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Analysis Of The Effectiveness Of LMWH Compared To UFH In COVID-19 Patients With Coagulation Disorders At Pasar Minggu Regional General Hospital

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ABSTRACT
Background: COVID-19 disease causes multiorgan damage and impacts the cardiovascular system. The Increase in death cases occurs due to coagulation disorders characterized by increased d-dimer parameters, bleeding, thrombocytopenia, and thrombosis. Objective: To analyze the effectiveness of the use of LMWH anticoagulants compared to UFH in COVID-19 patients with coagulation disorders in hospital. Methods: Observational retrospective data collected1with cross sectional design. Methods of collecting data on COVID-19 inpatients in the January-December 2021 period based on moderate, severe, and critical severity of the disease. The data used is medical record data and analysis using chi square. Results: The sample consisted of 6362patients who met the inclusion criteria with the largest difference in decrease D-dimer values in critical severity for LMWH (4.8 ug/ml) and UFH (4.0 ug/ml). Wilcoxon test analysis *showed that there was a significant difference between the use of LMWH and UFH based on the decrease in D-dimer values.

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INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus is the cause of an acute respiratory disease known as COVID-19. This disease begins as a viral infection that can damage multiple organs and lead to a cytokine storm phenomenon, which impacts the massive infection of blood vessels connecting major organs in the body (Rusdiana and Akbar, 2020).

On March 2, 2020, the first two cases of COVID-19 were announced in Indonesia. As of December 31, 2020, there were 743,196 confirmed cases with 22,138 deaths and 611,097 recoveries. Previous studies on the use of LMWH in adult inpatients with COVID-19 showed that the use of high-dose LMWH upon admission significantly reduced mortality in COVID-19 patients, and while non-heparin and low-dose LMWH treatments also resulted in higher major bleeding rates (Gonzalez-Porras et al., 2020).

Coagulation disorders are blood clotting (thrombus) disorders that occur in the vascular system throughout the body. Because it can dissolve thrombus by converting plasminogen

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into plasmin, an enzyme that breaks down fibrin, the administration of thrombolytics has a significant impact on the treatment of COVID-19 patients with coagulation issues. Fibrin is the main component of blood clots. It is especially used in patients with laboratory results showing elevated D-dimer, fibrinogen, and decreased platelets (Gonzalez-Porras et al., 2020). Therefore, there has been an increase in the use of anticoagulants, both LMWH and UFH, in COVID-19 patients with coagulation disorders.

This background led to the research on the effectiveness of using LMWH compared to UFH in COVID-19 patients with coagulation disorders at Pasar Minggu Regional General Hospital. The researcher hopes that the results of this study can benefit the hospital in determining the Clinical Pathway for coronavirus patients with coagulation issues based on the severity of the disease..

METHODS

The author used an observational method with a cross-sectional study design for this research. The study population consisted of COVID-19 inpatients at Pasar Minggu Regional General Hospital from September to October 2022. Data were retrospectively retrieved, and the sampling technique was purposive sampling. This study had inclusion criteria, which included: COVID-19 patients with confirmed coagulation disorders who were using UFH or LMWH, aged > 18 years, hospitalized for > 3 days, and with disease severity ranging from moderate to critical. The exclusion criteria were incomplete patient medical records, mild symptomatic COVID-19 patients, patients receiving more than one type of anticoagulant, and patients with a D-dimer test conducted only once. A p-value < 0.05 was used in the statistical test to determine the significance of the variables in the study. Data analysis was then performed using SPSS version 25 on the collected data.

RESULT AND DISCUSSION

Characteristics of the Patient

The results of the research revealed data from 836 COVID-19 patients with coagulation disorders at Pasar Minggu Regional General Hospital, consisting of 318 patients using LMWH anticoagulants, 318 patients using UFH anticoagulants, and 200 excluded patients. Among the 318 patients using LMWH, 95 had moderate severity, 103 had severe severity, and 120 had critical severity. Similarly, among the 318 UFH patients, 95 had moderate severity, 103 had severe severity, and 120 had critical severity. The 200 excluded patients consisted of 5 with mild COVID-19 severity, 100 receiving more than one type of anticoagulant, and 95 with only one D-dimer test, resulting in 636 patients as the study sample for statistical testing.

For patient characteristics, the majority (Table 1) of patients using LMWH anticoagulants were male (57.2%). The same trend was observed in the UFH anticoagulant group, where most patients were also male (57.9%).

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Table 1. Characteristics Research Subjects

Characteristics of the Patient		LMWH (N=318)	%	UFH (N=318)	%
Gender	Male	182	57,2%	184	57,9%
	Female	136	42,8%	134	42,1%
Comorbid	1 Comorbid	114	35,8%	98	30,8%
	>1 Comorbid	108	34,0%	95	29,9%
	None	96	30,2%	125	39,3%
Patient Age	*Mean*	54	-	46	-
	Std. Deviation	13,78	-	14,3	-

LMWH = low molecular weight heparin ; UFH = unfractionated heparin

The results of the study (Table 1) show that the majority of patients were male. This finding is in line with research conducted by Nasiri et al. (2020), which stated that the number of male COVID-19 patients is higher than female patients because testosterone has an immunosuppressive effect, while estrogen can enhance immunity. Several studies related to COVID-19 and SARS-CoV-2 infections have shown greater severity and mortality in males due to the coronavirus (Tang, Li, et al., 2020; Sakka et al., 2020; Nasiri et al., 2020). Higher mobility and lower adherence to protocols also contribute to males being the majority among COVID-19 patients (Setiadi, Panjaitan, and Aviatin, 2021).

Based on the number of comorbidities (Table 1), the majority of patients using LMWH anticoagulants had 1 comorbidity (35.8%), while the highest percentage of patients using UFH anticoagulants had no comorbidity (39.3%). The most common comorbidities were hypertension, diabetes mellitus, and cardiovascular disease. Studies indicate that hypertension impacts COVID-19 due to the binding of the SARS-CoV-2 virus to Angiotensin Converting Enzyme 2 (ACE2), which is a receptor for the COVID-19 virus in the lungs. This interaction allows the virus to penetrate into cells and replicate in host cells, leading to organ dysfunction and worsening COVID-19 infections (Choirunnisa Hekla, 2021; Gunawan et al., 2020; Zhang et al., 2020).

Based on the average age (Table 1), patients using LMWH anticoagulants had an average age of 54 years, while those using UFH anticoagulants had an average age of 46 years. Studies have shown that COVID-19 is more risky for the elderly due to their tendency to have chronic health problems, which increase the risk of COVID-19. In older adults, immune function tends to decline, particularly in fighting infections. Additionally, lung tissue loses its elasticity, leading to severe inflammation, making respiratory diseases like COVID-19 a major issue for elderly patients, as it causes organ damage (Elviani, Anwar, and Januar Sitorus, 2021).

Parameters for Decreasing D-dimer Values

The reduction in D-dimer value is the difference between the pre-anticoagulant use D-dimer result and the D-dimer result before stopping the anticoagulant use (post). Based on the Wilcoxon test (Table 2), it shows that in COVID-19 patients with coagulation disorders,

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those using LMWH anticoagulants compared to UFH showed a p-value of 0.000. This value indicates that the use of anticoagulants, both LMWH and UFH, has an effect on reducing pre- and post-D-dimer values in COVID-19 patients with coagulation disorders, regardless of whether the severity is moderate, severe, or critical.

In this study, it can be observed that the more severe the degree of COVID-19 in coagulation disorders, the higher the D-dimer values. Additionally, there were differences in D-dimer values, especially in severe, critical, and overall severity levels (Table 3), where there was a significant difference in D-dimer values, with a larger difference in D-dimer values for patients using LMWH compared to those using UFH. These results align with previous research showing that severe COVID-19 patients, whether they survived or died, exhibited variations in D-dimer values (Rusdiana and Akbar, 2020; Cheng et al., 2020; Wu et al., 2020).

The results of this study indicate that there is a significant difference between pre- and post-anticoagulant D-dimer values, which aligns with research conducted by Feri Setiadi at RSPI Prof. Dr. Sulianti Saroso. This is because anticoagulants can prevent thromboembolism and can be used to maintain organ perfusion. The use of LMWH via the subcutaneous route has been shown to be effective in reducing D-dimer levels in moderate to severe severity cases (Chandra et al., 2022).

The effect of administering LMWH anticoagulants is more favorable due to the longer half-life of the drug and better bioavailability compared to UFH. LMWH anticoagulants work by inhibiting blood clotting through the inhibition of activated factor Xa by antithrombin II, blocking the pathway that causes fibrinogen to convert into fibrin. This process prevents blood clot formation resulting from the conversion of fibrinogen into fibrin (Setiadi, Panjaitan, and Aviatin, 2021).

Table 2. Decreased D-dimer Based on Disease Severity

D-dimer Value	Normal Value (ug/ml)	LMWH Average	LMWH Std. Deviation	*P-value*	UFH Average	UFH Std. Deviation	*P-value*	*P-value wilcoxon*
Moderate Severity								
Pre	<0,5	2,5	3,89	0,000	0,9	1,30	0,000	0,000
Post		0,7	0,67		0,4	0,45		0,000
Difference		1,8	3,47	-	0,5	0,88	-	0,000
Degree of Severity								
Pre	<0,5	5,7	7,65	0,000	2,0	3,35	0,000	0,000
Post		1,4	2,00		0,6	0,34		0,000
Difference		4,3	7,09	-	1,4	3,28	-	0,000
Critical Severity Degree								
Pre	<0,5	6,1	6,09	0,000	5,1	8,21	0,000	0,000
Post		1,3	1,53		1,1	1,71		0,000
Difference		4,8	5,67	-	4,0	7,67	-	0,016

P-value = Significance Value

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Table 3. Decrease in D-dimer levels in patients using LMWH and UFH

D-dimer Value	Nilai Normal (ug/ml)	LMWH Average	LMWH Std. Deviation	*P-value*	UFH Average	UFH Std. Deviasi	*P-value*	*P-value Wilcoxon*
Pre	<0,5	4,9	6,30	0,000	2,8	5,71	0,000	0,000
Post		1,2	1,55		0,7	1,13		0,000
Difference		3,7	19,4		2,1	5,29		0,000

Bleeding

Based on the Chi-Square test, moderate severity showed that patients who did not experience bleeding (Table 4) with LMWH anticoagulant administration were fewer (90.5%) compared to UFH (93.7%) with a significance value of P=0.420. This means that at the moderate severity level, there is no difference in the use of either LMWH or UFH anticoagulants in relation to bleeding events. At the severe severity level, patients who did not experience bleeding with LMWH anticoagulant administration were fewer (71.8%) compared to UFH (76.7%) with a significance value of P=0.425. This value indicates that there is no difference in the use of LMWH and UFH anticoagulants regarding incidence of bleeding. Additionally, there were patients who did not experience bleeding with LMWH anticoagulants (61.7%) fewer compared to UFH (62.5%) with a significance value of P=0.894. This value suggests that at the critical severity level, there is also no difference in the use of LMWH or UFH anticoagulants in relation to incidence of bleeding.

According to previous studies, incidence of bleeding when using LMWH and UFH at the critical severity level are consistent with the findings of this study (Tang, Bai, et al., 2020) (Volteas et al., 2021) (He et al., 2018). Yodi et al. conducted a study and mentioned that factors such as age, comorbidities, medication dosage, prior use of antithrombotic agents, and the presence of trauma or previous surgeries can influence the bleeding risk in patients receiving LMWH, UFH, or other anticoagulants (Putra, Yodi, and Dalimunthe, 2022).

Table 4. The Incidence Of Bleeding Is Based On The Severity Of The Disease

Incidence Of Bleeding	LMWH (N=318)	%	UFH (N=318)	%	*P-value Chi Square*
Moderate Severity					
Occurred	9	9,5%	6	6,3%	0,420
Not Occur	86	90,5%	89	93,7%	
Degree of Severity					
Occurred	29	28,2%	24	23,3%	0,425
Not Occur	74	71,8%	79	76,7%	
Critical Severity Degree					
Occurred	46	38,3%	45	37,5%	0,894
Not Occur	74	61,7%	75	62,5%	

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Thrombocytopenia

Thrombocytopenia is a condition where patients experience a decrease in platelet count to <100 10^3/ul, as recorded in the doctor's diagnosis in the medical records. The research results (Table 5) obtained through the Chi-Square test based on data from patients who did not experience thrombocytopenia at moderate severity with LMWH anticoagulant administration showed 91.6%, which is lower compared to UFH at 98.9%, with a P-value of 0.017. The use of LMWH and UFH anticoagulants in relation to thrombocytopenia events, based on these results, indicates a significant difference. At the severe severity level, patients who did not experience thrombocytopenia with LMWH use accounted for 90.3%, which is lower than UFH at 91.3%, with a significance value of P=0.810. This value reflects that there is no difference in the use of either LMWH or UFH anticoagulants regarding thrombocytopenia events. Meanwhile, at the critical severity level, patients who did not experience thrombocytopenia with LMWH administration accounted for 93.3%, which is higher than UFH at 86.7%, with a significance value of P=0.085. This value indicates that at the critical severity level, there is no difference in the use of LMWH or UFH anticoagulants in relation to incidence of thrombocytopenia.

According to previous studies, the incidence of thrombocytopenia when using LMWH and UFH is comparable in terms of critical severity (Tang, Bai, et al., 2020). Other studies also explain that, overall, lower platelet counts occur in critically ill COVID-19 patients (Khan et al., 2020). In research by Mulyadi, it was mentioned that HIT occurs as a serious consequence of using UFH or LMWH due to the increased use of heparin, both for therapy and diagnosis. Patients at high risk for HIT include those with heparin antibody dependence, a history of HIT, previous heparin therapy, and those undergoing cardiovascular or orthopedic surgery. In critically ill patients, HIT occurred in 2.4% of those using LMWH and 7.4% of those using UFH (Mulyadi, and Soemarsono, 2018).

Table 5. Incidence Of Thrombocytopenia Is Based On The Severity Of The Disease

Incidence Of Thrombocytopenia	LMWH		UFH		*P-value*
	(N=318)	%	(N=318)	%	*Chi Square*
Moderate Severity					
Occurred	8	8,4%	1	1,1%	0,017
Not Occur	87	91,6%	94	98,9%	
Degree of Severity					
Occurred	10	9,7%	9	8,7%	0,810
Not Occur	93	90,3%	94	91,3%	
Critical Severity Degree					
Occurred	8	6,7%	16	13,3%	0,085
Not Occur	112	93,3%	104	86,7%	

Thrombotic

Thrombosis refers to the formation of blood clots (thrombus) in the arterial or venous blood vessels that occurs during hospitalization, based on the doctor's diagnosis and

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https://ejournal.seaninstitute.or.id/index.php/Ekonomi

recorded in the medical records. In this study (Table 6), the Chi-Square test shows that patients who did not experience thrombosis events with LMWH anticoagulant administration at moderate severity were fewer (91.6%) compared to UFH (100%), with no thrombosis events, and a P-value of 0.004. This value indicates that there is a difference in the use of anticoagulants regarding thrombosis events. At the severe severity level, patients who did not experience incidence of thrombosis with LMWH administration were fewer (89.3%) compared to UFH (98.1%), with a P-value of 0.01. This value suggests that there is a difference in the use of LMWH and UFH anticoagulants based on thrombosis events in COVID-19 patients with coagulation disorders. At the critical severity level, patients who did not experience thrombosis events with LMWH administration were fewer (86.7%) compared to UFH (97.5%). In COVID-19 patients with coagulation disorders, the P-value was 0.002. This value indicates that the use of anticoagulants affects incidence of thrombosis. COVID-19 patients with coagulation disorders who experienced thrombosis events with LMWH anticoagulant administration were higher compared to UFH at the critical severity level. These findings contradict previous research, which showed that incidence of thrombosis significantly occurred more often with UFH use compared to LMWH (Tang, Bai, et al., 2020).

The results of the study on the overall incidence of side effects (Table 7) based on the Chi-Square test can be interpreted to show that the data for patients who did not experience bleeding with LMWH anticoagulant administration was 73.6%, which is lower compared to UFH at 76.4%, with a P-value of 0.410. This value suggests that there is no effect of anticoagulant use on incidence of bleeding. Previous research has mentioned that patients using LMWH along with tissue plasminogen activator have a higher risk of bleeding compared to UFH (Thachil et al., 2020). Other studies have also indicated that the increased risk of bleeding is similar between LMWH, Fondaparinux, and UFH (Putra, Yodi, and Dalimunthe, 2022).

Table 7 shows that the data for patients who did not experience thrombocytopenia with LMWH anticoagulant administration was the same as with UFH, at 91.8%, with a P-value of 1.0. This value indicates that there is no effect of thrombocytopenia events in COVID-19 patients with coagulation disorders when using either LMWH or UFH anticoagulants. This study mentions that thrombocytopenia can be caused by the progression of infection and increased disease severity. The smaller molecular size of LMWH compared to UFH determines its affinity for PF4, making it less likely for LMWH to induce thrombocytopenia compared to UFH, which is consistent with previous research. Additionally, the occurrence of HIT antibodies in patients using UFH is greater in terms of anti-H-PF4 antibody formation compared to LMWH, as the larger molecules can form complexes with PF4 (Martel, Lee, and Wells, 2005).

Table 7 also shows that the data for patients who did not experience thrombosis events with LMWH anticoagulant administration was 89%, which is lower than UFH at 98.4%, with a significance value of P=0.000. These results suggest that the use of LMWH and UFH anticoagulants has an effect on thrombosis events in COVID-19 patients with coagulation disorders.

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https://ejournal.seaninstitute.or.id/index.php/Ekonomi

A study in Italy showed that complications from thromboembolic events, including venous thromboembolism (VTE), ischemic stroke, and acute coronary syndrome (ACS) or myocardial infarction, occurred in 8 ICU patients and 20 patients in general care units. Of the 44 patients monitored, pulmonary embolism occurred in 10 of 16 cases, and VTE occurred in 8 of 16 patients (Lodigiani et al., 2020). Both prophylactic and therapeutic anticoagulant therapy can prevent thrombosis and improve clinical outcomes, provided that hemostatic parameters are carefully monitored. Various factors contribute to thrombosis, including hypercoagulability, endothelialopathy, and excessive immune response (Sunggoro, Purwanto, and Hasan, 2020).

Table 6. Incidence Of Thrombosis Based On The Severity Of The Disease

Incidence Of Thrombosis	LMWH		UFH		*P-value*
	(N=318)	%	(N=318)	%	*Chi Square*
Moderate Severity					
Occurred	8	8,4%	-	0%	0,004
Not Occur	87	91,6%	95	100%	
Degree of Severity					
Occurred	11	10,7%	2	1,9%	0,010
Not Occur	92	89,3%	101	98,1%	
Critical Severity Degree					
Occurred	16	13,3%	3	2,5%	0,002
Not Occur	104	86,7%	117	97,5%	

Table 7. Incidence Of Side Effects In COVID-19 Patients Using LMWH Compared To UFH

Side Effect Incidence	LMWH		UFH		*P-value*
	(N=318)	%	(N=318)	%	
Incidence Of Bleeding					
Occurred	84	26,4%	75	23,6%	0,410
Not Occur	234	73,6%	243	76,4%	
Incidence Of Thrombocytopenia					
Occurred	26	8,2%	26	8,2%	1,000
Not Occur	292	91,8%	292	91,8%	
Incidence Of Thrombosis					
Occurred	35	11%	5	1,6%	0,000
Not Occur	283	89%	313	98,4%	

Recovery

Based on the data analysis (Table 8), it shows that patients who recovered with LMWH anticoagulant administration were 76.1%, higher compared to UFH at 71.7%, with a P-value of 0.206. This value indicates that the use of anticoagulants does not affect the recovery of COVID-19 patients with coagulation disorders. These results are similar to previous research,

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https://ejournal.seaninstitute.or.id/index.php/Ekonomi

which explained that there was no difference between the use of LMWH and UFH in terms of mortality at the critical severity level (Tang, Bai, et al., 2020). Additionally, based on statistical results, there was no difference in the effect of anticoagulant use on recovery; however, the study findings suggest that the recovery rate with LMWH use was higher compared to UFH use at severe to critical severity levels. These results align with previous studies, which state that patients receiving LMWH had a lower mortality rate compared to those receiving UFH (Volteas et al., 2021).

Table 8. Recovery Rate Of COVID-19 Patients Using LMWH Compared To UFH

Final Outcome	LMWH		UFH		*P-value*
	(N=318)	%	(N=318)	%	
Death	76	23,9%	90	28,3%	0,206
Recovery	242	76,1%	228	71,7%	

Length of stay (LOS)

The average length of stay (LOS) for COVID-19 patients using LMWH was 14 days, while those using UFH had a LOS of 11 days, as shown in Table 8. After analysis, a P-value of 0.000 was obtained, indicating that there is a difference in the LOS of patients with coagulation disorders when using LMWH or UFH anticoagulants in COVID-19 patients.

The results of the study show that a longer LOS is associated with the severity of the disease. This statement suggests that patients with severe COVID-19 are a factor contributing to the prolonged hospital stay, in line with previous research. Patients with severe conditions tend to have a longer LOS due to the need for more extended care and more intensive medical treatment (Fahmia, Helda, and Nursari, 2022).

Table 9. The Length Of Stay (LOS) Of COVID-19 Patients Using LMWH Compared To UFH.

LOS	LMWH (N)	UFH (N)	*P-value*
Mean (Day)	14	11	0,000
Std Deviation	7,88	5,55	-

LOS = *Length of stay*

CONCLUSION

This study aims to determine the effectiveness of anticoagulants in COVID-19 patients, where the use of LMWH is more effective than UFH based on the reduction of D-dimer levels. Regarding patient recovery, more patients using UFH recover compared to LMWH in moderate severity cases, whereas in severe and critical cases, more patients recover with LMWH than with UFH. For bleeding side effects, more patients using UFH did not experience bleeding compared to LMWH, while the incidence of thrombocytopenia was the same for both UFH and LMWH. Additionally, more patients using UFH did not experience thrombosis events compared to those using LMWH.

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