Commentary

COVID-19, thromboembolic risk and thromboprophylaxis: learning lessons from the bedside, awaiting evidence

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Over the past four months, COVID-19, the disease associated with the severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), emerged in Wuhan and the Hubei province of China[1] and spread worldwide, overwhelming healthcare systems and causing significant mortality. Among Western countries, Italy, and in particular the northern regions, were the first to have to face the COVID-19 epidemic emergency, at a time when knowledge about the disease was limited and little data about management and treatment were available in the literature.

Since the first reports from China, the presence of abnormalities of coagulation tests has been highlighted. These include mildly prolonged prothrombin time (PT) and reduced platelet count in most patients and, in particular, important increases in D-dimer, showing an association with the severity of illness and adverse clinical outcome[1-4] that is useful for risk stratification of patients at admission and over the clinical course of the disease[5]. These signs of coagulopathy, mimicking sepsis-induced disseminated intravascular coagulation (DIC)[4,6], reflect the activation of coagulation with thrombin generation and hyperfibrinolysis in this setting; the acute lung injury and hypoxia induce a massive inflammatory state due to macrophage and endothelial activation, resulting in the cytokine storm (IL-1, IL-6, IL-8, TNF-α) that dominates the second stage of COVID-19[7]. While describing the highly prevalent respiratory and cardiac complications[1-3], first publications on the outbreak of COVID-19 in China did not report thromboembolic events or the use of antithrombotic prophylaxis and treatment approaches; this could be consistent with the lower incidence of venous thromboembolism (VTE) in Asian populations[8] and the consequent lack of routine thromboprophylaxis. However, some Chinese authors described severe hypercoagulability, pulmonary microthrombosis, and the possible benefits of anticoagulation in COVID-19[9,10]. Tang and colleagues were the first to provide concrete clinical and outcome data. In their retrospective report on 449 patients with severe COVID-19, 22% received thromboprophylaxis for ≥7 days, mostly enoxaparin 40-60 mg daily or unfractionated heparin (UFH) 10,000-15,000 IU daily[11]. However, this study did not provide any information about occurrence of VTE. Despite an overall similar 28-day mortality in heparin users and non-users (30.3% *vs* 29.7%), heparin prophylaxis was associated with a significantly lower mortality in patients with sepsis-induced coagulopathy (SIC) score ≥4 (40.0% *vs* 64.2%; p=0.029) and in those with higher D-dimer, exceeding 3.0 mg/mL (6 times upper normal limit; 32.8% *vs* 52.4%; p=0.017)[11]. Thus, clinical benefits of heparin were detected in subgroups of patients with more relevant signs of coagulopathy. The lack of data about incidence of VTE, and the fact that assessment of

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risk and thromboprophylaxis was being overlooked, was recognised in a recent Chinese report, showing that among 1,026 hospitalised patients, 40% could be considered at high VTE risk according to the Padua Prediction Score[12] (≥4), but only 7% of those for whom data were available received anticoagulant drugs[13].

In parallel with the dramatic increase in clinical involvement in Italy and other western countries, radiological and pathological reports, and the experience of the intensive care units (ICU) revealed the growing need for more attention to be given to thrombotic risk and thromboembolic complications in COVID-19 patients[14-19]. Besides microvascular thrombosis in the lung, likely to reflect a vicious cycle of increasing localised thrombo-inflammatory mechanisms[20], venous thrombosis and pulmonary embolism also occur. In 81 Chinese patients with severe COVID-19 in the ICU setting who did not receive thromboprophylaxis, the prevalence of lower limb venous thrombosis (VT) was 25%[14]. Among VT patients, 40% (8 of 20) died. VT was associated with older age, lower lymphocyte counts, and, again, higher D-dimer, showing high specificity when the cut-off value of 3.0 mg/mL was considered[14]. Limitations of this study are its retrospective design and small patient population. Although it is perhaps rather daring to make any comparisons due to inherent differences in study design and the patients' age and ethnic background, this VTE rate is higher than those reported in the placebo groups of trials of thromboprophylaxis carried out on acutely ill patients[21]. In the first European study of 184 patients admitted to the ICU of three Dutch hospitals, all receiving low molecular weight (LMWH) thromboprophylaxis, 27% had confirmed symptomatic acute pulmonary embolism and/or deep-vein thrombosis and 3.7% arterial thrombotic events[15]. Again, taking into account the differences in study designs and populations, and in LMWH regimens, the rate of failure of thromboprophylaxis is much higher than that reported in critically ill patients in the ICU setting[22]. Consistent with this, in 26 consecutive patients from two French ICU who underwent systematic assessment of VTE (complete duplex ultrasound and targeted investigation for pulmonary embolism in those with persistent hypoxemia and secondary deterioration) receiving anticoagulation at doses defined according to their individual risk, the overall rate of VTE was 69% (18 of 26)[23]. Although only small patient groups were compared, the VTE rate was significantly higher in patients receiving prophylactic anticoagulation than in those on therapeutic doses (100% *vs* 56%; p=0.03)[23].

On the whole, there are still no rigorous data on VTE incidence in COVID-19 patients. However, the above findings are consistent with current observations from the ICU and sub-intensive settings, where clinicians recognise that the incidence of thromboembolic complications is probably even under-estimated, in particular in the case of rapid deterioration of the patient's clinical condition or a large increase in D-dimer, as few patients undergo diagnostic investigations, or even an autopsy in case of death. On the other hand, the acute respiratory infection and respiratory failure, together with prolonged bed rest, almost invariably identify a high VTE risk in COVID-19 patients[12], who frequently also present other risk factors such as age >70 years, comorbidities (cancer, obesity, acute heart failure) or previous history of VTE, further complicating their risk profile.

In this scenario, scientific societies and expert panels of coagulation and thrombosis[24-28] provided recommendations about stratification of VTE risk in hospitalised COVID-19 patients and strongly advised thromboprophylaxis with LMWH, UFH or fondaparinux at doses as defined in prescribing information and by the evidence available from acutely ill patients[29,30], unless contraindicated. The Italian Society for Thrombosis and Haemostasis (SISET) considers the possibility of giving intermediate-dose LMWH (i.e., enoxaparin 4,000 IU every 12 hours) on an individual basis in patients with multiple risk factors[25]. Increasing doses in overweight patients (>100 kg) or monitoring anti-Xa activity in specific situations, such as renal insufficiency, has been suggested by the Working Party on Haemostasis of the Swiss Society of Hematology[26]. Extended prophylaxis after discharge[25,28], or even before admission to hospital[25,27], should be considered after careful evaluation of the individual risk.

Interestingly, in the Dutch study above mentioned, thromboprophylaxis protocols were modified after approximately one month: LMWH doses were increased from 2,850 IU/day and 5,700 IU/day in obese subjects >100 kg to 5,700 IU in all patients at one hospital, and from 5,700 IU/day to 5,700 IU twice daily at another

hospital[15]. Indeed, clinicians are dealing with COVID-19 by extrapolating the evidence available in acutely/critically ill patients, but in the absence of specific data from good-quality studies. Thus, empirical intensifications of antithrombotic strategies have been considered as justified, borrowing experience from other settings with very high thrombotic risk[31-33] but often in the lack of rigorous evidence. Higher doses of heparin could be useful in the light of the reduction in mortality shown in patients with acute respiratory distress syndrome receiving LMWH, particularly in those treated with daily doses ≥5,000 IU[34]. These potential benefits of LMWH, consistent with its anti-inflammatory effects[35,36], or even the antiviral role studied in experimental models, including those of SARS-CoV-2[37,38], led some clinicians to increase doses up to full therapeutic anticoagulation. Putting these hotly debated issues to one side, in clinical practice, it is reasonable to consider risk-adjusted choices to prevent thromboembolic complications after careful consideration of the concurrent bleeding risk.

In this respect, following the suggestions from the SISET expert consensus[25] and the practical recommendations made by the Italian Federation of Centers for Thrombosis Diagnosis and Surveillance of Antithrombotic Treatments (FCSA)[39], many Italian centres have shared the approaches summarised in **Table I**. Moreover, as recently suggested, all patients already being treated with oral anticoagulants (both antivitamin K and direct oral anticoagulants) should switch to parenteral drugs at therapeutic levels in order to avoid the risk of over- or undertreatment[40].

Clinical trials are being designed and started, and national and international registries are collecting information in order to provide evidence which will help optimise antithrombotic strategies in COVID-19 patients. These studies should hopefully clarify the possible benefits of their use in terms of disease progression and patient outcome, within the frame of the management of anti-inflammatory and immunomodulating agents, aiming at affecting the thrombo-inflammatory vicious cycle that triggers microvascular thrombosis and overt VTE. While we wait for evidence-based approaches to be defined, we are constantly updating our strategies and implementing all that is being learnt so far as clinical experience of the disease continues to develop.

Table I - *Thromboemblic risk assessment, monitoring and antithrombotic strategies in COVID-19 patients*

Assessment of thromboembolic risk	• In all hospitalised patients with COVID-19, taking into account body mass index, individual risk factors for VTE, and the severity of the illness (SOFA score, need for oxygen treatment, mechanical ventilation). • Patients at highest risk are those with additional non-modifiable risk factors (i.e., cancer or chronic comorbidities), previous VTE or severe illness (SOFA score ≥4, severe hypoxia, ADRS).
Laboratory monitoring	• Platelet count, PT, APTT, fibrinogen and D-dimer, at least every 2-3 days. • Useful to assess bleeding risk and surveillance for DIC, to be considered particularly if clinical conditions deteriorate. In patients with sudden and/or marked increase of D-dimer, possible VTE should be investigated.
Thromboprophylaxis	• Advised in all patients, with at least standard doses of LMWH, UFH or fondaparinux, unless contraindicated (active bleeding, known bleeding disorders, platelet count <25×10^9/L). • In patients at highest risk, LMWH at adjusted doses is suggested, taking into account the concomitant bleeding risk: enoxaparin 4,000 IU if body weight <50 kg; 6,000 IU, 50-70 kg; 4,000 IU twice daily, 70-100 kg; 6,000 IU twice daily, >100 kg. • Particularly in patients in ICU, LMWH at intermediate doses (70 IU/kg twice daily) or UFH achieving approximately APTT ratio 2.0 or anti-Xa=0.5 IU/mL is suggested, considering the concurrent bleeding risk. In patients with kidney insufficiency, monitoring of anti-Xa activity is suggested, maintaining the upper prophylactic range (anti-Xa=0.4-0.5 IU/mL). As an alternative, UFH could be used with the same anti-Xa levels or APTT ratio approximately 1.5-2.0. • Fondaparinux can be used at standard doses (2.5 mg daily) if creatinine clearance is >50 mL/min; at lower dose (1.5 mg daily) in patients with creatinine clearance between 20 and 50 mL/min. • Mechanical thromboprophylaxis (elastic socks and intermittent pneumatic compression) can be used in patients at highest risk and should be considered if pharmacological prophylaxis is contraindicated. • Extension of thromboprophylaxis at hospital discharge should be advised, according to the individual risk, including active mobilisation and the persistence of inflammatory signs.

ADRS: acute distress respiratory syndrome; APTT: activated partial thromboplastin time; DIC: disseminated intravascular coagulation; ICU: intensive care unit; LMWH: low-molecular weight heparin; PT: prothrombin time; SOFA: sequential organ failure assessment; UFH: unfractionated heparin; VTE: venous thromboembolism.

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CONFLICT OF INTEREST DISCLOSURE

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