Sustained High D-Dimer in Outpatients Who Have Recovered from Mild to Moderate Coronavirus Disease 2019 (COVID-19)

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Over 1 year has passed since the beginning of the coronavirus disease 2019 (COVID-19) pandemic outbreak. Throughout this period of time, severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) has spread across the globe, causing a disease that generates high and fast rates of hospitalizations and deaths. It has been now well clarified that COVID-19 is not just a respiratory disease, but rather in the most severe cases is the result of inappropriate response of immune system precipitating a so-called "cytokine storm" and immunothrombosis, accompanied by vasculitis, micro- and macro-angiopathy, thromboembolism, and multiple organ damage, especially if prompt treatment is not undertaken.[1]

Very recently, the American Society of Hematology (ASH) released new guidelines for anticoagulation in COVID-19 patients.[2] In the context of "very low certainty of evidence," as stated, ASH confirmed recommendation for using prophylactic-intensity rather than intermediate-intensity or therapeutic-intensity anticoagulation in critical COVID-19 patients, without confirmed or suspected venous thromboembolism, consistent with some evidence that in critically ill patients, high dose anticoagulation does not exhibit the same benefit, and rather, can increase mortality.[3]

Several studies report high incidence of vascular thrombosis (arterial and venous thromboembolism, pulmonary and cardiac microthrombi, disseminated intravascular coagulation [DIC]) in patients with COVID-19. Elevated levels of some markers of coagulation activation are among the frequent findings in the most severe patients admitted to the intensive care unit (ICU). Most recently, the pathology of COVID-19-related coagulopathy has been unraveled.[4,5] A necropsy study revealed that 64% of cases of myocardial necrosis was due to microthrombi, related not directly to cardiac viral invasion, with distinct high levels of fibrin and terminal complement, different from thrombi found in epicardial coronary arteries during acute myocardial infarction.[4] Elevated D-dimer is likely the most appropriate marker of this type of fibrin-related micro-thrombosis, as the direct expression of plasmin activity on stabilized fibrin cross-links. The evidence of fibrin clots in the myocardial microcirculation and the high incidence of venous and arterial thromboembolic events in COVID-19 patients raise questions about the use of prophylactic, intermediate, or therapeutic-intensity low-molecular weight heparin (LMWH) in COVID-19 patients, independently of the overt clinical presentation of thromboembolism, prompting NHLBI to issue a public notice on preliminary results from three clinical trials showing clear benefit of high-dose anticoagulation over prophylactic intensity in moderately ill patients.[6]

The apparently contradictory current indications are actually consistent with the importance of using the right therapeutic decision according to the stage of the disease.[7] Heparin treatment may be of critical value during the formation of microthrombi, to prevent them and, therefore, before stage 3 (hyperinflammation) and probably even before stage 2, when the disease shifts from the phase of viral invasion toward the phase of hyperimmune response.[8] In addition, the use of prophylactic doses of LMWH or unfractionated heparin reduces the 28-day mortality in very sick COVID-19 patients (in the presence of D-dimer levels more than sixfold of the upper limit of normal or a Sepsis-Induced Coagulopathy score $\geq$4).[9] The thromboembolic risk extends for up to 6 weeks post-hospital discharge in high-risk medically ill patients, including patients with pneumonia and sepsis. A modified IMPROVE (International Medical Prevention Registry on Venous Thromboembolism) risk score, using established cut-offs plus elevated D-dimer ($>$2 times upper normal limit [UNL]) identifies patients at an almost threefold higher thromboembolic risk.[10] In these

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patients, significant benefits are reported when extending thromboprophylaxis.[10]

Based on this evidence, extended post-discharge thromboprophylaxis should be considered for all hospitalized patients with COVID-19 who meet high VTE risk criteria. The duration of post-discharge thromboprophylaxis is suggested to be at least 14 days.[11] Among the many laboratory-measurable prothrombotic biomarkers, D-dimer seems particularly effective in identifying impending thromboembolic activity.[12] Elevated D-dimer levels at admission or increasing D-dimer over time are both associated with increased mortality with COVID-19.[5]

Rising D-dimer after admission precedes multiple organ failure and overt DIC. Moreover, longer duration of hospital stay is associated with increasing D-dimer.[13] However, in the context of noncritical COVID-19, the value of monitoring D-dimer also in out-of-hospital mild/moderate disease remains unclear,[14] a question requiring prompt answer, given the efforts to identify predictors of severe disease at the early stages.[15]

We herein report evidence of persisting high D-dimer levels in 20% of the patients with mild to moderate COVID-19, who requested remote consultation and were, therefore, remotely followed at home. This is a series of 45 patients with mild to moderate COVID-19 (age 51 ± 14 years, 21 women).

Diagnosis of COVID-19 was confirmed in out-of-hospital private laboratories authorized to perform molecular tests, by nasal swab for nucleic acid amplification test to detect SARS-Cov-2 mRNA, using different techniques, mostly by the reverse transcription polymerase chain reaction (RT-PCR). D-dimer was measured using different immunoassays, giving different normal limits. Given the impossibility to directly compare D-dimer values produced with different methods,[16] the D-dimer value was expressed as the percent deviation from the upper normal limit (UNL) that every laboratory gave in their reports.

COVID-19 patients came to our observation at different times from beginning of symptoms. All patients were treated with indomethacin 75 to 150 mg/d according to the patient weight, omeprazole 20 mg/d, and enoxaparin 4000 IU/d. In 10 patients, in whom initial symptoms and signs of COVID-19 (anosmia/ageusia, sore throat, fever, fatigue, muscular pain, cold, dry cough, diarrhea, abdominal pain, shortness of breath in different combinations) persisted over 6 days (two of them in the subgroup with persistent high D-dimer), a 6-day course of prednisone 25 mg/bid was added.

After complete clinical recovery, restoration of a well-being and normalization of molecular swab, C-reactive protein, white blood cell count and fibrinogen level, D-dimer remained substantially elevated in nine patients (20%), with high levels persisting at 15 days after complete clinical and laboratory remission (►**Fig. 1**; note that the reported values are the percent increase referenced against the UNL specific for each laboratory). Patients with persistently high D-dimer had the same sex distribution (four women) as the subgroup with normal D-dimer but were slightly younger (47 ± 13 vs. 51 ± 13 years, $p = 0.05$).

Our study has obvious limitations, including that D-dimer was measured with a variety of methods, and thus not strictly comparable.[16] However, we believe that reporting data as a percent increase over the UNL represent a reasonable approach. Also, our empiric, clinical observation needs confirmation. However, the data suggests that D-dimer should be monitored also in mild-to-moderate COVID-19 patients, even if managed at home. In addition, our experience also raises several questions:

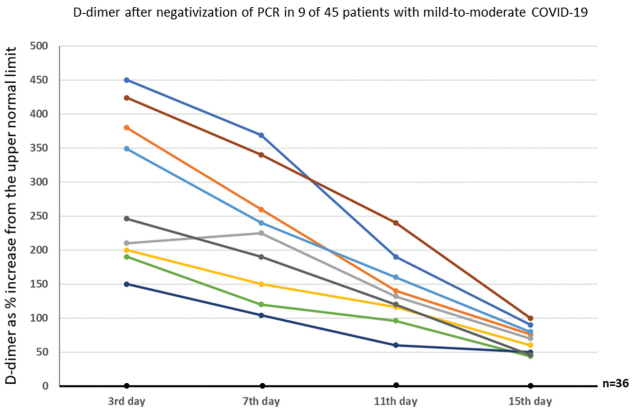

Fig. 1 D-dimer monitoring over 15 days, in 9 of 45 patients maintaining high values after clinical recovery and negativization of swab.

1. Should anticoagulation (e.g., LMWH) be administered in all mild-to-moderate COVID-19 patients or at least in those who exhibit elevated D-dimer (implying that in all patients D-dimer should be measured), and for how long?
2. Is prophylactic-intensity LMWH sufficient to prevent microthrombus formation that is clinically silent?
3. Finally, can persistence of elevated D-dimer beyond the clinical recovery be a track to understand mechanisms leading to the frequent long-term consequences of SARS-CoV-2 infection?[17]

All these questions need attention and well-designed observational studies.

Conflict of Interest
None declared.

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