 28-day mortality was found between heparin users and non-users (30.3 vs. 29.7%, p=0.910), low molecular weight heparin (LMWH) prophylaxis was associated with a significantly lower mortality in patients with sepsis-induced coagulopathy score ≥4 (users vs. non-users: 40 vs. 64.2%; p = 0.029) and in those with higher D-dimer levels (six times upper normal limit; users vs. non-users: 32.8 vs. 52.4%; p = 0.017) [51]. Another recent study examined two groups of patients, those with COVID-19 and those without COVID-19. The COVID-19 group with elevated D-dimer levels (>6 times the upper limit of normal) showed lower mortality rates with LMWH administration (40–60 mg of enoxaparin per day) or unfractionated heparin (UFH) (10,000–15,000 units/day) than those without heparin. Interestingly, there was no difference in mortality in the COVID-19-negative patients with the use of heparin when stratified by D-dimer level [52]. In addition to the anticoagulant effect, LMWH has been shown to have anti-inflammatory properties which could

Table 1: Management of coronavirus disease 2019 (COVID-19) coagulopathy.

Assessment of thromboembolic risk	References	Thromboprophylaxis	References
– Laboratory monitoring: platelet count, fibrinogen, PT, D-dimer, CRP, ferritin, IL-6.	[19, 23, 57]	– Use of standard prophylactic doses of LMWH, UFH or fondaparinux in all COVID-19 hospitalized patients (use mechanical thromboprophylaxis if pharmacological prophylaxis is contraindicated).	[19, 23, 41, 57, 58]
– Assessment of individual risk factors: immobilization, ICU setting; patients' age, previous VTE, BMI >30, active cancer or chronic comorbidities.	[19, 25, 41, 57]	– Use of intermediate dose of LMWH or UFH on an individual basis, considering patients' risk factors.	[19, 57, 58]
		– Use of prophylaxis for the entire duration of the hospital stay and for 7–14 after discharge in case of persisting VTE risk.	[25, 41, 57, 58]

PT, prothrombin time; CRP, C-reactive protein; IL-6, interleukin 6; BMI, body mass index; VTE, venous thromboembolism; LMWH, low molecular weight heparin; UFH, unfractionated heparin; ICU, intensive care unit.

improve its beneficial effect in COVID-19 patients, where pro-inflammatory cytokines are markedly increased [53]. Thus, considering the hypercoagulable state of patients with severe COVID-19 disease and the potential risk of thrombosis, several experts have recommended that all COVID-19 patients admitted to hospital should receive prophylactic treatment with LMWH, UFH or fondaparinux in the absence of medical contraindications [21, 22]. The WHO interim guidance statement recommends prophylactic daily LMWH, or twice daily subcutaneous UFH, in patients with suspected COVID-19 pneumonia [54]. However, the previously mentioned thromboembolic events occurring in COVID-19 patients despite VTE prophylaxis indicate that standard dose LMWH prophylaxis (i.e., enoxaparin 4,000 IU/day) in some cases may be not sufficiently protective. This awareness has led many centers to reconsider thromboprophylaxis, increasing the dose of anticoagulation from prophylactic to intermediate intensity doses (i.e., enoxaparin 4,000 IU twice daily) on an individual basis considering D-dimer and fibrinogen levels and other risk factors, including the ICU setting, patients' age and body mass index (BMI). Regarding to the latter issue, the possibility of increasing LMWH doses (i.e., enoxaparin 6,000 IU twice daily) in overweight patients (>100 kg) has been suggested [55]. Thromboprophylaxis should be administered for the entire duration of the hospital stay. Extended prophylaxis at home for 7–14 after hospital discharge should also been considered after careful evaluation of the individual thrombotic risk (patient's age, reduced mobility, previous VTE, BMI>30, active cancer or other prothrombotic comorbidities) [25]. All in all, the current clinical evidences from the literature indicate that patients with severe COVID-19 should be considered at a high risk of developing thromboembolic complications and thus necessitate of an "adequate" anticoagulant prophylaxis. However, dosage and timing of such thromboprophylaxis is yet to be established exactly and requires more information that unavoidably will arise from large, adequately powered, trials. Table 1 summarize the management of coagulopathy associated with COVID-19 based on the published literature data and on personal experience.

Conclusions

There is currently consisting evidence that severe COVID-19 is a systemic disease frequently associated with coagulopathy. The viral infection elicits endothelial dysfunction and systemic inflammatory response with the resulting imbalance between procoagulant and anticoagulant homeostatic pathways. This thromboinflammation is related with the severity and prognosis of the SARS-CoV-2 disease [56].

The management of coagulopathy associated with COVID-19 is particularly challenging and still in continuous evolution, according to the growing clinical experience. Concomitantly to the recommended laboratory monitoring of coagulopathy (i.e., D-dimer, fibrinogen, platelet count, PT), also inflammatory parameters (i.e., IL-6, C-reactive protein, ferritin, and procalcitonin) [19] are very useful to stratify patients' thrombotic risk, due to the close link between inflammation and coagulation. Given the thrombotic burden of COVID-19, thromboprophylaxis with LMWH is currently considered a therapeutic priority, taking into account also the anti-inflammatory properties of this anticoagulant agent [57], and is recommended by several guidelines from national and international scientific societies and panels of experts [23, 25, 27, 57, 58]. Anticoagulant prophylaxis should be, however,

personalized according to patients' thrombotic risk profile and SARS-CoV-2 disease characteristics. Clinical and laboratory data arising from upcoming trials will help us to better optimize the management of coagulopathy in critically ill COVID-19 patients with the aim of improving their clinical outcomes [59].

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