© 2023 Journal of Pharmacy & Pharmacognosy Research, 11 (6), 1106-1113, 2023
ISSN 0719-4250
https://jppres.com

DOI: https://doi.org/10.56499/jppres23.1683_11.6.1106

Original Article

Analysis of factors affecting enoxaparin effectiveness on coagulation, inflammation, and clinical outcomes in patients with COVID-19

[Análisis de los factores que afectan a la eficacia de la enoxaparina sobre la coagulación, la inflamación y los resultados clínicos en pacientes con COVID-19]

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Abstract

Context: Hypercoagulopathy is a COVID-19 extra-pulmonary manifestation has drawn the attention of the scientists due to its risk of thromboembolism. Enoxaparin is an anticoagulant used to prevent hypercoagulopathy. Many factors have been associated with enoxaparin effectiveness.

Aims: To analyze factors affecting enoxaparin effectiveness on coagulation, inflammation, and clinical outcomes.

Methods: This retrospective cohort study involved hospitalized adult patients with COVID-19 from November 2020 to April 2021. Patients' age, gender, body mass index (BMI), comorbidity, and laboratory results were extracted from medical records. Factors influencing enoxaparin efficacy on coagulation, inflammation, and clinical outcomes were analyzed using path analysis with SmartPLS 3.0 software. D-dimer and platelet values was determined as coagulation outcomes and C-reactive protein (CRP) value as an inflammation outcome. Clinical outcomes comprised of mortality, ventilator usage, and length of stay.

Results: A total of 269 patients fulfilled the inclusion criteria. Most of the subjects were male (58%), 66% had comorbidities, 48.3% were aged ≥60 years old, and 65.8% had a BMI ≥ 25 kg/m^2. Path analysis showed that age, BMI, and comorbidity affected disease severity ($p<0.05$). Disease severity strongly influenced enoxaparin dosage ($p=0.000$). Dosage affected platelet value, ventilator usage, and mortality ($p<0.05$). Gender did not influence disease severity, and dosage displayed no significant effect on length of stay, CRP, and D-dimer ($p>0.05$).

Conclusions: Dosage is the main factor influencing enoxaparin efficacy on coagulation, inflammation, and clinical outcomes. The dosage is strongly affected by disease severity, in which is predominantly influenced by age, BMI, and comorbidity.

Keywords: anticoagulant; blood coagulation; COVID-19; enoxaparin.

Resumen

Contexto: La hipercoagulopatía es una COVID-19 manifestación extrapulmonar que ha llamado la atención de los científicos por su riesgo de tromboembolismo. La enoxaparina es un anticoagulante utilizado para prevenir la hipercoagulopatía. Muchos factores se han asociado con la eficacia de la enoxaparina.

Objetivos: Analizar los factores que afectan a la eficacia de la enoxaparina sobre la coagulación, la inflamación y los resultados clínicos.

Métodos: Este estudio de cohortes retrospectivo incluyó pacientes adultos hospitalizados con COVID-19 desde noviembre de 2020 hasta abril de 2021. La edad, el sexo, el indice de masa corporal (IMC), la comorbilidad y los resultados de laboratorio de los pacientes se extrajeron de los registros médicos. Los factores que influyen en la eficacia de la enoxaparina sobre la coagulación, la inflamación y los resultados clínicos se analizaron mediante análisis de trayectorias con el software SmartPLS 3.0. Los valores de dímero D y plaquetas se determinaron como resultados de coagulación y el valor de C-reactive protein (CRP) como resultado de inflamación. Los resultados clínicos incluyeron la mortalidad, el uso de ventilador y la duración de la estancia.

Resultados: Un total de 269 pacientes cumplieron los criterios de inclusión. El sexo masculino predominó entre los sujetos (58%). El 66% de los pacientes presentaba comorbilidad, el 48,3% tenía una edad ≥60 años y el 65,8% un IMC ≥25 kg/m^2. El análisis mostró que la edad, el IMC y la comorbilidad afectaban a la gravedad de la enfermedad ($p<0,05$). La gravedad de la enfermedad influye fuertemente en la dosis de enoxaparina ($p=0,000$). La dosis afectó al valor plaquetario, el uso de ventilador y la mortalidad ($p<0,05$). El sexo no influyó en la gravedad de la enfermedad, y la dosis no mostró efectos significativos en la duración de la estancia hospitalaria ni en la PCR y el dímero D ($p>0,05$).

Conclusiones: El factor que influye en la eficacia de la enoxaparina sobre la coagulación, la inflamación y los resultados clínicos es la dosis, que se vio afectada positivamente por la gravedad de la enfermedad. La edad, el IMC y la comorbilidad afectaron a la gravedad de la enfermedad.

Palabras Clave: anticoagulantes; coagulación sanguínea; COVID-19; enoxaparina.

ARTICLE INFO
Received: May 7, 2023.
Accepted: September 26, 2023.
Available Online: October 31, 2023.

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INTRODUCTION

Recent studies state that hypercoagulopathy is a hematologic complication in patient with COVID-19 (Al-Samkari et al., 2020; Elrobaa and New, 2021; Giannis et al., 2020). This is particularly alarming because of the rise of thromboembolic event, which can lead to higher mortality and morbidity (Bilaloglu et al., 2020).

Patients with hypercoagulopathy displayed abnormal blood laboratory results, including a significant rise in D-dimer value, thrombocytopenia, and prothrombin time (PT) prolongation (Giannis et al., 2020). Higher D-dimer increases the risk of developing venous thromboembolic events (pulmonary embolism and deep vein thrombosis) and arterial thromboembolic events (ischemic stroke and myocardial infarction). A previous study by Bilaloglu et al. (2020) reported that the prevalence of thromboembolic events in intensive care unit (ICU) patients were 29.4% and in non-ICU patients 11.5%.

Enoxaparin is a low-molecular-weight heparin (LMWH) that is used as an anticoagulant to prevent a thromboembolic event in COVID-19 (Atallah et al., 2020; Jiménez-Soto et al., 2021; Pangarsa et al., 2020). However, evidence in terms of the effectiveness of enoxaparin on patient outcomes has been inconsistent. Several factors come to play when it comes to improving patient outcomes. Perepu et al. (2021) conducted a post hoc analysis between obese and non-obese patients who received prophylactic or therapeutic enoxaparin. The result showed that patients with obesity had a higher hazard ratio for mortality reaching 0.75 compared to 0.55 hazard ratio in non-obese patients. Another study by Zalivansky et al. (2021) showed that different enoxaparin dosages could influence patient outcomes. Zalivansky et al. (2021) found that therapeutic enoxaparin administration led to lower mortality (41%), venous thromboembolism (VTE) (11%), and ventilator requirements (4%) compared to prophylactic or intermediate doses. Oliynyk et al. (2021) also presented similar results, indicating a significant correlation between dosage type, gender, and D-dimer, and the risk of death and ventilator requirement ($p<0.05$) using three-factor logistic regression analysis.

In clinical setting, enoxaparin is often prescribed in three dosing regimens: prophylactic, intermediate, or therapeutic, and these dosing regimens were determined by disease severity (Atallah et al., 2020). Factors that are shown to predict the severity in COVID-19 patients include being of the male gender, obesity, advanced age, and comorbidities (Guan et al., 2020; Li et al., 2020).

Based on the abovementioned idea, it can be hypothesized that the enoxaparin outcome depends on the dosage used on each severity, which is often determined by factors such as age, gender, body mass index (BMI), and comorbidities. The goal of this study is to analyze the factors affecting enoxaparin effectiveness on patient outcomes (coagulation, inflammation, and clinical) by means of testing the theory through path analysis.

MATERIAL AND METHODS

Study design and population

The study design was observational-cohort, and data was collected retrospectively. The study was conducted at Rumah Sakit Santo Borromeus, a secondary hospital in Indonesia. The inclusion criteria were age ≥18 years old, patients who received enoxaparin during admission, patients who had baseline platelet >100.000/µL and glomerulus filtration rate (GFR) >30 mL/min. The exclusion criteria were patients who were pregnant, whose length of stay (LOS) was less than three days, and who experienced a change in therapy from enoxaparin to another anticoagulant during the treatment. Adult inpatients admitted from November 2020 to April 2021 who met the inclusion and the exclusion criteria were used as a study sample.

Data on patient characteristics (age, gender, BMI, and comorbidities), disease severity, enoxaparin dosage, D-dimer, platelet, C-reactive protein (CRP) value, mortality, LOS, and ventilator usage were collected to analyze factors influencing enoxaparin effectiveness on patient outcomes.

Three types of enoxaparin dosing regimens were administered for the patients: prophylactic, intermediate, and therapeutic. The prophylactic dose was 40 mg once daily for BMIs below 30 kg/m^2 or 60 mg once daily for BMIs ≥30 kg/m^2. The intermediate dose included enoxaparin 60 mg once daily for patients with a BMI below 30 kg/m^2 or 40 twice daily for those with BMI ≥30 kg/m^2. Patients with D-dimer values exceeding 1500 ng/mL received therapeutic enoxaparin (60 mg twice daily). The clinical outcomes were mortality, ventilator usage, and LOS. The coagulation outcome included D-dimer and platelet values, and the inflammation outcome included the CRP value (Suprapti et al., 2022)

Ethical clearance

The methodology of this study has been approved by the local ethics committee of Santo Borromeus Hospital with the approval letter number

017/KEPK/IX.2021. The local ethics committee waived the requirement for patient informed consent because there was no direct intervention to the patients and data was collected retrospectively from medical records.

Research variables

The variables examined in this study comprised of independent and dependent variables. The relationship between variables is describe as follows: (1) Age, BMI, gender, and comorbidities were the independent variables that cause a change in disease severity (dependent variable); (2) Disease severity also served as an independent variable that influences enoxaparin dosage; (3) Enoxaparin dosage was the independent variable influencing D-dimer, platelet, CRP, ventilator usage, mortality, and length of stay (dependent variables).

To summarize, disease severity and enoxaparin dosage were both independent and dependent variables.

Statistical analysis

Descriptive analysis was used to illustrate patient demographic including gender, BMI, comorbidities, enoxaparin dosage, and disease severity.

Path analysis was performed using SmartPLS 3.0 software to analyze various factors involved in the effectiveness of enoxaparin on coagulation, inflammation, and clinical outcomes. The first step was to construct a conceptual model based on the research variables. The next step was to perform the bootstrap technique to test the significance of each variable relationship. A *T*- value >1.96 and p-value <0.05 indicated a significant relationship. The R^2 value was reported to demonstrate the size of the dependent variable's variance that can be explained by its independent variable. The R^2 value of 0.75, 0.5, and 0.25 indicate strong, moderate, and weak explanatory power (Hair et al., 2021).

RESULTS

Patient characteristics

During the research period, 269 patients fulfilled the inclusion criteria. Table 1 provides patient characteristics involved in this study. The majority of patients were male (58%), and 48.3% were elderly (≥60 years old). More than half of the patients were categorized as obese (65.8%), and 66.2% were accompanied by comorbidity. The three most prevalent comorbidity among patients was hypertension (41%), diabetes mellitus (32%), and cardiovascular disease (21%). In this study, a patient could experienced one or more comorbidities. Most patients developed mild (45.0%) and moderate symptoms of COVID-19 (46.8%). While severe symptoms only accounted for 8.2%. Enoxaparin dosing is based on enoxaparin dosing guidelines for COVID-19 and the patients's clinical condition. Patients mostly received intermediate-dose enoxaparin of either 60 mg/day or 40 mg twice daily (45%), then followed by prophylactic dose of either 40 mg/day or 60 mg/day (35.7%) and therapeutic dose of 60 mg twice daily (19.3%). During treatment, adjustment to the dosage may be required due to the possibility of a deterioration in the patient's condition. In this study, a predominance of patients received intermediate dosage, primarily due to the fact that the majority of them experienced a moderate degree of COVID-19.

Path analysis

Fig. 1 illustrates the path analysis model of the factors influencing enoxaparin effectiveness on coagulation, inflammation, and clinical parameters. Table 2 provides the significance of each variable relationship and its R^2 value. Excluding gender, the results showed that age (β: 0.166; *T*-value: 2.689; p-value: 0.007), BMI (β: 0.095; *T*- value: 2.035; p-value: 0.042), and comorbidity (β: 0.298; *T*-value: 5.191; p-value: 0.000) positively affected disease severity. Comorbidity (β: 0.298) had a greater impact on disease severity, then followed by age (β: 0.166) and BMI (β: 0.095). In turn, the severity, as well, affected the enoxaparin dosage (β: 0.358; *T*-value: 6.938; p-value: 0.000). Dosage had a positive relationship on ventilator usage (β: 0.351; *T*-value: 6.150; p-value: 0.000) and mortality (β:0.356; *T*-value: 6.443; p-value :0.000) but had a negative relationship on platelet values (β: -0.152; *T*- value: 2.211; p-value: 0.027). However, dosage displayed no significant effect on D-dimer, CRP, and LOS (*T*-value <1.96 and p-values >0.05). The R^2 value of all the variables is under 0.25, which means the model has a weak explanatory power.

DISCUSSION

Few studies have observed factors influencing enoxaparin effectiveness on patient outcomes. To address this gap, it is fundamental to conduct path analysis to analyze factors influencing enoxaparin effectiveness on coagulation, inflammation, and clinical outcomes.

Path analysis revealed- age, BMI, and comorbidity positively influenced disease severity. This result indicates that with the increase of age, BMI, and the presence of comorbidity, patients are more likely to experience worsening of their illness. The result is supported by previous studies that shown older

Table 1. Patient demographic's profile (N = 269).

Characteristics	n	%
Gender		
Male	156	58.0
Female	113	42.0
Age		
18-59 years old	139	51.7
≥60 years old	130	48.3
BMI[a]		
Non-obese	92	34.2
Obese (BMI ≥ 25 kg/m^2)	177	65.8
Comorbidity		
Without comorbidity	91	33.8
With comorbidity	178	66.2
Enoxaparin dosage		
Prophylactic	96	35.7
Intermediate	121	45.0
Therapeutic	52	19.3
Disease severity		
Mild	121	45.0
Moderate	126	46.8
Severe	22	8.2

[a]BMI: Body Mass Index.

Table 2. Results of the path analysis and R^2 value.

Variable relationship	Path coefficient (β)	*T*-values	p-value	Conclusions	R^2
Age → severity	0.166	2.689	0.007	Significant	
BMI → severity	0.095	2.035	0.042	Significant	
					0.162
Comorbidity → severity	0.298	5.191	0.000	Significant	
Gender → severity	-0.003	0.055	0.956	Not Significant	
Severity → dosage	0.358	6.938	0.000	Significant	0.128
Dosage → LOS	0.037	0.568	0.570	Not Significant	0.001
Dosage → ventilator usage	0.351	6.150	0.000	Significant	0.123
Dosage → mortality	0.356	6.443	0.000	Significant	0.127
Dosage → D-dimer	-0.029	0.469	0.639	Not Significant	0.001
Dosage → platelet	-0.152	2.211	0.027	Significant	0.023
Dosage → CRP	-0.022	0.285	0.776	Not Significant	0.001

patients, patients with BMI 30 kg/m^2 or higher, and patients with multiple comorbidities are at a higher risk of developing severe disease (Barek et al., 2020; Cai et al., 2021; Guan et al., 2020).

Previous studies have reported age as a critical predictor of severe clinical outcomes in COVID-19 (Sharma et al., 2021; Starke et al., 2021). Patients aged 65 and older are 0.76 times more likely to develop

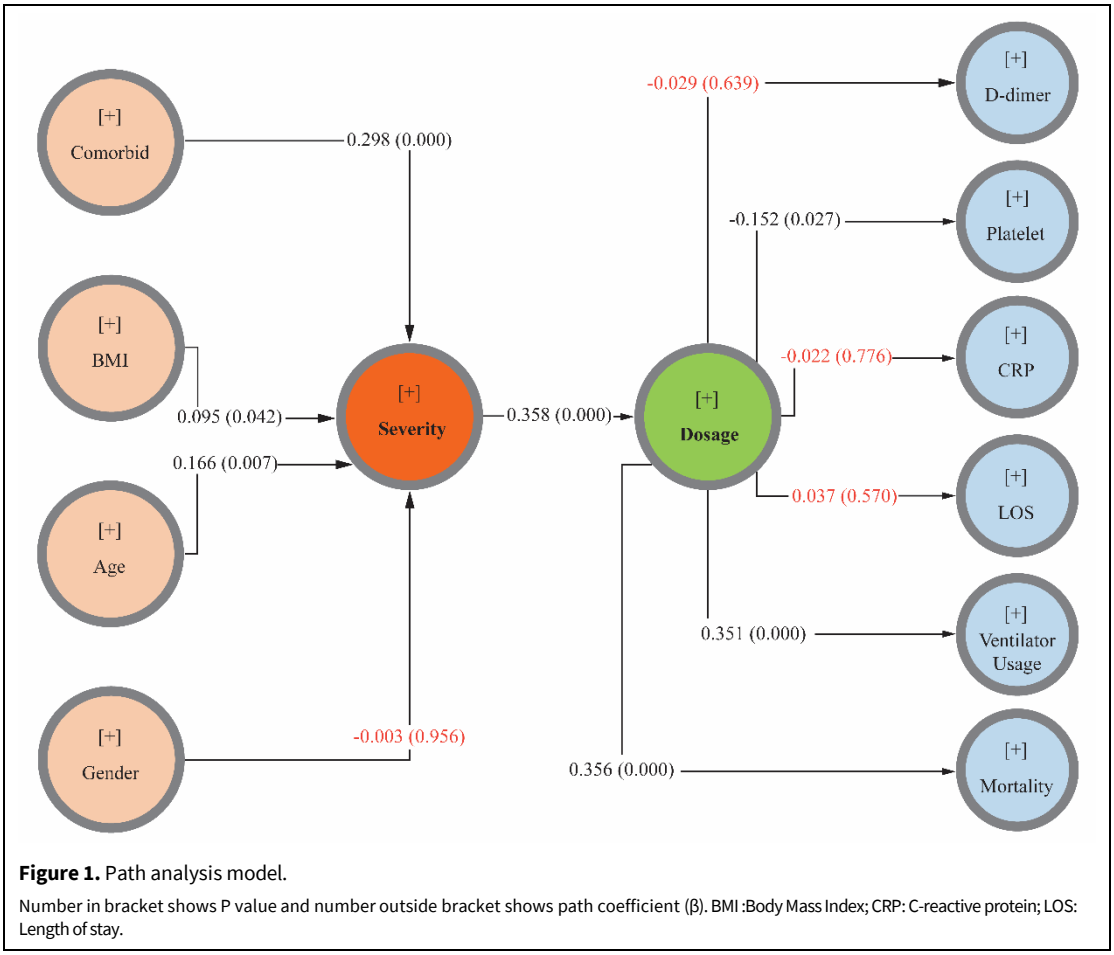

Figure 1. Path analysis model.

Number in bracket shows P value and number outside bracket shows path coefficient (β). BMI :Body Mass Index; CRP: C-reactive protein; LOS: Length of stay.

severe illness compared to those younger than 65 (Barek et al., 2020). This is due to the aging process, which can cause immune system dysfunction that leads to reduced patient resistance to the SARS-COV-2 virus (Bajaj et al., 2021). Moreover, patients with advanced age are often accompanied by comorbidities such as hypertension, diabetes, and cardiovascular disease that can exacerbate their disease severity (Wu and McGoogan, 2020).

Several studies reported that obesity is another risk factors affecting COVID-19 severity (Cai et al., 2021; Gao et al., 2021; Tamara and Tahapary, 2020). One meta-analysis study stated that patients with BMI >30 kg/m^2 are more prone to severe infections, use ventilators, and are more prone to hospitalization (Cai et al., 2021). Several mechanisms have explained the correlation between obesity with COVID-19 severity. The expression of ACE2 receptors, which are the 'entry point' of the SARS-COV-2 virus, is higher in the adipose tissue than in the lung tissue, thus increasing viral load. Adipose tissue contains many cytokines and pro- inflammatory hormones, so in obese patients, the baseline levels of CRP and IL-6 are already high before contracting COVID-19 (Gammone and D'Orazio, 2021). In addition, the condition of obesity also causes respiratory disorders (decreased FEV1, FVC, and diaphragm contractility) and metabolic syndrome (Gammone and D'Orazio, 2021). All these factors lead to worsening prognosis of obese patients with COVID-19.

In this analysis, it was found that comorbidity had a positive relationship and greater contribution to disease severity (β: 0.298). This result indicated that patients with more comorbidities tend to develop severe disease severity. This result is aligned with a previous report by Guan et al. (2020) who conducted a study on 1590 hospitalized patients in China. The report confirmed that patients with severe symptoms are more often accompanied by two or multiple comorbidities than patients with non-severe symptoms (40% *vs.* 29.4%). In addition, a study conducted in tertiary hospitals in Malang, Indonesia, further stated that 76.2% (16/21) of patients with severe symptoms had multiple comorbidities (Christanto et al., 2022).

The present study showed that gender does not influence disease severity (p: 0.956). This finding is in contradiction to the study conducted by Barek et al. (2020), which showed that gender difference is associated with the risk of developing severe disease (OR: 2.41; p<0.00001).

The present study also analyzed the relationship between disease severity to dosage and dosage to various patient outcomes. Path analysis indicates a positive relationship between disease severity and dosage, and between dosage and ventilator usage and mortality. It suggests that worsening disease severity may increase dosage administration, which leads to higher mortality and ventilator use. This finding can be explained through the hospital protocol for treating COVID-19 patients. Therapeutic dosage is directly administered to patients with severe conditions, while those who display milder conditions are given prophylactic and intermediate dosage. The results are supported by a study conducted by Elmelhat et al. (2020) on severe COVID-19. In the study, it is reported that the rate of patients in the therapeutic group who need mechanical ventilation reached 38.5% compared to 10% in the prophylactic group, and the difference is statistically significant. However, regarding mortality rate is where the findings differ. Elmelhat et al. (2020) stated that there was no significant difference in mortality rate between both groups. A similar result was also presented in Perepu et al. (2021), which showed no significant difference in mortality rate between prophylactic and intermediate enoxaparin (p: 0.31).

Thrombocytopenia is a hematologic disorder linked to COVID-19-associated-hyper coagulopathy and also a side effect of enoxaparin. Previous study suggested thrombocytopenia in COVID-19 was caused by decreased platelet production due to the cytokine storm and other mechanisms, such as lung injury and the formation of autoantibodies, which lead to increased platelet consumption and degradation (Xu et al., 2020).

This study shows a significant negative correlation between enoxaparin dosage and platelet improvement (β: -0.152; p: 0.027). The result suggests that every dosage regimen can increase platelet, and higher dosage did not worsen thrombocytopenia in COVID-19. There was a downward trend in platelet improvement as the dosage escalated toward the therapeutic level since patients who received therapeutic enoxaparin had already severe conditions, and higher enoxaparin dosage could not optimally improve platelet compared to the prophylactic and intermediate groups. The mechanism leading to thrombocytopenia was more pronounced in severe cases compared to those with mild and moderate one (Chen et al., 2020).

Based on the findings, dosage did not significantly affect D-dimer. Reduction in D-dimer value is not correlated with enoxaparin dosage escalation. Any regimens give the same value on D- dimer change, so no significant difference was noticeable in path analysis. Therapeutic enoxaparin could not compete with disease progression in patients with severe conditions, but still reduced D-dimer as the primary parameter of coagulopathy. Therefore, it can be concluded that enoxaparin has its limitation in reducing D-dimer.

This experiment showed that dosage escalation did not significantly reduce LOS. Patients in prophylactic, intermediate, and therapeutic groups exhibited a similar average length of stay. This study aligns with a study conducted in Dubai hospital, which enrolled 59 patients with severe COVID-19, in which therapeutic enoxaparin administration did not yield reduced hospital stays. On the contrary, patients in the therapeutic group had more extended hospital stays compared to the prophylactic group (mean hospital stay: 24.4 ± 13.5 *vs.* 15.6 ± 6.2 days, p:0.007) (Elmelhat et al., 2020).

Path analysis revealed that increased enoxaparin dosage did not significantly influence CRP value (β: -0.152; p: 0.776). This result indicated that any enoxaparin regimen was able to reduce CRP value, and its reduction is not associated with the amount of dosage administered.

Nonetheless, there are some limitations in the present study. Firstly, the model used in this study has weak explanatory power, as all variables have an R^2 value below 0.25 (Hair et al., 2021). Patient demographics (age, BMI, gender, and comorbidities) were only able to explain 16.6% variances in disease severity, while the remaining 83.4% were affected by unknown variables that were not included in this model. Other factors asides from demographic criteria, such as neutrophil, AST, LDH, and IL-6, may have a role in predicting disease severity (Gopaul et al., 2022; Qi et al., 2021; Zhang et al., 2020). Disease severity only explain for 12.8% variances in dosage. Other factors such as clearance creatinine, weight, and patient history of bleeding may also influence the enoxaparin dosage (Al- Samkari et al., 2020; Jiménez-Soto et al., 2021). Secondly, the study was conducted retrospectively and had a single-center design. Despite these limitations, as far as the author knows, this is the first study to use path analysis to identify factors contributing to enoxaparin effectiveness on coagulation, inflammation, and clinical outcomes.

CONCLUSION

Based on the results of the study, it can be concluded that the main factor influencing enoxaparin effectiveness on coagulation, inflammation and clinical outcomes is dosage, which is affected by disease severity – and age, BMI, and comorbidities affect the severity of the illness. Patients who are older, tend to

have a higher BMI, and more comorbidities, which will commonly result in a more serious medical condition. Thus, the more severe the case is, the higher the enoxaparin dosage needed, which will ultimately affect the patient outcome.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

The authors would like to thank Santo Borromeus Hospital for permission to conduct this research. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

Al-Samkari H, Leaf RS, Dzik WH, Carlson JCT, Fogerty AE, Waheed A, Goodarzi K, Bendapudi PK, Bornikova L, Gupta S, Leaf DE, Kuter DJ, Rosovsky RP (2020) COVID-19 and coagulation: Bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood 136(4): 489–500. https://doi.org/10.1182/blood.2020006520

Atallah B, Malla SI, AlMahmeed W (2020) Anticoagulation in COVID-19. Eur Heart J Cardiovasc Pharmacother 6: 260–261. https://doi.org/10.1093/ehjcvp/pvaa036

Bajaj V, Nirupa G, Sphilman AP, Wu SC, Choi CH, Moulton VR (2021) Aging, immunity, and COVID-19: How age influences the host immune response to Coronavirus infections? Front Physiol 11: 571416. https://doi.org/10.3389/fphys.2020.571416

Barek MA, Aziz MA, Islam MS (2020) Impact of age, sex, comorbidities and clinical symptoms on the severity of COVID-19 cases: A meta-analysis with 55 studies and 10014 cases. Heliyon 6(12): E05684. https://doi.org/10.1016/j.heliyon.2020.e05684

Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS (2020) Thrombosis in hospitalized patients with COVID-19 in a New York City health system. JAMA 324(8): 799–801. https://doi.org/10.1001/jama.2020.13372

Cai Z, Yang Y, Zhang J (2021) Obesity is associated with severe disease and mortality in patients with coronavirus disease 2019 (COVID-19): a meta-analysis. BMC Public Health 21(1): 1505. https://doi.org/10.1186/s12889-021-11546-6

Chen LD, Zhang ZY, Wei XJ, Cai YQ, Yao WZ, Wang MH, Huang QF, Zhang XB (2020) Association between cytokine profiles and lung injury in COVID-19 pneumonia. Respir Res 21(1): 201. https://doi.org/10.1186/s12931-020-01465-2

Christanto A, Listyoko AS, Putra NPP (2022) Analysis of comorbidity and its association with disease severity and mortality rate in hospitalized COVID-19 patients. J Respir Indo 42(1):18–25. https://doi.org/10.36497/jri.v42i1.27

Elmelhat A, Elbourai E, Dewedar H, Elgergawi T, Alkhanbouli M, Ahmed S, Malik Z, Nugud A, Mohammed S, Mohammad H, Husain A (2020) Comparison between prophylactic versus therapeutic doses of low-molecular-weight heparin in severely Ill Coronavirus disease 2019 patients in relation to disease progression and outcome. Dubai Med J 3(4): 162–169. https://doi.org/10.1159/000511163

Elrobaa IH, New KJ (2021) COVID-19: Pulmonary and extra pulmonary manifestations. Front Public Health 9: 711616. https://doi.org/10.3389/fpubh.2021.711616

Gammone MA, D'Orazio N (2021) COVID-19 and obesity: Overlapping of two pandemics. Obes Facts 14(6): 579–585. https://doi.org/10.1159/000518386

Gao M, Piernas C, Astbury NM, Hippisley-Cox J, O'Rahilly S, Aveyard P, Jebb SA (2021) Associations between body-mass index and COVID-19 severity in 6.9 million people in England: A prospective, community-based, cohort study. Lancet Diabetes Endocrinol 9(6): P350–359. https://doi.org/10.1016/s2213-8587(21)00089-9

Giannis D, Ziogas IA, Gianni P (2020) Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. J Clin Virol 127: 104362. https://doi.org/10.1016/j.jcv.2020.104362

Gopaul CD, Ventour D, Thomas D (2022) Laboratory predictors for COVID-19 Intensive Care Unit admissions in Trinidad and Tobago. Dialogues Heal Dec 1: 100022. https://doi.org/10.1016/j.dialog.2022.100022

Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, Liu XQ, Chen RC, Tang CL, Wang T, Ou CQ, Li L, Chen PY, Sang L, Wang W, Li JF, Li CC, Ou LM, Cheng B, Xiong S, Ni ZY, Xiang J, Hu Y, Liu L, Shan H, Lei CL, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Cheng LL, Ye F, Li SY, Zheng JP, Zhang NF, Zhong NS, He JX (2020) Comorbidity and its impact on 1590 patients with COVID-19 in China: A nationwide analysis. Eur Respir J 55: 2000547. https://doi.org/10.1183/13993003.00547-2020

Hair JF, Hult GTM, Ringle CM, Sarstedt M, Danks NP, Ray S (2021) An Introduction to Structural Equation Modeling. In: Partial Least Squares Structural Equation Modeling (PLS- SEM) Using R. Classroom Companion: Business. USA: Springer. https://doi.org/10.1007/978-3-030-80519-7_1

Jiménez-Soto R, Aguilar-Soto M, Rodríguez-Toledo CA, Camiro-Zúñiga A, Demichelis R; ARMII Study Group (2021) The impact of different prophylactic anticoagulation doses on the outcomes of patients with COVID-19. Thromb Res 202: 14–16. https://doi.org/10.1016/j.thromres.2021.02.031

Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY, Xing X, Xiang N, Wu Y, Li C, Chen Q, Li D, Liu T, Zhao J, Liu M, Tu W, Chen C, Jin L, Yang R, Wang Q, Zhou S, Wang R, Liu H, Luo Y, Liu Y, Shao G, Li H, Tao Z, Yang Y, Deng Z, Liu B, Ma Z, Zhang Y, Shi G, Lam TTY, Wu JT, Gao GF, Cowling BJ, Yang B, Leung GM, Feng Z (2020) Early transmission dynamics in Wuhan, China, of novel Coronavirus–infected pneumonia. N Engl J Med 382(13): 1199–1207. https://doi.org/10.1056/nejmoa2001316

Oliynyk O, Barg W, Slifirczyk A, Oliynyk Y, Dubrov S, Gurianov V, Rorat M (2021) Comparison of the effect of unfractionated heparin and enoxaparin sodium at different doses on the course of Covid-19-associated coagulopathy. Life 11(10): 1032. https://doi.org/10.3390/life11101032

Pangarsa EA, Setiawan B, Santosa D, Naibaho RM, Rizky DS, Suyono, Tobing ML, Suharti C (2020) Position paper from the Indonesian society of thrombosis and hemostasis (Inasth), Semarang chapter: Management of coagulopathy in COVID-19. Bali Med J 9(2): 482–488. https://doi.org/10.15562/bmj.v9i2.1841

Perepu US, Chambers I, Wahab A, Ten EP, Wu C, Dayal S, Sutamtewagul G, Bailey SR, Rosenstein LJ, Lentz SR (2021) Standard prophylactic versus intermediate dose enoxaparin in adults with severe COVID-19: A multi-center, open-label, randomized controlled trial. J Thromb Haemost 19(9): 2225–2234. https://doi.org/10.1111/jth.15450

Qi J, He D, Yang D, Wang M, Ma W, Cui H, Ye F, Wang F, Xu J, Li Z, Liu C, Wu J, Qi K, Wu R, Huang J, Liu S, Zhu Y (2021) Severity-associated markers and assessment model for predicting the severity of COVID-19: A retrospective study in

Hangzhou, China. BMC Infect Dis 21(1): 774. https://doi.org/10.1186/s12879-021-06509-6

Sharma J, Rajput R, Bhatia M, Arora P, Sood V (2021) Clinical predictors of COVID-19 severity and mortality: A perspective. Front Cell Infect Microbiol 11: 674277. https://doi.org/10.3389/fcimb.2021.674277

Starke KR, Reissig D, Petereit-Haack G, Schmauder S, Nienhaus A, Seidler A (2021) The isolated effect of age on the risk of COVID-19 severe outcomes: A systematic review with meta-analysis. BMJ Glob Health 6: e006434. https://doi.org/10.1136/bmjgh-2021-006434

Suprapti B, Debora L, Kusumawati D, Puspitasari AD, Natasya G, Arini MN, Aryanti LD (2022) Analysis of enoxaparin effectiveness based on COVID-19 severity: A study in a secondary hospital in Bandung, Indonesia. Indones J Pharm 33(3): 381–393. https://doi.org/10.22146/ijp.4133

Tamara A, Tahapary DL (2020) Obesity as a predictor for a poor prognosis of COVID-19: A systematic review. Diabetes Metab Syndr 14(4): 655–659 https://doi.org/10.1016/j.dsx.2020.05.020

Wu Z, McGoogan JM (2020) Characteristics of and important lessons from the Coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA 323(13): 1239–1242 https://doi.org/10.1001/jama.2020.2648

Xu P, Zhou Q, Xu J (2020) Mechanism of thrombocytopenia in COVID-19 patients. Ann Hematol 99(6): 1205–1208. https://doi.org/10.1007/s00277-020-04019-0

Zalivansky Y, Pereira L, Budovich A (2021) Enoxaparin use in hospitalized SARS-CoV-2- positive patients with elevated D-dimer: A pilot study. J Pharm Pract 36(3): 532–536. https://doi.org/10.1177/08971900211064184

Zhang J, Hao Y, Ou W, Ming F, Liang G, Qian Y, Cai Q, Dong S, Hu S, Wang W, Wei S (2020) Serum interleukin-6 is an indicator for severity in 901 patients with SARS-CoV-2 infection: a cohort study. J Transl Med 18: 406. https://doi.org/10.1186/s12967-020-02571-x

AUTHOR CONTRIBUTION:

Contribution	Suprapti B	Debora L	Safitri RA	Kusumawati D	Puspitasari AD
Concepts or ideas	x	x		x	x
Design	x	x		x	x
Definition of intellectual content	x	x			
Literature search		x	x		
Clinical trial		x		x	
Experimental studies		x		x	
Data acquisition		x		x	
Data analysis	x		x		x
Statistical analysis			x		
Manuscript preparation	x		x		
Manuscript editing	x	x	x	x	x
Manuscript review	x	x	x	x	x

Citation Format: Suprapti B, Debora L, Safitri RA, Kusumawati D, Puspitasari AD (2023) Analysis of factors affecting enoxaparin effectiveness on coagulation, inflammation, and clinical outcomes in patients with COVID-19. J Pharm Pharmacogn Res 11(6): 1106–113. https://doi.org/10.56499/jppres23.1683_11.6.1106