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HEPARIN VS ENOXAPARIN: EFFECTS ON D-DIMER AND HOSPITAL STAY IN COVID-19 PATIENTS

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Abstract: Comparative Analysis of Heparin and Enoxaparin in Modulating D-Dimer Levels and Hospitalization Duration in Hospitalized COVID-19 Patients. *Elevated d-dimer levels due to venous thromboembolism and hypercoagulability in covid-19 patients play a role in disease severity and poor clinical outcomes. This study aims to compare the effectiveness of heparin and enoxaparin, two recommended anticoagulants, in reducing d-dimer levels and hospital stay duration in hospitalized covid-19 patients. This retrospective cohort study involved 106 hospitalized covid-19 patients with abnormal d-dimer levels treated between March 2020 and March 2023. The assessment included changes in d-dimer levels and hospitalization duration. Statistical analyses were performed using stata software. Patients receiving enoxaparin were 5.913 times more likely to experience a reduction in d-dimer levels compared to those receiving heparin (p=0.021). While smoking status (or=0.034; p=0.001) and the number of comorbidities (or=11.247; p=0.018) were notable factors influencing d-dimer reduction, enoxaparin administration was linked to significantly longer hospitalization (p=0.024). The severity of covid-19 also had a substantial impact on hospital stays, with severe (β = 5.757; p= 0.004) and critical (β = 9.147; p <0.001) cases requiring extended care. Thus, enoxaparin demonstrates greater efficacy in reducing d-dimer levels in hospitalized covid-19 patients, though at the cost of prolonged hospital stays.*
Keywords : *Anticoagulant, COVID-19, D-Dimer, Enoxaparin, Heparin*

Abstrak: Analisis Perbandingan Efektivitas Heparin dan Enoxaparin Terhadap Modulasi Kadar D-Dimer dan Lama Rawat Inap Pada Pasien COVID-19 Rawat Inap. Peningkatan kadar D-dimer akibat tromboemboli vena dan hiperkoagulabilitas pada pasien COVID-19 berperan dalam meningkatkan keparahan penyakit serta luaran klinis yang buruk. Penelitian ini bertujuan untuk membandingkan efektivitas heparin dan enoxaparin, dua antikoagulan yang direkomendasikan, dalam menurunkan kadar D-dimer dan lama rawat inap pada pasien COVID-19. Studi kohort retrospektif ini melibatkan 106 pasien COVID-19 yang dirawat di rumah sakit dengan kadar D-dimer abnormal yang dirawat antara Maret 2020 dan Maret 2023. Penilaian yang dilakukan meliputi perubahan kadar D-dimer dan durasi rawat inap, yang dianalisis secara statistik menggunakan *software* STATA. Berdasarkan data yang diperoleh, pasien yang menerima enoxaparin memiliki kemungkinan 5,913 kali lebih besar mengalami penurunan kadar D-dimer dibandingkan pasien yang menerima heparin (p=0,021). Di samping itu, status merokok (OR=0,034; p=0,001) dan jumlah komorbiditas (OR=11,247; p=0,018) merupakan faktor penting yang memengaruhi penurunan kadar D-dimer. Namun demikian, penggunaan enoxaparin berhubungan dengan lama rawat inap yang lebih Panjang secara signifikan (p=0,024). Tingkat keparahan COVID-19 turut memberikan

pengaruh bermakna terhadap durasi rawat inap, di mana kasus berat (β = 5,757; p= 0,004) dan kritis (β = 9,147; p <0,001) membutuhkan waktu perawatan lebih lama. Kesimpulannya adalah enoxaparin menunjukkan efikasi yang lebih tinggi dalam menurunkan kadar D-dimer pada pasien COVID-19 yang dirawat inap, meskipun disertai dengan durasi rawat inap yang lebih panjang.
Kata Kunci : Antikoagulan, COVID-19, D-dimer, Enoxaparin, Heparin

INTRODUCTION

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had profound global health implications, leading to millions of infections and fatalities (Cascella et al., 2025). One significant complication associated with COVID-19 is the heightened risk of thromboembolic events, which contribute to morbidity and mortality (Raharjo et al., 2025; Malas et al., 2020). Thrombotic complications, including deep vein thrombosis (DVT) and pulmonary embolism (PE), have been frequently documented among hospitalized patients, particularly those with severe disease manifestations (Erben et al., 2021). Elevated D-dimer levels have emerged as a critical biomarker in COVID-19, reflecting increased fibrinolytic activity and coagulation system activation, thus correlating with the thrombotic events (Nopp et al., 2020; Zhan et al., 2021). Studies have consistently demonstrated a correlation between high D-dimer levels and adverse clinical outcomes, including prolonged hospitalization, higher ICU admission rates, and increased mortality. Given the prognostic implications of elevated D-dimer levels, timely and effective management of coagulopathy is essential in COVID-19 treatment (Zhang et al., 2022).

Current guidelines, including those from the American College of Chest Physicians (CHEST) recommend anticoagulation therapy as a standard intervention for hospitalized COVID-19 patients, emphasizing either low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) as preferred options (Zang et al., 2022). Among these, enoxaparin, a form of LMWH is frequently favored due to its predictable pharmacokinetics, ease of administration, and enhanced safety profile compared to UFH (Samuel et al., 2023; Padayachee et al., 2023).

While previous studies have been conducted, comparative studies specifically evaluating the effectiveness of heparin and enoxaparin in reducing D-dimer levels in COVID-19 patients remain limited, especially in Indonesian population (Pawlowski et al., 2021; Oliynyk et al., 2021). Additionally, variations in outcome measures have led to inconsistencies in findings. Therefore, this study aimed to compare the effectiveness of heparin and enoxaparin in reducing D-dimer levels and to evaluate their association with hospitalization duration among Indonesian hospitalized COVID-19 patients.

METHODS

Study Setting and Data Source

This study was a retrospective cohort study, with patients' medical records serving as the primary data source. The study population included hospitalized COVID-19 patients aged ≥ 26 years with abnormal D-dimer levels (> 500 ng/mL) who received either heparin or enoxaparin therapy. The study protocol had been approved by the Research Ethics Committee of Atma Jaya Catholic University of Indonesia, No. 05/04/KEP-FKIKUAJ/2023. The reporting of this study follows the STROBE checklist.

The inclusion criteria in this study encompass adult patients hospitalized at Atma Jaya Hospital between March 2020 and March 2023 who were confirmed with COVID-19. Eligible patients must have abnormal D-dimer levels (> 500 ng/mL) and have received either heparin or enoxaparin therapy. Additionally, patients must have undergone a

minimum of two D-dimer assessments during hospitalization. Meanwhile, the exclusion criteria comprise incomplete medical records, along with patients with underlying conditions such as cancer and pregnancy.

The samples were obtained based on predefined inclusion and exclusion criteria from the medical records of hospitalized COVID-19 patients with abnormal D-dimer levels at Atma Jaya Hospital from 2020 to 2023. The minimum sample size was determined using R Studio. The minimum sample size for the D-dimer outcome was 42 individuals, with a 5% significance level, 80% power, a 71% probability of D-dimer reduction (absolute differences) in the heparin group, and a 91% probability of D-dimer reduction in the enoxaparin group. For hospitalization duration, the minimal sample consisted of 84 patients, with a numerator degree of freedom of 4, a denominator degree of freedom of 79.45, an effect size of 0.15, a significance level of 5%, and a power of 80%. The minimum sample size of 84 was augmented by 10% to anticipate missing data, resulting in a final minimum sample size of 93.

This study includes two types of variables: independent and dependent variables. The independent variables for the outcome measure of D-dimer reduction include the type of anticoagulant administered (heparin or enoxaparin), age, sex, COVID-19 severity based on National Institute of Health (NIH), smoking status, and comorbidities. The D-dimer was measured using a turbidimetry immunoassay. For the outcome measure of hospitalization duration, the independent variables include the type of anticoagulant used (heparin or enoxaparin), age, D-dimer levels, COVID-19 severity, and comorbidities. The dependent variables in this study are D-dimer reduction and hospitalization duration, as they are influenced by independent variables.

Data Analysis

Univariate analysis was conducted to obtain a summary of data related to factors affecting the measured outcomes, including the type of anticoagulant administered, age, D-dimer levels, COVID-19 severity, sex, smoking status, and comorbidities. Furthermore, multivariate analysis was conducted to examine the correlation between independent and dependent variables. Logistic regression analysis was performed using STATA 15.1 software to evaluate D-dimer reduction, while multiple linear regression was applied to analyze hospitalization duration. The binary outcome of interest was D-dimer reduction, with independent variables including anticoagulant therapy, age, sex, smoking status, COVID-19 severity, and comorbidities. To enhance model accuracy, the backward elimination method was applied, systematically removing non-significant variables to identify the most optimal predictive model.

RESULTS

Sociodemographic Characteristics

A total of 106 hospitalized COVID-19 patients who received heparin or enoxaparin were selected from an initial cohort of 331 patients. The majority of those receiving heparin were female (52.78%), aged over 65 years (36.11%), non-smokers (87.50%), had no comorbidities (30.56%), and exhibited moderate COVID-19 severity (45.83%). Conversely, most patients receiving enoxaparin were male (55.88%), aged 46–55 years (26.47%) and 56–65 years (26.47%), non-smokers (88.24%), had multiple comorbidities (35.29%), and also exhibited moderate COVID-19 severity (35.29%) (Table 1).

Table 1. Sociodemographic characteristics

	Heparin n (%)	Enoxaparin n (%)
Sex		
Male	34 (47.22%)	19 (55.88%)
Female	38 (52.78%)	15 (44.12%)
Age (years)		
26-35	9 (12.50%)	4 (11.76%)
36-45	10 (13.89%)	5 (14.71%)
46-55	11 (15.28%)	9 (26.47%)
56-65	16 (22.22%)	9 (26.47%)
>65	26 (36.11%)	7 (20.59%)
Smoking Status		
Smoker	9 (12.50%)	4 (11.75%)
Non-smoker	63 (87.50%)	30 (88.24%)
Comorbidity		
No Comorbidity	22 (30.56%)	11 (32.35%)
Cardiovascular	6 (8.33%)	2 (5.88%)
Hypertension	12 (16.67%)	5 (14.71%)
Diabetes Mellitus	9 (12.50%)	2 (5.88%)
Obesity	3 (4.17%)	2 (5.88%)
>1 Comorbidity	20 (27.78%)	12 (35.28%)
COVID-19 severity		
Mild	24 (33.33%)	9 (26.47%)
Moderate	33 (45.83%)	12 (35.29%)
Severe	10 (13.89%)	8 (23.53%)
Critical	5 (6.94%)	5 (14.71%)

Effect of Anticoagulant Therapy on D-Dimer Reduction

Patients receiving heparin therapy (70.83%) exhibited a lower percentage of D-dimer reduction compared to those receiving enoxaparin therapy (91.18%) (Table 2).

Table 2. Effect of anticoagulant therapy on D-dimer reduction

Anticoagulant Therapy	Reduction in D-dimer		No reduction in D-dimer	
	n	%	n	%
Heparin	51	70.83	21	29.17
Enoxaparin	31	91.18	3	8.82

Effectiveness of Anticoagulant Therapy on Hospitalization Duration

Patients who received enoxaparin therapy spent five days longer in the hospital compared to those receiving heparin therapy (Table 3).

Table 3. Effectiveness of anticoagulant therapy on hospitalization duration

Anticoagulant Therapy	Average Hospitalization Duration
Heparin	12.67 days
Enoxaparin	17.24 days

Multivariate Data Analysis

The analysis of D-dimer reduction outcomes was conducted using logistic regression methodology, which yielded the odds ratio (OR), 95% confidence interval (CI), and p-value. The results revealed significant independent variables, including anticoagulant therapy, smoking status, and the presence of more than one comorbidity. Enoxaparin therapy was associated with an OR of 5.913 (95% CI: 1.310 – 26.694) and a p-value of 0.021. On the other hand, smoking was associated with an OR of 0.034 (95% CI: 0.005 – 0.228) and a p-value of 0.001. Patients with more than one comorbidity had an OR of 11.247 (95% CI: 1.510 – 83.748) and a p-value of 0.018. Other independent variables, including sex, age, and COVID-19 severity, were not found to be statistically significant in relation to D-dimer reduction, as their p-values exceeded 0.05 (Table 4).

Table 4. Analysis of factors influencing D-dimer level reduction

Factors	OR	95% CI	p-value
Anticoagulant Therapy			
Enoxaparin	5.913	1.310-26.694	0.021
Smoking Status			
Smoker	0.034	0.005-0.228	0.001
Comorbidity			
Cardiovascular	1.773	0.262-12.005	0.557
Hypertension	0.897	0.215-3.749	0.881
Diabetes Mellitus	3.192	0.422-24.136	0.261
Obesity	2.721	0.201-36.848	0.452
>1 Comorbidity	11.247	1.510-83.748	0.018

The analysis of hospitalization duration identified statistically significant independent variables, comprising anticoagulant therapy and COVID-19 severity at severe and critical levels, as key determinants of hospital length of stay. Enoxaparin therapy was associated with a coefficient of 3.181 (95% CI: 0.435 – 5.926) and a p-value of 0.024. Patients with severe COVID-19 had a coefficient of 5.757 (95% CI: 1.929 – 9.585) and a p-value of 0.004, while patients with critical COVID-19 had a coefficient of 9.147 (95% CI: 4.426 – 13.868) and a p-value of < 0.001. Other independent variables, including D-dimer reduction, age, and comorbidities, were not statistically significant in relation to hospital length of stay, as their p-values exceeded 0.05. This study utilized the backward elimination method; therefore, variables that were not statistically significant are not included (Table 5).

Table 5. Analysis of factors influencing hospitalization duration

Factors	β	95% CI	p-value
Anticoagulant Therapy			
Enoxaparin	3.181	0.435-5.926	0.024
COVID-19 Severity			
Moderate	0.545	-2.427-3.516	0.717
Severe	5.757	1.929-9.585	0.004
Critical	9.147	4.426-13.868	0.000

DISCUSSION

Our study, which analyzed 106 hospitalized COVID-19 patients with elevated D-dimer levels, demonstrated that enoxaparin was significantly more effective than heparin in reducing D-dimer levels (Table 2). Patients receiving enoxaparin had an odds ratio of 5.913 for experiencing a reduction in D-dimer levels compared to those treated with heparin (p = 0.021). These findings underscore enoxaparin's potential role in mitigating thrombotic risks associated with COVID-19, which is critical given the established relationship between elevated D-dimer levels and increased mortality rates in these patients (Chaiut et al., 2023).

The observed effectiveness of enoxaparin aligns with existing literature, including a cohort study (Al Sulaiman et al., 2022), which reported a higher rate of thrombosis in patients receiving heparin compared to those treated with enoxaparin (18.3% vs. 4.6%, p = 0.02). This suggests that enoxaparin may provide a better therapeutic approach in minimizing VTE events in hospitalized COVID-19 patients. The differences in efficacy can likely be attributed to the pharmacologic profiles of the two anticoagulants; enoxaparin has a preferential action against factor Xa, leading to a more targeted anticoagulant effect (Padayachee et al., 2023; Imbalzano et al., 2024).

However, our study also found that patients treated with enoxaparin experienced an average hospital stay 3.181 days longer than those receiving heparin (p = 0.024), as presented in Table 3. This finding contrasts with Pawlowski et al. (2021), who observed a longer hospitalization stay in heparin-treated patients; however, the difference was not statistically significant (p = 0.17). The discrepancy in findings may stem from variations in COVID-19 management guidelines, particularly isolation protocols, potentially introducing bias as patients with resolved symptoms may still require hospitalization (Indonesia Ministry of Health, 2019; Rees et al., 2020).

Notably, smoking status was a significant predictor of D-dimer reduction, with smokers exhibiting a reduced likelihood of achieving lower D-dimer levels (OR 0.034; p = 0.001) (Table 4). Smokers had an average probability of 0.034 times (95% CI: 0.005 - 0.228) lower for experiencing a reduction in D-dimer levels compared to non-smokers, indicating a lower likelihood of D-dimer reduction in smokers than in non-smokers. Similarly, a study by involving 1592 men and women aged 55-74 years investigating the association between D-dimer distribution and cardiovascular risk found that patients with a history of smoking exhibited higher D-dimer levels compared to non-smokers (Lee et al., 1995). This phenomenon is likely attributed to the effects of smoking, which elevates nicotine levels, subsequently increasing fibrinogen concentrations and promoting blood clot formation, thereby leading to higher D-dimer levels (Al-Dahy and Abed, 2022). The implications of these findings suggest that targeted interventions in smoking cessation might be beneficial, not only for overall health but also for improving outcomes in COVID-19 patients.

The presence of multiple comorbidities also significantly influenced D-dimer reduction (OR 11.247; p = 0.018). This finding is consistent with existing research that highlights the interaction between comorbidities and COVID-19 severity. Patients with multiple comorbidities may experience a more severe inflammatory response or altered coagulation states, leading to persistently elevated D-dimer levels (Djaharuddin et al., 2021; Sumarpo et al., 2025). This emphasizes the importance of managing comorbid conditions to potentially improve patient outcomes.

Additionally, our analysis highlighted the significant impact of COVID-19 severity on hospitalization duration. As shown in Table 5, patients with severe and critical cases had longer hospital stays (coefficients of 5.757 and

9.147, respectively, $p < 0.001$), a finding supported by Thai et al. (2020). This aligns with findings from Khajuria et al. (2021), who identified disease severity as a critical predictor of length of stay, reflecting the need for intensive care and monitoring in these patients.

Despite these findings, several limitations must be addressed. The retrospective nature of the study inherently carries potential biases related to data collection and documentation inconsistencies. Moreover, the lack of standardized post-treatment D-dimer assessments may have introduced variability in the measured outcomes. The subsequent issue is that D-dimer measurements are qualitative, specifically presenting a binary outcome. Future prospective studies with larger sample sizes, quantitative measurements, and standardized treatment protocols are warranted to validate these findings and explore the nuances of anticoagulation therapy in diverse hospitalized COVID-19 populations.

CONCLUSION

Our study suggests that while enoxaparin is associated with a significant reduction in D-dimer levels among hospitalized COVID-19 patients, its use is also linked to longer hospital stays compared to heparin. Understanding the complex relationships between anticoagulation therapy, smoking habits, comorbidities, and disease severity is essential for optimizing treatment strategies and improving clinical outcomes in this vulnerable population.

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