Original Article

Diagnostic Value of D-Dimer in COVID-19: A Meta-Analysis and Meta-Regression

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Abstract

The prognostic role of hypercoagulability in COVID-19 patients is ambiguous. D-dimer, may be regarded as a global marker of hemostasis activation in COVID-19. Our study was to assess the predictive value of D-dimer for the severity, mortality and incidence of venous thromboembolism (VTE) events in COVID-19 patients. PubMed, EMBASE, Cochrane Library and Web of Science databases were searched. The pooled diagnostic value (95% confidence interval [CI]) of D-dimer was evaluated with a bivariate mixed-effects binary regression modeling framework. Sensitivity analysis and meta regression were used to determine heterogeneity and test robustness. A Spearman rank correlation tested threshold effect caused by different cut offs and units in D-dimer reports. The pooled sensitivity of the prognostic performance of D-dimer for the severity, mortality and VTE in COVID-19 were 77% (95% CI: 73%-80%), 75% (95% CI: 65%-82%) and 90% (95% CI: 90%-90%) respectively, and the specificity were 71% (95% CI: 64%-77%), 83% (95% CI: 77%-87%) and 60% (95% CI: 60%-60%). D-dimer can predict severe and fatal cases of COVID-19 with moderate accuracy. It also shows high sensitivity but relatively low specificity for detecting COVID-19-related VTE events, indicating that it can be used to screen for patients with VTE.

Introduction

Since the outbreak of the pandemic in December 2019 in Wuhan, China, coronavirus disease 2019 (COVID-19) has affected over 120.77 million worldwide, and resulted in approximately 2,672,099 deaths. COVID-related mortality is largely associated with hypercoagulability and increased risk of venous thromboembolism (VTE) events, leading to thrombo-inflammation in severe conditions.[1] Therefore, coagulation biomarkers may indicate disease severity and mortality, and help determine patient triage, therapeutic strategies and prognosis supervision. D-dimer is the product of fibrin degradation, and plays a mechanistic role in thrombo-inflammation in COVID-19.[1] Several studies have correlated elevated D-dimer (prevalence up to 46.4%) with increased severity and adverse outcomes of COVID-19.[2-4] Patients with D-dimer >1000 ng/ml present a 20-fold higher mortality risk compared to those with lower D-dimer values.[3] Therefore, D-dimer is a potential screening tool for VTE in COVID-19 patients, and based on D-dimer elevation, adjusting therapeutic

anticoagulant doses is more beneficial to the patients compared to prophylactic doses.[5] Thus, D-dimer levels should be monitored in COVID patients early after admission.

However, the diagnostic value of D-dimer in predicting disease severity, mortality and VTE events in COVID-19 has not

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been elucidated yet, due to the small cohorts and the heterogeneity between studies. Up till now, most of studies didn't report harmonized D-dimer to single units. To recognize and verify its diagnostic performance in COVID-19, we systematically conducted a literature review and meta-analysis.

Materials and Methods

Literature Search

The systematic review and meta-analysis was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Supplementary Table 1). The registration number is CRD42021230446. Two authors (HTZ and HZC) independently searched the PubMed, Embase, Cochrane Library and the core collection of Web of Science databases for studies published till September 1, 2020, using the following items: "d-dimer," "diagnostic marker," "biomarker" and "laboratory test" for D-dimer combined with "Coronavirus," "Beta coronavirus," "SARS CoV-2" and "COVID-19." The search strategies are detailed in Supplementary Table 2. Additional studies were retrieved manually from the references.

Eligibility Criteria

Without any restrictions on time, language, ethnicity or geographical region, studies satisfying the following criteria were included: (1) assessment of the diagnostic utility of D-dimer in distinguishing in-hospital severity, mortality and VTE events in COVID-19 patients, (2) sufficient data to construct a 2 × 2 table to determine diagnostic accuracy of D-dimer, and (3) confirmed diagnosis of COVID-19 by either real time-polymerase chain reaction (RT-PCR) or radiological imaging, with at least one adequate D-dimer result. Studies on animal and cellular models, case reports, case series, conference abstracts or letters without sufficient data were excluded.

Data Extraction and Quality Assessment

Two independent authors (HTZ and HZC) separately screened the literature, and extracted and evaluated the data. Any discrepancies were resolved by consensus or a third opinion. The study number, first author's name, study region, sample size, inclusion and exclusion criteria, demographic features (age, sex, comorbidity and ethnicity), reference standard, D-dimer assay method, time for D-dimer test (at admission or hospitalization) and VTE prevalence were extracted into pre-designed charts. Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) was used to evaluate the study quality. Further details of the pooled studies were obtained by directly contacting the authors as per requirement.

Statistical Analysis

STATA V.16.0 (Stata Corporation, College Station, TX, USA) and Meta-DiSc V.1.4 (Unit of Clinical Biostatistics, Ramony Cajal Hospital, Madrid, Spain) was used to perform the meta-analysis. The primary outcomes were severity, mortality and VTE events in COVID-19 confirmed patients. A bivariate mixed-effects binary regression modeling framework was used to combine the pooled sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR−), and diagnostic ratios (DOR) with 95% CI. Significant heterogeneity was ascertained based on Cochrane's Q-statistic P value ≤ 0.10 or $I^2 > 50\%$. The summary receiver operator characteristics (SROC) curve and the area under the curve (AUC) were analyzed to appraise the overall diagnostic performance of D-dimer in COVID-19 confirmed patients. Sensitivity analysis and multiple regression analysis were performed to identify the potential origin of heterogeneity and test robustness. P value <0.05 (2 sided) was considered statistically significant. The publication bias was also assessed.

Results

Search Results and Characteristics of Studies

The results of the literature search are outlined in Figure 1. A total of 5557 articles published till September 1, 2020 were extracted from 4 databases. After removing duplicate studies (n = 2207) and irrelevant publications (n = 1048), 2302 articles were further analyzed, and the full-text of 69 were read. Thirty-nine full-text articles were eliminated on account of incomplete data or unrelated outcomes (severe/dead/VTE events). Thirty-three eligible studies met our inclusion criteria,[6-34] of which one was excluded due to the combined model of dyslipidemia and D-dimer levels for VTE prediction in COVID-19, and 3 due to insufficient data. Finally, 8 studies on the predictive power of D-dimer for disease severity,[6-13] 12 for mortality[6,11,14-23] and 12 for COVID-19-related VTE events[11,24-34] were included in the meta-analysis, which included 2014, 4468 and 2158 patients respectively. The main characteristics of the studies are summarized in Supplementary Table 3 and Supplementary Table 4. Most are retrospective studies (n = 27), one was prospective and one cross-sectional.

Study Quality

QUADAS-2 was used to assess the quality of the eligible studies, and indicated overall good quality, with positive results for at least 9/14 items (Figure S1).

Meta-Analysis of the Diagnostic Accuracy of D-Dimer for Disease Severity in COVID-19 Patients

The diagnostic sensitivity of D-dimer for severity in 2014 COVID-19 patients ranged from 43% to 100%, and the specificity was 57% to 89%. The pooled sensitivity and specificity were 77% (95% CI: 58%-89%) and 71% (95% CI: 64%-77%) respectively. The LR+ was 2.65 (95% CI: 2.22-3.17) and the LR− was 0.33 (95% CI: 0.18-0.61). The pooled DOR was 8 (95% CI: 4-17) and the AUC of SROC was 77% (95% CI: 73%-
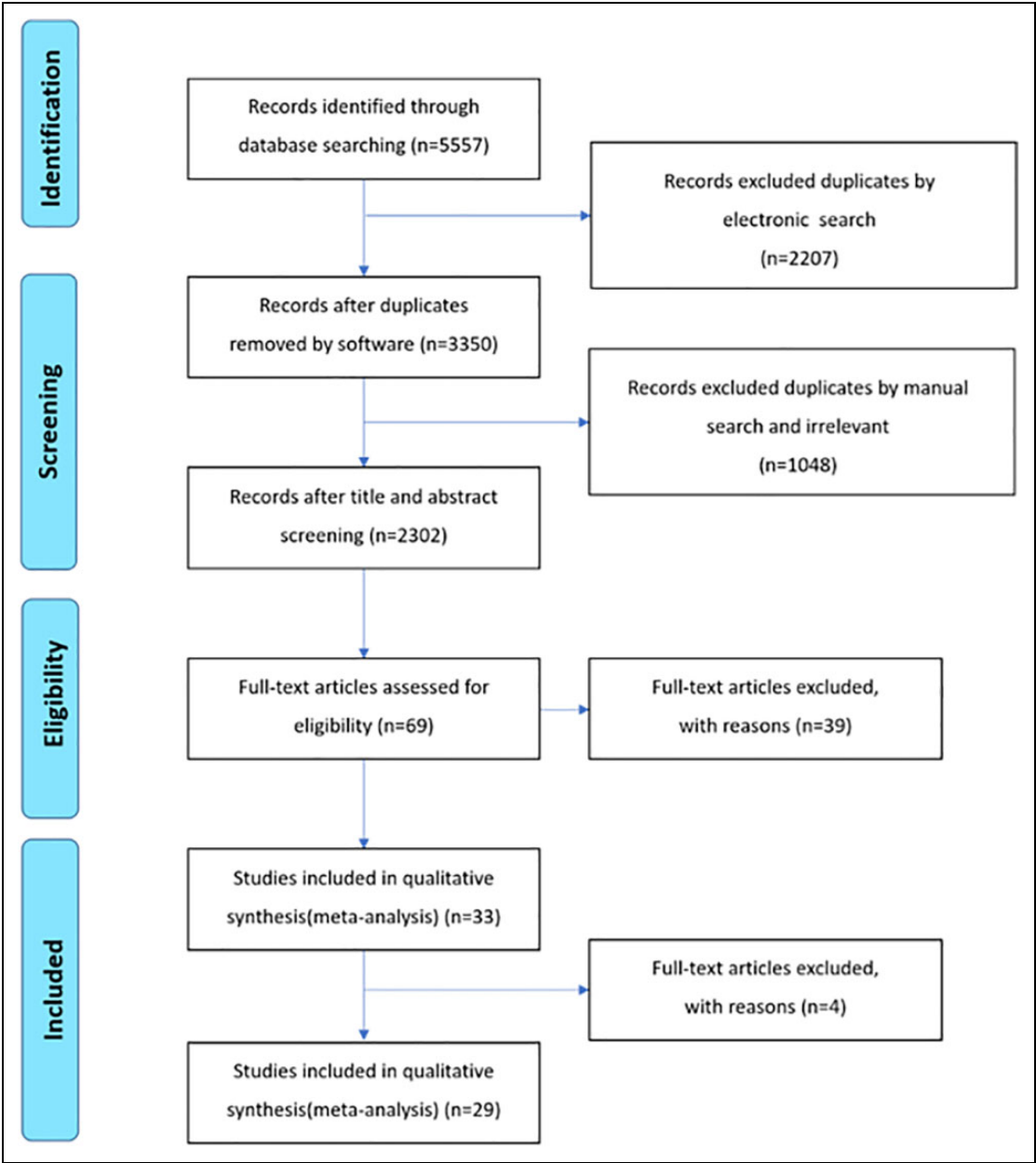
Figure 1. Flow diagram of studies included in the meta-analysis.

80%). The 95% confidence region of SROC was narrow and small, indicating the increased precision of studies in the pooled estimate. Forest plots of sensitivity and specificity, and the SROC curve are shown in Figure 2.

Meta-Analysis of the Diagnostic Accuracy of D-Dimer for Mortality in COVID-19 Patients

The diagnostic sensitivity and specificity of D-dimer for mortality in 4468 COVID-19 patients were 43% to 93% and 64% to 96% respectively, and the pooled estimates were 75% (95% CI: 65%-82%) and 83% (95% CI: 77%-87%). Comparing to severity, the LR+ was higher (4.35, 95% CI: 3.25-5.82) and the LR− was

comparable, (0.30, 95% CI: 0.22-0.42). The pooled DOR (14, 95% CI: 9-24) and the AUC of SROC (86%, 95% CI: 83%-89%) were higher than severity. Consistently, the narrow and small 95% confidence region of SROC indicated accuracy of the pooled estimate. The Forest plots and SROC curve are shown in Figure 3.

Meta-Analysis of the Diagnostic Accuracy of D-Dimer for VTE Events in COVID-19 Patients

The diagnostic sensitivity of D-dimer for VTE events in 2158 COVID-19 patients ranged from 67% to 100%, and the specificity from 29% to 89%. The pooled sensitivity and specificity were 90% (95% CI: 90%-90%) and 60% (95% CI: 60%-60%)
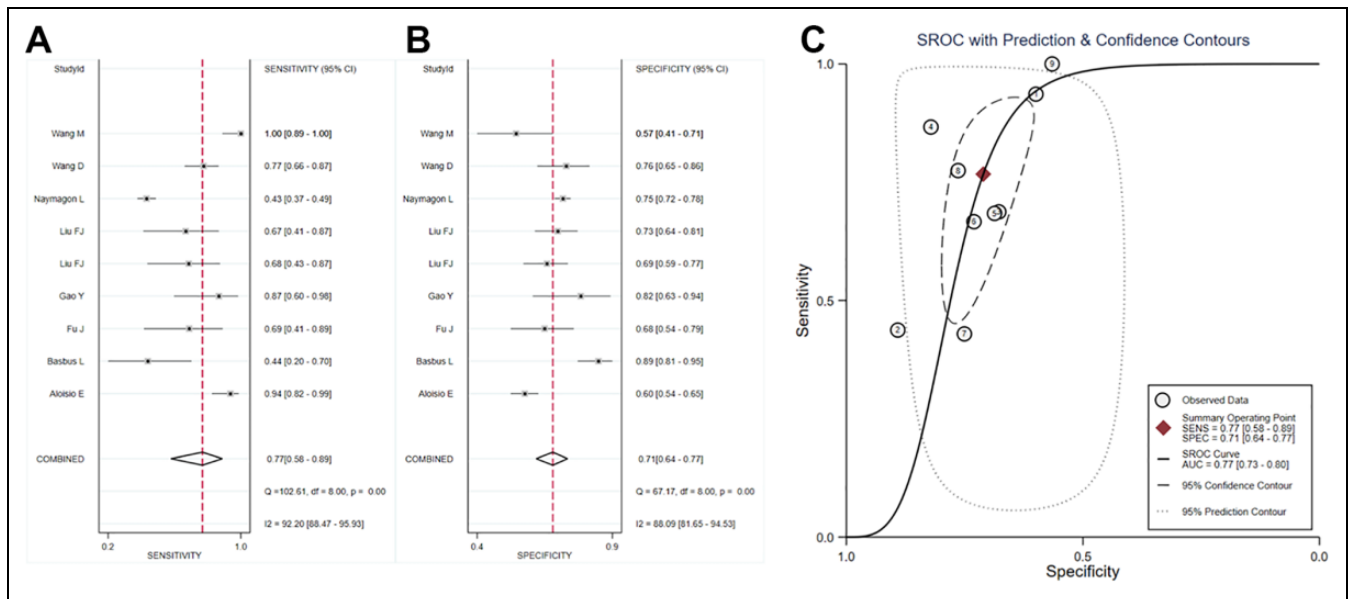
Figure 2. Forest plot and SROC of the accuracy of D-dimer for severity in COVID-19 patients.
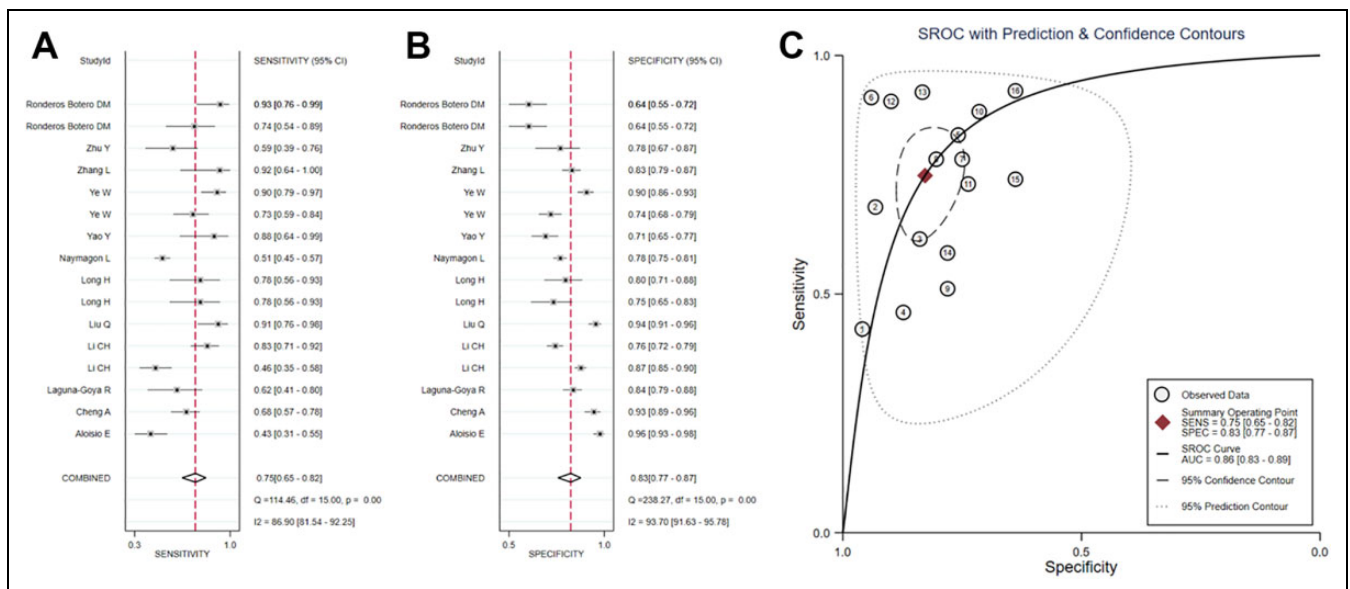

Figure 3. Forest plot and SROC of the accuracy of D-dimer for mortality in COVID-19 patients.

respectively. In this meta-analysis, LR+ and LR− showed slightly lower comparing to severity and mortality (2.24, 95% CI: 2.24-2.24; 0.16, 95% CI: 0.16-0.16, respectively). Similarly, the consistent pooled DOR was 14 (95% CI: 14-14) and the narrow and small AUC of SROC was 85% (95% CI: 81%-88%), which illustrated accurate pooled estimate. The Forest plots for pooled sensitivity and specificity, as well as the SROC curve are shown in Figure 4.

Multiple Regression and Exploration of Threshold Effect

Meta-regression analysis was performed to explore the potential origins of heterogeneity among the pooled studies.

The co-variates were country, study type, age, sex (percentage of males), patient inclusion and exclusion criteria, reference standards, time for D-dimer test, measurements of D-dimer, co-morbidity status, and clinical prevalence of VTE events.

For severity (Table 1 and Figure S2A), the reference standard (COVID-19 Diagnosis and Treatment Program Edition of China) and comorbidity status (percentage of diabetic patients) contributed to the heterogeneity in sensitivity ($P = 0.01$, $P = 0.00$, respectively), whereas country, sex and classification of severity outcome (admission to ICU/intubation/critical illness) led to heterogeneity in specificity ($P = 0.03$, $P = 0.03$, $P = 0.00$, respectively). Supplementary Table 5 showed the
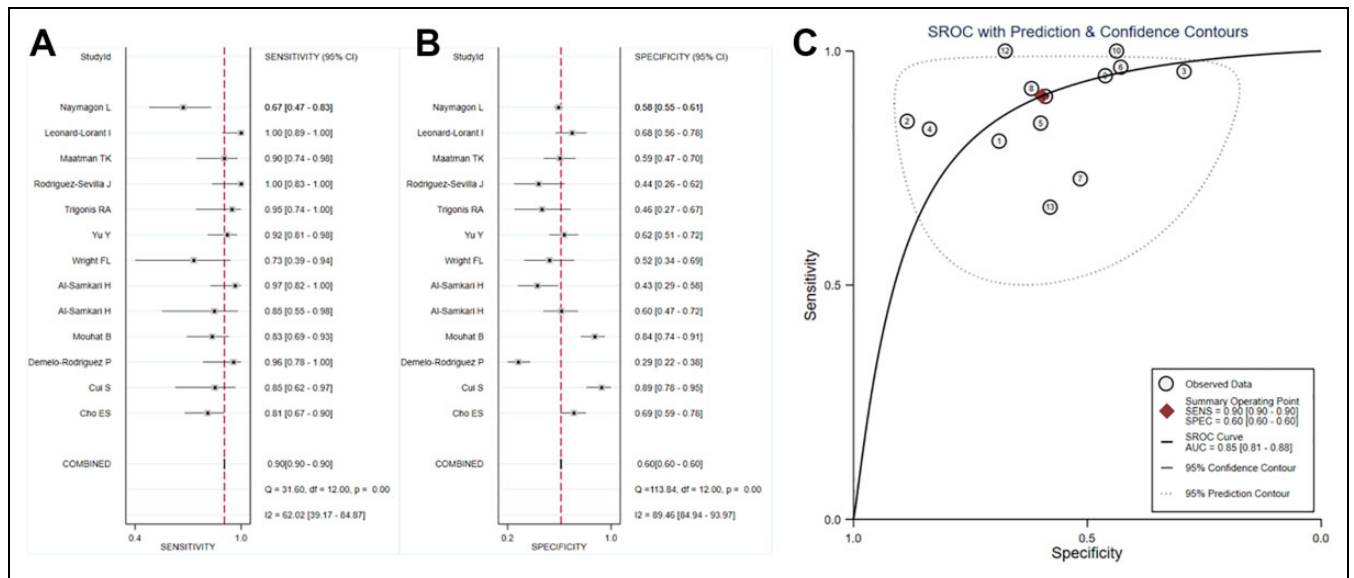
Figure 4. Forest plot and SROC of the accuracy of D-dimer for VTE events in COVID-19 patients.

results of sensitivity and specificity in meta-regression after adjusting the variable. For mortality (as shown in Table 1 and Figure S2B), country ($P = 0.03$) and exclusion of pregnancy ($P = 0.03$) led to heterogeneity in the diagnostic sensitivity, and the country ($P = 0.01$), mixed ($P = 0.00$) or single ($P = 0.02$) cohort patients (i.e. inclusion of mild/moderate/severe/critical COVID-19 patients), exclusion of no D-dimer test results ($P = 0.02$) and D-dimer test at peak level ($P = 0.00$) contributed to the heterogeneity in specificity. For VTE events (presented in Table 1 and Figure S2C), heterogeneity in sensitivity was attributed to the clinical prevalence of VTE ($P = 0.01$), whereas country ($P = 0.04$) was the source of heterogeneity in specificity.

Considering the heterogeneity of threshold (caused by different cut offs and D-dimer units) in individual study, we performed Spearman rank correlation to test the threshold effect and validated lack of threshold effect in this meta-analysis. The respective spearman correlation coefficients were 0.533 ($P = 0.139$), 0.283 ($P = 0.289$) and 0.368 ($P = 0.216$).

Exploration of Heterogeneity and Publication Bias

We conducted leave-one-out sensitivity analysis to explore the effect of every single study on the overall estimates, and the results indicated that our meta-analysis is stable (Supplementary Table 6 and Figure S3). We detected publication bias in the predictive role of D-dimer for mortality, as suggested by the asymmetric funnel plot and P values of 0.079 for Begg's test (Figure S4A), 0.000 for Egger's test (Figure S4B) and 0.04 for Deek's funnel plot (Figure S4C). However, the results of Begg's test should be interpreted with caution given small number of studies (<25). Additionally, a meta trim practice turns out the afterward heterogeneity (Q = 230.447, $P = 0.000$) is higher than it used to be (Q = 116.636, $P = 0.000$), suggesting adding imputed missing studies is more

likely to extend the distribution range of a meta-analysis and thus led to more heterogeneous of the whole set of studies (Figure S5). No publication bias was observed in the role of D-dimer for VTE events ($P = 0.95$ for Deek's funnel plot).

Discussion

Coagulation dysfunction in COVID-19 patients insidiously drives progression to severe illness and fatal outcome, and is characterized by elevated D-dimer and thrombi in the veins and arteries.[1] The high level of D-dimer in COVID-19 is triggered by excessive clots and hypoxemia. In addition, D-dimer elevation is frequently observed in COVID-19 patients with severe disease, and correlates significantly with mortality.[2,3] Since D-dimer is the product of fibrin degradation, its presence can predict pulmonary embolism and deep venous thrombosis (DVT).[35] In fact, COVID-19 patients with VTE events (both in deep venous thrombosis and pulmonary embolism) also exhibit high D-dimer levels in circulation.[6-34]

The limited availability of duplex ultrasound or computer tomography pulmonary angiography (CTPA) and ICU equipment for COVID-19 patients due to the present quarantine warrants a novel predictor of VTE events. A recent study on 191 COVID-19 patients reported that D-dimer levels greater than 1 mg/ml on admission correlate to 18-fold increase in mortality risk.[3] Furthermore, D-dimer >2600 ng/ml or more than 10 times higher than the upper limit of normal range calls for 4-extremity duplex ultrasound.[36] Although studies are increasingly focusing on the diagnostic performance of D-dimer for predicting the severity, mortality and VTE events in COVID-19, the results are ambiguous given the small study populations and heterogeneity between the studies. Therefore, we conducted a meta-analysis to assess the diagnostic value of D-dimer in COVID-19 patients.

Table 1. Meta-Regression for Factors Associated With Variation in Sensitivity and Specificity.[a]

Outcome		Variable	Sensitivity P value	Specificity P value
Severity	Country	Other Country except China	0.18	**0.03**
	Age		0.95	0.93
	Study type	Cross-sectional study	0.67	0.49
	Males		0.12	**0.03**
	Classification of outcome	Use of admission to ICU/intubation/critical illness for outcome	0.58	**0.00**
	Reference standard used	Not use COVID-19 reference standard of China	**0.01**	0.29
	Diabetes		**0.00**	0.14
	Chronic respiratory disease		0.42	0.79
Mortality	Country	Other Country except China	**0.03**	**0.01**
	Age		0.94	0.83
	Study type	Prospective study	0.47	0.66
	Males		0.08	0.48
	Recruitment criteria	Mixed patient selection	0.52	**0.00**
		Severe patients only	0.46	**0.02**
	Exclusion criteria	Study excluding no D-dimer results patients	0.15	**0.02**
		Study excluding pregnant patients	**0.03**	0.08
		Study excluding hematological system disease	0.10	0.10
	Time for index test	At admission (within 3 days)	0.67	0.10
		Peak value of D-dimer	0.89	**0.00**
		Other time	0.12	0.74
VTE events	Country	Other Country except China	0.55	**0.04**
	Age		0.93	0.97
	Study type	Prospective study	0.11	0.08
	Males		0.31	0.06
	Clinical prevalence of VTE		**0.01**	0.99
	Recruitment criteria	DVT patients only	0.09	0.70
		PE patients only	0.07	0.20
		VTE patients only	0.91	0.23
		Mixed patient selection	0.13	0.74
		Severe patients only	0.40	0.06
	Exclusion criteria	Study excluding prior VTE patients	0.23	0.84
		Study excluding therapeutic anticoagulation patients	0.10	0.20
	Reference standard used	Use CPTA for radiographic examination	0.08	0.31
		Use ultrasound for radiographic examination	0.27	0.72
	Time for index test	At admission	0.54	0.68
		Peak value of D-dimer	0.44	0.59
	Treatment prior to index test	No treatment prior	0.28	0.79
	Hypertension		0.71	0.13
	Diabetes		0.46	0.07
	Respiratory disease		0.80	0.59
	Smoking history		0.34	0.12

[a]Bold values represent $P < 0.05$ which means this variable is statistically correlated with sensitivity or specificity in meta-regression analysis.

D-dimer levels can distinguish severe COVID-19 patients with only moderate accuracy, as indicated by pooled sensitivity and specificity of 77% and 71% respectively, and AUC 77%. For predicting fatal outcome in COVID-19 patients, the pooled sensitivity, specificity and AUC were 75%, 83% and 86% respectively, suggesting a moderate chance of omission, relatively low risk of misdiagnosis and relatively high diagnostic accuracy. Finally, D-dimer can diagnose COVID-19 related VTE with high sensitivity (90%), low specificity (60%) and acceptable accuracy (AUC 85%). The respective pooled DORs for the above-mentioned analysis were 8 (95% CI: 4-17), 14

(95% CI: 9-24) and 14 (95% CI: 14-14), indicating that D-dimer can distinguish between mild and severe, fatal and non-fatal, and VTE and VTE-free cases of COVID-19.

Severity is not a solid endpoint as mortality in COVID-19 patients. In this analysis, we detailed described classification of severity in Supplementary Table 4. Definition of disease severity diversified according to different reference standard, which composed World Health Organization interim guidance for COVID-19, guidelines on the novel coronavirus-infected pneumonia diagnosis and treatment (issued by the National Health Commission of China), guidelines of national diagnosis and

treatment protocols for COVID-19 and the guidelines of American Thoracic Society. This source of heterogeneity of disease severity was confirmed by meta-regression analysis where the reference standard ($P = 0.01$) impact on the sensitivity and classification of severe outcome ($P = 0.00$) influenced specificity.

Threshold effect analysis only focused on true positive (TP), true negative (TN), false positive (FP) and false negative (FN) values to test diagnostic efficacy of D-dimer and distinguish if there exists heterogeneity caused by different cut offs and D-dimer units. On account of our analysis, we have identified that most of the pooled studies reported D-dimer using various units, such as D-dimer units (DDU), fibrinogen equivalent units (FEU) (~ 1.7-2.0 differences), mg/L or μg/mL. This may give rise to concerns whether it is correct or not to pool all the sensitivity and specificity data without taking that into account. To reassure this consideration, we conducted a Spearman rank correlation to test the threshold effect. Inexistence of threshold effect was unveiled by spearman correlation coefficients as 0.533 ($P = 0.139$), 0.283 ($P = 0.289$) and 0.368 ($P = 0.216$). Thus, each metric can be combined for further analysis.

We found substantial heterogeneity among the studies, and performed multiple meta-regression analysis to identify the sources. For severity, the reference standard ($P = 0.01$) and percentage of diabetic patients ($P = 0.00$) affected the sensitivity, whereas country ($P = 0.03$), percentage of males ($P = 0.03$) and classification of severe outcome ($P = 0.00$) contributed to the heterogeneity in specificity. For mortality, country ($P = 0.03$) and exclusion of pregnancy ($P = 0.03$) predicted heterogeneity in sensitivity, while that in specificity was attributed to no D-dimer test results ($P = 0.02$), country ($P = 0.01$), recruitment of mixed or single cohort patients ($P = 0.00$ for mixed, $P = 0.02$ for severe only), and D-dimer test at peak value ($P = 0.00$). The heterogeneity in the sensitivity and specificity of diagnosing VTE were respectively due to clinical prevalence of VTE ($P = 0.01$) and country ($P = 0.04$).

Additional research could help us to understand this heterogeneity further, Yao et al[19] retrospectively analyzed D-dimer upon admission and identified a cut off value >2.14 mg/ml predicting in-hospital mortality with a sensitivity of 88.2% and specificity of 71.3%. Creel-Bulos et al[37] rendered a comprehensive observation of D-dimer trajectories and represented a highly predictive value of a rise in D-dimer (>2000 ng/ml) of any 24 hours within 10 days with 75% sensitivity and 74% specificity while baseline value was not associated with VTE. A Chinese study composed of 1114 patients[38] mentioned the meaningfulness of last D-dimer test before discharge or death in prognosing death using a cut off value of 2.025 mg/L rather than the first test at admission, the AUC of which was 0.909. Through meticulously reading of these articles, we have discovered the main source of inconsistency including age, comorbidity rates, mean duration of hospitalization, exclusion criteria for conditions that increases D-dimer levels (pregnancy, cancer or post trauma and surgery status), as well as timing of D-dimer measurement (initial, peak or ultimate value), etc. In addition, lack of association between D-dimer and mortality in the study of Creel-Bulos et al[37] indicates anticoagulation treatment may potentially lead to decreased death and misunderstanding prognosis value of D-dimer. He and his colleges[38] also found participants with advanced age, male gender, dyspnea symptoms impact D-dimer value.

There can be several causes of heterogeneity. First, different reference standards can affect the sensitivity in discerning between severe and non-severe patients. Second, patients with diabetes have higher D-dimer levels and a significant higher risk of adverse prognosis, as well as shorter survival duration,[39] all of which influence diagnostic sensitivity. Third, males are more likely to develop severe illness and succumb, which can be attributed to the presence of androgens and angiotensin-converting enzyme 2 (ACE2) expression, along with a greater prevalence of unhealthy lifestyle choices like smoking, abuse alcohol and poor sleep.[40] Fourth, ethnicity can also affect diagnostic sensitivity and specificity due to the genetic predisposition to fatal comorbidities (diabetes, hypertension, asthma, etc.) and thrombotic events. For instance, polymorphism of mannose-binding lectin (MBL) genes and variations in ACE2 expression levels correlate to more severe and fatal outcomes in African American and Hispanic populations.[41] Fifth, exclusion of pregnancy may reduce sensitivity by removing false positive results and exclusion of no D-dimer test results may increase specificity by removing false negative results. Sixth, recruiting only severe patients can increase the probability of death compared to a mixed cohort of severe and mild cases. Likewise, measuring D-dimer at its peak also increases the possibility of patients for progressing to severe or critical illness, thrombotic events and fatal outcomes.[42] Finally, high clinical prevalence of VTE may avoid the potential diagnostic omission of VTE events in COVID-19 patients.

According to International Society on Thrombosis and Haemostasis (ISTH) guidance,[43] practice of utilizing thromboembolic prophylaxis is established for COVID-19 associated coagulopathy management, however, the optimal doses in severe COVID-19 patients based on increasing D-dimer values warrants adjustment and further investigation. Thus far, serial coagulation indices screening focused on D-dimer changes before and after anticoagulant as risk stratification is suggested. Dynamic alterations of D-dimer could demonstrate progression and prognosis of COVID-19. During 10 consecutive days of monitoring, D-dimer in admission escalated in improved and deteriorated groups after treatment and then gradually decreased in improved groups but remained high and fluctuated with disease progression in poor ones.[44] Coincidentally, initial elevated levels of D-dimer in baseline diminished after anticoagulant therapy with LMWH in DVT-COVID-19 patients and continuously higher than non-DVT-COVID-19 patients, indicating changes of D-dimer present an improvement in hypercoagulable state as well as a stable biomarker for anticoagulant effect in COVID-19 therapy.[45] Recently, researchers found D-dimer levels could affect anticoagulant doses. Prophylactic dose of heparin has been revealed its efficacy and better

prognosis among users with D-dimer >6 times the upper limit of normal value (ULN) by improving 28-day mortality than that of nonusers (32.8 vs 52.4%) while users with D-dimer ≤1 ULN of no benefit.[46] In comparison, another study unveiled improved survival rate in patients with D-dimer above 3000 ng/ml who administrated an intermediate dose of heparin than prophylactic doses.[47] Besides, prophylactic and therapeutic use of apixaban and enoxaparin prophylaxis is more beneficial in patients with D-dimer >10 μg/ml than UFH therapy while patients with D-dimer <1 μg/ml appears no benefit.[48] Benefit for extended thromboprophylaxis in the post-hospital discharge period (14-30 days) is also pronounced among patients with enhanced D-dimer >2 ULN and recognized 3-fold risk for VTE.[49] VTE risk stratification using very elevation of D-dimer may recommend intermediate or higher dose LMFH or UFH regimens.[50] Therefore, sequential measurement and careful assessment of D-dimer during disease worsening in addition to anticoagulation treatment may assist physicians to construct dynamic intervention, tailored prophylaxis or therapeutic doses and extended prophylaxis paradigms after hospitalization. We should apply D-dimer cautiously for anticoagulation considering the post-hoc feature of these studies and deficiency of clinical indications, its utility in adjusting antithrombotic strategies needs for prospective randomized controlled trails testing.

There are several limitations in our meta-analysis that ought to be considered. Although we conducted a meta-regression analysis to distinguish heterogeneity, much of it remains to be explained and reported. In addition, the funnel plots indicated publication bias in the predictive value of D-dimer for mortality, likely due to the fact that researchers would rather submit the favorable results, moreover, all the enrolled researches in our meta-analysis are published by September 1, 2020 which may also contribute to our publication bias. This publication bias may lead to overestimation of the pooled sensitivity and specificity. Data of race, comorbidities (respiratory failure, cardiovascular disease, smoking history, malignancy, previous VTE, etc.), pregnancy, recent surgery or trauma and anticoagulant treatment could not be retrieved, which may have led to missing values in meta-regression and omissions of covariates in the heterogeneity test. The test time, detection platform, cut offs and various units of D-dimer also potentially contributed to heterogeneity and bias. Availability of complete data on patient selection and exclusion, presence of comorbidities, treatment statistics of in-hospital COVID-19 patients, as well as the precise timing and method of D-dimer test would greatly reduce the bias in our estimates. In addition, although the existing heterogeneity can be partially explained by patient recruitment and methodological variance of individual studies, an exact conclusion cannot be drawn due to the lack of explanation for the remaining heterogeneity. Further studies with more comprehensive data can elucidate the diagnostic performance of D-dimer in COVID-19.

In conclusion, D-dimer can predict severe and fatal outcomes in COVID-19 patients with moderate sensitivity and specificity, and diagnose VTE with high sensitivity but low specificity. It is a suitable to employ this indicator as a pre-radiographic screening tool, VTE risk stratification indicator as well as a routine investigation after anticoagulant therapy for hospitalized patients with COVID-19.

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Supplemental Material

Supplemental material for this article is available online.

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