Elevated D-Dimer Levels Are Associated With Increased Risk of Mortality in Coronavirus Disease 2019:

A Systematic Review and Meta-Analysis

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Abstract: The 2019 novel coronavirus, declared a pandemic, has infected 2.6 million people as of April 27, 2020, and has resulted in the death of 181,938 people. D-dimer is an important prognostic tool, is often elevated in patients with severe coronavirus disease-19 (COVID-19) infection and in those who suffered death. In this systematic review, we aimed to investigate the prognostic role of D-dimer in COVID-19-infected patients. We searched PubMed, Medline, Embase, Ovid, and Cochrane for studies reporting admission D-dimer levels in COVID-19 patients and its effect on mortality. Eighteen studies (16 retrospective and 2 prospective) with a total of 3682 patients met the inclusion criteria. The pooled weighted mean difference (WMD) demonstrated significantly elevated D-dimer levels in patients who died versus those who survived (WMD, 6.13 mg/L; 95% confidence interval [CI] 4.16–8.11; $P < 0.001$). Similarly, the pooled mean D-dimer levels were significantly elevated in patients with severe COVID-19 infection (WMD, 0.54 mg/L; 95% CI 0.28–0.80; $P < 0.001$). The risk of mortality was fourfold higher in patients with positive D-dimer versus negative D-dimer (risk ratio, 4.11; 95% CI, 2.48–6.84; $P < 0.001$) and the risk of developing severe disease was twofold higher in patients with positive D-dimer levels versus negative D-dimer (risk ratio, 2.04; 95% CI, 1.34–3.11; $P < 0.001$). Our meta-analysis demonstrates that patients with COVID-19 infection presenting with elevated D-dimer levels have an increased risk of severe disease and mortality.

Key Words: 2019-nCoV, D-dimer, severe COVID-19, mortality

(*Cardiology in Review* 2020;28: 00–00)

The 2019 novel coronavirus (2019-nCoV) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first originated in late 2019 in Wuhan, China, and has since caused a substantial impact on mankind.[1] As of April 24, 2020, 2.6 million individuals have been infected with SARS-CoV-2 in 213 countries worldwide and 181,938 lives have been lost.[2] On December 31, 2019, China reported the outbreak to the World Health Organization (WHO). Subsequently, WHO officially declared the coronavirus disease 2019 (COVID-19) epidemic as a public health emergency of international concern.[3] The clinical features of COVID-19 vary from asymptomatic cases to severe infection, causing acute respiratory distress syndrome (ARDS), multisystem organ dysfunction, and death.[4]

There is uncertainty regarding the case fatality rate (CFR) of COVID-19 infection. The overall CFR for COVID-19 was reported at about 2% in China and 7.2% in Italy (likely due to the higher mean age of the overall population in the latter).[5] The CFR is very high in patients with severe COVID-19 infection, as high as 50% or more in patients admitted to the intensive care unit (ICU).[6] Due to high mortality in critically-ill COVID-19 patients, the detection of biomarkers that may help identify at-risk patients earlier in their course of illness becomes crucial. D-dimer is a biomarker that has emerged as an important prognostic tool, with findings of elevated levels in critically-ill patients and those deceased. In this systematic review, we aimed to investigate the prognostic role of admission D-dimer levels in patients hospitalized with COVID-19.

METHODS

Search Strategy

The reporting of this systematic review and meta-analysis complies with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines (Supplement Table 1, http://links.lww.com/CIR/A21).[7]

The initial search strategy was developed by 2 authors (S.S. and S.P.). We performed a systematic search, without language restriction, using PubMed, EMBASE, SCOPUS, Google Scholar, and 2 preprint servers (https://www.medrxiv.org and https://www.ssrn.com/index.cfm/en/coronavirus) from inception to April 16, 2020, for studies that reported D-dimer levels in COVID-19 patients. We utilized the "related articles" function in PubMed to find relevant articles that were missed by the initial search. Also, reference lists of the included studies were hand-searched to further locate relevant articles that were missed in the primary search. We used the following keywords and medical subject heading: "COVID-19," "SARS-CoV-2," "Wuhan coronavirus," "Coronavirus 2019," "2019 n-CoV," "D-dimer," "laboratory."

Study Selection and Data Extraction

To be included in our systematic review and meta-analysis, the study had to fulfill the following criteria: (1) reported D-dimer levels in COVID-19 patients according to severity or including mortality as a clinical outcome; (2) included human subjects; and (3) studies in the English language. Single-arm studies, case reports, editorials, or systematic reviews were excluded. Two investigators (S.S. and S.P.)

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Disclosure: The authors have no conflicts of interest and funding to report.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.cardiologyinreview.com).

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ISSN: 1061-5377/17/2806-0000
DOI: 10.1097/CRD.0000000000000330

independently performed the literature search and screened all titles and full-text versions of all relevant studies that met study inclusion criteria.

The data from included studies were extracted using a standardized protocol and a data extraction form. Any discrepancies between the 2 investigators were resolved through consultation with the senior investigator (J.G.). Two independent reviewers (S.S. and S.P.) extracted the following data from the eligible studies: author name, study design, publication year, follow-up duration, number of patients, age, gender, diabetes mellitus (DM), hypertension, coronary artery disease (CAD), acute cardiac injury, arrhythmias, shock, and outcomes. The Newcastle Ottawa Risk bias assessment tool was used to appraise the quality of the included studies (Supplement Table 2, http://links.lww.com/CIR/A21).

OUTCOMES

Clinical Outcomes

The primary outcome of interest in our study was all-cause mortality and severity of COVID-19.

STATISTICAL ANALYSIS

For binary data, the Mantel-Haenszel (MH) risk ratio (RR) random-effects model (DerSimonian and Laird method) was used to summarize data between the 2 groups.[8] For continuous data (e.g., D-dimer), studies that reported as the median and interquartile range, we first used the Wan method to estimate the mean and standard deviations.[9] We then calculated the pooled weighted difference in means (WMD) using a random-effects model to evaluate the association of levels of D-dimer between the 2 groups. Higgins I-squared (I^2) statistic was used to assess the test of heterogeneity. A value of I^2 of 0%–25% represented insignificant heterogeneity, 26%–50% represented low heterogeneity, 51%–75% represented moderate heterogeneity, and more than 75% represented high heterogeneity.[10] A prespecified random-effects metaregression analysis was conducted for the primary outcome in relation to the baseline demographics, comorbid conditions, biomarkers to test the relationship between D-dimer and disease severity, and all-cause mortality. Publication bias was formally assessed using funnel plots and Egger's linear regression test of funnel plot asymmetry. A 2-tailed $P < 0.05$ was considered statistically significant. Statistical analysis was performed using Comprehensive Meta-Analysis version 3.0 (Biostat Solutions, Inc. [BSSI], Frederick, MD).

RESULTS

Search Results

A total of 920 citations were identified during the initial search (Fig. 1). Nine hundred and two records were excluded. After a detailed evaluation of these studies, 12 studies met the inclusion criteria. We also included 6 manuscripts from 2 preprint servers (https://www.medrxiv.org and https://www.ssrn.com/index.cfm/en/coronavirus), to accommodate the rapidly evolving nature of information for COVID. We acknowledge that the manuscripts from these 2 sources are not peer reviewed. Eighteen articles of 3682 patients were included in the final analysis.

Study Characteristics

This systematic review and meta-analysis of 18 studies incorporated a total of 3682 patients. Six articles compared D-dimer levels upon admission in patients who survived versus those who died,[11–16] 1 article compared patients with elevated D-dimer level with those with normal D-dimer levels,[17] and 11 articles compared severe versus nonsevere COVID-19 patients.[18–28] All studies were retrospective[12–27] except 2, which were prospective,[11,28] and all were conducted in China in the year 2020.

Positive D-dimer was defined as a value above the normal reference range. Five studies[11,12,14,19,26] considered levels ≥ 0.5 mg/L as abnormal, 5 studies[13,17,18,23,27] used > 0.5 mg/L as an abnormal value, 3 studies[15,20,28] considered levels > 0.55 mg/L as abnormal, 2 studies[21,24] considered levels > 0.243 mg/L as abnormal, and 3 studies[16,22,25] gave only mean values of D-dimer (which were then used to calculate pooled WMD). The assay used to measure D-dimer was mentioned in only 1 study.[17] Wherever necessary, the unit for D-dimer was converted to mg/L. Severe COVID-19 disease was defined in a patient with a respiratory rate ≥ 30 beats/min (resting state) or a mean oxygen saturation of ≤ 93% on room air or an arterial blood oxygen partial pressure (Pa_{O_2})/oxygen concentration (Fi_{O_2}) ≤ 300 mm Hg and was consistent across all studies. The severe group included patients with severe COVID-19 and/or those needing ICU care for acute respiratory failure requiring mechanical ventilation, or for shock, or multiorgan failure. Survived patients were defined as those who were discharged from the hospital following recovery, were still in-hospital at the end of follow-up period (6 studies),[11–13,15–17] or those patients who survived at least 28 days from admission (1 study).[14]

Table 1 summarizes the baseline characteristics of 6 studies,[11–17] which compared dead versus survived patients, and 1 study which compared patients with elevated D-dimer versus normal D-dimer levels. Among the 6 studies which compared dead versus survived patients, the mean age of the study population in this group was 62.5 ± 14.8 years, and 56.3% were males. Overall, hypertension was the most common comorbidity (36.6%), followed by DM (16.8%) and CAD (11.7%). Shock was observed in 8.9% of patients.

Table 2 summarizes the baseline characteristics of 11 studies[18–28] that compared severe versus nonsevere COVID-19 patients. The mean age of the study population was 49.9 ± 17.2 years, and 54.6% were males. Overall, hypertension was the most common comorbidity (18.8%), followed by DM (9.2%) and CAD (3.9%). Shock was observed in 3.6% of patients, of which 2% of patients had septic shock. Shock was undefined in the other patients.

All-Cause Mortality

The data for D-dimer levels were available in 5 studies.[11,13–16] The pooled mean D-dimer levels were significantly elevated in patients who died versus those who survived (WMD, 6.13 mg/L; 95% CI, 4.16–8.11; $P \leq 0.001$; $I^2 = 81.41\%$) (Fig. 2). No publication bias was observed (Egger's $P = 0.39$, Supplement Figure 1, http://links.lww.com/CIR/A20). A meta-regression analysis demonstrated no significant associations between age, male sex, hypertension, DM, CAD, C-reactive protein, and troponin in COVID-19-infected patients who died versus those who survived (Table 3).

The risk of mortality was fourfold in patients with positive D-dimer versus negative D-dimer (21% vs 4.9%; RR, 4.11; 95% CI, 2.48–6.84; $P \leq 0.001$, respectively). The test for heterogeneity was nonsignificant ($I^2 = 0\%$) (Fig. 3). No publication bias was observed (Egger's $P = 0.26$; Supplement Figure 2, http://links.lww.com/CIR/A20).

Severity of COVID-19

The data for D-dimer levels were available in 9 studies.[19–25,27,28] The pooled mean D-dimer levels were significantly elevated in patients with severe COVID-19 infection (WMD, 0.54 mg/L; 95% CI, 0.28–0.8; $P \leq 0.001$; $I^2 = 90.74\%$) (Fig. 4A). No publication bias was observed (Egger's $P = 0.13$; Supplement Figure 3, http://links.lww.com/CIR/A20). Meta-regression analysis showed a significant association between CAD, C-reactive protein, and severe COVID-19 disease, but the results were not significant for age, male sex, and

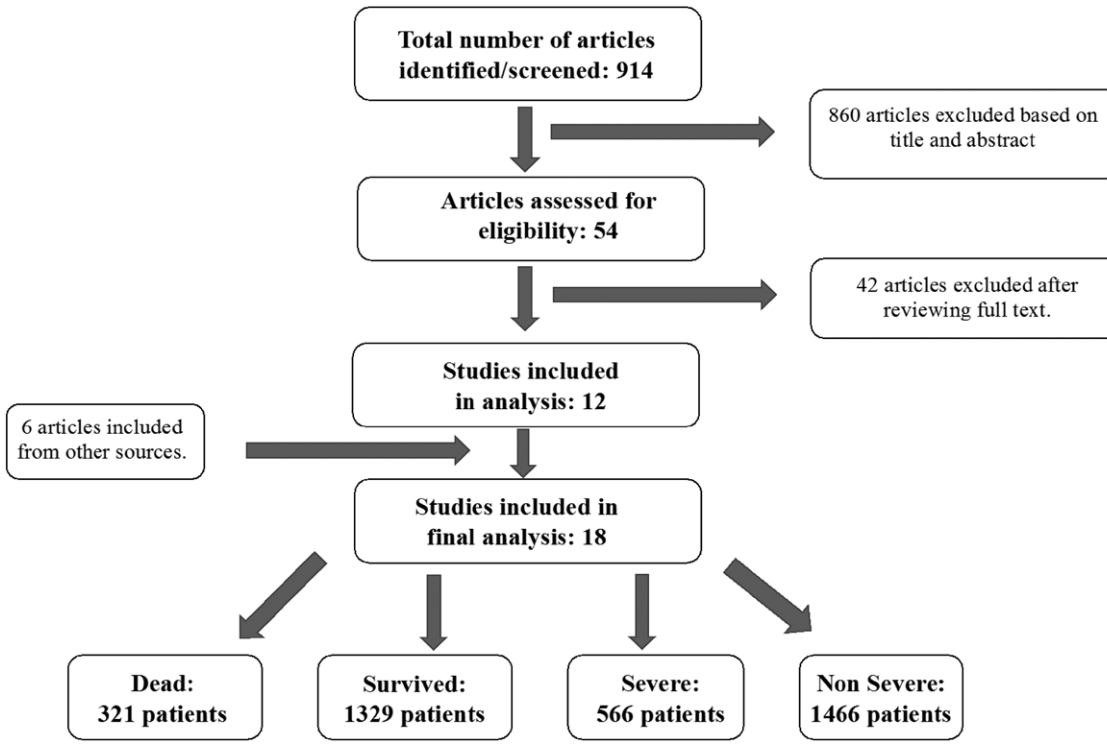

FIGURE 1. Flow diagram illustrating the systematic search of studies

comorbidities (hypertension, DM, troponin levels) (Table 4; Fig. 4B and 4C).

The risk of developing severe disease was twofold higher in patients with a positive D-dimer level versus negative D-dimer level (40.74% vs 21.98%; RR, 2.04; 95% CI, 1.34–3.11; $P \leq 0.001$; $I^2 = 81.83\%$, respectively) (Fig. 5). No publication bias was observed (Egger's $P = 0.16$; Supplement Figure 4, http://links.lww.com/CIR/A20). A sensitivity analysis was performed by removing 1 study at a time (n-1 analysis) to investigate the high heterogeneity. No significant change in the findings was observed with the sensitivity analysis.

DISCUSSION

Elevated D-dimer is one of the abnormal laboratory parameters found in patients with COVID-19 infection. D-dimer is the fibrin degradation product released upon cleavage of cross-linked fibrin by plasmin, often utilized in diagnosing disseminated intravascular coagulation in those with low and intermediate pretest probability for deep vein thrombosis (DVT) and pulmonary embolism (PE).[29] Historically, the role of D-dimer is limited due to its nonspecificity, with elevated levels often seen with advanced age, African American race, female sex, active malignancy, surgery, pregnancy, immobility, cocaine use, connective tissue disorders, end-stage renal disease, and prior thromboembolic disease.[30] More recently, D-dimer has been explored to identify patients thought to develop severe COVID-19 infection earlier in their course of illness. A previous meta-analysis comprising 4 studies demonstrated elevated D-dimer levels in patients with severe COVID-19 infection compared with those with the nonsevere disease.[31] However, this meta-analysis was limited by a relatively small sample size, and it failed to answer the clinically relevant question regarding the prognostic value of D-dimer in predicting severe COVID-19 infection and mortality. Our meta-analysis comprising 18 studies evaluated the prognostic role of D-dimer in COVID-19-infected patients, and is the largest to date, to the best of our knowledge. The key findings of our pooled analysis are: (1) the D-dimer levels were higher in patients with severe COVID-19 infection and those who succumbed to death, compared with nonsevere disease and those who survived, respectively; (2) patients with elevated D-dimer levels were at an increased risk of developing severe COVID-19 infection and increased all-cause mortality compared with those with normal D-dimer levels.

Zhou et al[13] reported that D-dimer levels >1 mg/L on admission in COVID-19-infected patients were independently associated with increased odds of mortality, a finding that echoes with our pooled analysis. Also, patients with advanced age, higher Sequential Organ Failure Assessment score, elevated troponin, and B-type natriuretic peptide have been associated with poor outcomes and mortality in COVID-19 infection.[13,32,33] Furthermore, using a higher cutoff value of D-dimer (levels >2 mg/L) predicted in-hospital mortality even better, as noted by Zhang et al,[17] with a sensitivity of 92.3% and a specificity of 83.3% after adjusting for age, gender, and comorbidities. Besides, studies have shown that rising D-dimer levels during the course of hospitalization were associated with worse long-term outcomes.[12,13]

The prognostic value of D-dimer, as seen in COVID-19 infection, has also been noted in sepsis and other infections (like pneumonia or influenza). Patients with sepsis who had elevated D-dimer levels on admission demonstrated a higher 28-day mortality.[34] Likewise, elevated D-dimer levels may help predict severe community-acquired pneumonia.[35] Elevated D-dimer was also noted in the 2009 novel influenza A (H1N1) infection among critically-ill patients and those who died.[36] Other than infections, elevated D-dimer levels have been associated with adverse clinical outcomes in numerous cardiovascular conditions (like CAD and congestive heart failure).[37,38]

TABLE 1. Baseline Characteristics of Studies Included in the Meta-Analysis Comparing COVID-19-Infected Patients Who Died Versus Patients Who Survived

Study Name	Study Type	Country	Study Period	Age (yr)	Male	Groups	N	Diabetes	Hypertension	Coronary Artery Disease	Shock
Zhang et al[17]	Retrospective	China	January 12–March 15, 2020	62 (IQR 48–69)	169	Overall	343	47 (13.7%)	76 (22.2%)	19 (5.5%)	NR
Wang et al[15]	Retrospective	China	January 1–February 6, 2020	69 (IQR 65–76)	166	Survived	274	43 (15.7%)	106 (38.7%)	NR	5 (1.8%)
						Dead	65	11 (16.9%)	32 (49.2%)	NR	3 (4.6%)
Tang et al[14]	Retrospective	China	January 1–February 13, 2020	65.1 ± 12.0	268	Survived	315	NR	NR	NR	NR
						Dead	134	NR	NR	NR	NR
Zhou et al[13]	Retrospective	China	December 29, 2019–February 1, 2020	56 (IQR 46–67)	119	Survived	137	19 (13.9%)	32 (23.4%)	2 (1.5%)	NR
						Dead	54	17 (31.5%)	26 (48.1%)	13 (24.1%)	38 (70.4%)
Du et al[11]	Prospective	China	December 25, 2019–February 7, 2020	57.6 ± 13.7	97	Survived	158	27 (17.1%)	45 (28.5%)	NR	NR
						Dead	21	6 (28.6%)	13 (61.9%)	NR	NR
Cao et al[12]	Retrospective	China	January 3–Febrauary 1, 2020	54 (IQR 37–67)	53	Survived	85	5 (5.9%)	17 (20%)	NR	3 (3.5%)
						Dead	17	6 (35.2%)	11(64.7%)	NR	7 (41.2%)
Zhang et al[16]	Retrospective	China	December 25, 2019–February 15, 2020	70.58 ± 13.38	33	Survived	31	5 (16.1%)	20 (64.5%)	9 (29%)	NR
						Dead	17	5 (29.4%)	12 (70.6%)	4 (23.5%)	NR

COVID-19 indicates coronavirus disease 2019; N, number; IQR, interquartile range; NR, not reported.

TABLE 2. Baseline Characteristics of Studies Included in the Meta-Analysis Comparing Severe Versus Nonsevere COVID-19-Infected Patients

Study Name	Study Type	Country	Study Period	Age (yr)	Male	Groups	N	Diabetes	Hypertension	Coronary Artery Disease	Shock
Deng et al[20]	Retrospective	China	January 6–February 20, 2020	65 (IQR 49–70.8)	57	Nonsevere	45	5 (11.1%)	12 (26.7%)	4 (8.9%)	NR
						Severe	67	14 (20.9%)	24 (35.8%)	11 (16.4%)	NR
Chen et al[19]	Retrospective	China	December–January 27, 2020	56 (IQR 50–65)	17	Nonsevere	10	1 (10%)	1 (10%)	NR	NR
						Severe	11	2 (18.2%)	4 (36.4%)	NR	1 (9.1%)
Zhang et al[21]	Retrospective	China	January 16–February 3, 2020	57 (range 25–87)	71	Nonsevere	82	9 (11%)	20 (24.4%)	3 (3.7%)	NR
						Severe	58	8 (13.8%)	22 (37.9%)	4 (6.9%)	NR
Qian et al[24]	Retrospective	China	January 20–February 11, 2020	50 (IQR 36.5–57)	37	Nonsevere	82	8 (8.8%)	15 (16.5%)	NR	NR
						Severe	9			NR	NR
Cai et al[27]	Retrospective	China	January 11–February 9, 2020	47 (IQR 33–61)	149	Nonsevere	240	19 (6.4%)	38 (12.8%)	NR	NR
						Severe	58			NR	NR
Ji et al[28]	Prospective	China	January 20–February 16, 2020	43.6 ± 17.1	31	Nonsevere	34	NR	NR	NR	NR
						Severe	15	NR	NR	NR	NR
Lu et al[22]	Retrospective	China	January 20–February 19, 2020	NR	NR	Nonsevere	243	15 (6.2%)	42 (17.3%)	10 (4.1%)	NR
						Severe	22	6 (27.3%)	10 (45.5%)	4 (18.2%)	NR
Ma et al[23]	Retrospective	China	January 21–March 2, 2020	48 (IQR 42.3–62.5)	48	Nonsevere	64	3 (4.7%)	8 (12.5%)	NR	NR
						Severe	20	7 (35%)	4 (20%)	NR	NR
Hu et al[18]	Retrospective	China	January 8–February 20, 2020	61 (range 23–91)	166	Nonsevere	151	14 (9.3%)	39 (25.8%)	NR	4 (2.6%)
						Severe	172	33 (19.2%)	66 (38.4%)	NR	39 (22.7%)
Wan et al[25]	Retrospective	China	January 23–February 8, 2020	47 (IQR 36–55)	72	Nonsevere	95	3 (3.2%)	9 (9.5%)	NR	0 (0%)
						Severe	40	9 (22.5%)	4 (10%)	NR	1 (2.5%)
Guan et al[26]	Retrospective	China	December 11, 2019–January 29, 2020	47 (IQR 35–58)	637	Nonsevere	926	53 (5.7%)	124 (13.4%)	17 (1.8%)	1 (0.10%)
						Severe	173	28 (16.2%)	41 (23.7%)	10 (5.8%)	11 (6.4%)

COVID-19 indicates coronavirus disease 2019; N, number; IQR, interquartile range; NR, not reported.

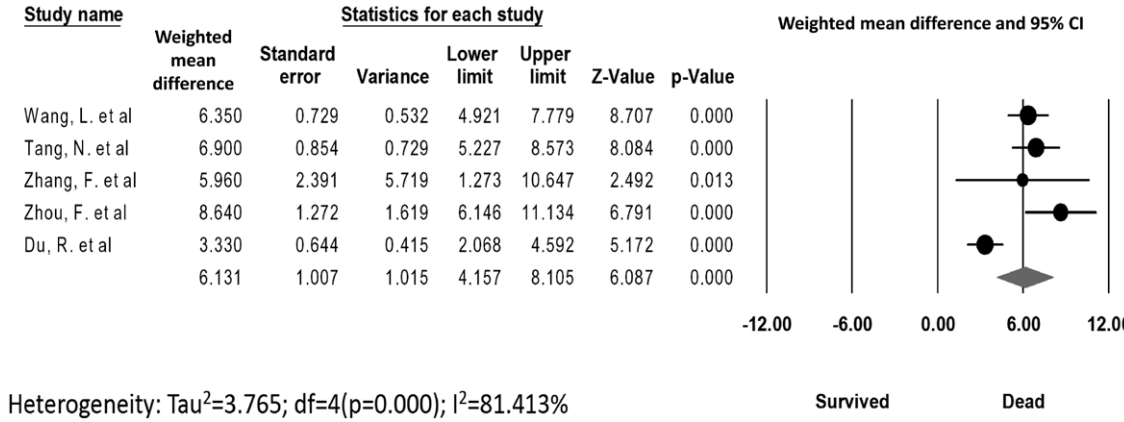

FIGURE 2. D-Dimer levels. The Forest plot for pooled weighted mean difference in D-dimer levels in dead versus survived COVID-19 patients. COVID-19 indicates coronavirus disease 2019.

TABLE 3. Metaregression of Baseline Characteristics with Weighted Mean Difference in D-Dimer Levels in COVID-19 Patients—Dead Versus Survived

Dead versus survived COVID-19	Metaregression						
	Weighted mean difference (95% CI)	Age	Male	Hypertension	Diabetes	CAD	Troponin
D-dimer levels	6.13 (4.16–8.11), $P < 0.001$	$\beta = 0.02$, $P = 0.91$	$\beta = 0.05$, $P = 0.62$	$\beta = -0.002$, $P = 0.98$	$\beta = 0.15$, $P = 0.82$	$\beta = -0.12$, $P = 0.25$	$\beta = 201.41$, $P = 0.53$

COVID-19 indicates coronavirus disease 2019; CI, confidence interval; CAD, coronary artery disease.

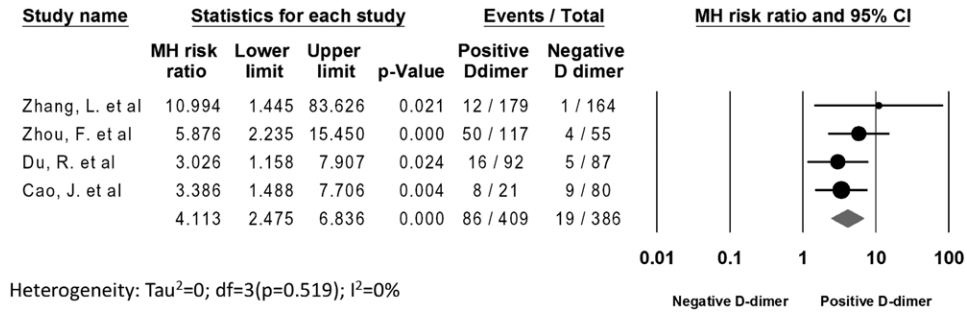

FIGURE 3. All-cause mortality. The Forest plot shows the outcomes of the individual trials as well as the aggregate.

Nonetheless, in our analysis, patients who died as a result of COVID-19 infection were noted to have elevated D-dimer levels even after adjusting for age and comorbidities. However, no single cutoff value (both in COVID and non-COVID illnesses) has been identified to predict adverse outcomes consistently.

There has been evidence regarding an increased incidence of venous thromboembolic events (VTE), including DVT and PE, in patients with severe COVID-19 infection.[39] One study proposed that D-dimer levels > 1.5 mg/L may help detect VTE events with a sensitivity of 85.0% and specificity of 88.5%; however, results should be interpreted with caution due to small sample size and lack of external validation.[40] It remains unclear at this time if this is a direct consequence of SARS-CoV-2 infection or a due to cytokine storm resulting in the systemic inflammatory response syndrome, as seen in other viral infections.[41–44] A similar pattern of changes in coagulation cascade with increased prothrombotic state and incidences of DVT and PE were also noted with the coronavirus responsible for Middle Eastern Respiratory Syndrome (MERS-CoV) and SARS-CoV-1.[45] The risk of VTE is generally high in critically-ill patients, but the risk appears to be higher in patients infected with SARS-CoV-2.

While hypercoagulability could be one of the reasons for elevated D-dimer levels in severe COVID-19 infection, these patients may also have several other reasons for D-dimer elevation, including renal dysfunction, disseminated intravascular coagulation, atrial fibrillation, stroke, acute coronary syndrome, infection, and acute upper gastrointestinal bleed, especially among those admitted to the ICU. Furthermore, D-dimer has low specificity to detect VTE in critically-ill patients.[46] Thus, imaging studies to diagnose

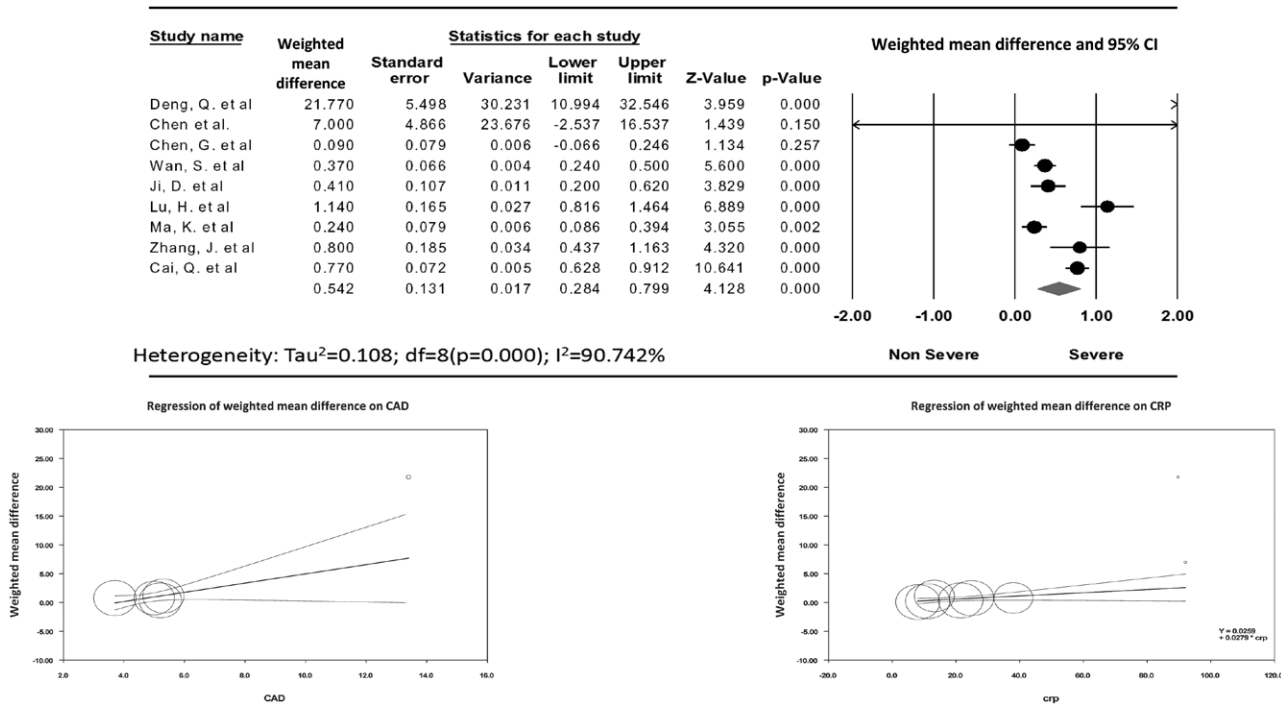

FIGURE 4. Disease severity. A, The Forest plot for pooled weighted mean difference in D-dimer levels in severe versus nonsevere COVID-19 patients, followed by random-effects meta-regression analysis plots depicting the relationship between weighted mean differences in D-dimer levels (on *y*-axis) and (B) CAD and (C) CRP. Each included study is represented by a circle, the size of which is proportional to its respective weight in the analysis. The line indicates the predicted effects (regression line). There was significant association between CAD (β = 0.8, *P* = 0.02), and CRP levels (β = 0.02, *P* = 0.03) and mean differences in D-dimer levels. COVID-19 indicates coronavirus disease 2019; CAD, coronary artery disease; CRP, C-reactive protein.

TABLE 4. Metaregression of Baseline Characteristics with Weighted Mean Difference in D-Dimer Levels in Severe Versus Nonsevere COVID-19-Infected Patients

Severe vs nonsevere COVID-19	Metaregression						
	Weighted mean difference (95% CI)	Age	Male	Hypertension	Diabetes	CAD*	CRP*	Troponin
D-Dimer levels	0.54 (0.28–0.80), $P < 0.001$	β = 0.03, $P = 0.31$	β = 0.008, $P = 0.68$	β = 0.03, $P = 0.2$	β = −0.01, $P = 0.84$	β = 0.8, $P = 0.02$	β = 0.02, $P = 0.03$	β = 105.63, $P = 0.06$

COVID-19 indicates coronavirus disease 2019; CI, confidence interval; CAD, coronary artery disease; CRP, C-reactive protein.
*Indicates statistically significant value.

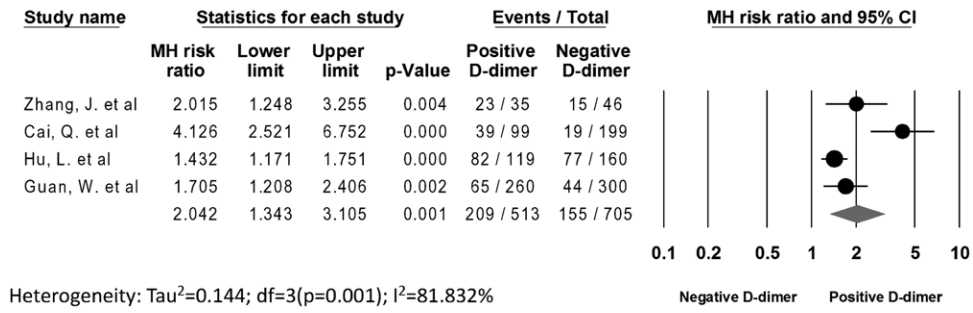

FIGURE 5. The Forest plot demonstrating the risk ratio of positive D-dimer with severity.

DVT or PE should only be pursued if clinically warranted.[40] Perhaps, empirically treating all COVID-19 patients with intermediate or full (therapeutic) doses of anticoagulation to prevent microvascular thrombosis[14,47] might be beneficial (provided a thorough risk-benefit assessment is performed given these patients are also at-risk of spontaneous bleeding). However, our study was not designed to assess this difference.

Our study has a few important limitations. First, all studies included in our meta-analysis were from China, while currently the United States and Europe have the majority of COVID-19 cases. However, the preliminary reports from the United States and Europe have shown similar trends in COVID-19 infection in terms of clinical presentation and outcomes.[5,48] Our pooled analysis provides the best available data regarding trends of D-dimer levels in patients with COVID-19 infection, and the likelihood of developing severe infection or mortality in patients with elevated D-dimer levels. Second, all studies included in our analysis were either prospective or retrospective reports, which is currently the best available evidence, and therefore, subject to potential confounding and publication bias. Third, high heterogeneity was observed between studies in our pooled analysis. Fourth, details on trends of D-dimer over the course of hospitalization were not available. Fifth, the normal reference range of D-dimer varied slightly among studies, and details regarding the assays used to measure D-dimer were not available in most studies. Sixth, trends in D-dimer levels for COVID-19 patients never hospitalized remain unknown. Finally, patient-level data to perform additional detailed analysis were not available.

CONCLUSIONS

Our meta-analysis demonstrates that patients with COVID-19 presenting with elevated D-dimer levels have an increased risk of severe disease and mortality.

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