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BRIEF REPORT

D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19

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Abstract

Background: The outbreak of the coronavirus disease 2019 (Covid-19) has shown a global spreading trend. Early and effective predictors of clinical outcomes are urgently needed to improve management of Covid-19 patients.

Objective: The aim of the present study was to evaluate whether elevated D-dimer levels could predict mortality in patients with Covid-19.

Methods: Patients with laboratory confirmed Covid-19 were retrospective enrolled in Wuhan Asia General Hospital from January 12, 2020, to March 15, 2020. D-dimer levels on admission and death events were collected to calculate the optimum cutoff using receiver operating characteristic curves. According to the cutoff, the subjects were divided into two groups. Then the in-hospital mortality between two groups were compared to assess the predictive value of D-dimer level.

Results: A total of 343 eligible patients were enrolled in the study. The optimum cutoff value of D-dimer to predict in-hospital mortality was 2.0 μg/mL with a sensitivity of 92.3% and a specificity of 83.3%. There were 67 patients with D-dimer ≥2.0 μg/mL, and 267 patients with D-dimer <2.0 μg/mL on admission. 13 deaths occurred during hospitalization. Patients with D-dimer levels ≥2.0 μg/mL had a higher incidence of mortality when comparing with those who with D-dimer levels <2.0 μg/mL (12/67 vs 1/267, $P < .001$; hazard ratio, 51.5; 95% confidence interval, 12.9-206.7).

Conclusions: D-dimer on admission greater than 2.0 μg/mL (fourfold increase) could effectively predict in-hospital mortality in patients with Covid-19, which indicated D-dimer could be an early and helpful marker to improve management of Covid-19 patients. (Chinese Clinical Trial Registry: ChiCTR2000031428).

KEYWORDS

coronavirus disease, D-dimer, mortality, prognosis, SARS-CoV-2

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L.Z. and X.Y. contributed equally to this work.

2 | INTRODUCTION

The novel coronavirus, designated SARS-CoV-2, has caused a global outbreak of respiratory illness termed coronavirus disease 2019 (Covid-19) since December 2019, and is still spreading quickly in more than 100 countries.[1-3] There have been more than 600,000 patients with confirmed Covid-19 worldwide by the end of March 2020.[3-5] One of the key issues has been the very high volume of patients presenting to health centers or hospitals during the outbreak. It clearly overwhelms the human and mechanistic capacities available, especially the need for critical care support. As such, risk stratification measures would clearly be helpful.[5,6] Therefore, early and effective predictors of clinical outcomes are urgent needed for risk stratification of Covid-19 patients. D-dimer originates from the formation and lysis of cross-linked fibrin and reflects activation of coagulation and fibrinolysis.[7] It has been reported that Covid-19 was associated with hemostatic abnormalities, and markedly elevated D-dimer levels were observed in those nonsurvivors.[8] However, the prognosis value and the optimal cutoff value for D-dimer on admission to predict mortality have not been well evaluated.

Essentials

- Measuring D-dimer had been recommended for Covid-19 patients, however, the optimal cutoff for D-dimer remains to be well-established.
- D-dimer = 2.0 μg/ml (fourfold increase) on admission might be the optimum cutoff to predict in-hospital mortality for Covid-19.
- The in-hospital mortality was significant higher in patients with D-dimer ≥ 2.0 μg/ml than those who had D-dimer < 2.0 μg/ml on admission.
- Among routine tests, D-dimer might be the best early marker to improve management of Covid-19 patients.

3 | METHODS

3.1 | Study design and participants

The study was a retrospective study conducted in Wuhan Asia General Hospital (Wuhan, China), which was a designated hospital for Covid-19 patients. Adult (aged 18 years or older) patients with laboratory-confirmed Covid-19 between January 12, 2020, and March 15, 2020, were retrospectively screened. The diagnosis of Covid-19 was according to World Health Organization interim guidance[9] and confirmed by RNA detection of the SARS-CoV-2 in onsite clinical laboratory. A total of 343 participants who had a D-dimer level on admission and had a definite outcome (dead or survival) were enrolled. The study was approved and the requirement for informed consent was waived by the Ethics Commission (WAGHMEC-KY-202004).

3.2 | Data collection

All clinical, laboratory, and outcome data were extracted from electronic medical records using a standardized data collection form. All data were checked by two physicians (S.Y. and X.L.), and a third researcher (Z.L.) adjudicated any difference in interpretation between the two primary reviewers.

3.3 | Laboratory assay and intervention

Blood samples were collected within 24 hours after admission to perform routine laboratory tests, such as blood count, coagulation profile, and serum biochemical tests (including renal and liver function) in an onsite laboratory. D-dimer was determined on CS5100 automatic coagulation analyzer (Sysmex, Kobe, Japan) by using a latex-enhanced photometric immunoassay (Siemens, Marburg, Germany). Inter- and intra-day variability coefficients were 3.41% and 4.22%. The laboratory reference range was 0 to 0.5 μg/mL. The D-dimer result was expressed in μg/mL fibrinogen equivalent unit. All measurements were done within 2 hours after blood sampling.

3.4 | Statistical analysis

Continuous and categorical variables were presented as mean ± standard deviation or median (interquartile range [IQR]), as appropriate. Categorical variables were presented as n (%). Event frequencies were compared with chi-squared test. Other comparisons between two groups were made with unpaired Student *t* test or Mann-Whitney *U* test. The optimal D-dimer cutoff point and C-statistic of routine tests were evaluated by receiver operator characteristic (ROC) curve. The outcomes were compared by Kaplan-Meier survival analysis. Hazard ratio (HR) and 95% confidential interval (95% CI) were calculated by log-rank tests. The prognostic values of D-dimer and clinical variables were analyzed with Cox-proportional hazard models. A value of $P < .05$ was accepted as statistically significant. The statistical software package MedCalc Statistical Software (version 16.2, Ostend, Belgium) was used for analyses.

4 | RESULTS

4.1 | Baseline characteristics and establishing optimum cutoff value for D-dimer

Of 343 eligible patients, the median age was 62 years (IQR, 48-69), ranging from 18 years to 92 years. A total of 37.6% (129/343) patients were older than 65 years and 50.3% (174/343) patients were

TABLE 1 Baseline characteristics of 343 patients with Covid-19

Variable	Total n = 343	D-dimer < 2.0 n = 276	D-dimer ≥2.0 n = 67	*P* Value
Age (IQR), y	62.0 (48.0, 69.0)	59.0 (43.5, 68.0)	70.0 (62.2, 76.0)	<.001
Age > 65, n (%), y	129 (37.6)	88 (33.0)	41 (53.9)	<.001
Female, n (%)	174 (50.7)	145 (54.3)	29 (38.2)	.22
Underlying conditions, n (%)	120 (35.0)	79 (29.6)	41 (53.9)	<.001
Diabetes, n (%)	47 (13.7)	31 (11.6)	16 (21.1)	.007
Hypertension, n (%)	76 (22.2)	50 (18.7)	26 (34.2)	<.001
Coronary heart disease, n (%)	19 (5.5)	11 (4.1)	8 (10.5)	.02
COPD, n (%)	8 (2.3)	4 (1.5)	4 (5.3)	.05
Cancer, n (%)	9 (2.6)	5 (1.9)	4 (5.3)	.08
Stroke history, n (%)	8 (2.3)	2 (0.7)	6 (7.9)	<.001
Chronic kidney disease, n (%)	4 (1.2)	4 (1.5)	0 (0.0)	1.0
Atrial fibrillation, n (%)	4 (1.2)	2 (0.7)	2 (2.6)	.17
Chronic liver disease, n (%)	6 (1.7)	5 (1.9)	1 (1.3)	1.0
Routine tests on admission				
White blood cell, 10^9/L	6.66 ± 4.27	6.47 ± 4.38	7.44 ± 3.72	.09
Lymphocyte, 10^9/L (IQR)	1.36 (0.88, 1.76)	1.44 (1.03, 1.83)	0.83 (0.58, 1.24)	<.001
Neutrophil, 10^9/L (IQR)	3.68 (2.80, 5.06)	3.51 (2.71, 4.81)	4.71 (3.42, 7.32)	<.001
Hemoglobin, 10^9/L (IQR)	127 (115, 137)	127 (117, 139)	122 (110, 134)	.003
Platelet, 10^9/L	242.8 ± 92.3	249.3 ± 88.6	216 ± 102.7	.009
CRP, mg/L (IQR)	3.22 (0.34, 22.5)	1.69 (0.32, 16.6)	13.6(1.77, 62.8)	<.001
Direct bilirubin	4.82 ± 1.46	4.83 ± 1.49	4.76 ± 1.34	.74
ALT, U/mL	28 (16, 49)	28 (16, 47)	30.5 (17, 60)	.34
Creatinine, μmol/L (IQR)	72 (59, 85)	70 (59, 83)	76 (64, 99)	.026
Prothrombin time, s (IQR)	11.7(11.2, 12.3)	11.6 (11.1, 12.2)	12.3 (11.6, 13.1)	<.001
aPTT, s	29.4 ± 4.5	29.6 ± 4.3	28.8 ± 5.2	.21
Fibrinogen, g/L (IQR)	4.1(3.1, 5.1)	4.1(3.1, 5.1)	4.3(3.2, 5.6)	.54
D-dimer, μg/mL (IQR)	0.54 (0.20, 1.41)	0.41 (0.15, 0.69)	4.76 (2.99, 11.9)	<.001
D-dimer ≤0.5 μg/mL, n (%)	164	/	/	/
Hospital stay, d	29 (21, 30)	29 (22, 30)	29 (19, 30)	.31
Nonsurvivors, n (%)	13 (3.8)	1 (0.4)	12 (15.8)	<.001

Note: Data are mean ± standard deviation, median (IQR), n (%). *P* values were calculated by *t* test, Mann-Whitney *U* test, chi-squared test, or Fisher exact test, as appropriate.

Abbreviations: ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; COPD, chronic obstructive pulmonary disease; CRP, C-reaction protein; IQR, interquartile range.

female. Listed in Table 1 are the basic clinical characteristics of the patients, including age, gender, comorbidities, and routine laboratory results on admission. A total of 13 all-cause deaths occurred during hospitalization. The optimum cutoff value for D-dimer to predict all-cause deaths was 2.0 μg/mL using ROC curve (Figure 1) with a sensitivity of 92.3% and a specificity of 83.3%. Area under the ROC curve for all-cause deaths was 0.89. Among routine laboratory tests, D-dimer has the highest C-index to predict in-hospital mortality in Covid-19 patients (Table 2). Besides, The C-indices indicates lymphocyte, prothrombin time, and C-reaction protein are also strong predictors for these patients (Table 2).

According to the optimum cutoff value, 276 patients' D-dimer levels on admission were less than 2.0 μg/mL, and 67 patients had D-dimer levels over 2.0 μg/mL. Compared with those patients with D-dimer levels below 2.0 μg/mL, patients with D-dimer levels ≥2.0 μg/mL had a higher incidence of underlying disease, such as diabetes ($P = .007$), hypertension ($P < .001$), coronary heart disease ($P = .02$), and stroke history ($P < .001$). Additionally, lower level of lymphocyte ($P < .001$), hemoglobin ($P = .003$), platelet count ($P = .009$), and higher level of neutrophil ($P < .001$), C-reactive protein ($P < .001$), and prothrombin time ($P < .001$) were also observed in those with D-dimer levels ≥2.0 μg/mL.

4.2 | High D-dimer levels to predict mortality

A total of 13 death events occurred during hospitalization, 12 of which were observed among patients with D-dimer levels ≥2.0 μg/mL on admission as compared with only one such event in those with negative D-dimer levels (<2.0 μg/mL) on admission (12/67 vs 1/276). Kaplan-Meier survival curves (Figure 2) for D-dimer levels showed that D-dimer level ≥2.0μg/mL was the significant predictor of subsequent deaths (P < .001; HR, 51.5; 95% CI, 12.9-206.7). Statistical significance of separation between two groups was achieved at 7 days. Cox proportional hazard analysis showed that high D-dimer level was also a significant determinant (P = .003, adjusted HR, 22.4; 95% CI, 2.86-175.7) after adjustment of gender, age, with or without underlying disease.

5 | DISCUSSION

The main finding of this study is that D-dimer on admission greater than 2.0 μg/mL was the independent predictor of in hospital death for patients with Covid-19. This finding provides a well-established cutoff value to identify those patients with Covid-19 who have poor prognosis at an early stage.

D-dimer elevation has been reported to be one of the most common laboratory findings noted in Covid-19 patients requiring hospitalization. Guan and colleagues analyzed 1099 patients with laboratory-confirmed Covid-19 from more than 550 hospitals in China,[5] and found the nonsurvivors had a significantly higher D-dimer (median, 2.12 μg/mL) than that of survivors (median, 0.61 μg/mL). Similarly, Ning et al also observed abnormal coagulation results, especially markedly elevated D-dimer in deaths with Covid-19.[8] Fei et al conducted a retrospective study involved 191 patients with Covid-19,[10] and found that D-dimer greater than 1 μg/mL on admission was associated with in-hospital death (HR, 18.42; 95% CI, 2.64-128.55). Huang and colleagues showed D-dimer levels on admission were higher in patients needing critical care support than those who did not require it (median, 0.5 μg/mL).[1] However, these previous studies did not provide well evaluated cutoff for D-dimer. Therefore, a recent guidance on recognition and management of coagulopathy in Covid-19 from International Society of Thrombosis and Haemostasis "arbitrarily defined markedly raised D-dimers on admission as three-four folds increas.e"[6] In current study, a clear cutoff value (2.0 μg/mL, fourfold increase) for D-dimer was well established by ROC curve. Notably, of 12 nonsurvivors with D-dimers ≥2.0 μg/mL, 7 had no severity symptoms on admission. Thus, for patients who have markedly raised D-dimers (cutoff, 2.0 μg/mL; four-fold increase), admission to hospital and closely monitoring should be considered even in the absence of other severity symptoms.

Elevation of D-dimer indicated a hypercoagulable state in patient with Covid-19, which might be attributed to several reasons as follows. First, virus infections are usually accompanied by an aggressive

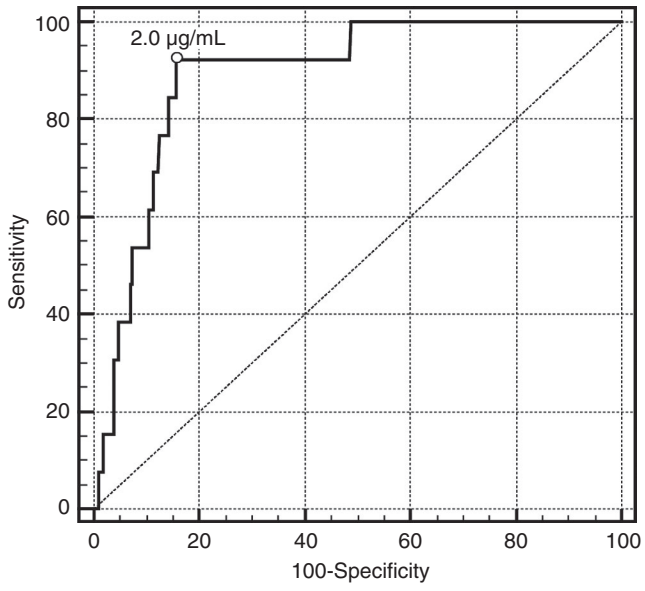

FIGURE 1 Receiver operator characteristic curve for D-dimer to predict deaths. The optimum cutoff point, identified as the point closest to upper left corner, was 2.0 μg/mL with 92.3% sensitivity and 83.3% specificity. Area under receiver operator characteristic curve for mortality was 0.89

TABLE 2 C-statistic of routine tests to predict mortality in patients with Covid-19

Routine Laboratory Tests	C-index	95% CI
D-dimer	0.883	0.842-0.916
Lymphocyte	0.872	0.832-0.906
Prothrombin time	0.858	0.814-0.895
C-reaction protein	0.844	0.799-0.882
Platelet	0.781	0.734-0.824
Neutrophil	0.773	0.725-0.817
White blood cell	0.625	0.571-0.676
Hemoglobin	0.583	0.528-0.635
Creatinine	0.567	0.510-0.623

Abbreviation: CI, confidential interval.

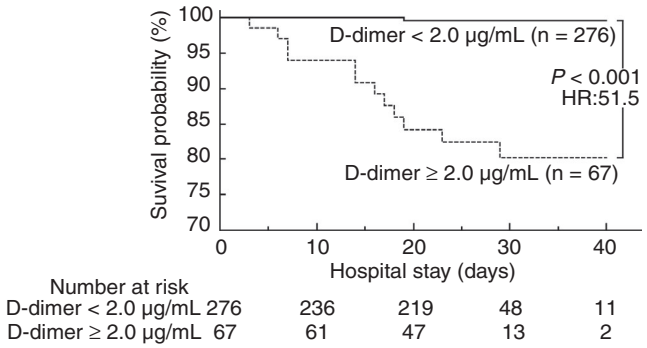

FIGURE 2 Kaplan-Meier survival curves for D-dimer levels on admission. Statistical significance of separation between two groups was achieved at 7 days after admission. HR, hazard ratio.

pro-inflammatory response and insufficient control of an anti-inflammatory response.[11] It might induce the dysfunction of endothelial cells, resulting in excess thrombin generation.[12] Second, the hypoxia found in severe Covid-19 can stimulate thrombosis through not only increasing blood viscosity, but also a hypoxia-inducible transcription factor-dependent signaling pathway.[13,14] Third, hospitalized patients, especially severe patients with Covid-19, were more prone to have older ages, underlying conditions, long-term bed rest, and invasive treatment, which were all risk factors of hypercoagulation or thrombosis.[15-17] As evidence, the lung organ dissection of critical patient with Covid-19 have reported occlusion and microthrombosis formation in pulmonary small vessels.[18] Fourth, some patients might develop to sepsis-induced coagulopathy or even disseminated intravascular coagulation.[8,19] Elevated D-dimer was always associated with unfavorable events.[20,21] Previously, the lack of specificity has been regarded as a disadvantage of D-dimer.[7] However, low specificity has been transformed into one of its advantages in the evaluation of prognosis.

This study has several limitations. First, our study might have selection bias because it was a single-center, retrospective study, even if it had sufficient power to detect the significant differences between groups in mortality. Despite our efforts to include all qualified patients, some patients still excluded in enrollment because of absence of D-dimer levels on admission. Second, because of differences in patient size and medical resources, the lengths from illness onset to admission of the included patients might not be representative, which might influence D-dimer levels on admission. In addition, the half-life of D-dimer was approximately 8 hours[22]; therefore, dynamic measurement of D-dimer will reveal more information. Third, the fully adjusted model analysis for HR was not performed, given the low number of events. Fourth, a multiple-parameter prediction model including D-dimer and other variables might provide better predictive ability for Covid-19 patients.

6 | CONCLUSION

D-dimer on admission greater than 2.0 μg/mL (fourfold increase) could effectively predict in-hospital mortality in patients with Covid-19, which indicated D-dimer could be an early and helpful marker to improve management of Covid-19 patients.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest regarding this article.

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AUTHOR CONTRIBUTIONS

Litao Zhang drafted the manuscript; Litao Zhang, Xinsheng Yan, Haiyan Liu, Xintian Liu, and Zejin Liu collected and analyzed the data; Litao Zhang and Qingkun Fan interpreted the data; and Litao Zhang and Zhenlu Zhang designed the study.

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