

Elevated D-dimer and Adverse In-hospital Outcomes in COVID-19 Patients and Synergism with Hyperglycemia

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Aim: One of the most common laboratory findings in COVID-19 patients has been observed to be hypercoagulability with elevated D-dimer levels. An activation of thrombosis may be generated by hyperglycemia. We aimed to explore the association between D-dimer and in-hospital outcomes, and evaluate the synergistic effect between elevated D-dimer and hyperglycemia on COVID-19 prognosis.

Methods: A retrospective cohort study was undertaken with 2467 COVID-19 inpatients. D-dimer and fasting blood glucose (FBG) on admission and adverse in-hospital outcomes (events of death and aggravated severity) were collected. Cox proportional risk model was performed to assess the association of D-dimer and adverse in-hospital outcomes, and the combined effects of D-dimer and FBG.

Results: Among these COVID-19 patients, 1100 (44.6%) patients had high D-dimer (≥ 0.50 mg/L). Patients with high D-dimer were older, with higher FBG (≥ 7.00 mmol/L), and had significantly higher adjusted risk of adverse in-hospital outcomes when comparing with those who with D-dimer < 0.50 mg/L (hazard ratio, 2.73; 95% confidence interval, 1.46–5.11). Moreover, patients with high FBG and D-dimer levels had an increasing risk (hazard ratio, 5.72; 95% confidence interval: 2.65–12.34) than those with normal FBG and D-dimer.

Conclusion: Risk of adverse in-hospital outcomes is higher among patients with high D-dimer levels. Additionally, this study found for the first time that elevated D-dimer and hyperglycemia had a synergistic effect on COVID-19 prognosis, and this risk was independent of diabetes history.

Keywords: D-dimer, hyperglycemia, in-hospital outcomes, COVID-19, cohort study

Introduction

Coronavirus disease 2019 (COVID-19) is a global pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that has resulted in the loss of over 5.00 million people so far.¹ Despite the fact that the vaccine has been developed, the accompanying mutation of the virus brings new uncertainties and challenges to the prevention and treatment of the disease. Therefore, there is an urgent need to identify reliable biomarkers for early diagnosis, effective treatment and judgment in the prognosis of COVID-19.

Recent research suggests that thrombosis impacts the prognosis of people with COVID-19² and that D-dimer, a widely recognized biomarker for thromboembolism and a prognostic marker for critical patients, should be regarded seriously.³ Additionally, many COVID-19 patients have been shown to have significantly higher D-dimers, which have been linked to increased mortality in these patients.⁴⁻⁸ However, not all COVID-19 clinical studies have consistently found elevated D-dimer levels.⁹ Furthermore, existing research suggests that hyperglycemia may cause thrombus activation through different pathways.^{10,11} Considering the close relationship between D-dimer and hyperglycemia, whether there exists a synergistic association of elevated D-dimer and blood glucose levels with COVID-19 prognosis needs further elucidation. Therefore, we aimed to investigate the association between admission D-dimer levels and adverse in-hospital outcomes among a large cohort of patients hospitalized with COVID-19, and further evaluate the combined effects of D-dimer and fasting blood glucose (FBG) levels.

Methods

Study Design and Participants

We performed this prospective cohort study from February 4 to April 14, 2020, in one hospital of Wu Han, including all of the COVID-19 inpatients. Patients were diagnosed with COVID-19 based on typical clinical symptoms and chest CT findings and/or positive results of COVID-19 RNA and/or gene. Initially, 3059 patients with COVID-19 infection were enrolled in this study, but 12 patients were not treated in this hospital for other complications. After excluding participants who had incomplete D-dimer data ($n = 537$), incomplete FBG data ($n = 39$), D-dimer outlier ($n=1$) and under the age of 18 ($n=3$), 2467 participants were eligible for the current study (Figure 1). The study protocol was approved by the Institution Ethics Committee of PLA general hospital, which was conducted in conformity with the Declaration of Helsinki. This study was retrospective research, which just collected previous data from the hospital system, and the study did not include any personal information or privacy. For these reasons, the requirement for informed consent from the patients was waived. Data were used anonymously, with strict respect for the confidentiality of the patients included.

Data Collection

All records of admission, diagnosis and treatment process and discharge were extracted from electronic medical records using a standardized data collection form. And the related data we collected included demographic information, medical history, computed tomography (CT) description, symptoms and laboratory examination. The extracted contents were conducted by trained engineers who used Python and randomly selected 5% to double check by trained physicians to ensure accuracy.

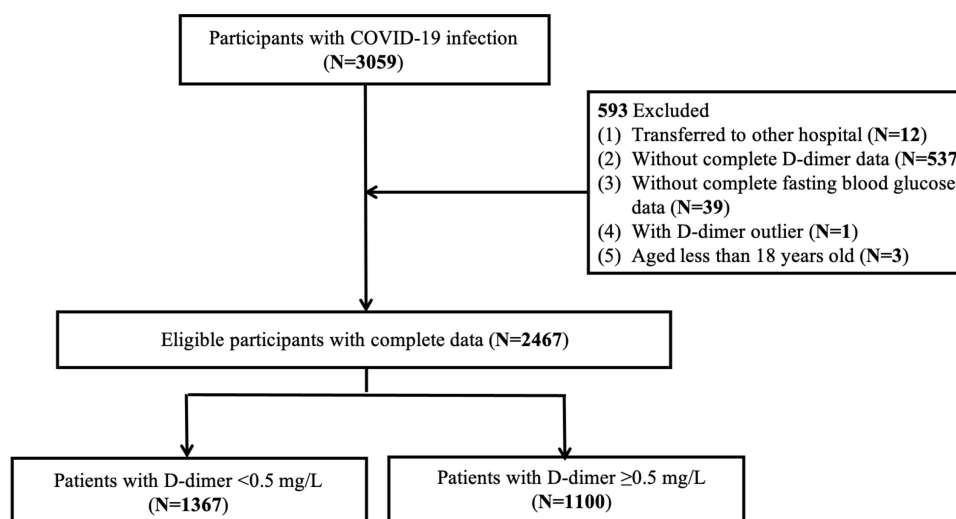


Figure 1 Flowchart for selection of the study patients.

Definition of D-dimer and Fasting Blood Glucose Grouping

In total, 2469 patients had laboratory examinations within 24 hours of admission and were categorized into either the normal (<0.50 mg/L) or the high (≥ 0.50 mg/L) D-dimer group according to the laboratory reference. D-dimer was determined on CS5100 automatic coagulation analyzer (Sysmex, Kobe, Japan) by using a latex-enhanced photometric immunoassay (Siemens, Marburg, Germany).¹² And to specifically assess the combined effects of FBG and D-dimer on adverse in-hospital outcomes, we also divided the patients into two groups with a cut point of 7.00 mmol/L. FBG test was conducted by a laboratory plasma measurement.

Definition of Adverse In-hospital Outcomes

The main endpoint was the composite outcome of death and aggravated severity during hospitalization. The severity of COVID-19 and treatment for all patients were determined using the Chinese National Health Committee's COVID-19 diagnosis and treatment guidelines (5th–7th edition).⁵ When patients met one of the following criteria, they were diagnosed with severe COVID-19: (1) respiratory failure needing mechanical ventilation; (2) shock; (3) other organ failure that requires monitoring and treatment in an intensive care unit (ICU). Criteria COVID-19 was diagnosed when the patients met one of the following criteria: (1) respiratory distress (≥ 30 beats per min); (2) finger oxygen saturation $\leq 93\%$ at rest; (3) ratio of arterial partial pressure of oxygen (PaO₂) to oxygen concentration (FiO₂) ≤ 300 mmHg; (4) more than 50% progression of the lesion in pulmonary imaging over 24–48h. Moderate or mild patients were diagnosed with COVID-19 who lacked severe or critical features. The final diagnosis was made by doctors during patients' hospitalization and was recorded in both inpatient medical records and the database of this program.

Definition of Other Variables

Diabetes, hypertension, chronic bronchitis or chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD) and cerebrovascular disease were defined based on the patient's self-reported medical history, medication taken, or the doctor's diagnosis of discharge determined in accordance with relevant guidelines. History of respiratory disease was defined as patients who had chronic bronchitis or COPD. History of cardiovascular and cerebrovascular disease was defined as CHD or cerebrovascular disease.

Statistical Analysis

Continuous variables, expressed as mean \pm standard deviation (SD) or as median with interquartile range (IQR) if not normally distributed, were compared using the unpaired Student *t*-test, Mann–Whitney *U*-test, or One-way analysis of variance, as appropriate. Categorical variables were expressed as count (percent) and tested by Chi-Square test. The univariate and multivariable Cox proportional risk model was used to calculate the hazard ratio (HR) of D-dimer levels for follow-up adverse in-hospital outcomes with COVID-19. In multivariable analyses, age, gender, disease of admission, history of hypertension, diabetes, respiratory and cardiovascular and cerebrovascular disease, white blood cell, hemoglobin, high-sensitivity C-reactive protein (hs-CRP), creatinine, albumin and aspartate aminotransferase (AST) were adjusted. Considering that FBG was an important influence on D-dimer levels and adverse in-hospital outcomes, we also generated 2 \times 2 combinations between D-dimer and FBG levels to assess if there exists a synergistic effect between D-dimer and FBG levels that increases the risk of adverse in-hospital outcomes. Predefined subgroups stratified by age (65 years as the cutoff to define the elderly and the non-elderly group) and diabetes were conducted. Statistical analyses were performed using SPSS Statistics version 24.0 (IBM Corporation, Armonk, NY, United States) and Stata 14.0 (Stata, College Station, TX, USA). Two-tailed *p* values of less than 0.05 were considered statistically significant.

Results

Demographic, Symptomatic and Clinical Laboratory Characteristics of Inpatients

A total of 2467 inpatients with COVID-19 were included in our analysis, with 51.4% (1269) males and average aged 59.0 \pm 14.4 years. D-dimer had a skewed distribution with median (interquartile range) values of 0.43 mg/L (0.21–0.91 mg/L). Among all inpatients, a total of 1100 (44.6%) had high D-dimer levels (≥ 0.50 mg/L) (Table 1).

Table 1 General Characteristics of Patients with COVID-19

	Total (N=2467)	D-dimer <0.50 mg/L (N=1367)	D-dimer ≥0.50 mg/L (N=1100)	P value
Age (years), mean±SD	59.0±14.4	53.8±13.5	65.5±12.8	<0.001
Male, n (%)	1269(51.4)	705(51.6)	564(51.3)	0.903
BMI (kg/m ²), mean±SD	24.2±3.6	24.3±3.6	24.1±3.8	0.380
Hospitalization days, median (IQR)	13(8–20)	12(7–17)	16(10–23)	<0.001
Disease type of admission, n(%)				<0.001
Mild–moderate	1760(71.3)	1114(81.5)	646(58.7)	
Severe	673(27.3)	252(18.4)	421(38.3)	
Critical	34(1.4)	1 (0.1)	33(3.0)	
Signs and Symptoms				
DBP (mmHg), mean±SD	81±11	82±11	80±11	<0.001
SBP (mmHg), mean±SD	130±16	130±16	130±16	0.403
Fever, n(%)	2082(84.4)	1132(82.8)	950(86.4)	0.016
Dry cough, n(%)	1272(51.6)	681(49.8)	591(53.7)	0.057
Dyspnea, n(%)	350(14.2)	129(9.4)	221(20.1)	<0.001
Muscle ache, n(%)	525(21.3)	259(18.9)	266(24.2)	0.002
CT description				
Ground-glass opacity, n(%)	1506(61.0)	827(60.5)	679(61.7)	0.561
Patch shadow, n(%)	1658(67.2)	892(65.3)	766(69.6)	0.022
Comorbidities				
Diabetes, n(%)	449(18.2)	217(15.9)	232(21.1)	0.001
Hypertension, n(%)	892(36.2)	407(29.8)	485(44.1)	<0.001
History of respiratory disease, n(%)	116(4.7)	31(2.3)	85(7.7)	<0.001
History of cardiovascular and cerebrovascular disease, n(%)	378(15.3)	133(9.7)	245(22.3)	<0.001
Blood routine				
Hemoglobin (g/L), mean±SD	123.80±17.79	128.76±15.43	117.63±18.59	<0.001
White blood cell count (×10 ⁹ /L), median (IQR)	5.70(4.70–7.10)	5.60(4.70–6.80)	6.00(4.80–7.50)	<0.001
Lymphocyte percentage (%), median (IQR)	26.70(19.70–32.90)	29.20(23.70–34.45)	22.40(14.60–29.60)	<0.001
Neutrophil percentage (%), mean±SD	63.38±11.57	60.15±9.35	67.39±12.76	<0.001
Platelet count (×10 ⁹ /L), median (IQR)	222.00(179.00–273.00)	219.00(182.00–266.00)	227.00(176.00–286.00)	0.162
Biochemical detection				
hs-CRP (mg/L), median(IQR)	2.25(0.81–8.87)	1.27(0.55–3.15)	5.93(1.76–10.00)	<0.001
BUN (mmol/L), median(IQR)	4.42(3.62–5.53)	4.22(3.53–5.10)	4.78(3.80–6.13)	<0.001
Uric acid (mmol/L), median(IQR)	278.00(223.00–340.00)	288.00(237.00–350.00)	262.00(202.00–328.00)	<0.001
Creatinine (mmol/L), median(IQR)	64.50(55.20–76.10)	64.00(54.80–74.90)	65.30(55.80–78.18)	0.014
Albumin (g/L), mean±SD	37.37±4.51	39.22±3.58	35.08±4.48	<0.001
ALT (IU/L), median(IQR)	22.70(14.60–37.40)	22.70(14.70–37.70)	22.65(14.50–37.20)	0.779
AST (IU/L), median(IQR)	19.60(15.60–26.70)	18.50(15.20–25.10)	20.75(16.10–30.45)	<0.001
LDH (IU/L), median(IQR)	179.10(152.00–217.30)	164.80(144.20–190.20)	203.20(172.63–262.95)	<0.001
TBIL (IU/L), median(IQR)	9.60(7.40–12.40)	9.50(7.50–12.20)	9.65(7.20–12.80)	0.451
DBIL (IU/L), median(IQR)	3.40(2.50–4.50)	3.20(2.50–4.10)	3.60(2.60–5.00)	0.001
Fibrinogen (g/L), median(IQR)	2.97(2.62–3.39)	2.85(2.55–3.14)	3.21(2.80–3.68)	<0.001
FBG (mmol/L), median(IQR)	4.92(4.49–5.74)	4.76(4.40–5.36)	5.19(4.61–6.29)	<0.001

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, urea nitrogen; DBIL, direct bilirubin; DBP, diastolic blood pressure; FBG, fasting blood glucose; hs-CRP, high-sensitivity C-reactive protein; LDH, lactate dehydrogenase; SBP, systolic blood pressure; TBIL, total bilirubin.

Patients with high D-dimer levels were older, with a high proportion of signs and symptoms such as fever, dyspnea, muscle ache and CT description with ground-glass opacity, and had a higher frequency of previous diseases. Of these inpatients with high D-dimer levels, 21.1% and 44.1% had previously diagnosed diabetes and hypertension, respectively, higher than that of patients with normal D-dimer. In addition, patients with high D-dimer levels had a higher proportion

of history of respiratory ($P<0.001$), cardiovascular and cerebrovascular disease ($P<0.001$). Most of the laboratory characteristics in the two D-dimer groups revealed significant differences in addition to platelet count, alanine aminotransferase and total bilirubin (Table 1). Levels of white blood cell count, hs-CRP, urea nitrogen, creatinine, AST, lactate dehydrogenase, direct bilirubin and FBG were significantly higher, whereas hemoglobin and albumin were lower in subjects with high D-dimer levels ($P<0.05$). Additionally, the high D-dimer group was characterized by high fibrinogen levels, which reflected the hypercoagulable state ($P<0.05$).

Prevalence of High D-dimer Level in Patients with COVID-19

The prevalence of high D-dimer levels increased significantly with age in total patients and each sex subgroup ($P<0.001$). Moreover, patients with higher FBG (≥ 7.00 mmol/L) had a higher prevalence of high D-dimer levels than those with normal FBG (<7.00 mmol/L) (42.3% versus 58.3%, $P<0.001$). Similar distributions were found in males and females (Table 2).

Association Between D-dimer Levels, FBG Levels and the Adverse In-hospital Outcomes

A total of 118 (4.4%) inpatients developed adverse outcomes during their hospital stay. And the rates of adverse outcomes were much higher in patients with higher D-dimer levels (Table 3). Multivariate Cox proportional risk model revealed that the risk of adverse in-hospital outcomes increased by 8% (HR 1.08, 95% CI 1.04–1.13) with the increment of 1 mg/L of D-dimer. Then, we compared the in-hospital outcomes between patients with high D-dimer levels (≥ 0.50 mg/L) and normal D-dimer levels. The results showed that D-dimer ≥ 0.50 mg/L was significantly associated with an increased risk of adverse in-hospital outcomes (HR 2.73, 95% CI 1.46–5.11). In addition, when D-dimer was considered as a quartile variable, the risk of adverse in-hospital outcomes was an upward trend with the increase of the quartile of D-dimer ($P_{\text{trend}}<0.001$) (Table 3).

Supplement Table 1 depicts the relationship between FBG level and the risk of adverse in-hospital outcomes. As a continuous variable, every unit increase of FBG was associated with a 1.10-fold higher risk of adverse in-hospital outcomes (95% CI 1.04–1.17). Consistently, when patients were divided into two groups based on the guideline, FBG ≥ 7.00 mmol/L was associated with an increased HR (2.29, 95% CI 1.45–3.63) for adverse in-hospital outcomes compared with FBG <7.00 mmol/L.

And an apparent association was also found in elderly patients with high D-dimer (≥ 0.50 mg/L) and high FBG (≥ 7.00 mmol/L) for adverse outcomes, the adjusted HR was 3.89 (95% CI 1.15–13.14) and 2.54 (95% CI 1.44–4.47), respectively. However, no significance was observed in the non-elderly after full adjustments (Supplement Table 2).

Synergic Effect of Elevated D-dimer and FBG on Adverse In-hospital Outcomes

Combined group analyses showed that high level of FBG and D-dimer had a synergic effect on the adverse in-hospital outcomes, with an increasing risk of adverse in-hospital outcomes (HR 5.72; 95% CI 2.65–12.34) than those with normal levels of FBG and D-dimer. Patients with D-dimer ≥ 0.50 mg/L and FBG ≥ 7.00 mmol/L were also significantly associated

Table 2 Prevalence of High D-Dimer Level in Patients with Different Ages and Fasting Blood Glucose

	D-dimer ≥ 0.50 mg/L			P value
	All Inpatients (n=1100)	Male (n=564)	Female (n=536)	
Age (years)				<0.001
<45	74(17.9%)	45(18.2%)	29(17.4%)	
45–64	400(36.2%)	195(36.9%)	205(35.7%)	
65–74	372(56.9%)	194(57.4%)	178(56.3%)	
≥ 75	254(86.1%)	130(83.9%)	124(88.6%)	
Fasting blood glucose (mmol/L)				<0.001
<7.00	892(42.3%)	459(42.3%)	433(42.2%)	
≥ 7.00	208(58.3%)	105(57.1%)	103(59.5%)	

Table 3 HRs and 95% CI of Risks of Adverse In-Hospital Outcomes Associated with D-Dimer Levels

Valid	Rate of Adverse In-Hospital Outcomes	HR (95% CI)			
		Model 1	Model 2	Model 3	Model 4
Continuous Variable					
D-dimer level	118(4.8%)	1.12(1.09–1.16)	1.11(1.07–1.15)	1.11(1.11–1.14)	1.08 (1.04–1.13)
Categorical variable					
Binary variable					
Normal level (<0.50mg/L)	14(1.0%)	1	1	1	1
High level (≥0.50mg/L)	104(9.4%)	4.91(2.79–8.65)	3.89 (2.16–7.01)	3.83 (2.12–6.92)	2.73 (1.46–5.11)
Quartile variable					
Q1 (<0.21mg/L)	3(0.5%)	1	1	1	1
Q2 (0.21–0.42mg/L)	5(0.8%)	1.30(0.31–5.43)	1.16 (0.28–4.87)	1.16(0.28–4.86)	1.36(0.32–5.81)
Q3 (0.43–0.90mg/L)	31(5.0%)	5.37(1.63–17.63)	4.15(1.24–13.90)	4.26(1.27–14.31)	3.28 (0.95–11.36)
Q4 (≥0.91mg/L)	79(12.7%)	10.33 (3.23–33.01)	7.56(2.29–24.92)	7.48 (2.26–24.80)	5.63 (1.64–19.30)
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001

Notes: Model 1 no adjustment for any covariates. Model 2 adjusted for age, gender. Model 3 additionally adjusted for history of hypertension, diabetes, respiratory and cardiovascular and cerebrovascular disease on the basis of Model 2. Model 4 additionally adjusted for disease type of admission, white blood cell count, hemoglobin, hs-CRP, creatinine, albumin and AST on the basis of Model 3.

Abbreviations: AST, aspartate aminotransferase; CI, confidence interval; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein.

with a 2.30-fold higher risk of adverse in-hospital outcomes (95% CI 1.16–4.54); however, the HR was attenuated, relative to those with elevated D-dimer and FBG (Figure 2). Similar synergic effects were found in the non-elderly and elderly (Supplement Table 3). And the synergic effect of elevated D-dimer and FBG on adverse in-hospital outcomes

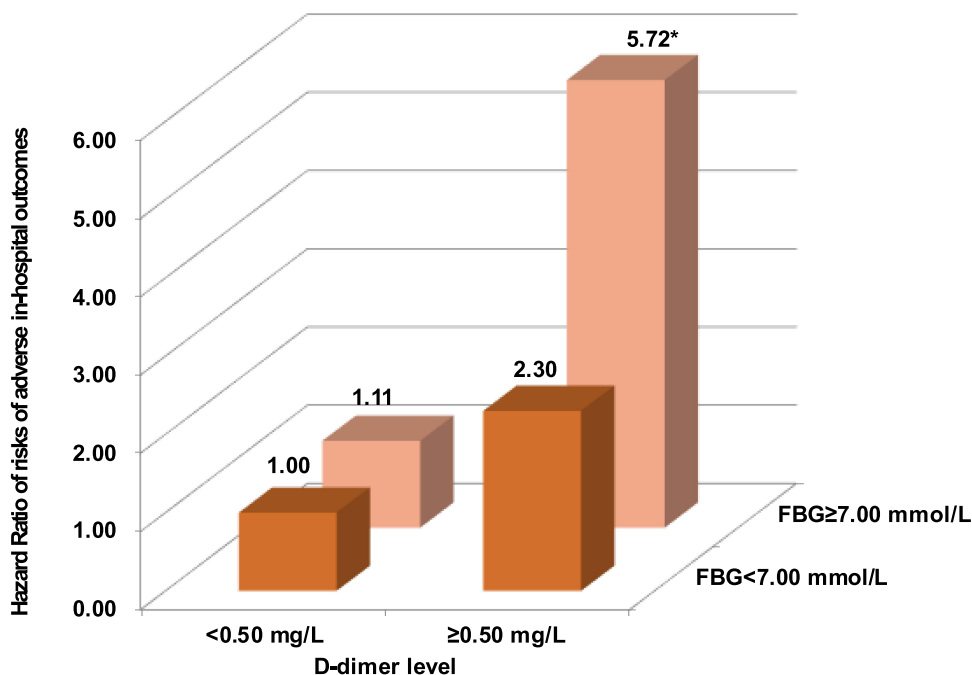


Figure 2 Cox regression analysis of combined subgroups of D-dimer and FBG levels on the risk of adverse in-hospital outcomes. All substantial models are additionally adjusted for age, gender, disease type of admission, history of hypertension, diabetes, respiratory and cardiovascular and cerebrovascular disease, white blood cell count, hemoglobin, hs-CRP, creatinine, albumin and AST. * $P < 0.05$. The subgroup with D-dimer <0.50 mg/L and FBG <7.00 mmol/L was defined as the reference group. There were 12(1.0%), 66(7.4%), 2(1.3%), and 38(18.3%) adverse in-hospital outcomes in the subgroup with D-dimer <0.50 mg/L and FBG <7.00 mmol/L, the subgroup with D-dimer ≥0.50 mg/L and FBG <7.00 mmol/L, the subgroup with D-dimer <0.50 mg/L and FBG ≥7.00 mmol/L and the subgroup with D-dimer ≥0.50 mg/L and FBG ≥7.00 mmol/L, respectively.

Abbreviations: AST, aspartate aminotransferase; FBG, fasting blood glucose; hs-CRP, high-sensitivity C-reactive protein.

were not substantially changed after excluding patients with diabetes, although some of the effects were borderline significant due to the smaller sample size ([Supplement Table 4](#)).

Discussion

In this retrospective cohort study based on 2467 Chinese COVID-19 patients, we found that D-dimer level at admission was a predictor of adverse in-hospital outcomes. COVID-19 patients with D-dimer ≥ 0.50 mg/L had a substantially high risk for adverse in-hospital outcomes compared with patients with D-dimer < 0.50 mg/L, especially in the elderly. Moreover, our study revealed for the first time that the synergic effect of elevated D-dimer and hyperglycemia could further increase the risk of adverse in-hospital outcomes, and this risk was independent of the history of diabetes.

Many previous studies, including meta-regression analysis, have found that D-dimer was associated with comorbidities, hospitalization, complications, and outcomes. Most of the conclusions tended to be consistent that patients with higher D-dimer levels were at high risk of COVID-19 adverse outcomes. A study of 343 COVID-19 inpatients from Wuhan Asia General Hospital reported that D-dimer on admission higher than $2.0 \mu\text{g/mL}$ was the independent predictor of in-hospital death (HR 51.5; 95% CI 12.9–206.7).⁴ However, this conclusion was drawn based on only 13 death events, difficult to guarantee the stability of the results. Another two studies also reported that high D-dimer levels predicted poor prognosis, whereas the chosen cutoffs of D-dimer of the two studies were different and it was unclear why these specific cutoffs were chosen.^{5,8} In addition, some studies found that the patients who were admitted to ICU or nonsurvivors had significantly higher D-dimer levels.^{6,13,14} However, the sample size may restrict the interpretation of these findings, although a recent meta-regression analysis revealed that the discharge rate was negatively related to D-dimer, demonstrating the capability of D-dimer to serve as a prognostic variate for outcomes.³ Our study extended previous findings with a larger sample size and got similar results, both for D-dimer as a continuous variable and as a categorical variable. Moreover, the cutoff of 0.50 mg/L we chose was based on the laboratory reference, which may be more instructive in the selection of treatment options.

Moreover, some studies showed COVID-19 was associated with an increased risk of arterial and venous thrombosis.^{14–17} And the fact that patients with COVID-19 typically have considerably increased D-dimer levels indicated a hypercoagulable state, which might be attributed to several reasons as follows. First, thrombosis with associated inflammation (thromboinflammation) occurs with virus infections, leading to the loss of the normal antithrombotic and anti-inflammatory functions of endothelial cells.¹⁸ Second, most patients with COVID-19 are characterized by dyspnea, especially in severe cases. And it has been previously reported that thrombosis increases under hypoxic conditions in animal models and human populations.¹⁹ Third, immobilization, mechanical ventilation and the use of central venous catheters during a patient's hospital stay could increase the probability of thrombosis.^{20,21} In addition, the stress of COVID-19 may increase the secretion of stress hyperglycemia, and further induce prothrombotic state associated with hyperglycemia.²²

Studies have shown that COVID-19 patients with diabetes were more likely to develop a hypercoagulable state, as evidenced by elevated D-dimer and fibrinogen, and the relationship was influenced by blood glucose control,^{23,24} which is possibly associated with an imbalance between clotting factors and fibrinolysis.²⁵ However, most of the previous studies did not address the prognostic impact of combined hyperglycemia and high D-dimer levels, focusing only on the prognostic impact of hyperglycemia or diabetes. However, the relationship between hyperglycemia and prognosis in our study was consistent with previous studies.^{26,27} Only a few studies have found a significant correlation between D-dimer levels and hyperglycemia or diabetes.^{28–30} Furthermore, our study showed that hyperglycemia (FBG $\geq 7.00 \text{ mmol/L}$) had a synergistic effect with elevated D-dimer levels, which further increased the risk of adverse in-hospital outcomes, and this risk was independent of the history of diabetes. We observed that patients with normal D-dimer who had hyperglycemia did not present higher risk of adverse in-hospital outcomes compared with those with normoglycemia (HR 1.11; 95% CI 0.24–5.08). However, patients with high D-dimer levels, no matter with hyperglycemia, showed a higher risk of adverse in-hospital outcomes compared with those with normal D-dimer and FBG, the adjusted HR was 2.30 (95% CI 1.16–4.54) and 5.72 (95% CI 2.65–12.34), respectively. The highest risk was seen in patients with both high D-dimer and hyperglycemia. To take the argument a bit further, these results illustrated that the adverse effects of hyperglycemia on COVID-19 might be associated with a prothrombotic state induced by hyperglycemia, and may

provide new ideas for the clinical treatment of COVID-19, that is, anticoagulation should be accompanied by a focus on constant monitoring of blood glucose in order to prevent the synergistic effect of hyperglycemia and hypercoagulable state. Meanwhile, the risk was independent of diabetes and also indicated the need to pay more attention to the glycemic status on admission, rather than the diabetes history alone, to determine the need for glucose-lowering therapy.

Of even greater interest, we also found this result in older patients ≥ 65 years of age, which has never been mentioned in previous studies. Although previous studies have suggested that D-dimer is physiologically elevated in the elderly and the threshold for pulmonary embolism diagnosis should be increased according to age.³¹ However, our study found that using 0.50 mg/L as the cutoff point, the risk of greater than 0.50 mg/L has been significantly enhanced. Therefore, given that the elderly are more likely to have hyperglycemia and coagulation problems compared with the younger, the results imply that more attention should be paid to blood glucose and D-dimer levels when dealing with elderly COVID-19 patients.

However, several possible limitations of the present study warrant special consideration. First, despite this being a cohort study with a full sample from one center, some patients still excluded from enrollment because of the absence of D-dimer and FBG levels on admission. Second, because both D-dimer and FBG levels were measured on admission, namely at the same time cross-section, it was not possible to further explore whether hyperglycemia contributed to the elevated D-dimer and thus to the poor prognosis. Third, our study only explored admission D-dimer levels but failed to analyze the differences in D-dimer levels at multiple time points and their trends over time. Therefore, more studies with dynamic monitoring data are needed. Finally, we collected all data during hospitalization without a long-term follow-up after discharge.

In conclusion, our findings suggest that D-dimer levels at admission were a predictor of adverse in-hospital outcomes, and the synergic effect of elevated D-dimer and hyperglycemia could further increase the risk of adverse in-hospital outcomes, especially in the elderly, and this risk was independent of the history of diabetes. Hence, more attention should be paid to blood glucose and D-dimer levels of COVID-19 patients regardless of their history of thrombosis or diabetes, which might be very useful for better management of COVID-19.

Data Sharing Statement

The database of the current study is not publicly available.

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Disclosure

The authors have no conflicts of interest to declare.

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