Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

D-dimer measurement in COVID-19: Silver bullet or clinical distraction?

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Coronavirus disease 2019 (COVID-19), the severe infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has now spread all over the world, infecting several millions of people and causing nearly 1 million casualties to date. According to our current understanding of this insidious pathology, the disease develops through a continuum of different phases [1]. The lower respiratory tract is primarily involved, with development of interstitial pneumonia, most often bilateral, and progression towards acute respiratory distress syndrome (ARDS) in a certain number of patients (i.e., between 5 and 10%). In a subset of either genetically or phenotypically predisposed patients (i.e., older and/or immobilized subjects, or those carrying important co-morbidities such as overweight/obesity, hypertension, immune system depression, cardiovascular and respiratory disorders, diabetes, cancer and so forth), the infection spreads systemically, affecting many other organs and finally progressing towards multiple organ failure (MOF). A pro-thrombotic state, frequently evolving with development of both venous and arterial thrombotic episodes, is now regarded as a key aspect characterizing the unfavorable progression of COVID-19 [2]. Clinical, radiological or even post-mortem studies show that episodes of venous thromboembolism (VTE) can be found in nearly one third of patients with severe forms of COVID-19, whilst the presence of micro- and macro-vascular thrombi within pulmonary vessels accompanies the paradigmatic picture of diffuse alveolar damage (DAD) seen in most patients dying from COVID-19 [3,4]. Owing to the important role played by thrombosis in fostering an adverse clinical progression, the identification of early and accurate predictors of worse outcome seems hence pivotal for establishing the most appropriate anticoagulant treatment in patients with SARS-CoV-2 infection.

Increased D-dimer values are commonly found in patients with COVID-19 [5], and an increased plasma concentration of this biomarker over the conventional diagnostic thresholds has been found as significant predictor of disease severity in recent meta-analyses [6,7].

In an article published in this issue of the Journal [8], Choi and colleagues provides further insights on the important relationship between D-dimer and COVID-19. The authors carried out a retrospective observational cohort study in two hospitals in Manhattan (New York, US), recruiting all consecutive adult patients hospitalized for COVID-19 during nearly 2.5 months (i.e., between March 3 and May 15, 2020). The final study population consisted of 1739 patients (median age, 66.5 years; 59% men), who underwent VTE testing (at physicians' discretion) by means of compression ultrasound (CUS) or computed tomography pulmonary angiogram (CTPA). Overall, 123 patients (7%) were found to have documented VTE throughout their hospital stay, averaging 136 cumulative VTE episodes (95 of deep vein thrombosis and 41 of pulmonary embolism, respectively). The relatively low prevalence of VTE compared to previous reports is not surprising, since all patients underwent standard or even intermediate-dose thromboprophylaxis early during their hospital stay. In multivariate analysis, enhanced odds ratio (OR) of VTE was found for black race (OR, 2.66), need for mechanical ventilation upon admission (OR, 2.25), as well as for increased values of prothrombin time (OR per every 1 second increase, 1.02) and D-dimer (OR for every 1000 ng/mL increase, 1.09). Notably, D-dimer values displayed good efficiency for identifying VTE, exhibiting an area under the curve (ACU) as high as 0.79 (95% confidence interval, 0.75–0.83) and likelihood ratios of VTE escalating in parallel with increasing D-dimer values (e.g., 0.14 for D-dimer < 1000 ng/mL vs. 4.10 for D-dimer > 7500 ng/mL).

Some notable drawbacks can be identified in the study of Choi et al., along with those listed by the authors. Although routine VTE screening is not currently recommended in critically ill COVID-19 patients, in this original investigation VTE testing was only ordered at physicians' discretion. This may have led to missing a number of asymptomatic VTE episodes [9], which may have thus contributed to bias the diagnostic performance of D-dimer. Another critical aspect is that D-dimer performance was calculated on the value obtained upon hospital admission, whereby recent evidence demonstrates that either the “peak” or “delta” values may more efficiently predict VTE. In the study of Maatman et al. [10], for example, the peak D-dimer value during hospital stay was associated with nearly 90% sensitivity for diagnosing VTE in patients hospitalized with COVID-19, whilst the admission value only displayed 64% sensitivity. Naymagon et al. also showed that COVID-19 patients with stable D-dimer values during hospital stay had approximately 80% lower risk of developing VTE compared to those with increasing concentration (OR, 0.18; 95% confidence interval, 0.05–0.68) [11]. It is also noteworthy that increased D-dimer values in patients with COVID-19 cannot be solely attributed to VTE episodes,

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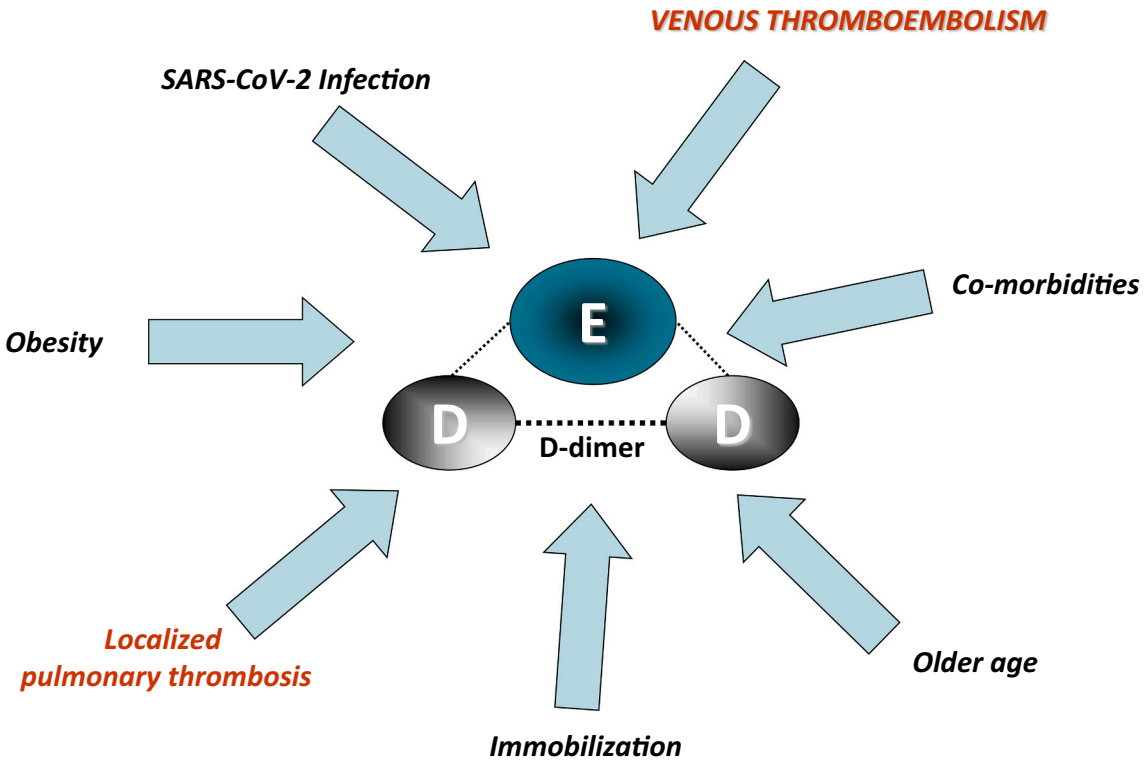

Fig. 1. Potential underlying causes of increased D-dimer values in patients with coronavirus disease 2019 (COVID-19).
SARS-CoV-2, severe acute respiratory syndrome coronavirus disease 2.

but will recognize different etiologies (Fig. 1), such as the viral infection itself, the presence of clinical and demographical variables frequently associated with enhanced D-dimer values (e.g., older age, obesity, cardiovascular disease) [12], but also to the evidence that localized pulmonary thrombosis, rather than embolization, is commonplace in patients with severe COVID-19 illness and necessitates specific therapeutic treatment [13]. Thus, a higher threshold than standardly used for VTE exclusion will be required in COVID-19 patients. This threshold may be 4× or higher. In the new study, a cut-off of 1000 ng/mL (D-dimer units) indicated a low post-test probability of VTE for values < 1000 ng/mL, which compares with a normal cut-off of 250 ng/mL for most D-dimer kits using D-dimer units. Even here, however, using a cut off of 1000 ng/mL would have led to 7/271 (2.6%) patients with VTE being potentially missed.

A final critical aspect is the methodology used for measuring D-dimer in the two hospitals in Manhattan, which differed in the two study sites (one used ACL HemosIL D-dimer and the other Diagnostica Stago reagents), and which will also differ from methods used at other hospitals. This thus represents another potential source of bias, whereby standardization of D-dimer measurement is a foremost aspect in test results interpretation [14]. Importantly, the straightforward adoption of the D-dimer cutoffs identified in the study of Choi et al. is generally unfeasible, and in our opinion unadvisable, due to the multiple analytical techniques that are currently available for measuring this biomarker.

Conversely, the results presented by Choi et al. are in keeping with previous evidence on this matter, which would attribute a relevant diagnostic and prognostic value to routine D-dimer assessment in patients with SARS-CoV-2 infection. This would open a debate as to whether D-dimer values should be part of a routine panel of laboratory tests offered to all patients hospitalized for (or even with) COVID-19 [15]. This practice carries some theoretical advantages, such as increased likelihood of identifying patients with VTE episodes and possibility to adapt the anticoagulant regimen according to D-dimer values, but may also carry some obvious drawbacks, such as increased healthcare costs and risk of overdiagnosing and overtreating asymptomatic patients with less clinically relevant thrombotic episodes. Although further evidence, based on solid cost-effectiveness analyses, would be needed to make definitive conclusions on this matter, it is undeniable that routine D-dimer measurement may currently help identifying a subset of COVID-19 patients at enhanced risk of unfavorable progression, who may then benefit from more extensive assessment and tailored treatment. The ideal cut-off for use in patient stratification needs more definitive investigation, and may differ according to the method used. In theory, there are also 28 possible reporting units for D-dimer [16], though the number is likely closer to 5 for units preferred by the major D-dimer manufacturers [17]. Irrespective, D-dimer reporting in the COVID-19 era remains problematic [14,17], and we hope that future studies, like the recent report [11], will clearly identify what methods and units are being reported, in order to enable clearer comparison of findings.

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