The Predictive Value of D-Dimer and DPR for in-Hospital Mortality in Patients with COVID-19

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Short Report

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Abstract

Background: The aim of this study was to explore the predictive value of D-dimer and D-dimer to platelet ratio (DPR) on admission in COVID-19 patients.

Methods: This is a retrospective cohort study of confirmed COVID-19 patients that were admitted to the Renmin Hospital of Wuhan University from January 30, 2020 to February 15, 2020. The baseline clinical and laboratory parameters were collected.

Results: 264 COVID-19 patients were enrolled in this study, of whom 52 died during hospitalization and 212 were discharged from the hospital. Receiver operating characteristic (ROC) curve analysis demonstrated that the area under curve (AUC) of D-dimer was 0.818 with a sensitivity of 75.0% and a specificity of 78.3%, and the AUC of DPR was 0.847 with a sensitivity of 84.6% and a specificity of 75.5% for the prediction of in-hospital mortality on admission. Patients with higher D-dimer or DPR levels were associated with higher mortality risk, compared to those who lower levels. The multivariable Cox regression indicated that in-hospital mortality was associated with age (hazard ratio (HR) 1.034, 95% confidence interval (CI) 1.011-1.058, *P*=0.003), gender (HR 0.553, 95% CI 0.313-0.976; *P*=0.041), coronary heart disease (HR 2.315, 95% CI 1.276-4.200; *P*=0.006), elevated D-dimer (HR 6.111, 95% CI 3.095-12.068; *P*<0.001), and elevated DPR (HR 7.158, 95% CI 3.633-14.101; *P*<0.001).

Conclusions: DPR levels seem to be slightly better at predicting mortality than D-dimer, and elevated D-dimer and DPR can both be considered independent risk factors of the death in COVID-19 patients.

Background

Since the first case of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 was reported in Wuhan, Hubei Province in December 2019, COVID-19 has dramatically spread across the world [1–3]. As of 23th June, 2020, 9106594 cases have been diagnosed with COVID-19, and 469039 patients died of this disease over the world. Most of mild and common patients exhibit a good prognosis and present with milder clinical symptoms, while severe and critical patients might rapidly develop acute respiratory distress syndrome, acute respiratory failure, multiple organ failure, and other fatal complications, which cause a high mortality rate [4, 5]. At present, COVID-19 lacks specific and effective drugs and vaccines. Therefore, it has great clinical significance to investigate risk factors of prognosis for COVID-19 patients. some studies reported that patients with COVID-19 commonly developed hemostatic abnormality with elevated D-dimer and decreased platelet levels in those non-survivors, and the D-dimer was significantly associated with severe disease and higher mortality [6–11]. However, the prognosis value for D-dimer to platelet ratio (DPR) on admission to predict in-hospital mortality has not yet been reported. The aim of this study was to investigate the potential predictive value of D-dimer and DPR for in-hospital mortality in patients with COVID-19.

Methods

Study design and participants

A retrospective study was conducted in Renmin Hospital of Wuhan University (Wuhan, China), which served as designated hospital for COVID-19 patients diagnosis and treatment. The COVID-19 was confirmed by RNA detection of the SARS-CoV-2 using the diagnostic criteria defined in the World Health Organization (WHO) interim guidance [12]. We excluded patients if they were younger 18 years of age, pregnant women, died on admission, with missing data or were transferred to other designated hospitals. Therefore, a total of 264 patients hospitalized from January 30 to February 15, 2020 were included in the final analysis and the final follow-up date was April 27, 2020. All enrolled inpatients had a definite outcome (dead or discharged). The current study was conducted in accordance with the Declaration of Helsinki Principles, and was approved by the Ethics Committee of Renmin Hospital of Wuhan University. (WDRY2019-K056). The requirement for written informed patient consent was waived because of the anonymous nature of the data.

Data Collection

Two investigators (PD and BQ) independently extracted data including demographic data, comorbidities, laboratory data and outcome data from all of the included studies using a standardized data collection form for analysis and, all data of the patients were checked by two investigators (ZK and LY) independently to verify data accuracy.

The hematological parameters (including red blood cell count, platelet (PLT) count, hemoglobin, white blood cell, lymphocytecount, neutrophil count, and monocyte count) were determined using XN-9000 Hematology Analyzer (Sysmex, Kobe, Japan). The ADVIA 2400 Clinical Chemistry System (Siemens, Erlangen, Germany) was used to measure the albumin, alanine aminotransferase, aspartate aminotransferase, creatine kinase, creatinine, lactate dehydrogenase, total bilirubin, and blood urea nitrogen. The plasma D-dimer was measured by CA7000 Coagulation Analyzer (Sysmex, Kobe, Japan), and the normal upper limit range of plasma D-dimer was below 0.5 mg/L. Blood samples were collected within 4 hours on admission.

Statistical analysis.

Categorical data were presented as n(%) and analysed using χ^2 tests. Normally distributed continuous variables are presented as means ± standard deviations (SD), whereas non-normally distributed variables, as median and interquartile ranges (IQR), and the unpaired Studentst - $test$ or $Ma \cap$ - $Whit \neq y$s U test was used for two-groups comparisons of values.

Receiver operating characteristic (ROC) curve analysis was used for calculating the optimal cut-off values, sensitivity, and specificity of D-dimer and DPR. Survival analysis was assessed using the Kaplan-Meier method and compared using log-rank tests. Then, univariate and multivariate Cox proportional

uate the survival hazard using Cox proportional hazard model

with a forward stepwise procedure. All *P*-values were two-sided, with P values less than 0.05 indicating statistical significance. All statistical analyses and graphical representations of the data were performed using GraphPad Prism 7 software (San Diego, CA, USA) and SPSS 21.0 (SPSS Inc, Chicago, IL, USA).

Results

Participants' characteristics

The basic characteristics for all participants were shown in Table 1. Of 264 eligible patients, the median age was 64.5 years (IQR, 53.3–74.0 years), ranging from 26 years to 94 years. The patients in non-survival group were much older than those in survivor group ($P < 0.001$). 50.8% (134/264) patients were female. The median time from admission to discharge was 38.0 days (IQR 29.0-47.8), whereas the median time to death was 5.0 days (IQR 3.0-10.8). The most prevalent clinical symptoms recorded in the COVID-19 patients on admission were fever (93.6%), cough (77.3%), sputum production (22.0%) and fatigue (21.2%). The results also showed that more patients in non-survival group had hypertension (51.9% vs. 34.4%, $P = 0.02$) and coronary heart diseas (34.6% vs. 6.6%, $P < 0.001$), and that there was no difference in the incidence of diabetes, chronic obstructive lung disease, carcinoma, chronic kidney disease, and chronic liver disease between the two groups ($P > 0.05$).

Table 1
Baseline clinical and laboratory characteristics of of patients on admission

	total (264)	survival (212)	non-survival (52)	*P*-value
Total	264	212	52	
Male, n(%)	130 (49.2)	97 (45.8)	33 (63.5)	0.022
Age, years	64.5 (53.3–74.0)	62.5 (52.0–70.0)	74.5 (65.3–81.8)	< 0.001
Time from hospital admission to outcome, days	35.0 (20.0-44.8)	38.0 (29.0-47.8)	5.0 (3.0-10.8)	< 0.001
Comorbidity				
Hypertension (n[%])	100 (37.9)	73 (34.4)	27 (51.9)	0.02
Diabetes, n(%)	41 (15.5)	33 (15.6)	8 (15.4)	0.964
Coronary heart diseas, n(%)	32 (12.1)	14 (6.6)	18 (34.6)	< 0.001
Chronic obstructive lung disease, n(%)	8 (3.0)	6 (2.8)	2 (3.8)	0.702
Carcinoma, n(%)	12 (4.5)	9 (4.2)	3 (5.8)	0.637
Chronic kidney disease n(%)	9 (3.4)	7 (3.3)	2 (3.8)	0.847
Chronic liver disease n(%)	14 (5.3)	10 (4.7)	4 (7.7)	0.392
Other n(%)	80 (30.3)	66 (31.1)	14 (26.9)	0.554
symptom				
Fever (temperature ≥ 37.3℃) n(%)	247 (93.6)	197 (92.9)	50 (96.2)	0.538
Cough n(%)	204 (77.3)	160 (75.5)	44 (84.6)	0.159
Sputum n(%)	58 (22.0)	46 (21.7)	12 (23.1)	0.830
Myalgia n(%)	32 (12.1)	25 (11.8)	7 (13.5)	0.741
Fatigue n(%)	56 (21.2)	44 (20.8)	12 (23.1)	0.714

nter-quartile range.

	total (264)	survival (212)	non-survival (52)	*P*-value
Diarrhoea n(%)	10 (3.8)	7 (3.3)	3 (5.8)	0.419
Nausea or vomiting n(%)	8 (3.0)	6 (2.8)	2 (3.8)	0.658
Albumin, g/L	35.6 ± 4.4	36.3 ± 4.0	32.7 ± 5.0	< 0.001
Alanine aminotransferase, U/L	26.5 (18.0-47.8)	26.5 (18.0–46.0)	26.5 (18.3–57.5)	0.564
Aspartate aminotransferase, U/L	31.0 (23.0–47.0)	29.0 (23.0–41.0)	49.0 (28.3–74.8)	< 0.001
Creatine kinase, U/L	66.0 (38.3-113.8)	61.5 (37.3-106.8)	85.0 (57.0-140.8)	0.005
Creatinine, μmol/L	60.5 (50.3–79.0)	59.0 (50.0–72.0)	74.5 (52.0-112.8)	0.005
Lactate dehydrogenase, U/L	307.0 (233.0-436.8)	282.5 (224.3–381.0)	544.0 (367.3-748.8)	< 0.001
Total bilirubin, μmol/L	10.2 (7.9–15.1)	9.6 (7.5–14.0)	15.2 (10.1–24.2)	< 0.001
Blood urea nitrogen, mmol/L	5.2 (4.0-8.2)	4.9 (3.8–7.2)	8.9 (6.6–15.8)	< 0.001
Prothrombin time, s	12.2 (11.6–12.7)	12.0 (11.5–12.6)	12.7 (12.0-13.8)	< 0.001
Red blood cell, × 1012/L	4.0 ± 0.6	4.0 ± 0.6	4.0 ± 0.7	0.603
Hemoglobin, g/dL	123.4 ± 17.2	123.0 ± 16.2	124.9 ± 21.1	0.549
White blood cell, × 109/L	5.9 (4.0-8.1)	5.4 (3.7–7.2)	8.7 (5.8–13.5)	< 0.001
Lymphocyte, × 109/L	0.9 (0.6–1.2)	0.9 (0.7–1.3)	0.6 (0.4–0.9)	< 0.001
Neutrophil, × 109/L	4.4 (2.4–6.5)	3.9 (2.3–5.5)	7.7 (4.7–11.9)	< 0.001
Monocyte, × 109/L	0.4 (0.3–0.6)	0.4 (0.3–0.6)	0.4 (0.3–0.5)	0.617
Platelet, × 109/L	204.0 (155.3-269.8)	212.0 (162.0-275.0)	181.5 (107.3-227.5)	< 0.001
D-dimer, mg/L	1.1 (0.5–4.1)	0.9 (0.4–1.9)	7.1 (1.7–17.1)	< 0.001

nter-quartile range.

	total (264)	survival (212)	non-survival (52)	*P*-value
DPR × 10^3	5.3 (2.5–19.0)	3.5 (2.1–9.7)	38.3 (11.5-104.7)	< 0.001
Abbreviation: DPR, D-dimer/Platelet; IQR: inter-quartile range.				

Routine blood test showed that white blood cell and neutrophil counts were considerably higher whereas lymphocyte and PLT counts were remarkably lower in the non-survivor group than those in the survivor group. In terms of blood coagulation indexes, the non-survivor group showed significantly higher D-dimer and prothrombin time compared with the survivor group. Meanwhile, aspartate aminotransferase, creatine kinase, creatinine, lactate dehydrogenase, total bilirubin, and blood urea nitrogen were remarkably higher whereas serum albumin was significantly lower in the non-survivor group than those in the survivor group (Table 1).

Analysis of the efficiency of D-dimer and DPR in the predicting the risk of in-hospital mortality

ROC curves were constructed to evaluate predictive value of in-hospital mortality of D-dimer and DPR in patients with COVID-19 on admission (Fig. 1). The results showed that the area under curve (AUC) of D-dimer and DPR were 0.818 (95% confidence interval (CI): 0.759–0.878) and 0.847 (95%CI: 0.795–0.899), respectively. The optimal cutoff value were 2.145 μg/L and 0.010 for D-dimer and DPR. The highest sensitivity and specificity of D-dimer and DPR for predicting in-hospital mortality were 75.0% and 78.3%, and 84.6% and 75.5, respectively.

Association Of D-dimer And Dpr With In-hospital Mortality

To identify the independent risk factors associated with in-hospital mortality in. COVID-19 patients on admission, Kaplan-Meier univariate survival analysis and multivariate Cox regression were used to determine prognostic factors. Figure 2 showed that the survival period of patients with high levels of D-dimer and DPR were both significantly shorter compared to those with low levels ($P < 0.001$). Furthermore, we selected risk factors (Mainly clinical features) that differed between the survival and non-survival group for univariate Cox regression analysis. On univariate analysis, Elevated D-dimer and DPR along with four other variables (age, gender, hypertension, and coronary heart disease) were significantly related to shorter survival. Next, we selected the risk factors identified by the univariate analysis described above for multivariate Cox regression analysis of survival. Multivariate analysis demonstrated that independent predictors of in-hospital mortality in COVID-19 patients on admission were age (hazard ratio (HR), 1.034; 95% CI, 1.011–1.053; $P = 0.003$), gender (HR, 0.553; 95% CI, 0.313–0.976; $P = 0.041$), coronary heart disease (HR, 2.315; 95% CI, 1.276-4.200; $P = 0.006$), elevated D-dimer (HR 6.111, 95% CI 3.095–12.068; $P < 0.001$), and elevated DPR (HR 7.158, 95% CI 3.633–14.101; $P < 0.001$) (Table 2).

Table 2
Univariate and multivariate cox regression analysis of mortality risk factors for patients with COVID-19

	Univariate		Multivariate	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Age	1.056 (1.032–1.081)	< 0.001	1.034 (1.011–1.058)	0.003
Gender	0.516 (0.294–0.908)	0.022	0.553 (0.313–0.976)	0.041
Hypertension	1.926 (1.118–3.319)	0.018		
Coronary heart disease	4.546 (2.563–8.065)	< 0.001	2.315 (1.276-4.200)	0.006
D-dimer	7.722 (4.119–14.480)	< 0.001	6.111 (3.095–12.068)	< 0.001
DPR	8.522 (4.377–16.592)	< 0.001	7.158 (3.633–14.101)	< 0.001
Abbreviation: DPR, D-dimer/Platelet; HR, hazard ratio; CI, confidence interval.				

Discussion

This study, to our best knowledge, was the first to simultaneously explore the predictive value of in-hospital mortality for both D-dimer and DPR in patients with COVID-19. In this retrospective cohort study, The main finding is that elevated D-dimer and DPR on admission can were considered independent risk predictors of the death in COVID-19 patients. This finding provides a well-established cutoff value to identify those patients with COVID-19 who have poor prognosis at an early stage.

There have been several reports about the roles of D-dimer in COVID-19 patients. Huang and colleagues showed D-dimer levels on admission were higher in patients needing critical care support than those who did not require it [9]. Similarly, Fu and colleagues retrospectively analyzed 75 confirmed COVID-19 adult patients in Suzhou and found that D-dimer levels of the severe group was higher than the mild/moderate on days 1, 4 and 14 [7]. Guan and colleagues analyzed 1099 patients with laboratory-confirmed Covid-19 from over 550 hospitals in China, and found the non-survivors had a significantly higher D-dimer than that of survivors [10]. Meanwhile, Tang N et al also observed abnormal coagulation results, especially markedly elevated D-dimer in deaths with COVID-19 [6]. Zhou F et al conducted a retrospective study involved 191 patients with COVID-19, and found that increasing odds of in-hospital death associated with elevated D-dimer on admission [11]. Similarly, Zhang L et al showed that elevated D-dimer on admission could effectively predict in-hospital mortality in patients with COVID-19 [8]. Our current results are consistent with the findings from the previous studies that investigated the roles of D-dimer in COVID-19 pattients [6–11]. In this study, ROC curve analysis revealed that the optimal cut-off value of D-dimer at 2.145 μg/L had 75.0% sensitivity and 78.3% specificity, and the AUC of D-dimer was 0.818. The results presented in this study also confirmed that elevated D-dimer on admission might be regarded as an independent prognostic indicator in COVID-19 patients. Meanwhile, ROC curve for DPR was also well

established. The optimal cut-off value was 0.010 with a sensitivity of 84.6% and a specificity of 75.5%, the AUC of DPR was 0.847.

The above results showed that diagnostic performance of DPR was slightly better than D-dimer for predicting in-hospital mortality of COVID-19. There might be several reasons for this finding. First, The D-dimer levels were gradually and dramatically elevated in COVID-19 patients, which reflects that the in-vivo blood is in the hypercoagulable and hyperfibrinolytic state. Virus infections usually results in proinflammatory cytokine induction and in a pronounced inflammatory response, which might cause endothelial cell dysfunction and subsequently contribute to the activation of coagulation system [13, 14]. Second, not only can severe COVID-19 increase blood viscosity, but also activate hypoxia-inducible transcription factor-dependent signaling pathways to promote thrombosis [15, 16]. Third, severe patients with COVID-19, most of them were elderly, poor underlying conditions, long-term bedridden and invasive treatment, which were all potential factors for promoting thrombosis [17–19]. Forth, some severe COVID-19 patients progressed into sepsis, and sepsis caused abnormal blood coagulation function or even disseminated intravascular coagulation [20]. As evidence, recent pulmonary autopsy study demonstrated that the occlusion and micro-thrombosis of pulmonary small vessels occurred COVID-19 patients [21]. Furthermore, the study also showed that the levels of PLT in patients with COVID-19 were abnormal. Some severe patients with COVID-19 had coagulation dysfunction, which might provoke rapid consumption of platelets, resulting in thrombocytopenia [22, 23]. In addition, COVID-19 is an Inflammatory disease, and inflammation might cause excessive consumption of platelets. The synergism of elevated D-dimer and decreased platelet would improve the diagnostic value of DPR in COVID-19 patients. The above-mentioned reasons may explain why the diagnostic value of DPR was slightly better than D-dimer for predicting in-hospital mortality of COVID-19.

We acknowledged that this study has the following limitations. First, our study was a retrospective, single-center study with a relatively small number of enrolled patients. Second, It is of great significance for monitoring the progress of the disease if we detect D-dimer and DPR levels at the different time points. However, D-dimer and DPR levels cannot be measured multiple times due to the poor conditions. Third, This study only included cases of Chinese patients diagnosed with COVID-19, and the generalizability of the results to other ethnicities might be limited. Forth, we did not collect treatment-related information, which may play crucial role in the prognosis of patients.

Conclusions

The current study provides convincing evidence that elevated D-dimer and DPR levels on admission were independent risk factors, and the predictive value of DPR is may slightly superior to D-dimer. Further researches with a larger number of patients are needed to confirm our findings.

Abbreviations

COVID-19

Coronavirus disease 2019; DPR:D-dimer to platelet ratio; WHO:World Health Organization; PLT:Platelet; SD:Standard deviations; IQR:Interquartile ranges; ROC:Receiver operating characteristic; AUC:Area under the curve; CI:Confidence interval; HR:Hazard ratio

Declarations

Acknowledgements

Not applicable.

Authors' contributions: Supervision: LY; study concept and design: PD, MX, BQ, ZK, and LY; drafting of the manuscript: PD, MX, BQ, and LY; collection, analysis, or interpretation of data: BQ, ZK, BY, and XX; and technical or material support: BQ and PD. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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Availability of data and materials

All datasets are presented in the main paper. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Ethics approval and consent to participate

The study was approved by the by the Ethics Committee of Renmin Hospital of Wuhan University (WDRY2019-K056) and Hubei University of Medicine. The requirement for written informed patient consent was waived because of the anonymous nature of the data.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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Figures

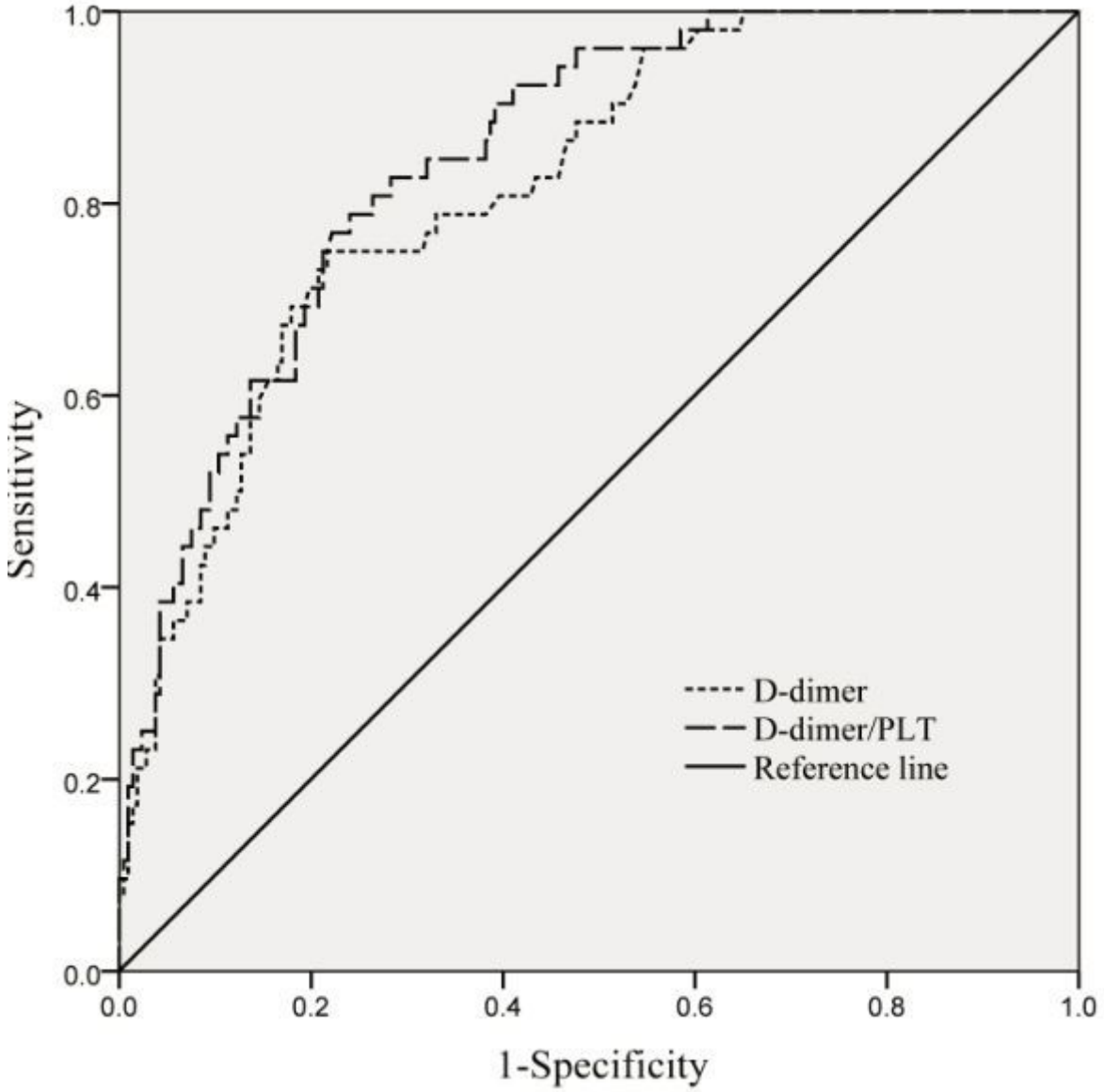

Figure 1

Receiver operator characteristic curve for D-dimer and D-dimer/PLT to predict in-hospital mortality.

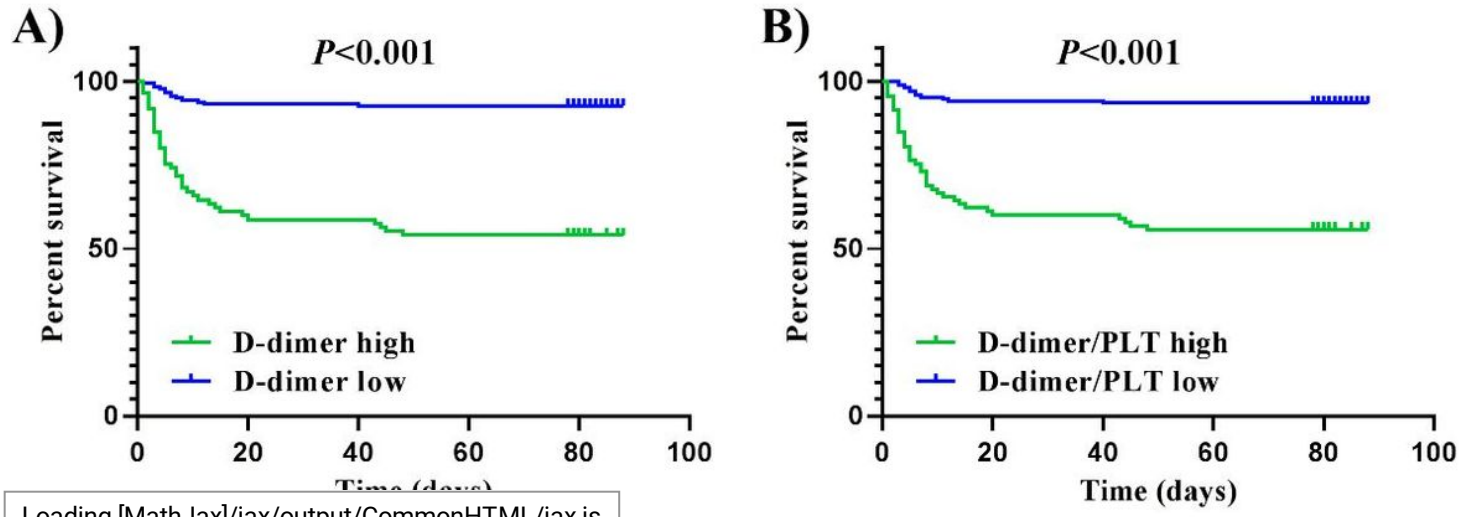

Figure 2

Kaplan-Meier curves of survival analysis. A) Kaplan-Meier curve demonstrating survival of COVID-19 patients by D-dimer levels. B) Kaplan-Meier curve demonstrating survival of COVID-19 patients by D-dimer/PLT levels. P values for survival analysis are derived by the log-rank test. D-dimer high and low are defined as the levels of D-dimer greater than 2.145 μg/L and and less than 2.145 μg/L, respectively. D-dimer/PLT high and low are defined as the levels of D-dimer/PLT greater than 0.010 and less than 0.010, respectively.