Indonesian Journal of Pharmacy

VOL 32 (3) 2022: 381–393 | REVIEW ARTICLE

Analysis of Enoxaparin Effectiveness Based on COVID-19 Severity: A Study in a Secondary Hospital in Bandung, Indonesia

Liana Debora[1,4], Budi Suprapti[2]*, Dewi Kusumawati[3], Arina Dery PS[2], Gabriella Nathasya T[1], Mustika Novi Arini[4] and Lusiana Dwi Aryanti[4]

1. Magister of Clinical Pharmacy Program, Campus B Universitas Airlangga Surabaya, Jalan Dharmawangsa Dalam, Surabaya 60286, Indonesia
2. Faculty of Pharmacy Department, Campus B Universitas Airlangga Surabaya, Jalan Dharmawangsa Dalam, Surabaya 60286, Indonesia
3. Intensive Care Unit Department, Santo Borromeus Hospital, Bandung, Jawa Barat 40132, Indonesia
4. Pharmacy Department, Santo Borromeus Hospital, Bandung, Jawa Barat 40132, Indonesia

Submitted: 26-02-2022
Revised: 18-06-2022
Accepted: 05-07-2022

*Corresponding author
Budi Suprapti

Email:
budiprapti@yahoo.co.id

ABSTRACT

Li Coagulopathy is a common predictor of mortality in COVID-19. Meanwhile, enoxaparin is an anticoagulant with anti-inflammatory, endothelial protection, and viral antagonist properties. Therefore, thromboprophylaxis with enoxaparin in COVID-19 is common in clinical settings. This study aims to assess enoxaparin's efficacy across different severity levels by examining its effect on primary outcomes comprising Length of stay (LOS), invasive mechanical ventilation, and mortality as well as secondary in the form of D-dimer, platelets, C-reactive protein (CRP), Neutrophil Lymphocyte Ratio (NLR), and Absolute Lymphocyte Count (ALC). During hospitalization, 269 patients received enoxaparin across varying severity levels comprising mild, moderate, and severe, while the Wilcoxon test was used to analyze the efficacy in each group. Additionally, the differences in patient characteristic profiles across the severity levels were determined using the Kruskal-Wallis test. The increase in mortality rate and the need for mechanical ventilation were directly proportional to the level of severity. D-dimer decreased from 1308.87 ng/ml to 979.83 ng/ml (p=<0,001) as well as from 1758.41 ng/ml to 1510.68 ng/ml (p=<0,001) in the mild and moderate levels respectively. The platelet increased from 225.65 to 369.39 $x10^3$/µl (p=<0,001) in mild and 256.77 to 398.97 $x10^3$/µl (p=<0,001) in moderate. Moreover, CRP improved in both mild 52.62 to 49.58 mg/l (p=0.031) and moderate 92.99 to 42.66 mg/l, (p=<0,001). Based on the results, enoxaparin effectively improves D-dimer, platelet, and CRP levels in mild and moderate but not in severe conditions, however, no effect was found on LOS, NLR, and ALC.

Keywords: Enoxaparin, COVID-19, D-Dimer, Platelet, C-reactive protein

INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) was first detected in China and then spread rapidly into an epidemic in Hubei province. Currently, the pandemic has spread around the world. A total of 340 million confirmed cases and over 5.5 million deaths were recorded by the end of January 2022 (CDC, 2022; WHO, 2022). According to several reports, coagulopathy plays a role in the severity of COVID-19 patients (Elbeddini *et al*., 2020; Tang *et al*., 2020; Zhou *et al*., 2021). Initially, a cytokine storm initiates coagulopathy during COVID-19 infection, then it progresses into disseminated intravascular coagulation (DIC) or pulmonary embolism, both of which can lead to acute respiratory distress syndrome (ARDS) (Kamel *et al*., 2021; Lopes *et al*., 2021; Spyropoulos *et al*., 2021).

Coagulopathy is one of the COVID-19 infection signs and can determine illness severity (Tang *et al*., 2020). Numerous studies stated that people who died from COVID-19 infection had coagulation problems. These patients mostly have high levels of D-dimer, pulmonary embolism (PE),

and vein thromboembolism (VTE), which are all signs of coagulopathy (Elbeddini *et al*., 2020; Iba *et al*., 2020; Tang *et al*., 2020; Zhou *et al*., 2021). Coagulopathy develops in the patients due to interactions between pro-inflammatory factors produced by infected cells, platelet hyperactivity, and endothelial cell damage (Vajari *et al*., 2021).

A meta-analysis study reported that COVID-19 patients with DIC and coagulopathy were at an increased risk of death, accompanied by high D-dimer levels (Parisi *et al*., 2021; Zhou *et al*., 2021). With a sensitivity and specificity of 70.6% and 78.4%, the D-dimer cut-off level of 1500 ng/ml might accurately predict the severity of COVID-19 infection (Poudel *et al*., 2021). In total, 71.4% of patients who died from COVID-19 met the DIC criteria, while only 0.6% survived with DIC conditions (Arachchillage & Laffan, 2020). Furthermore, several studies reported that an average of 41.18% with the range 17.5% - 85% of intensive care unit (ICU) patients with COVID-19 infection experienced thromboembolism (Price *et al*., 2020; Rusdiana & Akbar, 2020). ICU patients with an average D-dimer of 3,950 ng/mL (1,150 - 10,960 ng/mL) ended up with mortality, while those with an average of 490 ng/mL (310 – 1,180 ng/dL) survived (Arachchillage & Laffan, 2020). These findings indicate that high D-dimer levels are associated with an increased risk of coagulopathy and the severity of COVID-19 infection.

Additionally, several guidelines from the American College of Cardiology (ACC), British Thoracic Society (BTS), International Society on Thrombosis and Haemostasis (ISTH), Swedish Society of Hematology (SSH), and Indonesian Society of Thrombosis and Haemostasis (InaSTH) recommend the use of Unfractionated Heparin (UFH), Low Molecular Weight Heparin (LMWH), Fondaparinux, or Direct Oral Anticoagulant (DOAC), except for contraindications *(*Jiménez-Soto *et al.,* 2021*;* Pangarsa *et al.,* 2020*;* Price *et al.,* 2020*;* Rosovsky *et a*l., 2020). Enoxaparin is one of the most often prescribed anticoagulants with a prophylactic dose of 40 to 60 mg once daily (depending on Body Mass Index/BMI), an intermediate of 40 mg twice daily, or a therapeutic of 60 mg twice daily subcutaneously.

Anticoagulants can lower mortality in COVID-19 patients with a coagulopathy caused by sepsis, a condition known as sepsis-induced coagulopathy (SIC), with SIC values > 3 (p=0.029) and D-dimer levels >3,000 ng/dL (Tang *et al*., 2020). In patients with D-dimer levels of >1,500 ng/mL which is three times the normal upper limit, treatment with LMWH (enoxaparin) can reduce the levels after three weeks (Cardillo *et al*., 2021). Anticoagulant therapy, particularly enoxaparin, has been shown to lower mortality without increasing the risk of bleeding. Consequently, anticoagulants are prescribed to all inpatients in line with the levels of D-dimer and platelet levels, as well as the risk of bleeding (Elbeddini *et al*., 2020; Langer *et al*., 2020; Pangarsa *et a*l., 2020; Rentsch *et al*., 2021; Rosovsky *et al*., 2020; Sunggoro *et al*., 2020; Zhang *et al*., 2020).

SARS-CoV-2 infection is also associated with a cytokine storm which is defined as elevated plasma concentrations of various cytokines (Han *et al*., 2020). During the severe stages of COVID-19 infection, a massive and sudden storm of cytokines plays a significant role in pulmonary and extrapulmonary injury (Billett *et al*., 2020; Han *et al*., 2020). Acute respiratory failure with severe hypoxemia is the primary clinical presentation of a severe condition, which ultimately requires mechanical ventilation (Berlin *et al*., 2020). Previous studies suggest that intermediate and therapeutic doses do not differ significantly in reducing mechanical ventilation support (Jiménez-Soto *et al*., 2021). Therapeutic doses of enoxaparin for 14 days in ICU patients decreased the length of mechanical ventilation support and increased the P/F ratio (Lemos *et al*., 2020). Furthermore, a study revealed that the length of stay (LOS) for patients taking prophylactic anticoagulants is approximately 11 to 12 days (Kirkup *et al*., 2021). Infectious conditions accompanied by comorbidities and advanced age are examples of poorer clinical conditions that necessitate longer LOS for patients on enoxaparin (Vaughn *et al*., 2021).

Platelet damage by the immune complex and the formation of thrombi and microthrombi in the lungs contribute to substantial use of platelets in Covid-19 infection. Therefore, an improvement in platelet levels in anticoagulant-treated patients is indicative of improved clinical conditions (Albani *et al*., 2020; Jiménez-Soto *et al*., 2021). There were no statistically significant differences between patients who received enoxaparin and those who did not. This is demonstrated by the lack of a correlation between enoxaparin administration and a reduction in CRP levels. This is because the disease further progresses under severe conditions, particularly complex inflammations caused by COVID-19 infection, which impair enoxaparin's anti-inflammatory capabilities (Shi *et al*., 2020).

According to a meta-analysis study, heparin is an effective anti-inflammatory agent that reduces inflammatory biomarkers and improves patient conditions (Mousavi *et al*., 2015). Also, multiple pathways have been used to demonstrate the anti-inflammatory properties of enoxaparin. The anti-inflammatory effects of heparin and its derivatives are as diverse as their biological effects (Vitiello & Ferrara, 2021). A study reported an increase in lymphocytes in patients with clinical improvement following enoxaparin administration (Shi *et al*., 2020).

Enoxaparin acts as an anticoagulant by reversibly bonding with antithrombin III, inhibiting the activation of factors X and Xa (thrombin), and preventing fibrin formation (Costanzo *et al*., 2020; Rosovsky *et al*., 2020). It is the most widely used anticoagulant compared to UFH and Fondaparinux due to its safer pharmacokinetics and pharmaco-dynamic profiles (Iba *et al*., 2020). Enoxaparin also has a bioavailability nearly identical to fondaparinux, which is >90%, but it is superior to UFH, which has a 30-40% (Fareed *et al*., 2003; Kluwer, 2022b; Nutescu *et al*., 2016). Additionally, it has a shorter half-life of 4 to 7 hours than fondaparinux, having 17 to 21 hours (Fareed *et al*., 2003; Kluwer, 2022b). Healthcare professionals immediately use protamine as an antidote to stop bleeding caused by enoxaparin's adverse effects. In comparison, fondaparinux does not have an antidote (Iba *et al*., 2020; Nutescu *et al*., 2016).

Thromboprophylaxis with enoxaparin in COVID-19 is common in clinical settings, including at Santo Borromeus Hospital in Bandung. Enoxaparin is recommended by the Indonesian Society of Thrombosis and Haemostasis (InaSTH) for patients with D-dimer >1500 ng/mL or SIC >4 and IMPROVE score >7 (Sunggoro *et al*., 2020). In some countries, including Indonesia, enoxaparin has been administered subcutaneously at prophylactic doses of 40 to 60 mg once daily, intermediate 40 mg twice daily, or therapeutic 60 mg twice daily. However, studies on enoxaparin's effectiveness, particularly in the Indonesian population, are lacking. Therefore, this study aims to examine the effect of enoxaparin administration in COVID-19 patients with varying severity.

MATERIAL AND METHODS

Ethics Statement

The methodology of this study was approved by the Health Research Ethics Committee of Santo Borromeus Hospital with the number 017/KEPK/IX.2021.

Participants and Data Sources

This study employed a retrospective observational cohort design to evaluate the effectiveness of enoxaparin on the primary and secondary outcomes. Sampling was carried out on the total population, while adult patients with COVID-19 who received enoxaparin during hospitalization at Santo Borromeus Hospital from November 2020 to April 2021 were included in this study. A total of 269 patients were selected, while samples were collected from October to November 2021. Patients of all severity levels received enoxaparin subcutaneously except for contraindications. The standard dose of prophylaxis used was 40 mg once daily for BMI <30 kg/m^2 or 60 mg for BMI ≥30 kg/m^2. The intermediate dose was 40 mg twice daily for BMI ≥30 kg/m^2 or 60 mg once daily for BMI <30 kg/m^2, while the therapeutic was 60 mg twice daily.

Data on demography which includes gender, age, and BMI; treatment comprising the start and stop dates of enoxaparin administration, dose, and other medications received; as well as outcomes including mortality, ventilator usage, length of stay, D-dimer, platelet, CRP, NLR, and ALC were extracted from electronic medical records, and then recorded into a data collection form. All patients with COVID-19 met the inclusion criteria, which include [1] aged ≥18 years; [2] receiving enoxaparin during treatment; [3] platelet >100.000/µL; [4] GFR >30 ml/min. Meanwhile, the exclusion criteria are [1] pregnancy; [2] switching to another anticoagulant such as heparin or fondaparinux; [3] LOS <3 days.

The severity of illness was defined by the clinical condition and the amount of oxygen required as follows: [1] mild: no oxygen supplementation required, [2] moderate: oxygen supplementation ≤30 L/min required, and [3] severe: oxygen supplementation >30 L/min or needed mechanical ventilation.

Statistical Analysis

The Wilcoxon test was used to analyze the efficacy of enoxaparin administration in each severity group, while the Kruskal-Wallis test was used to compare patient characteristic profiles across severity levels.

RESULT AND DISCUSSION

Patients infected with SARS-CoV-2 can have a variety of clinical manifestations, ranging from no symptoms to critical illness and categorize into mild, moderate, and severe. A total of 269

patients were hospitalized for confirmed COVID-19 cases and met the inclusion criteria. Enoxaparin was administered subcutaneously to examine the efficacy during hospitalization at Santo Borromeus Hospital from November 2020 to April 2021.

Patient Characteristics Based on COVID-19 Severity Levels

Table I summarizes patient characteristics according to severity levels. These include age, BMI, gender, comorbidities, dose, duration of use, and treatment regimen. The severity of the illness differed significantly with age as demonstrated by p<0.001. Patients with higher BMI experienced more severe conditions (p=0.026), while comorbidities also varied with severity (p<0.001). Furthermore, enoxaparin dosing differed significantly across severity levels with p<0.001 (Table I).

There were differences in age between the severity categories as indicated in Table I. The most severe condition was experienced by the age of >60 years specifically 65 years. This is consistent with a previous study which stated that COVID-19 patients over the age of 60 have a higher severity and mortality rate (Albani *et al*., 2020). Old age is one of the risk factors due to the declining immune system function and a tendency to have more comorbidities, hence, defenses against COVID-19 are weaker than at a young age (Albani *et al*., 2020; Li *et al*., 2021). In SARS and MERS, old age is a significant independent predictor of mortality. Another study on Macaques inoculated with SARS-CoV showed that more aged samples had a more robust response to viral infection than younger adults due to increased differential expression of inflammation-related genes and decreased type I interferon (Smits *et al*., 2010).

According to some studies, obesity is another factor that influences the severity of COVID-19 patients (Al-Samkari *et al*., 2021; Hendren *et al*., 2021; Mennuni *et al*., 2021). It causes increased endothelial dysfunction and elevated expression of ACE-2 receptors, causing adipose tissue to change into a virus carrier (Li *et al*., 2021). The average severe patient had a BMI of 28.02 kg/m^2, moderate 26.54 kg/m^2, and mild 25.66 kg/m^2 (p=0.026) (Table I).

Gender did not differ in the various severity groups as demonstrated by p=0.731. This result is contrary to several previous studies which found gender differences in the severity group. Although global epidemiological data indicate a similar prevalence of virus infection in men and women, a clear sex-related difference in disease severity has been described (Pivonello *et al*., 2021). Clinical outcomes showed that men had a higher severity and fatality rate for the COVID-19 infection than women (Mukherjee & Pahan, 2021), while women had better outcomes. Furthermore, sex has been shown to impact SARS-CoV-2 infection as well as the severity and outcome of COVID-19 (Pivonello *et al*., 2021). Numerous studies revealed that men and women have significantly varied clinical severity and outcomes *(*Abate *et al., 2020;* Jin *et al., 2020;* Peckham *et al*., 2020; Simegn *et al*., 2021; Zhang *et al*., 2022).

Comorbidity differed among the severity groups as indicated by p<0.001, based on the results, the majority of patients undergoing treatment have comorbidities. The severe group had a higher proportion of comorbidities compared to others. Hypertension was the most common comorbidity both independently and in combination with others, followed by Diabetes Mellitus and Cardiovascular Disease. The higher the number of comorbidities, the greater the severity level. Several chronic diseases, including hypertension, Diabetes Mellitus, coronary heart disease, and chronic obstructive pulmonary disease, are frequently fatal (Chen *et al*., 2020). The results are also consistent with several previous studies which found that comorbidities play a role in the severity of COVID-19 patients (Elbeddini *et al*., 2020; Langer *et al*., 2020; Wang *et al*., 2021).

A study which included 487 COVID-19 hospitalized patients in China, discovered that hypertension is related to the severity of the disease (Shi *et al*., 2020). Additionally, 48% of COVID-19 patients with comorbid hypertension did not survive hospitalization in the Wuhan population *(*Zhou *et al*., 2020). ACE and ACE2 work together to keep blood pressure hemo-dynamically stable in the Renin-Angiotensin-Aldosterone System (RAAS). When the SARS-CoV-2 virus binds to the ACE2 receptor, the activity in the infected organ decreases (Li *et al*., 2020), thereby altering the balance of ACE and ACE2, leading to over expression of angiotensin-II, which culminates in vasoconstriction and increased blood pressure, in hypertensive patients. High ACE2 expression also increases the risk of COVID-19 severity (Gemmati & Tisato, 2020).

Table I. Patient Characteristics Based on COVID-19 Severity

Parameters	Mild (N=121)	Moderate (N=126)	Severe (N=22)	P-value[a]
Age (years)	54 (20-85)	60 (21-90)	65 (41-84)	**<0.001**
BMI (kg/m^2)	25.66 (17.4-51.2)	26.54	28.02	**0.026**
Gender				
•Male	71	74	11	0.731
•Female	50	52	11	
Comorbidities				
•Without Comorbid	56	32	3	**<0.001**
•1 Comorbid	51	39	5	
•2 Comorbid	13	45	13	
•3 Comorbid	1	10	1	
Enoxaparin Dose				
•Prophylactic	56	38	2	**<0.001**
•Intermediate	60	53	9	
•Therapeutic	5	35	11	
Subcutaneous Enoxaparin Use Duration (days)	7.5 (2-10)	8.4 (4-20)	9.5 (3-23)	0.129
Treatment regimen				
•Main Therapy[b] + Antibiotic	52	35	4	0.199
•Main Therapy[b] + Antibiotic + Corticosteroid	21	38	10	
•Main Therapy[b] + Antibiotic + Corticosteroid + NSAID	21	21	4	
•Main Therapy[b] + Antibiotic + NSAID	8	9	3	
•Main Therapy[b]				
•Main Therapy[b] + Corticosteroid	8	6		
•Main Therapy[b] + NSAID	5	6		
•Main Therapy[b] +Corticosteroid + NSAID	4	4	1	
•Main Therapy[b] + Antibiotic + Corticosteroid + NSAID + IvIG	1 1	4 1		

Note: [a]Kruskal-Wallis Test; [b]Main Therapy: antipyretic (acetaminophen), antiviral (favipiravir or remdesivir), antitussive or expectorant, vitamin C, vitamin D, vitamin B complex, zinc; NSAID (nonsteroidal anti-inflammatory drugs); IVIG (Intravenous immunoglobulin)

Based on the results, enoxaparin doses differed significantly across severity levels with p<0.001. The majority of patients were in moderate condition, followed by mild and severe. Patients who received prophylactic and intermediate doses were mainly in mild-moderate states, while those that received therapeutic were mostly in moderate-severe conditions (Table I). The enoxaparin was administered at the recommended dose listed in the guidelines (Dutt *et al*., 2020; Jiménez-Soto *et al*., 2021; Mennuni *et al*., 2021; Motta *et al*., 2020; Perepu *et al*., 2021; Spyropoulos *et al*., 2021).

COVID-19 patients are at a higher risk of venous thromboembolism (VTE), hence, prophylactic doses of anticoagulants, such as low molecular weight heparin (LMWH) or unfractionated heparin, can be administered. Based on previous recommendations, prophylactic and therapeutic doses are to be used in moderate and mild conditions. Meanwhile, prophylactic doses are recommended for patients in severe conditions (National Institutes of Health, 2021).

There was no significant difference in the enoxaparin duration of use in mild, moderate, and

severe conditions with p=0.129 (Table I). The treatment with enoxaparin ranged from 2 to 23 days. The procedure in mild conditions ranged from 2 to 10 days, while it varied between 3 to 23 days in moderate to severe patients. Aside from enoxaparin, there was no significant difference in other treatments received by patients in the mild, moderate, and severe groups as demonstrated by p=0.199. The most common treatments received are main therapy and antibiotics. Antipyretics such as acetaminophen, antiviral in the form of favipiravir or remdesivir, as well as antitussive or expectorant, vitamin C, D, B complex, and zinc were the mainstays of treatment administered orally or intravenously. Common antibiotics include azithromycin, levofloxacin, and ceftriaxone.

Furthermore, enoxaparin had no significant drug interactions with main therapy, antibiotics, antihypertension, antidiabetics, or lipid-lowering agents (statins). The drug interaction between enoxaparin and non-steroidal anti-inflammatory drugs (NSAIDs) has been linked to an increase in the risk of bleeding. When concomitant administration is unavoidable, signs and symptoms of bleeding must be monitored closely (Kluwer, 2022a; Liverpool Drug Interactions Group, 2022). However, the manifestation of this drug interaction did not occur in this study.

The Effects of Enoxaparin Administration on Primary and Secondary Outcomes Based on COVID-19 Severity

The severity of the patient's condition determines the length of stay (LOS), based on the results, the comparison of LOS in mild, moderate, and severe conditions showed no significant difference as demonstrated in Table II. Despite being statistically insignificant, it was found that the greater the severity, the longer the LOS. Clinically, an additional day of hospitalization increases the medical costs and is related to the clinical improvement. Consequently, the length of stay increases as the severity becomes more intense. Another study stated that patients who received enoxaparin required a longer stay due to a more severe clinical condition which necessitated a longer course of treatment, such as infectious conditions with comorbidities or old age (Vaughn *et al*., 2021).

The use of mechanical ventilation increases as the severity worsens (Zhu *et al*., 2020). The use of mechanical ventilation during the treatment period occurred mainly in 90.9% of patients with severe conditions. Meanwhile, it was 15.9% and 2.5% in those with moderate and mild conditions (Table II). Similar to SARS-CoV or MERS-CoV infections, some patients infected with 2019-nCoV developed acute respiratory distress syndrome with characteristic changes in the pulmonary ground glass on imaging. In most severe conditions, SARS-CoV-2 infection is also associated with a cytokine storm, defined by elevated plasma concentrations of various cytokines (Han *et al*., 2020). During the severe stages of COVID-19 infection, a massive and sudden storm of cytokines plays a significant role in pulmonary and extrapulmonary injury (Billett *et al*., 2020; Han *et al*., 2020).

Acute respiratory failure with chronic hypoxemia is the primary clinical presentation of a severe condition, which ultimately requires mechanical ventilation (Berlin *et al*., 2020). Additionally, the post-mortem examination revealed a high prevalence of pulmonary microvascular platelet-fibrin thrombi, implying that coagulopathy might contribute to respiratory failure and death in COVID-19 even in the absence of a clinical diagnosis of thromboembolism (Perepu *et al*., 2021).

Based on the results, mortality was lower, while the survival rate was higher in patients with mild to moderate conditions. However, the mortality rate was higher than the survival rate in patients with severe infections (Table II). Patients with severe conditions had the highest percentage of mortality 81.8%, followed by moderate 15.9%, and mild 1.6% as shown in Table II. Although there was no difference in LOS, patients with severe conditions had the highest mortality rate. This is consistent with a previous study stating that the mortality rate increases as the severity worsens (Zhu *et al*., 2020).

Excess bloodstream cytokine might potentially increase the risk of thrombosis and multi-organ failure (Billett *et al*., 2020; Han *et al*., 2020). Clotting cascade abnormalities, such as thrombocytopenia and increased D-dimer levels, are common in patients with severe COVID-19 and are associated with an increased risk of death. Patients are recommended to receive standard thromboprophylaxis, for instance, subcutaneous low-molecular-weight heparin except for contraindications (Moores *et al*., 2020; Wang *et al*., 2020)

Table II. The Effects of Enoxaparin Administration on Primary and Secondary Outcome Based on The Severity Level of COVID-19

Outcome	**Severity Level**		
Primary	**Mild (N=121)**	**Moderate (N=126)**	**Severe (N=22)**
LOS (days)	12 (4-32)	13 (6-28)	14 (3-29)
P-value[a]		0.191	
Invasive Mechanical Ventilation – n (%)			
Yes	3 (2.5)	20 (15.9)	20 (90.9)
No	118 (97.5)	106 (84.1)	2 (9.1)
Mortality – n (%)			
Death	2 (1.6)	20 (15.9)	17 (81.8)
Survive	119 (98.4)	106 (84.1)	
Secondary			
D-dimer (ng/mL) (Mean (SD)			
Initial	1308.87(1496.13)	1758.41 (2062.09)	2656.14 (2220.04)
Final	979.83 (1136.12)	1510.68 (2061.18)	2800.27 (2080.89)
P-value[b]	***<0.001***	***0.002***	*0.918*
Platelet (10^3/µL)) (Mean (SD)			
Initial	225.65 (90.75)	256.77 (115.77)	270.59 (76.09)
Final	368.39 (132.03)	398.97 (160.48)	274.74 (97.71)
P-value[b]	***<0.001***	***<0.001***	*0.546*
CRP (mg/L)) (Mean (SD)			
Initial	52.62 (46.35)	92.99 (62.49)	142.07 (74.18)
Final	49.58 (93.41)	42.66 (54.99)	105.65 (94.99)
P-value[b]	***0.031***	***<0,001***	*0.193*
NLR) (Mean (SD)			
Initial	4.32 (3.76)	6.72 (5.39)	10.65 (6.12)
Final	6.23 (6.33)	10.85 (12.77)	28.88 (22.55)
P-value[b]	***0.039***	***0.012***	***0.003***
ALC (10^3/µL)) (Mean (SD)			
Initial	1280.88 (447.76)	1172.71 (603.60)	1036.14 (323.88)
Final	1314.66 (559.48)	1221.89 (664.17)	745.74 (468.89)
P-value[b]	*0.218*	*0.341*	*0.102*

Note : [a]Kruskal-Wallis Test, [b]Wilcoxon test, LOS (Length of Stay), CRP (C-reactive protein), NLR (Neutrophil-to-Lymphocyte Ratio), ALC (absolute lymphocyte count)

Based on laboratory markers, COVID-19 patients tend to have lymphopenia, defined by lymphocyte level <1000/µL and associated with increased severity. The platelets are typically normal or slightly reduced (Singhal, 2020). Moreover, the majority of patients have an increased neutrophil-lymphocyte ratio (NLR), higher levels of C-reactive protein (CRP), liver function (AST/ALT), D-dimer status, erythrocyte sedimentation rate (ESR), procalcitonin (PCT) level, and impaired kidney function (Ouassou *et al*., 2020; Singhal, 2020).

The normal D-dimer concentration is 0 - 0.5 mg/L or <500 ng/mL (Yao *et al*., 2020). This must be interpreted with caution in elderly patients and patients with accompanying diseases such as liver disorders, diabetes mellitus, or cardiovascular disease since D-dimer levels rise even in the absence of infection or inflammation (PDPI *et al*., 2020; Zhan *et al*., 2021). In Covid-19, D-dimers have sensitivities of 77%, 75%, and 90%, respectively, and specificities of 71%, 83%, and 60% (Yao *et al*., 2020; Zhan *et al*., 2021). The use of enoxaparin was significantly effective under mild and moderate conditions, with a significant decrease in D-dimer as demonstrated by p<0.001 and p=0.002 (Table II).

There was a difference between the initial and final D-dimer levels before and after enoxaparin administration in the mild and

moderate conditions. However, enoxaparin did not reduce D-dimer in severe conditions as demonstrated by p=0.918. Therefore, additional investigation is required in patients with severe infections due to the rapid worsening of the disease. Deteriorating kidney conditions necessitate switching from enoxaparin to UFH, particularly in patients with severe conditions who require intensive care. During the hospitalization, the D-dimer level and incidence of bleeding are closely monitored.

Furthermore, platelet levels increased significantly in the mild and moderate ($p<0.001$) but not in severe conditions ($p=0.546$). Theoretically, the use of enoxaparin might decrease platelets (thrombocytopenia), but this was not observed in this study. The improvement in platelet levels indicates improved clinical conditions as well as recovery from infectious diseases, considering that in COVID-19 infection, platelets are used extensively due to the damage caused by immune complexes and the formation of thrombi and microthrombi in the lungs (Albani *et al*., 2020; Jiménez-Soto *et al*., 2021). Each 50.000/µL increase in platelet concentration lowers the risk of death by 40% (Vajari *et al*., 2021; Liu *et al*., 2020).

There was also a decrease in CRP levels among patients with mild and moderate conditions ($p<0.05$). This is evidenced by the difference between the initial and final CRP level before and after receiving enoxaparin (Table II). However, the decrease in severe conditions is not statistically significant as demonstrated by $p=0.193$ (Table II). This result is in line with Shi *et al*., who discovered no effect of decreased CRP following enoxaparin administration in patients with severe conditions. This is because the patient's disease progresses under severe conditions, particularly complex inflammatory conditions caused by COVID-19 infection, which impair enoxaparin's anti-inflammatory properties, most notably in CRP parameters (Shi *et al*., 2020).

Enoxaparin administration significantly increased NLR levels across all severity groups as demonstrated by $p<0.005$ (Table II). This increase indicates an ongoing inflammatory process, as there is no improvement in NLR parameters following enoxaparin administration. Several mechanisms demonstrate enoxaparin's anti-inflammatory effects, heparin and its derivatives exert diverse anti-inflammatory and other biological effects (Vitiello & Ferrara, 2021). According to a meta-analysis study, heparin is an effective anti-inflammatory agent that lowers inflammatory biomarkers and improves patients' conditions (Mousavi *et al*., 2015). Furthermore, the results showed that enoxaparin cannot reduce NLR (Table II).

Enoxaparin did not affect the ALC level, this is contrary to previous studies which reported an increase in the ALC level of COVID-19 patients. The treatment with enoxaparin in varying severity levels had no significant effect as demonstrated by $p>0.05$ (Table II). These indicate that enoxaparin does not affect lymphocyte counts. Meanwhile, these results are in contrast with a previous study conducted by Shi et al. which reported an increase in lymphocytes in patients with clinical improvement after enoxaparin treatment. The anti-inflammatory effects of enoxaparin can reduce IL-6 levels in COVID-19 patients, while an increase in TNF-α and IL-6 during a cytokine storm causes lymphopenia (Shi *et al*., 2020).

NLR values typically decrease followed by an increase in lymphocytes as a sign of inflammatory improvement (Selanno *et al*., 2021). Therefore, predicting the severity of a COVID-19 infection is possible with the help of NLR and ALC. NLR has a sensitivity of 91.8% and a specificity of 66.4%, while that of ALC are 81.6% and 64.8% respectively (Selanno *et al*., 2021). Given that the NLR and ALC levels did not improve, they are not reliable indicators of clinical improvement in COVID-19 patients. This study has certain limitations, first, it was conducted in only one hospital. Secondly, the findings are limited by the sample size and single-center design.

CONCLUSION

The increase in mortality rate and the need for mechanical ventilation are directly proportional to a high level of severity. Meanwhile, the greater the severity, the higher the mortality rate and the need for mechanical ventilation. Based on the results, enoxaparin significantly improved D-dimer, CRP, and platelet levels in mild and moderate patients but not in severe conditions. There was also no effect on the LOS, NLR, and ALC levels.

ACKNOWLEDGMENT

The authors are grateful to the director of Santo Borromeus Hospital Bandung for granting the permission to conduct this study.

REFERENCES

Abate, B. B., Kassie, A. M., Kassaw, M. W., Aragie, T. G., & Masresha, S. A. (2020). Sex difference in coronavirus disease (COVID-19): A systematic review and meta-analysis. *BMJ Open*, *10*(10), 1–10. https://doi.org/10.1136/bmjopen-2020-040129

Al-Samkari, H., Gupta, S., Leaf, R. K., Wang, W., Rosovsky, R. P., Brenner, S. K., … Leaf, D. E. (2021). Thrombosis, bleeding, and the observational effect of early therapeutic anticoagulation on survival in critically ill patients with covid-19. *Annals of Internal Medicine*, *174*(5), 622–632. https://doi.org/10.7326/M20-6739

Albani, F., Sepe, L., Fusina, F., Prezioso, C., Baronio, M., Caminiti, F., … Natalini, G. (2020). Thromboprophylaxis with enoxaparin is associated with a lower death rate in patients hospitalized with SARS-CoV-2 infection. A cohort study. *eClinicalMedicine*, *27*(April), 100562. https://doi.org/10.1016/j.eclinm.2020.100562

Arachchillage, D. R. J., & Laffan, M. (2020). Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *Journal of Thrombosis and Haemostasis*, *18*(5), 1233–1234. https://doi.org/10.1111/jth.14820

Berlin, D. A., Gulick, R. M., & Martinez, F. J. (2020). Severe Covid-19. *New England Journal of Medicine*, *383*(25), 2451–2460. https://doi.org/10.1056/nejmcp2009575

Billett, H. H., Reyes-Gil, M., Szymanski, J., Ikemura, K., Stahl, L. R., Lo, Y., … Bellin, E. (2020). Anticoagulation in COVID-19: Effect of Enoxaparin, Heparin, and Apixaban on Mortality. *Thrombosis and Haemostasis*, *120*(12), 1691–1699. https://doi.org/10.1055/s-0040-1720978

Cardillo, G., Viggiano, G. V., Russo, V., Mangiacapra, S., Cavalli, A., Castaldo, G., … Di Micco, P. (2021). Antithrombotic and anti-inflammatory effects of fondaparinux and enoxaparin in hospitalized COVID-19 patients: The FONDENOXAVID study. *Journal of Blood Medicine*, *12*, 69–75. https://doi.org/10.2147/JBM.S285214

CDC. (2022). *Covid-19*. Retrieved February 14, 2022, from https://www.cdc.gov/coronavirus/2019-nCoV/index.html

Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., … Zhang, L. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet*, *395*(10223), 507–513. https://doi.org/10.1016/S0140-6736(20)30211-7

Costanzo, L., Palumbo, F. P., Ardita, G., Antignani, P. L., Arosio, E., & Failla, G. (2020). Coagulopathy, thromboembolic complications, and the use of heparin in COVID-19 pneumonia. *Journal of Vascular Surgery: Venous and Lymphatic Disorders*, *8*(5), 711–716. https://doi.org/10.1016/j.jvsv.2020.05.018

Dutt, T., Simcox, D., Downey, C., McLenaghan, D., King, C., Gautam, M., … Burhan, H. (2020). Thromboprophylaxis in COVID-19: Anti-FXa - The missing factor? *American Journal of Respiratory and Critical Care Medicine*, *202*(3), 455–457. https://doi.org/10.1164/rccm.202005-1654LE

Elbeddini, A., Gerochi, R., & Elshahawi, A. (2020). Evaluation of the prophylaxis and treatment of COVID-associated coagulopathy. *Journal of Pharmaceutical Policy and Practice*, *13*(1), 1–9. https://doi.org/10.1186/s40545-020-00274-8

Fareed, J., Hoppensteadt, D., Walenga, J., Iqbal, O., Ma, Q., Jeske, W., & Sheikh, T. (2003). Pharmacodynamic and pharmacokinetic properties of enoxaparin: Implications for clinical practice. *Clinical Pharmacokinetics*, *42*(12), 1043–1057. https://doi.org/10.2165/00003088-200342120-00003

Gemmati, D., & Tisato, V. (2020). *Genetic Hypothesis and Pharmacogenetics Side of Renin-Angiotensin-System in COVID-19*. *11*(9), 1–17. https://doi.org/10.3390/genes11091044

Han, H., Ma, Q., Li, C., Liu, R., Zhao, L., Wang, W., … Xia, Y. (2020). Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. *Emerging Microbes and Infections*, *9*(1), 1123–1130. https://doi.org/10.1080/22221751.2020.1770129

Hendren, N. S., De Lemos, J. A., Ayers, C., Das, S. R., Rao, A., Carter, S., … Grodin, J. L. (2021). Association of Body Mass Index and Age with Morbidity and Mortality in Patients

Hospitalized with COVID-19: Results from the American Heart Association COVID-19 Cardiovascular Disease Registry. *Circulation*, 135–144. https://doi.org/10.1161/CIRCULATIONAHA.120.051936

Iba, T., Levy, J. H., Connors, J. M., Warkentin, T. E., Thachil, J., & Levi, M. (2020). The unique characteristics of COVID-19 coagulopathy. *Critical Care*, *24*(1), 4–11. https://doi.org/10.1186/s13054-020-03077-0

Jiménez-Soto, R., Aguilar-Soto, M., Rodríguez-Toledo, C. A., Camiro-Zúñiga, A., & Demichelis, R. (2021). The impact of different prophylactic anticoagulation doses on the outcomes of patients with COVID-19. *Thrombosis Research*, *202*(December 2020), 14–16. https://doi.org/10.1016/j.thromres.2021.02.031

Jin, J., Bai, P., He, W., Wu, F., Liu, X., Han, D., & Liu, S. (2020). Gender Differences in Patients With COVID-19 : Focus on Severity and Mortality. *Frontiers in Public Health*, *8*(152), 1–6. https://doi.org/10.3389/fpubh.2020.00152

Kamel, A. M., Sobhy, M., Magdy, N., Sabry, N., & Farid, S. (2021). Anticoagulation outcomes in hospitalized Covid-19 patients: A systematic review and meta-analysis of case-control and cohort studies. *Reviews in Medical Virology*, *31*(3). https://doi.org/10.1002/rmv.2180

Kirkup, C., Pawlowski, C., Puranik, A., Conrad, I., O'Horo, J. C., Gomaa, D., … Soundararajan, V. (2021). Healthcare disparities among anticoagulation therapies for severe COVID-19 patients in the multi-site VIRUS registry. *Journal of Medical Virology*, *93*(7), 4303–4318. https://doi.org/10.1002/jmv.26918

Kluwer, W. (2022a). *Enoxaparin : Drug Interactions*. Retrieved February 12, 2022, from https://online.lexi.com/lco/action/interact/globalid/6105

Kluwer, W. (2022b). *Enoxaparin (Lexi-Drugs)*. Retrieved February 10, 2022, from https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6820?cesid=6hYfqL8KCGL&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Denoxaparin%26t%3Dname%26va%3Denoxaparin#phk

Langer, F., Kluge, S., Klamroth, R., & Oldenburg, J. (2020). Coagulopathy in COVID-19 and Its Implication for Safe and Efficacious Thromboprophylaxis. *Hamostaseologie*, *40*(3), 264–269. https://doi.org/10.1055/a-1178-3551

Lemos, A. C. B., do Espírito Santo, D. A., Salvetti, M. C., Gilio, R. N., Agra, L. B., Pazin-Filho, A., & Miranda, C. H. (2020). Therapeutic versus prophylactic anticoagulation for severe COVID-19: A randomized phase II clinical trial (HESACOVID). *Thrombosis Research*, *196*, 359–366. https://doi.org/10.1016/j.thromres.2020.09.026

Li, X., Xu, S., Yu, M., Wang, K., Tao, Y., Zhou, Y., Shi, J., Zhou, M., Wu, B., Yang, Z., Zhang, C., Yue, J., Zhang, Z., Renz, H., Liu, X., Xie, J., Xie, M., & Zhao, J. (2020). Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. *Journal of Allergy and Clinical Immunology*, *146*(1), 110–118. https://doi.org/10.1016/j.jaci.2020.04.006

Li, X., Zhong, X., Wang, Y., Zeng, X., Luo, T., & Liu, Q. (2021). Clinical determinants of the severity of COVID-19: A systematic review and meta-analysis. *PLoS ONE*, *16*(5 May), 1–21. https://doi.org/10.1371/journal.pone.0250602

Liu, Y., Sun, W., Guo, Y., Chen, L., Zhang, L., Zhao, S., Long, D., & Yu, L. (2020). Association between platelet parameters and mortality in coronavirus disease 2019: Retrospective cohort study. *Platelets*, *31*(4), 490–496. https://doi.org/10.1080/09537104.2020.1754383

Liverpool Drug Interactions Group. (2022). Interactions with experimental COVID-19 Antiviral Therapies. *University of Liverpool*, *February*, 1–6. Retrieved February 4, 2022, from www.covid19-druginteractions.org

Lopes, R. D., de Barros e Silva, P. G. M., Furtado, R. H. M., Macedo, A. V. S., Bronhara, B., (2021). Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. *The Lancet*, *397*(10291), 2253–2263. https://doi.org/10.1016/S0140-6736(21)01203-4

Mennuni, M. G., Renda, G., Grisafi, L., Rognoni, A., Colombo, C., Lio, V., … Patti, G. (2021). Clinical outcome with different doses of low-molecular-weight heparin in patients hospitalized for COVID-19. *Journal of*

Thrombosis and Thrombolysis, *52*(3), 782–790. https://doi.org/10.1007/s11239-021-02401-x

Moores, L. K., Tritschler, T., Brosnahan, S., Carrier, M., Collen, J. F., Doerschug, K., … Wells, P. (2020). Prevention, Diagnosis, and Treatment of VTE in Patients With Coronavirus Disease 2019: CHEST Guideline and Expert Panel Report. *Chest*, *158*(3), 1143–1163. https://doi.org/10.1016/j.chest.2020.05.559

Motta, J. K., Ogunnaike, R. O., Shah, R., Stroever, S., Cedeño, H. V., Thapa, S. K., … Hegde, A. (2020). Clinical Outcomes With the Use of Prophylactic Versus Therapeutic Anticoagulation in Coronavirus Disease 2019. *Critical Care Explorations*, *2*(12), e0309. https://doi.org/10.1097/cce.0000000000000309

Mousavi, S., Moradi, M., Khorshidahmad, T., & Motamedi, M. (2015). Anti-inflammatory effects of heparin and its derivatives: A systematic review. *Advances in Pharmacological Sciences*, *2015*. https://doi.org/10.1155/2015/507151

Mukherjee, S., & Pahan, K. (2021). Is COVID-19 Gender-sensitive? *Journal of Neuroimmune Pharmacology*, *16*, 38–47. https://doi.org/10.1007/s11481-020-09974-z

National Institutes of Health. (2021). Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19). *NIH 2019*, 1–243. Retrieved February 14, 2022, from https://www.covid19treatmentguidelines.nih.gov/

Nutescu, E. A., Burnett, A., Fanikos, J., Spinler, S., & Wittkowsky, A. (2016). Pharmacology of anticoagulants used in the treatment of venous thromboembolism. *Journal of Thrombosis and Thrombolysis*, *41*(1), 15–31. https://doi.org/10.1007/s11239-015-1314-3

Ouassou, H., Kharchoufa, L., Bouhrim, M., Daoudi, N. E., Imtara, H., Bencheikh, N., … Bnouham, M. (2020). The Pathogenesis of Coronavirus Disease 2019 (COVID-19): Evaluation and Prevention. *Journal of Immunology Research*, *2020*, 1–7. https://doi.org/10.1155/2020/1357983

Pangarsa, E. A., Setiawan, B., Santosa, D., Naibaho, R. M., Rizky, D., Suyono, Tobing, M. L., & Suharti, C. (2020). Position paper from the indonesian society of thrombosis and hemostasis (Inasth), semarang chapter: Management of coagulopathy in COVID-19. *Bali Medical Journal*, *9*(2), 482–488. https://doi.org/10.15562/bmj.v9i2.1841

Parisi, R., Costanzo, S., Di Castelnuovo, A., De Gaetano, G., Donati, M. B., & Iacoviello, L. (2021). Different Anticoagulant Regimens, Mortality, and Bleeding in Hospitalized Patients with COVID-19: A Systematic Review and an Updated Meta-Analysis. *Seminars in Thrombosis and Hemostasis*, *47*(4), 372–391. https://doi.org/10.1055/s-0041-1726034

PDPI, PERKI, PAPDI, PERDATIN, & IDAI. (2020). Pedoman tatalaksana COVID-19 Edisi 3 Desember 2020. In *Pedoman Tatalaksana COVID-19*. Retrieved December 16, 2022, from https://www.papdi.or.id/download/983-pedoman-tatalaksana-covid-19-edisi-3-desember-2020

Peckham, H., de Gruijter, N. M., Raine, C., Radziszewska, A., Ciurtin, C., Wedderburn, L. R., … Deakin, C. T. (2020). Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. *Nature Communications*, *11*(1), 1–10. https://doi.org/10.1038/s41467-020-19741-6

Perepu, U. S., Chambers, I., Wahab, A., Ten Eyck, P., Wu, C., Dayal, S., … Lentz, S. R. (2021). Standard prophylactic versus intermediate dose enoxaparin in adults with severe COVID-19: A multi-center, open-label, randomized controlled trial. *Journal of Thrombosis and Haemostasis*, *19*(9), 2225–2234. https://doi.org/10.1111/jth.15450

Pivonello, R., Auriemma, S., & Pivonello, C. (2021). Sex Disparities in COVID-19 Severity and Outcome : Are Men Weaker or Women Stronger ? *Neuroendocrinology*, *111*, 1066–1085. https://doi.org/10.1159/000513346

Poudel, A., Poudel, Y., Adhikari, A., Aryal, B. B., Dangol, D., Bajracharya, T., … Gautam, R. (2021). D-dimer as a biomarker for assessment of COVID-19 prognosis: D-dimer levels on admission and its role in predicting disease outcome in hospitalized patients with COVID-19. *PLoS ONE*, *16*(8 August 2021), 1–13. https://doi.org/10.1371/journal.pone.0256744

Price, L. C., McCabe, C., Garfield, B., & Wort, S. J. (2020). Thrombosis and COVID-19 pneumonia: The clot thickens! *European Respiratory Journal*, *56*(1). https://doi.org/10.1183/13993003.01608-2020

Rentsch, C. T., Beckman, J. A., Tomlinson, L., Gellad, W. F., Alcorn, C., Kidwai-Khan, F., … Freiberg, M. S. (2021). Early initiation of prophylactic anticoagulation for prevention of coronavirus disease 2019 mortality in patients admitted to hospital in the United States: Cohort study. *The BMJ*, *372*. https://doi.org/10.1136/bmj.n311

Rosovsky, R. P., Sanfilippo, K. M., Wang, T. F., Rajan, S. K., Shah, S., Martin, K. A., … Baumann Kreuziger, L. (2020). Anticoagulation practice patterns in COVID-19: A global survey. *Research and Practice in Thrombosis and Haemostasis*, *4*(6), 969–983. https://doi.org/10.1002/rth2.12414

Rusdiana, T., & Akbar, R. (2020). Perkembangan Terkini Terapi Antikoagulan Pada Pasien Covid-19 Bergejala Berat. *Jurnal Sains Farmasi & Klinis*, *7*(3), 244. https://doi.org/10.25077/jsfk.7.3.244-250.2020

Selanno, Y., Widaningsih, Y., Esa, T., & Arif, M. (2021). Analysis of Neutrophil Lymphocyte Ratio and Absolute Lymphocyte Count as Predictors of Severity of COVID-19 Patients. *Indonesian Journal of Clinical Pathology and Medical Laboratory*, *27*(2), 184–189. https://doi.org/10.24293/ijcpml.v27i2.1738

Shi, C., Wang, C., Wang, H., Yang, C., Cai, F., Zeng, F., … Zhang, Y. (2020). The Potential of Low Molecular Weight Heparin to Mitigate Cytokine Storm in Severe COVID-19 Patients: A Retrospective Cohort Study. *Clinical and Translational Science*, *13*(6), 1087–1095. https://doi.org/10.1111/cts.12880

Simegn, A., Mesfin, D., Minuye, B., Ayanaw, B., & Muche, T. (2021). Sex and Gender Differences for Severity and Mortality from COVID-19 : Rapid Evidence Synthesis for the Implication of Health Equity in Access Policies. *Health Science Journal*, *15*(8), 1–3.

Singhal, T. (2020). A Review of Coronavirus Disease-2019 (COVID-19). *Indian Journal of Pediatrics*, *87*(4), 281–286. https://doi.org/10.1007/s12098-020-03263-6

Smits, S. L., De Lang, A., Van Den Brand, J. M. A., Leijten, L. M., Van Ijcken, W. F., Eijkemans, M. J. C., … Haagmans, B. L. (2010). Exacerbated innate host response to SARS-CoV in aged non-human primates. *PLoS Pathogens*, *6*(2). https://doi.org/10.1371/journal.ppat.1000756

Spyropoulos, A. C., Goldin, M., Giannis, D., Diab, W., Wang, J., Khanijo, S., … Weitz, J. I. (2021). Efficacy and Safety of Therapeutic-Dose Heparin vs Standard Prophylactic or Intermediate-Dose Heparins for Thromboprophylaxis in High-risk Hospitalized Patients with COVID-19: The HEP-COVID Randomized Clinical Trial. *JAMA Internal Medicine*, *181*(12), 1612–1620. https://doi.org/10.1001/jamainternmed.2021.6203

Sunggoro, A. J., Purwanto, I., & Hasan, M. (2020). Trombosis pada corona virus disease (COVID-19). *Jurnal Kedokteran Syiah Kuala*, *20*(3), 191–198. https://doi.org/10.24815/jks.v20i3.18689

Tang, N., Bai, H., Chen, X., Gong, J., Li, D., & Sun, Z. (2020). Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *Journal of Thrombosis and Haemostasis*, *18*(5), 1094–1099. https://doi.org/10.1111/jth.14817

Vajari, M. K., Shirin, M., Pourbagheri-Sigaroodi, A., Akbari, M. E., Abolghasemi, H., & Bashash, D. (2021). COVID-19-related coagulopathy: A review of pathophysiology and pharmaceutical management. *Cell Biology International*, *45*(9), 1832–1850. https://doi.org/10.1002/cbin.11623

Vaughn, V. M., Yost, M., Abshire, C., Flanders, S. A., Paje, D., Grant, P., … Barnes, G. D. (2021). Trends in Venous Thromboembolism Anticoagulation in Patients Hospitalized with COVID-19. *JAMA Network Open*, *4*(6), 1–13. https://doi.org/10.1001/jamanetworkopen.2021.11788

Vitiello, A., & Ferrara, F. (2021). Low Molecular Weight Heparin, Anti-inflammatory/Immunoregulatory and Antiviral Effects, a Short Update. *Cardiovascular Drugs and Therapy*. https://doi.org/10.1007/s10557-021-07251-6

Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., … Peng, Z. (2020). Clinical Characteristics of

138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA - Journal of the American Medical Association*, *323*(11), 1061–1069. https://doi.org/10.1001/jama.2020.1585

Wang, X., Zhang, H., Du, H., Ma, R., Nan, Y., & Zhang, T. (2021). Risk Factors for COVID-19 in Patients with Hypertension. *Canadian Journal of Infectious Diseases and Medical Microbiology*, *2021*. https://doi.org/10.1155/2021/5515941

WHO. (2022). *Coronavirus disease (COVID-19) pandemic*. Retrieved February 14, 2022, from https://www.who.int/emergencies/diseases/novel-coronavirus-2019

Yao, Y., Cao, J., Wang, Q., Shi, Q., Liu, K., Luo, Z., … Hu, B. (2020). D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: A case control study. *Journal of Intensive Care*, *8*(1), 1–11. https://doi.org/10.1186/s40560-020-00466-z

Zhan, H., Chen, H., Liu, C., Cheng, L., Yan, S., Li, H., & Li, Y. (2021). Diagnostic Value of D-Dimer in COVID-19: A Meta-Analysis and Meta-Regression. *Clinical and Applied Thrombosis/Hemostasis*, *27*. https://doi.org/10.1177/10760296211010976

Zhang, J., Dong, X., Liu, G., & Gao, Y. (2022). Risk and Protective Factors for COVID - 19 Morbidity , Severity , and Mortality. *Clinical Reviews in Allergy & Immunology*. https://doi.org/10.1007/s12016-022-08921-5

Zhang, L., Feng, X., Zhang, D., Jiang, C., Mei, H., Wang, J., … Xie, M. (2020). Deep Vein Thrombosis in Hospitalized Patients with COVID-19 in Wuhan, China: Prevalence, Risk Factors, and Outcome. *Circulation*, *142*(2), 114–128. https://doi.org/10.1161/CIRCULATIONAHA.120.046702

Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., … Cao, B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet*, *395*(10229), 1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3

Zhou, X., Cheng, Z., Luo, L., Zhu, Y., Lin, W., Ming, Z., … Hu, Y. (2021). Incidence and impact of disseminated intravascular coagulation in COVID-19 a systematic review and meta-analysis. *Thrombosis Research*, *201*(November 2020), 23–29. https://doi.org/10.1016/j.thromres.2021.02.010

Zhu, Z., Cai, T., Fan, L., Lou, K., Hua, X., Huang, Z., & Gao, G. (2020). Clinical value of immune-inflammatory parameters to assess the severity of coronavirus disease 2019. *International Journal of Infectious Diseases*, *95*, 332–339. https://doi.org/10.1016/j.ijid.2020.04.041