D-dimer is Associated with Severity of Coronavirus Disease 2019: A Pooled Analysis

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The study was performed in accordance with the Declaration of Helsinki and with the term of local legislation.

Overall, 80 documents could be initially identified based on our search criteria. 77 of which ought to be excluded after title, abstract, or full text reading; since they were review articles (n = 6), commentaries, or other editorial material (n = 1), they did not deal with COVID-19 disease (n = 62), or did not express the difference of D-dimer values in COVID-19 patients with or without severe disease (n = 8). One additional study could be identified from the reference list of selected articles and another one was published while the article was under revision so that a total number of five studies could finally be included in our analysis.6–10 Four of these five studies reported median and IQR values of D-dimer,6–9 while the remaining only showed the proportion of patients with D-dimer values above the locally defined diagnostic cut-off.9

In the first study, Huang et al reported clinical and laboratory data of 41 patients hospitalized with laboratory-confirmed COVID-198 and observed that D-dimer values were nearly fivefold higher in those with severe disease (median: 2.4 mg/L; IQR: 0.6–14.4 mg/L) than in those without (median: 0.5 mg/L; IQR: 0.3–0.8 mg/L; p = 0.004). Tang et al also studied 183 patients with COVID-197 and found that D-dimer values were nearly 3.5-fold higher in those with severe disease (median: 2.12 mg/L; IQR: 0.77–5.27 mg/L) than in those without (median: 0.61 mg/L; IQR: 0.35–1.29 mg/L; p < 0.001). In the third study, published by Wang et al and including 138 patients hospitalized for COVID-19,8 D-dimer values were nearly 2.5-fold higher in patients with severe disease (median: 4.14 mg/L; IQR: 1.91–13.2 mg/L) than in those without (median: 1.66 mg/L; IQR: 1.01–2.85 mg/L; p < 0.001). In the third study, Zhou et al studied 191 patients with COVID-199 and found that D-dimer values were nearly ninefold higher in...
patients who died (median: 5.2 mg/L; IQR: 1.5–21.1 mg/L) than in those who survived (median: 0.6 mg/L; IQR: 0.3–1.0 mg/L; p < 0.001). In the study of Guan et al, who extracted data on 1,099 patients with laboratory-confirmed COVID-19 infection from 552 hospitals located in 30 Chinese territories, the risk of having D-dimer values above the locally defined cut-off (i.e., ≥0.5 mg/L) was more frequent in patients with severe disease (65/109, i.e., 59.6%) than in those without (195/451, i.e., 43.2%; p = 0.002). The WMD of the four studies which reported continuous values (totaling 553 patients, 22% with severe disease) is summarized in Fig. 1, showing that D-dimer values are considerably higher in COVID-19 patients with severe disease than in those without (WMD: 2.97 mg/L; 95% CI: 2.47–3.46 mg/L). The heterogeneity across the studies was found to be relatively high (i.e., I², 94%; p < 0.001).

Recent literature data show that D-dimer values are frequently enhanced in patients with COVID-19, being variably observed in 36 to 43% of positive cases. Nonetheless, what clearly emerges from the results of our pooled analysis is that D-dimer values are even higher in patients with severe COVID-19 than in those with milder forms and therefore, D-dimer measurement may be associated with evolution toward worse clinical picture, though serial measurement would not be easily feasible at present in COVID-19 patients. Notably, Tang et al also recently highlighted that the vast majority of COVID-19 patients who died during hospital stay fulfilled the criteria for diagnosing disseminated intravascular coagulation (71.6 vs. 0.6% in survivors). Although D-dimer elevations recognize multifactorial etiology, our findings would lead us to conclude that D-dimer elevations and disseminated coagulopathy may be commonplace in patients with severe forms of COVID-19 as in other severe infections disease such as systemic human immunodeficiency virus, Ebola, and Chikungunya virus so that urgent studies shall be planned to define whether adjunctive antithrombotic therapies (e.g., anticoagulants, antithrombin or thrombomodulin) may be helpful in patients with severe COVID-19.

Conflict of Interest
None declared.

References