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REVIEW ARTICLE

# Elevated D-dimer is associated with severity of COVID-19: A systematic review and meta-analysis

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ABSTRACT

With the rapid increase of COVID-19 cases, identifying case severity has become a critical issue for hospital admission and intensive care treatment. Given that pre-existing comorbidities play a significant role in the severity, emerging evidence indicates coagulopathy becomes an independent condition that causes respiratory distress in COVID-19.

In this metanalysis, relevant literatures reporting D-dimer, a coagulation byproduct, in COVID-19 cases were synthesized and statistically analyzed to test if the D-dimer level can predict case severity and mortality.

The analysis found that D-dimer levels were higher in non-survivors/severe than in survivors/non-severe, (MD 0.64, 95% CI 0.52 to 0.75; participants = 5957, $I^2$ = 98%). Subgroup analysis showed MD between non-survivors and survivors was MD 3.48 µg/mL (95% CI 2.69 to 4.27; participants = 1799; studies = 7; $I^2$ = 86%) with Z-score 8.64, p<0.0001. In meta-regression, a significant correlation was observed between increased plasma mean D-dimer level with increased proportion case severity ($P$=0.046) and mortality ($P$=0.009).

Overall, the study found that the D-dimer level index can be a predictor of risk for case severity and mortality in COVID-19 patients. The test is rapid and inexpensive and can help clinicians prioritize medical care other than deciding therapeutic options for clinical goals.

**Keywords:** COVID-19; SARS-CoV-2; D-dimer; Coagulopathy; Risk; Management; Systematic Review; Meta-Analysis.

## 1. Introduction

Covid-19 is a respiratory disease. Caused by the virus SARS-CoV-2, the disease has triggered colossal suffering in the health of the global community. Rapid transmissibility, lack of effective treatment, and lesser-known pathogenicity have made this outbreak the deadliest in recent history. Early January 2020, high-throughput genome sequence analysis revealed that a new coronavirus came into existence in Wuhan, China. On March 11, 2020, the outbreak was designated a pandemic by the World Health Organization (WHO).

The pathogenicity of the disease has been elucidated at a rapid pace. The key structural components responsible for the pathogenicity of coronavirus strains include the membrane, envelope, nucleocapsid, and spike proteins [1]. Although SARS-CoV-2 and other coronaviruses, SARS-CoV and Middle East respiratory syndrome CoV (MERS-CoV) are highly similar genetically and at the protein production level, there are significant differences between them [2].

Targeting the same respiratory tract, with many common symptoms such as fever, fatigue, dry cough, anorexia, myalgia, dyspnea, SARS-CoV-2 shares genetic identity with SARS-CoV and MERS-CoV 79% and 50%, respectively [3]. Given the relationship between the SARS-CoV-2 and the SARS-CoV or MERS-CoV, further research will explain what part of the genome structure makes the SARS-CoV-2 so deadly in humans.

As of June 15, 2020, there have been more than 8 million confirmed cases and 439,051 deaths worldwide, with a case fatality rate of over 5.4% so far. Though a significant population (40%) among confirmed cases remain asymptomatic and do not seek any medical care, a greater population develop symptoms [4]. The clinical features manifested in the majority of confirmed cases primarily include lower respiratory tract illness with fever, dry cough, fatigue, and shortness of breath. Given that preexistence comorbidities such as hypertension, diabetes, and cardiac diseases may play a great role in the severity of the disease, it has been hypothesized that SARS-CoV-2 induced intravascular lung thrombosis and its progression and evolution could induce the fast worsening of the clinical condition of the patients, which may eventually result in death [5]. More importantly, recent studies indicated that death due to the severe SARS-Cov-2 was often associated with the presence of coagulopathy and disseminated intravascular coagulation (DIC), wherein excess mortality has been to be associated with a high level of D-dimer (>1 µg/mL) [6].

D-dimer is a byproduct of blood coagulation and breakdown processes and shows activation of both thrombotic and fibrinolytic pathways. Once blood is coagulated, plasma enzyme plasmin slowly cleaves fibrin to break down clots and releases D-dimer into the blood. The D-dimer level can be evaluated using various commercially available kits. The testing based on monoclonal antibodies is rapid, inexpensive, easily accessible, and reproducible. An increased level of plasma D-dimer indicates the presence of significant blood clot formation and its degrading in the human body [7]. The higher the D-dimer level, the greater the possibility of deep vein thrombosis (DVT) or pulmonary embolism (PE) [8], the conditions manifested in many COVID-19 patients in an included study [9] and beyond.

Several studies have reported increased D-dimer values in COVID-19 patients, although the prognostic value of D-dimer levels, particularly in patients who require urgent medical care or treatment modifications, is not well described [10-12]. Thus, this meta-analysis was performed to investigate if the measurement of the D-dimer level is associated with the prognosis of patients with COVID-19 and to predict case severity and mortality of the disease.

Here, we presented evidence that the plasma D-dimer level could be closely linked to the severity and mortality of COVID-19 infection.

## 2. Methods

### 2.1. Search criteria

A comprehensive literature search was conducted in PubMed, ScienceDirect, and Google Scholar. Keyword "D-dimer" was used with "novel coronavirus", "COVID-19", "2019-nCoV", "SARS-CoV-2," "coronavirus", "pneumonia", "nCoV", "SARS-CoV-2", "COVID", "prognosis", "death", "mortality", "laboratory", "dimer" and "coagulation" either alone or in combinations,

dated up to May 31, 2020. This search was restricted to the articles published in English language and participants in the original studies were adult only (age >18 years).

### 2.2. Article selection

After pulling all literature in Endnote X6 software, first, the duplicates were removed. Then, reviewing the title and abstract, the literature was shortlisted. Next, the full text of all these studies was analyzed. Original cohort studies reporting D-dimer levels

separately in COVID-19 patients in two cohorts, 1) severe vs. non-severe and 2) survivors vs. non-survivors, were finally included in the meta-analysis. Case reports, comments, letters to the editors, and reviews were excluded.

### 2.3. Data extraction

The selected articles were extracted for the following data: first author, second author, year of publication, number of participants, gender, age, D-dimer levels, and outcomes of studies (severe, non-severe, survival, death). 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, were also collected.

### 2.4. Statistical analysis

In the analysis, a random-effect model was applied to allow for heterogeneity in individual studies. Pooled results of proportion at their respective 95% confidence intervals (CI) presented in the analysis were calculated using the DerSimonian–Laird method. The Inverse-Variance method was used for the comparison of mean difference (MD) with a 95% confidence interval (CI), and the Random Effects model was used for calculation. Heterogenicity was evaluated with Q-test and *I2* statistics. Data that was not expressed as mean and standard deviation was extrapolated from the sample size, median, and interquartile range (IQR) using Hozo's calculation method[13]. The meta-analysis was performed using RevMan version 5.4. A meta-regression was performed on Open-Open Meta Analyst (CEBM, University of Oxford, Oxford, UK).

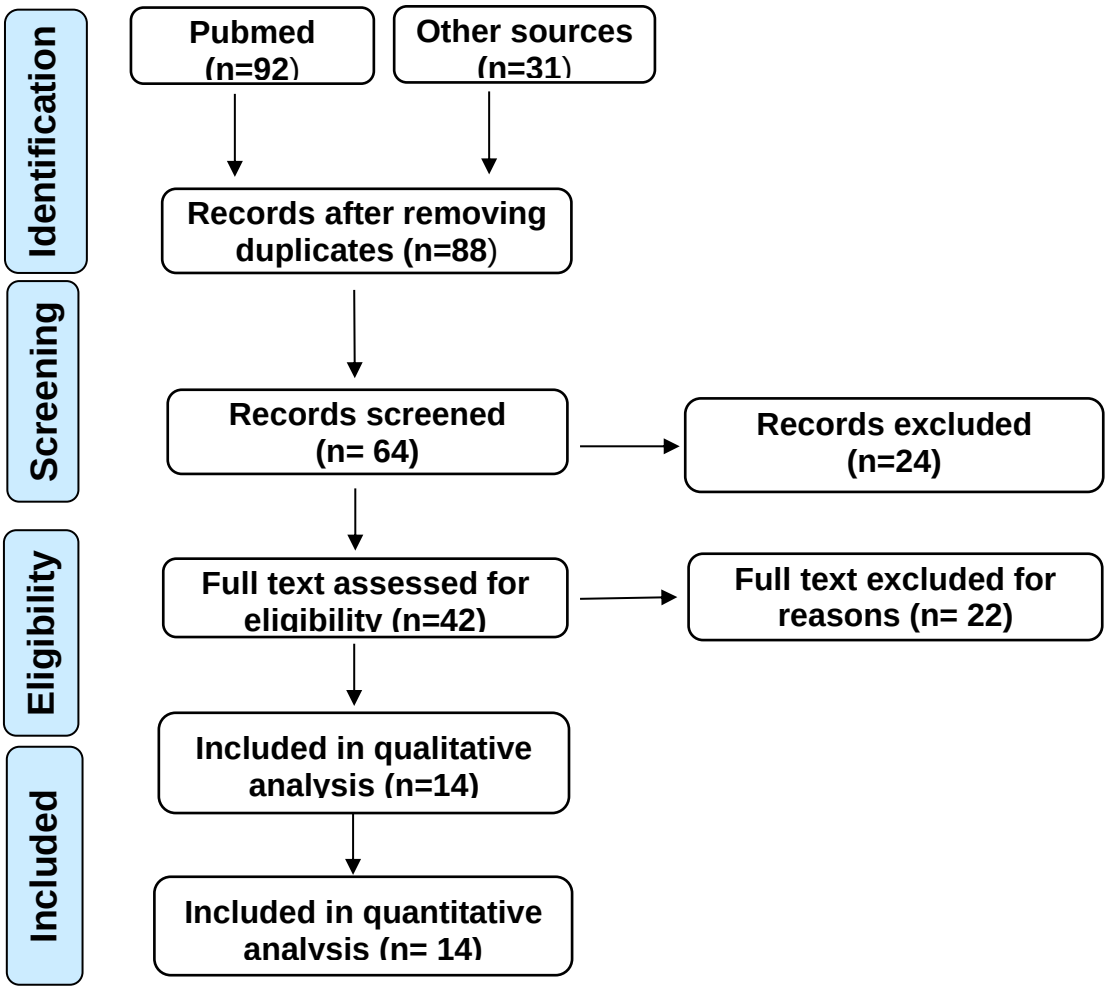


**Figure 1.** PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flow chart of the included studies

**Table 1. Characteristics of the studies included in the meta-analysis**

| Studies | Number of patients (#n) | Sex (male %) | Age (years) | Outcomes, #n (diseased - severe/survivors - non-severe) | Non-survivors - Severe (%) | Country |
|---|---|---|---|---|---|---|
| **Wang, He et al. 2020** [14] | 339 | 49 | 69 (65-76) | Dead/Survival, 65/274 | 19.2 | China |
| **Tang, Li et al. 2020** [15] | 183 | 53.6 | 54.1 ± 16.2 | Non-survivors/survivors, 21/162 | 11.5 | China |
| **Chen, Wu et al. 2020** [16] | 274 | 62 | 62 (44.0-70.0 | Death/Recovered, 113/161 | 41.2 | China |
| **Wang, Lu et al. 2020** [17] | 344 | 52 | 64 (52-72) | Non-survivor/Survivor, 133/211 | 38.7 | China |
| **Tang, Bai et al. 2020** [9] | 449 | 59.7 | 65.1 ± 12.0 | Non-survivor/Survivors, 134/315 | 29.8 | China |
| **Zhang, Liu et al. 2020** [18] | 19 | 57.9 | 73 (38–91) | Non-survivors/Survivor 8/11 | 42.1 | China |
| **Zhou, Yu et al. 2020** [19] | 191 | 62 | 56 (46-–67) | Non-survivors/Survivors, 54/137 | 28.3 | China |
| **Chen, Zheng et al. 2020** [20] | 145 | 54.9 | 45.3 (±13.6) | Severe/Non-severe, 43/102 | 29.7 | China |
| **Fu, Kong et al. 2020** [21] | 75 | 60 | 46.6 ± 14 | Severe/Mild, 16/59 | 21.3 | China |
| **Wan, Xiang et al. 2020** [22] | 135 | 53.3 | 47 (36-55) | Severe/Mild, 40/95 | 36.3 | China |
| **Zhang, Dong et al. 2020** [23] | 140 | 50.7 | 57 (25-87) | Severe/Non-severe, 58/82 | 19.5 | China |
| **Zhang, Hu et al. 2020** [24] | 221 | 48.9 | 55.0 (39.0–66.5) | Severe/Non-severe, 55/166 | 41.4 | China |
| **Zhu, Cai et al. 2020** [25] | 127 | 35.43 | 50.90± 15.26 | Severe/Non-severe, 16/111 | 24.9 | China |
| **Petrilli, Jones et al. 2020** [26] | 2729 | 61.3 | 63 (51-74) | Critical/Non-critical, 1739/990 | 12.6 | USA |

## 3. Results

### 3.1 Data search

The search retrieved 123 articles, of which 35 were duplicates. After reviewing the title and abstract, 42 articles were assessed for full-text review. Finally, 14 articles were found to be consistent with full inclusion criteria and were included in the qualitative synthesis and meta-analysis (Figure 1). The main characteristics of the included studies are summarized in Table 1. All studies were retrospective, thirteen studies were conducted in China, and one study was originated in the USA. The median age of the participants ranged from 45.3 to 73 years, with a male proportion of 57.8%.

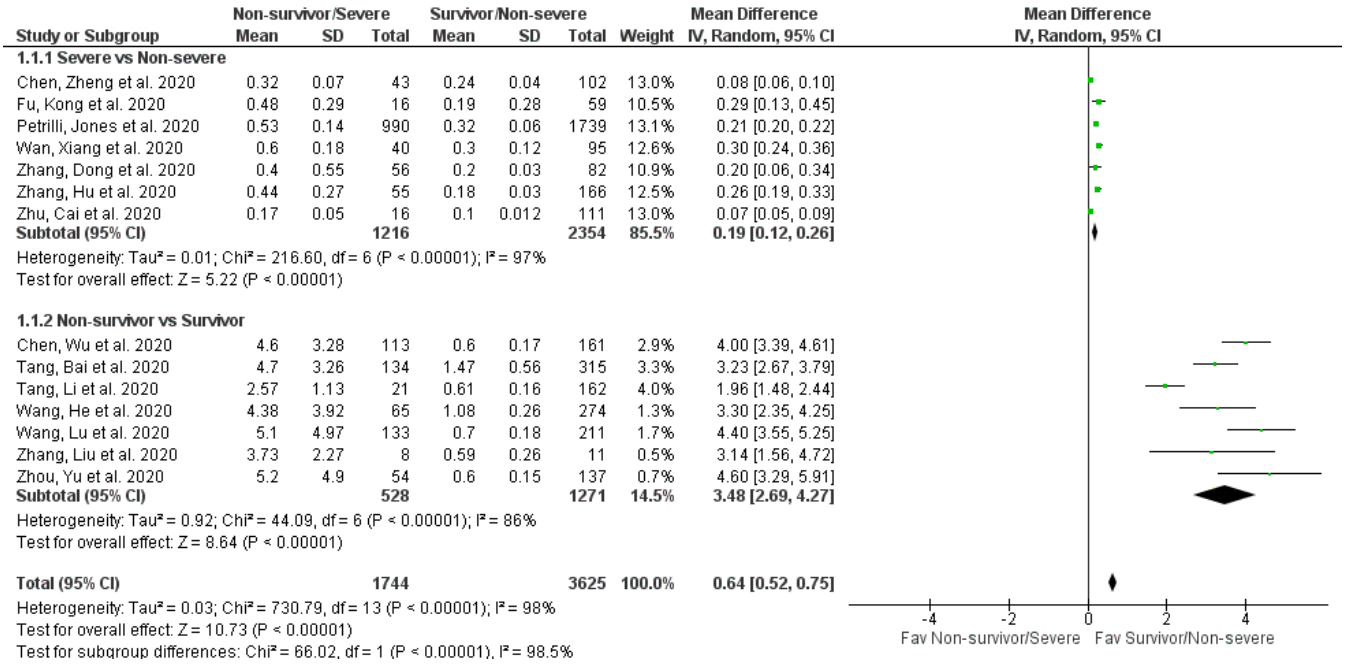


**Figure 2.** A forest plot comparing mean difference of plasma D-dimer level between non-survivor/severe vs. survivors/non-severe COVID-19 patients in the fourteen included studies. CI, confidence interval

### 3.2. Characteristics and quality of studies

A total of 5371 participants were enrolled in the studies. However, D-dimer data was available for 5369 patients. Among the studies, as many as seven studies involving 3570 participants reported D-dimer levels in the severe vs. non-severe COVID-19 cohort. An equal number of studies with 1799 participants assessed the level of D-dimer in the survivor vs. non-survivor cohort. The prevalence of non-survivor/severe cases was 28.4 % (95% CI: 22.9-33.9%, *P* <0.001), wherein non-survivor cases accounted for 10.8% (95% CI: 8.6% 13.1%, *P* < 0.001), across the studies.

### 3.3. Quantitative data synthesis

The meta-analysis of 14 studies showed the mean plasma D-dimer level in diseased/severe group was 1.77 µg/mL, which is significantly higher than the non-severe/survivors' groups 0.53 µg/mL and the difference is significant (MD 0.64, 95% CI 0.52 to 0.75; participants = 5369; studies = 14; $I^2$ = 98%).

In subgroup analysis, plasma D-dimer level in severe vs non-severe cohort, mean plasma D-dimer level in severe cases was 0.51 µg/mL, which is significantly higher (MD 0.19, 95% CI 0.12 to 0.26; participants = 3570; studies = 7; $I^2$ = 97%) than the non-severe (0.29 µg/mL) patients. In survivors vs. non-survivor cohort, the mean plasma D-dimer level in diseased group was 4.69 µg/mL (2.12 to 21.1 µg/mL) which is 4.99-fold higher than survivors 0.94 µg/mL (0.3 to 4.16 µg/mL) and the difference is statistically significant (MD 3.48, 95% CI 2.69 to 4.27; participants = 1799; studies = 7; $I^2$ = 86%).

We performed a meta-regression analysis to explore the relationship between individual D-dimer values and the increased likelihood of case severity or mortality. The meta-regression demonstrated increased mean D-dimer is closely related with an increased likelihood of severity (Q: 0.378 CI: 0.007 0.749, *P*= 0.046), Figure 3, and mortality (Q: 0.082, CI: 0.020 to 0.144, *P*= 0.009), Figure 4.

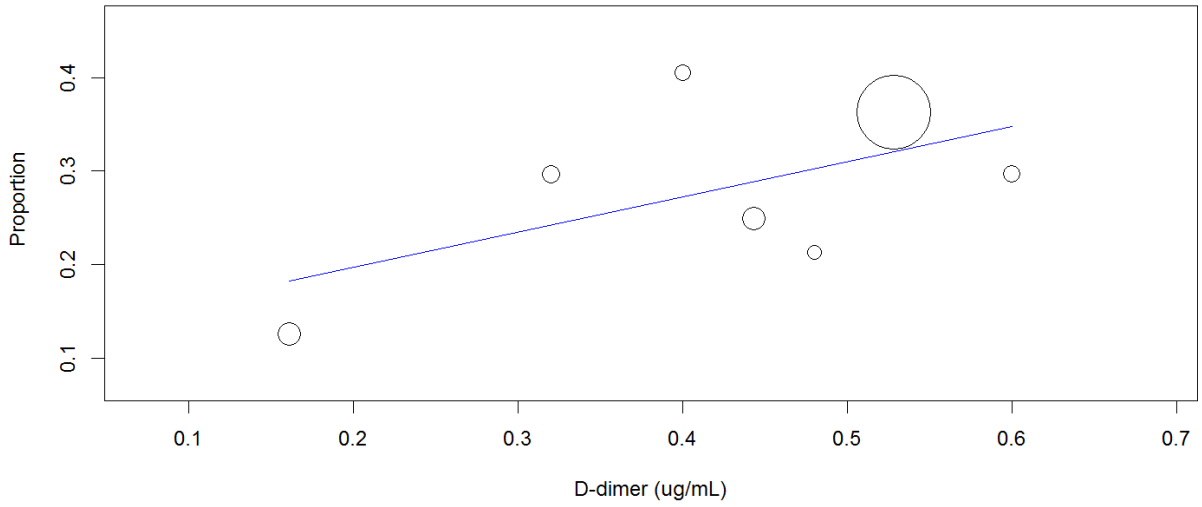


Figure 3. A scatter plot demonstrating the association of plasma D-dimer and severity

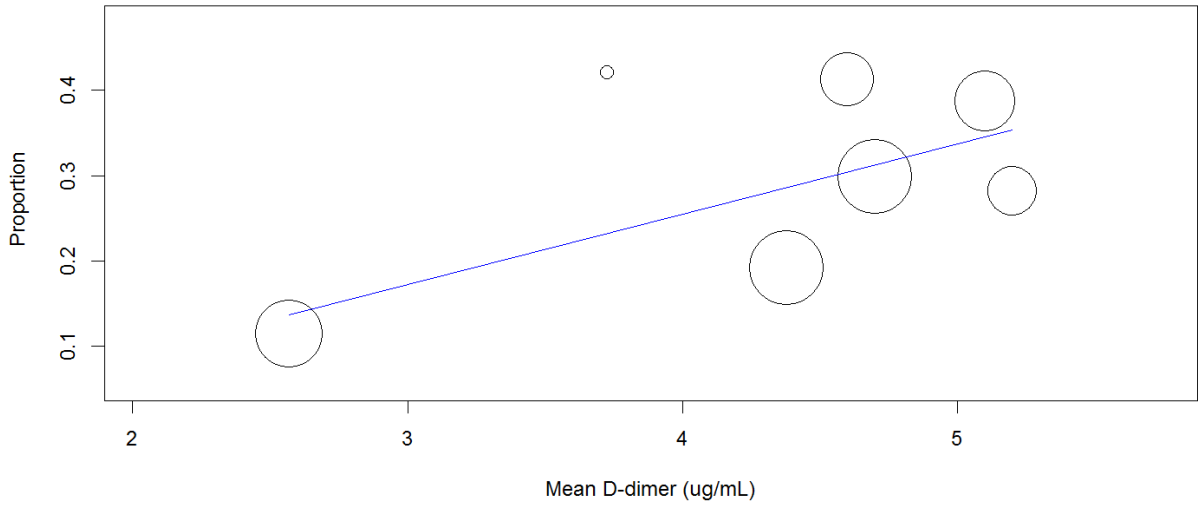


Figure 4. A scatter plot demonstrating the association of plasma D-dimer and mortality

**4. Discussion**

Coronaviruses are enveloped viruses that have a single-strand positive-sense RNA of 26 to 32 kb in length within its structures. The family, called *Coronaviridae*, has at least seven strains of coronavirus. Two of them have caused severe respiratory illness in humans in the past: SARS-CoV from 2002 to 2003, MARS-CoV in 2013. In the middle of December 2019, the virus that caused an acute respiratory outbreak in Wuhan, China, was named SARS-CoV-2, and the disease was termed COVID-19 by WHO. Similar to SARS-CoV, SARS-CoV-2 primarily targets the respiratory system, where the virus enters host epithelium cells via the ACE2 receptor.

With the rapid increase of infection, case severity determination has become an important component of providing effective medical care for COVID-19 patients. It helps clinicians to determine if the patient needs an urgent and intensive care facility. In the case of a limited facility, it may help clinicians prioritize the case who needs immediate care. Also,

determining severity helps clinicians to determine what medical equipment and medicine the patient need for the clinical goal. Along with pre-existing comorbidity such as hypertension, diabetes, respiratory disease, routine blood profile/biochemistry/immunology analysis results such as increased white blood cell (WBC), decreased lymphocyte and platelet counts, higher IL-6 and IL-10 levels are associated with both severe and fatal COVID-19 cases, for review see [27].

This meta-analysis assessed the clinical data of 5,369 COVID-19 patients and found that patients presenting more severe symptoms and patients exhibiting a higher risk of mortality have higher levels of D-dimer levels.

The key finding of this concise meta-analysis is that D-dimer values were significantly elevated in non-survivor/severe cases than in survivors/non-severe cases. Also, the level of D-dimer was markedly higher in studies having mortality as an outcome in comparison to the survivability. The evidence provided in this analysis shows that investigating the D-dimer level in COVID-19 infected patients could be an effective parameter for determining risk and severity in the infected patients. The findings of this study are in accordance with the findings of several previous analyses where elevated D-dimer levels are shown to be associated with an increased risk of adverse clinical outcomes [12, 28].

D-dimer is a byproduct of active blood coagulation and degradation process. Activation of blood coagulation decreases blood flow, resulting in hypoxia leading to multiple organ failure and death, characteristic manifestations of severe and fatal COVID-19 cases. In several previous reviews the biomarker appears to be an important prognostic factor in predicting mortality in COVID-19 cases. Investigating clinical data of 1355 hospitalized COVID-19 cases included in six independent studies, Sakka et al. showed a mean difference of 3.59 µg/L (95% CI 2.79–4.40 µg/L) in D-dimer levels between non-survivors and survivors [12]. Bansal et al found the value as 2.5 µg/L (95% CI, 0.62-4.41 µg/ml) while investigating three retrospective studies wherein mortality was shown as an outcome measure [28].

This meta-analysis, to the best of available information, is the first analysis that systematically compared D-dimer abnormalities in both a severity and mortality cohort and determined a statistically significant relationship between the variables. In accordance with the aforementioned studies and the observation that shows coagulopathy—development of miro-clots in lung tissues have been shown to be associated with COVID-19 disease severity [29], in the current study a significantly greater increases for D-dimer were observed in non-survivors vs. survivors (MD 3.48 µg/mL) as compared to severe vs. non-severe cases (MD 0.19 µg/mL), respectively. Both of the values are equally important for monitoring clinical prognosis in COVID-19 patients during hospital admission and throughout making a medical decision. Given the observation—the higher the D-dimer level greater the proportion of severe and deceased cases, plasma D-dimer level, statistically, could be a significant predictor of clinical deterioration of cases leading to case severity and death in hospitalized COVID-19 cases.

Understanding the mechanism involved in the elevated D-dimer values in patients with SARS-CoV-2 infection having worse clinical outcomes is necessary to provide optimal care as well as to minimize the disease severity in hospitalized patients. Several plausible reasons have been described to be involved in the coagulation activation and for elevated D-dimer over the normal value of 0.5 µg/ml in severe SARS-CoV-2 infected cases.

First, the virus may cause acute lung injury, or the symptoms of ARDS can alone increase the incidence of disseminated intravascular coagulation (DIC) [15]. It is also believed that the virus causes injuries to the inner endothelial lining of blood vessels that triggers the release and activation of coagulation factors. Other contributing factors include the release of various cytokines and inflammatory factors in response to a viral infection—a study mentioned [30]. Even more, acute cardiac injury, heart failure, and acute renal injury increase the risk of worse outcomes, increasing the level of D-dimer in elderly patients [31].

Several limitations exist in this meta-analysis. The most important was the presence of high heterogenicity among the studies. This can be explained due to the different populations of the participants, the presence of different comorbidity, and variation in the follow-up process. Also, the laboratory value might have influenced the results, as different laboratories have different normal range settings based on the method and local data. These limitations need to be kept in mind to interpret the test results. Sample size, exploitation of data from median and range, strict selection criteria, and covering studies that originated in only China and the USA are among the other limitations of the study.

Despite limitations, this study has shown that the D-dimer level could be a predictor of case severity and death as in both instances positive coefficient (Q) signifies there is a linear relationship between the variables, when value of D-dimer increases population in severe or mortal cases increases. The finding of this study, therefore, may potentially be useful in creating a therapeutic intervention. At the time of hospital admission and during the treatment process, measurement of D-dimer could provide a therapeutic option, as in one study, Tang et al. reported that heparin treatment reduced mortality of COVID-19 patients with elevated D-dimer [9]. Developing a scoring system involving D-dimer would help clinicians select patients at risk for developing severity and mortality. However, the conclusion of this study needs to be verified with more studies involving larger samples sized.

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**Conflict of interest**

The authors declare no relevant involvements or financial association with any organization or entity that may cause a conflict of interest with the subject matter addressed in this article.

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