



Elevated D-dimer levels on admission are associated with severity and increased risk of mortality in COVID-19: A systematic review and meta-analysis

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ABSTRACT

Background: In this systematic review and meta-analysis, we aimed to investigate the correlation of D-dimer levels measured on admission with disease severity and the risk of death in patients with coronavirus disease 2019 (COVID-19) pneumonia.

Materials and methods: We performed a comprehensive literature search from several databases. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in abstracting data and assessing validity. Quality assessment was performed using the Newcastle-Ottawa quality assessment scale (NOS). D-dimer levels were pooled and compared between severe/non-severe and surviving/non-surviving patient groups. Weighted mean difference (WMD), risk ratios (RRs) and 95% confidence intervals (CIs) were analyzed.

Results: Thirty-nine studies reported on D-dimer levels in 5750 non-severe and 2063 severe patients and 16 studies reported on D-dimer levels in 2783 surviving and 697 non-surviving cases. D-dimer levels were significantly higher in patients with severe clinical status (WMD: 0.45 mg/L, 95% CI: 0.34–0.56; $p < 0.0001$). Non-surviving patients had significantly higher D-dimer levels compared to surviving patients (WMD: 5.32 mg/L, 95% CI: 3.90–6.73; $p < 0.0001$). D-dimer levels above the upper limit of normal (ULN) was associated with higher risk of severity (RR: 1.58, 95% CI: 1.25–2.00; $p < 0.0001$) and mortality (RR: 1.82, 95% CI: 1.40–2.37; $p < 0.0001$).

Conclusion: Increased levels of D-dimer levels measured on admission are significantly correlated with the severity of COVID-19 pneumonia and may predict mortality in hospitalized patients.

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1. Introduction

In December 2019, an outbreak of coronavirus disease 2019 (COVID-19) occurred in Wuhan, Hubei Province, China and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been designated as the pathogen. COVID-19 has inflicted millions of people worldwide, but definite prognostic factors and treatment regimens could not be adequately defined [1]. COVID-19 manifests with enteric, hepatic, nephrotic, neurological and cardiac symptoms, causing multiple organ failure and a high risk of death [2]. Arterial and venous thrombotic

complications and coagulopathies including disseminated intravascular coagulopathy (DIC) have become a major cause of morbidity and mortality particularly in patients with comorbid conditions, prolonged hospitalization, intensive care unit (ICU) admission, and mechanical ventilation (MV). Excessive inflammation, platelet activation, endothelial dysfunction, and stasis play a significant role in the development of thrombotic complications. D-dimer is the degradation product of fibrin and reflects the activation of both thrombotic and fibrinolytic pathways. Many descriptive studies have reported elevated D-dimer levels in COVID-19 patients although the prognostic value of D-dimer levels, particularly those measured on admission and the threshold levels for treatment modifications, have not been well described [3–6]. In this systematic review and meta-analysis, we aimed to investigate the

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prognostic value of D-dimer levels measured on admission in COVID-19 patients.

2. Materials and methods

This analysis was planned based on the current MOOSE (Meta-analysis of Observational Studies in Epidemiology) and PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) guidelines in order to perform a comprehensive systematic review and meta-analysis [7,8]. As the study was a meta-analysis, no approval from the institutional review board was required. Severe patients were accepted to have any of the following criteria: [1] respiratory distress (respiratory rate ≥ 30 breaths per min); [2] oxygen saturation at rest $\leq 93\%$; [3] ratio of the partial pressure of arterial oxygen (PaO₂) to the fractional concentration of oxygen inspired air (FiO₂) (Pao₂:FiO₂, ≤ 300 mmHg); or [4] critical complication (respiratory failure and need for mechanical ventilation, septic shock, and/or multiple organ dysfunction/failure and intensive care unit admission requirement) [9].

2.1. Literature search

Two independent investigators (B.G. and A.A.) searched the electronic databases including Medline, Google Scholar, and Scopus between December 12, 2019 and April 25, 2020 using the key words “coronavirus”, “pneumonia”, “nCoV”, “SARS-CoV-2”, “COVID*”, “prognosis”, “death”, “mortality”, “laboratory”, “dimer” and “coagulation” either alone or in combinations. Moreover, medRxiv (<https://www.medrxiv.org>), SSRN (<https://www.ssrn.com>) and the reference lists of all studies were identified. This search was restricted to adults (>18 years of age) and the English language. Reviews and reference lists of retrieved articles were hand searched for potentially relevant publication not previously identified in the database search.

2.2. Article selection

Retrieved studies were reviewed by two investigators (B.G. and H.A.B.) using a standardized data collection form. In case of disagreement, a consensus was reached by a third reviewer (AA). The title, abstract, and the full text of all these studies were analyzed. Among these studies, those reporting on the D-dimer values measured on admission in COVID-19 patients and those comparing non-severe and severe patients and surviving and non-surviving patients were included in the meta-analysis. Exclusion criteria included [1] case reports and case series, [2] unclear grouping of the study population (e.g. comparison according to presence of frailty, obesity, diabetes mellitus or comparison between different regions or countries), [3] laboratory parameters that were not measured during initial evaluation or on admission, and [4] the studies reporting only on the results of surviving, non-surviving, or ICU patients.

2.3. Data extraction

Extracted data included age, sex, sample size, sample characteristics, D-dimer levels, odds ratio (OR) of D-dimer levels for the development of severe disease or mortality as well as the other study characteristics of the included studies. The country of origin, authors, and the enrollment periods of the studies were reviewed to exclude duplicate publications of the same cohort. Mean and standard deviation of D-dimer values were extrapolated from the sample size, median, and interquartile range (IQR) as previously defined [10,11]. In the studies that presented the data using graphs only, GetData Graph Digitizer 2.24 (<http://getdata-graphdigitizer.com/>) software was used to digitize and extract the data.

2.4. Quality assessment

The methodological quality of retrospective studies was assessed by the modified Newcastle–Ottawa scale (NOS) which consists of three domains: [1] subject selection, [2] comparability of the study groups, and [3] the assessment of outcome(s) [12]. A score of 0–9 was allocated to each study except for randomized clinical trials. Observational studies with an NOS score ≥ 6 were accepted as high-quality.

2.5. Statistical analysis

A meta-analysis was performed based on the calculation of weighted mean difference (WMD) and 95% confidence interval (95% CI) of D-dimer values in COVID-19 patients with or without severe disease and surviving and non-surviving patients. To determine heterogeneity across the studies, an a priori decision was made to select the random-effects model that could allow more conservative estimates in scenarios with heterogeneity. To investigate categorical variables, risk ratios (RRs) and 95% CIs were calculated from the number of cases in each group and the total sample size. In the studies reporting the outcomes using OR, the ORs were pooled using a random-effects model by the method of DerSimonian and Laird [13]. The Cochran's Q and Higgins's I² statistics were used to estimate heterogeneity. Publication bias was estimated using funnel plots and Begg's rank correlation test and Egger's linear regression test [14,15]. In order to define any source of heterogeneity, sensitivity analysis was performed by excluding each study and rerunning the meta-analysis. RevMan 5.3 (The Cochrane Collaboration) and MetaXL, software Version 5.3 (EpiGear International PtyLtd., Sunrise Beach, Australia) were used for performing this analysis.

3. Results

3.1. Characteristics of included studies

The study selection process was illustrated in Fig. 1. Of the initial 1625 records, 1281 remained after the removal of duplicates. After screening the titles and abstracts, 123 studies remained for full-text assessment while 69 were subsequently excluded (Fig. 1). Fifty-four studies met the meta-analysis inclusion criteria, all of which were retrospective observational studies. The demographic and baseline parameters and the NOS scores in the included studies were shown in Supplementary Table S1. Thirty-nine studies compared the D-dimer levels between a total of 5759 severe and 2063 non-severe patients [16–54]. Sixteen studies compared the D-dimer levels between a total of 2783 surviving and 697 non-surviving patients [39,55–69]. All the studies except for one were performed outside China [64]. Fourteen studies reported the number of cases with a D-dimer level above the upper limit of normal (ULN) in each group and analyzed the D-dimer levels as categorical variables [16,20,23–25,33,35,39,44,46,50,51,60,67]. Thirteen studies reported on predictors of severity and eight other studies reported on predictors of mortality using logistic regression analysis; however, only four studies analyzed D-dimer levels using a multivariate regression model. The time from the onset of symptoms to hospital admission was longer in more severe and non-surviving patients.

3.2. Quantitative data synthesis

The meta-analysis of 34 studies showed significantly higher D-dimer levels on admission in patients with a severe clinical condition (WMD: 0.45 mg/L, 95% CI: 0.34–0.56; $p < 0.0001$) (Fig. 2). This effect size was robust in sensitivity analysis and the omission of a single study did not significantly change the overall estimated effect size. When the analysis was repeated using the fixed-effects model, significant results were obtained (WMD: 0.20 mg/L, 95% CI: 0.17–0.23; $p < 0.0001$). When the D-dimer levels were analyzed as binary variables using data from 12 studies and 828 severe and 1757 non-severe patients, the presence of

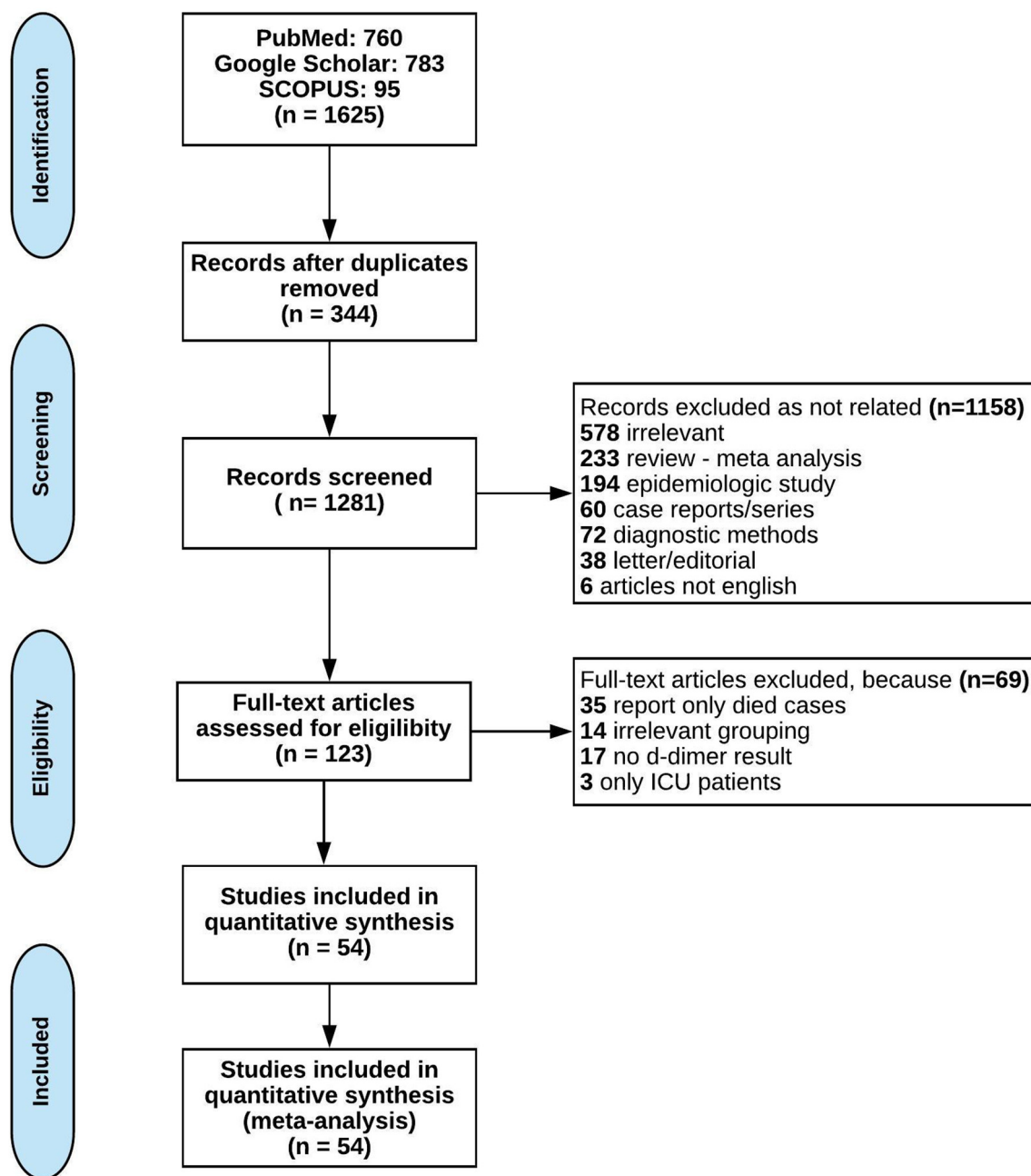


Fig. 1. Pooled ORs of the univariate regression analysis of severity for d-dimer as a continuous variable.

D-dimer levels above ULN was significantly associated with disease severity (RR: 1.58, 95% CI: 1.25–2.00; $p < 0.0001$) (Fig. 3).

The meta-analysis of 16 studies showed significantly higher levels of D-dimer on admission in non-surviving patients compared to surviving patients (WMD: 5.32 mg/L, 95% CI: 3.90–6.73; $p < 0.0001$) (Fig. 4). When the analysis was repeated using the fixed-effects model, significant results were obtained (WMD: 1.87 mg/L, 95% CI: 1.54–2.21; $p < 0.0001$). When the D-dimer levels were analyzed as binary variables using data from 3 studies and 358 surviving and 259 non-surviving patients, the presence of D-dimer levels above ULN was significantly associated with mortality (RR: 1.82, 95% CI: 1.40–2.37; $p < 0.0001$) (Fig. 5).

In our study, the D-dimer levels were used as continuous variables in logistic regression analysis for the prediction of clinical outcomes in remarkably few studies. We pooled ORs from univariate and multivariate regression analyses for the prediction of clinical outcomes using admission D-dimer levels as continuous variables; however, the pooled ORs

for each comparison did not reach statistical significance (Supplementary Figs. S1–S3).

3.3. Meta-regression

We performed a meta-regression analysis to investigate the effect of the time from the onset of symptoms to hospital admission on D-dimer levels due to the fact that the patients in severe and non-surviving groups were admitted to hospital at a later period when compared to non-severe and surviving groups (Supplementary Table S1). The ratio of the mean duration of this time period in severe/non-severe and surviving/non-surviving groups was accepted as the covariate for the meta-regression analysis.

Eighteen studies compared the time from the onset of symptoms to hospital admission between severe and non-severe patients. In the meta-regression analysis, we did not find a significant correlation

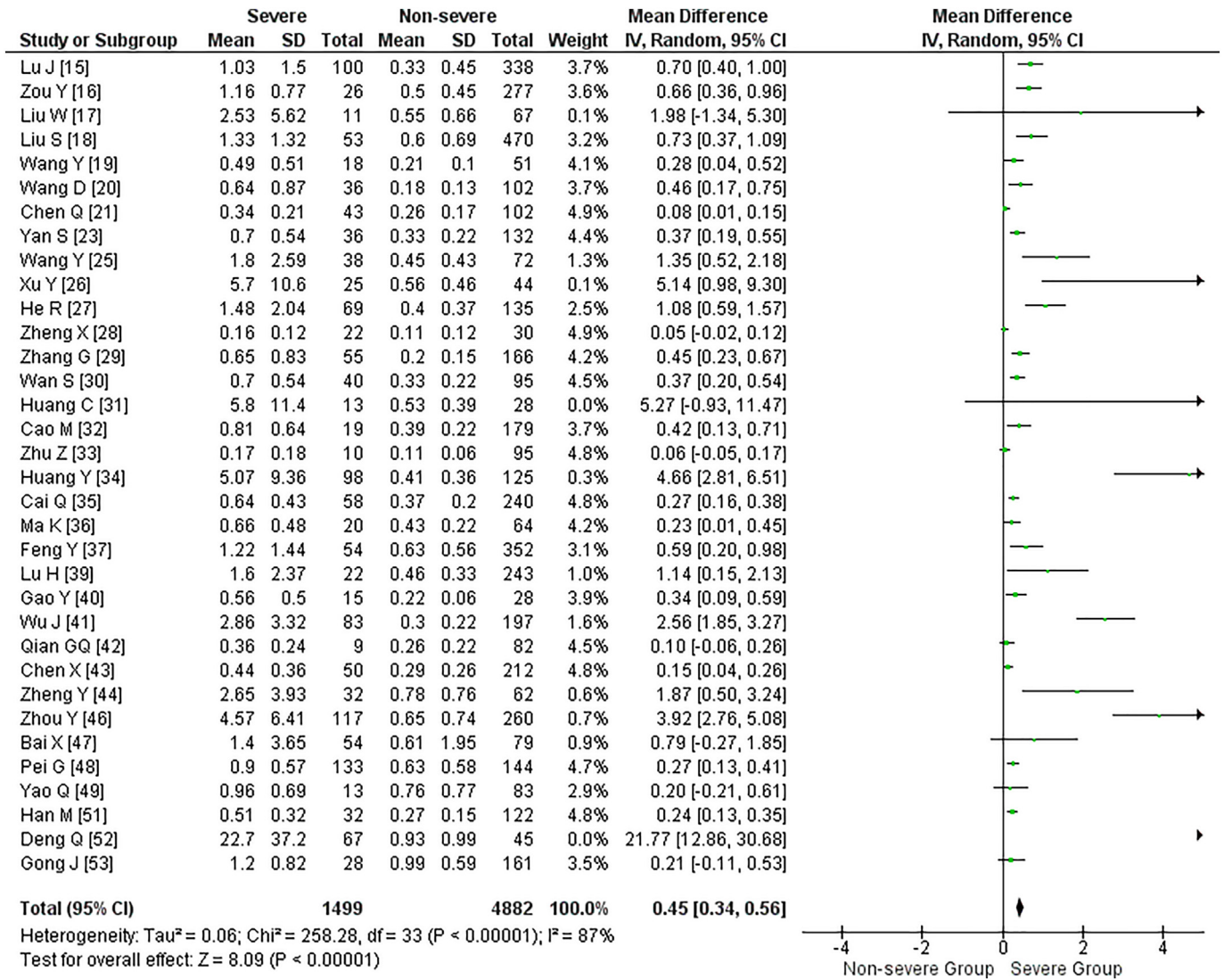


Fig. 2. Pooled ORs of the univariate regression analysis of mortality for d-dimer as a continuous variable.

between symptom duration and D-dimer difference ($\beta = 0.248$, $p = 0.075$) (Supplementary Fig. S4). The same analysis was performed for six studies that reported time intervals in surviving and

non-surviving patients. The admission time was found to have a significant effect on the D-dimer levels assessed on admission ($\beta = 27.646$, $p < 0.01$) (Supplementary Fig. S5).

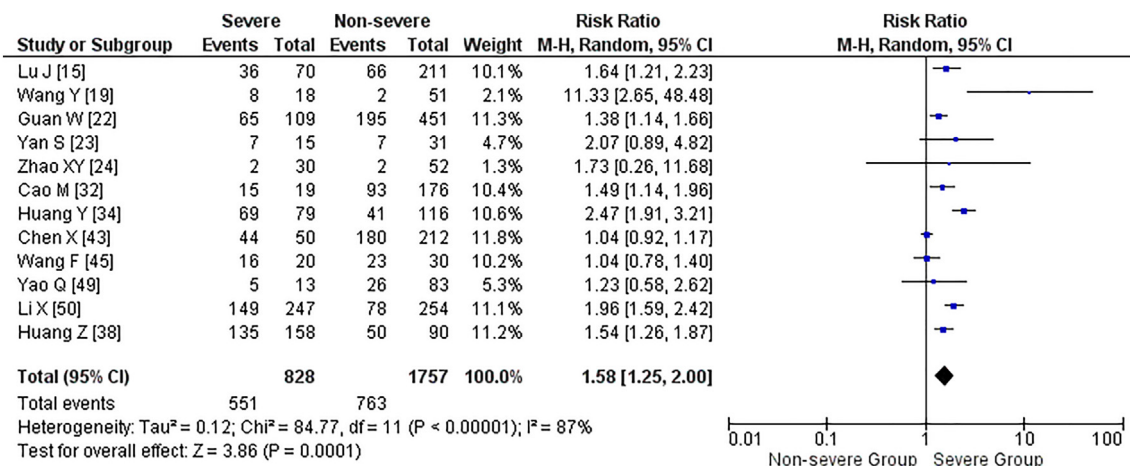


Fig. 3. Pooled ORs of the multivariate regression analysis of mortality for d-dimer as a continuous variable.

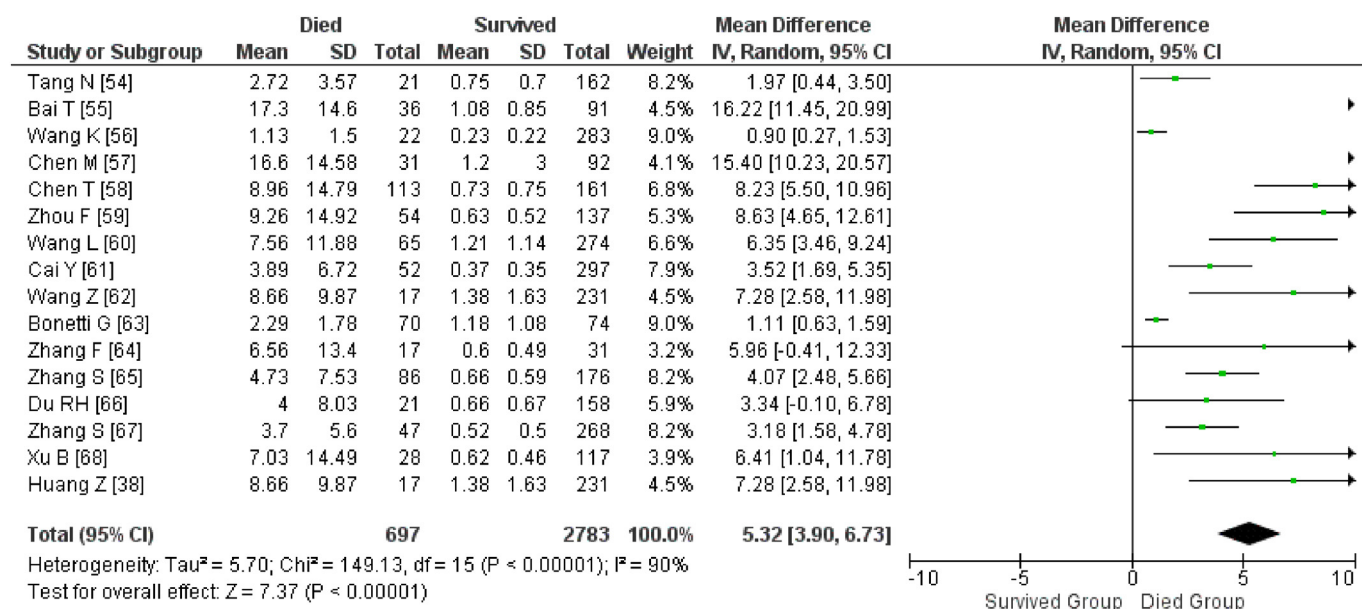


Fig. 4. Meta-regression analysis of pooled SMD of admission CRP levels in severe and non-severe patients including ratio of time from symptom onset to hospital admission in severe and non-severe patients as the covariate of the model.

3.4. Publication bias

The funnel-plot analysis showed a symmetrical shape for all outcomes, indicating a low risk of publication bias in severe and non-severe patients with no indication of small-study effects (Egger's test, $p = 0.987$; Begg's test, $p = 0.953$) (Supplementary Fig. S6). However, the funnel-plot analysis showed an asymmetrical shape for the studies included, i.e. in the comparison of surviving and non-surviving patients with an indication of small-study effects (Egger's test, $p = 0.008$; Begg's test, $p = 0.019$) (Supplementary Fig. S6).

4. Discussion

The present meta-analysis evaluated the clinical data of 11,054 COVID-19 patients and indicated that patients with more severe presenting symptoms and patients with a higher risk of mortality have higher levels of D-dimer levels on admission. The clinical progress of COVID-19 may vary from asymptomatic disease to rapid progression to death due to acute respiratory distress syndrome (ARDS) and thromboembolic and hemorrhagic complications. The findings of this meta-analysis provide robust evidence that D-dimer levels may be used for risk stratification of patients with COVID-19. In emergency settings, risk stratification is as important as diagnosis especially if testing all patients with suspected COVID-19 is not possible. Reverse transcription polymerase chain reaction assays usually yield results within 24 h which is relatively long for triage of suspected COVID-19 patients. However, d-dimer testing is widely available and results can be obtained

within 1 h. D-dimer testing may be reserved for all patients with suspected COVID-19 in emergency departments.

Coronavirus disease 2019 (COVID-19) is a viral respiratory disease caused by SARS-CoV-2 and ARDS has been shown in 20–41%, acute cardiac damage in 7.2%, shock in 8.7% of COVID-19 patients [70–72]. Cardiovascular manifestations include nonspecific electrocardiographic changes and elevated levels of cardiac biomarkers such as troponin and systolic dysfunction on echocardiography. Patients with severe COVID-19 infection usually start with respiratory failure then rapidly proceed to systemic complications and multiple organ failure. Therefore, prompt risk stratification is needed in such patients to initiate more aggressive treatment regimens.

In severe COVID-19, a number of conditions including sepsis, complement activation, cytokine storm, endothelial damage, and inflammatory and microthrombotic pathway activation predispose patients to thrombosis and coagulopathy. D-dimer is a well-known and widely used laboratory parameter for evaluating thrombotic events. The prognostic value of D-dimer levels have been shown in different clinical conditions including acute PE [73,74]. The frequency of D-dimer elevation has been reported to be 36–43% in COVID-19 patients [75]. Lippi et al. pooled the analysis of four studies and reported that the D-dimer levels were considerably higher in severe COVID-19 patients (WMD: 2.97 mg/L; 95% CI: 2.47–3.46 mg/L; $p < 0.001$) [76]. In our study, this finding was confirmed in a much larger population (WMD: 0.45 mg/L, 95% CI: 0.34–0.56; $p < 0.0001$) and patients with elevated D-dimer levels had 1.58 times higher risk for progression to more severe clinical status. In addition, it was also found that the D-dimer levels were higher

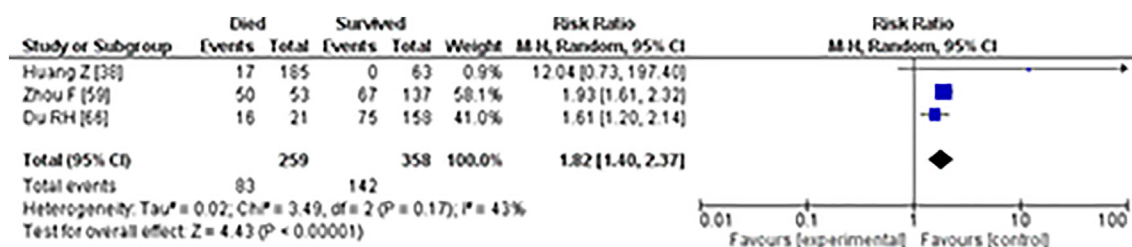


Fig. 5. Meta-regression analysis of pooled SMD of admission CRP levels in died and survived patients including ratio of time from symptom onset to hospital admission in died and survived patients as the covariate of the model.

in non-surviving patients compared to surviving patients (WMD: 5.32 mg/L, 95% CI: 3.90–6.73; $p < 0.0001$) and also patients with elevated D-dimer levels had 1.82 fold higher risk for mortality compared to other patients. However, when we pooled the ORs from the regression analyses of clinical outcomes, we found that most of the studies did not perform a regression analysis. Only three studies reported on ORs of multivariate analysis for prediction of mortality by using D-dimer levels as continuous variables. Nevertheless, the pooled ORs did not reach statistical significance in the analysis. Accordingly, we cannot report on the prognostic value of D-dimer levels in the prediction of severity or mortality adjusted to other properties of study populations. In addition, the frequency of patients with hypoxemia and/or mechanical ventilation have not been reported comparing between normal and elevated dimer patient groups in the included studies. Thus, this data could not be extracted from the articles.

The progress of COVID-19 is remarkably fast in severe and fatal patients. Zhou et al. reported that the median time from the onset of symptoms to hospital admission was 11 days and the mean time from the onset of symptoms to death was 18.5 days in non-surviving patients. Previous studies have reported on a progressive elevation of D-dimer levels during hospitalization in non-surviving patients compared to surviving patients [55,60]. In the meta-regression analysis, we found that the time from the onset of symptoms to hospital admission had a significant effect on pooled D-dimer levels in non-surviving patients compared to surviving patients. These findings implicate that D-dimer levels assessed on admission may be a strong risk indicator in COVID-19 patients and may indicate early initiation of therapeutic anticoagulation particularly in patients with severe clinical symptoms.

Although therapeutic anticoagulation seems to have clinical benefits in COVID-19 patients, routine anticoagulation is not recommended by international societies since there have been no randomized control trials to date [70,72,77]. Recently, Paranjpe et al. compared in-hospital mortality between 1987 patients without any anticoagulation and 786 patients with treatment-dose anticoagulation and found no significant difference between the two groups with regard to in-hospital mortality (22.8% and 22.5%, respectively). The authors also noted that only 1.9% of the anticoagulated patients developed bleeding events after the initiation of anticoagulation therapy, although there was no significant difference between the two groups with regard to the incidence of bleeding events [78]. In that study, however, the incidence of DIC, D-dimer levels, and the indications for anticoagulant therapy were not reported.

5. Conclusion

The prognosis of COVID-19 is poor in some group of patients. Unfortunately, an effective, globally accepted treatment algorithm for the treatment of COVID-19 has not yet been established. Additionally, the importance of anticoagulant therapy is increasing, as thrombotic events play a major role in mortality. This meta-analysis showed that elevated D-dimer levels are strongly associated with disease severity and increased mortality. Future studies are warranted to investigate whether anticoagulation treatment strategies reduce morbidity and mortality in COVID-19. Future studies are warranted to investigate the clinical benefit of d-dimer directed anticoagulant treatment regimens in COVID-19.

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Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ajem.2020.09.018>.

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