

Relationship of D-dimer with severity and mortality in SARS-CoV-2 patients : A meta-analysis

Johanes Nugroho^{1,2}  | Ardyan Wardhana³  | Irma Maghfirah² | Eka Prasetya Budi Mulia² | Dita Aulia Rachmi² | Maya Qurota A'yun² | Imanita Septianda²

¹Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

²Dr. Soetomo General Hospital, Surabaya, Indonesia

³Faculty of Medicine, Universitas Surabaya, Surabaya, Indonesia

Correspondence

Johanes Nugroho, Department of Cardiology and Vascular Medicine, Faculty of Medicine Universitas Airlangga, Dr. Soetomo General Hospital, Surabaya, 60285, Indonesia.
Email: j.nugroho.eko@fk.unair.ac.id

Abstract

Introduction: The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a pandemic. Many studies have shown that several laboratory parameters are related to disease severity and mortality in SARS-CoV-2 cases. This meta-analysis aimed to determine the relationship of a prognostic factor, D-dimer, with disease severity, need for intensive care unit (ICU) care, and mortality in SARS-CoV-2 patients.

Methods: A systematic search for all observational studies and trials involving adult patients with SARS-CoV-2 that had any data related to D-dimer on admission was conducted using PubMed, Science Direct, Scopus, ProQuest, and MedRxiv databases. We performed random-effects inverse-variance weighting analysis using mean difference (MD) of D-dimer values for outcomes such as disease severity, mortality, and need for ICU care.

Results: A total of 29 studies (4,328 patients) were included in this meta-analysis, which revealed a higher mean of D-dimer levels on admission in severe patients than in nonsevere patients (MD = 0.95, [95% confidence interval (CI): 0.61-1.28], $P < .05$; $I^2 = 90\%$). The nonsurvivor group had a higher pooled MD of D-dimer values on admission (MD = 5.54 [95% CI: 3.40-7.67], $P < .05$; $I^2 = 90\%$). Patients who needed ICU admission had insignificantly higher D-dimer values than patients who did not need ICU admission (MD = 0.29, [95% CI: -0.05 to 0.63], $P = .10$; $I^2 = 71\%$).

Conclusion: Elevated D-dimer levels on admission were associated with an increased risk of disease severity and mortality in patients with SARS-CoV-2 infection.

KEYWORDS

D-dimer, laboratory, mortality, prognostic factor, SARS-CoV-2, severity

1 | INTRODUCTION

A new viral pneumonia was first detected in Wuhan, China, and was found to be caused by a novel coronavirus, later identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), that has since then caused a pandemic. Previous reports have shown that certain laboratory parameters correlated with disease

severity and mortality in SARS-CoV-2 infection.¹ The levels of D-dimer, an important prognostic factor, were found to be higher in patients with a clinically severe case of SARS-CoV-2 than in nonsevere cases.² A better understanding of this prognostic factor can help physicians predict the disease severity and need for intensive care unit (ICU) care in patients infected with SARS-CoV-2. This meta-analysis aimed to determine the relationship

of D-dimer with disease severity and mortality in SARS-CoV-2 patients.

2 | METHODS

We conducted this study following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We selected all observational studies and trials involving adult patients with SARS-CoV-2 that had any data on D-dimer values for comparing different groups: severe vs. nonsevere; ICU vs. non-ICU; survivor vs. nonsurvivor. We excluded any study that did not have the required data, collect D-dimer data on admission, and report D-dimer data in numerical values.

A systematic literature search was carried out after receiving approval from the Institutional Review Board. Five different databases (PubMed, Science Direct, Scopus, ProQuest, and MedRxiv) were used to perform a systematic search of all the literature using the keywords "intensive" and "laboratory" and "COVID-19" or "coronavirus 2019" or "2019-nCoV" or "SARS-CoV-2," in the title, abstract, and medical subject heading (MeSH). We used "laboratory" as a search term instead of D-dimer because earlier studies did not consider D-dimer as an important factor, and hence, this factor was reported as data related to the laboratory report on admission. D-dimer levels were neither mentioned nor discussed separately in these reports. The reference lists of the studies included were screened to identify additional studies relevant to D-dimer.

Three investigators independently screened and assessed titles and abstracts before full-text retrieval. The other two authors reviewed the papers for final inclusion and extracted data including authors, year of publication, location, study design, peer-reviewed publication status, disease severity measurement, and D-dimer levels in each comparison group.

The primary outcome in our meta-analysis was the D-dimer levels on admission based on the severity of the case. We used all definition of severity. If the study categorized disease severity into three or four groups, we combined all the data found in the mild and moderate group into one group as nonsevere; severe and critical groups were combined into one group as severe. The average of their mean and standard deviation was calculated using the formula in Table 7.7.a of the Cochrane Handbook.³ The secondary outcomes were D-dimer levels on admission based on mortality and intensive care need.

Two authors independently assessed the methodological quality assessment using the National Heart Lung and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. We conducted the meta-analysis using the mean difference (MD) for D-dimer levels. Mean and standard deviation values were extrapolated from the sample size, median, and interquartile range (IQR), according to Wan et al⁴ We employed a fixed-effects and inverse-variance weighting using Review Manager (RevMan v5.3 2014). We carried out a subgroup analysis based on study design. We performed a sensitivity analysis based on peer

review and age difference status. We evaluated inter- and intrastudy heterogeneity using the I^2 statistic. We applied a random-effects meta-analysis if the heterogeneity is significant.

3 | RESULT

We identified a total of 111 records from the PubMed database, 488 records from the ScienceDirect database, 20 records from the ProQuest database, 42 records from the Scopus database, 846 records from the MedRxiv database, and 127 records from other sources as shown in Figure 1. One-hundred and fifty-one other studies were excluded because of incorrect population (4 studies), irrelevant exposure (83 studies), irrelevant outcome (42 studies), study not reported in English (1 study), D-dimer values not collected on admission (9 studies), and irrelevant severity criteria (12 studies). We excluded the study of Levy et al from our analysis because D-dimer measurements were missing in 78% of the patients and there was no information regarding the proportion of those missing in each group.⁵ Twenty-nine studies (4,328 patients) were included in the analysis.⁶⁻³⁴

The baseline characteristics of the included studies are presented in Supplementary file 1. Twenty-six studies were retrospective, and three studies were prospective observational. Fifteen studies have already undergone peer review.^{6,12,14,16,18-21,24,25,27,30,31,33,34} One study provided a comparison between groups for disease severity and mortality.¹¹ Most of the studies classified the disease severity according to the National Health Commission of the People's Republic of China. Only three studies considered subjects of similar age in both groups.^{28,30,33}

Among the 29 studies included in this meta-analysis, most did not identify whether D-dimer values were reported as D-dimer units (DDU) or fibrinogen equivalent units (FEU). Only 3 studies clearly stated using FEU.^{20,22,30} Nine studies did not report the normal cut-off value of D-dimer (Supplementary file 1).

We assessed all studies wherein all outcomes were obtained using a good and fair methodology (Supplementary file 1). None of the studies that were considered had any flaws in the analyses. The analyses were rigorous, and the conclusions drawn by the studies were credible. However, most studies did not assess exposure prior to outcome measurement and may have lacked sufficient timeframe for the outcomes to occur because of their cross-sectional design.

Random-effects meta-analysis revealed a higher mean of D-dimer levels on admission in severe patients than in nonsevere patients as shown in Table 1 (14 studies, MD = 0.95, [95% CI: 0.61-1.28], $P < .05$; $I^2 = 90\%$). Subgroup analysis based on the study design showed a similar result in both subgroups. Sensitivity analysis based on the peer-reviewed status from 6 studies showed an MD of 0.68 with 95% CI 0.26-1.10 and $I^2 = 86\%$ (Supplementary file 2).

Nonsurvivor group had a pooled higher mean difference of D-dimer values on admission as shown in Table 1 (9 studies, MD = 5.54 [95% CI: 3.40-7.67], $P < .05$; $I^2 = 90\%$) than survivor groups. Sensitivity analysis showed similar result (5 studies,

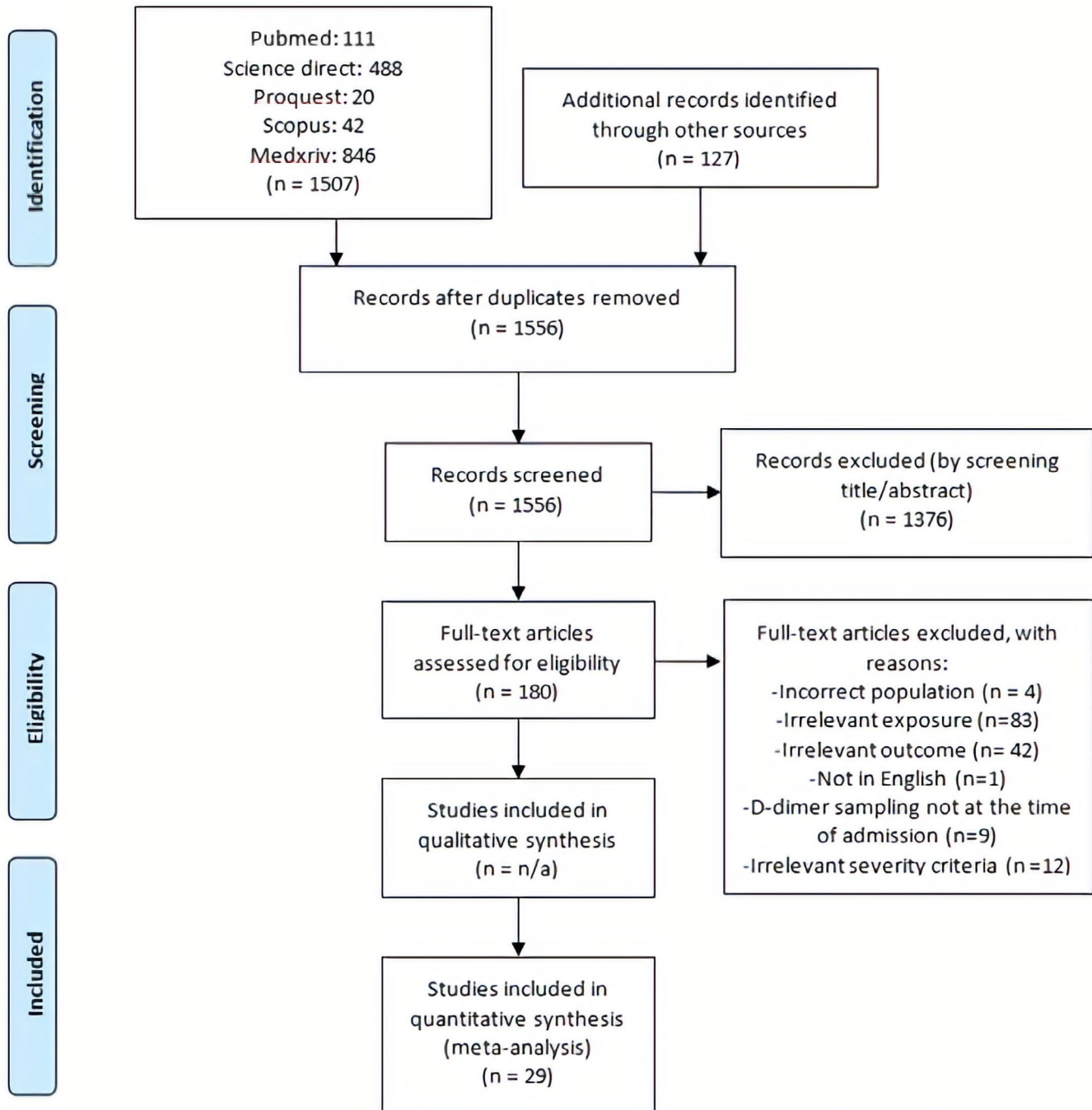


FIGURE 1 Study flow chart (as per PRISMA guideline)

MD = 5.78, [95% CI: 2.94-8.63], $P < .05$; $I^2 = 84\%$) when we excluded nonpeer-reviewed studies. We did not perform a subgroup analysis based on study design because all included studies were retrospective observational.

Patients with need for ICU care had higher D-dimer values on admission than patients who did not need ICU care (seven studies, MD = 0.29, [95% CI: -0.05 to 0.63], $P = .10$; $I^2 = 71\%$) as shown in Table 1. Sensitivity analysis showed a similar result when we excluded studies that had significant age differences pertaining to participants estimates (3 studies, MD = 4.35, [95% CI: -2.31 to 11.01], $P = .20$; $I^2 = 81\%$). However, the effect estimates changed and were

found to be significant without improvement in heterogeneity (4 studies, MD = 0.48, [95% CI: 0.21-0.76], $P < .05$; $I^2 = 66\%$) when we excluded nonpeer-reviewed studies.

4 | DISCUSSION

This meta-analysis showed that increasing D-dimer levels on admission were significantly associated with increased disease severity and mortality. The results obtained were similar to the results reported previously in two other systematic reviews.^{35,36} Pooled

TABLE 1 Summary of findings

Outcomes	Studies	Participants	Effect Estimates	P	I2
Severity	14	2190	0.95 [0.61, 1.28]	<.05	90%
Retrospective	11	1557	1.30 [0.78, 1.82]	<.05	91%
Prospective	3	633	0.54 [0.05, 1.04]	<.05	90%
Sensitivity analysis	6	775	0.29 [-0.05, 0.63]	<.05	86%
Mortality	9	1808	5.54 [3.40, 7.67]	<.05	90%
Sensitivity analysis ^a	5	851	5.78 [2.94, 8.63]	<.05	84%
Needs of ICU	7	657	0.29 [-0.05, 0.63]	.1	71%
Sensitivity analysis ^a	4	241	0.48 [0.21, 0.76]	<.05	66%
Sensitivity analysis ^b	3	89	4.35 [-2.31, 11.01]	.2	81%

^aSensitivity analysis based on peer-reviewed status.

^bSensitivity analysis based on age difference status.

analysis by Shah et al demonstrated that patients who had D-dimer levels more than 0.5 mg/L had a twofold higher risk of developing a severe case of the disease and fourfold higher risk of mortality than those who had D-dimer levels less than 0.5 mg/L.³⁶ Higher cut-off value of D-dimer (>2 mg/L) was considered to be even better in predicting in-hospital mortality in SARS-CoV-2 with a sensitivity of 92.3% and a specificity of 83.3% after adjusting for age, gender, and comorbidities.³⁷

Our study also showed that patients with a need for ICU care had nonsignificant higher D-dimer values on admission than patients who did not need ICU care. An earlier study demonstrated that there was an increased incidence of thrombotic complications in patients treated in the ICU.³⁸ Hypercoagulability state was also found in patients admitted to ICU where D-dimer levels were drastically increased.³⁹ At the late stages of SARS-CoV-2, levels of fibrin-related markers (D-dimer and fibrin degradation product) were either moderately or markedly elevated in all cases of death suggesting a common coagulation activation and secondary hyperfibrinolysis condition in these patients.²⁴

Histopathology studies on the lung biopsy of critical patients with SARS-CoV-2 revealed the presence of occlusion and microthrombosis formation in pulmonary small vessels.⁴⁰ The exact mechanism responsible for coagulopathy in SARS-CoV-2 patients is not yet identified. Whether SARS-CoV-2 can directly attack vascular endothelial cells expressing high levels of angiotensin-converting enzyme 2 (ACE2) leading to abnormal coagulation and sepsis is an aspect that still needs to be explored.

Our meta-analysis suggests that elevated D-dimer levels can be a marker of poor prognosis in patients with coronavirus disease (COVID-19). During a pandemic, risk stratification in triage is

necessary, and D-dimer can be one of the potential indicators in the case of high-risk patients. However, only the presence of elevated D-dimer only is not a reason enough to start the administration of therapeutic anticoagulants.

To the best of our knowledge, this meta-analysis conducted using 29 different studies is the largest that evaluates the prognostic role of D-dimer on admission in SARS-CoV-2 patients. However, several limitations should be noted in our study. First, there was substantial heterogeneity across studies. Most of the studies included were retrospective with relatively small sample size. Second, the variation in reporting the unit of D-dimer inevitably might affect our interpretation and analysis of the D-dimer data. Third, the analysis in this study was performed during the pandemic; researchers conducting studies in many areas affected by SARS-CoV-2 have not published their data as yet. Most of the studies included were from mainland China, while the remaining three studies were from the USA. Ethnic and geographical differences could distort the results of the analysis.

5 | CONCLUSIONS

Our meta-analysis demonstrated that elevated D-dimer levels on admission were associated with an increased risk of disease severity and mortality in SARS-CoV-2 infection.

ACKNOWLEDGEMENT

This work did not receive specific funding, but was performed as part of Johannes Nugroho employment at the Department of Cardiology and Vascular Medicine, Universitas Airlangga/Dr Soetomo General Hospital, East Java, Indonesia.

CONFLICT OF INTEREST

(If present, give more details): The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be considered as a potential conflict of interests.

AUTHOR CONTRIBUTIONS

JN involved in conceptualization, methodology, writing-review and editing, and supervision. AW involved in conceptualization, data analysis, manuscript writing-review and editing. IM involved in screening, data extraction, investigation, data analysis, and writing-original draft. EM involved in screening, data extraction, investigation, and writing-original draft. MA involved in screening, investigation, data extraction, writing-original draft, and project administration. DR and IS involved in investigation, data analysis, quality assessment, and writing-original draft.

IEC APPROVAL

Dr Soetomo General Hospital Surabaya Ethical Committee in Health Research (0005/LOE/301A.2/05/2020).

TRIAL REGISTRY

UMIN Clinical Trial Registry (UMIN ID 000 040 433).

DATA AVAILABILITY STATEMENT

The data supporting this meta-analysis are from previously reported studies and data sets, which have been cited.

ORCID

Johanes Nugroho  <https://orcid.org/0000-0002-3501-1872>
 Ardyan Wardhana  <https://orcid.org/0000-0003-4048-2414>

REFERENCES

- Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clin Chem Lab Med*. 2020;/j/cclm.ahead-of-print/cclm-2020-0188/cclm-2020-0188.xml
- Mattiuzzi C, Lippi G. Which lessons shall we learn from the 2019 novel coronavirus outbreak? *Ann Transl Med*. 2020;8:48.
- Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0. The Cochrane Collaboration; 2011 [cited 2020 May 10]. Available from: <https://handbook-5-1.cochrane.org/>
- Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14(1):1-13.
- Levy TJ, Richardson S, Coppa K, et al. Estimating survival of hospitalized COVID-19 patients from admission information. *medRxiv*. 2020;2020.04.22.20075416.
- Cai Q, Huang D, Ou P, et al. COVID-19 in a designated infectious diseases hospital outside Hubei Province, China. *Allergy*. 2020. <https://doi.org/10.1111/all.14309>
- Chen X, Zheng F, Qing Y, et al. Epidemiological and clinical features of 291 cases with coronavirus disease 2019 in areas adjacent to Hubei, China: a double-center observational study. *medRxiv* 2020;2020.03.03.20030353.
- Han Y, Zhang H, Mu S, et al. Lactate dehydrogenase, a risk factor of severe COVID-19 patients: a retrospective and observational study. *medRxiv* 2020;2020.03.24.20040162.
- Li Z, Wu M, Yao J, et al. Caution on kidney dysfunctions of COVID-19 patients. *medRxiv*. 2020;2020.02.08.20021212.
- Liu L, Gao J. Clinical characteristics of 51 patients discharged from hospital with COVID-19 in Chongqing, China. *medRxiv*. 2020;;2020.02.20.20025536.
- Luo X, Xia H, Yang W, et al. Characteristics of patients with COVID-19 during epidemic ongoing outbreak in Wuhan, China. *medRxiv*. 2020;2020.03.19.20033175.
- Qian G-Q, Yang N-B, Ding F, et al. Epidemiologic and clinical characteristics of 91 hospitalized patients with COVID-19 in Zhejiang, China: a retrospective, multi-centre case series. *QJM*. 2020;113(7):474-481
- Shi P, Ren G, Yang J, et al. Clinical characteristics of imported and second-generation COVID-19 cases outside Wuhan, China: a multi-center retrospective study. *medRxiv*. 2020;2020.04.19.20071472.
- Zhang G, Hu C, Luo L, et al. Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan. *China. J Clin Virol*. 2020;127:104364.
- Zhang H, Wang X, Fu Z, et al. Potential factors for prediction of disease severity of COVID-19 patients. *medRxiv*. 2020;2020.03.20.20039818.
- Zhang J-J, Dong X, Cao Y-Y, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan China. *Allergy*. 2020;75:1730-1741.
- Zhou Y, Yang Z, Guo Y, et al. A new predictor of disease severity in patients with COVID-19 in Wuhan, China. *medRxiv*. 2020;2020.03.24.20042119.
- Chen G, Wu DI, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest*. 2020;130:2620-2629.
- Sun Y, Dong Y, Wang L, et al. Characteristics and prognostic factors of disease severity in patients with COVID-19: the Beijing experience. *J Autoimmun*. 2020;112:102473.
- Yan Y, Yang Y, Wang F, et al. Clinical characteristics and outcomes of patients with severe covid-19 with diabetes. *BMJ Open Diabetes Res Care*. 2020;8:e001343.
- Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;368:m1091.
- Chen X, Liu Z. Early prediction of mortality risk among severe COVID-19 patients using machine learning. *medRxiv*. 2020;2020.04.13.20064329.
- Paranjpe I, Russak A, De Freitas JK, et al. Clinical characteristics of hospitalized Covid-19 patients in New York City. *medRxiv*. 2020;2020.04.19.20062117.
- Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18(4):844-847.
- Tu WJ, Cao J, Yu L, Hu X, Liu Q. Clinicolaboratory study of 25 fatal cases of COVID-19 in Wuhan. *Intensive Care Med*. 2020;1-4.
- Zhang F, Yang D, Li J, et al. Myocardial injury is associated with in-hospital mortality of confirmed or suspected COVID-19 in Wuhan, China: a single center retrospective cohort study. *medRxiv*. 2020;2020.03.21.20040121.
- Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study [published correction appears in *Lancet*. 2020 Mar 28;395(10229):1038]. *Lancet*. 2020;395:1054-1062.
- Lau FH, Majumder R, Torabi R, et al. Vitamin D insufficiency is prevalent in severe COVID-19. *medRxiv*. 2020;2020.04.24.20075838.
- Zhou J, Sun J, Cao Z, Wang W, Huang K, Zheng F, et al. Epidemiological and clinical features of 201 COVID-19 patients in Changsha, China. *Res Sq*. 16 March 2020, Preprint 2020;(version 1). <https://doi.org/10.21203/rs.3.rs-17313/v1>
- Wang F, Yang Y, Dong K, et al. Clinical characteristics of 28 patients with diabetes and Covid-19 in Wuhan, China. *Endocr Pract*. 2020.

31. Lei S, Jiang F, Su W, et al. Clinical characteristics and outcomes of patients undergoing surgeries during the incubation period of COVID-19 infection. *EClinicalMedicine*. 2020;100331.
32. Cao M, Zhang D, Wang Y, et al. Clinical features of patients infected with the 2019 novel coronavirus (COVID-19) in Shanghai China. *medRxiv*. 2020;2020.03.04.20030395.
33. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan China. *Lancet*. 2020;395:497-506.
34. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061-1069.
35. Lippi G, Favaloro EJ. D-dimer is associated with severity of coronavirus disease 2019: a pooled analysis [Letter to Editor]. *Thromb Haemost*. 2020;120(05):876-878.
36. Shah S, Shah K, Patel SB, et al. Elevated D-dimer levels are associated with increased risk of mortality in COVID-19: A systematic review and meta-analysis. *medRxiv*. 2020;2020.04.29.20085407.
37. Zhang L, Yan X, Fan Q, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19 [published online ahead of print, 2020 Apr 19]. *J Thromb Haemost*. 2020. <https://doi.org/10.1111/jth.14859>
38. Klok FA, Kruij MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. 2020;S0049-3848(20)30120-1.
39. Panigada M, Bottino N, Tagliabue P, et al. Hypercoagulability of COVID-19 patients in intensive care unit. A report of thromboelastography findings and other parameters of hemostasis. *J Thromb Haemost*. 2020. <https://doi.org/10.1111/jth.14850>
40. Luo W, Yu H, Gou J, et al. Clinical pathology of critical patient with novel coronavirus pneumonia (COVID 19). *Preprints*. 2020;2020020407. <https://doi.org/10.20944/preprints202004.0004.v1>

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Nugroho J, Wardhana A, Maghfirah I, et al. Relationship of D-dimer with severity and mortality in SARS-CoV-2 patients : A meta-analysis. *Int J Lab Hematol*. 2020;00:1-6. <https://doi.org/10.1111/ijlh.13336>