An overview of the role of D-dimer in COVID-19: elevated D-dimer level is associated with disease severity

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Abstract

The great number of patients presenting to health centers or hospitals during the outbreak of coronavirus disease 2019 (COVID-19) overwhelms the need for critical care support. Early and effective predictors for clinical outcomes are urgently needed for risk stratification. Critically ill patients often develop coagulation disorders, in particular hypercoagulation. Elevated D-dimer is a prominent indicator for the initial coagulopathy of COVID-19. To estimate whether D-dimer is associated with the severity of COVID-19, we performed the analysis of D-dimer abnormalities in patients with COVID-19. The data demonstrated that D-dimer levels were significantly higher in deceased patients than in survivors (weighted mean difference(WMD): 3.70mg/L, 95% confidence interval(CI):1.41–5.98mg/L), and the levels in severe patients were also higher than those in mild cases (WMD: 0.39mg/L, 95% CI: 0.22–0.55mg/L). Therefore, we conclude that elevated D-dimer level is related to the severity and poor prognosis of patients with COVID-19.

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Short title: An overview of the role of D-dimer in COVID-19

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Abstract

The great number of patients presenting to health centers or hospitals during the outbreak of coronavirus disease 2019 (COVID-19) overwhelms the need for critical care support. Early and effective predictors for clinical outcomes are urgently needed for risk stratification. Critically ill patients often develop coagulation disorders, in particular hypercoagulation. Elevated D-dimer is a prominent indicator for the initial coagulopathy of COVID-19. To estimate whether D-dimer is associated with the severity of COVID-19, we performed the analysis of D-dimer abnormalities in patients with COVID-19. The data demonstrated that D-dimer levels were significantly higher in deceased patients than in survivors (weighted mean difference(WMD): 3.70mg/L, 95% confidence interval(CI):1.41–5.98mg/L), and the levels in severe patients were also higher than those in mild cases (WMD: 0.39mg/L, 95% CI: 0.22–0.55mg/L). Therefore, we conclude that elevated D-dimer level is related to the severity and poor prognosis of patients with COVID-19. (145 words)

Key words : COVID-19, D-dimer, Coagulopathy, Severity

Introduction

Since December 2019, the outbreak of COVID-19 put the health authorities of the whole world on high alert. According to the latest statistics released by the World Health Organization on June 17,2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has already infected over 8 million people from over 200 countries worldwide, causing more than 400,000 deaths("World Health Organization.,"). SARS-CoV-2 can cause serious diseases, including acute respiratory distress and occasionally associated with multiple organ dysfunction failure(Mattiuzzi & Lippi, 2020). During the course of SARS-CoV-2 infection, critical patients developed uncorrectable coagulation dysfunction. Existence of disseminated intravascular coagulation is common in deaths with COVID-19(Tang, Li, Wang, & Sun, 2020). The initial coagulopathy of COVID-19 is accompanied with prominent elevation of D-dimer and fibrin/fibrinogen degradation products(Connors & Levy, 2020). Also, markedly elevated D-dimer levels were reported in the deceased patients(Tang et al., 2020), suggesting that elevated D-dimer is closely related to poor prognosis. In this review, we studied the roles of D-dimer in infections, then performed the analysis of D-dimer abnormalities in patients with COVID-19 to better estimate the role of D-dimer in predicting the prognosis of SARS-CoV-2 infected patients.

General roles of D-dimer in infections

On-admission, D-dimer level is usually used to predict disease severity and mortality in endocarditis and severe patients without obvious disseminated intravascular coagulation(Shorr, Trotta, Alkins, Hanzel, & Diehl, 1999; Turak et al., 2014). A cohort study by Michael et al. found that patients with bacteremia had a higher risk of in-hospital mortality on the first day of positive blood culture with elevated D-dimer levels(Schwameis et al., 2015). Elevated D-dimer levels have also been reported in patients with acute lung injury and acute respiratory distress syndrome(Wenzel et al., 2002). Lee et al. had reported the clinical and laboratory features of 138 cases of suspected SARS in Hong Kong, which was striking that 45% of the patients had elevated D-dimer levels(Lee et al., 2003). Notably, most SARS-CoV-2 infected patients with systemic inflammatory response syndrome are associated with significantly elevated D-dimer, especially in critically ill patients (Mehta et al., 2020). In a study of 1099 patients with COVID-19 from over 550 hospitals in China, a D-dimer [?]0.5 mg/L was noted in 260/560 (46.4%) patients, and about 60% of severe patients have elevated D-dimer(Guan et al., 2020). Furthermore, markedly elevated D-dimer levels were also observed in the deceased patients with COVID-19 (Tang et al., 2020).

D-dimer is associated with severity of COVID-19

Given the important roles of D-dimer in infections, we speculated that D-dimer can be used to track the severity of COVID-19. To address this hypothesis, we reviewed studies that reported information on the difference of D-dimer values from COVID-19 patients with different backgrounds (i.e., those who need mechanical ventilation, or intensive care unit (ICU) admission, or those who died) from December 1, 2019 to June 10, 2020, without language restriction. Based on these literatures, we performed a pooled analysis with calculation of WMD and 95% CI of D-dimer values between deceased patients and survivors with COVID-19(Du et al., 2020; Fogarty et al., 2020; Tang et al., 2020; Wu et al., 2020; Yan et al., 2020; J. Zhang et al., 2020; Zhou et al., 2020)(subgroup 1, consisting 7 studies, characteristics presented in **Table 1**), and between COVID-19 patients with or without severe disease(G. Chen et al., 2020; Q. Chen et al., 2020; Huang, Wang, & Li, 2020; Ji et al., 2020; M. Liu et al., 2020; Liu, Liao, Wan, Xiang, & Zhang, 2020; Wei et al., 2020; Wu et al., 2020; Xie et al., 2020; J. J. Zhang et al., 2020; Zheng et al., 2020; Zhu et al., 2020; Zou et al., 2020)(subgroup 2, consisting 13 studies, characteristics presented in **Table 2**), using R software Version 3.6.3. The severe group met any of the following criteria: (a) Increased breathing rate ([?]30 beats/min), (b) resting-state oxygen saturation [?]93%, (c) arterial partial pressure of oxygen/oxygen concentration[?]300mm Hg("Diagnosis and Treatment of Pneumonia Caused by SARS-CoV-2(version 7).National Health Commission of the People's Republic of China,"), or (d) respiratory failure, mechanical ventilation, shock, or other functional organ failure requiring ICU monitoring and treatment. Mean and standard deviation were extrapolated from sample size, median, and interquartile range according to Wan et al.(Wan, Wang, Liu, & Tong, 2014) and Luo et al.(Luo, Wan, Liu, & Tong, 2018).

The WMD of subgroup 1 (597 patients in total, 32% were deceased patients) was summarized in**Figure 1,** showing that D-dimer levels were significantly higher in deceased patients than those in survivors with COVID-19 (WMD: 3.70mg/L, 95% CI: 1.41–5.98mg/L), the heterogeneity of subgroup 1 was relatively high (I-square(I^2), 86%; p< 0.01). The WMD of subgroup 2 (1172 patients in total, 35% with severe disease) was summarized in **Figure 2,** showing that D-dimer levels in severe patients were higher than those in the mild cases (WMD: 0.39mg/L, 95% CI: 0.22–0.55mg/L), while the heterogeneity of subgroup 2 was relatively high (I^2, 84%; p< 0.01).

Vigilance against elevated D-dimer levels

D-dimer level at the time of hospital admission is a risk predictor for the development of acute respiratory distress syndrome, ICU admission and death(Huang et al., 2020; Wu et al., 2020). An observational study in COVID-19 patients with elevated D-dimer levels showed that the 28-day mortality of heparin treated patients was lower than those from non-treated ones(Zhou et al., 2020). In a trial consisting of 31 patients with COVID-19, dipyridamole supplementation was associated with significantly decreased concentration of D-dimers, increased lymphocytes and platelet recovery in the circulation, suggesting markedly improved clinical outcomes(X. Liu et al., 2020). Similarly, Escher et al. also reported that the "decrease" of D-dimer levels (from 6.26 mg/L to 1.94 mg/L) in a patient after escalating the treatment dose of anticoagulation reflected clinical improvement(Escher, Breakey, & Lammle, 2020).

High concentration of D-dimer indicates a hypercoagulable state in patients with COVID-19, which is closely related to thromboembolism(Kline, Garrett, Sarmiento, Strachan, & Courtney, 2020). Cui et al. used a D-dimer cut-off of 1.5 μg/mL for predicting venous thromboembolism and demonstrating sensitivity of 85.0%, specificity of 88.5% and negative predictive value of 94.7%(Cui, Chen, Li, Liu, & Wang, 2020). The Swiss Society of Hematology proposed that for patients in ICU with a large increase of D-dimer, severe inflammation, or signs of hepatic, or renal dysfunction or imminent respiratory failure, intermediate or therapeutic dosing of low molecular weight heparin or unfractionated heparin should be applied based on the bleeding risk(Casini et al., 2020). As for venous thromboembolism prophylaxis, many centers have increased the dose of anticoagulation as a risk-adapted strategy based on the levels of D-dimer, fibrinogen, ICU location, or other factors associated with increased risk(Connors & Levy, 2020).

Conclusion

In this work, we performed a pooled analysis for D-dimer abnormalities that occurred in association with COVID-19 based on published data, found that D-dimer levels were considerably higher in severe or deceased patients than in mild ones or survivors with COVID-19, suggesting that elevated D-dimer level is closely related to the severity and poor prognosis of patients. Thereby, we conclude that D-dimer can be used as the early and effective predictor for the judgment of the disease severity, which is of great importance in clinical use. However, larger prospective studies are needed in the future to classify the mechanism how SARS-CoV-2 caused hypercoagulation, in particular elevated D-dimer levels.

Our review has several limitations. First, most of the studies reported the change of D-dimer levels are observational studies, and there are few longitudinal comparison studies. In addition, only one literature which we analyzed is not derived from studies of Chinese patients. Since race and ethnicity have major effects upon thrombotic risk (Liao et al., 2014; White & Keenan, 2009), data from other countries need to be updated.

Notes

Ethical Statement: No ethical approval was required as this is a review article with no original research data.

Data availability statement: The data that support the findings of this study are available on request from the corresponding author.

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Author contributions: Yu Hu and Shanshan Luo designed the study; Moran Wang and Shengling Ma collected the data, and wrote the paper; Yu Hu and Shanshan Luo analyzed the data and modified the grammatical structure of the article; all authors reviewed the paper and approved the final manuscript.

Potential conflicts of interest: The authors declare no conflicts of interest.

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Table 1. D-dimer values between deceased patients and survivors with coronavirus disease 2019.

Study	Country	All patients	Deceased patients	Survivors	D-dimer (mg/L)	D-dimer (mg/L)	D-dimer (mg/L)
					Deceased patients	Survivors	P values
Du.R(Du et al., 2020)	China	179	21	158	1.1(0.4-10.5)	0.5(0.3-1.2)	0.011
Fogarty.H(Fogarty et al., 2020)	Ireland	83	33	50	1.003 (0.537-1.782)	0.804 (0.513-1.29)	0.018
Tang.N(Tang et al., 2020)	China	183	21	162	2.12 (0.77-5.27)	0.61 (0.35-1.29)	<0.001
Wu.C(Wu et al., 2020)	China	84	44	40	3.95 (1.15-10.96)	0.49 (0.31-1.18)	0.001
Yan.YL(Yan et al., 2020)	China	48	9	39	4.95 (1.80-21)	0.41 (0.26-0.89)	<0.001
Zhang.JP(J. Zhang et al., 2020)	China	19	8	11	2.15(1.4-9.2)	0.48 (0.42-0.97)	<0.05
Zhou.F(Zhou et al., 2020)	China	191	54	137	5.2 (1.5-21.1)	0.6(0.3–1.0)	<0.0001

Data are median (interquartile range); P values comparing deceased patients and survivors with coronavirus disease 2019 are from χ^2 test, Fisher's exact test, or Mann-Whitney U test.

Study	Country	All patients	Severe	Non- severe	D-dimer (mg/L)	D-dimer (mg/L)	D-dimer (mg/L)
					Severe	Non-severe	P values
Chen.G(G. Chen et al., 2020)	China	21	11	10	8.2 ±9.0	0.4±0.3	0.025
Chen.QQ(Q. Chen et al., 2020)	China	145	43	102	0.32 (0.21-0.49)	0.24 (0.16-0.39)	0.110
Huang.C(Huang et al., 2020)	China	41	13	28	2.4(0.6-14.4)	0.5 (0.3-0.8)	0.004
Ji.D(Ji et al., 2020)	China	208	40	168	0.48 (0.31-0.75)	0.24 (0.19-0.43)	<0.001

Study	Country	All patients	Severe	Non- severe	D-dimer (mg/L)	D-dimer (mg/L)	D-dimer (mg/L)
Liu.M(M. Liu et al., 2020)	China	30	4	26	1.54±1.22	0.26±0.08	<0.001
Liu.Y(Y. Liu et al., 2020)	China	76	30	46	1(0.33-2.42)	0.26 (0.16-0.45)	<0.001
Wei.YY(Wei et al., 2020)	China	167	30	137	0.35 (0.23-0.58)	0.26 (0.19-0.51)	0.106
Wu.C(Wu et al., 2020)	China	201	84	117	1.16 (0.46-5.37)	0.52 (0.33-0.93)	<0.001
Xie JJ(Xie et al., 2020)	China	56	34	22	0.59 (0.22-1.0)	0.34 (0.22-0.54)	0.180
Zhang.JJ(J. J. Zhang et al., 2020)	China	138	56	82	0.4 (0.2-2.4)	0.2 (0.1-0.3)	<0.001
Zheng.Y(Zheng et al., 2020)	China	94	32	62	2.65±3.93	0.78±0.76	0.000
Zhu.Z(Zhu et al., 2020)	China	105	10	95	0.161 (0.074-0.283)	0.1 (0.082-0.158)	0.195
Zou.Y(Zou et al., 2020)	China	303	26	277	1.04 (0.73-1.72)	0.43 (0.31-0.77)	<0.001

Table 2. D-dimer values between severe and non-severe patients with coronavirus disease 2019.

Data are median (interquartile range) and mean±standard deviation; P values comparing severe and non-severe patients with coronavirus disease 2019 are from χ^2 test, Fisher's exact test, or Mann-Whitney U test.

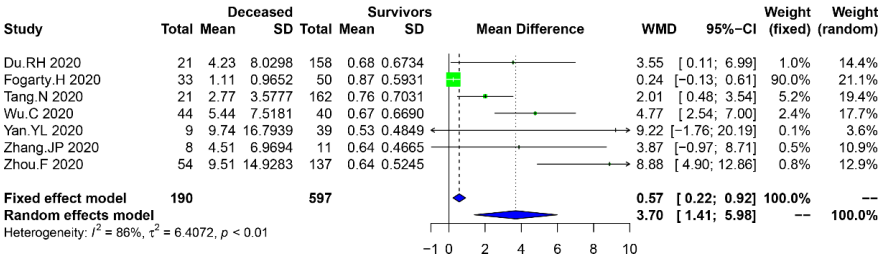

Figure 1.Weighted mean difference and 95% confidence interval of D-dimer values between deceased patients and survivors with coronavirus disease 2019.

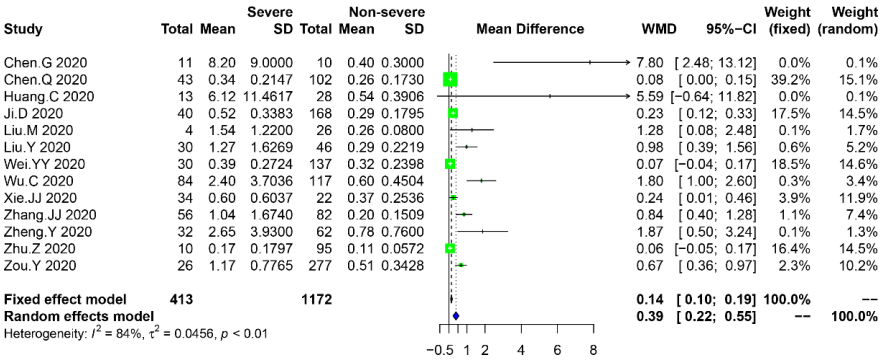

Figure 2. Weighted mean difference and 95% confidence interval of D-dimer values between severe and non-severe patients with coronavirus disease 2019.