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Meta-Analysis

Meta-Analysis: The Effect of D-Dimer on Mortality in Patients with COVID-19

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ABSTRACT

Background: The severity of COVID-19 can be detected by examining elevated levels of CRP, ferritin, IL-6 and LDH. Elevated D-dimer levels are often found in patients with severe COVID-19 which can predict the occurrence of ARDS (Acute Respiratory Distress Syndrome) and patient mortality. The purpose of this study was to determine how much influence D-dimer levels had on mortality of COVID-19 patients.
Subjects and Method: This study used a systematic review and meta-analysis with following PICO, population: patients with a clinical diagnosis of COVID-19. Intervention: high D-dimer level. Comparison: low D-dimer level. Outcome: mortality. The data used were obtained from scientific research articles from Pubmed, Google Scholar, Science Direct, and Proquest electronic databases with a cohort design in 2020 until 2022 and report on aOR in multivariate analysis. The keywords used in the search for scientific articles were "D-dimer level" OR "D-dimer" AND "COVID-19" AND "mortality". The selection of articles is done by using PRISMA flow diagram. Data were analyzed using Review Manager software version 5.4.1.
Results: A total of 12 studies with a cohort design that met the criteria from Asia, America, and Europe were selected for a systematic review and meta-analysis. Based on the meta-analysis, it was found that increased levels of D-dimer (>0.5 g/mL) increased mortality in COVID-19 patients by 6.40 times compared to low levels of D-dimer (≤0.5 g/mL) and was statistically significant (aOR = 6.40; 95% CI= 4.51 to 9.08; p<0.001).
Conclusion: Elevated levels of D-dimer may increase mortality risk in COVID-19 patients.

Keywords: d-dimer level, d-dimer, covid-19, mortality.

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BACKGROUND

COVID-19 or Coronavirus Disease is a disease caused by the SARS Cov-2 virus. The first case of infection with the COVID-19 disease outbreak was reported in December 2019 in Wuhan, China and its spread throughout the world.

In general, the COVID-19 virus is transmitted through droplets from the nose or mouth of an infected person and inhaled by others. The clinical symptoms of COVID-19 vary, such as fever, cough, shortness of breath, headache, and sore throat. Patients may also experience severe clinical manifestations including severe pneumonia, sepsis,

septic shock, acute respiratory distress syndrome (ARDS), and Multiple Organ Dysfunction Syndrome (MODS). Patients with advanced age (>65 years), smoking, comorbid hypertension, diabetes, cardiovascular disease, chronic obstructive pulmonary disease, and malignancy have a higher risk of experiencing a more severe disease degree and higher mortality if infected with COVID-19 (Willim et al, 2020).

Although COVID-19 generally has respiratory symptoms, a study by Levi et al. (2020) reported that patients with severe symptoms often have coagulation disorders or coagulopathy that mimic other systemic coagulation disorders associated with a few infections such as disseminated intravascular coagulation and thrombotic microangiopathy. This is associated with a significant increase in mortality in COVID-19 patients. Hyperinflammation in COVID-19 results in increased activation of the coagulation cascade and overproduction of thrombin. Coagulopathy in COVID-19 can causes prothrombotic conditions that can increase the risk of venous and arterial thrombosis and thromboembolism (Henry et al, 2020).

The severity of COVID-19 can be detected by examining elevated levels of CRP, ferritin, IL-6 and LDH. Elevated D-dimer levels indicate hypercoagulability and secondary hyperfibrinolysis. In addition, elevated levels of D-dimer may indicate the clinical severity of COVID-19 patients. Increased coagulopathy and D-dimer levels were reported in 3.75 – 68.0% of COVID-19 cases.

Normal levels of fibrinogen are between 2 until 4 milligrams per milliliter (mg/mL). D-dimer levels were assessed by immunoturbidimetric assay with a reference range of 0-0.50 milligrams per liter (mg/L). D-dimer levels appear normal or slightly elevated at early onset. D-dimer levels increase in severe and critical degrees, so it is used as a prognostic marker of hospital mortality (Willim et al, 2020).

A person who is normal or in good health has low circulating levels of D-dimer, whereas an increase in D-dimer levels can be a marker of suspicion of thrombosis (Berger et al., 2020). Elevated D-dimer levels are often found in severe COVID-19 patients which can predict the occurrence of ARDS (Acute Respiratory Distress Syndrome) and patient mortality (Iba et al., 2020). Research conducted by Yao et al. (2020) reported a significant relationship between D-dimer levels and the severity of COVID-19 based on clinical stage, oxygen saturation, and lung area affected. D-dimer levels that exceed >2.4 g/mL FEU can be a marker of mortality rates.

A number of scientific studies that show the relationship between D-dimer levels with the severity and mortality of confirmed COVID-19 patients encourage researchers to conduct meta-analysis studies. Researchers are interested in conducting existing research, combining and drawing conclusions from previous scientific research reports that specifically discuss the relationship between D-dimer levels and mortality in COVID-19 patients.

SUBJECTS AND METHOD

1. Study Design

This study uses a systematic review and meta-analysis method. The data used were obtained from scientific research articles from the Pubmed, Google Scholar, Science Direct, and Proquest electronic databases in the range of 2020 to 2022. The keywords used in the search for scientific articles were "D-dimer level" OR "D-dimer" AND “COVID-19” AND “mortality”.

2. Steps of Meta-Analysis

Meta-analysis is carried out through 5 steps as follows:

1) Formulate research questions in PICO (Population, Intervention, Comparison and Outcome).
2) Searching for primary study articles from various databases including Google Scholar and Science Direct.
3) Perform screening and conduct critical quality primary studies.
4) Perform data extraction and enter the estimated effect of each primary study into the RevMan 5.3 application.
5) Interpret the results and draw conclusions

3. Inclusion Criteria

The inclusion criteria in this study were full-text articles with a cohort design in 2020 to 2022 using an English, research subjects in articles are covering all countries, races, genders and ages, final results of research data analysis reported using adjusted odd ratio (aOR) and confidence interval (CI).

4. Exclusion Criteria

Exclusion criteria in this study were articles that had previously been meta-analyzed, duplicated articles, less than 100 research subjects, and preprint journals.

5. Definition Operational of Variable

The article search was carried out by considering the eligibility criteria determined using the PICO model. Population: patients with a clinical diagnosis of COVID-19. Intervention: high D-dimer levels. Comparison: low D-dimer levels. Outcome: mortality.

High D-dimer levels is having a high D-dimer level more than 0.5.

6. Study Instruments

The research was guided by the PRISMA flow diagram and the quality research on the research in this study was carried out based on the CASP Systematic Review Checklist worksheet from the Critical Appraisal Skills Program in the cohort study design.

7. Data Analysis

Data analysis was performed using Review Manager software version 5.4.1. Odds ratio with 95% CI calculated from adjusted OR. Forest plots are used to describe effect sizes and Funnel plots are used to describe publication bias. The analysis was carried out by looking for the heterogeneity consistency value (I2) from the selected research results.

RESULTS

The article searches used were obtained from the Pubmed, Google Scholar, Science Direct, and Proquest electronic databases published in the range of 2020 to 2022. The keywords used in the scientific article search were "D-dimer level" OR "D-dimer" AND " COVID-19" AND "mortality". The process of selecting and reviewing articles is carried out using the PRISMA flow diagram.

In this meta-analysis, a number of articles with a cohort research design will be used. The initial search results obtained a number of 7208 articles from a predetermined database. After deleting the duplicate articles obtained 4745 articles. At screening stage, 68 articles were obtained by issuing 4677 articles because the articles did not meet the criteria on the grounds that they were irrelevant, not a cohort design, and not full text. The researcher reviewed the 68 articles that had been obtained and found 28 eligible articles. After that, 40 articles were excluded on the grounds that the outcome was not mortality, did not include the aOR, the results did not include CI, and the research subjects were less than 100. The articles that were included in the qualitative synthesis were 18 articles, then 12 articles were selected again that met the criteria. In these 12 articles, a quantitative synthesis of meta-analysis will be carried out

Research related to the effect of D-dimer levels on mortality of COVID-19 patients in this study consisted of 12 studies from 3 continents, namely Asia; America;

and Europe. 8 studies from the Asian continent are all from China; 4 studies came from the Americas, 2 from the United States and 1 from Latin America; and 1 study from the European continent, namely from Italy. The distribution of the description of the research area is depicted on the map (Figure 2).

Quality research in research in this study was carried out based on the CASP Cohort Study Checklist worksheet from the Critical Appraisal Skills Program in the cohort study design with 12 steps as follows:

1. Does this research address a clearly focused problem?
2. Was the cohort organized in an appropriate way?
3. Is exposure accurately measured to minimize bias?
4. Are results measured accurately to minimize bias?
5. Has the author identified all confounding factors?
6. Was the follow-up of the subject sufficiently complete and long enough?
7. What are the results of this study?
8. How precise is the result?
9. Are the results reliable?
10. Can the results be applied?
11. Are the results of this study consistent with other available evidence?
12. What are the implications of this study for practice

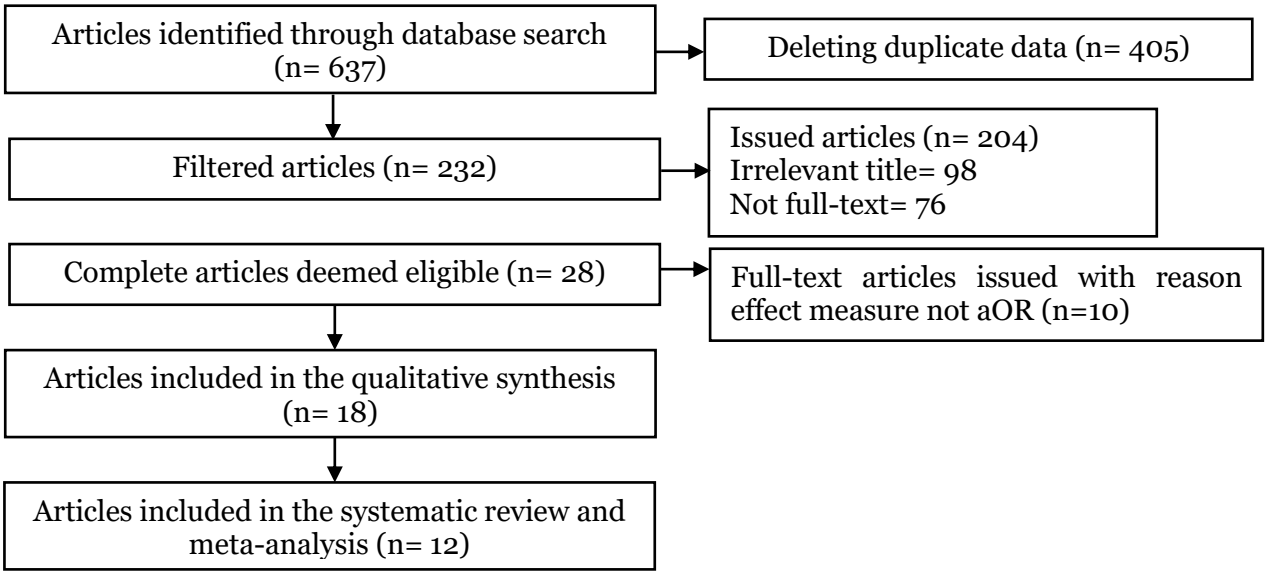

Figure 1. PRISMA Flowchart

After assessing quality of the study, the 12 articles were divided into 2 categories according to the independent variables included in the quantitative synthesis meta-analysis using RevMan 5.4.1.

The interpretation of the results meta-analysis conducted with Review Manager software version 5.4.1 can be seen through the forest plot. Based on the meta-analysis for prospective and retrospective cohort studies that have been described through forest plots (Figure 3), it can be seen that there is a moderate level of heterogeneity (I2= 61%; p<0.001), so the data analysis in the forest plot uses a random effects model. Based on the meta-analysis, it was found that an increase in D-dimer levels (>0.5 g/mL) increased the mortality risk of COVID-19 patients by 6.40 times compared to low D-dimer levels (≤0.5 g/mL) and was statistically

significant (OR= 6.40; 95% CI= 4.51 to 9.08; p< 0.001).

Based on the funnel plots in (Figure 4), it can be concluded that there is a publication bias characterized by the asymmetry of the left and right plots. The funnel plot shows there are 6 plots on the left and 4 plots on the right. The plots on the left are between standard errors of 0 and 1, while the plots on the right side are also between standard errors of 0 and 1. Bias can also be inferred from the imbalance in the distance between studies on the left and right plots.

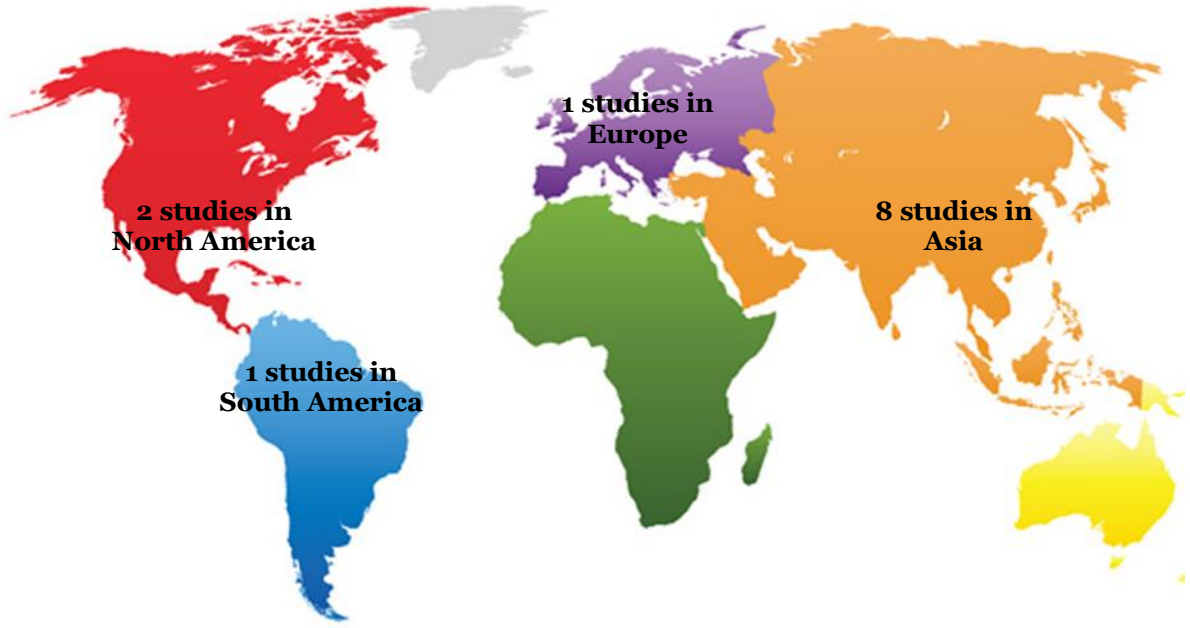

Figure 2. Map of Study Area

Table 1. Critical Appraisal of primary studies entered using the Joanna Briggs Institute (JBI) assessment

Study	Criteria												
	1	2	3	4	5	6	7	8	9	10	11	12	Total
Zhou et al. (2020)	1	1	1	1	1	1	1	1	1	1	1	1	12
Yao et al. (2020)	1	1	1	1	1	1	1	1	1	1	1	1	12
Du et al. (2020)	1	1	1	1	1	1	1	1	1	1	1	1	12
Tu et al. (2020)	1	1	0	1	0	1	1	1	1	1	1	1	10
Luo et al. (2020)	1	1	1	1	0	0	1	1	1	1	1	1	10
Cao et al. (2020)	1	1	1	1	0	0	1	1	1	1	1	1	10
Paranjpe et al. (2020)	1	1	1	1	1	1	1	1	1	1	1	1	12
Gomez-Mesa et al. (2021)	1	1	0	1	0	1	1	1	1	1	1	1	10
Mikami et al. (2020)	1	1	1	1	1	0	1	1	1	1	1	1	11
Li et al. (2020)	1	1	1	1	1	0	1	1	1	1	1	1	11
Giacomelli et al. (2020)	1	1	1	1	1	1	1	1	1	1	1	1	12
Wei et al. (2020)	1	1	1	1	1	1	1	1	1	1	1	1	12

Note: 1=yes, 0=no

Table 3. Description of the primary studies included in the meta-analysis

Author (year)	Country	Study Design	Sample	P	I	C	O	aOR (95%CI)
Zhou et al. (2020)	China	Retrospective Cohort	191	COVID-19 patients	D-dimer >0.5	D-dimer ≤0.5	Mortality	9.51 (3.23 to 28.06)
Yao et al. (2020)	China	Retrospective Cohort	108	COVID-19 patients	D-dimer >0.5	D-dimer ≤0.5	Mortality	6.29 (1.59 to 24.88)
Du et al. (2020)	China	Prospective Cohort	179	COVID-19 patients	D-dimer >0.5	D-dimer ≤0.5	Mortality	3.45 (1.21 to 9.88)
Tu et al. (2020)	China	Retrospective Cohort	174	COVID-19 patients	D-dimer >0.5	D-dimer ≤0.5	Mortality	16.18 (2.13 to 122.82)
Luo et al. (2020)	China	Retrospective Cohort	403	COVID-19 patients	D-dimer >0.5	D-dimer ≤0.5	Mortality	29.09 (10.34 to 81.82)
Cao et al. (2020)	China	Retrospective Cohort	102	COVID-19 patients	D-dimer >0.5	D-dimer ≤0.5	Mortality	4.51 (1.48 to 13.70)
Paranjpe et al. (2020)	United States of America	Retrospective Cohort	399	COVID-19 patients	D-dimer >0.5	D-dimer ≤0.5	Mortality	4.89 (3.07 to 7.78)
Gomez-Mesa et al. (2021)	Latin America	Retrospective Cohort	191	COVID-19 patients	D-dimer >0.5	D-dimer ≤0.5	Mortality	14.14 (6.31 to 31.70)
Mikami et al. (2020)	United States of America	Retrospective Cohort	1955	COVID-19 patients	D-dimer >0.5	D-dimer ≤0.5	Mortality	6.81 (5.47 to 8.49)
Li et al. (2020)	China	Retrospective Cohort	501	COVID-19 patients	D-dimer >0.5	D-dimer ≤0.5	Mortality	3.43 (2.37 to 4.96)
Giacomelli et al. (2020)	Italy	Retrospective Cohort	233	COVID-19 patients	D-dimer >0.5	D-dimer ≤0.5	Mortality	4.08 (0.94 to 17.82)
Wei et al. (2020)	China	Retrospective Cohort	229	COVID-19 patients	D-dimer >0.5	D-dimer ≤0.5	Mortality	3.62 (0.75 to 17.42)

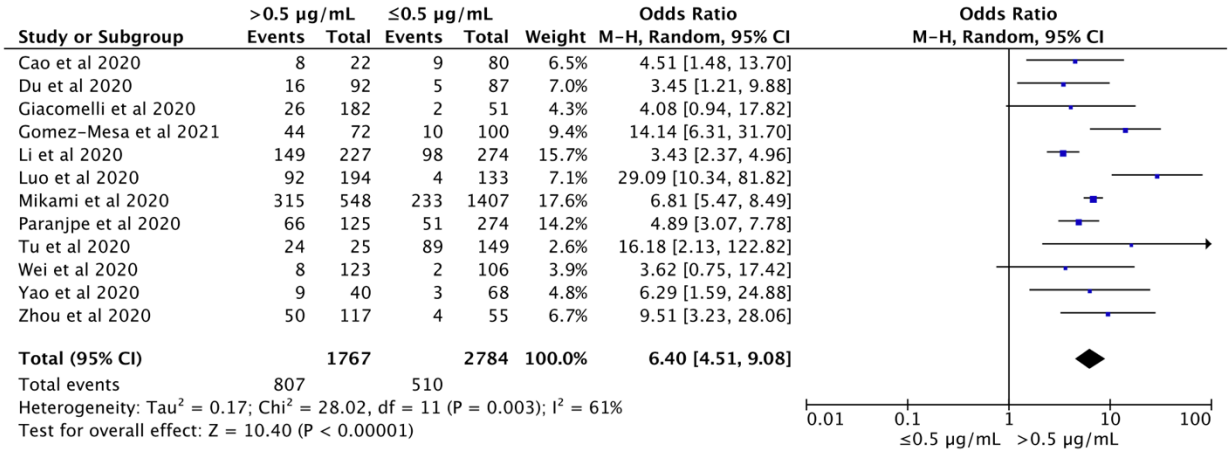

Figure 3. Forest Plot Analysis of the Effect of D-dimer Levels on Mortality of COVID-19 Patients

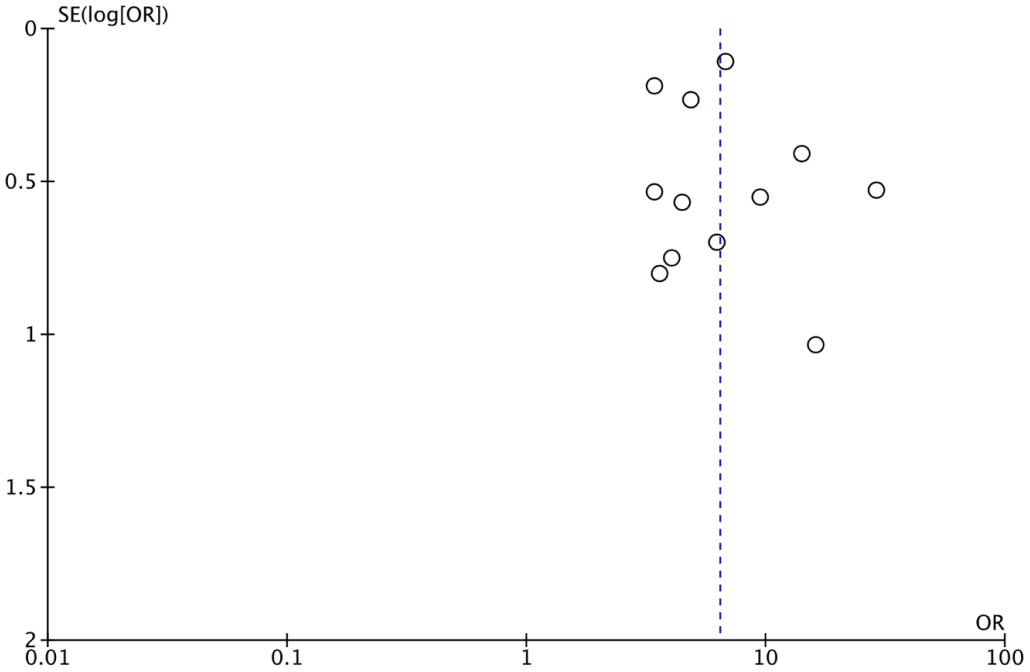

Figure 4. Funnel Plot Analysis of the Effect of D-dimer Levels on Mortality of COVID-19 Patients

DISCUSSION

This systematic review and meta-analysis discusses the effect of D-dimer levels on mortality in COVID-19 patients. The dependent variable studied was the mortality of COVID-19 patients. Research is considered important because it can strengthen evidence of clinical findings and laboratory characteristics that can be a risk factor for increasing mortality of COVID-19 patients. The results of primary studies conducted by systematic reviews and meta-analyses show that an epidemiological study with a larger sample and different demographic characteristics can describe the effect of D-dimer levels on mortality in COVID-19 patients.

COVID-19 affects the hematopoiesis and hemostasis system significantly. Lymphopenia is the most common laboratory finding. An increase in the ratio of neutron-

phils and lymphocytes has prognostic value in COVID-19 disease. Inflammatory parameters such as C-reactive protein (CRP), lactate dehydrogenase (LDH), and IL-6 have been reported to be elevated in COVID-19. In addition, other biomarkers such as ferritin and procalcitonin were also found to be elevated in COVID-19. Parameters of coagulation disorders that can be found in COVID-19 include increased D-dimer concentrations, prolonged prothrombin time (PT) or activated partial thromboplastin time (a-PTT), increased fibrinogen, and thrombocytopenia (Terpos et al., 2020).

D-dimer is a product of fibrin degradation formed in the process of degradation of blood clots by fibrinolysis. Elevated blood levels of D-dimer are predictors of suspected thrombosis found in deep vein thrombosis, pulmonary embolism, arterial thrombosis, DIC, pregnancy, inflammation, cancer, chronic liver disease, trauma, surgery, and vasculitis. Elevated D-dimer is often found in severe COVID-19 patients and is a marker of ARDS condition, need for intensive care unit care, and mortality. The study by Zhou et al. (2020) showed that an increase in D-dimer >1.0 l/mL was the most likely predictor of mortality in COVID-19 patients. Another study by Cui et al. (2020) showed that D-dimer >1.5 l/mL was a predictor of venous thromboembolism in COVID-19 patients with a sensitivity rate of 85% and specificity of 88.5%.

Effect of D-dimer Levels on Mortality of COVID-19 Patients

This systematic review and meta-analysis analyzed 12 articles with a cohort study design (10 retrospective articles and 2 prospective articles). The results showed that an increase in D-dimer levels (>0.5 g/mL) increased the risk of mortality in COVID-19 patients by 6.40 times compared to low D-dimer levels (≤0.5 g/mL) and was statistically significant (OR= 6.40; 95% CI = 4.51 to 9.08; p<0.001)

This study is in line with research by Nugroho et al. (2020) which showed that increased levels of D-dimer at admission were associated with a 5.54 times increased risk of disease severity and death in SARS-CoV-2 infection with aOR= 5.54 and 95% CI= 3.40 to 7.67. This study showed a significant relationship between increased levels of D-dimer at hospital admission and mortality in COVID-19 patients.

Milenkovic et al. (2021) reported that a D-dimer 760 ng/mL on admission to the ICU can effectively predict in-hospital mortality in COVID-19 patients. In the case of COVID-19 patients with D-dimer measured at 0.5 mg/L, the risk of death was 7.325-fold greater. The prognostic value of D-dimer is important in infection. Higher mortality rates have been demonstrated in patients with sepsis with high levels of D-dimer. Similarly, it has been reported that high levels of D-dimer can be helpful in predicting the severity of community pneumonia.

Pya et al. (2021) showed that an increase in D-dimer levels >0.5 g/mL increased the risk of mortality by 5.13 times in COVID-19 patients. Meanwhile, Hayiroglu et al. (2020), reported that the mean level of D-dimer obtained during the first five days of hospitalization was an independent predictor in mortality COVID-19 patients.

The severity or mortality of COVID-19 alone can be detected by examining the levels of D-dimer, but also by examining the levels of CRP, ferritin, IL-6 and LDH. There is an increasing trend of these predictors in severe cases of COVID-19 (Grobler et al., 2020).

AUTHORS CONTRIBUTION

Yusuf Ryadi as the main researcher who chose the topic, conducted a search for data collection in this study. Yulia Lanti Retno

Dewi and Hanung Prasetya conducted data analysis and reviewed research documents.

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CONFLICT OF INTEREST

There is no conflict of interest of this study.

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