D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study

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Research Article

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Abstract

Background: Over 240000 cases of coronavirus disease-19 (COVID-19) has been reported since Dec. 2019. We aim to assess the use of D-dimer as a biomarker for disease severity and clinical outcome in COVID-19 patients.

Methods: We retrospectively analyzed the clinical, laboratory, and radiological characteristics of 248 consecutive cases of COVID-19 in Renmin Hospital of Wuhan University, Wuhan, China from Jan 28 to Mar 08, 2020. Correlations of D-dimer upon admission with clinical staging, radiological staging, and in-hospital mortality were analyzed. Receiver operating characteristics curve was used to determine the optimal cutoff level for D-dimer that discriminated those survivors versus non-survivors during hospitalization.

Results: D-dimer elevation (≥0.50mg/L) was seen in 74.6% (185/248) of the patients. Pulmonary embolism and deep vein thrombosis were ruled out in patients with high probability of thrombosis. D-dimer levels significantly increased with increasing severity of COVID-19 as determined by clinical staging (Kendall's tau_b = 0.374, P=0.000) and chest CT staging (Kendall's tau_b = 0.378, P=0.000). In-hospital mortality rate was 6.9%. Median D-dimer level in non-survivors (n=17) was significantly higher than in survivors (n=231) [6.21 (3.79-16.01) mg/L versus 1.02 (0.47-2.66) mg/L, P=0.000]. D-dimer level of >2.14 mg/L predicted in-hospital mortality with a sensitivity of 88.2% and specificity of 71.3% (AUC 0.85; 95% CI=0.77-0.92).

Conclusions: D-dimer is commonly elevated in patients with COVID-19. D-dimer levels correlate with disease severity and is a reliable prognostic marker for in-hospital mortality in patients admitted for COVID-19.

Background

Coronavirus disease–19 (COVID–19) is the disease caused by 2019-nCoV/SARS-CoV–2, a novel β coronavirus of group 2B.[1] The illness ranges from asymptomatic or mild infection to severe respiratory tract infections in humans such as those seen in severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Presentations include fever, coughing, dyspnea, watery diarrhea, myalgia, severe lymphopenia, prolonged coagulation profiles, cardiac disease and sudden death.[2, 3]

Since the emergence in Wuhan, Hubei province, China in Dec. 2019, COVID–19 has increased rapidly in China and progressed worldwide. On January 30th 2020, WHO declared the outbreak as a Public Health Emergency of International Concern (PHEIC). As of Mar. 20, Over 81000 cases have been confirmed in China and over 160000 cases overseas, including in Italy, Iran, South Korea, Spain, USA, Australia, etc.

Coagulopathy were reported and d-dimer elevations were seen in 3.75–68.0% of the COVID–19 patients. [2, 4, 5] Previous studies in community acquired pneumonia (CAP) and chronic obstructive pulmonary disease (COPD) patients have shown that D-dimer level is higher in severe cases and may be used as a

prognostic biomarker[6–8] and D-dimer>1ug/ml is one of the risk factors for mortality in adult inpatients with COVID–19.[5] However, the role of D-dimer in COVID–19 patients has not been fully investigated. In this study, we showed D-dimer levels in patient groups stratified by clinical, imaging staging, in-hospital death and assessed the role of D-dimer as a biomarker for disease severity and clinical outcome.

Methods

Patients:

We enrolled patients of confirmed COVID–19 referred to the Renmin Hospital of Wuhan University (Wuhan, China), a designated center prioritized in treating critical illness, from Jan 28 to Mar 08, 2020. Confirmed cases was defined as those with epidemiological history, consistent with two clinical manifestations, and microbiological evidence (respiratory or blood specimens positive for SARS-CoV–2 by real-time reverse-transcription-polymerase- chain-reaction (RT-PCR) assay or virus gene sequencing) according to the Novel Coronavirus Pneumonia Diagnosis and Treatment Guideline (6th ed.) (in Chinese) published by the National Health Commission of China.[9] Exclusion criteria included pregnancy, cancer, hematologic malignancy, chronic liver disease, acute coronary syndrome, surgery or trauma within 30 days, and patients without D-dimer testing upon admission. We retrospectively collected demographic, clinical data, laboratory parameters, chest CT imaging, and prognosis through electronic nursing and medical records using standardized data collection form. This study was approved by the institutional ethics board of Renmin Hospital of Wuhan University (No. WDRY2020-K048).

Laboratory and imaging methods:

Complete blood count, coagulation profile, renal and liver function, creatine kinase, electrolytes, myocardial enzymes, CD4 and CD8 cell counts, C-reactive protein, and procalcitonin were collected routinely on admission. D-dimer level is tested using Immunoturbidimetric Assay with reference range of 0–0.50mg/L (Sysmex, CS5100). Doppler ultrasound and CT pulmonary angiography were done for any patients with high clinical suspicion of pulmonary embolism/ deep vein thrombosis (PE/DVT). Chest CT scan were done for all inpatients.

Severity assessment:

Clinically, severity of the COVID–19 patients was classified into mild, moderate, severe, and critically ill according to the Novel Coronavirus Pneumonia Diagnosis and Treatment Guideline (6th ed.) by the National Health Commission of China (Supplement table 1)[9]. Radiologically, the area of affected lungs consistent with viral pneumonia in each patient's first chest CT after admission was measured and classified into ≤30%, 31–50%, and ≥50% of total lung area. The scores of CURB–65 for community acquired pneumonia and Well's rule [10] and the revised Geneva score[11] for assessing pulmonary embolism (PE) risk for each patient were documented.

Statistics:

Continuous data accorded with normal distribution and homogeneity of variance were expressed as mean ± SD and compared by independent samples t-test, or expressed as median (25th—75th percentile) and compared by Wilcoxon rank sum test. Categorical variables were expressed as number (percentage) and compared by Chi-square tests. And ordinal categorical variables were compared by Wilcoxon rank-sum test. Correlations of D-dimer with clinical staging, chest CT staging and in-hospital mortality were evaluated by Kendall's tau_b coefficient analysis. To assess the predictive value of D-dimer, receiver operating characteristics (ROC) analysis was conducted with calculations of the area under the ROC curve (AUC), sensitivity and specificity. Statistical analyses were performed with SPSS (v.22.0; SPSS Inc., Chicago, IL, USA) and P value less than 0.05 was considered statistically significant.

Results

As a designated referral center for the novel coronavirus infection, all the patients hospitalized were confirmed with RT-PCR. After excluding subjects using the exclusion criteria, we included 248 consecutive inpatients between Jan. 28th and Mar. 8th, 2020, in the final analysis. The mean age of the 248 patients was 63.0±13.4years, ranging from 27 years to 88 years. The average time from illness onset to admission was 11.5±5.1days. Nearly one third of the patients had comorbidities, with hypertension being the most common (31.5%), followed by diabetes mellitus (17.7%).

Mild to moderately cases, severe cases, and critically ill cases accounted for 36.3%, 43.5%, and 20.2% of the patients respectively. Using the revised Geneva score, none belonged to the high probability group for risk of PE. Four patients belonged to the high probability group using the Well's rule. Fortunately, they were ruled out of PE/VTE by Doppler ultrasonography and CT pulmonary angiography. 17 patients died during hospitalization. D-dimer elevation (≥0.50mg/L) was seen in 74.6% (185/248) of the patients. The comparison of demographic and clinical characteristics between the normal D-dimer group and elevated D-dimer group are shown in Table 1. Major laboratory markers and chest imaging features upon admission were recorded (Table 2). 35.5%, 31.0%, and 33.5% of the patients had affected lungs of ≤30%, 31–50%, and ≥50% of the total area. The predominant changes seen were ground glass opacity (54.0%), followed by patchy consolidation (21.4%), fibrous stripes (12.9%), and irregular consolidated nodules (11.7%).

The distributions of D-dimer levels among patients with different clinical staging, chest CT staging, and who survived and deceased during hospitalization are presented in Figure 1–3. On admission, D-dimer levels significantly increased with increasing severity of COVID–19 as determined by clinical staging (Kendall's tau_b = 0.374, P = 0.000) and chest CT staging (Kendall's tau_b = 0.378, P = 0.000). Median D-dimer levels showed an about 7-fold increase from moderate to critically ill patients (4.76[2.02–13.30]mg/L versus 0.6[0.33–1.49] mg/L, P = 0.000), and a 5 fold increase from patients with ≤30% affected lung area to ≥50% change respectively (3.93[1.28–12.31]mg/L versus 0.6[0.33–1.42], P = 0.042). All of those who did not survive had increased D-dimer level upon admission. When compared between patients who survived and who died during hospitalization, a significantly higher D-dimer level

was detected in non-survivors versus survivors (6.21[3.79–16.01] mg/L versus 1.02[0.47–2.66] mg/L, P = 0047).

ROC analysis identified D-dimer >2.14 mg/L upon admission as the optimal cutoff level to discriminate survivors from non-survivors (area under the ROC 0.85, standard error 0.037; 95% confidence interval [CI] 0.77–0.92, P = 0.000; Figure 5). 32.7% of the included patients had a D-dimer of >2.14 mg/L. For predicting in-hospital mortality, D-dimer level above 2.14 mg/L had a sensitivity of 88.2% and specificity of 71.3%% (Table 3).

Discussion

We demonstrated that in patients diagnosed with COVID–19, D-dimer elevation upon admission was common and was associated with both increased disease severity and in-hospital mortality.

D-dimers are one of the fragments produced when plasmin cleaves fibrin to break down clots. The assays are routinely used as part of a diagnostic algorithm to exclude the diagnosis of thrombosis. However, any pathologic or non-pathologic process that increases fibrin production or breakdown also increases plasma D-dimer levels. [12] Examples include deep vein thrombosis/ pulmonary embolism, arterial thrombosis, disseminated intravascular coagulation, and conditions such as pregnancy, inflammation, cancer, chronic liver diseases, post trauma and surgery status, vasculitis. Among adults admitted to the emergency room, infections, instead of VTE/PE, are the most common reason for D-dimer elevation.[13] In the present study, D-dimer elevation was seen in 74.6% of the patient, but no patient had confirmed PE/DVT, which supports the application of D-dimer in COVID–19 not just as a diagnostic tool for thromboembolism.

Several studies have shown that D-dimer levels are associated with severity of community-acquired pneumonia and clinical outcome. [6, 14] However, D-dimer has not been used as a biomarker for viral pneumonia.[15, 16] Though D-dimer elevation has been observed in articles describing the clinical features of COVID–19, whether the level of D-dimer is a marker of severity has not been examined. In the present study, there is a significant correlation between D-dimer levels and severity stratified by the area of affected lungs on chest CT, as well as clinical staging according to the interim guideline. In addition, a higher percentage of D-dimer elevation was seen in the present study than previously reported.[2, 4] This may be due to the higher percentage of severe/ critically ill cases referred to our hospital, which is another demonstration of the correlation between D-dimer level and disease severity. This suggests that the assay may be used early as a marker of severity before chest CT scans, or as a complement to CT and clinical staging.

In-hospital mortality was also associated with increased D-dimer levels, suggesting that the assay may be used as a single useful biomarker for clinical outcome in patients with COVID–19. When using the cutoff value of 2.14, the clinical value of D-dimer levels upon admission for in-hospital mortality has an AUC of 0.846. The sensitivity and specificity are 88.2% and 71.3%, respectively. Which suggest that patients with D-dimer levels below 2.14mg/L have a low risk of death. More importantly, an elevated D-

dimer level on admission (>2.14 mg/L) may identify patients at higher risk for in-hospital mortality and therefore inform physicians about suitable candidates for intensive care and early intervention.

In SARS-COV–2 infection, dysregulation of coagulation/anti-coagulation cascades result in worsening lung pathology.[17] In influenza, the pathogenesis by augmenting viral replication and immune pathogenesis can be attributed to an aberrant coagulation system, including both the cellular and protein components.[18] The pathological features of COVID–19 include diffuse alveolar damage with cellular fibromyxoid exudates, desquamation of pneumocytes and hyaline membrane formation, pulmonary oedema with hyaline membrane formation, and interstitial mononuclear inflammatory infiltrates, dominated by lymphocytes, which greatly resemble those seen in SARS and MERS coronavirus infection. [19] [20] Presumably, the observed D-dimer elevation signify a hyperfibrinolysis state and increased inflammatory burden induced in 2019-nCoV infection. Whether this warrants anticoagulation therapy in COVID–19 patients needs further exploration.

This study has some limitations. First, the study is retrospective in nature. The patients included were not systematically assessed for the presence of PE/DVT, but only when clinically suspected. Second, the current study was done in a single center. The overall mortality (6.9%) was lower comparted with that reported in other studies done in Wuhan,[2, 5] and considerably higher than those reported by other provinces.[4, 21] Further researches may be needed when extrapolated to wider patient population. Third, we did not look into the value of serial D-dimer monitoring in assessing COVID–19 patients.

Conclusions

In conclusion, D-dimer levels are commonly elevated in patients infected with SARS-CoV–2. Significantly higher levels are found in those with critical illness and may be used as a prognostic marker for in-hospital mortality.

List Of Abbreviations

COVID–19: coronavirus disease–19; SARS: severe acute respiratory syndrome; MERS: Middle East respiratory syndrome; PHEIC: Public Health Emergency of International Concern; CAP: community acquired pneumonia; COPD: chronic obstructive pulmonary disease; PE: pulmonary embolism; DVT: deep vein thrombosis

Declarations

Ethics approval and consent to participate: This study was approved by the institutional ethics board of Renmin Hospital of Wuhan University (No. WDRY2020-K048).

Consent for publication: Not applicable

Availability of data and materials: The dataset supporting the conclusions of this article is included within the article and its additional files.

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Author's contributions:

YY and JC: contributed in the conception, design, acquisition and analysis, interpretation of data, and writing of the manuscript. QW, KL, ZL, XC, KY: contributed in the design, acquisition and analysis of data. ZH and BH: contributed to the conception, design of the work, analysis of data, interpretation of data, and revision of the manuscript. All authors have approved the submitted version. All authors have agreed to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved and the resolution documented in the literature.

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Tables

Table 1. Comparison of demographic and clinical characteristics between COVID-19 patients with normal and elevated D-dimers.

	Normal D-dimer, n=63	Elevated D-dimer, n=185	P value
Age (yrs.)	58.0±14.4	64.6±12.6	0.001
Male gender (%)	32 (50.8)	103 (55.7)	0.502
Underlying disease, n (%)			
Hypertension	12 (19.0)	66 (35.7)	0.014
Diabetes mellitus	7 (11.1)	37 (20.0)	0.319
Coronary artery disease	3 (4.8)	9 (4.9)	1.000
Chronic kidney disease	0 (0)	6 (3.2)	
Chronic obstructive pulmonary disease	0 (0)	4 (2.2)	
Time since disease onset (days)	10.5±4.8	11.8±5.1	0.069
Highest temperature (℃)	38.1±0.9	38.1±1.0	0.948
Clinical staging at admission, n (%)			0.000
Mild-moderate	40 (63.5)	50 (27.0)	
Severe	20 (31.7)	88 (47.6)	
Critically ill	3 (4.8)	47 (25.4)	
Wells score, n (%)			0.230
<2 points	60 (95.2)	167 (90.3)	
2-6 points	2 (3.2)	15 (8.1)	
>6 points	1 (1.6)	3 (1.6)	
Geneva score, n (%)			0.105
0-3 points	34 (54.0)	78 (42.2)	
4-10 points	29 (46.0)	107 (57.8)	
≥11 points	0	0	
CURB-65, n (%)			0.008
score 0	30 (47.62)	64 (34.59)	
score 1	25 (39.68)	68 (36.76)	
score 2	5 (7.94)	20 (10.81)	
score 3	3 (4.76)	17 (9.19)	
score 4	0 (0)	15 (8.11)	
score 5	0 (0)	1 (0.54)	
In-hospital mortality, n (%)	0	17 (9.2)	0.008

Table 2. Comparison of laboratory value and imaging characteristics between COVID-19 patients with normal and elevated D-dimers.

	Normal D-dimer, n=63	Elevated D-dimer, n=185	P value
D-dimer (mg/L)	0.35 (0.23-0.42)	1.69 (0.91-5.06)	0.000
PaO2 (mm Hg)	71.63±14.81	67.37±14.48	0.147
PaCO2 (mm Hg)	42.5±8.38	40.13±7.07	0.112
White blood cell count ($\times10^9$/L)	4.99±2.44	6.71±3.13	0.000
Lymphocyte count ($\times10^9$/L)	1.3±0.59	1.03±0.60	0.002
Neutrophil count ($\times10^9$/L)	3.12±2.17	5.11±3.13	0.000
Hemoglobin (g/L)	128.7±13.3	122.6±16.8	0.010
Platelet count (10^9/L)	221.9±82.9	232.9±92.6	0.405
CD4 (cells/mm^3)	337 (165.5-560.5)	263 (109.0-429.5)	0.326
CD8 (cells/mm^3)	229 (92-367)	123 (48.25-226.25)	0.122
C-reactive protein (mg/L)	8.5 (5-35.85)	48.4 (10.98-92.25)	0.000
Procalcitonin (ng/mL)	0.05 (0.03-0.08)	0.08 (0.04-0.18)	0.000
Total bilirubin (μmol/L)	10.0 (6.7-13.0)	11.7 (8.6-15.5)	0.050
Combined bilirubin (μmol/L)	3.4 (2.6-5.0)	4.3 (3.3-6.1)	0.030
Alanine aminotransferase (U/L)	21.0 (13.0-39.0)	28.5 (19.0-55.3)	0.001
Aspartate aminotransferase (U/L)	24.0 (17.0-34.5)	33.5 (21.0-49.0)	0.001
alkaline phosphatase (U/L)	60.4±17.0	77.7±40.3	0.000
Gamma-glutamyl Transferase (U/L)	30.0(13.5-47.0)	33.5(23.0-68.3)	0.001
Lactate dehydrogenase (IU/L)	250.41±90.4	356.11±185.28	0.000
Serum creatinine (mmol/L)	64.0 (54.0-77.0)	64 (52.0-74.0)	0.715
eGFR (ml/[min*1.73m^2])	97.15±13.99	88.64±24.94	0.001
Blood glucose (mmol/L)	6.49±3.34	7.12±3.94	0.257
Creatine kinase (U/L)	75.0 (50-132.5)	58.5 (33-87.5)	0.057
Cardiac troponin I (ug/L)	0.01 (0.01-0.01)	0.01 (0.01-0.02)	0.000
B-type natriuretic peptide (pg/mL)	44.45 (18.15-147.6)	222.25 (87.69-461.83)	0.000
Area of affected lung on Chest CT, n (%)			0.000
≤30%	37 (58.7)	51 (27.6)	
31%-50%	16 (25.4)	61 (33.0)	
≥50%	10 (15.9)	73 (39.4)	
Predominant feature on Chest CT, n (%)			0.287

Ground glass opacities	40 (63.5)	94 (50.8)	
Patchy consolidations	12 (19.1)	41 (22.2)	
Fibrous stripes	4 (6.3)	25 (13.5)	
Irregular solid nodules	7 (11.1)	25 (13.5)	
Pericardial effusion, n (%)	1 (1.6)	4 (2.2)	0.800

Table 3. Test characteristics of D-dimer for predicting in-hospital mortality with the optimal sensitivity and specificity scorers

Cutoff point for D-dimer (mg/L)	2.14
Area under curve	0.85
95% CI	0.77-0.92
Subjects with d-dimer > 2.14mg/L (%)	77 (31.2%)
Sensitivity (%)	88.2
Specificity (%)	71.3
Likelihood ratio	3.08

Figures

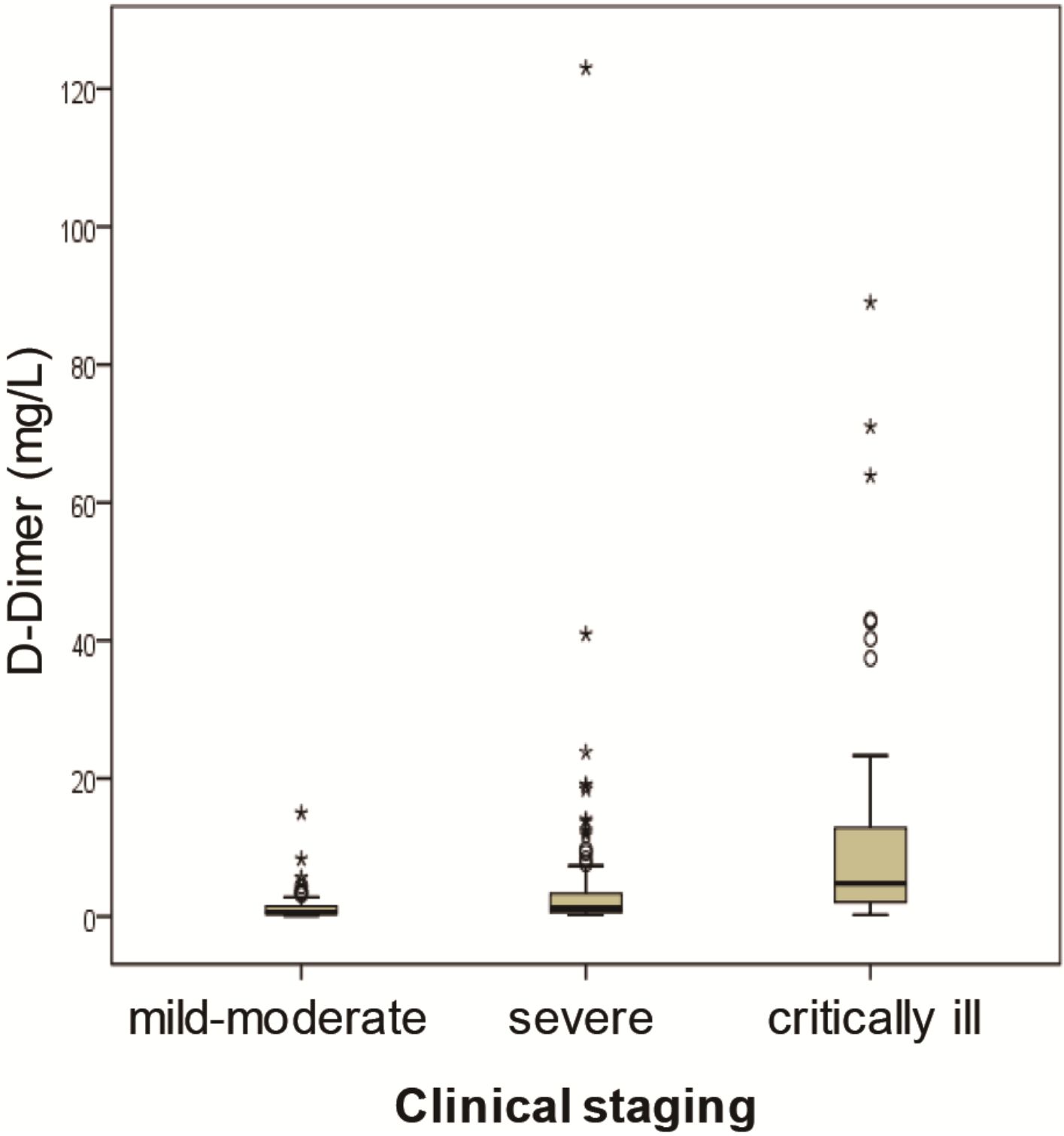

Figure 1

Correlations of D-dimer levels with clinical staging.

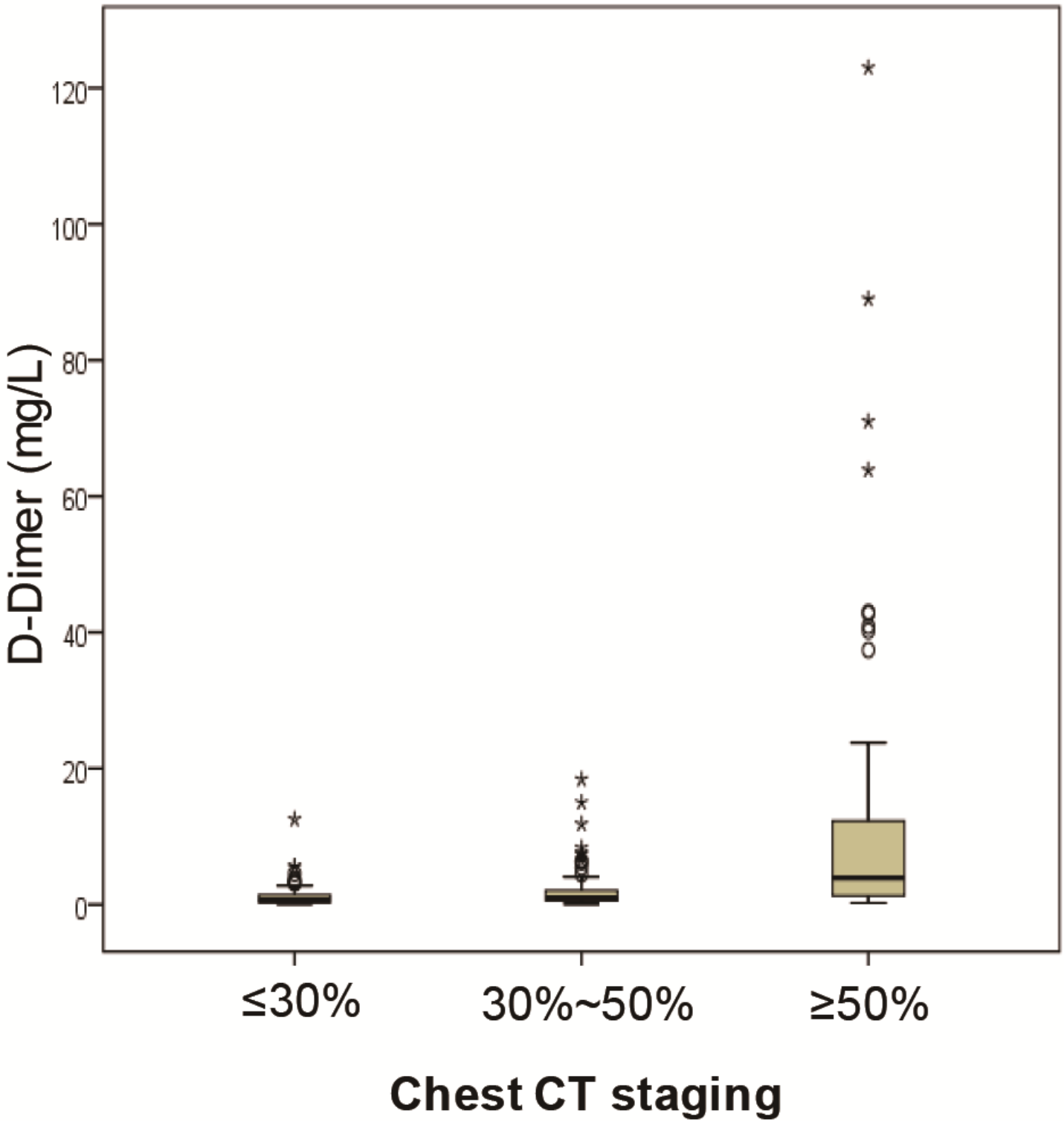

Figure 2

Correlations of D-dimer levels with chest CT staging according to area of affected lungs.

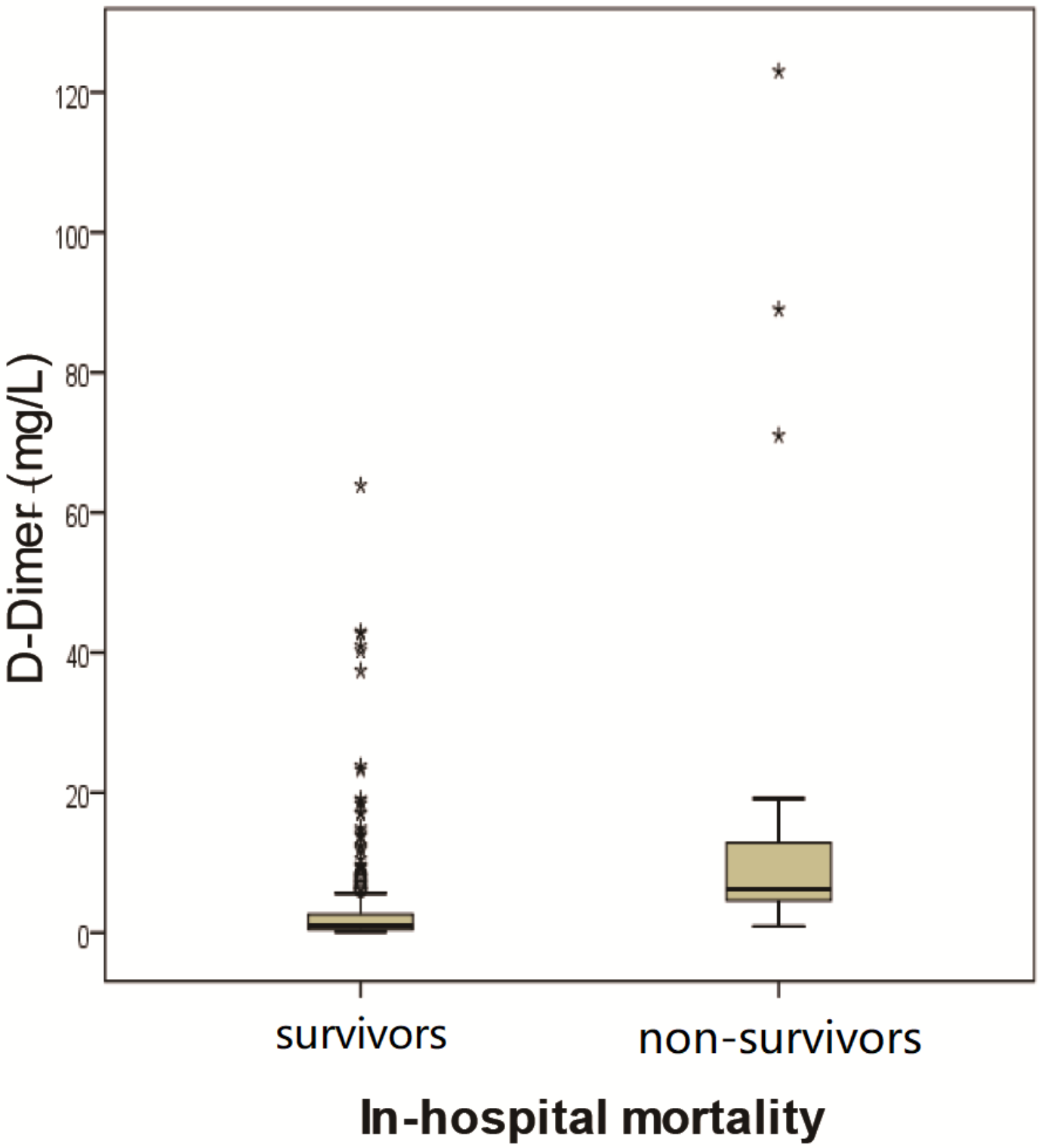

Figure 3

Correlations of D-dimer levels with in-hospital mortality.

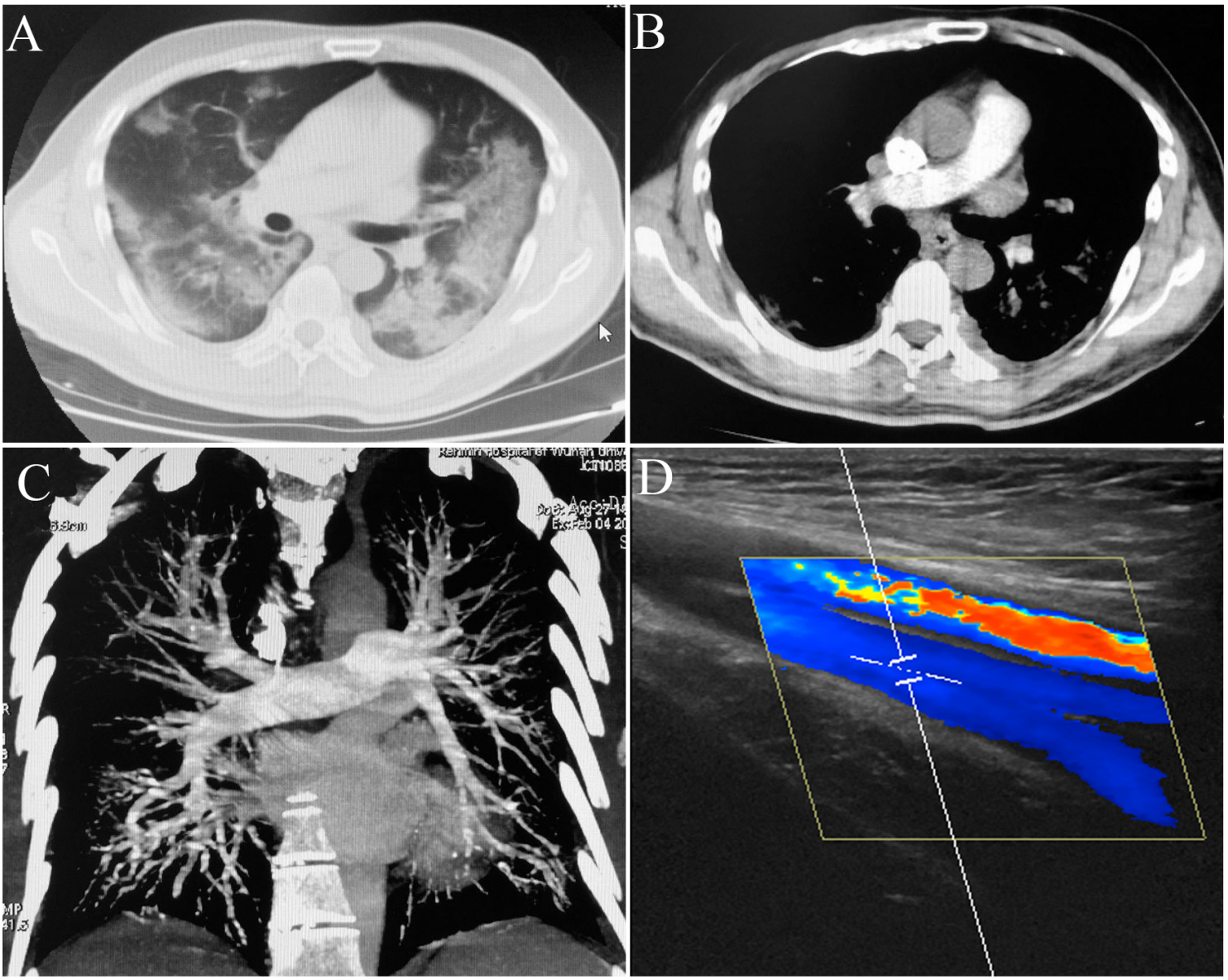

Figure 4

A 59-year-old male diagnosed with COVID-19 who presented with fever, coughing, and hemoptysis. Chest CT upon admission showing ground glass opacities and patchy consolidation (A). He had an elevated D-dimer level of 9.43mg/L. Well's score, Geneva score, and CURB65 score were 7, 7, and 2 respectively. Well's score suggested high probability of pulmonary embolism. CT pulmonary angiography (B, C) and Doppler ultrasonography (D) were then carried out and ruled out pulmonary embolism and deep vein thrombosis in the lower extremities.

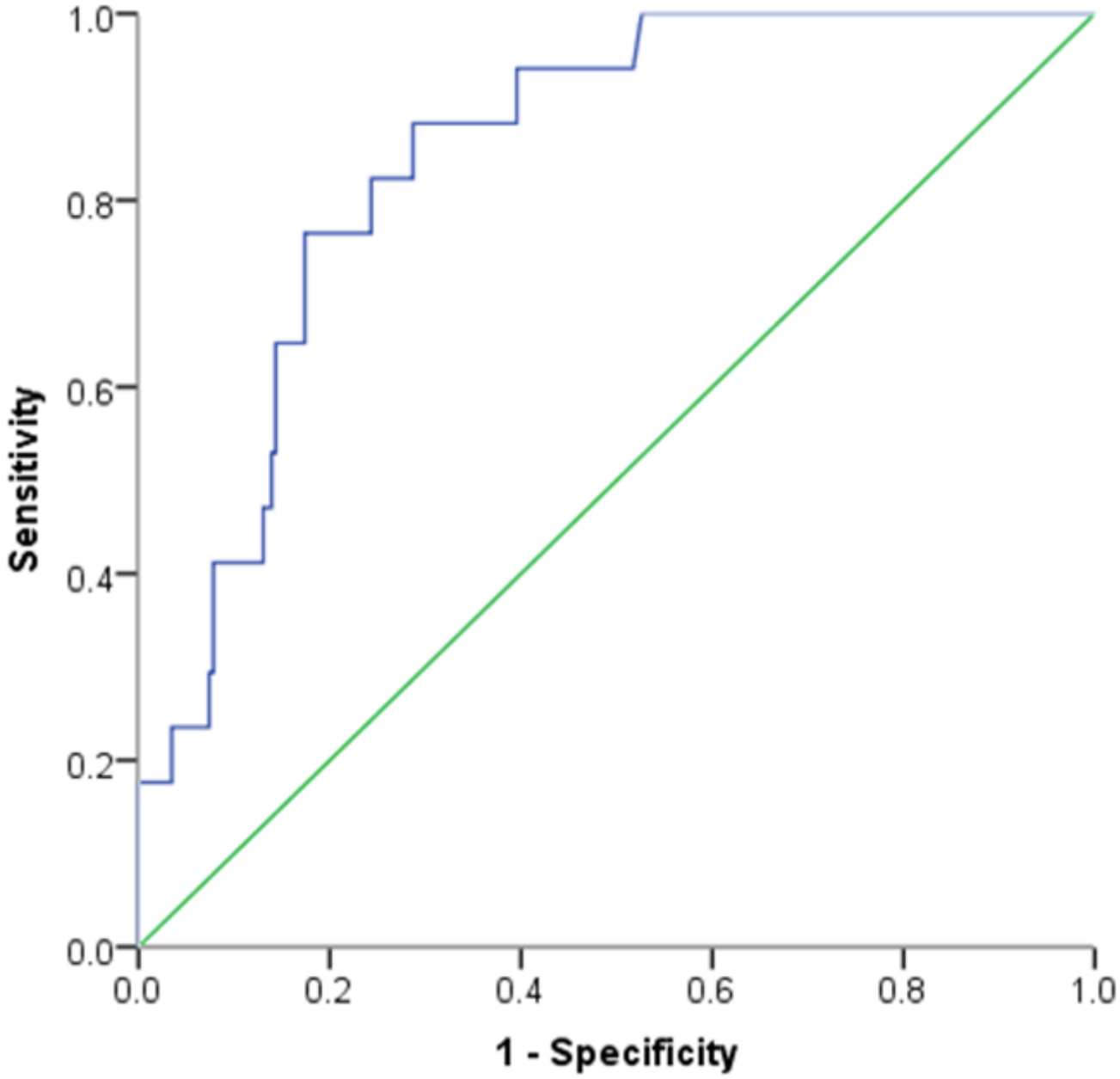

Figure 5

Receiver operating characteristics curve for D-dimer as parameter for predicting in-hospital mortality in COVID-19 patients.

Supplementary Files

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- Supplement20200402.docx