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The safety of fondaparinux, enoxaparin, and unfractionated heparin in COVID-19 patients

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ABSTRACT

The coagulopathy, a hematological disorder affecting blood clotting, carries an elevated risk of thrombosis and mortality in COVID-19 patients. Fondaparinux, enoxaparin, and unfractionated heparin (UFH) are potential treatments for reducing coagulopathy in COVID-19 patients. Nonetheless, anticoagulant administration increases the risk of bleeding-related adverse effects. This study aimed to evaluate the safety profile of fondaparinux, enoxaparin, and UFH in COVID-19 patients. The safety was evaluated based on the prevalence of major and minor bleeding events from the data of medical records collected retrospectively from October 2022 to December 2021 at Kediri District Hospital. The Chi-square analysis and multiple logistic regression were employed to establish associations between variables. Out of the 315 patients who meet the inclusion criteria, 35 patients (11.1%) exhibited bleeding, 11 patients (3.5%) experienced major bleeding, while 24 patients (7.6%) encountered minor bleeding. No significantly different in bleeding events both major and minor bleeding among the groups receiving fondaparinux, enoxaparin, and UFH were observed (p> 0.05). The UFH emerged as the most common anticoagulant associated with bleeding incidents. The multivariate analysis revealed that age ≥ 60 yr and concomitant medication with ketorolac influenced bleeding incidence. The monitoring of bleeding events on the use of anticoagulants is necessary.

ABSTRAK

Koagulopati merupakan suatu gangguan sistem pembekuan darah yang berkaitan dengan peningkatan risiko terjadinya trombosis serta peningkatan mortalitas pada pasien COVID-19. Terapi antikoagulan fondaparinux, enoxaparin atau *unfractionated heparin* (UFH) dapat diberikan pada pasien COVID-19 untuk menurunkan kejadian koagulopati. Namun, penggunaan antikoagulan berkaitan dengan risiko terjadinya efek samping perdarahan. Tujuan penelitian ini adalah untuk mengevaluasi keamanan penggunaan fondaparinux, enoxaparin serta UFH pada pasien COVID-19. Keamanan obat dinilai berdasarkan prevalensi kejadian perdarahan besar dan kecil dari data rekam medis yang dikumpulkan secara retrospektif pada bulan Oktober 2022 hingga Desember 2021 di RSUD Kediri. Analisis *Chi-square* dan regresi logistik berganda dilakukan untuk mengetahui hubungan antar variabel penelitian. Dari 315 pasien yang memenuhi kriteria inklusi, 35 pasien (11,1%) mengalami pendaharan yang meliputi 11 pasien (3,5%) mengalami perdarahan mayor dan 24 pasien (7,6%) mengalami perdarahan minor. Tidak ada perbedaan signifikan antara kejadian perdarahan baik pada perdarahan mayor maupun minor pada kelompok fondaparinux, enoxaparin dan UFH (p> 0,05). UFH merupakan antikoagulan yang paling sering menyebabkan perdarahan. Berdasarkan analisis multivariat, didapatkan hasil bahwa pasien dengan usia ≥ 60 tahun dan pengobatan bersamaan dengan ketorolac merupakan faktor yang mempengaruhi kejadian perdarahan. Pemantauan kejadian perdarahan pada penggunaan antikoagulan diperlukan.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), a severe acute respiratory syndrome, initially emerged in Wuhan, China, in late 2019 and spread to various countries worldwide.[1] On March 2, 2020, Indonesia reported its first two cases of COVID-19. As of May 31, 2023, Indonesia had recorded 6,807,085 confirmed COVID-19 cases, with approximately 161,762 associated deaths.[2]

Coagulopathy presents a common manifestation among patients diagnosed with COVID-19, and its presence correlates with poor prognosis.[3-5] The intense inflammatory response leads to thromboinflammation through cytokine storm, complement activation, and endotheliitis.[6,7] Several laboratory parameters, including D-dimer, neutrophil count, lymphocyte count, NLR, and platelet count have been identified as markers correlating with disease severity and are used to assess coagulopathy.[8-10] Thrombotic complications were observed in 31% of COVID-19 patients treated in the ICU, with 27% experiencing venous thromboembolism and 3.7% suffering from arterial thromboembolic events.[11]

COVID-19-induced coagulopathy has resulted from a combination of inflammation and thrombosis. Anticoagulant therapy can be given to COVID-19 patients with thrombosis who have no contraindications to anticoagulants. The International Society on Thrombosis and Haemostasis (ISTH) has established an algorithm for managing coagulopathy in COVID-19 based on simple laboratory markers. The American College of Chest Physicians (CHEST) and ISTH guidelines recommend anticoagulant therapy to treat coagulopathy in COVID-19 patients. Before administering anticoagulants, clinicians should evaluate the patient's condition using the VTE PADUA assessment and the IMPROVE score. The International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) score assesses hospital bleeding incidence and identifies admission-related risk factors associated with bleeding during hospitalization. Anticoagulants have been shown to effectively reduce the occurrence of venous thromboembolism (VTE) by as much as 95%. However, paying particular attention to the potential risk of bleeding associated with these medications is crucial.

Extensive research on the safety of anticoagulants in COVID-19 has not been widely conducted in Indonesia. Haswan *et al.*[12] reported that direct oral anticoagulants (DOAC) such as rivaroxaban and edoxaban are safer than low molecule weight heparin (LMWH) such as enoxaparin in COVID-19 patients. However, another study reported no significant difference in the major bleeding rate and clinically relevant non-major bleeding (CRNMB) between fondaparinux and unfractionated heparin (UFH).[13]

This study aimed to evaluate the safety of fondaparinux, enoxaparin, and UFH therapy in patients with COVID-19 and analyze factors associated with bleeding events. The results of this study are expected can help to monitor anticoagulant use in COVID-19 patients.

MATERIAL AND METHODS

Study design and samples

It was an observational study with a cohort design through retrospective data tracking of the medical records of COVID-19 patients at the Kediri District Hospital, Kediri, East Java started from October 2020 to December 2021 who met the inclusion and exclusion criteria. The inclusion criteria included 1) patients

whose COVID-19 infections were confirmed by real-time polymerase chain reaction (RT-PCR) with mild, moderate, and severe degrees; 2) aged 18-85 yr; and 3) length of stay ≥ 3 d. The exclusion criteria included 1) pregnant women;[14,15] and 2) incomplete medical record data.

The COVID-19 severity classification based on the patient's clinical condition from the World Health Organization (WHO) guidelines as follows 1) mild-symptomatic patients who does not require oxygen supplementation; 2) moderate - patients presenting with clinical signs of pneumonia (fever, cough, dyspnea, rapid breathing) but without signs of severe pneumonia, and with SpO2 ≥90% on room air, and 3) severe - patients with clinical signs of pneumonia (fever, cough, dyspnea), along with one of the following: respiratory rate >30 breaths/min, severe respiratory distress, or SpO2 <90% on room air.[2] The protocol of the study was approved by the Health Research Ethics Committee of the Health Research Ethics Committee with the number of 423/3688/418.67/2023.

Safety evaluation

The safety analysis of the anticoagulant therapy was assessed based on the incidence of bleeding observed during the patient's hospitalization obtained from the patient's medical records. The bleeding was classified into major and minor bleeding based on the ISTH criteria. The major bleeding is defined when one of the following conditions is met 1) fatal bleeding; 2) bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, or intramuscular; 3) hemorrhage with a hemoglobin decrease of ≥ 2 g/dL; 4) hemorrhage required transfusion of at least two bags of red blood cells. In contrast, the minor bleeding does not meet the criteria for major bleeding, hemoglobin depletion < 2 g/dL, or bleeding requiring one bag of blood transfusion.[16,17]

Statistical analysis

Data was analyzed using the IBM SPSS Statistics program, version 26. Descriptive statistics, such as tables and percentages (%), were used to present the characteristics of each subject. The descriptive presentation was also used to present the side effects of bleeding in each anticoagulant group. The bivariate and multivariate analyses were performed to determine the significance of each factor's impact on bleeding events. The Chi-square test or Fisher's exact test was employed, followed by multiple logistic regression analysis. The study utilized a 95% confidence interval (95%CI) and a significance level of 5%. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

In the period of October 2020 to December 2021, 315 COVID-19 patients who met the inclusion and exclusion criteria involved in this study. They consisted of patients receiving fondaparinux (164 patients or 52.1%), enoxaparin (103 patients or 32.7%), and UFH (48 patients or 15.2%). The characteristics of the patients are presented in TABLE 1. Almost patients (207 patients or 65.7%) aged between 18 and 60 yr. The youngest patient was 18 y.o., while the oldest patient was 84 y.o. and the mean of patients age was 53 y.o. Among the patients involved in this study, 159 (50.5%) were male, and 156 (49.5%) were female. A total of 191 patients (60.6%) had comorbidities, with the most prevalent being diabetes mellitus (36.5%) followed by hypertension (20.6%).

TABLE 1. Characteristics of COVID-19 patients receiving anticoagulants at Kediri District Hospital.

Parameters	Fondaparinux (n=164)	Enoxaparin (n=103)	UFH (n=48)	Total (n=315)	p
Age [median (min-max) yr]	54 (18-83)	56 (26-84)	55 (35-79)	53 (18-84)	
• 18-59 [n (%)]	104 (63.4)	71 (68.9)	32 (66.7)	207 (65.7)	0.645
• ≥ 60 [n (%)]	60 (36.6)	32 (31.1)	16 (33.3)	108 (34.3)	
Gender [n (%)]					
• Male	89 (54.3)	41 (39.8)	29 (60.4)	159 (50.5)	0.023
• Female	75 (45.7)	62 (60.2)	19 (39.6)	156 (49.5)	
Disease severity [n (%)]					
• Mild	29 (17.7)	8 (7.8)	3 (6.3)	40 (12.7)	
• Moderate	38 (23.2)	21 (20.4)	25 (52.1)	84 (26.7)	0.000
• Severe	97 (59.1)	74 (71.8)	20 (41.7)	191 (60.6)	
Smoking history [n (%)]					
• Yes	25 (15.2)	15 (14.6)	11 (22.9)	51 (16.2)	0.385
• No	139 (84.8)	88 (85.4)	37 (77.1)	264 (83.8)	
Comorbidities [n (%)]					
• DM	54 (32.9)	43 (41.7)	18 (37.5)	115 (36.5)	0.342
• Hypertension	28 (17.1)	32 (31.1)	5 (10.4)	65 (20.6)	0.004
• CHF	8 (4.9)	11 (10.7)	1 (2.1)	20 (6.3)	0.085
• CAD	9 (5.5)	7 (6.8)	1 (2.1)	17 (5.4)	0.556
• CKD	0 (0.0)	4 (3.9)	4 (8.3)	8 (2.5)	0.001
• Stroke	6 (3.7)	5 (4.9)	3 (6.3)	14 (4.4)	0.569
• Other comorbidities	14 (8.5)	7 (6.8)	3 (6.3)	24 (7.6)	0.839
• Without comorbid	78 (47.6)	30 (29.1)	16 (33.3)	124 (39.4)	0.007
Other treatment [n (%)]					
• Antivirus	163 (99,4)	99 (96.1)	48 (100)	310 (98,4)	0.073
• Antibiotic	152 (92.7)	96 (93.2)	43 (89.6)	291 (92.4)	0.741
• Corticosteroid	108 (65.9)	67 (65.0)	31 (64.6)	206 (65.4)	0.975
• Vitamin	164 (100)	102 (99)	47 (97.9)	313 (99.4)	0.126
• Plasma convalesens	7 (4.3)	3 (2.9)	9 (18.8)	19 (6.0)	0.002
• Comorbid therapy	91 (55.5)	68 (66.0)	31 (64.6)	190 (60.3)	0.186
• Symptomatic therapy	156 (95.1)	93 (90.3)	47 (97.9)	296 (94.0)	0.165
• Antiplatelet	9 (5.5)	11 (10.7)	1 (2.1)	21 (6.7)	0.112
Mortality [n (%)]					
• Alive	105 (64.0)	77 (74.8)	25 (52.1)	207 (65.7)	0.019
• Death	59 (36.0)	26 (25.2)	23 (47.9)	108 (34.3)	
LoS [median (min-max) d]	11 (3-32)	12 (4-34)	11 (4-26)	12 (3-34)	0.161

Note: UFH: unfractionated heparin; DM: diabetes mellitus; CHF: congestive heart failure; CAD: coronary artery disease; CKD: chronic kidney disease; LoS: length of stay.

The bleeding incidence in the COVID-19 patients based on anticoagulant use is presented in TABLE 2. As much as 35 patients (11.1%) experienced bleeding which consisted of major bleeding (11 patients or 3.5%) and minor bleeding (24 patients or 7.6%). However, no significantly difference in the bleeding incidence was observed, both in major and minor bleeding among the administration fondaparinux, enoxaparin, and UFH ($p > 0.05$). Notably, UFH was associated with the highest bleeding cases, with 9 patients (18.8%) experiencing bleeding. Furthermore, the mortality rate was higher in the bleeding group (57.1%) compared to the non-bleeding group (42.9%).

The doses of anticoagulants administration to COVID-19 patients are presented on TABLE 3. The most frequent prescribed dose of fondaparinux was 2.5 mg, given subcutaneously every 24 hr, which is classified as an intermediate dose category. Enoxaparin was commonly administered at 6000 units subcutaneously every 12 hr, classified as the therapeutic dose.

TABLE 2. Bleeding incidence [n (%)] based on anticoagulant use in COVID-19 patients

Bleeding incidence	Total (n=315)	Fondaparinux (n=164)	Enoxaparin (n=103)	UFH (n=48)	p
Total bleeding	35 (11.1)	16 (9.8)	10 (9.7)	9 (18.8)	0.188
Major bleeding	11 (3.5)	5 (3.0)	3 (2.9)	3 (6.3)	0.537
Minor bleeding	24 (7.6)	11 (6.7)	7 (6.8)	6 (12.5)	0.417

TABLE 3. Dosage of anticoagulants given to COVID-19 patients

Anticoagulant dose	Major bleeding (n=11)	Minor bleeding (n=24)	No bleeding (n=280)	Total (n=315)
Fondaparinux [n (%)]				
• 2.5 mg every 24 hr	4 (3.6)	7 (6.4)	99 (90.0)	110
• Initial 7.5 mg, then 2.5 mg, then 24 hr	1 (1.9)	4 (7.4)	49 (90.7)	54
Enoxaparin [n (%)]				
• 4000 units, then 24 hr	1 (4.3)	1 (4.3)	21 (91.4)	23
• 6000 units, then 24 hr	0 (0.0)	2 (7.4)	25 (92.6)	27
• 4000 units, then 12 hr	0 (0.0)	0 (0.0)	3 (100.0)	3
• 6000 units, then 12 hr	2 (3.9)	4 (7.8)	45 (88.3)	51
UFH [n (%)]				
• Initial IV bolus 5000 units, then infuse 20.000 units	0 (0.0)	1 (14.3)	6 (85.7)	7
• Initial IV bolus 5000 units, then infuse 25.000 units	0 (0.0)	0 (0.0)	2 (100.0)	2
• Initial IV bolus 5000 units, then 7500 units every 12 hr	2 (12.5)	2 (12.5)	12 (75.0)	16
• 5000 units every 12 hr	0 (0.0)	2 (14.3)	12 (85.7)	14
• 7500 units every 12 hr	1 (12.5)	1 (12.5)	6 (75.0)	8

Note: unfractionated heparin

The types of major bleeding observed in COVID-19 patients are presented on TABLE 4. The mean reduction of hemoglobin concentration was approximately 3.4 g/dL. The most prevalent type of bleeding observed was gastrointestinal bleeding. Among the patients, 27.3% presented with melena, while 45.4% had hematemesis. The incidence of bleeding varied based on the severity of COVID-19. Among patients with mild COVID-19, the bleeding was 0% (0 out of 39 patients). Among patients with moderate COVID-19, the incidence of bleeding was 5.9% (5 out of 85 patients). Among patients with severe COVID-19, the incidence of bleeding was 15.7% (30 out of 191 patients).

The variables associated with the bleeding incidence are presented in TABLE 5. Age was significantly associated with the incidence of bleeding. The age of COVID-19 patients who experienced bleeding (60.86±10.46 y.o.) was significantly higher than those without bleeding (51.89±13.59 y.o.; p = 0.000). Furthermore, the elderly patients (≥60 y.o.) had a higher risk of bleeding compared to younger patients (18-59 y.o.) (OR = 3.328; 95%CI: 1.616-6.850; p= 0.001). The proportion of bleeding in the elderly patients (19.4%) was also higher than younger patients (6.8%; p= 0.001).

The multivariate analyses of the risk factors of the bleeding of COVID-19 patients are presented in TABLE 6. The elderly patients (≥ 60 y.o.) and concomitant with ketorolac were significantly associated with the bleeding incidence. The elderly patients had a 2.917 times higher risk of bleeding compared to younger patients (OR = 2.917; 95% CI: 1.352-6.294; p= 0.006). Moreover, concomitant with ketorolac had a 6.288 times higher risk of bleeding compared to those without ketorolac (OR = 6.288; 95% CI: 1.142-34.624; p = 0.035).

TABLE 4. Major bleeding types [n (%)] that occur in the anticoagulant group

Major bleeding types	Total incidence (n=11)
Melena	3 (27.3)
Hematemesis	5 (45.4)
Hematuria	2 (18.2)
Hemoptysis	1 (9.1)

TABLE 5. Bivariate analysis of factors influencing the incidence of bleeding in COVID-19 patients

Parameters	Bleeding (n=35)	No bleeding (n=280)	p	OR	95%CI
Age	60.86±10.46	51.89±13.59	0.000		
• ≥ 60 [n (%) yr]	21(19.4)	87 (80.6)	0.001	3.328	1.616-6.850
• 18-59 [n (%) yr]	14 (6.8)	193 (93.2)			
Gender [n (%)]					
• Male	20 (12.6)	139 (87.4)	0.403	1.353	0.665-2.749
• Female	15 (9.6)	141(90.4)			
Disease severity [n (%)]					
• Mild	1 (2.5)	39 (97.5)	0.005		
• Moderate	4 (4.8)	80 (95.2)		1.95	0.211-18.035
• Severe	30 (15.7)	161 (84.3)		7.267	0.961-54.937
Comorbidities [n (%)]					
• No comorbid	5 (4.0)	119 (96.0)	0.001	0.225	0.085-0.598
• 1 comorbid	17 (13.3)	111 (86.7)	0.311	1.438	0.711-2.910
• 2 comorbidities	9 (20.0)	36 (80.0)	0.040	2.346	1.018-5.407
• ≥ 2 comorbidities	4 (22.2)	14 (77.8)	0.126	2.452	0.760-7.913
Other treatment [n (%)]					
• Antivirus	34 (11.0)	276 (89.0)	0.447	0.493	0.054-4.537
• Antibiotic	35 (12.0)	256 (88.0)	0.090	0.880	0.843-0.918
• Corticosteroid	23 (11.2)	183 (88.8)	0.967	1.016	0.485-2.130
• Vitamin	35 (11.2)	278 (88.8)	1.000	0.888	0.854-0.924
• Plasma convalesens	3 (15.8)	16 (84.2)	0.454	1.547	0.427-5.600
• Comorbid therapy	26 (13.7)	164 (86.3)	0.073	2.043	0.923-4.522
• Symptomatic therapy	35 (11.8)	261 (88.2)	0.146	0.882	0.846-0.919
• Antiplatelet	2 (9.5)	19 (90.5)	1.000	0.833	0.186-3.736
NSAIDs					
• Metamizole	29 (11.9)	215 (88.1)	0.418	1.461	0.581-3.673
• Ketorolac	3 (42.9)	4 (57.1)	0.032	6.469	1.385-30.206
• Ketoprofen	0 (0)	3 (100)	1.000	1.126	1.083-1.172

Note: NSAIDs: non steroid analgesics anti-inflammatory drugs

TABLE 6. Multivariate analysis of factors influencing the incidence of bleeding in COVID-19 patients

Factors	p	OR	95% Cl
Disease Severity			
• Moderate	0.820	1.302	0.134-12.622
• Severe	0.156	4.489	0.563-35.767
Comorbid			
• No comorbid	0.026	0.211	0.053-0.832
• Two comorbidities	0.339	1.618	0.604-4.335
• ≥ 2 comorbidities	0.525	1.531	0.411-5.699
Elderly (age ≥ 60 yr)	0.006	2.917	1.352-6.294
Concomitant medication with ketorolac	0.035	6.288	1.142-34.624
Comorbid therapy	0.366	0.565	0.164-1.947

DISCUSSION

This study was conducted to evaluate the safety of fondaparinux, enoxaparin, and UFH therapy in COVID-19 patients. The results are summarized as follows 1) no significant differences were observed in major and minor bleeding among the three anticoagulants evaluated; 2) UFH was associated with the highest incidence of bleeding; 3) among the patients involved in this study, 35 (11.1%) had bleeding consisting of major bleeding (11 patients or 3.5%) and minor bleeding (24 patients or 7.6%); 4) the gastrointestinal tract was the most frequently affected organ of bleeding; 5) patients aged ≥ 60 yr had a 2.917 times higher risk of bleeding compared to patients aged 18-59 yr; 6) concomitant medication with ketorolac was associated with a 6.288 times higher risk of bleeding.

Among the three anticoagulants evaluated, UFH was associated with the highest incidence of bleeding (9 patients or 18.8%). This result is in line with a study conducted by Pawlowski *et al.*[18] reporting that the incidence of bleeding is higher in patients receiving UFH than those receiving enoxaparin. The risk factors of bleeding in COVID-19 patients can be influenced by various factors such as age, sex, history of previous bleeding, kidney function, body weight, risk of falling or trauma, prior surgery, and alcohol consumption.[19]

The number of patients who experienced bleeding was not significantly different in the fondaparinux and enoxaparin groups (TABLE 2). This result is in line with a study conducted by Russo *et al.*[20] reporting that there is no significantly difference in overall bleeding events, including major and minor bleeding, between COVID-19 patients treated with fondaparinux and those treated with enoxaparin.

The difference in bleeding incidence between UFH and enoxaparin can be attributed to variations in their pharmacokinetics and biological properties. Enoxaparin, a low molecular weight heparin (LMWH), has lower protein binding properties than UFH. Unfractionated heparin comprises highly sulfated polysaccharide chains with a molecular weight ranging from 3,000 to 30,000 Da. Unfractionated heparin inhibits thrombin via an antithrombin-dependent mechanism and activates factor X (Xa). It binds to antithrombin (AT) with high affinity via a pentasaccharide. Since it inactivates thrombin, UFH prevents fibrin formation and inhibits thrombin-induced activation of platelets

and factors V and VIII. The bleeding occurs because UFH has a saccharide fragment with high antithrombin activity. Unfractionated heparin may also lead to side effects such as HIT (heparin-induced thrombocytopenia) and allergic reactions.[21,22]

Compared to UFH, LMWH exhibits a more favorable pharmacodynamic and pharmacokinetic profile, predictable anticoagulant response, and fewer side effects. As a result, routine monitoring of anticoagulant activity and dose adjustment is not typically required. The bioavailability of LMWH after subcutaneous injection approaches 100%. The peak of anti-factor-Xa activity is observed approximately 3-4 hr after administering a subcutaneous dose.[23]

Low molecule weight heparin, with an average molecular weight of 4500-5000 Da, has a lower ability to inactivate thrombin than UFH. Lower LMWH inactivates thrombin because it has smaller fragments that cannot bind AT and thrombin together. LMWH has a longer half-life and a lower risk of thrombocytopenia. It is important to note that despite the lower frequency of bleeding events associated with LMWH compared to UFH, attention should still be given to its antithrombin activity.[21,22]

The dosage of anticoagulant use in COVID-19 patients (TABLE 3). The most commonly used dose of fondaparinux is 2.5 mg administered subcutaneously once every 24 hr, which is classified as an intermediate dose category. Similarly, the most frequently used dose of enoxaparin is 6000 units administered subcutaneously every 12 hr, which is classified as a therapeutic dose category. Previous studies have reported that among COVID-19 patients receiving anticoagulants at intermediate or therapeutic doses for VTE prevention, 5.7% experienced major bleeding, and 6.7% experienced minor bleeding. The mortality rate was twice as high in the group with major bleeding compared to the non-bleeding group. Additionally, therapeutic anticoagulant doses, critical illness, and elevated levels of D-dimer and ferritin were significantly associated with an increased risk of bleeding.[24]

The study conducted by the INSPIRATION Investigators compared intermediate and standard prophylactic doses regarding bleeding events. The intermediate dose of enoxaparin was 1 mg/kg per d, whereas the standard prophylactic dose was 40 mg per d. The results showed that 7 patients (2.5%) in the intermediate-dose group experienced major bleeding, compared to 4 patients (1.4%) in the standard-dose prophylactic group. Clinically relevant non-major bleeding occurred in 12 patients (4.3%) in the intermediate-dose group and five patients (1.7%) in the standard-dose prophylactic group.[25] Another study by Lopes *et al*.,[26] found that therapeutic doses of anticoagulants increased the risk of bleeding compared to prophylactic doses in hospitalized patients with COVID-19 and elevated D-dimer concentrations (RR=3.64; 95%CI: 1.061-8.250).

Gastrointestinal bleeding was reported to be the most common type of bleeding (TABLE 4). This finding is consistent with previous studies that reported gastrointestinal bleeding as the most prevalent complication in COVID-19 patients, followed by surgery-related and intracranial bleeding. Nakamura *et al*.[27] reported that 2.0% patients among 2,882 COVID-19 patients involved in their study experienced major bleeding, with gastrointestinal bleeding being the most common type (44%). In addition, gastric ulcers were the most common cause of gastrointestinal bleeding in patients with COVID-19.[28] To prevent the risk of gastrointestinal bleeding, some drugs such as proton pump inhibitors (PPIs) could be recommended.

In this study, the risk factors associated with the bleeding incidence included age, comorbidities, and concurrent with ketorolac were reported (TABLE 5). Nakamura *et al*.[27] reported that a history of bleeding, the severity of COVID-19, and the administration of

anticoagulants are the independent risk factors of bleeding in COVID-10 patients. These risk factors were associated with poor clinical outcomes, such as increased mortality rates. Therefore, risk assessment of bleeding is essential when using anticoagulants to improve outcomes in COVID-19 patients.[27]

The elderly patients (≥ 60 y.o.) was significantly associated with the bleeding incidence in this study. The elderly patients had a 2.917 times higher risk of bleeding compared to younger patients (TABLE 6). In contrast, a previous study reported that age is not the risk factor of bleeding in COVID-19 patients. Furthermore, concomitant with ketorolac had a 6.288 times higher risk of bleeding compared to those without ketorolac (TABLE 6). Interaction between ketorolac and anticoagulants is well known. Ketorolac potentially enhances the anticoagulant effects resulting the increase of bleeding. Therefore, the administration of these two drugs together is not recommended.[29]

CONCLUSION

In conclusion, there is no different in bleeding events both major and minor bleeding among the groups receiving fondaparinux, enoxaparin, and UFH in COVID-19 patients. Unfractionated heparin has a greater chance of bleeding compared to fondaparinux and enoxaparin. Age ≥ 60 yr and concomitant with ketorolac are the risk factors of bleeding in COVID-19 patients. Monitoring of the side effects of bleeding in COVID-19 patients during anticoagulants administration is recommended.

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REFERENCES

1. Zhu H, Wei L, Niu P. The novel coronavirus outbreak in Wuhan, China. Glob Health Res Policy 2020; 5(1):6. https://doi.org/10.1186/s41256-020-00135-6
2. World Health Organization. Living guidance for clinical management of COVID-19: living guidance. Published November 23, 2021. Accessed June 5, 2023. https://covid19.who.int/table
3. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, *et al*. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020; 382(18):1708-20. https://doi.org/10.1056/NEJMoa2002032
4. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395(10223):497-506. https://doi.org/10.1016/S0140-6736(20)30183-5
5. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395(10229):1054-62. https://doi.org/10.1016/S0140-6736(20)30566-3
6. Campbell CM, Kahwash R. Will complement inhibition be the new target in treating COVID-19 related systemic thrombosis? Circulation 2020; 141(22):1739-41. https://doi.org/10.1161/CIRCULATIONAHA.120.047419
7. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, *et al*. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020; 395(10234):1417-8. https://doi.org/10.1016/S0140-6736(20)30937-5
8. Fan BE, Chong VCL, Chan SSW,

Lim GH, Lim KGE, Tan GB, *et al*. Hematologic parameters in patients with COVID-19 infection. Am J Hematol 2020; 95(6):E131-4. https://doi.org/10.1002/ajh.25774
9. Lagunas-Rangel FA. Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. J Med Virol 2020; 92(10):1733-4. https://doi.org/10.1002/jmv.25819
10. Yang X, Yang Q, Wang Y, Wu Y, Xu J, Yu Y, *et al*. Thrombocytopenia and its association with mortality in patients with COVID-19. J Thromb Haemost 2020; 18(6):1469-72. https://doi.org/10.1111/jth.14848
11. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, *et al*. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020; 191:145-7. https://doi.org/10.1016/j.thromres.2020.04.013
12. Haswan D, Yasin NM, Pinzon RT. Perbandingan efektivitas dan keamanan penggunaan *direct oral anticoagulants* (rivaroxaban, edoxaban) dan *low molecular weight heparin* (enoxaparin) pada pasien COVID-19 di Rumah Sakit Bethesda, Yogyakarta. [Thesis]. Yogyakarta: Universitas Gadjah Mada; 2022.
13. Adrian LH, Hutomo SA, Negari ADS. Efficacy and safety of fondaparinux versus unfractionated heparin in patients hospitalised with severe COVID-19 pneumonia and coagulopathy: a randomised, open-label clinical trial. Eur Heart J 2022; 43(Supplement_1):ehab849.169. https://doi.org/10.1093/eurheartj/ehab849.169
14. Saeed K, Áinle FN. Standardizing definitions for bleeding events in studies including pregnant women: a call to action. Res Pract Thromb Haemost 2022; 6(7):e12822. https://doi.org/10.1002/rth2.12822
15. Simard C, Gerstein L, Cafaro T, Filion KB, Douros A, Malhame I, *et al*. Bleeding in women with venous thromboembolism during pregnancy: a systematic review of the literature. Res Pract Thromb Haemost 2022; 6(6):e12801. https://doi.org/10.1002/rth2.12801
16. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005; 3(4):692-4. https://doi.org/10.1111/j.1538-7836.2005.01204.x
17. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost 2015; 13(11):2119-26. https://doi.org/10.1111/jth.13140
18. Pawlowski C, Venkatakrishnan AJ, Kirkup C, Berner G, Puranik A, O'Horo JC, *et al*. Enoxaparin is associated with lower rates of mortality than unfractionated heparin in hospitalized COVID-19 patients. EClinicalMedicine 2021; 33:100774. https://doi.org/10.1016/j.eclinm.2021.100774
19. Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141(2 Suppl):e24S-e43S. https://doi.org/10.1378/chest.11-2291
20. Russo V, Cardillo G, Viggiano GV, Mangiacapra S, Cavalli A, Fontanella A, *et al*. Fondaparinux use in patients with COVID-19: a preliminary multicenter real-world experience. J Cardiovasc Pharmacol 2020; 76(4):369-71. https://doi.org/10.1097/

FJC.0000000000000893
21. Hirsh J, Anand SS, Halperin JL, Fuster V. Mechanism of action and pharmacology of unfractionated heparin. Arterioscler Thromb Vasc Biol 2001; 21(7):1094-6. https://doi.org/10.1161/hq0701.093686
22. Liu Z, Ji S, Sheng J, Wang F. Pharmacological effects and clinical applications of ultra low molecular weight heparins. Drug Discov Ther 2014; 8(1):1-10. https://doi.org/10.5582/ddt.8.1
23. Fareed J, Hoppensteadt D, Walenga J, Iqbal O, Ma Q, Jeske W, *et al*. Pharmacodynamic and pharmacokinetic properties of enoxaparin. Clin Pharmacokinet 2003; 42(12):1043-57. https://doi.org/10.2165/00003088-200342120-00003
24. Demelo-Rodriguez P, Farfán-Sedano AI, Pedrajas JM, Llamas P, Sigüenza P, Jaras MJ, *et al*. Bleeding risk in hospitalized patients with COVID-19 receiving intermediate- or therapeutic doses of thromboprophylaxis. J Thromb Haemost 2021; 19(8):1981-9. https://doi.org/10.1111/jth.15400
25. Sadeghipour P, Talasaz AH, Rashidi F, Sharif-Kashani B, Beigmohammadi MT, Farrokhpour M, *et al*. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: the INSPIRATION Randomized Clinical Trial. JAMA 2021; 325(16):1620-30. https://doi.org/10.1001/jama.2021.4152
26. Lopes RD, de Baros E Silva PGM, Furtado RHM, Macedo AVS, Bronhara B, Damiani LP, *et al*. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. Lancet 2021; 397(10291):2253-63. https://doi.org/10.1016/S0140-6736(21)01203-4
27. Nakamura J, Tsujino I, Yachi S, Takeyama M, Nishimoto Y, Konno S, *et al*. Incidence, risk factors, and clinical impact of major bleeding in hospitalized patients with COVID-19: a sub-analysis of the CLOT-COVID Study. Thromb J 2022; 20(1):53. https://doi.org/10.1186/s12959-022-00414-x
28. Mauro A, De Grazia F, Lenti MV, Penagini R, Frego R, Ardizzone S, *et al*. Upper gastrointestinal bleeding in COVID-19 inpatients: Incidence and management in a multicenter experience from Northern Italy. Clin Res Hepatol Gastroenterol 2021; 45(3):101521. https://doi.org/10.1016/j.clinre.2020.07.025
29. Medscape. Drug interactions checker - medscape drug reference database. Published 2023. Accessed June 26, 2023. https://reference.medscape.com/drug-interactionchecker