

Literature Review of D-Dimer Levels on Disease Severity and Mortality, Along with Benefits of Anticoagulants in Covid-19 Patients

Maria Immaculata Iwo^{1,*}, Bhakti Pratiwi¹, Karenina Octavienne Sunny²

¹ Pharmacology Clinical Pharmacy Research Group, School of Pharmacy, Institut Teknologi Bandung, Indonesia 40132; maria@fa.itb.ac.id (M.I.I.); bhaktipratiwi@itb.ac.id (B.P.); kareninaoctv@gmail.com (K.O.S.);

² School of Pharmacy, Institut Teknologi Bandung, Indonesia 40132;

* Correspondence: maria@fa.itb.ac.id (M.I.I.);

Scopus Author ID 7801542533

Received: 20.07.2022; Accepted: 24.11.2022; Published: 6.01.2023

Abstract: Since December 2019, the COVID-19 pandemic has continued to spread across the world. Elevated D-dimer has known to have occurred in COVID-19 patients, which was associated with hypercoagulable conditions and could lead to various complications. This literature study aims to identify the effect of increasing D-dimer on the severity, mortality, and other outcomes and the benefits of anticoagulants used in COVID-19 patients. The research was conducted from February 17, 2021, to July 28, 2021, through PubMed, Scopus, and Clinical Trials.gov databases. It was then updated on November 1, 2022, and 116 articles were obtained for this study. The results showed that increased D-dimer was associated as a risk factor for severity, disease progression, and mortality and could predict several outcomes, such as the need for intensive care, cardiac injury, respiratory failure, and thromboembolic events. Several studies suggested the benefit of using prophylactic anticoagulants in COVID-19 patients, but there was insufficient evidence showing that higher doses of anticoagulants were beneficial.

Keywords: covid-19; D-dimer; anticoagulant; coagulation; thrombosis.

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1. Introduction

In December 2019, an infection by a novel coronavirus that transmits rapidly through humans happened in Wuhan, China. The International Committee on Taxonomy of Viruses (ICTV) named this virus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), and the World Health Organization (WHO) named this disease Coronavirus Disease 2019 (COVID-19) [1]. The SARS-CoV-2 is a positive-sense single-stranded RNA virus whose genome could be detected with RT-PCR. In March 2020, WHO stated COVID-19 was a pandemic outbreak [2].

Based on WHO data, on August 25, 2021, more than 213 million COVID-19 cases were confirmed, and more than 4.4 million deaths were caused by COVID-19. The highest number of confirmed cases happened in America, with 82 million cases; Europe, more than 64 million cases; and Southeast Asia, with more than 40 million cases. Meanwhile, more than 4 million cases have been confirmed, and more than 129 thousand death cases caused by COVID-19 happened in Indonesia [3].

Coagulation parameters, including D-dimer in COVID-19 patients, may increase due to an exaggerated inflammatory response such as a cytokine storm [4]. D-dimer is a biological marker of coagulation and fibrinolysis activation to assess thrombotic activity. It is commonly used to help confirm the diagnosis of venous thromboembolism (VTE), such as deep vein thrombosis (DVT) and pulmonary embolism (PE), and disseminated intravascular coagulation (DIC) [5]. In severe SARS-CoV-2 infection, proinflammatory cytokines release is uncontrolled, which causes endothelial cell dysfunction and increases procoagulant conditions [6].

The increase in D-dimer is associated with disease severity and mortality in COVID-19 patients [7]. In a study involving 1,099 patients in China, 46.4% of COVID-19 patients had elevated D-dimer levels of ≥ 0.5 mg/L, with a higher proportion in patients with severe COVID-19 and patients who require admission to the intensive care unit (ICU), mechanical ventilation, to death [8]. Based on Han *et al.* (2020), the mean D-dimer level in COVID-19 patients was higher than in healthy subjects (10.36 vs. 0.26 mg/L; $P < 0.001$). The D-dimer mean also increased proportionally to the severity of the disease, i.e., mild-moderate (2.14 ± 2.88 mg/L), severe (19.11 ± 35.48 mg/L), and critical (20.04 ± 32.39 mg/L). Meanwhile, a study in Indonesia by Mardewi & Yustiani (2021) stated that the D-dimer mean of COVID-19 patients treated at the Bali Mandara Hospital was 2.6 ± 6.5 mg/L with 23.7% of patients had an increase in D-dimer up to ≥ 2.0 mg/L. Therefore, D-dimer levels can be used as one of the parameters that can help patient management [11].

The International Society on Thrombosis and Haemostasis (ISTH) recommends giving thromboprophylaxis with low-molecular-weight heparin (LMWH), unfractionated heparin (UFH), or Fondaparinux to hospitalized COVID-19 patients who have no contraindications. Meanwhile, COVID-19 patients who require intensive care and are at high risk can be considered for administering a moderate dose of LMWH [12]. Enoxaparin or Nadroparin are generally given types of heparin [13]. However, in several studies that have been carried out, there is not strong enough evidence to determine the risks and benefits of anticoagulant prophylaxis for hospitalized patients with COVID-19 [14]. Therefore, this literature study aims to identify the effect of increased D-dimer levels on the disease severity, the possible disease outcome, and mortality of COVID-19 patients, as well as to identify the benefits of using anticoagulants in COVID-19 patients.

2. Materials and Methods

This research is a descriptive study of 115 articles which are grouped into 20 articles regarding the effect of D-dimer on disease severity, 39 articles regarding the effect of D-dimer on mortality, 40 articles regarding the effect of D-dimer on the disease outcome of COVID-19 patients, and 16 articles regarding the benefits of anticoagulants in COVID-19 patients. The literature search was carried out from February 17, 2021, to July 28, 2021. Then, the data was updated on November 1, 2022.

This literature was searched on the PubMed and Scopus databases. The keywords ("d-dimer") AND ("covid-19" OR "sars-cov-2" OR "2019-ncov" OR "coronavirus disease 2019" OR "novel coronavirus 2019") AND ("severity" OR "mortality" OR "outcome") are used to search articles regarding the effect of D-dimer on disease severity, mortality and other outcomes in COVID-19 patients. Meanwhile, to obtain articles related to the benefits of using anticoagulants in COVID-19 patients, used the keywords ("d-dimer") AND ("covid-19" OR "sars-cov-2" OR "2019-ncov" OR "coronavirus disease 2019" OR "novel coronavirus 2019")

AND ("anticoagulant"). A search was also conducted on ClinicalTrials.gov, a database of clinical trials from various countries, to provide information on the safety, quality, and efficacy of drugs to obtain additional information regarding the use of anticoagulants in COVID-19 patients. The search was conducted using the keyword "covid-19" and other terms "anticoagulant".

The literature search from national journals and/or Indonesian journals using Google Scholar with the keywords "d-dimer" and "covid-19 patients" obtained 81 results. However, no relevant articles met the eligibility criteria after screening by title, abstract, inclusion, and exclusion criteria.

The COVID-19 disease severity classification is according to the [15] and the "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia" published by [16].

Table 1. COVID-19 disease severity classification.

Disease Severity	Criteria Based on WHO	Criteria Based on NHC
Mild	Undergo the signs and symptoms of COVID-19 without experiencing hypoxia or pneumonia.	Undergo the signs and symptoms of COVID-19 without developing pneumonia.
Moderate	Undergo signs and symptoms of pneumonia such as fever, cough, dyspnea, and rapid respiratory rate, but oxygen saturation (SpO ₂) ≥90%.	Undergo fever and respiratory symptoms with pneumonia.
Severe	In adults, it meets one of the following criteria: - SpO ₂ <90%; however, SpO ₂ of 90-94% in patients with normal lung conditions is an early sign of severe disease; - Respiration rate >30 breaths/minute; and - Signs of severe respiratory distress.	In adults, it meets one of the following criteria: - Respiration rate ≥30 breaths/min; - SpO ₂ at rest ≤93%; - The ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO ₂ /FiO ₂) ≤300 mmHg; - The chest X-ray showed lesions >50% for 24-48 hours.
Critical	ARDS, sepsis, septic shock, or other conditions require mechanical ventilation or other life support therapy.	Respiratory failure, mechanical ventilation, shock, and organ failure require intensive care (ICU).

Sources: [15, 16]

The inclusion criteria used for articles from PubMed, Scopus, Google Scholar, and ClinicalTrials.gov are: Journal that discusses the effect of D-dimer and the use of anticoagulants in patients with COVID-19; Scopus-indexed journal in English with a rank of Q1 to Q3; SINTA-accredited national or Indonesian journal with a rank of S1 to S3.

The exclusion criteria used for articles from PubMed, Scopus, Google Scholar, and ClinicalTrials.gov are: Comments, letters to the editor, opinions, reviews, recommendations, and guidelines, and case reports; Studies that do not analyze the effect of D-dimer levels in COVID-19 patients or studies on the use of anticoagulants in COVID-19 patients without involving the D-dimer parameters; Studies using normal limits for D-dimer levels other than <500 ng/mL. According to the American Haematological Community (ASH), the D-dimer level limit for a healthy person is generally less than 500 ng/mL, but for someone over 50 years old, it can be adjusted to 10 times their age [17]; Studies involving patients diagnosed with COVID-19 without confirmation using RT-PCR or patients diagnosed through serologic/antibody testing.

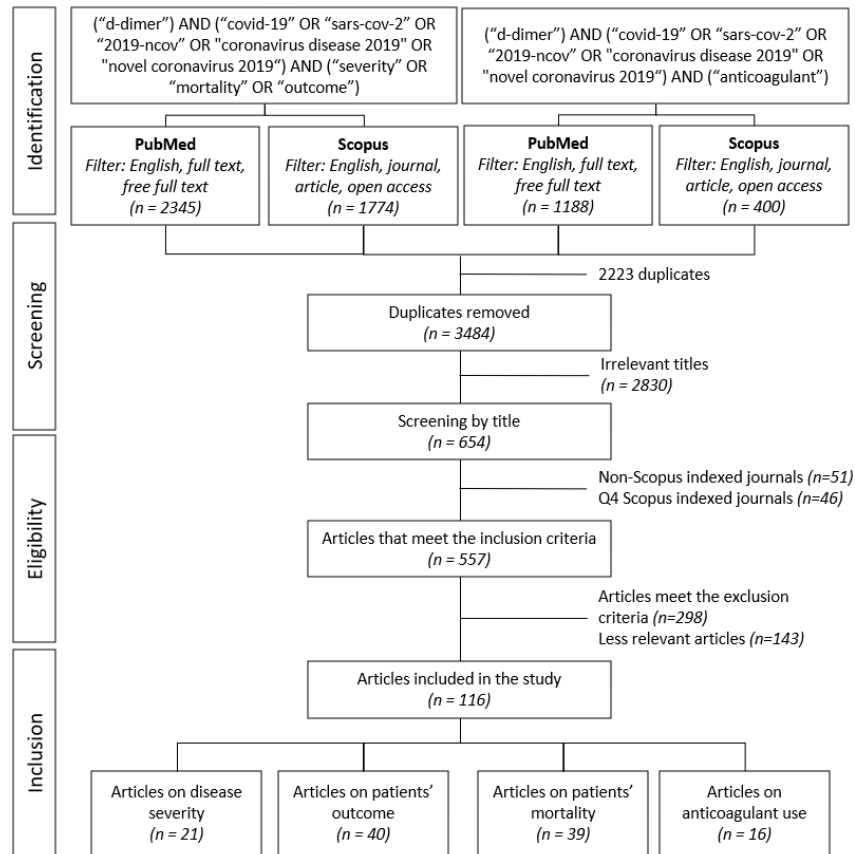


Figure 1. Literature search flow from PubMed and Scopus.

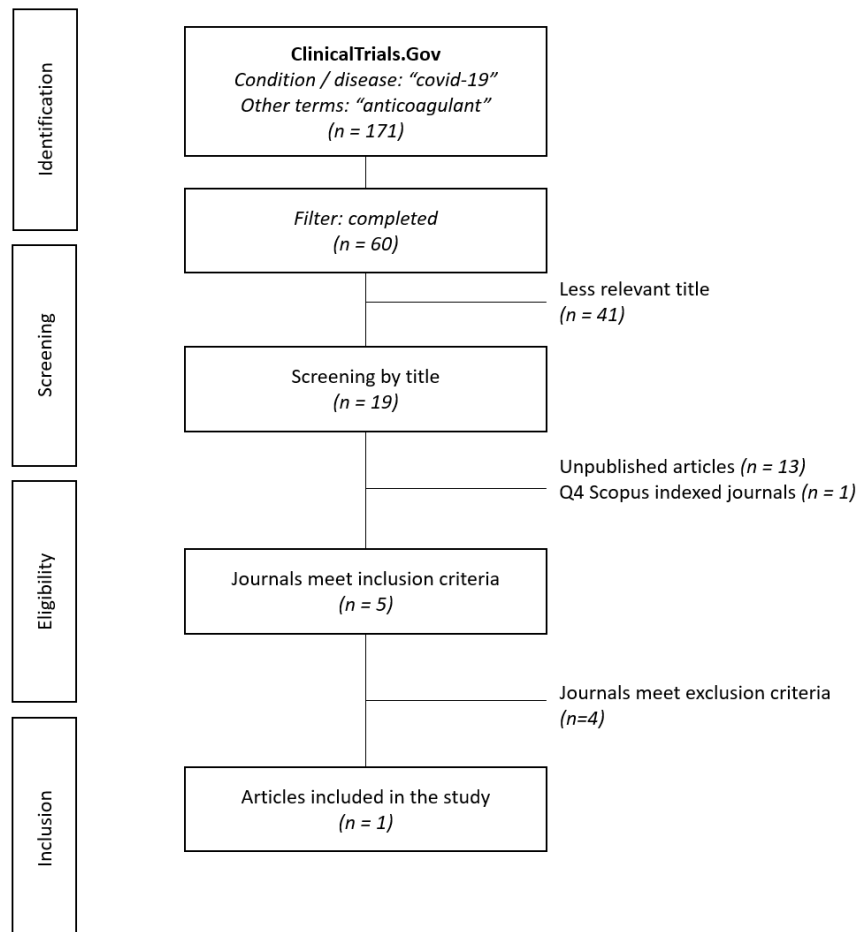


Figure 2. Literature search flow from ClinicalTrials.gov.

3. Results and Discussion

3.1. Literature search results.

The literature search found 100 articles related to D-dimer in COVID-19 patients grouped by the outcome measured in patients (Table 2). In addition, 16 journals were also found related to the benefits of using anticoagulants in COVID-19 patients.

Table 2. Classification of literature search results.

No.	Study Classifications	Number of Studies
1.	Effect of increased D-dimer on the COVID-19 severity	21
2.	Effect of increased D-dimer on acute kidney injury	2
3.	Effect of increased D-dimer on the need for admission to the ICU	4
4.	Effect of increased D-dimer on the incidence of cardiac injury	1
	Effect of increased D-dimer on cytokine storm	1
5.	Effect of increased D-dimer on the duration of hospitalization in the ICU	2
5.	Effect of increased D-dimer on the need for mechanical ventilation	2
6.	Effect of increased D-dimer on organ dysfunction	1
7.	Effect of increased D-dimer on respiratory failure	2
9.	Effect of increased D-dimer on thromboembolic events	25
9.	Effect of increased D-dimer on mortality of COVID-19 patients	39
10.	Benefits of using anticoagulants in COVID-19 patients	16

3.2. D-dimer formation mechanism.

D-dimer is a marker product of coagulation activation and fibrinolysis that can be measured through blood or plasma [5]. D-dimer is formed from the degradation of cross-linked fibrin in the process of fibrinolysis and requires the activity of thrombin, factor XIIIa, and plasmin. So, an increase in D-dimer can indicate intravascular coagulation because it can only be formed after thrombin formation and degradation of cross-linked fibrin [18]. Therefore, D-dimer can be used as an initial strategy in the diagnosis of venous thromboembolism (VTE), such as deep vein thrombosis (DVT) and pulmonary embolism (PE) [17].

Usually, D-dimer is absent in the blood unless coagulation occurs [19]. However, in healthy humans, D-dimer can also be detected in small amounts because, under normal physiological conditions, about 2-3% of fibrinogen will be converted to fibrin [20]. Although it has good sensitivity, the specificity of D-dimer is not suitable for detecting fibrinolysis [21] because its levels can also increase in several conditions such as elderly, cancer, postoperative, sepsis, pregnancy, trauma, burns, inflammation, and chronic renal failure [22]. Once formed, D-dimer will circulate in plasma and then be excreted through the reticuloendothelial system and kidneys with a half-life of 8 hours [5].

D-dimer is a final product of fibrin degradation as the product of cross-linking by factor XIII in the D domain of the fibrin polymer adjacent to each other [23]. Dissolved fibrinogen in plasma glycoproteins consists of 3 pairs of polypeptide chains ($A\alpha$ -, $B\beta$, and γ -) that connect the two outermost D domains to the central E domain. D-dimer formation begins with the breakdown of fibrinogen E domain polymerization sites enzymatically by thrombin, forming fibrin monomers and fibrinopeptides A and B. Fibrin monomers bind to each other to form a soluble network, then together with thrombin and factor XIII form factor XIIIa [20]. Calcium ions (Ca^{2+}) in high concentrations also play a role in the activation of factor XIIIa. Factor XIIIa plays a role in maintaining the stability of blood clots through cross-linking of α - dan γ - chains on fibrin, as well as maintaining clots formed from fibrinolysis by plasmin through cross-linking of $\alpha 2$ -antiplasmin with fibrin [24].

Plasminogen will be activated by urokinase (uPA) and tissue plasminogen activator (tPA) to become plasmin [25]. Activated plasmin will degrade the fibrin polymer to produce an E fragment and two D fragment molecules that form dimers through covalent bonds called D-dimers [26].

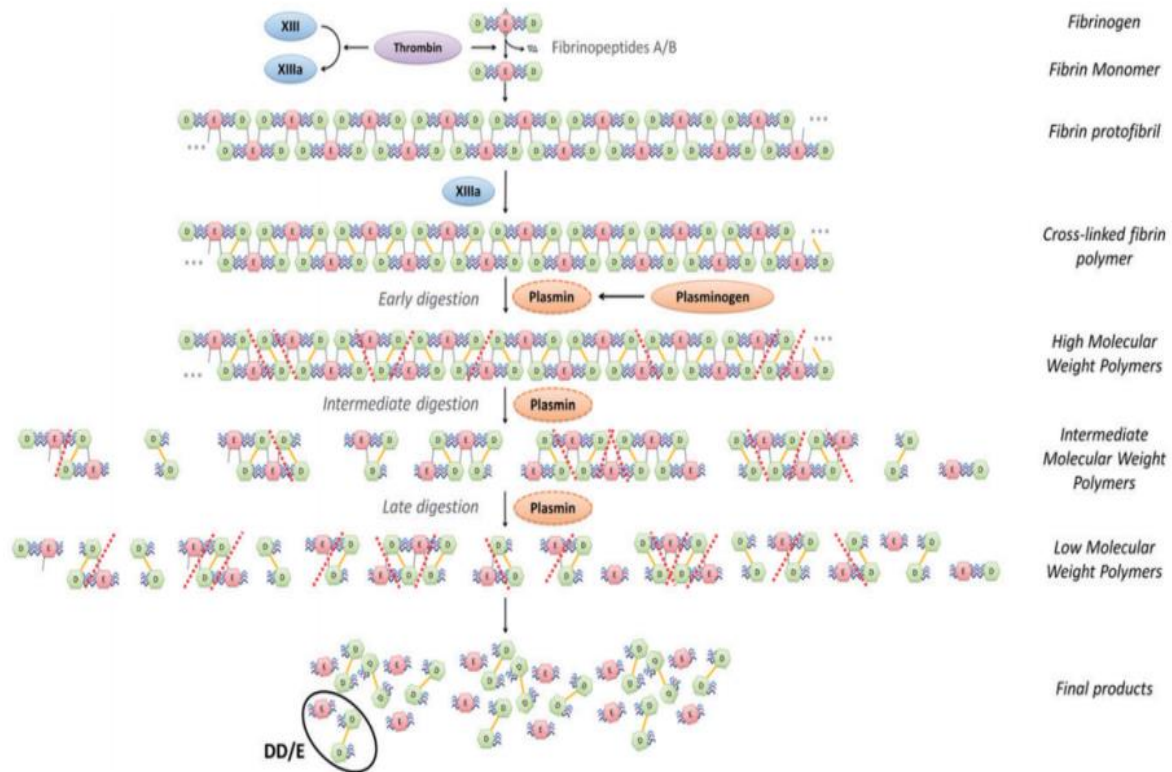


Figure 3. D-dimer formation mechanism [20].

Infectious conditions can induce the production of procoagulant compounds and trigger platelet adhesion, thereby affecting the coagulation pathway, platelet function, and fibrinolysis, leading to increased levels of D-dimer [27]. Pathogens can activate monocytes to release cytokines, chemokines, and other chemical mediators and activate platelets, neutrophils, and endothelial cells. Neutrophils will express tissue factors and trigger the activation of coagulation [28]. Most viruses can also directly infect endothelial cells, triggering tissue factors' expression, coagulation, and fibrinolytic pathways [29].

Several infectious conditions that can increase D-dimer levels include Zika and Chikungunya virus infections [27], hepatitis B infection [30], Ebola virus infection [31], HIV infection [32,33], *S. pneumonia*, and *N. meningitidis* infection [34].

3.3. Increased d-dimer mechanism in covid-19 patients.

D-dimer is produced by fibrin hydrolysis, which can reflect the effect of infection on the coagulation system [35]. The mechanism for the increased D-dimer levels is still unknown, whether it is due to the SARS-CoV-2 virus or to a systemic inflammatory response that produces a cytokine storm due to viral infection [12]. Activation of the coagulation system is a common occurrence in infected patients [36]. Coagulation is one of the immune functions against severe infection, so the increased D-dimer in severe COVID-19 patients is associated with a mechanism for accelerating the response to infection [37]. The increase in D-dimer indicates the formation of microemboli, which can cause mortality in COVID-19 patients [38].

When SARS-CoV-2 enters the body, the innate immune system activates. However, excessive activation will cause a "cytokine storm" and activate the coagulation system resulting in excessive thrombosis [39]. Elevated D-dimer in COVID-19 patients may signal coagulation activation due to viremia and a "cytokine storm" [40].

SARS-CoV-2 can infect endothelial cells via the ACE-2 receptor, causing the release of large amounts of plasminogen activator [41]. Endothelial cells form the surface layer between blood and tissues and play an important role in regulating permeability, inflammatory reactions, coagulation balance, and angiogenesis [42]. When SARS-CoV-2 enters endothelial cells through endocytosis, the infected cells will lose their physiological function ability and experience damage that will cause changes in procoagulant conditions, immunothrombosis, and organ formation malfunctions. Stimulated endothelial cells can also increase circulating clotting factors such as fibrinogen, factor VIII, and von Willebrand factor [43].

SARS-CoV-2 can cause injury to various organs through systemic inflammation or direct attack through the ACE-2 receptor [44]. The ACE-2 and TMPRSS2 receptors play an essential role in the entry of SARS-CoV-2 into the body. Various body organs express them and tissues, including the nasal cavity, lower respiratory tract epithelial cells (pneumocytes), endothelial cells, neurons, enterocytes, cardiomyocytes, hepatocytes, and kidneys [45]. Accumulated SARS-CoV-2 in the lungs can trigger a systemic inflammatory response by causing capillary leakage and viremia that can induce a "cytokine storm" [46,47]. "Cytokine storm" can activate the coagulation system and cause an increase in D-dimer [48]. SARS-CoV-2 can cause an inflammatory reaction that produces cytokines such as IL-6, IL-8, and TNF- α [49]. Proinflammatory cytokines such as IL-6 and TNF- α can induce the expression of tissue factors on the surface of endothelial cells and monocytes that can initiate the coagulation pathway [41]. Disruption of endothelial cells' anti-thrombotic and anti-inflammatory functions may be accompanied by activation of platelets and the complement system [50].

Inflammation can cause thrombosis and increased oxygen consumption, triggering hypoxia [51]. Hypoxia can increase blood viscosity, increase the inflammatory response, and trigger thrombosis [52]. Increased D-dimer indicates that respiratory failure in COVID-19 patients can occur due to microvascular thrombosis [53]. Activation of the coagulation system can lead to the formation of small thrombosis and ischemia in the pulmonary capillaries, thereby inhibiting gas and blood exchange in the lungs and triggering dyspnea, ARDS, and DIC [54]. Excessive thrombosis in small vessels and microvasculature has been confirmed histologically as a pathological change in the lungs of hospitalized COVID-19 patients [55]. An autopsy performed on a patient who died from COVID-19 showed abnormal bleeding and thrombosis in the lung tissue [56].

3.4. Effect of increased d-dimer on the covid-19 severity.

A total of 19 articles about the effect of increased D-dimer on the COVID-19 severity were included. The studies were carried out in various countries, including 12 studies in China, 2 studies in Saudi Arabia, and 1 study each in the Netherlands, Austria, Morocco, Pakistan, Poland, and Greece, involving patients ranging in age from 18 years to the elderly (≥ 60 years).

Table 3. Literature study results on the effect of Increased D-dimer on the COVID-19 severity.

Study Results	Number of Subjects	References
D-dimer levels were significantly higher in patients with severe or critical COVID-19 than in patients with mild or moderate symptoms.	3218	[36,37,57–65]
D-dimer levels in patients with mild COVID-19 were significantly lower than in patients with moderate symptoms.	401	[66]
In patients with or without comorbidities, D-dimer levels were higher in patients with severe/critical symptoms.	201	[61]
D-dimer is a factor associated with the severity of COVID-19 in patients with cancer.	751	[67]
The level of D-dimer is a factor that influences the severity of COVID-19 in patients with chronic hepatitis B.	436	[68]
D-dimer levels can predict the severity of COVID-19 in elderly patients.	262	[60]
D-dimer levels increase significantly in proportion to the severity of COVID-19.	709	[46,69,70]
D-dimer levels are related to the disease progression of COVID-19 patients becoming more severe.	1846	[36,71,72]
Patients who experienced disease progression from mild to severe symptoms had higher D-dimer levels compared to patients who tended to be stable or improve insignificantly.	348	[73]
Increased D-dimer levels can be a prognostic severity factor in COVID-19 patients.	112	[74]
D-dimer levels >650 ng/mL can predict disease severity in the elderly.	110	[63]
The highest D-dimer levels during hospitalization were associated with severe COVID-19.	100	[65]

3.5. The effect of increased d-dimer on the covid-19 patient's outcome.

A total of 40 articles about the increased D-dimer in COVID-19 patients were included. Increased D-dimer can cause disease progression to an undesirable outcome, i.e., acute kidney injury, admission to the ICU, cytokine storm, the need for mechanical ventilation, cardiac injury, organ dysfunction, respiratory failure, and thromboembolic events. The study was carried out in various countries, including the United States, China, Italy, Spain, Saudi Arabia, England, France, Poland, Germany, United Arab Emirates, Portugal, Turkey, Croatia, Japan, Bahrain, Russia, Finland, and Brazil.

Table 4. Literature study results on the effect of increased D-dimer on COVID-19 patients' outcomes.

Outcome	Study Results	Number of Subjects	References
Acute kidney injury	The cut-off value of 500 ng/mL D-dimer levels at hospital admission can predict acute kidney injury in COVID-19 patients with a sensitivity of 90.0% and a specificity of 86.7%. D-dimer levels are higher in moderate and mild COVID-19 symptoms with acute kidney injury than without acute kidney injury.	348	[75]
	Patients with high D-dimer levels are associated with acute kidney injury development compared with normal D-dimer levels.	353	[76]
Admission to ICU	D-dimer levels in COVID-19 patients requiring intensive care (ICU) are higher than in patients not treated in the ICU.	1110	[48,77–79]
	D-dimer levels are a risk factor for patient admission to the ICU.	213	[48]
	D-dimer level of 700 ng/mL can predict the need for intensive care in patients.	560	[77]
Cardiac injury	D-dimer is a factor associated with the occurrence of cardiac injury in COVID-19 patients, and the D-dimer level in patients with cardiac injury is higher than in patients who do not.	181	[44]
Cytokine storm	D-dimer levels >2100 ng/mL are a risk factor for COVID-19-associated cytokine storms.	458	[80]
Length of stay in ICU	Each 1 ng/mL increase in D-dimer levels was associated with an increased period of ICU stay.	331	[81]
	Elevated D-dimer levels were associated with admission to the ICU and longer stay in ICU for COVID-19 patients.	78	[82]

Outcome	Study Results	Number of Subjects	References
Need for mechanical ventilation	D-dimer levels 3 days after hospital admission were associated with the need for mechanical ventilation.	135	[83]
	D-dimer levels in patients requiring mechanical ventilation were higher than in patients not requiring it.	129	[84]
Organ dysfunction	Rapid progression of organ dysfunction may occur in patients with D-dimer levels 1000-4000 ng/mL within 4-7 days after ICU admission. High D-dimer levels are also associated with significantly higher 14-day mortality rate in the ICU.	158	[85]
Respiratory failure	D-dimer levels in patients with respiratory failure were higher than in patients without respiratory failure in the form of ARDS and ARF.	257	[54,86]
	An increase in D-dimer levels was associated with a significant decrease in the PaO ₂ :FiO ₂ ratio.	76	[87]
Thrombo-embolic events	D-dimer levels >3000 ng/mL at admission are a risk factor for thromboembolic events with a sensitivity of 40.6% and specificity of 85.7%.	243	[88]
	Elevated D-dimer levels to >2500 ng/mL at baseline can predict thrombotic complications during hospitalization.	400	[89]
DVT (deep vein thrombosis)	D-dimer levels in patients with DVT were higher than in patients without DVT.	316	[90–92]
	D-dimer levels of ≥5000 ng/mL on hospital admission can predict DVT in COVID-19 patients.	200	[92]
	The D-dimer level limit of 2450 ng/mL can predict DVT in patients with a sensitivity of 70.6% and a specificity of 59.5%.	71	[90]
	D-dimer levels >2000 ng/mL can predict the occurrence of DVT with a sensitivity of 95% and specificity of 46%.	45	[91]
PE (pulmonary embolism)	The levels of D-dimer in patients with PE were higher than in patients without PE.	2162	[52,87,93–99]
	Levels of D-dimer upon hospital admission can predict the occurrence of PE in COVID-19 patients.	689	[94]
	D-dimer levels >4800 ng/mL can predict the occurrence of PE in COVID-19 patients with a sensitivity of 75% and specificity of 78%.	214	[95]
	D-dimer level >3000 ng/mL can predict PE in mechanically ventilated patients.	160	[100]
	D-dimer levels of ≥3000 ng/mL at admission are associated with the risk of PE in COVID-19 patients.	88	[96]
	D-dimer level >2500 ng/mL can predict PE with 80% sensitivity and 51% specificity.	30	[52]
	D-dimer levels ≥2000 ng/mL are associated with the risk of PE in COVID-19 patients during hospitalization.	86	[101]
	The D-dimer level limit of 2495 ng/mL can predict PE in COVID-19 patients.	193	[99]
	D-dimer levels of 1000 ng/mL at hospital admission were associated with an increased risk of developing PE.	76	[87]
	Using a limit value of >1000 ng/mL has better specificity than 500 ng/mL with an insignificant decrease in sensitivity.	300	[98]
	D-dimer levels can predict PE in COVID-19 patients but do not affect mortality rates in patients with PE.	159	[97]
VTE (venous thromboembolism)	D-dimer levels in patients with VTE were higher than in patients without VTE.	10,227	[102–109]
	There was no significant difference in D-dimer levels between patients who had VTE and those who did not.	259	[103]
	D-dimer levels >3300 ng/mL can predict VTE in COVID-19 patients.	92	[106]
	A higher D-dimer level of 3000 ng/mL predicted the occurrence of VTE better than 2000 ng/mL.	115	[104]
	D-dimer levels >2190 ng/mL can predict VTE with a sensitivity of 67.9% and a specificity of 66.3%.	4014	[110]
	A cut-off values of D-dimer 2000 ng/mL can predict VTE in COVID-19 patients.	102	[109]
	D-dimer levels of 1500 ng/mL can predict VTE with a sensitivity of 85.0% and a specificity of 88.5%.	81	[108]
	D-dimer level ≥1000 ng/mL is a risk factor for VTE in COVID-19 patients.	85	[107]
	The D-dimer level limit of 1100 ng/mL at admission could predict the incidence of VTE in patients with a sensitivity of 49%	9386	[102]

Outcome	Study Results	Number of Subjects	References
	and a specificity of 72%. Meanwhile, the 4700 ng/mL limit has a sensitivity of 27% and a specificity of 95%.		

3.6. The effect of increased d-dimer on mortality of covid-19 patients.

High D-dimer levels are associated with clotting disorders, microthrombi formation, PE, and acute myocardial infarction that can cause hypoxemia, respiratory failure, DIC, and even mortality [35]. The literature search results included 39 articles about the effect of D-dimer levels in predicting mortality in COVID-19 patients. The studies were carried out in various countries, including China, the United States, Belgium, India, Italy, Kuwait, Saudi Arabia, Mexico, Croatia, Indonesia, France, Spain, and Turkey.

Table 5. Literature studies results on the effect of increased D-dimer on COVID-19 patients' mortality.

Study Results	Number of Subjects	References
D-dimer levels were higher in deceased patients than in patients who survived or managed to be discharged from the hospital.	16,551	[35,38,51,111–131]
D-dimer levels were higher in deceased patients within 90 days of admission to the ICU.	4244	[132]
D-dimer levels are a risk factor associated with 28-day mortality in critically ill COVID-19 patients.	733	[129]
In patients with severe and critical COVID-19, D-dimer levels in deceased patients increased significantly on day 7 and could predict mortality in patients.	753	[128]
Patients with higher levels of D-dimer have a higher risk of mortality.	326	[111]
A peak D-dimer of 2070 ng/mL can predict mortality in COVID-19 patients with a sensitivity of 72% and a specificity of 70%.	15,250	[133]
The D-dimer level limit of 2025 ng/mL can be used as a prognosis for patients' mortality.	1114	[51]
The D-dimer level limit of 2000 ng/mL is a risk factor for mortality in COVID-19 patients.	7216	[11,134,135]
D-dimer levels >1880 ng/mL with static lung function less than 41 mL/cmH ₂ O may increase the risk of 28-day mortality in mechanically ventilated patients.	643	[136]
D-dimer levels >1200 ng/mL are a risk factor associated with mortality.	103	[118]
D-dimer levels >1128 ng/mL at admission are associated with a worse prognosis and can predict in-hospital mortality in patients with or without VTE.	1154	[137]
After adjustment for potential confounders, D-dimer levels ≥1112 ng/mL at admission increase the risk of 30-day all-cause death in COVID-19 patients.	196	[123]
D-dimer levels >1116 ng/mL can predict mortality in COVID-19 patients.	893	[138]
D-dimer levels >1000 ng/mL increase mortality risk in COVID-19 patients.	1380	[38,112,114,117,139]
A cut-off value of the mean D-dimer levels of 779 ng/mL can predict in-hospital mortality in COVID-19 patients with a sensitivity of 77% and specificity of 83%.	240	[140]
D-dimer levels >500 ng/mL at admission are associated with increased mortality risk and can predict mortality in COVID-19 patients.	2936	[130,141,142]
D-dimer levels of 410 ng/mL can predict mortality in COVID-19 patients with a sensitivity of 93.9% and a specificity of 97.4%.	217	[122]
An increase in D-dimer, every 500 ng/mL in critically ill COVID-19 patients, can increase mortality risk by 1.05 times.	3418	[143]
D-dimer levels at admission were less effective in predicting mortality during hospitalization, but peak D-dimer levels ≥2010 ng/mL during hospitalization could predict mortality in COVID-19 patients.	483	[144]
In intubated patients, D-dimer levels were higher in deceased patients than in survivors, but further analysis showed that high D-dimer levels had no significant effect on patients' mortality.	79	[145]

Table 6. Results of the Literature Study on the Benefits of Using Anticoagulants in Patients with COVID-19

Study Method	Number of Subjects	Drug Type	Dose	Administration Route	Study Results	References
Meta-analysis of RCT	5753	Enoxaparin	Therapeutic dose: 1mg/kg every 12 hours Moderate dose: 1 mg/kg/day Prophylaxis: 40 mg/day	Subcutaneous injection	In patients with high D-dimer levels, high doses of anticoagulants did not significantly reduce mortality risk compared to prophylactic doses.	[146]
RCT, open-label, multicenter	614	Rivaroxaban	Therapeutic dose: 20 mg/day	Oral	Patients with elevated D-dimer levels who received therapeutic doses of Rivaroxaban and Enoxaparin had no improvement in clinical outcome at 30 days and had an increased risk of bleeding compared with prophylactic doses.	[147]
		Enoxaparin	Therapeutic dose: 1 mg/kg every 12 hours Prophylactic dose: 40-60 mg every 12-24 hours	Subcutaneous injection		
		Fondaparinux	Prophylactic dose: 2.5 mg/day	Subcutaneous injection		
		UFH	Therapeutic dose: up to an anti-Xa concentration of 0.3-0.7 IU/mL or aPTT 1.5-2.5 times the average mean value Prophylactic dose: 5000-7500 U every 8-12 hours	Infusion		
RCT, open-label, multicenter	465	Enoxaparin	Therapeutic dose: 1 mg/kg every 12 hours or 1.5 mg/kg every 24 hours Prophylactic dose: 40 mg/kg every 24 hours (BMI <40) or every 12 hours (BMI ≥40)	Subcutaneous injection	The study included participants with baseline D-dimer level 2.3-fold above the upper limit of normal (ULN). Patients who receive therapeutic heparin have lower D-dimer levels compared with patients who receive prophylactic heparin after a median of 1.5 days assessment (OR=0.88, P=0.03), but there was no significant lower incidence of death, mechanical ventilation, or ICU admission in therapeutic heparin group compared with prophylactic heparin group.	[148]
		Dalteparin	Therapeutic dose: 200 U/kg every 24 hours or 100 IU/kg every 12 hours Prophylactic dose: 5000 U every 24 hours (BMI <40) or every 12 hours (BMI ≥40)	Subcutaneous injection		
		Tinzaparin	Therapeutic dose: 175 U/kg every 24 hours Prophylactic dose: 4500 U every 24 hours (BMI <40) or 9000 U every 24 hours (BMI ≥40)	Subcutaneous injection		

Study Method	Number of Subjects	Drug Type	Dose	Administration Route	Study Results	References
		UFH	Therapeutic dose: titrate to specific anti-Xa or aPTT values Prophylactic dose: 5000-7500 U every 8-12 hours	IV bolus with continuous infusion Subcutaneous injection		
		Fondaparinux	Prophylactic dose: 2.5 mg every 24 hours (BMI <40)	Subcutaneous injection		
RCT, double-blind, multicenter	253	Enoxaparin	Therapeutic dose: 1 mg/kg every 12 hours (CrCl 30 mL/min/1.73m ²) or 0.5 mg/kg every 12 hours (CrCl 15-29 mL/min/1.73m ²) Standard dose: 30-40 mg every 12-24 hours	Subcutaneous injection	In patients with elevated D-dimer levels up to 4 times the upper limit normal, therapeutic doses of LMWH can reduce the risk of thromboembolism and mortality compared with standard doses of LMWH or UFH. Therapeutic doses of LMWH reduced the incidence of thromboembolism and mortality significantly in patients not admitted to the ICU compared to patients admitted to the ICU.	[149]
		UFH	Standard dose: 22,500 IU (divided into 2-3 times/day)	Subcutaneous injection		
		Dalteparin	Standard dose: 2500-5000 IU/day	Subcutaneous injection		
Cohort, retrospective, multicenter	100	Enoxaparin	40-60 mg/day	Subcutaneous injection	Fondaparinux and Enoxaparin can reduce D-dimer levels in COVID-19 patients after 3 weeks of receiving treatment.	[150]
		Fondaparinux	2,5 mg/day	Subcutaneous injection		
Case-control, retrospective, single-center	75	Enoxaparin	40 mg/day	Subcutaneous injection	The patient's D-dimer concentration decreased significantly after receiving heparin, while the group of patients who did not receive anticoagulants experienced an increase in D-dimer within 5 days.	[39]
		LMWH	100 U/kg every 12 hours	Subcutaneous injection		
Cohort, retrospective, multicenter	525	Enoxaparin	40 mg/day or every 12 hours Minimum 7 days	Subcutaneous injection	Patients who received LMWH had a lower mortality rate. Using LMWH can improve survival in patients with D-dimer levels >5 times the upper limit normal levels.	[151]
Cohort, retrospective, single-center	449	Enoxaparin	40-60 mg/day	Subcutaneous injection	Giving heparin to patients with severe COVID-19 with D-dimer levels reaching 3000 g/mL can reduce mortality risk by 20%.	[152]
		UFH	10,000-15,000 U/day Minimum 7 days	Subcutaneous injection		
Cohort, retrospective, single-center	2450	Apixaban	Prophylaxis: 2.5 mg every 12 hours	Subcutaneous injection	A significant benefit in reducing mortality was obtained in patients with D-dimer 1000 ng/mL to <3000 ng/mL and D-dimer levels >10,000 ng/mL who received	[153]

Study Method	Number of Subjects	Drug Type	Dose	Administration Route	Study Results	References
		Enoxaparin	Therapeutic dose: 2.5-5 mg every 12 hours Prophylaxis: 0.5 mg/kg every 12 hours or 1.0 mg/kg/day or 30-60 mg/day	Subcutaneous injection	Apixaban prophylaxis, Apixaban therapy, Enoxaparin prophylaxis. Meanwhile, UFH and Enoxaparin therapy did not provide significant benefits in patients. Anticoagulants did not significantly benefit patients with D-dimer levels <1000 ng/mL.	
		UFH	Therapeutic dose: 1mg/kg every 12 hours or 1.5mg/kg/day Prophylaxis: 4000-10,000 U every 8-12 hours	Subcutaneous injection		
Cohort, retrospective, multicenter	152	Tinzaparin	Low dose: 2500-4500 IU Moderate dose: >4500 IU to <175 IU/kg High dose: 175 IU/kg	Subcutaneous injection	In the analysis with a 28-day outcome, the median peak of D-dimer decreased in patients receiving the higher dose.	[154]
		Dalteparin	Low dose: 5000 IU Moderate dose: >5000 IU to <200 IU/kg High dose: 200 IU/kg	Subcutaneous injection		
Cohort, retrospective, single-center	56	Enoxaparin	Prophylaxis: 40 mg/day	Subcutaneous injection	There was no significant difference in the incidence of thromboembolism in patients receiving UFH by infusion versus subcutaneous UFH prophylaxis. However, the median increase in D-dimer levels from day 1 to 7 in the group of patients receiving UFH prophylaxis was higher than that of patients receiving UFH infusion.	[155]
		UFH	Prophylaxis: 5000 U every 8 or 12 hours Infusion: 8 U/kg/hour with monitoring every 6 hours to reach aPTT of 40-60 seconds	Subcutaneous injection Infusion		
Cohort, retrospective, single-center	45	Enoxaparin	Full dose: 1 mg/kg every 12 hours or 1.5 mg/kg every 24 hours Moderate dose: 0.5 mg/kg every 12 hours or 1 mg/kg every 24 hours Prophylaxis: 40 mg every 24 hours	Subcutaneous injection	In patients with elevated D-dimer levels, complete or moderate doses of anticoagulation had an insignificantly lower risk of VTE and mortality than prophylactic doses. Administration of full-dose anticoagulation can significantly reduce the risk of intubation compared to moderate or prophylactic doses.	[156]
Cohort, retrospective, single-center	225	Apixaban	Prophylaxis: 2.5 mg every 12 hours Therapeutic dose: 5 mg every 12 hours	Oral	Anticoagulant prophylaxis can significantly reduce D-dimer levels. Therapeutic doses can reduce D-dimer levels but not significantly.	[157]
		Enoxaparin		Subcutaneous injection		

Study Method	Number of Subjects	Drug Type	Dose	Administration Route	Study Results	References
		UFH	Prophylaxis: 40 mg/day at BMI <40, GFR 30 or 30 mg every 12 hours at BMI 40 Therapeutic dose: 1-5 mg/kg/day or 1 mg/kg every 12 hours 80 U/kg bolus then 18 U/kg/hour or 5000 U bolus then 1300 U/hour	Intravenous injection then infusion		
Cohort, prospective, single-center	74	Enoxaparin Heparin Fondaparinux	Prophylaxis: 80 U/kg/day Moderate dose: >80 to <200 U/kg/day Therapeutic dose: 100 U/kg every 12 hours Prophylaxis: 5000 U every 8 hours Moderate dose: >15,000 to <25,000 U/day Therapeutic dose: 12,500 U every 8-12 hours Prophylaxis: 2.5 mg/day Moderate dose: 5mg / 24 hours	Subcutaneous injection Subcutaneous injection Subcutaneous injection	Higher doses did not affect D-dimer levels, mortality rates, and duration of hospitalization in COVID-19 patients.	[158]
Cohort, prospective, single-center	40	Enoxaparin UFH	0.5 mg/kg every 12 hours 7500 U every 8 hours	Subcutaneous injection Subcutaneous injection	Anticoagulation with LMWH and UFH could not benefit patients, indicated by the significant increase of median D-dimer level up to 7 days after admission.	[159]
Cohort, retrospective, multicenter	844	Direct oral vitamin K antagonists and anticoagulants	N/A	Oral	Patients who had received oral anticoagulants before hospitalization had lower D-dimer levels at admission than those who did not receive anticoagulants. The use of heparin in COVID-19 patients with acute hypoxemic respiratory failure (AHRF) is associated with an increased chance of survival and successful discharge from the hospital.	[160]

3.7. Benefits of using anticoagulants in covid-19 patients.

Theoretically, using anticoagulants such as LMWH can inhibit blood coagulation, reduce inflammation, inhibit platelet aggregation, prevent thrombosis, and inhibit the progression of coagulopathy to DIC. However, the administration timing, type, and dose to patients still need to be confirmed by randomized controlled trials (RCTs), and it is possible that patients with severe, highly progressive coagulopathy may no longer benefit from anticoagulants [134]. In a literature search on the benefits of using anticoagulants in COVID-19 patients, 16 articles were carried out in various countries, including the United States, China, Italy, Sweden, Brazil, Canada, Ireland, Saudi Arabia, and the United Arab Emirates

4. Conclusions

Increased levels of D-dimer in COVID-19 patients can increase the need for intensive care, the risk of respiratory failure, and the risk of thromboembolic events, which is associated as a risk factor for disease severity, disease worsening, and mortality. A prophylactic dose of anticoagulants may provide benefits for COVID-19 patients. However, there is no firm evidence of more significant benefits from high-dose anticoagulation. In addition, ISTH does not recommend changing the anticoagulant dosing regimen based on D-dimer levels. The most widely used type of anticoagulant is Enoxaparin.

COVID-19 patients need to check their D-dimer levels, indicating disease severity and worsening. Giving anticoagulants to COVID-19 patients can be done by paying attention to interactions with other drugs.

Funding

This research received no external funding and no funding to report.

Acknowledgments

Highly acknowledge the lecturers who have provided support and advice in this research.

Conflicts of Interest

The authors declare no conflict of interest in this research.

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