Association between D-dimer level and chest CT severity score in patients with SARS-COV-2 pneumonia

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Research Article

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Abstract

The elevated level of D-dimer and its relationship with poor outcomes in COVID-19 pneumonia patients have been demonstrated. In addition to a hypercoagulable state, D-dimer is also a biomarker of inflammation. We investigated the relationship between D-dimer level and chest computed tomography (CT) severity score, which could reflect the severity of inflammation in COVID-19 pneumonia patients. We retrospectively enrolled 86 consecutive COVID-19 pneumonia patients. CT severity scores were computed to quantify the overall lung involvement. The D-dimer level among CT score tertiles and the association of the D-dimer level with CT score were analyzed. Our results showed that the median D-dimer level was 0.70 mg/L (IQR: 0.35-1.76). 49 patients (57.0%) had D-dimer level above the normal range (≤ 0.55mg/L). The D-dimer levels were significantly different across CT score tertiles (0.37 mg/l [IQR, 0.31-0.87], 0.66 mg/l [IQR, 0.39-1.43], 1.83 mg/l [IQR, 0.85-4.41], P<0.001). The natural logarithm of the D-dimer level was significantly associated with the CT score (r_s =0.586, P <0.001). In conclusion, the D-dimer level may predict the severity of inflammation of COVID-19 pneumonia prior to coagulopathy/thrombosis. This could be an additional explanation for the mechanism of elevated D-dimer level predicting higher mortality.

Introduction

Since the outbreak of coronavirus disease 2019 (COVID-19) worldwide, studies from different countries have consistently found elevated levels of D-dimer in patients with SARS-COV-2 pneumonia[1,2]. Furthermore, several studies also demonstrated that a higher level of D-dimer was associated with in-hospital mortality[3,4]. The most suggested mechanism was that the hypercoagulable state, which could be reflected by an elevated D-dimer level, might lead to thrombotic events, resulting in poor outcomes. However, the coagulopathy was thought to result from local and systemic inflammation caused by the coronavirus. Also, D-dimer is known as a biomarker of inflammation[5]. Therefore, we proposed the hypothesis that the D-dimer level may predict the severity of inflammation rather than directly reflect the hypercoagulable state in patients with SARS-COV-2 pneumonia. Chest computed tomography (CT) involvement extent is the most visual parameter, which could reflect the severity of inflammation[6]. In this study, we investigated the relationship between D-dimer level and CT severity score in patients with SARS-COV-2 pneumonia.

Results

Comparison of clinical characteristics between patients with D-dimer ≤0.55mg/L and >0.55mg/L

Of the 98 patients confirmed SARS-COV-2 pneumonia, 86 (87.8%) patients was finally included in this study. Their median age was 61 years (IQR: 47-69), and 50 (58.1%) of them were female. The median D-dimer level was 0.70 mg/L (IQR: 0.35-1.76). 49 patients (57.0%) had D-dimer level above the normal range (≤ 0.55mg/L). Patients with elevated D-dimer level had older age (67 yrs [IQR: 60.0-73.0] vs 49 yrs [IQR: 40.0-61.5]; P< 0.001), higher level of C-reactive protein (35.8 mg/L [IQR: 5.0-95.6] vs 5.0 mg/L [IQR: 5.0-28.0]; P=0.005) and NT-proBNP (160.7 pg/ml [IQR: 82.5-375.0] vs 28.5 pg/ml [IQR: 14.4-90.8]; P <0.001). (Table 1)

Comparison of radiographic findings between patients with D-dimer ≤0.55mg/L and >0.55mg/L

A total of 76 patients had a high-resolution chest CT scan during the study period. The median CT score was 8.0 (IQR 6.0-13.0). Patients with elevated D-dimer level had significantly higher CT score (10.0 [IQR 6.3-14.8] VS 6.0 [IQR, 4.0-9.8], P<0.001) and higher incidence of fibrosis on chest CT images (77.3% vs. 46.9%, P=0.006) than patients with normal D-dimer level (Table 2). The D-dimer levels were significantly different across CT score tertiles (0.37 mg/l [IQR, 0.31-0.87], 0.66 mg/l [IQR, 0.39-1.43], 1.83 mg/l [IQR, 0.85-4.41], for tertile 1 to 3, respectively; P<0.001) (Figure l, A). The natural logarithm of the D-dimer level was significantly associated with the CT score (r_S =0.586, P <0.001) (Figure l, B).

Comparison of clinical events between patients with D-dimer ≤0.55mg/L and >0.55mg/L

Patients with elevated D-dimer levels had a higher rate of mechanical ventilation (12.2% vs. 0.0%, P=0.035) than the ones with D-dimer level below 0.55mg/L. Four patients had pulmonary thromboembolism (PTE) in this study, whose D-dimer levels were all above 0.55 mg/L (Table 3). There was one patient died during the study period who had segmental PTE.

Discussion

In our study, the median D-dimer level of total patients was 0.7 mg/L. This is close to the level previously reported by Zhou et al. (0.8 mg/L)[2] in Wuhan but lower than the one by Cummings et al. in New York (1.6 ug/ml)[4], whose study population were all critical cases. There were 58% of patients in our study had elevated D-dimer levels. Their chest CT severity scores were higher than those with normal range D-dimer level, and more patients had lung fibrosis (77.3%). Furthermore, we also found that the D-dimer level was well correlated with the chest CT score. Since a recent study has proved the chest CT score could be an imaging tool for assessing the severity of SARS-COV-2 pneumonia[7,8], our findings would lead us to conclude that D-dimer level could be a biomarker for severe SARS-COV-2 pneumonia by paralleling with the inflammation involvement extent in lungs which was reflected by chest CT score. The more frequent presence of lung fibrosis in these patients was also evidence of more extensive and severe inflammation response and lung injury.

The relationship between D-dimer level and coagulopathy/thrombosis in COVID-19 patients has been widely confirmed. However, whether the time points of D-dimer elevation and coagulopathy/thrombosis present were consistent has not been fully addressed. Based on our findings in which the D-dimer level's time point was matched to the time of CT scan, we have reasons to speculate that the D-dimer level may predict the severity of inflammation prior to coagulopathy/thrombosis. Uncontrolled inflammation response itself could result in severe lung injury and sequentially aggravate coagulopathy/thrombosis and then lead to poor outcomes, even death. This could be an additional explanation for the mechanism of elevated D-dimer level predicting higher mortality. Further researches are needed to investigate the relationship between the dynamics of D-dimer level and severity of inflammation and coagulopathy.

Methods

For this retrospective, single-center study, we enrolled consecutive patients from February 9 to March 4, 2020, in a COVID-19 ward of Renmin Hospital of Wuhan University (East Branch) in Wuhan, which is a government-assigned center for COVID-19 treatment. The diagnosis was confirmed by microbiological and radiographic findings following the World Health Organization (WHO) interim guidance[9] and the Fifth Revised Trial Version of the Novel Coronavirus Pneumonia Diagnosis and Treatment Guidance in China[10]. The observed time of this study ended on April 7. Only the patients who had D-dimer results during the study period were included. The study was approved by the Clinical Rearech Ethics Committee of West China Hospital (2020-226), and the requirement for written informed consent was waived by the Ethics Committee.

Demographic data, vital signs, laboratory test reports on admission, and outcomes were obtained from the patients' electronic medical records and scrutinized by investigators. Attending physicians in respiratory medicine reviewed the first high-resolution chest CT images of the patients for analyzing the radiographic patterns such as ground-glass opacities (GGOs), consolidation, fibrosis, and pleural effusion, and for computing CT severity score to quantify overall lung involvement. Each lung was divided into three lung zones. Each lung zone (total of six lung zones) was assigned a score that was based on the following: score 0, 0% involvement; 1, 0–25%; 2, 25–50%; 3, 50-75%; and 4, >75%. Summation of scores provided overall lung involvement (maximal CT score for both lungs was 24). D-dimer levels at the time point most nearby the date of CT were obtained in patients with high-resolution chest CT.

Data were expressed as the median and interquartile range (IQR [25th to 75th percentiles]) for continuous variables due to the skewed distribution (tested by the Shapiro-Wilk normality test) and as count and percentage for categorical variables. T-test or Mann-Whitney U test was used to analyze the differences between the D-dimer $\leq$ 0.55mg/L and D-dimer > 0.55mg/L groups for continuous variables. $\chi 2$ test was used for categorical variables. The difference of D-dimer levels among CT score tertiles was tested using the Kruskal-Wallis test. Spearman's correlation coefficient was used to measure the association of the natural logarithm of the D-dimer level with CT score. All the statistical analyses were performed with the use of IBM SPSS Statistics software (version 26.0).

All the methods above were carried out in accordance with relevant guidelines and regulations.

Declarations

Author contributions

LW and YP contributed to the study design, data acquisition, data analysis, and interpretation; LW and LY contributed to the manuscript; LY contributed to data analysis and interpretation. LB and ZXH contributed to data acquisition. All authors have approved the version of the manuscript submitted.

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Conflict of Interest

We declare no conflicts of interest and financial disclosures associated with this manuscript.

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Tables

Table 1. Comparison of clinical characteristics between patients with D-dimer ≤0.55mg/L and >0.55mg/L

Characteristic	All patients (N=86)	D-dimer ≤0.55mg/L (N=37)	D-dimer >0.55mg/L (N=49)	*P* value
Age, yrs	61.0 (47.0-69.0)	49.0 (40.0-61.5)	67.0 (60.0-73.0)	< 0.001
Female, n (%)	50 (58.1)	20 (54.1)	30 (61.2)	0.505
Coexisting illnesses				
Hypertension, n (%)	18 (20.9)	3 (8.1)	15 (30.6)	0.011
Diabetes, n (%)	4 (4.7)	2 (5.4)	2 (4.1)	1.000
IHD, n (%)	1 (1.2)	0 (0.0)	1 (2.0)	1.000
COPD, n (%)	4 (4.7)	2 (5.4)	2 (4.1)	1.000
Cancer	3 (3.5)	1 (2.7)	2 (4.1)	1.000
Vital signs				
Temperature, °C	36.5 (36.4-36.7)	36.5 (36.3-36.7)	36.6 (36.4-36.7)	0.371
Respiratory rate, /min	20.0 (18.0-21.0)	20.0 (18.0-22.0)	20.0 (18.0-21.0)	0.661
Heart rates, beats/min	86.0 (78.0-97.0)	92.0 (78.0-99.5)	82.5 (76.5-93.8)	0.165
SBP, mmHg	128.0 (119.0-136.0)	122.0 (114.5-132.0)	130.0 (122.0-143.0)	0.011
DBP, mmHg	78.0 (73.0-83.5)	75.5 (71.5-80.0)	78.0 (75.0-89.0)	0.034
Laboratory findings				
White cell count, /mm^3	5300 (4095-6608)	5170 (3900-6050)	5660 (4225-7265)	0.090
Hemoglobin, g/L	124.0(113.8-136.3)	125.0(116.0-140.0)	120.0(107.5-131.5)	0.039
Hematocrit	0.36 (0.32-0.39)	0.37 (0.35-0.40)	0.35 (0.32-0.38)	0.006
Platelet count, /mm^3	234,000 (171,500-283,500)	231,000 (169,000-272,500)	241,000 (177,500-289,500)	0.547
D-dimer	0.70 (0.35-1.76)	0.32 (0.23-0.41)	1.55 (1.03-4.05)	< 0.001
CD4+ cell	453 (262-588)	462 (350-625)	432 (226-578)	0.298
CD8+ cell	244 (151-385)	306 (184-497)	213 (114-339)	0.011
Creatinine, μmol/L	59.5 (47.8-71.0)	61.0 (48.0-72.0)	58.0 (47.0-70.0)	0.814
ALT, U/L	22.0 (15.0-38.3)	27.0 (14.0-40.5)	20.0 (15.0-29.5)	0.445
AST, U/L	24.0 (18.0-34.5)	24.0 (17.5-31.5)	24.0 (18.0-37.5)	0.831
Albumin, g/L	37.7 (34.6-41.0)	39.7 (37.5-42.7)	36.2 (32.3-39.5)	< 0.001
Sodium, mmol/L	142 (138-145)	142 (140-145)	142 (137-146)	-
Procalcitonin, ng/mL	0.04 (0.03-0.07)	0.04 (0.03-0.06)	0.04 (0.03-0.09)	0.368
CRP, mg/L	11.5 (5.0-48.9)	5.0 (5.0-28.0)	35.8 (5.0-95.6)	0.005
CK-MB, U/L	1.0 (0.6-1.5)	0.9 (0.6-1.2)	1.1 (0.8-1.8)	0.006
hs-cTnI > 99^{th} percentile URL	8 (9.4)	2 (5.6)	6 (12.2)	0.504
NT-proBNP, pg/ml	88.0 (30.4-257.7)	28.5(14.4-90.8)	160.7 (82.5-375.0)	< 0.001
NT-proBNP >300 pg/ml	20 (23.3)	3 (8.1)	17 (34.7)	0.004
Oxygenation index	365.1(272.3-476.8)	447.6(300.0-478.8)	341(248.5-428.6)	0.285
Oxygenation index <300	16 (32.0)	4(26.7)	12(34.3)	0.597

CT score	8.0(6.0-13.0)	6.0 (4.0-9.8)	10.0 (6.3-14.8)	< 0.001

Data are expressed as median (interquartile range) or counts and percentages, as appropriate.

Abbreviation: IHD, Ischemic heart disease; COPD, Chronic obstructive pulmonary disease; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CRP, C-reactive protein; CK-MB, Creative kinase MB; hs-cTnI, high-sensitivity cardiac troponin I; URL, upper reference limit; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CT, computed tomography.

The composite endpoint was the composite of mechanical ventilation requirement, ECMO requirement, or all-cause death.

Table 2. Comparison of radiographic findings between patients with D-dimer ≤0.55mg/L and >0.55mg/L

Radiographic finding	All	D-dimer ≤0.55mg/L	D-dimer >0.55mg/L	*P* value
	(n=76)	(n=32)	(n=44)	
CT score	8.0(6.0-13.0)	6.0 (4.0-9.8)	10.0 (6.3-14.8)	< 0.001
More than two lobes involvement	75 (98.7)	31 (96.9)	44 (100.0)	0.421
Pleural effusion	2 (2.6)	0 (0.0)	2 (4.5)	0.506
Ground-glass opacity	75 (98.7)	31 (96.9)	44 (100.0)	0.421
Consolidation	56 (73.7)	25 (78.1)	31 (70.5)	0.453
Fibrosis	49 (64.5)	15 (46.9)	34 (77.3)	0.006

Data are expressed as counts and percentages. The Pearson Chi-Square or Fisher's Exact Test was used to test the difference between D-dimer groups, as appropriate.

Table 3. Comparison of clinical events between patients with D-dimer ≤0.55mg/L and >0.55mg/L

Clinical events	All	D-dimer ≤0.55mg/L	D-dimer >0.55mg/L	*P* value
	(n=86)	(n=37)	(n=49)	
Thrombotic events	4 (4.7)	0 (0.0)	4 (8.2)	0.131
Mechanical ventilation requirement	6 (7.0)	0 (0.0)	6 (12.2)	0.035
ECMO requirement	2 (2.3)	0 (0.0)	2 (4.1)	0.504
All-cause Death	1 (1.2)	0 (0.0)	1 (2.0)	1.000
Composite endpoint	6 (7.0)	0 (0.0)	6 (12.2)	0.035

Data are expressed as counts and percentages. The Pearson Chi-Square or Fisher's Exact Test was used to test the difference between D-dimer groups, as appropriate.

Abbreviation: ECMO, extracorporeal membrane oxygenation; The composite endpoint was the composite of mechanical ventilation requirement, ECMO requirement, or all-cause death.

Figures

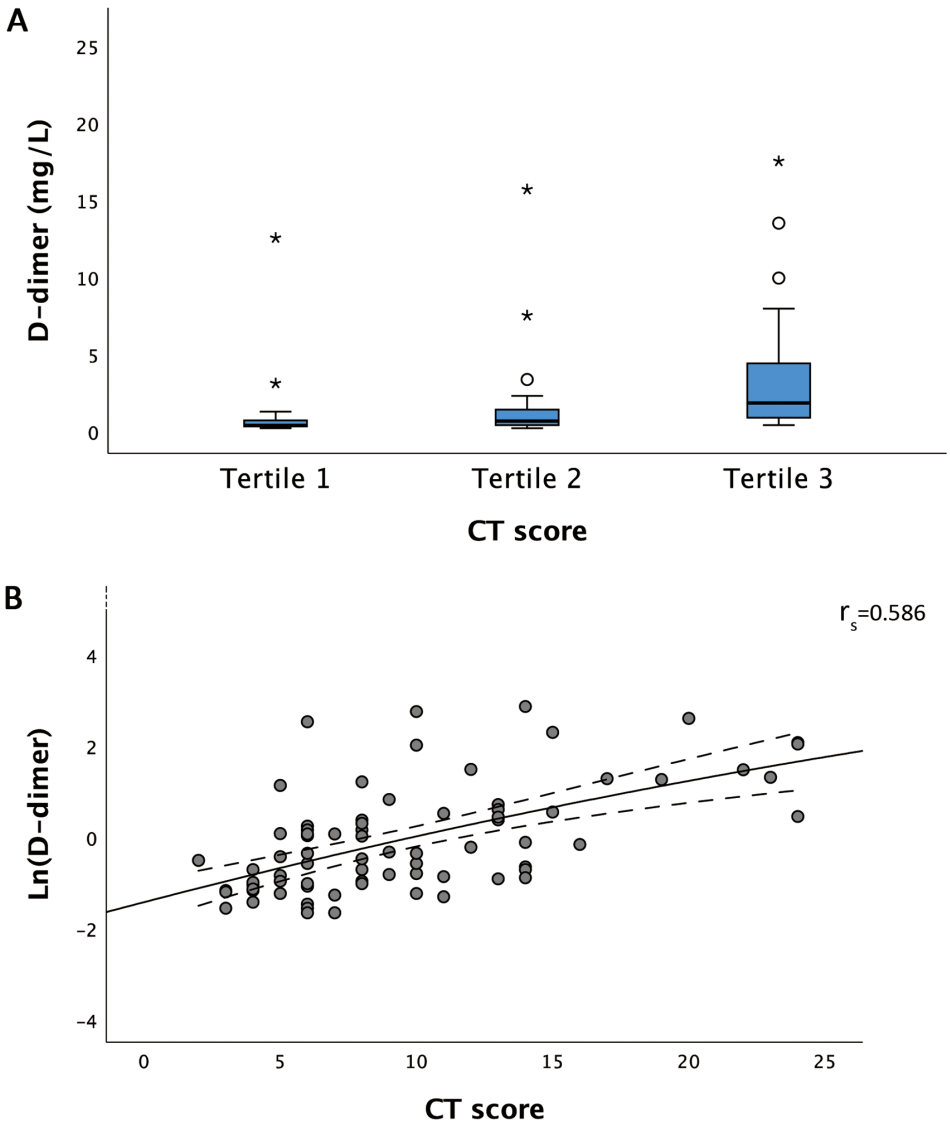

Figure 1

Panel A, The boxplot showing a significant difference in D-dimer levels across CT score tertiles (P<0.001). Panel B, The scatterplot was showing that the natural logarithm of the D-dimer level was significantly associated with CT score (rs =0.586, P<0.001).