Position paper

COVID-19 and haemostasis: a position paper from Italian Society on Thrombosis and Haemostasis (SISET)

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The ongoing pandemic of Coronavirus disease 2019 (COVID-19) is severely challenging healthcare systems all around the world, with the need to provide intensive care to a previously inconceivable number of patients.

The clinical spectrum of the disease is very wide, ranging from minor, unspecific symptoms, such as fever, dry cough and diarrhoea, sometimes combined with mild pneumonia and mild dyspnoea, to severe pneumonia with dyspnoea, tachypnoea and disturbed gas exchange, leading in approximately 5% of infected patients to severe lung dysfunction, a need for ventilation, shock or multiple (extra pulmonary) organ failure[1].

Among the several clinical and biochemical parameters associated with poor prognosis, increased D-dimer levels have gained particular attention as a predictor of the development of acute respiratory distress syndrome (ARDS), the need for admission to an intensive care unit (ICU) or death[1-5]. On the other hand, disease severity also correlates with pro-inflammatory cytokines (i.e., IL-2, IL6, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A and TNF-α), although it is not yet clear what is the cause of such a cytokine storm[6]. These findings are consistent with the already demonstrated close connection between thrombosis and inflammation[7,8], two processes that mutually reinforce each other. Indeed, both coagulation factors (pro- and anti-coagulants)[9-11] and platelets[12-14] are directly implicated in the modulation of the host immune response, displaying proinflammatory functions that are independent from their haemostatic effects. All the above issues have been instrumental in spreading the feeling that COVID-19 is associated with the classical syndrome named disseminated intravascular coagulation (DIC) and the subsequent consumption coagulopathy. Moreover, it has been shown that heparin, beside its anticoagulant effects, also displays an anti-inflammatory action, various immunomodulatory properties, and protects glycocalyx from shedding[15]. It has also been suggested that dipyridamole, an antiplatelet drug with antiviral and antioxidant properties, has beneficial effects in patients with COVID-19[16].

Despite such a tight interconnection between inflammation and haemostasis abnormalities, no good evidence is available of the efficacy/safety of heparin and/or antiplatelet agents on sepsis patients, and many issues remain to be addressed, such as the proper timing, dosages and administration scheme of antithrombotic drugs[17-19]. Nevertheless, very recent data showed that low molecular weight heparin (LMWH) or unfractionated heparin (UFH) at prophylactic doses are associated with a reduced 28-day mortality in more severe COVID-19 patients displaying a sepsis-induced coagulopathy (SIC) score ≥4 (40.0% *vs* 64.2%, p=0.029) or D-dimer levels >6-fold the upper limit of

normal (32.8% *vs* 52.4%, p=0.017)[20]. Relevant to this, increased D-dimer levels have already been demonstrated to be associated with a poorer outcome in other cohorts of sepsis patients[21], although very recently published data have questioned the prognostic utility of the standard D-dimer test in this setting[22]. In addition, the reported D-dimer cut-off in a Chinese population cannot be applied to all populations. Indeed, the median age of Chinese patients is significantly lower than the Italian ones, and age significantly correlates with D-dimer levels. Therefore, we cannot translate the D-dimer cut-off adopted by those authors[2] to the Italian population. It would be advisable to launch an effort aimed at quickly collecting data on coagulation parameters in COVID-19 patients in Italy, as well as in other countries involved in the pandemic.

Although there is no confirmed evidence as yet from the laboratory, it is plausible that the plasma of these patients is hypercoagulable, as suggested by preliminary laboratory information and many clinical observations. Indeed, physicians in the ICU often share the clinical observation that patients with COVID-19 are very hypercoagulable, and that the rate of micro-pulmonary embolism is probably higher than that reported, due to the inherent problems of imaging technology or in performing autopsies.

It is also possible that a pulmonary embolism is already present in more severely ill COVID-19 patients before hospitalisation, thus explaining the reported ineffectiveness of prophylactic doses of heparins during their hospital stay.

The hypothesis of improving the clinical outcome of COVID-19 patients by simple and inexpensive antithrombotic drugs is very attractive, but several issues need to be addressed and clarified before adopting an aggressive anticoagulation approach. They include the appropriate timing of start of treatment, and the type and dosage of drug, while the impact of concomitant medications that are often taken by these subjects should also be taken into consideration. Moreover, it should be noted that approximately 50% of those patients who have died of COVID-19 in Italy had three or more comorbidities such as atrial fibrillation or ischaemic heart disease, often requiring anticoagulant or antiplatelet treatment; the management of these is particularly challenging due to the potential interactions of concomitant therapies, namely direct oral anticoagulants (DOAC)[23]. The picture is further complicated by the observation that chronic kidney disease is among the most prevalent underlying diseases in hospitalised patients[24] and that acute kidney injury is a common finding in deceased patients[25]; these two conditions have a strong impact on the activity of heparins and DOAC.

While the scientific community is waiting for more robust evidence from properly designed clinical trials with strong end points, the Italian Society on Thrombosis and Haemostasis aims to provide some recommendations, based on expert consensus, for the management of the haemostasis derangement in COVID-19 patients.

- In the general management of patients, the monitoring of laboratory tests should always include haemostasis function and platelet count; deep vein thrombosis (DVT) ultrasound screening should be carried out whenever feasible.
- It is highly recommended that standardised procedures be adopted to collect clinical and laboratory data on all hospitalised patients in order to improve our understanding of the natural history of the disease.
- The use of LMWH, UFH, or fondaparinux at doses indicated for prophylaxis of venous thromboembolism (VTE) is strongly advised in all COVID-19 hospitalised patients; patients with anticoagulant contraindications should be treated with limb compression.
- Thromboprophylaxis should be administered for the entire duration of the hospital stay. This should also be maintained 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 (i.e., reduced mobility, body mass index (BMI) >30, previous VTE, active cancer, etc.).
- The use of intermediate-dose LMWH (i.e., enoxaparin 4,000 IU subcutaneously every 12 hours) can be considered on an individual basis in patients with multiple risk factors for VTE (i.e., BMI >30, previous VTE, active cancer, etc.).
- The use of therapeutic doses of UFH or LMWH, although a reasonable approach, is currently not supported by evidence outside of established diagnoses of VTE or as a bridging strategy in patients on vitamin k antagonists (VKA), and cannot be recommended as a standard treatment for all COVID-19 patients. In this respect, randomised clinical trials comparing efficacy/safety of higher doses of LMWH or UFH to those adopted for

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prophylactic use are urgently needed. To improve their clinical usefulness, it is advisable that these trials adopt simple and clear protocols, and that they are run by large collaborative efforts, hopefully supported by the Italian drug agency (AIFA).

- In patients requiring therapeutic doses of LMWH or under DOAC, renal function should be monitored and anti-factor Xa or plasma DOAC levels should be tested.
- Both VKA and DOAC display significant interference with concomitant antiviral treatment to which the COVID-19 patients are subjected. An individualised patient-based approach is recommended, aimed at balancing the risk/benefit ratio of the various antithrombotic strategies, taking into consideration the underlying hypercoagulable state.
- Tight co-operation between all the specialists involved in the treatment of COVID-19 patients is also recommended.

The Authors declare no conflicts of interest.

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