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Predictive value of D-dimer in the clinical outcome of severe COVID19 patients: Are we giving it too much credit?

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Abstract

Background: COVID-19 is a new form of acute respiratory failure leading to multiorgan failure and ICU admission. Gathered evidence suggests that a 3-fold rise in D-dimer concentrations may be linked to poor prognosis and higher mortality.

Purpose: To describe D-dimer admission profile in severe ICU COVID19 patients and its predictive role in outcomes and mortality.

Methods: **S**ingle-center retrospective cohort study. All adult patients admitted to ICU with COVID19 were divided into 3 groups: (1) Lower-values group (D-dimer levels < 3-fold normal range value [NRV] [500ng/mL]), Intermediate-values group (D-dimer ≥3-fold and <10-fold NRV) and Higher-value group (≥10-fold NRV).

Results: 118 patients (mean age 63 years, 73% males) were included (N = 73 Lower-values group, N = 31 Intermediate-values group; N = 11 Higher-values group). Mortality was not different between groups (p = 0.51). Kaplan-Meier survival curves revealed no differences (p = 0.52) between groups, nor it was verified even when gender, age, ICU length of stay, and SOFA score were considered as covariables.

Conclusions: In severe COVID19 patients, the D-dimer profile does not retain a predictive value regarding patients' survivability and should not be used as a surrogate of disease severity.

Keywords

COVID19, D-dimer, mortality rate, critical care

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Introduction

COVID-19 is a new and complex form of hypoxemic acute respiratory failure caused by the new SARS-CoV-2, ultimately leading to severe acute respiratory distress syndrome, multiorgan failure, and death. Evidence collected collectively worldwide has shed light on several pathophysiological mechanisms and has identified a potentially pro-coagulant state, which is biochemically detected by prolonged prothrombin, increased fibrinogen and high D-dimer levels.[1] These biological markers potentially represent clear signs of activation of coagulation pathways and thrombosis, pointed as preponderant in the early stages of the disease.[2]

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Actual European Society of Cardiology and American Society of hematology guidelines currently recommend the use of highly sensitive assays of d-dimer serum level to exclude venous thromboembolism due to its high negative predictive value.[3,4] COVID19 patients frequently present a high titer of d-dimer serum levels at admission and during the hospital stay. In fact, a 3 to 4-fold rise in D-dimer concentrations has even been associated with the development of more severe acute respiratory distress syndrome, a higher risk for admission to intensive care unit (ICU), and a poor prognosis.[5-8]

Therefore, it has been hypothesized that this biomarker may be used in severe COVID19 patients with acute respiratory failure to predict disease severity and signaling subsets of patients with higher mortality rates, independent of the occurrence of venous thromboembolism events.[9-11]

This study aimed to describe the D-dimer admission profile in severe COVID19 patients admitted to ICU and analyze its predictive role regarding clinical outcomes and mortality rate.

Methods

Study Design and Population

A single-center prospective observational cohort study was conducted over a 9-month consecutive period between March 2020 and January 2021. Data were collected from consecutive adult patients, admitted to ICU, using patients' electronic medical records, in Centro Hospitalar Lisboa Ocidental, in Lisbon, Portugal. The study was approved by the National Ethics Committee for Clinical Research (reference REC: 2020_EO_02).

Eligibility criteria included (1) age equal to or above 18 years old, (2) COVID19 respiratory infection diagnosed using clinical and radiological criteria of pulmonary involvement with a SARS-CoV-2 positive RT-PCR test, and (3) admission to an ICU with multiorgan failure secondary to COVID19 pneumonia, described as the development of potentially reversible physiological derangement involving two or more organ systems or change in baseline of Sequential Organ Failure Assessment (SOFA) score of 2 points or more.

Patients included in the analysis were further divided according to D dimer serum levels at admission into three groups: Lower-values group (D-dimer levels at ICU admission < 3-fold normal range value [500ng/mL]), Intermediate-values group (D-dimer levels at ICU admission ≥3-fold and <10-fold normal range value) and Higher-value group (D-dimer levels at ICU admission ≥10-fold normal range value).

All patients received low molecular weight heparin therapy, either with prophylactic or therapeutic dose, according to formal clinical indication.

Data Collection and End-Points

Patient demographic characteristics were recorded at baseline for all patients including comorbidities and SOFA score at admission. Daily measurements of vital signs (including minimum mean arterial pressure and maximum respiratory rate), ventilation variables (including minimum ratio partial pressure arterial oxygen and the fraction of inspired oxygen and time of ventilation in prone position), hemodynamic support (including the use of vasopressor therapy and maximum dosage of vasopressor support), renal replacement therapy, laboratory variables (including d-dimer, hemoglobin, troponin I, lactate, C-reactive protein, and procalcitonin levels), prescribed therapies (remdesivir and dexamethasone) and outcomes (discharge alive or death in ICU) were also collected for every admitted patient to statistical analysis.

Primary outcomes included in-hospital mortality and 28-day mortality. As secondary outcomes, ventilator-free days and vasopressor-free days at day 28 were determined.

Statistical Analysis

All Gaussian distributed variables were expressed as mean (SD), and nonnormally distributed variables as median (interquartile range [IQR]). Categorical variables were expressed as numbers and percentages.

Chi-square test was used for categorical variables, and t-test and Kruskal-Wallis were used on continuous variables for statistical assessment of outcomes between groups. Kaplan-Meier survival curve and log-rank test were also obtained to ascertain and compare survival between groups.

Cox proportional hazards regression analysis was performed. Univariate analysis was performed first and only variables showing significant results in univariate analysis were included in calculating the adjusted hazard ratio.

To assess the ability of the d-dimer serum level in predicting the primary endpoints, diagnostic performances were calculated and receiver operating characteristic (ROC) curves were constructed to ascertain the corresponding area under the ROC curve (AUROC).

In all the hypothesis tests, a p-value of less than 0.05 was considered for statistical significance and usual confidence intervals of 95% were chosen.

Results

In total, 118 patients were included during the study period, 76 (64.4%) in the Lower-values group, 31 (26.3%) in the Intermediate-values group, and 11 (9.3%) in the Higher-value group. Patients' baseline characteristics are summarized in Table 1.

The population analyzed had a mean age of 63.3 (± 13.1) years, with 73.7% of males (87 patients), a mean body mass index of 28.2 (± 4.9) and a mean length of COVID19 symptoms at UCI admission of 8.6 days, without differences across the three groups.

The Lower-values, the Intermediate-values and the Higher-values groups were not different in what concerns the need for hemodynamic support, respiratory support and renal replacement therapy. Similarly, they did not differ statistically

Table 1. Demographic and primary clinical characteristics in the Lower-values group, Intermediate-values group and Higher-values group.

	Lower-values group (n = 76)	Intermediate-values group (n = 31)	Higher-values group (n = 11)	p
Age, years (mean ± sd)	63.2 ± 13	64.5 ± 12.6	59.8 ± 15.6	0.641
Gender, males (n, %)	58 (76.3%)	20 (64.5%)	9 (81.8%)	0.369
Body mass index (mean ± sd)	27.9 ± 5.1	28.7 ± 5.1	28.1 ± 4.3	0.813
Length of COVID19 symptoms at ICU admission, days (mean ± sd)	9.3 ± 6.9	7.4 ± 4.4	7.7 ± 6	0.522
SOFA at admission (median [IQR])	4 (2;7)	4 (2;8)	7 (2.5; 8.75)	0.609
Mechanical Ventilation (n, %)	43 (56.6%)	18 (58%)	7 (63.6%)	0.905
Length of mechanical ventilation, days (median [IQR])	4.5 (0; 17.8)	4 (0;19)	7 (0; 17)	0.982
Minimum paO2/FiO2 registered (mean ± sd)	133.4 ± 81.7	139.6 ± 94.3	118.8 ± 79.5	0.868
Ventilation in prone position, hours (median [IQR])	58.3 (0; 105.3)	74.6 (0; 82)	55.5 (0; 72)	0.699
Vasopressor Support (n, %)	41 (53.9%)	19 (61.2%)	7 (63.6%)	0.699
Minimum Blood Pressure registered, mm Hg (mean ± sd)	53.7 ± 9.7	56.6 ± 14.2	54.1 ± 11.9	0.856
Maximum dose of Vasopressor therapy, µg/Kg (median [IQR]	6.6 [0; 26.4]	9.9 [0;23.1]	13.4 [0; 39.6]	0.675
Maximum serum lactate level, mg/dL [median [IQR]	1.9 [1.4; 2.6]	1.7 [0.9; 2.5]	1.8 [1.6; 3.1]	0.238
Maximum troponin level, ng/mL [median [IQR]]	28.5 [11.3; 76.8]	47 [13; 93]	33 [15; 194]	0.577
Minimum hemoglobin level, g/dL [mean ± sd]	9.7 ± 2.5	10 ± 2.4	9.8 ± 2.9	0.777
Minimum platelet count registered, $\times 10^3$/uL [mean ± sd]	179 ± 78.3	181 ± 82.7	150 ± 98.7	0.639
C-Reactive protein, mg/dL [mean ± sd]	26.7 ± 11.9	24.4 ± 9.9	21.3 ± 9.9	0.287
Procalcitonin, ng/mL [median [IQR]	1 [0.2; 5.8]	1.1 [0.3; 3.3]	0.95 [0.24; 15.3]	0.795
Remdesivir [n, %]	41 [54%]	12 [38.7%]	2 [18.2%]	0.05
Corticosteroid therapy [n, %]	26 [34%]	9 [29%]	3 [27.3%]	0.816
Renal support therapy [n, %]	18 [23.6%]	8 [25.8%]	5 [45.5%]	0.308

*IQR denotes Interquartile range.

in biomarkers serum levels registered during ICU stay, such as maximum lactate, C-reactive protein and procalcitonin, and minimum hemoglobin and platelet count. In contrast, the maximum d-dimer level registered during ICU stay was different in the three analyzed groups (6463 ng/mL vs 9377 ng/mL vs 32114ng/mL, respectively, $p < 0.0001$).

The analysis of the defined primary outcomes revealed overall in-hospital mortality of 23.7% (28 patients) (Table 2). Despite the trend to higher in-hospital mortality in the Higher-values group, these values did not differ between the groups (21% in the Lower-values group vs 25.8% in the Intermediate-values group vs 36.4% in the Higher-values group, $p = 0.510$). The Kaplan-Meier survival curves at day 28 showed no difference between the 3 groups (log-rank test of 0.524) (Figure 1).

The results of univariate Cox regression performed considering d-dimer serum level at ICU admission or maximum d-dimer serum level registered also did not show any significant hazard ratios when analyzed individually (hazard ratio 1.000, 95% Confidence Interval [CI]I 1.0-1.0, with $p = 0.583$ and $p = 0.706$ respectively), or even when adjusted for gender, age, ICU length of stay and SOFA score at admission.

In order to account for a small sample in the Higher-values group, another survival analysis was made dividing patients according to d-dimer levels at ICU admission < 3-fold normal range value versus >3-fold normal range value. Mortality was not different between these two groups (mortality rate 14,5% vs 19%, respectively, $p = 0.517$).

In the analyses of the secondary outcomes, the collected data did not show statistical difference between the three groups in ventilator free-days and vasopressor free-days at day 28 ($p = 0.692$ and $p = 0.699$, respectively).

The AUROC curves for prediction of 28-day mortality rate by d-dimer serum level at ICU admission and maximum d-dimer serum level registered were constructed and are present in Figure 2. The AUROC for d-dimer serum level at ICU admission was 0,57 (95% CI: 0.422-0.714) and for maximum d-dimer serum level registered was 0.47 (95% CI: 0.314-0.616).

Discussion

Due to the complexity of COVID19 pathophysiology and the uncertainty still surrounding this disease, it has become preponderant the identification of reliable clinical biomarkers to correctly and promptly identify patients more prone to poor outcomes and with higher mortality rates. The previously collected data has indicated a high tier of d-dimer serum level on COVID19 patients and has linked the COVID19 driven pro-inflammatory state and hypoxia to the unregulated activation of the coagulation cascade and the hypoxia-inducible transcription factor-dependent signaling pathway.[12] This evidence has motivated an increasing number of heterogeneous studies with not agreeable results regarding the ability of d-dimer serum levels in predicting poor prognosis and mortality in COVID19 patients.[13-16]

Table 2. Primary and secondary outcomes in Lower-values group, Intermediate-values group and Higher-values group.

	Lower-values group (n = 76)	Intermediate-values group (n = 31)	Higher-values group (n = 11)	p
D-dimer levels at ICU admission, ng/mL (mean ± sd)	902 ± 328.9	2455 ± 951.8	25711 ± 23529	**<0.0001**
Maximum D-dimer level registered, ng/mL (median [IQR])	2096 (1272; 6938)	4516 (2428; 10711)	23529 (16514; 57742)	**<0.0001**
Ventilator free-days at day 28 (mean ± sd)	15.9 ± 12.3	14.7 ± 12.2	13.5 ± 12.2	0.692
Vasopressor free-days at day 28 (mean ± sd)	17.7 ± 12.2	17.1 ± 12.2	16.2 ± 13.1	0.699
ICU length of stay, days (mean ± sd)	15.8 ± 13.8	13.5 ± 11.4	13.1 ± 8.7	0.774
In-Hospital mortality rate (n, %)	16 (21%)	8 (25.8%)	4 (36.4%)	0.510

* IQR denotes Interquartile range.

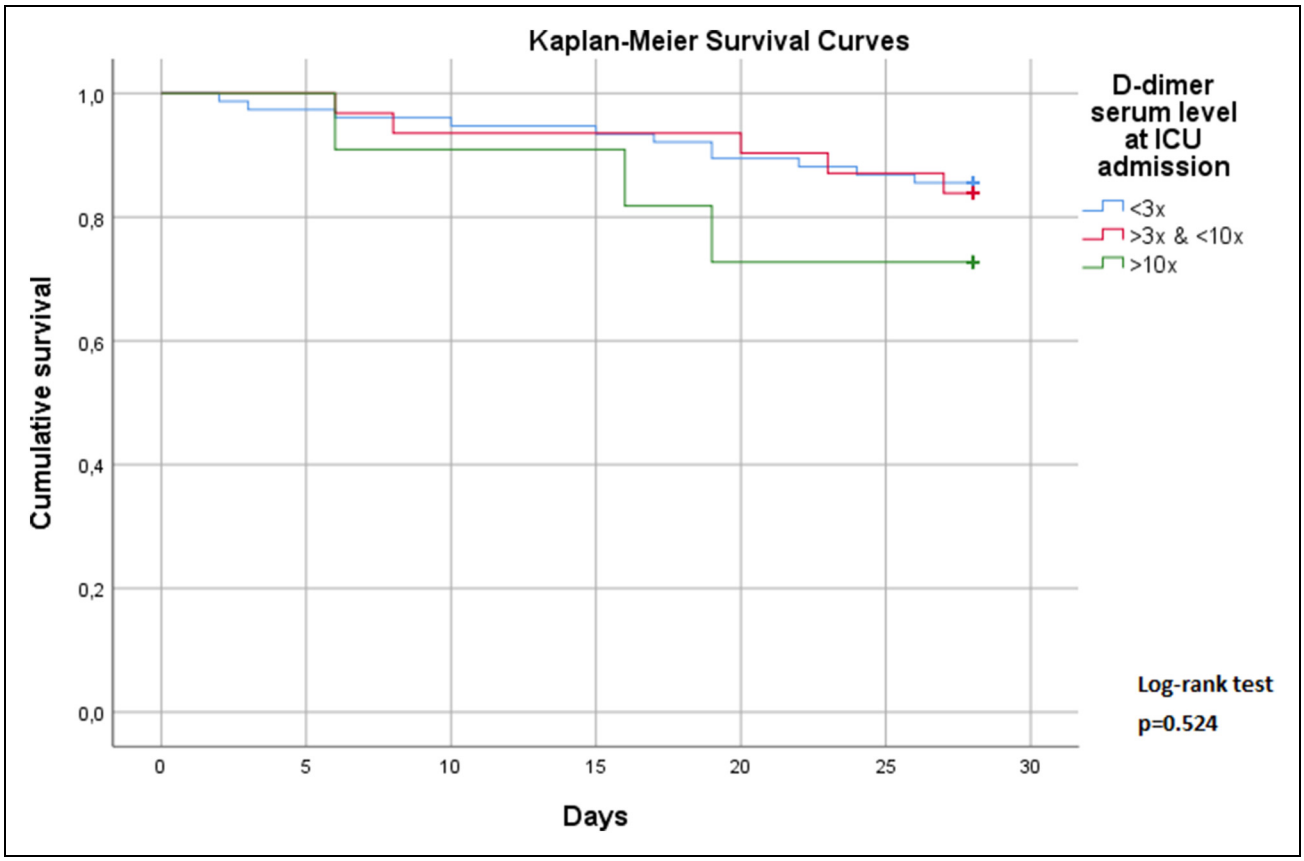

Figure 1. Kaplan-Meier Survival curves of Lower-values group, Intermediate-values group and Higher-values group.

Our study clearly shows that d-dimer serum levels are not a good surrogate marker of severity in COVID19 patients nor does it reliably stratify patients according to risk mortality. Irrespective of the d-dimer level at ICU admission or maximum d-dimer level registered during ICU length of stay, patients analyzed did not differ at in-hospital mortality, at 28-day mortality or secondary outcomes as ventilation-free days and vasopressor-free days. Furthermore, patients in the three groups did not differ in the rate of hemodynamic, respiratory and renal support therapies and they were comparable in age, gender, body mass index, SOFA score at admission, length of COVID symptoms at ICU admission and ICU length of stay.

A meta-analysis done by Gungor et al. concluded that patients with elevated d-dimer on admission had a higher mortality risk (relative risk 1.82) and disease severity (relative risk of 1.58) when compared to patients with d-dimer levels in the normal range values. However, the authors report a high heterogeneity of the analyzed retrospective observational studies and an inability to truly ascertain the prognostic value of d-dimer serum level when adjusted to other properties of the studied population (as age, respiratory and vasopressor support) due to lack of data available on patients' characteristics in those studies.[17] Another similar meta-analysis also described worse clinical outcomes in

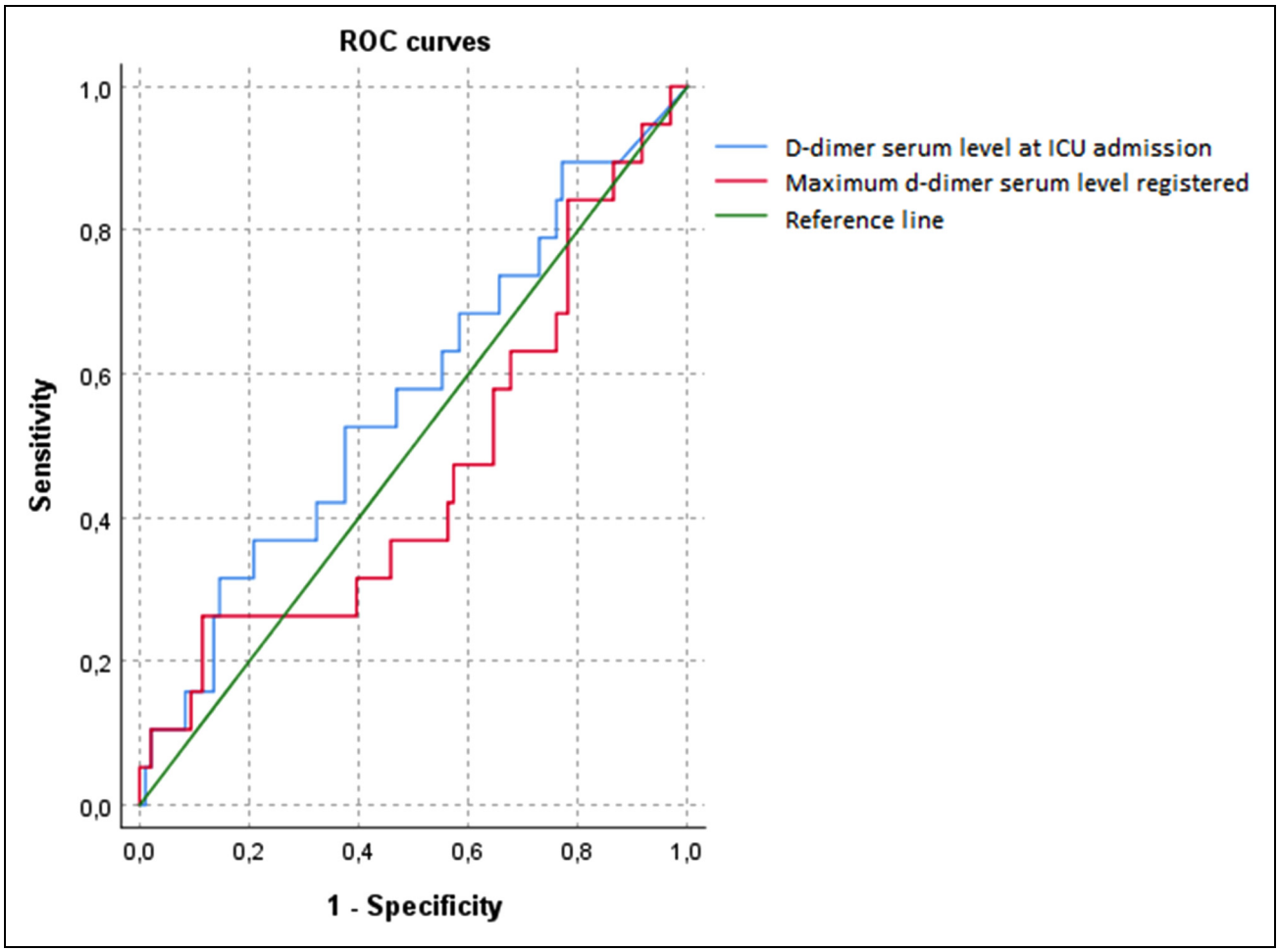

Figure 2. ROC curves for prediction of 28-day mortality rate by d-dimer serum level at ICU admission and maximum d-dimer serum level registered.

COVID19 patients with elevated d-dimer serum levels.[18] In this study the reported clinical outcome referred to a composition of all-cause mortality, ICU admission and acute respiratory distress syndrome occurrence and the heterogeneity index of the studies included was found to be relatively high (I2 statistic 98%). Our study suggests that the magnitude d-dimer serum level is not associated with a higher mortality or poorer outcomes, even in COVID patients comparable in their baseline, clinical and therapeutical characteristics.

Several studies have also attempted to ascertain the accuracy of d-dimer serum levels in defining the prognosis of COVID19 patients, although with contrasting results. Poudel A. et al. recently reported a value of AUC of ROC curve of d-dimer serum levels of 0.807.[19] However, our data describe a poor ability of d-dimer serum level at admission (AUC 0.57) and maximum d-dimer level registered during ICU length of stay (AUC 0.47) to predict survivability of severe COVID19 patients. These reported values are in accordance with the majority of published data defining a poor discriminatory ability of d-dimer serum levels with AUC <0.7.[13-15]

Our study provides evidence that d-dimer serum level is not a good predictor of in-hospital mortality of COVID19 patients and probably stands as a derived inflammatory biomarker, rather than a severity index. This is further reinforced by recent evidence that has shown that d-dimer serum level in COVID19 patients is not reliably associated with pulmonary embolism and this VTE event occurrence probably does not increase patients' mortality, considering its usual involvement of smaller pulmonary arteries.[20] Therefore, our data suggest that d-dimers should not be used for clinical-decision making, including anticoagulation therapy without formal clinical indication, or to limit adequate resuscitation and therapeutic support to these patients, considering its inability to correctly define their poor outcome.

Recent data has hypothesized that linear modeling of d-dimer serum levels during hospital admission may offer a better prognostic value than admission to d-dimer serum level *per se,*[21] but more evidence is required.

This study strengthens its results with a robust structure and data prospectively collected. Moreover, the homogeneity of supportive care across the compared groups limits some

potential biases on the analyzed outcomes. Furthermore, this study has taken into account time from illness presentation to ICU admission and has used the same d-dimer measurement method, limiting bias due to the use of different equipment and methods. However, it is not without some limitations. It is a single-center study, with relatively small sample size. Moreover, the potential complications during ICU stay that could justify high d-dimer levels, not directly related to COVID19 infection, were not registered.

Conclusion

In severe COVID19 patients, the d-dimer serum level profile does not accurately predict poor outcomes and mortality rate, and therefore we suggest that it should not be used for clinical-decision making or to limit adequate resuscitation and therapeutic support to these patients. Considering the importance of early recognition of severe COVID19 patients to improve their survival, d-dimer serum level determination does not add clinical value to individual clinical evaluation in patients' risk stratification.

Author Contributions

JPC contributed to Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Roles/Writing – original draft; Writing – review & editing. LC contributed to Conceptualization; Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Roles/Writing – original draft; Writing – review & editing. VC, RM, and PM contributed to Conceptualization; Data curation; Investigation; Roles/Writing – original draft. LM, PF, AT, CP, DN, BV, VM, and CT contributed to Conceptualization; Data curation; Investigation. PP contributed to Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Roles/Writing – original draft; Writing – review & editing.

Availability of Data and Materials

The datasets generated and/or analysed during the current study are not publicly available due to privacy issues, but are available from the corresponding author on reasonable request

Ethics Approval and Consent to Participate

The study was approved by the Portuguese National Ethics Committee for Clinical Research (reference REC: 2020_EO_02)

Declaration of Conflicting Interests

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References

1. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. *Jama*. 2020;324(8):782-793.
2. Osuchowski MF, Winkler MS, Skirecki T, et al. The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity. *Lancet Respir Med*. 2021;9(6):622-642.
3. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European respiratory society (ERS): the task force for the diagnosis and management of acute pulmonary embolism of the European society of cardiology (ESC). *Eur Respir J*. 2019;54(3):9–54.
4. Ortel TL, Neumann I, Ageno W, et al. American Society of hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv*. 2020;4(19):4693-4738.
5. Conte G, Cei M, Evangelista I, et al. The meaning of D-dimer value in COVID-19. *Clin Appl Thromb Hemost*. 2021;27(27):10760296211017668.
6. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062.
7. Wu Z, McGoogan JM. Characteristics of and important lessons From the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases From the Chinese center for disease control and prevention. *Jama*. 2020;323(13):1239-1242.
8. Yao Y, Cao J, Wang Q, et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. *J Intensive Care*. 2020;8(8):8–49.
9. Thachil J, Tang N, Gando S, et al. ISTH Interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost*. 2020;18(18):1023-1026.
10. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-Art review. *J Am Coll Cardiol*. 2020;75(23):2950-2973.
11. Rostami M, Mansouritorghabeh H. D-dimer level in COVID-19 infection: a systematic review. *Expert Rev Hematol*. 2020;13(11):1265-1275.
12. Wool GD, Miller JL. The impact of COVID-19 disease on platelets and coagulation. *Pathobiology*. 2021;88(1):15-27.
13. Soni M, Gopalakrishnan R, Vaishya R, Prabu P. D-dimer level is a useful predictor for mortality in patients with COVID-19: analysis of 483 cases. *Diabetes Metab Syndr*. 2020;14(6):2245-2249.
14. Naymagon L, Zubizarreta N, Feld J, et al. Admission D-dimer levels, D-dimer trends, and outcomes in COVID-19. *Thromb Res*. 2020;196(196):99-105.

15. He X, Yao F, Chen J, et al. The poor prognosis and influencing factors of high D-dimer levels for COVID-19 patients. *Sci Rep*. 2021;11(1):1830.
16. Oualim S, Abdeladim S, Ouarradi AE, et al. Elevated levels of D-dimer in patients with COVID-19: prognosis value. *Pan Afr Med J*. 2020;35(Suppl 2):105.
17. Gungor B, Atici A, Baycan OF, et al. Elevated D-dimer levels on admission are associated with severity and increased risk of mortality in COVID-19: a systematic review and meta-analysis. *Am J Emerg Med*. 2021;39(39):173-179.
18. Bansal A, Singh AD, Jain V, et al. The association of D-dimers with mortality, intensive care unit admission or acute respiratory distress syndrome in patients hospitalized with coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. *Heart Lung*. 2021;50(1):9-12.
19. Poudel A, Poudel Y, Adhikari A, et al. D-dimer as a biomarker for assessment of COVID-19 prognosis: d-dimer levels on admission and its role in predicting disease outcome in hospitalized patients with COVID-19. *PLoS One*. 2021;16(8):e0256744.
20. Miró Ò, Jiménez S, Mebazaa A, et al. Pulmonary embolism in patients with COVID-19: incidence, risk factors, clinical characteristics, and outcome. *Eur Heart J*. 2021;42(33):3127-3142.
21. Qeadan F, Tingey B, Gu LY, Packard AH, Erdei E, Saeed AI. Prognostic values of Serum ferritin and D-dimer trajectory in patients with COVID-19. *Viruses*. 2021;13(3). doi:10.3390/v13030419