

The Meaning of D-Dimer value in Covid-19

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Coronavirus disease 2019 (COVID-19) caused by the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) is an ongoing global health emergency.¹ The clinical spectrum of SARS-CoV-2 infection ranges from asymptomatic infection to critical illness and death. In COVID-19 disease coagulopathy is frequently reported, being more prevalent in critically ill patients; indeed, SARS-CoV-2 may predispose patients to thrombotic disease, both in the venous and arterial circulation, due to excessive inflammation, platelet activation, endothelial dysfunction, and stasis.² Increased prevalence of antiphospholipid antibodies was also reported.³ Elevated D-dimer values correlate with a poor prognosis,⁴ with the development of acute respiratory distress syndrome (ARDS), and with the risk for admission to intensive care unit.⁵

The increase in the value of D-dimer is the most sensitive change in coagulation parameters in COVID-19 and indicate a greater risk for the development of thrombosis; nevertheless, D-dimer is a marker of fibrinolysis, and only a proxy for ongoing thrombosis, and it is already known that its specificity for venous thromboembolism is low. Moreover, since the D-dimer is known to be a mixture of fragments of different weight, and tests may report results in terms of weight for units of volume or as fibrinogen equivalent units (FEU). So, it may be not correct to compare results between different tests⁶. In arterial thromboembolism D-dimer has a marginal role, if any. Therefore, the use of heparin in the treatment of COVID-19 disease, should play a fundamental role, and prophylactic doses of low molecular weight heparin (LMWH) or unfractionated heparin (UFH) were associated with a reduced 28-day mortality in more severe COVID-19 patients.⁷

Consequently, the International Society of Thrombosis and Haemostasis (ISTH) recommended systematic pharmacological thromboprophylaxis in all patients who require hospital admission for COVID-19 disease.⁸ Also in a position paper from Italian Society on Thrombosis and Haemostasis (SISST), the use of LMWH, UFH, or fondaparinux at doses indicated for prophylaxis of venous thromboembolism (VTE) was strongly advised in all COVID-19 hospitalized patients.⁹ However, these recommendations are largely derived on the experience

from trials in medical patients without COVID-19. Moreover, it is not known if antithrombotic prophylaxis in COVID-19 patients should be guided by risk assessment models (the standard practice in nonsurgical admitted patients before the current pandemic), or by D-dimer levels, or instead by clinical judgement alone.

In a retrospective cohort study conducted in 2 French centers,¹⁰ consecutive patients hospitalized in medical wards non-ICU with confirmed COVID-19 and adequate thromboprophylaxis were enrolled and subjected to systematic low limb venous duplex ultrasonography. D-dimers at baseline were significantly higher in patients with deep venous thrombosis (DVT) ($P < 0.001$). The negative predictive value of a baseline D-dimer level $< 1.0 \mu\text{g/ml}$ was 90% for VTE and 98% for pulmonary embolism (PE). The positive predictive value for VTE was 44% and 67% for D-dimer level $\geq 1.0 \mu\text{g/ml}$ and $\geq 3 \mu\text{g/ml}$, respectively. Increased D-dimer concentrations of more than $1.0 \mu\text{g/ml}$ predict the risk of VTE.

In an other prospective study, 165 consecutive patients hospitalized in non-intensive care units with diagnosis of COVID-19 pneumonia and D-dimer $> 1000 \text{ ng/ml}$ were screened for asymptomatic DVT with complete compression doppler ultrasound.¹¹ All but 3 patients were received standard doses of thromboprophylaxis. Twenty-three patients were diagnosed with DVT (of whom only one had proximal DVT, and 7 patients had bilateral distal DVT). In these kind of patients the D-dimer value was higher than other patients: 4527 ng/ml vs 2050 ng/ml ; $P < 0.001$. Therefore, in patients with COVID-19 disease, higher cut-off levels for D-dimer might be necessary

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for the diagnosis of DVT. In reality, this may be a too narrow view of coagulopathy in COVID-19. In fact, autopsy studies have shown the presence of diffuse microthrombosis, which cannot be recognized with normal ultrasound or radiological methods, while they are instead expressed by multiorganic dysfunction.¹² Therefore, the only finding in patients with COVID-19 disease, of high values of D-dimer, does not necessarily indicate a diagnosis of DVT. However, a particularly significant increase of D-dimer value in COVID-19 patients deserves further investigation in order to rule out a possible DVT.

Instead, in the diagnosis of VTE, in the absence of concomitant COVID-19 disease, the negative predictive value of D-dimer testing is high, and a normal D-dimer level renders acute PE or DVT unlikely. On the other hand, the positive predictive value of elevated D-dimer levels is low and D-dimer testing is not useful for confirmation of PE.¹³

Thus, in COVID-19 disease, D-dimer concentration provides important information on the prognosis of COVID-19 patients. Whether management based on risk stratification using D-dimers improves the risk benefit ratio of increased dose anticoagulant interventions remains unclear. Some clinicians use D-dimer value to determine the intensity of antithrombotic prophylaxis in these kind of patients; furthermore, some studies highlighted that decrease in D-dimer levels could correlate with a clinical improvement of the patients, offering an option for downgrading the anticoagulation intensity; finally, although the role of D-dimers in guiding treatment of COVID-19 is attractive, clinicians should be aware of the details of their local D-dimer tests before implementing standard cut-offs provided by others.¹⁴

Author Contributions

N. Mumoli, G. Conte and M. Cei were responsible for study concept. G. Conte, N. Mumoli, J. Vitale, M. Cei, I. Evangelista, A. Colombo, and A. Mazzone were responsible for acquisition of data. N. Mumoli, M. Cei, and G. Conte drafted the manuscript. N. Mumoli, G. Conte, and M. Cei were responsible for critical revision of the manuscript for important intellectual content. All authors had full access to the data and take responsibility for the accuracy of the data analysis.



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