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

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ABSTRACT

Coagulopathy is a common predictor of mortality in COVID-19. Meanwhile, enoxaparin is an anticoagulant with anti-inflammatory, endothelial protection, and viral antagonistic 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, 209 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 x10^9/µl (p=<0.001) in mild and 256.77 to 398.97 x10^9/µl (p=<0.001) in moderate. Moreover, CRP improved in both mild 52.62 to 42.66 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; X. 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; X. 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 (Kohansal 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 (Paris et al., 2021; X. 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 (Arachchilage & 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 (Arachchilage & 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 al., 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 al., 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 (Alhani 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 pharmacodynamic 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/m² or 60 mg for BMI ≥30 kg/m². The intermediate dose was 40 mg twice daily for BMI ≥30 kg/m² or 60 mg once daily for BMI <30 kg/m², while the therapeutic was 60 mg twice daily.

Data on demographics 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 Borrormeo 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; Xinyang 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 (Xinyang Li et al., 2021). The average severe patient had a BMI of 28.02 kg/m², moderate 26.54 kg/m², and mild 25.66 kg/m² (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; Simmon et al., 2021; J. 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; X. 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 (F. Zhou et al., 2020). ACE and ACE2 work together to keep blood pressure hemodynamically 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 (Xiaochen 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).
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 (Table I).
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; D. Wang et al., 2020)
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 severe groups.
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% (Kohansal 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 \( p=0.198 \) (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 can not 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.
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