Type of the Paper (Review article)

The Association of D-Dimer with COVID-19: A Systematic Review

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Received: 17 December, 2024 Reviewed: 12 April, 2025

Accepted: 23 June, 2025 Published online: 20 September 2025

Abstract:

Background: To monitor, prognosis, and formulate treatment algorithms for COVID-19, it is essential to identify severe infection parameters.

Objectives: Using D-dimer levels to measure COVID-19 severity, this study aims to investigate the association between severity and D-dimer levels.

Methods: The review included eight papers that fulfilled the inclusion criteria of patients with an association of D-dimer with COVID-19 who were COVID-19 individuals and were free from cancer, pregnancy, hematologic malignancy, acute coronary syndrome, chronic liver disease, or surgery. Nevertheless, the quality of the studies that were included was generally satisfactory.

Results: This study examined the association between COVID-19 and D-dimer levels in affected patients. Eight studies were incorporated, encompassing a total of 2,916 participants. The findings indicated a notable positive relationship between COVID-19 and D-dimer levels in affected patients. This indicates that D-Dimer levels could serve as a valuable indicator for evaluating SARS-CoV-2 in these individuals.

Conclusion: In severe cases of COVID-19, elevated D-dimer levels are associated with the disease. COVID-19 patients may exhibit these laboratory markers, indicating deteriorating health and unfavorable outcomes. However, due to variations in study designs and patient characteristics, further research is needed to establish standardized thresholds and refine treatment approaches. Integrating D-dimer measurements with other biomarkers and clinical evaluations can improve early detection of high-risk patients and optimize therapeutic strategies.

Keywords: Coronavirus-2; Severe Acute Respiratory Syndrome; D-dimer

1. Introduction

Infective respiratory droplets are transmitted from surfaces and infected individuals through contact with the respiratory mucosa and conjunctiva [1]. A patient may be contagious for 2 to 14 days after exposure during incubation. Research on animal-to-human transmission is ongoing, acknowledging the presence of analogous coronaviruses in birds, bats, and rodents [2]. COVID-19-infected individuals had mild to severe respiratory symptoms, primarily dyspnea and cough [3]. About 14% of patients experienced severe illness, which included respiratory failure, cardiovascular problems, septic shock, acute liver injury, and multi-organ failure [4]. The risk of severe disease was elevated in older individuals and those with underlying co-morbidities such as chronic respiratory diseases, diabetes, and immunocompromised states [5]. For patients with severe illnesses or complications, intensive care units (ICUs) with mechanical ventilation are recommended.

However, intensive care beds are significantly undersupplied compared to the overall population [6]. Additionally, 39% of hospital prescription expenditures go toward ICU services, 25% to equipment, and 13% to laboratory investigations [7]. Various anti-inflammatory, anti-malarial medications, including chloroquine phosphate and hydroxychloroquine sulfate, are currently being tested for specific hospitalized patients with SARS-CoV-2. PCR analysis of viral RNA in respiratory specimens and exposure risk assessment are essential for diagnosing the disease [8]. Several other studies have focused on assessing the severity of a patient's disease and predicting their outcomes; thrombocytopenia, complete blood count, D-dimer, and procalcitonin levels all correlate with severe COVID-19 [9].

Additional research indicated that D-dimer contributes to the prognosis of SARS-CoV-2 [10]. This study evaluates the correlation between severe SARS-CoV-2 and various laboratory indicators. Given the illness load and the constrained resources and capabilities of healthcare institutions, it is essential to identify characteristics that facilitate the risk assessment of clinical conditions to predict severe consequences.

2. Subjects and Methods

2.1.Study approach

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews (PRISMA) protocols (**Figure 1**) [11]. Literature searches were conducted comprehensively utilizing PubMed, the WHO-Virtual Health Library, and the electronic databases of ScienceDirect, with no limitations on date or language. The terms employed in the review included "SARS-CoV-2," "COVID-19," "2019 nCoV," and "D-Dimer" to guarantee that no potentially relevant articles were overlooked.

2.2.Criteria for eligibility

Additionally, we examined the references cited by the articles identified in this search. The variables extracted include the first author, study design, publication year, country, participant numbers in non-severe and severe disease, and laboratory index (specifically d-dimer levels) across various groupings. If additional information is required, we will reach out to the corresponding author via email. In the absence of a response, the study will be excluded. The interquartile range (IQR) of stratified data was transformed into mean ±Standers deviation (SD) utilizing mathematical formulas for meta-analysis. Our search for eligible randomized trials found none that could be used with the Cochrane Risk of Bias tool. The non-randomized research assessed bias utilizing the Newcastle-Ottawa scale (**Figure 1**).

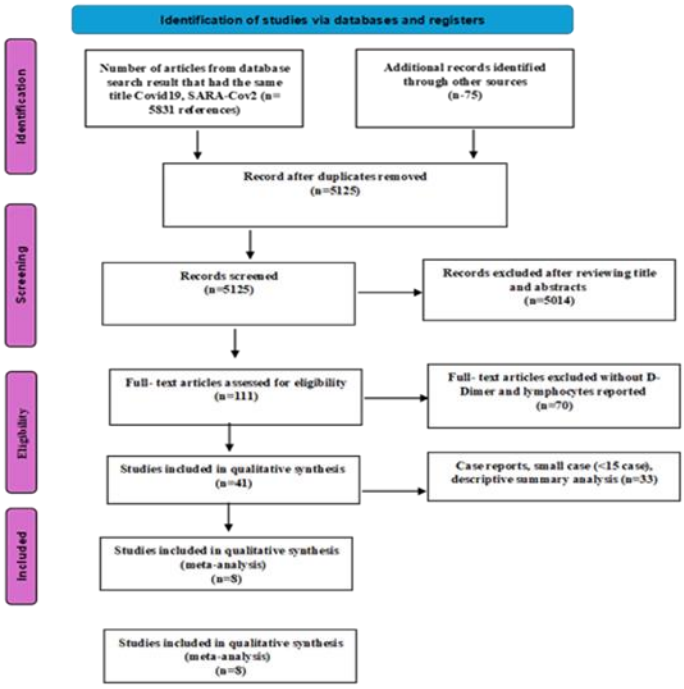

Figure 1: The process flowchart for selecting studies and conducting the systematic literature review.

Inclusion criteria

The investigations included individuals classified as confirmed cases, characterized by an epidemiological history and microbiological evidence, namely blood specimens or respiratory that SARS-CoV-2 test results were positive using RT-PCR testing or viral gene sequencing.

Exclusion criteria

Cancer, pregnancy, hematologic malignancy, acute coronary syndrome, chronic liver disease, surgery, and patients who were admitted without undergoing D-dimer testing.

2.3. Study selection

Both the full-text and abstracts underwent conventional, blind review. Selected publications' references to pertinent studies were reviewed for potential inclusion. The Excel program was utilized. Moreover, any differences among scholars were settled by senior contributors before final clearance.

2.4. Data extraction

Before the screening, the search results from each database were pooled, and duplicates were eliminated. Initial screening of the title and abstract was done, full texts of chosen articles were retrieved, eligibility was double-checked using a predetermined

eligibility form, and data were collected using a predefined form. The authors, working independently, carried out the citation screening and extraction, and conflicts were reviewed and resolved through consensus.

The authors evaluated the included papers for quality and bias risk, including using the Newcastle-Ottawa Scale.

2.5. Statistical analysis

The random effect model was employed to account for heterogeneity. The fixed-effect model was utilized at certain instances. The asymmetric funnel plot suggested publication bias in the papers, which the scientists assessed using Egger's test and funnel plots. A sensitivity analysis was done to analyze the records' different sources. This study assigned a significance level of $p < 0.05$.

3. Results

2.6.Study features and literature research

Figure 1 shows that a total of 5831 articles were identified, with 8 included in our analysis. The fundamental attributes of the papers incorporated in the article are as follows (**Table 1**). A total of 8 articles were disseminated in the year 2022. Four studies were conducted in China, alongside two from the United States, one from Turkey, and one from Nepal. Eight studies were categorized based on their severity and non-severity classifications. The articles elucidated the D-dimer levels observed in cases afflicted with SARS-CoV-2. Every study included in the analysis received a high-quality rating based on the NOS scores (**Table 1**).

Table 1. Summary of included papers.

Study ID	Country	Study Design	Study Population	Inclusion and exclusion criteria	Conclusion
Yao, *et al.* [12]	China	Case-control study	Patient with confirmed COVID-19	**Inclusion criteria** The National Health Commission of China's Novel Coronavirus Pneumonia Diagnosis (NHCCNP) and Applied Rules (6th ed.) (Chinese) required a history, two clinical manifestations, and	COVID-19 patients often have elevated D-dimer. Critically ill individuals have elevated levels, which could serve as a prognostic indicator for death in hospitals.

				COVID-19 real-time RT-PCR testing positive blood specimens. **Exclusion criteria** included haematological, oncological, chronic liver diseases, surgery, or pregnancy.	
Ozen, *et al.* [13]	Turkey	Case-control study	Patient with confirmed COVID-19	**Inclusion criteria** NHCCNP and Applied Rules (14 ed.) (Turkey) required a history, two clinical manifestations, and COVID-19 real-time RT-PCR testing, positive blood specimens. **Exclusion criteria**: haematological, oncological, chronic liver diseases, surgery, or pregnancy	COVID-19 pneumonia severity is tightly linked to D-dimer, which increases radiological or clinical deterioration. We believe SARS-CoV-2 patients' D-dimer affects prognosis, but further research is required.
Naymagon, *et al.* [14]	USA	Case-control study	Patient with confirmed COVID-19	**Inclusion criteria** NHCCNP and Applied Rules (6th ed.) (Chinese) required a history, two clinical manifestations, and COVID-19 real-time RT-PCR testing positive blood specimens. **Exclusion criteria** haematological, oncological, chronic liver diseases, surgery, or pregnancy	Higher admission of SARS-CoV-2 patients with increased D-dimer and trends had a greater risk of all-cause mortality, intubation, and VTE. D-dimer alone does not predict SARS-CoV-2 in the short or long term. High D-dimers in SARS-CoV-2 patients may be attributable to thrombotic load, inflammation, or both. More study is required. D-dimers should also be included in multifactorial diagnostic paradigms and clinical decision-making.
Poudel, *et al.* [15]	Nepal	Case-control study	Patient with confirmed COVID-19	**Inclusion criteria** An epidemiological history that matched two clinical signs and microbiological evidence was characteristic of confirmed cases. **Exclusion criteria included** A patient without documented D-dimer levels at entry, a patient who has had further infections, a patient who has taken an anticoagulant previously, a patient who has experienced a deep vein thrombosis, and a patient who has not recorded conclusive results (mortality or survival).	COVID-19 patients' deaths may be accurately predicted by measuring their admission D-dimer levels. Thus, D-dimer is a simple and affordable COVID-19 prognostic laboratory indication.
He, et al. [10]	China	Retrospective study	Patient with confirmed COVID-19	**Inclusion criteria** SARS-CoV-2 positive COVID-19 individuals **Exclusion criteria included**	This multi-centre experiment used D-dimer to diagnose and prognose COVID-19. The best D-

				Pregnancy patients	dimer death risk threshold is 2.025 mg/L. After grouping by D-dimer, age, gender (male), dyspnea, and underneath disorders like coronary heart disease, hypertension, and cerebrovascular disease, diabetes influenced patient prognosis. The above factors enhance COVID-19 mortality. DIC secondary fibrinolysis prevention reduces COVID-19 mortality with D-dimer monitoring, early thrombotic identification, and thromboembolism and hemorrhage prevention
Zhang, *et al.* [16]	China	Retrospective study	Patient with confirmed SARS-CoV-2	**Inclusion criteria** SARS-CoV-2 positive COVID-19 individuals	A fourfold rise in D-dimer on arrival may predict in-hospital mortality in SARS-CoV-2 cases, suggesting it may be a useful marker for better care of these patients.
Nemec, *et al.* [17]	USA	Retrospective study	Patient with confirmed COVID-19	**Inclusion criteria** SARS-CoV-2 positive COVID-19 individuals	This retrospective analysis supports worldwide research linking D-dimer to SARS-CoV-2 results. Higher admission and peak D-dimer readings are related to poorer clinical outcomes, including intubation and death. Therapeutic anticoagulation's effect on D-dimer trends might be studied further.
Yu, *et al.* [18]	China	Retrospective study	Patient with confirmed COVID-19	**Inclusion criteria** SARS-CoV-2 positive COVID-19 individuals **Exclusion criteria included** Patients having secondary infections (bacterial and fungal) or no pre-treatment lab results were eliminated. A minimum of two positive SARS-CoV-2 RT-PCR tests confirmed COVID-19. This study also eliminated patients without or with negative SARS-CoV-2 tests.	Increased baseline D-dimer levels in SARS-CoV-2 patients indicate inflammation but not thrombosis. With SARS-CoV-2 medication, D-dimer should change. Anticoagulants target D-dimer and inflammatory factor abnormalities. For venous thromboembolism prevention in SARS-CoV-2 cases, the VTE score may be better than baseline D-dimer levels, although further study is required.

2.7.Notable Publication Bias Arising from Varied Study Designs

This finding was accompanied by a notable publication bias, quantified at 91.6%. The random-effects filled funnel plot (P<0.001) (Figure 2A) supports this observation, further validated by both Egger's at *P*<0.001 and Begg's tests at P=0.003, as illustrated in Figures 2B-C. We posited that the level of D-dimer might act as a significant correlate for clinical characteristics (**Table 2**)

Table 2: Bias Risk Assessment Using Newcastle-Ottawa Scale.

Study ID	Country	Year	Journal	Newcastle–Ottawa Scale
Yao et al	China	2020	Journal of Intensive Care	Good quality
Ozen et al	Turkey	2021	American Journal of Emergency Medicine	Good quality
Naymagon et al	USA	2020	Thrombosis Research	Good quality
Poudel et al	Nepal	2021	Plos one	Good quality
He et al	China	2021	Scientific Reports	Good quality
Zhang et al.	China	2020	Journal of Thrombosis and Haemostasis	Good quality
Nemec et al.	USA	2022	The American Surgeon	Good quality
Yu et al.	China	2020	Journal of Thrombosis and Thrombolysis	Good quality

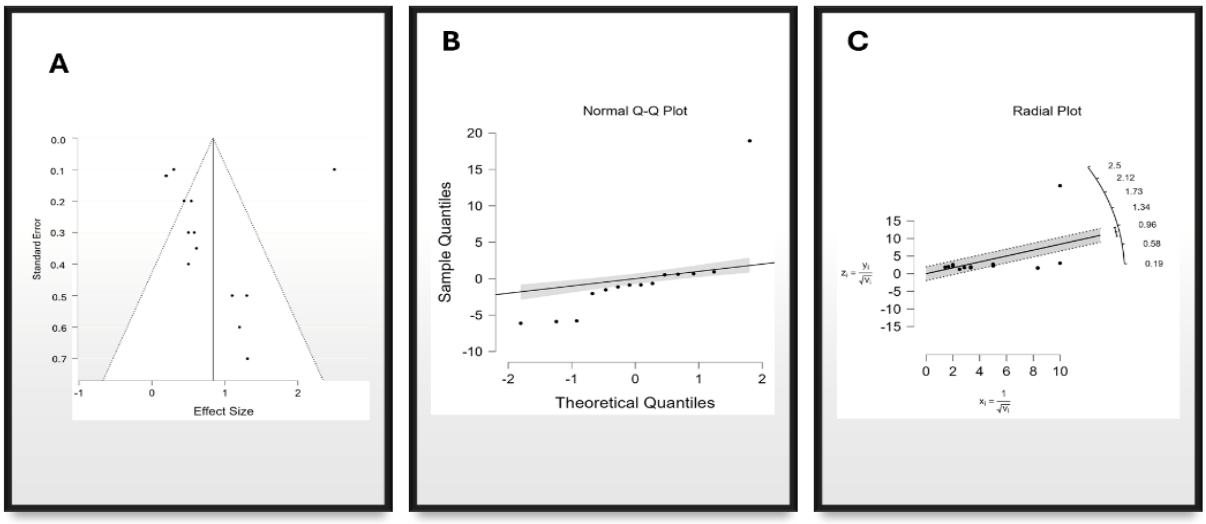

Figure 2. (A) Filled funnel plot. (B, C) Egger's publication bias plot.

4. Discussion

Recent researchers, clinicians, and months have diligently sought to comprehend COVID-19, a virus that has impacted numerous nations and persists in disseminating within the community [19,20]. Our investigation intended to examine currently available data, assess Clinical outcomes, and identify laboratory blood parameters that could serve as indicators of disease severity. Many working theories have emerged regarding the management of cases that test positive for COVID-19, particularly concerning the biological markers that may be employed to evaluate their condition. 12 to 14 No multiple regression routine diagnostic equation exists to screen patients with positive PCR findings for symptomatic COVID-19 infections on the day of presentation to a healthcare institution [21,22].

During the hospitalization of laboratory-confirmed COVID-19 cases, this review presented a meta-analysis of all published English articles. Based on contemporary literature, we derived prevalent hematological indicators used to assess clinical severity and disease progression in this cohort. Fifteen to 17. It was noted that prevalent markers impacting patient outcomes included acute phase reactants and WBCs. Notably, D-dimer levels exhibited patterns that could indicate whether a patient would experience a mild-to-moderate disease progression instead of a severe trajectory or potential mortality. Lymphopenia, neutropenia, and raised D-dimer quantities were distinctly correlated with disease progression, whereas patients exhibiting mild-to-moderate disease demonstrated only moderate alterations in these parameters. Several studies have examined these values in isolation, yet a comprehensive comparison remains absent.

COVID-19 infection severity was correlated with raised D-dimer levels in this meta-analysis [23]. Samprathi and Jayashree [24] observed that biomarkers and D-dimer exhibit significant elevation during the systemic inflammation phase of 2019 nCoV, with excessive hyperinflammation potentially resulting in multiple organ failure and cardiopulmonary collapse. Many studies indicate that the blood coagulation function experiences considerable activation during severe 2019 nCoV infections, potentially linked to the prolonged inflammatory response triggered by the release of D-dimer due to viral invasion [25,26]. Recent evidence from lung

pathological anatomy has revealed the presence of microthrombosis in critically ill patients and pulmonary small vessel occlusion suffering from 2019-nCoV [27]. In terms of coagulation markers, D-dimer levels are pronounced and dynamically elevated.

Nevertheless, the causes of increased serum D-dimer levels are diverse and complex. The pronounced inflammatory response observed in patients suffering from severe 2019-nCoV could potentially elevate the risk of thromboembolic disease, elucidating the rise in serum d-dimer levels [28]. The coagulopathy associated with COVID-19 warrants careful consideration and appropriate intervention. It is recommended that an anticoagulant be administered to all patients diagnosed with 2019 nCoV in the absence of contraindications [29].

The correlation between age and improved levels of D-dimer in 2019 nCoV cases upon admission is either an independent or a covariate prognostic indicator for the disease outcomes. As a function of the levels of D-dimer's threshold value (0.5 μg/mL), it exhibits age-related variability among healthy populations [30]. The disparity in the level of D-dimer between males and females is negligible within a healthy demographic [31]. According to 2019 nCoV studies, levels of D-dimer are positively associated with the percentage of male patients, indicating that males are more likely to have severe incidents than females.

As a result of our systematic review, we found that rising D-dimers were correlated with various immune responses following infection with COVID-19. Furthermore, the timeline for the PCR utilized to revert to a negative result is correlated with the D-dimer [32]. A downregulation of the protective Ang1-7/Mas/ACE2 axis occurs when spike proteins from COVID-19 interact with ACE2 receptors in host cells. The result is a greater expression of PAI-1 [33]. Albumin is both an anticoagulant and an antiplatelet agent, enhancing vascular permeability [34]. This mechanism appears to elucidate the association between elevated hypoalbuminemia and D-dimer.

The findings revealed a significant positive correlation between raised D-dimer at mortality and admission, underscoring the prognostic importance of raised D-dimer as a measure of heightened mortality risk. The affirmative association additionally supports this observed relationship between levels of D-dimer and the duration from admission to

onset, the necessity for ventilation, and the time required for PCR test results to revert to negative [35,36]. Furthermore, a noteworthy correlation exists, indicating that an improvement in D-dimer is inversely related to the likelihood of patient discharge. The data indicate that timely clearance and admission of the COVID-19 virus could mitigate severity and decrease fatal outcomes by inhibiting inflammation and hyperfibrinolysis. Numerous reviews have established D-dimer's prognostic value [37]. Individuals experiencing severe SARS-CoV-2 may exhibit a prolonged duration of illness compared to those with mild cases. The correlation between D-dimer and the duration from onset to admission is substantiated by the data presented in Table 1. Conversely, the advancement of the disease could be significantly accelerated in patients who are critically ill upon admission. We have carried out a systematic review to elucidate the correlation between the rising levels of D-dimer and various clinical multi-variants for the first time. This research elucidates: 1) The associations between levels of D-dimer and various clinical variables suggest a potential causal or indirect connection. 2) A limited number of variables associated with D-dimer have been validated or may identify fatal events and in-hospital mortality as prognostic biomarkers. 3) Significantly heightened D-dimer levels appear to arise from hyperfibrinolysis, primarily within the other organs and pulmonary capillaries. A notable rise in levels of D-dimer levels may correlate with thromboembolism and an increased risk of mortality. In contrast, we deduce that a consistent decrease observed through daily assessments typically indicates a path toward recovery. Given that COVID-19 represents a novel disease, most studies are characterized as patient series, single-center, descriptive, and observational, retrospective [38]. Most of the articles incorporated originate from Asia and China, the regions where the pandemic was initially identified. Diversity within cohorts is evident among seniors and children, correlating with various co-morbidities and complications [39]. The variability in grouping strategies across studies presents a significant obstacle to systematic review. This includes distinctions such as ICU versus ARDS, non-ICU versus control, non-ARDS versus SARS-CoV-2, non-survivor versus survivor, severe versus non-severe, non-VTE versus VTE, deaths versus recoveries, as well as classifications of mild versus moderate and moderate versus severe, alongside regular versus abnormal

D-dimer levels, among others [40,41]. It is essential to consider the potential deviations that may arise before and after testing concerning the methodology employed for D-dimer assessments. It is important to highlight that the D-dimer level may not be a biomarker linked to all clinical outcomes upon admission [42].

5. Conclusion

This systematic review found that a range of clinical factors, such as organ damage, preexisting conditions, abnormal glucose levels, inflammation, overall outcomes, and complications, may influence increased D-dimer levels. The clinical trial significance of raised levels of D-dimer may be complex and varied.

Conflict of interests: No conflict of interest.
Funding: This research is not funded.
Ethical consideration: Before the research began, the Faculty of Medicine, Fayoum University's ethics committee approved (number M535; Session: 81; Date: April 11, 2021). The legal guardians of every person in this research signed informed written permission.
Authors' contributions: LEA: Protocol/project development, Data collection and management, manuscript writing/editing. RAA: Data analysis, manuscript writing, and editing. ASA: Data management, Manuscript writing/editing. MAH: Protocol/project development, Data analysis, Manuscript writing /editing. MAA: Data management, Manuscript writing/editing. LAA: Data management, Manuscript writing/editing. All authors have read and approved the manuscript.
AI declaration: Not applicable

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