

## D-DIMER AS A PREDICTOR OF MORTALITY PROGNOSIS IN COVID-19 PATIENTS: SYSTEMATIC REVIEWS

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### ABSTRACT

Corona Virus Disease 19 or Covid-19 is an infectious disease caused by the coronavirus officially named SARS-CoV-2. In December 2019, an outbreak of the COVID-19 disease was first discovered in Wuhan City of China's Hube Province and spread throughout the world. On March 11, 2020, WHO declared Covid-19 a pandemic. COVID-related deaths are largely associated with hypercoagulability and an increased risk of venous thromboembolic events (VTE), leading to thrombotic inflammation in severe conditions. The literature review writing approach used is *Systematic Literature Review* ( SLR ) with the PRISMA method without meta-analysis. This literature review is carried out to obtain relevant information by searching articles on online databases derived from Scopus. The keywords used for searching related articles are *d-dimer, Covid-19, and mortality*. Based on the literature study conducted, there are 6 articles that support the discovery of D-Dimer as a predictor of the death of COVID-19 hospitalized patients. *The cut off* of D-Dimer levels used in each study varied according to the characteristics of the study patients.

**Keywords** : COVID-19, death, D-dimer, mortality, pandemic

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### 1. INTRODUCTION

Corona Virus Disease 19 or what is known as Covid-19 is an infectious disease caused by ole corona virus which is officially named SARS-CoV-2. This virus was named SARS- CoV because of its genome homology.<sup>1</sup> Coronaviruses are large, positive single-stranded RNA (+ ssRNA ) viruses of the Coronaviridae family . Coronaviruses can infect a variety of vertebrates, including bats, birds, pangolins, snakes, mice and humans.<sup>2,3</sup>

Since December 2019, the Covid-19 disease outbreak was first discovered in Wuhan City, Hube Province , China and spread throughout the world. On March 11 2020, WHO declared Covid-19 a pandemic.<sup>4</sup> The Covid-19 pandemic which has spread throughout the world has even caused deaths. COVID-related deaths are mostly associated with hypercoagulability and increased risk of venous thromboembolic (VTE) events, leading to inflammatory thrombosis in severe conditions.<sup>5</sup> Thrombotic arterial and venous complications and coagulopathies include.

*Disseminated Intravascular Coagulation* ( DIC ) has become a major cause of morbidity and mortality, especially in patients with comorbid conditions, prolonged hospitalization, *intensive care admission Care Unit* (ICU), and mechanical ventilation. Excessive inflammation, platelet activation , endothelial dysfunction, and stasis play important roles in the development of thrombotic complications. D-dimer is a product of fibrin degradation and reflects the activation of thrombotic and fibrinolytic pathways.<sup>6-10</sup>

D-dimer is a product of fibrin degradation, originating from the formation and lysis of fibrin cross-links and reflecting the activation of coagulation and fibrinolysis . Among the clinical and biochemical parameters associated with poor prognosis, elevated D-dimer levels appear to be predictive of acute respiratory distress syndrome (ARDS), need for admission to the intensive care unit (ICU) or death. <sup>11-13</sup> A study has reported that Covid-19 is associated with hemostatic

abnormalities and increased D-dimer levels which are associated with patient mortality.<sup>13,14</sup> For this reason, writing literature This review aims to discuss D-Dimer as a prognosis for death in Covid-19 patients.

## **2. METHOD**

Approach to writing literature The review used is *Systematic Literature Reviews* (SLR) using the PRISMA method ( *Preferred Reporting Items for Systematic Reviews and Meta- analysis* ) without meta-analysis. Literature This review was carried out to obtain relevant information by searching for articles in the database online which comes from Scopus . The keywords used to search for related articles are *d-dimer, Covid-19, mortality* . The procedure used in this research is *Systematic Reviews* from *University of Maryland Libraries* , namely:

### **1. Identify the research question**

This research question is "What is the influence of D-Dimer levels as a predictor of mortality prognosis for Covid-19 patients?"

### **2. Determine inclusion criteria**

The inclusion criteria in this study used the PICO ( *Population , Intervention , Comparison , Outcome* ) approach. Inclusion criteria consist of: (a) Articles

published in 2020-2022; (b) Articles published in International Journals; (c) The articles used are articles with relevant retrospective cohort studies.

### **3. Article search**

Keywords used in *the database Scopus* is “ *D-Dimer AND mortality patient Covid-19*”, “*Prognosis AND D-Dimer AND Mortality AND Covid-19*”.

### **4. Article selection**

At the article selection stage, the PRISMA flow diagram is used to filter the articles to be selected. Article selection was first carried out by screening the titles and abstracts to exclude articles that did not meet the inclusion criteria.

### **5. Critically examine the article**

Critically review the article using the STROBE ( *Strengthening* ) *guide the reporting of observational studies in epidemiology* ) according to the cohort study design.

### **6. Extracting articles**

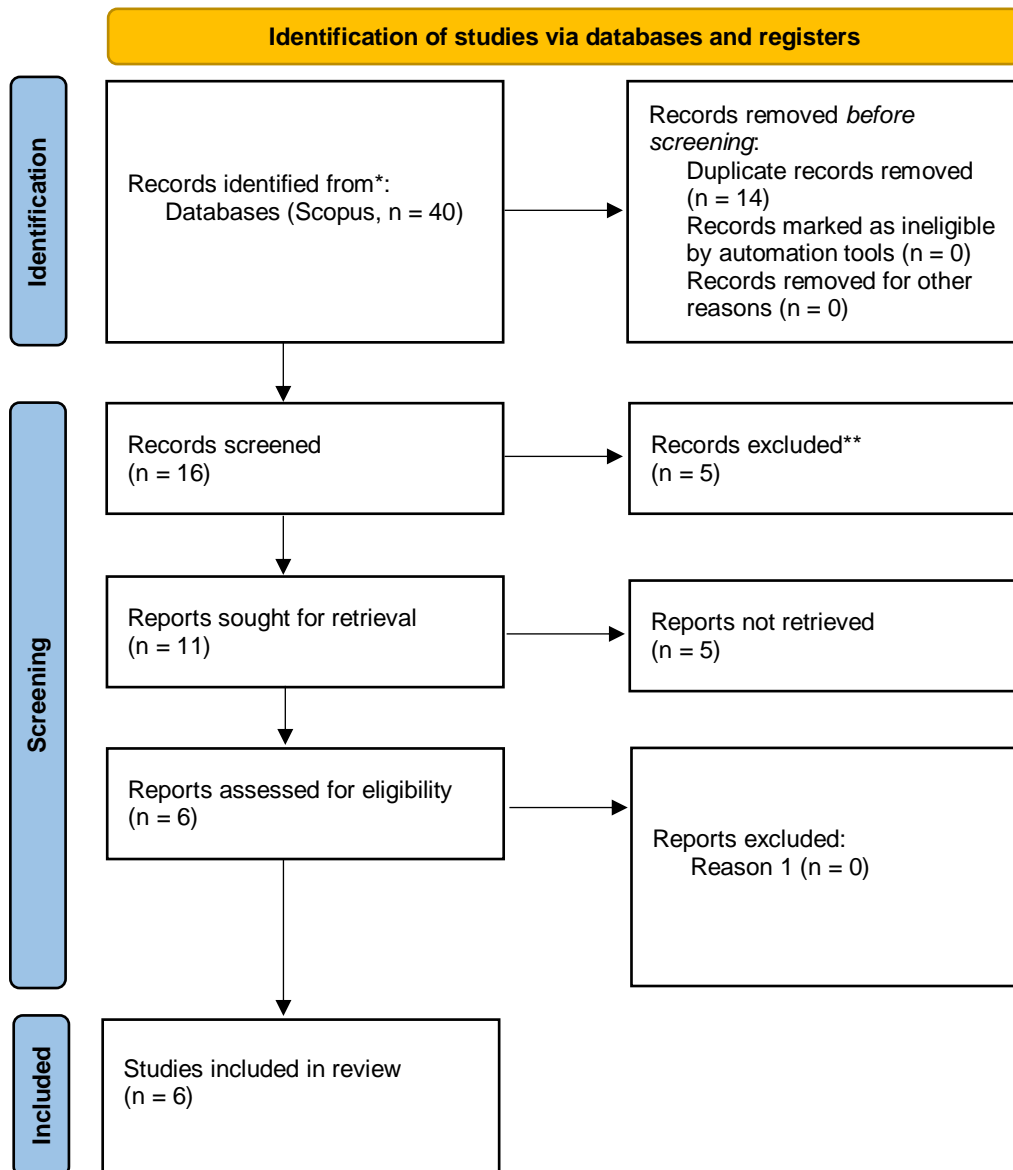
At the article extraction stage, a brief review table is used which consists of the author's name, journal information, title and findings.

### **7. Synthesis of articles**

*Synthesis* guidelines *Without Meta-analysis* ( SwiM ).

### 3. RESULTS

Found 40 articles relevant to keywords from *the database* Scopus . The following is a PRISMA diagram carried out in the article search process presented in **Figure 1** .



**Figure 1. Flow diagram**

The extraction results from 6 articles are presented in **table 1** .

**Table 1. Article Extraction Results**

No.	Author , Title , Journal	Method Design	Results
1.	Milenkovic , M., Hadzibegovic , A., Kovac , M., Jovanovic , B., Stanisavljevic , J., Djikic , M., Sijan , D., Ladjevic , N., Palibrk , I., Djukanovic , M., Velickovic , J., Ratkovic , S., Brajkovic , M., Popadic , V., Klasnja , S., Toskovic , B., Zdravkovic , D., Crnokrak , B., Markovic , O., Bjekic-Macut , J ., ... Zdravkovic , M. (2022). D-dimer, CRP, PCT, and IL-6 Levels at Admission to ICU Can Predict In-Hospital Mortality in Patients with COVID-19 Pneumonia. <i>Oxidative medicine and cellular longevity</i> , 2022 , 8997709. <a href="https://doi.org/10.1155/2022/8997709">https://doi.org/10.1155/2022/8997709</a> <sup>15</sup>	Retrospective Cohort Study	Our study proved that D-dimer concentrations above 760 ng / mL FEU, measured on admission to the ICU, were associated with a higher risk of death during hospitalization. The cutoff value of D-Dimer is 760 ng / mL FEU (Sn 63.4%, To 57.1%). D-dimer = 760 ng / mL was a statistically significant predictor of in-hospital mortality. C-Index = 0.64, 95% CI = 0.57-0.7.
2 .	Selcuk , M., Cinar , T., Gunay , N., Keskin , M., Cicek , V., Kilic , S., Asal, S., & Orhan , A.L. (2021). Comparison of D-dimer Level Measured on the Third Day of Hospitalization with Admission D-dimer Level in Predicting In-hospital Mortality in COVID-19 Patients . <i>Medeniyet medical journal</i> , 36 (1), 1–6. <a href="https://doi.org/10.5222/MMJ.2021.07348">https://doi.org/10.5222/MMJ.2021.07348</a> <sup>16</sup>	Retrospective Study	The ideal value for D-dimer levels on the 3rd day of hospitalization is 774 q/ mL (area under curve (AUC): 0.903, 95% CI: 0.836-0.968; p<0.01) with sensitivity of 83.2% and specificity of 83.6%. It was noted that D-dimer levels on day 3 of hospitalization had higher sensitivity (83.2% vs. 67.6%, respectively) and AUC values than D-dimer levels on admission (0.903 vs. 0.799, respectively). .
3.	Chocron , R., Duceau , B., Gendron , N., Ezzouhairi , N., Khider , L., Trimaille , A., Goudot , G., Weizman , O., Alsac , J.M., Pommier , T., Bory , O., Cellier , J., Philippe , A., Geneste , L., Ben Abdallah, I., Panagides , V., El Batti , S., Marsou , W., Juvin , P., Deney , A. , ... Critical COVID-19 France investigators (2021). D-dimer at hospital admission for COVID-19 are associated with in-hospital mortality , independent of venous thromboembolism : Insights from a French multicenter cohort studies. <i>Archives of cardiovascular diseases</i> , 114 (5), 381–393. <a href="https://doi.org/10.1016/j.acvd.2021.02.003">https://doi.org/10.1016/j.acvd.2021.02.003</a> <sup>17</sup>	Multicenter Retrospective Observational Study	off value for D-dimer on admission with the best prognostic ability of in-hospital mortality was 1128 ng / mL according to the ROC curve, with a sensitivity of 71.1% (95% confidence interval [CI] 62—78), specificity of 55, 6% (95% CI 52-58), positive predictive value 15.8% (95% CI 13-19) and negative predictive value 94.3% (95% CI 92-96). The area under the curve for in-hospital mortality was 64.9% (95% CI 60-69). ( <i>p-value</i> = 0.026; OR=1.88; 95%CI=1.08-3.30)
4.	Soni, M., Gopalakrishnan , R., Vaishya , R., & Prabu, P. (2020). D -dimer levels are useful predictor for mortality	Retrospective Study	Elevated D-dimer (0.50 mg /ml) was seen in 80.1% (387/483) of hospitalized patients. Median D-dimer value among

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<p>in patients with COVID-19: Analysis of 483 cases . <i>Diabetes &amp; metabolism syndromes</i> , 14 (6), 2245–2249. <a href="https://doi.org/10.1016/j.dsx.2020.11.007">https://doi.org/10.1016/j.dsx.2020.11.007</a><sup>18</sup></p>	<p>non-survivors was 6.34 mg/ml and 0.94 mg/ml among survivors. Kaplan- Meier survival curves for D-dimer levels showed that a D-dimer level of 2.01 mg/ml was a significant predictor of subsequent death (P &lt; 0.01; HR, 3.165; 95% CI, 2.013-4.977). High D-dimer values (0.50 mg/ml) were observed in 72 of 75 (96%) cases with fatal outcome. Fifty-six of 75 cases (74.67%) had D-dimer levels of 2.01 mg/ml.</p>
<p>5. Boknäs , N., Laine , C., Hillarp , A., Macwan , A.S., Gustafsson , K.M., Lindahl , T.L., &amp; Holmström , M. (2022). Associations between hemostatic markers and mortality in COVID-19 - Compounding effects of D-dimer, antithrombin and PAP complex . <i>Thrombosis research</i> , 213 , 97–104. <a href="https://doi.org/10.1016/j.thromres.2022.03.013">https://doi.org/10.1016/j.thromres.2022.03.013</a><sup>19</sup></p>	<p>Single-center cohort studies</p> <p>In COVID-19+ patients, we found a marked increase in von factor plasma levels Willebrand ( vWF ) and fibrinogen. Excess mortality was observed in COVID-19+ patients with deviations of the following hemostatic markers: high D-dimer, low antithrombin, or low plasmin-antiplasmin (PAP) complex formation, with Odds Ratios (OR) for death 4.7 (95% confidence interval (CI95) 1.7–12.9; p = 0.003 for D-dimer &gt;0.5 mg /L, 5.9 (CI95 1.8–19 .7; p = 0.004) for antithrombin (AT) 0.85 kIU /l and 4.9 (CI95 1.3–18.3 ; p = 0.019) for PAP &lt; 1000 g/L COVID-19+ with combined defects in markers of fibrinolysis and coagulation, with an OR for death of 15.7 (CI95 4.3–57; p &lt; 0.001) for patients with PAP &lt;1000 g/L and D-dimer &gt;0.5 mg /L and 15.5 (CI 95% 2.8-87, p = 0.002) for patients with PAP &lt;1000 g/L and AT 0.85 kIU /L We observed an increase in the fraction of incompletely degraded D-Dimer fragments in COVID-19+ patients with low PAP, indicating impaired fibrinolytic breakdown of fibrin cross-links.</p>
<p>6. Zhang , L., Yan, X., Fan , Q., Liu, H., Liu, X., Liu, Z., &amp; Zhang , Z. (2020). D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. <i>Journal of thrombosis and haemostasis : JTH</i> , 18 (6), 1324–1329. <a href="https://doi.org/10.1111/jth.14859">https://doi.org/10.1111/jth.14859</a><sup>8</sup></p>	<p>Retrospective Study</p> <p>A total of 343 eligible patients were enrolled in this study. The optimum D-dimer cutoff value for predicting in-hospital mortality is 2.0 g/ mL with a sensitivity of 92.3% and a specificity of 83.3%. There were 67 patients with D-dimer 2.0 g/ mL , and 267 patients with D-dimer &lt;2.0 g/ mL at admission. 13 deaths occurred during hospitalization. Patients with D-dimer levels 2.0 g/ mL had a higher incidence of death when compared with those with D-dimer levels &lt;2.0 g/ mL (12/67 vs 1/267, P &lt; .001; hazard ratio , 51, 5 ; 95% confidence interval, 12.9-206.7).</p>

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#### **4. DISCUSSION**

D-Dimer is a biomarker of fibrin formation and degradation that can be measured in whole blood or plasma. Healthy individuals have low circulating levels of D-Dimer, whereas elevated circulating levels of D-Dimer are found in conditions associated with thrombosis. D-Dimer is a soluble degradation product derived from plasmin from cross-linked fibrin.<sup>20,21</sup> The process begins when thrombin produced by the coagulation system converts dissolved fibrinogen into fibrin monomers. D-Dimer has been studied extensively for the diagnosis of venous thromboembolism (VTE). D-dimer has also been evaluated to determine the optimal duration of anticoagulation in VTE patients, to diagnose and monitor intravascular coagulation disseminated disease (DIC), and to identify medical patients at high risk for VTE.<sup>21</sup>

High serum D-Dimer levels are not a specific disease, but are usually associated with several medical conditions such as infection, inflammation, and pregnancy.<sup>22</sup> During the Covid-19 pandemic, D-Dimer > 0.5 µg/ mL was first reported as a prognostic indicator in a retrospective analysis with a large cohort from China.<sup>23</sup> D-Dimer elevation has been reported as one of the most common findings from laboratory examination results that occur in hospitalized Covid-19 patients. D-Dimer was identified as a soluble product<sup>8</sup> of plasmin-mediated fibrin breakdown triggered after initiation of the coagulation and fibrinolysis cascade.<sup>24</sup> In the period before the Covid-19 pandemic, D-Dimer in the normal range had been shown to have higher sensitivity but much lower specificity for predicting thromboembolic conditions.<sup>25</sup>

Several previous studies have proven that high D-Dimer levels are more common in Covid-19 patients who do not survive than in patients who survive. Research conducted by Guan et al who conducted research on 1,099 patients with confirmed cases of Covid-19 at more than 550

hospitals in China found that patients who did not survive had much higher D-Dimer (median 2.12 µg/ mL ) than patients who survived ( mean 0.61 µg/ mL ).<sup>26</sup> This is also supported by research conducted by Zhou et al who found that D-Dimer levels > 1 µg/ mL were a predictor of death in patients hospitalized due to Covid-19 [ Odds Ratio (OR) = 18.42; 95%CI = 2.64-128.55; *p-value* = 0.0033].<sup>24</sup>

Several studies in this literature study found that increasing D-Dimer was a predictor of death in Covid-19 patients. Retrospective cohort study conducted by Milenkovic et al (2022) proved that D-dimer concentrations above 760 ng / mL FEU, measured on admission to the ICU, were associated with a higher risk of death during hospitalization. The cutoff value of D-Dimer is 760 ng / mL FEU (Sn 63.4%, To 57.1%). D-dimer = 760 ng / mL was a statistically significant predictor of in-hospital mortality. C-Index = 0.64, 95%CI = 0.57-0.7.<sup>15</sup> Research conducted by Selcuk et al (2021) found that the ideal value for D-dimer levels on the 3rd day of hospitalization was 774 q/ mL (area under curve (AUC): 0.903, 95% CI: 0.836-0.968; *p*<0.01) with sensitivity of 83.2% and specificity of 83.6%.<sup>16</sup> Furthermore, research conducted by Chocron et al (2021) found that the optimal cut-off value for D-dimer on admission with the best prognostic ability of in-hospital mortality was 1128 ng / mL according to the ROC curve, with a sensitivity of 71.1% (95% confidence interval [CI] 62- 78 ), specificity 55.6% (95% CI 52-58), positive predictive value 15.8% (95% CI 13-19) and negative predictive value 94.3% (95% CI 92-96). The area under the curve for in-hospital mortality was 64.9% (95% CI 60-69). ( *p-value* = 0.026; OR=1.88; 95%CI=1.08-3.30).<sup>17</sup> Research conducted by Soni et al (2020) showed that a D-dimer level of 2.01 mg /ml was a significant predictor of subsequent death (*P* < 0.01; HR, 3.165; 95% CI, 2.013-4.977).<sup>18</sup> Single-center cohort study conducted by Boknäs et al

found that higher mortality was observed in COVID-19+ patients with deviations in the following hemostatic markers: high D-dimer, low antithrombin, or plasmin complex formation for D-dimer >0.5 mg /L, 5.9 (CI 95% = 1.8–19.7; p = 0.004).<sup>19</sup> Furthermore, research conducted by Zhang et al (2020) found that the optimum D-dimer cutoff value for predicting in-hospital mortality was 2.0 g/ mL with a sensitivity of 92.3% and a specificity of 83.3%.<sup>8</sup>

D-Dimer is a fragment produced by cleavage of fibrin by plasmin during clot dissolution.<sup>27</sup> Therefore, high admission D-Dimer may give rise to increased fibrinolysis, some evidence of intravascular coagulation and thrombotic disease, and indicate cytokine storm, tissue damage or the potential for sepsis as seen in severe clinical manifestations of Covid-19.<sup>28,29</sup> Recent evidence also shows that patients with severe Covid-19 have an increased incidence of pulmonary and *deep embolism veins thrombosis* (DVT) during the clinical course of the disease.<sup>30–33</sup> A limitation in writing this literature study is that the database may not include all existing database sources.

## 5. CONCLUSION

COVID-related deaths are mostly associated with hypercoagulability and increased risk of venous thromboembolic (VTE) events, leading to inflammatory thrombosis in severe conditions. D-dimer is a product of fibrin degradation and reflects the activation of thrombotic and fibrinolytic pathways. COVID-related deaths are mostly associated with hypercoagulability and increased risk of venous thromboembolic (VTE) events, leading to inflammatory thrombosis in severe conditions. D-dimer is a product of fibrin degradation and reflects the activation of thrombotic and fibrinolytic pathways. Research conducted by Guan et al and Zhou et al have proven increased D-Dimer levels as a predictor deaths of Covid-19 patients who are hospitalized. Based on a literature

study conducted, there are 6 articles that support the discovery of D-Dimer as a predictor of death in hospitalized Covid-19 patients. *The cut off* level of D-Dimer used in each study varies according to the characteristics of the study patients.

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