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Original Article

Efficacy of therapeutic-dose heparin for severe COVID-19 patients at COVID-19 Emergency Hospital Jakarta

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Abstract

Introduction: Arterial and venous thrombotic events in COVID-19 cause significant morbidity and mortality. For optimal thromboprophylaxis treatment for hospitalized patients, especially those with severe COVID-19 symptoms, it is still unclear whether to use full- or therapeutic-dose versus prophylactic-dose anticoagulation therapy. The study aim was to evaluate the efficacy and safety of unfractionated heparin (UFH) for thromboprophylaxis in severe degree of COVID-19.

Methodology: In this cross-sectional study, the medical records of 160 COVID-19 patients at the COVID-19 Emergency Hospital Wisma Atlet, Jakarta, from March to August 2021, were collected. The predetermined inclusion criteria for patients were severe COVID-19 infection; age > 18 years; positive D-dimer level > 400 ng/mL; high-flow nasal cannula (HFNC) oxygenation; IMPROVE bleeding risk score < 7; and willingness to participate in the study. The primary outcome was activated partial thromboplastin time (APTT) target achievement, oxygenation changed to nasal cannula or ended with room air, mortality rate, and the principal safety criterion was presence of bleeding.

Results: Of 160 subjects, 63.8% were male and 45.6% were aged 45-59 years old. Obesity was the most common comorbidity at 45.6% Among all subjects, 9.4% experienced bleeding, with hematuria being the most frequent type at 66.7%. All subjects released HFNC, and no deaths were reported.

Conclusions: It can be concluded that administration of therapeutic doses of heparin in patients with severe COVID-19 had a low risk of bleeding and no patients were reported to have died. However, further investigation is needed to determine the long-term effects of therapeutic doses of anticoagulants.

Key words: Therapeutic-dose heparin; thromboprophylaxis; severe COVID-19.

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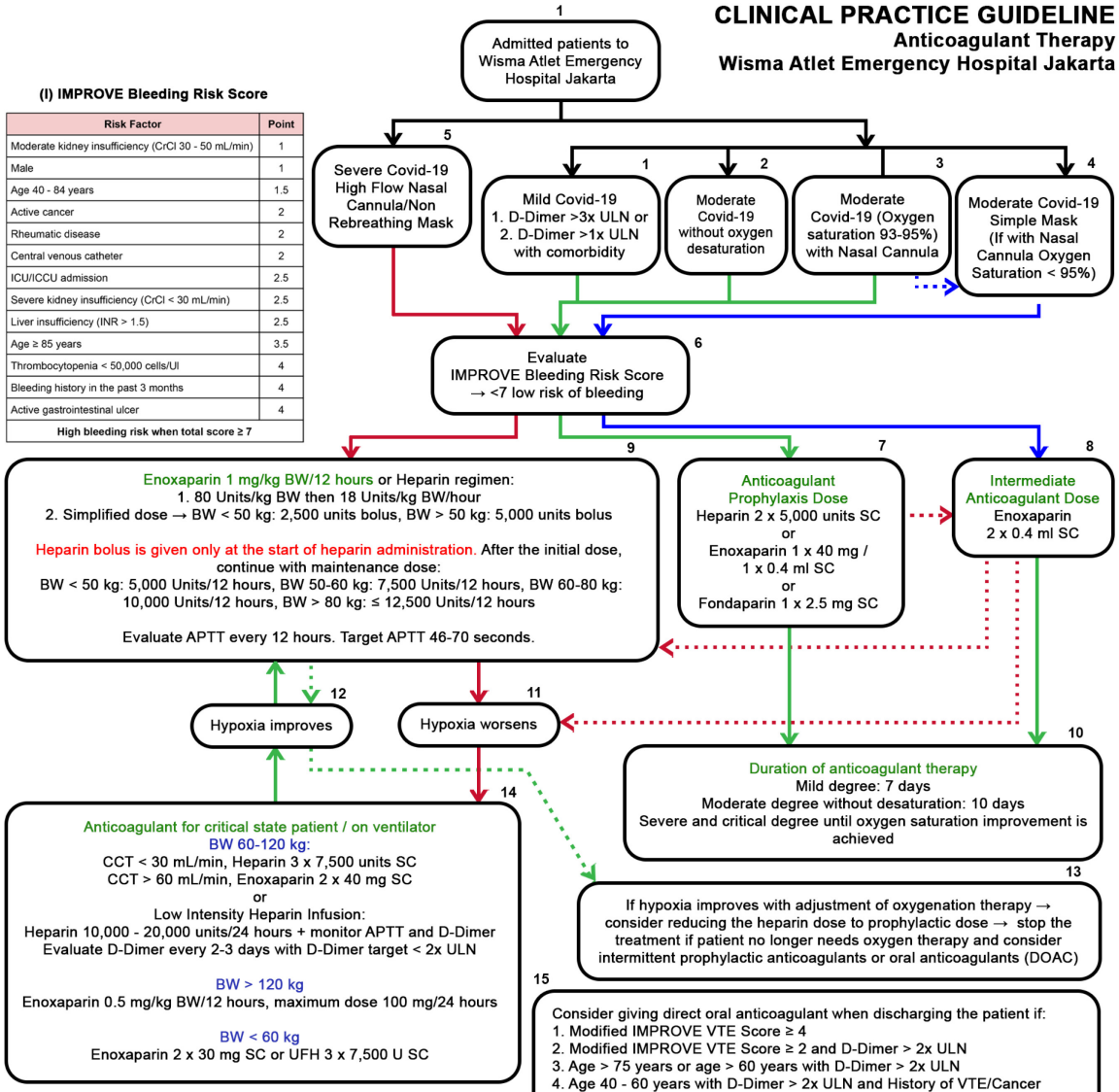
Introduction

COVID-19, a disease caused by the SARS-CoV-2 virus, was declared a global pandemic by the World Health Organization (WHO) on March 11, 2020. The immune response to SARS-CoV-2 involves Toll-like receptors (TLRs) binding to RNA as antigens, initiating a signaling cascade that leads to systemic inflammatory reactions and stimulates endothelial dysfunction. This mechanism reduces the production of natural anticoagulants, such as antithrombin III (AT III), protein C, and protein S, promoting hypercoagulability and thrombus formation in the veins causing complications that include deep-vein thrombosis (DVT) and microvascular occlusion. The occlusion results in acute respiratory distress syndrome (ARDS) and respiratory failure [1-4].

D-dimer is a biomarker of activated coagulation and fibrinolysis. Elevated levels ≥ 500 ng/mL correlate positively with disease severity and mortality in COVID-19 patients. In a retrospective study conducted in India by Soni *et al*., out of 483 of COVID-19 hospitalized patients, 80.1% exhibited increased D-dimer levels (≥ 500 ng/mL). High D-dimer levels (≥ 500 ng/mL) were observed in 96% of deaths, with an average of 6340 ng/mL, compared to 940 ng/mL in survivors [5]. A higher proportion of deaths occurred in patients with co-morbidities (89.0%), where the most common disease was diabetes mellitus (66%). High

Figure 1. Clinical practice guideline for anticoagulant therapy at COVID-19 Emergency Hospital, Wisma Atlet Jakarta.



median D-dimer values were significantly found in those with obesity (980 ng/mL) and diabetes mellitus (1,680 ng/mL) [6,7]. This corresponds to another study by Buwono *et al*., which found that elevated D-dimer level correlates to higher prevalence of pneumonia in COVID-19 patients [8].

According to the National COVID-19 Therapy Guideline established by the Indonesian Ministry of Health, severe-degree COVID-19 patient criteria include clinical signs of pneumonia with one of the following: respiratory rate more than 30 bpm, severe respiratory distress or oxygen saturation (SpO2) less than 93% in room air or patient requires a non-rebreathing mask (NRM) or high-flow nasal cannula (HFNC) oxygen [7].

Based on guidelines, successful evaluation for COVID-19 patients given standard treatments, including anticoagulant therapy, involves assessing clinical improvement in symptoms such as shortness of breath, oxygen saturation, and heart rate (HR). Once a reduction in shortness of breath is observed, oxygen saturation exceeds 95%, and HR is below 23 bpm, transitioning from HFNC to nasal cannula oxygenation therapy is considered. This assessment is repeated 2–3 days later, and when oxygen saturation remains above 95% and HR is below 23 bpm, the patient can be taken off oxygen therapy [7].

At Wisma Atlet COVID-19 Emergency Hospital, the choice of anticoagulants administered was determined by the type of oxygen therapy provided to the patient. All severe-degree COVID-19 patients were given a therapeutic dose of anticoagulant, which is a bolus UFH 80 units/kg body weight (BW), followed by a drip of 18 units/kg BW/hour. The activated Partial Thromboplastin Time (APTT) examinations are conducted every 12 hours, with a target range of 46-70 seconds. UFH dose adjustments are made based on APTT results. When APTT falls within the target range, periodic APTT examinations are continued every 12 hours to maintain the appropriate dosage. Another option for anticoagulant therapy in COVID-19 patients receiving NRM or HFNC oxygenation therapy was low-molecular weight heparin (LMWH) enoxaparin at a dosage of 1 mg/kg/12 hours. The response to enoxaparin therapy was monitored through D-dimer testing every 3 or 4 days, aiming for a D-dimer level below two times the highest normal value [8].

At the beginning of the COVID-19 pandemic, providing anticoagulant therapy at referred hospitals in Indonesia was based on D-dimer level. The IMPROVE bleeding risk score is designed to estimate the risk of bleeding in acutely ill hospitalized patients in whom anticoagulation treatment is being considered. The IMPROVE score was based on the patient's sex, age, history of having renal failure, rheumatic disease, liver insufficiency, thrombocytopenia, gastrointestinal ulcer, and cancer. An IMPROVE score below 7 indicates a low risk of bleeding, in which case anticoagulant therapy is initiated [7] (Figure 1).

Initially, the management of heparin administration in patients with severe COVID-19 primarily focused on prophylactic and intermediate doses due to concerns about increased bleeding risk associated with therapeutic doses [9]. However, studies done by Canoglu & Saylan, the REMAP-CAP meta-analysis, Spyropoulos, RAPID meta-analysis, and D'Ardes *et al.*, showed that therapeutic-dose heparin carried minimal bleeding risk, shortened ICU stays, and reduced the risk of death compared with prophylactic doses [9-13]. A case study conducted at Diponegoro National Hospital involving patients suffering from severe COVID-19 with ARDS and hypertension demonstrated that administering therapeutic doses of UFH for 12 days improved their clinical conditions, as indicated by a significant increase in the PaO_2/FiO_2 ratio [14]. A retrospective cohort study of 19 severely ill patients in a Japanese hospital reported shorter ICU stays for those who received therapeutic-dose heparin and there were no reports of thromboembolism or organ failure [15]. Furthermore, Shi *et al*. examined 449 severe cases in China and found lower mortality rates (32.8% vs 52.4%, $p = 0.017$) among those with D-dimer levels > 6 times the normal value who had received therapeutic low-molecular-weight heparin (LMWH) compared to their untreated counterparts [16].

Considering the disparities between existing guidelines and several reported results concerning heparin administration in severe COVID-19 patients, this study aimed to determine the efficacy and safety of administering full-dose therapeutic UFH anticoagulants for thromboprophylaxis in severe-degree COVID-19 patients at The National COVID-19 Emergency Hospital Wisma Atlet Kemayoran Jakarta, Indonesia.

Methodology

Study design and participant

A cross-sectional design was employed in this study of 160 COVID-19 patients whose data were collected from Intensive Care Unit (ICU) medical records of The National COVID-19 Emergency Hospital Wisma Atlet Kemayoran Jakarta, Indonesia from April to July 2021. All patients met the following inclusion criteria: severe COVID-19 infection and receiving HFNC oxygenation, age > 18 years, D-dimer level > 400 ng/ml, IMPROVE

bleeding risk score < 7, and willingness to participate in this study. Those with incomplete data or using oxygenation methods other than HFNC were excluded. Routine laboratory analysis for clotting disorders started with platelet count, prothrombin time (PT), and APTT.

All subjects who met inclusion criteria directly received a therapeutic dose of UFH 80 units/kg body weight (BW), followed by a drip of 18 units/kg BW/hour, and their condition was monitored.

The usage of therapeutic-dose UFH was similar in all patients, with success being the achievement of an APTT target 1.5-2.5× that of the APTT control. UFH dose adjustments were made based on APTT results and for geriatric patients. When the APTT fell within the target range, periodic APTT examinations were continued every 12 hours to maintain the appropriate dosage.

The main side-effect of heparin is bleeding. The most common types of bleeding were hematuria (red-colored urine), hematoma (a solid swelling of clotted blood under the skin), epistaxis (nasal bleeding), hematemesis (blood vomiting) and melena (coffee-ground-colored stools).

In this study, the initial condition of subjects was analyzed as primary data, with data taken on completed treatment being analyzed as secondary data.

The primary efficacy outcome was APTT target achievement, oxygenation being changed to nasal cannula or switching to room air, and mortality rate, and the principal safety outcome was presence of bleeding.

The collected data comprised various variables such as gender, age, D-dimer values, risk factors or comorbidities, length of stay, and incidence and forms of bleeding.

Ethics considerations

The study protocol was accepted by the Health Research Ethics Committee Wisma Atlet COVID-19 Emergency Hospital Jakarta, Indonesia, with registry number 039/KERSDCWA/2021. All methods were carried out in accordance with relevant guidelines and regulations in the Declaration of Helsinki. Informed consent was acquired from each subject before completing the questionnaire. All data obtained and used in this study will be kept confidential.

Statistical analysis

Data were analyzed to assess the efficacy of administering therapeutic heparin doses on the incidence of bleeding and patient mortality rates. The characteristics and comorbidities of the respondents, as well as the proportion of successful therapeutic doses of UFH administration and the incidence of bleeding, were presented in tabular form with frequency values (%).

Results

Characteristics of subjects

As shown in Table 1, there was a total of 160 subjects, 102 male (63.8%) and 58 female (36.3%). The mode age group was 45-59 years old, accounting for 73 (45.6%) subjects, and the mean age was 48 years. Elderly patients or subjects > 60 years old were 29

Table 1. Characteristics of subjects.

Characteristic	N	%
Gender		
Male	102	63.8
Female	58	36.3
Age (years)		
18-29	10	6.3
30-44	48	30.0
45-59	73	45.6
60 and above	29	18.1
Baseline D-dimer level		
< 400 ng/mL	23	14.3
≥ 400 ng/mL	137	85.6
Comorbidity		
Obesity	73	45.6
Heart disease and hypertension	56	35.0
Diabetes mellitus	34	21.3
Chronic kidney disease (CKD), stage III	1	0.6
CVD stroke	6	3.8
Lung disease (asthma or COPD)	3	1.9
Dyslipidemia	1	0.6

Table 2. Bleeding incidence by number of comorbidities.

No. comorbidities	Incidence of bleeding	
	n	%
None	3	20.00
One	9	60.00
Two	1	6.70
Three	2	13.30

(18.1 %). All subjects were admitted as severe COVID-19 patients and all of them received the same oxygen supplementation (HFNC). The cut off D-dimer level for severe COVID-19 in the hospital was 400 ng/ml.

The majority of patients included have D-dimer score ≥ 400 ng/mL, accounting for 137 (85.6%) subjects. The average D-dimer level was 9512 ng/mL, while there were two patients with D-dimer score of 540,800 ng/mL and 760,988 ng/mL, but median D-dimer was 840 ng/ml.

In this study, all subjects who received heparin therapy had IMPROVE bleeding risk scores less than 7. Heparin was not given if platelet counts were < 25,000/µl. Patients with platelet counts of 25,000-50,000/µl were given heparin provided they had an IMPROVE score less than 7, but otherwise there was no incident of bleeding that led to death.

Among the various risk factors analyzed, obesity was the most prevalent, affecting 73 subjects (45.6%), followed by hypertension (56 subjects, 35%) and diabetes (34 subjects, 21.3%) (Table 1). There were 55 subjects having two comorbidities, 11 had three comorbidities and two had four comorbidities.

All subjects had APTT target achievement, were released from HFNC and changed to nasal cannula or room air. The average length of stay was 10 days.

Bleeding incidence

Figure 2 shows the incidence of bleeding in 15 out of 160 subjects (9.4%), with the most common bleeding being hematuria in 10 (66.7%) subjects. Other types of bleeding were epistaxis, hematoma, and hematemesis.

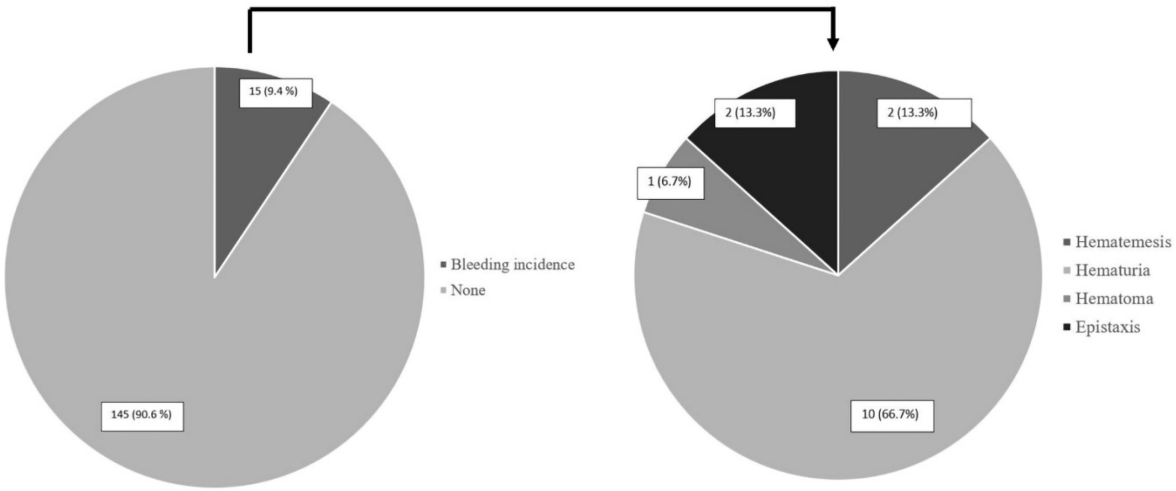
Patient comorbidities and bleeding rate

As shown in Table 2, patients with one comorbidity had the highest incidence of bleeding complications, accounting for 9 out of 15 (60%) subjects. There was no reported death from severe COVID-19 patients who received therapeutic-dose heparin among the different groups of co-morbidities.

Discussion

The demographic profile of subjects was similar to other studies, such as REMAP-CAP with 72% male with an average D-dimer level of 823 ng/mL [10]. The mean of the subjects in this study were aged 48 years, this finding is different from other studies in which the mean of critically ill COVID-19 patients were aged 60 or above; the age difference in this study corresponds to the lower mortality rate compared to other studies [1]. The high prevalence of male patients with severe COVID-19 can be affected by the process of downregulation of the ACE2 enzyme, which is more prevalent in females. In females, the hormone estrogen

Figure 2. Bleeding incidences and types of bleeding after administering therapeutic doses heparin.



acts as an anti-inflammatory agent and causes increased expression of ACE2 enzymes, which may lead to a better prognosis in female COVID-19 patients than males [16]. In addition, patients with severe-degree COVID-19 experience a coagulopathy process caused by excess inflammation which is characterized by increased levels of D-dimer [3].

Patients with comorbidities such as obesity, hypertension, or diabetes mellitus often experience chronic coagulopathy due to systemic inflammation. Prolonged inflammatory processes can activate prothrombotic signal pathways, stimulating the coagulation cascade. Additionally, patients with comorbidities have higher levels of plasminogen activator inhibitor-1 (PAI-1), an inhibitor of fibrinolysis. Excessive PAI-1 can increase fibrin deposition in blood vessels, leading to occlusion. These risk factors contribute to the exacerbation of coagulopathy in COVID-19-related inflammation [2,3]. However, there was no difference in the type of bleeding between the three comorbidities.

Our study showed that obesity was the most prevalent comorbidity. Obesity is associated with low-grade inflammation, atherosclerosis, immobility, and stasis, which may all potentially lead to thrombosis. Additionally, support for a biological link between obesity and coagulation arises from observational studies showing higher levels of procoagulant factors with increasing body weight. Obesity is associated with higher levels of coagulation factors VII, VIII, IX and XII and von Willebrand factor (VWF), higher levels of fibrinogen and plasminogen activator inhibitor-1 (PAI-1) activity, and inversely associated with tissue plasminogen activator (t-PA) activity and the activated protein C (APC) ratio [17].

In this study, patients with heart disease and hypertension exhibited the highest incidence of bleeding complications, accounting for 40% of bleeding complications, followed by diabetes and obesity. This could be attributed to the potential of anticoagulant administration to amplify the risk of rupture and bleeding in individuals with chronic heart disease who have blood vessel aneurysms.

Hypertension and diabetes mellitus are closely associated with bleeding risk in patients, especially in those receiving anticoagulant therapy. Bleeding refers to a common and severe complication of anticoagulant therapy with a reported incidence of bleeding events between 1 and 7.4% per year [18].

As a form of coagulopathy management in patients with severe COVID-19 cases, heparin therapeutic doses at 80 units/kg BW and a continuous drip at 18 units/kg BW/hour were administered, with monitoring bleeding risk. Bleeding occurred in 15 out of 160 patients (9.4%) who received the therapeutic doses, with hematuria being the most common form of bleeding, in 10 individuals (67%). These results aligned with a study by Nugroho *et al*. which reported a low incidence of bleeding after administering therapeutic doses of anticoagulants [14]. Sardu *et al*. also showed that SARS-CoV-2 affects different organs and leads to multi-organ damage and failure [2]. Bozorgmehr *et al*. reported that acute kidney injury (AKI) occurred among almost 6% of the patients with COVID-19. However, the exact mechanism leading to kidney injury is still unknown [19]. Hematuria and proteinuria are the most common signs of AKI among patients infected with SARS-CoV-2 virus [20]. This bleeding complication may occur not only because of the microvascular damage associated with the infection but also because of the anticoagulation treatment, especially at therapeutic doses [19, 20]. Bleeding risk must be evaluated on a case-by-case basis. Fibrinogen may be a useful biomarker for early detection risk of bleeding risk [20,21].

Our study was consistent with a randomized controlled trial conducted by the RAPID team on 465 severe COVID-19 patients in 2020-2021 [12]. Furthermore, Sholzberg *et al*., found lower major bleeding incidence in a group that received UFH therapeutic doses (0.9%) compared to those that received prophylactic doses (1.7%) (odds ratio = 0.52; 95% CI = 0.09 to 2.85; $p = 0.69$) [12].

The number of comorbidities in this study did not correlate with the incidence of bleeding. Although age, use of antithrombotic drugs, and medication history might influence the incidence of bleeding. For example, in patients with heart problems, patients have the possibility of taking an antithrombotic for a long period of time [21].

In this study, the average length of stay was 10 days. This was similar to the results of a study by D'Ardes *et al*., who found reduced length of stay between patients receiving anticoagulant and patients not receiving anticoagulant during their hospital admission [13]. At the end of the treatment period, there was no reported death among severe grade COVID-19 individuals receiving UFH therapeutic doses. These results were consistent with a randomized controlled trial conducted by the RAPID team on 465 severe COVID-19 patients in 2020-2021, which reported a lower percentage of patient deaths in the group receiving therapeutic anticoagulant doses (1.8%) compared to those receiving prophylactic doses (7.6%) [12]. These results indicated

that the mortality rate was lower in individuals who received therapeutic doses of anticoagulants compared to prophylactic doses [9-13]. Li *et al*., examined 42 COVID-19 patients in Huazhong, China, and discovered that besides improving coagulation function, heparin exerts anti-inflammatory effects by the reducing levels and activity of IL-6, a proinflammatory cytokine involved in hyperinflammatory reactions triggered by SARS-CoV-2 infection. This occurs because heparin binds to IL-6, preventing its interaction with the surface IL-6 receptor (SIL-6R) on host cells. The inhibition of IL-6 signal transduction in host cells subsequently mitigates the degree of inflammation [22].

This study is limited to the description result of UFH administration without analyzing the correlation of patient comorbidities with UFH and their efficacy, complication and safety.

Conclusions

In summary, a total of 160 subjects participated in this study, and obesity was the most common comorbidity among them. Among all patients, 9.4% experienced bleeding, with hematuria being the most frequent type. Subjects with heart disease and hypertension had the highest incidence of bleeding, accounting for 40% of cases. Recent management of anticoagulant administration in patients with severe COVID-19 primarily focused on prophylactic and intermediate doses due to concerns about increased bleeding risk associated with therapeutic doses. However, this study showed the administration of therapeutic doses of UFH in severe COVID-19 patients with HFNC oxygen therapy upon hospitalization had a low risk of bleeding and no patient reported death. Further investigation is needed to determine efficacy and safety following the administration of therapeutic doses of anticoagulants.

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Author contribution

Conceptualization: Hendarto H, Akbar FN, Buwono PH, Tadjoedin H; Data curation: Buwono PH, Ismail E, Halida M, Rakhmawati N; Formal analysis: Hendarto H, Akbar FN, Buwono PH, Ismail E, Halida M, Rakhmawati N, Tadjoedin H; Funding acquisition: None. Methodology: Hendarto H, Akbar FN, Buwono PH; Writing – original draft: Hendarto H, Akbar FN, Yasmin PA; Writing – review and editing: Hendarto H, Akbar FN, Buwono PH, Yasmin PA.

References

1. Liu J, Li J, Arnold K, Pawlinski R, Key NS (2020) Using heparin molecules to manage COVID-2019. Res Pract Thromb Haemost 4: 518-523. doi: 10.1002/rth2.12353.
2. Sardu C, Gambardella J, Morelli MB, Wang X, Marfella R, Santulli G (2020) Hypertension, thrombosis, kidney failure, and diabetes:is COVID-19 an endothelial disease? acomprehensive evaluation of clinical and basic evidence. J Clin Med 9: 1417. doi: 10.3390/jcm9051417.
3. Dechamps M, De Poortere J, Martin M, Gatto L, Daumerie A., Bouzin C, Octave M, Ginion A, Robaux V, Pirotton L, Bodart J, Gerard L, Montiel V, Campion A, Gruson D, Van Dievoet MA, Douxfils J, Haguet H, Morimont L, Derive M, Beauloye C (2022) Inflammation-induced coagulopathy substantially differs between COVID-19v9 and septic shock: a prospective observational study. Front Med (Lausanne) 8: 780750. doi: 10.3389/fmed.2021.780750.
4. Akbar F, Risahmawati, Fitriyah N, Hendarto H (2023) Adverse events following immunization (AEFI) with CoronaVac COVID-19 vaccine among clinical clerkship students at the Faculty of Medicine, Syarif Hidayatullah State Islamic University, Jakarta, Indonesia. Bangladesh J Med Sci 22: 545-552. doi: 10.3329/bjms.v 22i3.65319.
5. Soni M, Gopalakrishnan R, Vaishya R, Prabu P (2020) Ddimer level is a useful predictor for mortality in patients with COVID-19: analysis of 483 cases. Diabetes Metab Syndr 14: 2245-2249. doi: 10.1016/j.dsx.2020.11.007.
6. Mehanna O, El Askary A, Ali E, El Esawy B, FathAlla T, Gharib AF (2020) Impact of obesity and its associated comorbid conditions on COVID-19 presentation. Diabetes Metab Syndr Obes 14: 409-415. doi: 10.2147/DMSO.S287779.
7. Decision of the Minister of Health of the Republic of Indonesia number HK.01.07/MENKES/243/2022 regarding clinical management of corona virus disease 2019 (COVID-19) in health service facilities. [Article in Indonesian].
8. Buwono PW, Akbar FN, Hendarto H, Parlindungan F, Khomeini A, Prasetyo AHT, Nufus H, Niswara C, Suseno D, Syahlan RH, Sumampouw F, Agustin SN, Widjojoatmojo NC, Lukman J, Hidayat A, Sunggoro AJ, Ghanie A (2022) Association between serum d-dimer levels and COVID-19 severity among vaccinated and non-vaccinated individuals. Mal J Med Health Sci 18(SUPP16): 67-71.
9. Spyropoulos AC, Goldin M, Giannis D, Diab W, Wang J, Khanijo S, Mignatti A, Gianos E, Cohen M, Sharifova G, Lund JM, Tafur A, Lewis PA, Cohoon KP, Rahman H, Sison CP, Lesser ML, Ochani K, Agrawal N, Hsia J, Anderson VE, Bonaca M, Halperin JL, Weitz JI, HEP-COVID Investigators (2021) Efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19. JAMA Intern Med 181: 1612-1620. doi: 10.1001/jamainternmed.2021.6203.
10. REMAP-CAP Investigators; ACTIV-4a Investigators; ATTACC Investigators; Goligher EC, Bradbury CA, McVerry BJ, Lawler PR, Berger JS, Gong MN, Carrier M, Reynolds HR, Kumar A, Turgeon AF, Kornblith LZ, Kahn SR, Marshall JC, Kim KS, Houston BL, Derde LPG, Cushman M, Tritschler T, Angus DC, Godoy LC, McQuilten Z, Kirwan BA, Farkouh ME, Brooks MM, Lewis RJ, Berry LR, Lorenzi E, Gordon AC,

Ahuja T, Al-Beidh F, Annane D, Arabi YM, Aryal D, Baumann Kreuziger L, Beane A, Bhimani Z, Bihari S, Billett HH, Bond L, Bonten M, Brunkhorst F, Buxton M, Buzgau A, Castellucci LA, Chekuri S, Chen JT, Cheng AC, Chkhikvadze T, Coiffard B, Contreras A, Costantini TW, de Brouwer S, Detry MA, Duggal A, Džavík V, Effron MB, Eng HF, Escobedo J, Estcourt LJ, Everett BM, Fergusson DA, Fitzgerald M, Fowler RA, Froess JD, Fu Z, Galanaud JP, Galen BT, Gandotra S, Girard TD, Goodman AL, Goossens H, Green C, Greenstein YY, Gross PL, Haniffa R, Hegde SM, Hendrickson CM, Higgins AM, Hindenburg AA, Hope AA, Horowitz JM, Horvat CM, Huang DT, Hudock K, Hunt BJ, Husain M, Hyzy RC, Jacobson JR, Jayakumar D, Keller NM, Khan A, Kim Y, Kindzelski A, King AJ, Knudson MM, Kornblith AE, Kutcher ME, Laffan MA, Lamontagne F, Le Gal G, Leeper CM, Leifer ES, Lim G, Gallego Lima F, Linstrum K, Litton E, Lopez-Sendon J, Lother SA, Marten N, Saud Marinez A, Martinez M, Mateos Garcia E, Mavromichalis S, McAuley DF, McDonald EG, McGlothlin A, McGuinness SP, Middeldorp S, Montgomery SK, Mouncey PR, Murthy S, Nair GB, Nair R, Nichol AD, Nicolau JC, Nunez-Garcia B, Park JJ, Park PK, Parke RL, Parker JC, Parnia S, Paul JD, Pompilio M, Quigley JG, Rosenson RS, Rost NS, Rowan K, Santos FO, Santos M, Santos MO, Satterwhite L, Saunders CT, Schreiber J, Schutgens REG, Seymour CW, Siegal DM, Silva DG Jr, Singhal AB, Slutsky AS, Solvason D, Stanworth SJ, Turner AM, van Bentum-Puijk W, van de Veerdonk FL, van Diepen S, Vazquez-Grande G, Wahid L, Wareham V, Widmer RJ, Wilson JG, Yuriditsky E, Zhong Y, Berry SM, McArthur CJ, Neal MD, Hochman JS, Webb SA, Zarychanski R (2021) Therapeutic anticoagulation with heparin in critically ill patients with COVID-19. N Engl J Med 385: 777-789. doi: 10.1056/NEJMoa2103417.

11. Canoglu K, Saylan B (2020) Therapeutic dosing of low-molecular-weight heparin may decrease mortality in patients with severe COVID-19 infection. Ann Saudi Med 40 : 462-468. doi: 10.5144/0256-4947.2020.462.
12. Sholzberg M, Tang GH, Rahhal H, AlHamzah M, Kreuziger LB, Áinle FN, Alomran F, Alayed K, Alsheef M, AlSumait F, Pompilio CE, Sperlich C, Tangri S, Tang T, Jaksa P, Suryanarayan D, Almarshoodi M, Castellucci LA, James PD, Lillicrap D, Carrier M, Beckett A, Colovos C, Jayakar J, Arsenault MP, Wu C, Doyon K, Andreou ER, Dounaevskaia V, Tseng EK, Lim G, Fralick M, Middeldorp S, Lee AYY, Zuo F, da Costa BR, Thorpe KE, Negri EM, Cushman M, Jüni P; RAPID trial investigators (2021) Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with COVID-19 -19 admitted to hospital: RAPID randomised clinical trial. BMJ 375: n2400. doi: 10.1136/bmj.n2400.
13. D'Ardes D, Carrarini C, Russo M, Dono F, Speranza R, Digiovanni A, Martinotti G, Di Iorio A, Onofrj M, Cipollone F, Bonanni L. (2021) Low molecular weight heparin in COVID-19 patients prevents delirium and shortens hospitalization. Neurol Sci 42: 1527-1530. doi: 10.1007/s10072-020-04887-4.
14. Nugroho TE, Mochamat M, Famila M (2020) Use of High Dose Heparin in COVID-19 Patients with ARDS and Hypertension in the Intensive Care Unit (ICU). JAI (Indonesian Journal of Anesthesiology) 12: 104-111. [Article in Indonesian]. doi: 10.14710/jai. v12i3.34246.
15. Takayama W, Endo A, Otomo Y (2020) Anticoagulation therapy using unfractionated heparin at a therapeutic dose for coronavirus disease 2019 patients with severe pneumonia: a retrospective historical control study. Acute Med Surg 8: e679. doi: 10.1002/ams2.679.
16. Shi, C, Wang, C, Wang, H, Yang, C, Cai, F, Zeng, F, Cheng, F, Liu, Y, Zhou, T, Deng, B, Vlodavsky, I, Li, J P, Zhang, Y (2020) The potential of low molecular weight heparin to mitigate cytokine storm in severe COVID-19 patients: a retrospective cohort study. Clin Transl Sci 13: 1087-1095. doi: 10.1111/cts.12880.
17. Gagliardi, M.C., Tieri, P, Ortona, E. Ruggieri A (2020) ACE2 expression and sex disparity in COVID-19. Cell Death Discov 6: 37. doi: 10.1038/s41420-020-0276-1.
18. Zhang Z, Zhai Z, Yang Y, Wan J, Xie W, Zhu J, Shen YH, Wang C (2017) Diabetes mellitus is associated with increased bleeding in pulmonary embolism receiving conventional anticoagulant therapy: findings from a "real-world" study. J Thromb Thrombolysis 43: 540-549. doi: 10.1007/s11239-017-1473-5.
19. Bozorgmehr R, Tajabadi Z (2021) Hemoptysis and hematuria as the initial symptoms of COVID-19: a case report. Tanaffos 20: 75-78.
20. Thomas MR, Scully M. (2022) Clinical features of thrombosis and bleeding in COVID-19. Blood 140: 184-195. doi: 10.1182/blood.2021012247.
21. Lip GY, Felmeden DC, Dwivedi G (2011) Antiplatelet agents and anticoagulants for hypertension. Cochrane Database Syst Rev 2011: CD003186. doi: 10.1002/14651858.CD003186.pub3.
22. Li X, Li T, Wang H (2021) Treatment and prognosis of COVID-19: current scenario and prospects (Review). Exp Ther Med 21: 3. doi: 10.3892/etm.2020.9435.

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