ISSN No:-2456-2165

Correlation of Low Molecular Weight Heparin Thromboprophylaxis Use on D-Dimer Level and PaO2/FiO2 Ratio in Covid-19 Patients

Romulus Sianipar*, Akhyar Hamonangan Nasution**, Ade Winata**
*Resident of Anaesthesiology and Intensive Therapy, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
**Departement of Anaesthesiology and Intensive Therapy, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

Abstract:-

Background: Respiratory failure and coagulopathy are life-threatening complications caused by COVID-19 because of a cytokine storm. Low-molecular-weight heparin (LMWH) is the most common anticoagulant used in hospitals. Apart from its potential as an anticoagulant, it also has anti-inflammatory and antiviral effects, so we believe that we can use it as a thromboprophylaxis in COVID-19 cases.

Objective: To determine the relationship between the use of LMWH thromboprophylaxis on D-Dimer and the PF ratio in COVID-19 patients.

Methods: This study is an observational analytic study with a retrospective cohort design carried out in the isolation room and ICU of RSUP HAM. The study subjects were ≥ 18 years old patients who were confirmed positive for COVID-19 based on RT-PCR results and received anticoagulants for seven days. We divided the study subjects into two groups, the LMWH (+) group, which received 0.5 cc/day enoxaparin subcutaneously for seven days, and the non-LMWH group who received other types of anticoagulants. We took blood samples for blood gas analysis and d-dimer test before giving the intervention, 5 and 7 days after administration. Comparative analysis of PF ratio and d-dimer levels before and after the Paired t-test analyzed the intervention.

Results: 34 study subjects comprising 20 men and 14 women followed this study. The mean baseline PF ratio was lower in the LMWH (+) group and increased consistently until day 7. There were differences in the PF ratio before and after thromboprophylaxis in both groups (p = 0.022; 0.018). The baseline D-dimer level was higher in the LMWH (+) group and decreased until day 7 with a more significant reduction difference than the non-LMWH group. There was a significant difference found before and after thromboprophylaxis in both groups (p = 0.016; 0.034).

Conclusion: There was a significant relationship between using LMWH thromboprophylaxis in increasing the PF ratio and reducing D-dimer levels in COVID-19 patients.

***Keywords:-** PF Ratio, D-Dimer, Thromboprophylaxis, COVID-19.*

I. INTRODUCTION

Corona Virus Disease 2019 (COVID-19) is an RNA virus, with a distinctive appearance under the electron microscope like a crown because of glycoprotein spikes on the envelope.[1] The first reported COVID-19 observed in December 2019 was 54 people in Wuhan, China, and has now spread throughout the world affecting 28,530,904 people in 215 countries with a global death of 916,478 as of 12 September 2020. The severity of infection is increasing because of the ability of human-to-human transmission, especially through contact and droplets. In addition, they can also transmit it through aerosols and secretions on various surfaces and cause infection.

Common clinical manifestations included fever (88.7%), cough (67.8%), fatigue (38.1%), sputum production (33.4%), shortness of breath (18.6%), sore throat (13.9%), and headaches (13.6%). In addition, some patients presented with gastrointestinal symptoms, with diarrhea (3.8%) and vomiting (5.0%). The elderly and people with underlying diseases are susceptible to infection and are susceptible to a poor prognosis, which may be associated with acute respiratory distress syndrome (ARDS) and cytokine storm. Most adults or children with SARS-CoV-2 infection show mild flu-like symptoms and some patients are in critical condition and quickly develop acute respiratory distress syndrome, respiratory failure, multiple organ failure, and even death.[2]

On the results of laboratory tests, most of the patients had decreased white blood cell count and lymphocytopenia. But in severe patients, the neutrophil count, D-dimer, blood urea, and creatinine levels are significantly higher, and the lymphocyte count continues to decline.[3] Similar to other viral respiratory diseases, such as influenza, severe lymphopenia can occur in individuals with COVID-19 19 when SARS-CoV-2 infects and kills T lymphocyte cells. In addition, the viral inflammatory response, comprising both innate and adaptive immune responses (comprising humoral and cellular immunity), impairs lymphopoiesis and enhances lymphocyte apoptosis. In the later stages of infection, when viral replication is accelerated, the integrity of the epithelial-endothelial barrier is compromised.

Currently, there are no specific management recommendations for COVID-19 patients, including antivirals or vaccines. China's National Health Commission (NHC) has investigated several drugs that have the potential to treat SARS-CoV-2 infection, including interferon-alpha (IFN-α), lopinavir/ritonavir (LPV/r), ribavirin (RBV), chloroquine phosphate (CLQ/r), CQ), remdesvir and umifenovir (arbidol).[3] Thromboembolic prophylaxis with subcutaneous low molecular weight heparin (LMWH) is recommended for all hospitalized patients with COVID-19.[4] Wang's study showed the mean neutrophil to lymphocyte ratio (NLR) and d-dimer levels in COVID-19 patients were 5.99 and 1.96, while the patients who went home in good health and died were 8.46 + 0.83 vs 16.16 + 3.15 and 1.25 + 0.29 vs 3.19 + 1.27. This change appeared to be statistically significant ($p<0.05$).[4] NLR is an independent risk factor for severe disease. An increase in the severity of COVID-19 disease was seen in 75.8% of patients during hospitalization having an NLR >2,973.

The increase in cases of COVID-19 is increasingly unstoppable. The best way to reduce the number of COVID-19 cases is to prevent uninfected people and maximize COVID-19 testing for COVID-19 patients. In COVID-19 patients, there were significant changes in laboratory results compared to non-COVID-19 patients, such as an increase in NLR, procalcitonin, and D-dimer and a decrease in the PF ratio. This parameter can speed up the detection of COVID-19 patients.

Several recent studies have shown the effectiveness of using LMWH in COVID-19 patients for thromboprophylaxis, besides that it also has benefits in improving abnormal laboratory results of COVID-19 patients. This research has the potential to be an effective treatment for COVID-19 and can increase the effectiveness of treatment and reduce complications for COVID-19 patients, where currently no definitive therapy has been found. Therefore, researchers are interested in raising the relationship between the use of LMWH d-dimer thromboprophylaxis and the PF ratio in COVID-19 patients.

II. METHODS

This study is a retrospective cohort study to prove the relationship between LMWH thromboprophylaxis with PF ratio and D-dimer levels in COVID-19 patients. We conducted this research at the Medical Record Installation and negative pressure isolation room at Haji Adam Malik General Hospital (RSUP HAM) from December 2020 to July 2021. The study population was all patients with confirmed COVID-19 by RT-PCR examination. The medical records taken are medical records from March 2021 to June 2021.

We took research subjects with consecutive sampling techniques until the number of research subjects was met. The inclusion criteria in this study were patients aged 18 years, positive results on the COVID-19 RT-PCR examination, the case group receiving anticoagulants for 7 days, and study subjects who did not receive anticoagulants and antiplatelet therapy before being confirmed positive for COVID-19 by RT-PCR. While the exclusion criteria for this study were incomplete medical records, research subjects who had received LMWH, anticoagulant, and antiplatelet therapy before being confirmed positive for COVID-19 by RT-PCR, and study subjects undergoing thrombolytic therapy or percutaneous coronary intervention (PCI). The drop-out criteria in this study was a change in anticoagulant thromboprophylaxis therapy during the follow-up period.

Based on the calculation of the sample size, the largest number of research subjects was 17 in each group, namely the group given LMWH and the group given other anticoagulants such as UFH so that the total research subjects amounted to 34 samples. After obtaining approval from the Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara, and the Ethics Committee of the Haji Adam Malik General Hospital Medan, research samples were taken from medical records at Haji Adam Malik General Hospital Medan. The study population that met the inclusion and exclusion criteria, and was divided into 2 groups, namely the LMWH (+) and non-LMWH groups. Recording of identity as gender, age, and comorbid diseases of research subjects. Collecting and recording laboratory data consisting of AGDA results and D-dimer levels before the intervention, 5 and 7 days after the intervention. From the AGDA results, we obtained data regarding PaO2, while we calculated FiO2 depending on the type of oxygen supplementation obtained and the oxygen flow given. The FiO2 for NIV for both continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BPAP) is 21-100%.

For research permission, approval was obtained from the research subject and the Ethics Committee of the Faculty of Medicine, University of North Sumatra, and the Ethics Committee of the Haji Adam Malik General Hospital Medan which will conduct an assessment of the feasibility of the research proposal. We carried data analysis out using a computer program, namely SPSS (Statistical Package for Social Science). We arranged demographic data in a frequency distribution table. Inferential data analysis to test the hypothesis using the Paired t-test. We consider the data significant if the p-value <0.05.

III. RESULTS

The characteristics of the research subjects are shown as frequency, average with standard deviation, and homogeneity test is performed which is shown in Table 1. The results of the homogeneity test showed that the characteristics of the research subjects based on age, gender, and type of oxygen therapy showed that p> 0.05 which means that the research subjects were homogeneous.

Table 1. Distribution of research subject characteristics

Characteristics	LMWH (+)	Non LMWH	p
Age (years)	59,24 ± 13,89	40,29 ± 14,64	0,891[a]
Gender (n, %)			
Male	9 (52,9%)	11 (64,7%)	0,486[b]

Female	8 (47,1%)	6 (35,3%)	
Oxygen Therapy(n, %)			
Nasal canule	3 (17,6%)	6 (35,3%)	0,220[b]
Rebreathing mask	3 (17,6%)	6 (35,3%)	
Non-rebreathing mask (NRM)	6 (35,3%)	4 (23,5%)	
High flow nasal cannula (HFNC)	2 (11,8%)	1 (5,9%)	
Non-invasive ventilation (NIV)	3 (17,6%)	0 (0%)	

[a] Independent T-test [b] Chi-square test

Based on Table 1, the mean age of the study subjects in the LMWH (+) group was older than the non-LMWH group (59.24 ± 13.89 vs. 40.29 ± 14.4 years). The majority of research subjects in both groups were male with a greater proportion found in the non-LMWH group (52.9% vs. 64.7%), while the proportion of female study subjects was greater in the LMWH (+) group (47.1% vs. 35.3%). The results showed that we found the proportion of nasal cannula used to be greater in the non-LMWH group than the LMWH (+) group (35.3% vs 17.6%). We can also find the same proportion of trend in using rebreathing masks.

A total of 6 people (35.3%) research subjects received a non-rebreathing mask (NRM) in the LMWH (+) group, while only 4 people used NRM in the non-LMWH group. Research subjects in the LMWH (+) group used more High Flow Nasal Cannula (HFNC) and non-invasive ventilation (NIV) compared to the non-LMWH group, where 2 people (11.8%) in the LMWH (+) group and 1 person (5.9%) used HFNC and only 3 people (17.6%) used NIV in the LMWH (+) group and none of the study subjects in the non-LMWH group used NIV. Associated with the relationship between the use of LMWH thromboprophylaxis on the PF ratio, the normality test of the PF ratio between groups showed a p-value > 0.05 so the data were normally distributed, so the statistical test used was the PAIRED T-test to compare the PF ratio before and after LMWH administration.

Table 2. Comparison of PF ratio between groups.

PF ratio (mmHg)	*Baseline*	Day-5	Day-7
LMWH (+)	239,04 ± 111,57	299 ± 114,51	346,59 ± 101,11
Non LMWH	306,43 ± 81,94	348,63 ± 85,81	390,22 ± 79,68

The PF ratio was obtained from the results of the division of PaO2 and FiO2 obtained from the AGDA results. The baseline PF ratio in the LMWH (+) group was higher than in the non-LMWH group (239.04 ± 111.57 vs. 306.43 ± 81.94 mmHg). On day 5 there was an increase in the PF ratio and also increased again on day 7, where a higher PF ratio was found in the LMWH (+) group.

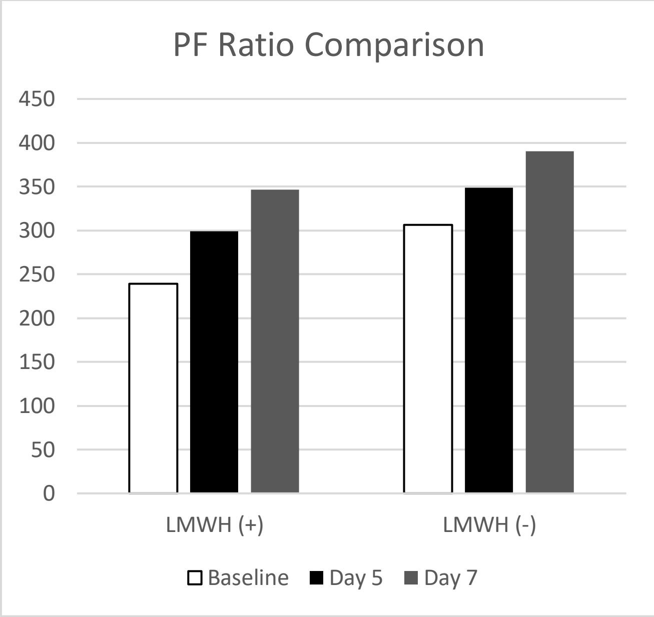

Figure 1. Comparison graph of PF ratio between groups.

Based on Figure 1, there were differences in the PF ratio before and after the intervention on day 5 and 7, where the PF ratio increased from baseline and continued to increase until day 7. In table 3, it shows that the LMWH (+) group has levels of higher baseline D-dimer than the non-LMWH group (2,537.94 ± 1,939.33 vs. 1,236 ± 741.92). The level of d-dimer after thromboprophylaxis decreased until day 7 (1,099 ± 877.94 vs 499.41 ± 205 ng/ml) with a greater difference in the decrease in the LMWH (+) group. We found significant differences in the levels of d-dimer before and after thromboprophylaxis in the two groups (p = 0.016; 0.034).

Table 3. The relationship between LMWH administration on the PF ratio on the fifth day.

PF ratio (mmHg)	*Baseline*	Day-5	Sig (2tailed)	P-value
LMWH (+)	239,04 ± 111,57	299 ± 114,51	0.000	0.000

*Tpaired

Based on statistical analysis using the T-paired test, the study showed that there was a significant relationship (p = 0.000) from the use of LMWH on increasing the PF ratio on the fifth day.

Table 4. The relationship between LMWH administration on the PF ratio on the seventh day.

PF ratio (mmHg)	*Baseline*	Day-7	Sig (2tailed)	P-value
LMWH (+)	239,04 ± 111,57	346,59 ± 101,11	0.000	0.000

*Tpaired

Based on statistical analysis using the T-paired test, the study showed that there was a significant relationship (p = 0.000) from the use of LMWH on the increase in PF ratio on the seventh day from the average value of 239.04 increased to

ISSN No:-2456-2165

346.59 after administering LMWH anticoagulant prophylaxis for seven days.

Table 5. The relationship of non-LMWH administration on the PF ratio on the fifth day.

PF ratio (mmHg)	*Baseline*	Day-5	Sig (2tailed)	P-value
non LMWH	306,43 ± 81,94	348,63 ± 85,81	0.000	0.000

*Tpaired

Based on statistical analysis using the T-paired test, the study showed that there was a significant relationship (p = 0.00) from the use of non-LMWH also had an effect on increasing the PF ratio on the fifth day.

Table 6. The relationship of non-LMWH administration on the PF ratio on the seventh day.

PF ratio (mmHg)	*Baseline*	Day-7	Sig (2tailed)	P-value
Non LMWH	306,43 ± 81,94	390,22 ± 79,68	0.000	0.000

*Tpaired

Based on statistical analysis using the T-paired test, the study showed that there was a significant relationship (p = 0.00) from the use of non-LMWH on the increase in the PF ratio on the seventh day from the average value of 306.43 increased to 390,22 after the administration of non-LMWH anticoagulant prophylaxis. for seven days. Table 7 shows that the LMWH (+) group had higher baseline D-dimer levels than the non-LMWH group (2,537.94 ± 1,939.33 vs. 1,236 ± 741.92). The level of d-dimer after thromboprophylaxis decreased until Day-7 (1,099 ± 877.94 vs 499.41 ± 205 ng/ml) with a greater difference in decrease found in the LMWH (+) group.

Table 7. Comparison of D-dimer levels between groups.

D-dimer (ng/ml)	*Baseline*	Day-5	Day-7
LMWH (+)	2.537,94 ± 1.939,33	1.692,94 ± 1.172,8	1.099 ± 877,94
Non LMWH	1.236 ± 741,92	904,12 ± 376,22	499,41 ± 204,99

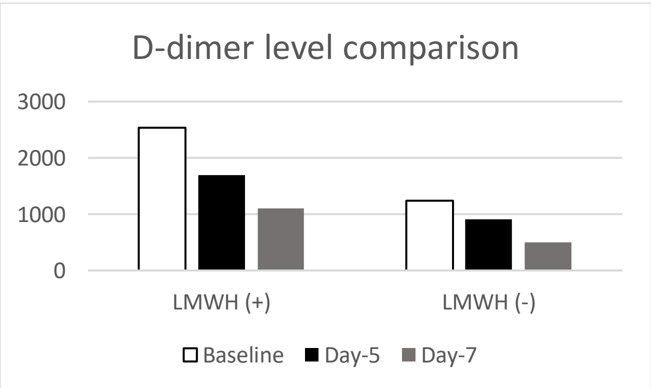

Figure 2. Comparison graph of D-dimer levels between groups.

Based on Figure 2, it was found that the D-dimer level experienced a greater decrease after LMWH thromboprophylaxis was given than the non-LMWH group.

Table 8. The relationship between LMWH administration on the value of D-Dimer on the fifth day.

PF ratio (mmHg)	*Baseline*	Day-5	Sig (2tailed)	P-value
LMWH (+)	2.537,94 ± 1.939,33	1.692,94 ± 1.172,8	0.001	0.000

*Tpaired

Based on statistical analysis using the T-paired test, the study showed that there was a significant relationship (p = 0.000) from the use of LMWH on the decrease in D-Dimer values on the fifth day.

Table 9. The relationship between LMWH administration on the value of D-Dimer on the seventh day.

PF ratio (mmHg)	*Baseline*	Day-7	Sig (2tailed)	P-value
LMWH (+)	2.537,94 ± 1.939,33	1.099 ± 877,94	0.000	0.000

*Tpaired

Based on statistical analysis using the T-paired test, the study showed that there was a significant relationship (p = 0.000) from the use of LMWH on the decrease in the value of D-Dimer on the seventh day from the average value of 2,537.94 decreased to 1,099 after administration of LMWH anticoagulant prophylaxis for seven days.

Table 10. The relationship of non-LMWH administration on the value of D-Dimer on the fifth day.

PF ratio (mmHg)	*Baseline*	Day-5	Sig (2tailed)	P-value
Non LMWH	1.236 ± 741,92	904,12 ± 376,22	0.003	0.000

*Tpaired

Based on statistical analysis using the T-paired test, the study showed that there was a significant relationship (p = 0.00) also from the use of non-LMWH on the decrease in D-Dimer values on the fifth day.

Table 11. Relationship of non-LMWH administration on the value of D-Dimer on the seventh day.

PF ratio (mmHg)	*Baseline*	Day-7	Sig (2tailed)	P-value
Non LMWH	1.236 ± 741,92	499,41 ± 204,99	0.000	0.059

*Tpaired

Based on statistical analysis using the T-paired test, the study showed that there was no significant relationship from the use of non-LMWH on the decrease in D-Dimer values on the seventh day (p=0.059). In table 12, based on the length of stay, it turns out that the LMWH (+) group had a longer average length of stay than the non-LMWH (14.08 ± 1.44 vs. 13.81 ± 0.91). Based on statistical analysis using the independent T-test, the study showed that there was no significant relationship between the use of LMWH and non-LMWH (p=0.548) on length of stay..

Table 12 Comparison of length of stay between groups and the relationship between anticoagulant administration and length of stay

Group	Length of stay	P-value
LMWH (+)	14,08 ± 1,44	0.548
Non LMWH	13,81 ± 0,91	

*T-test independent

In table 13, based on the mortality rate, it turns out that the LMWH (+) group who died had a higher mortality rate than the non-LMWH group, namely 5 people (29.4%) and 1 person (16.7%) who died. Based on statistical analysis using Fisher's exact test, the study showed that there was no significant relationship between the use of LMWH and non-LMWH (p = 0.175) on the mortality rate.

Table 13. Comparison of mortality rates between groups and the relationship between anticoagulation and mortality rates.

Group	Alive	Dead	Total	p-value
LMWH(+)	12 (70,6%)	5 (29,4%)	17	
Non LMWH	16 (94,1%)	1 (5,9%)	17	0,175
Total	28 (82,4%)	6 (17,6%)	34	

*Fisher exact test

IV. DISCUSSION

The results showed that the research subjects in the LMWH (+) group had an older mean age than non-LMWH (59.24 ± 13.89 vs. 40.29 ± 14.4 years) and most of the study subjects in both groups were male. Similar results can also be found in the study of Stabile et al which showed that study subjects who received a therapeutic dose of LMWH had an older mean age than the group that did not receive a therapeutic dose (69.4 ± 11.9 vs. 69.2 ± 9.5 years). In addition, men in the group receiving the therapeutic dose of LMWH dominated the proportion of study subjects (69.5% vs. 65.9%).[5] Shi et al. study also showed the same results, where study subjects who received LMWH had an age range of wider range, namely from the age of 42 years to 91 years with the majority of patients being male (62%).[6]

Based on the use of oxygen therapy, 35.3% of study subjects used NRM in the LMWH (+) group, while the largest proportion was found in the use of nasal cannula and rebreathing masks in the non-LMWH group. The use of HFNC and NIV breathing apparatus was also more common in the LMWH (+) group. Sadeghipour's study also showed that the group of study subjects who received LMWH had the highest proportion of NRM use (33.6%) followed by NIV (29.7%) and intubation with ETT (20.3%).[7]

The ratio of arterial partial pressure of oxygen (PaO2) to inspired partial pressure of oxygen (FiO2) or current PF ratio was used to assess the severity of respiratory failure in patients with ARDS and correlated with mortality. We have recently proposed the PF ratio to be used as a prognostic parameter in COVID-19 patients.[8] The results of this study showed that there was a significant difference in the PF ratio before and after the intervention in the two groups (p = 0.022 and 0.018) with a trend of increasing PF ratio on the day of the intervention. 5th and 7th post-administration.[9] The results of the study Negri et al, reported that the PF ratio increased significantly after 72 hours after starting anticoagulation from 254 ± 90 to 325 ± 80 mmHg (p = 0.013), and 92% of patients were discharged with an old median hospitalization for 11 days and there were no bleeding complications or fatal events.[10]

In addition, the results of Lemos et al. study also showed that there was a significant increase in the PF ratio of enoxaparin administration from baseline to day 14 of administration (p=0.0004). The results also reported that patients receiving enoxaparin had a higher weaning success rate from mechanical ventilation (hazard ratio/HR 4.0; p = 0.031) and had a longer ventilator-free period (median 15 days; p = 0.028) compared to the control group.[11] Gu et al. study stated that the PF ratio was an independent predictor of death in COVID-19 with an odds ratio (OR) of 0.974.[12]

COVID-19-associated hypoxia can cause vasoconstriction and low blood flow that contribute to endothelial injury. Hypoxia can also shift the basic antithrombotic and anti-inflammatory phenotype of the endothelium to a procoagulant and proinflammatory phenotype. Endothelial injury triggers the release of Ultra-large von Willebrand factor (ULVWF) which acts as a bridge between endothelial injury and platelet activation and triggers platelet aggregation and initiation of thrombogenesis in the microvasculature, which can lead to microthrombus formation. Primary viral infection causes alveolar injury and significant production of proinflammatory cytokines in COVID-19 patients. Activation and recruitment of mononuclear cells and neutrophils lead to increased damage to lung tissue and vascular endothelium. Hypoxia, endothelial injury, and a sustained inflammatory response increase the procoagulant state that can lead to pulmonary vascular micro thrombosis, triggering an increase in the PF ratio and the development of ARDS and respiratory failure.[11]

In this condition, the administration of LMWH is proven to provide significant perfusion in the alveoli, inhibiting oxidative stress, inflammation, apoptosis, and increasing antioxidant activity, resulting in an improvement in pathological conditions through the HIF-1α signaling mechanism, where one effect is increasing oxygenation (PF ratio).[12] However, several studies have assessed that there is a lack of the PF ratio, namely it does not consider the level of respiratory muscle effort and hyperventilation of patients with hypoxemia and does not discriminate against patients according to hypocapnia.[13]

A significant difference in D-dimer levels was also found after LMWH administration, where there was a decrease in D-dimer levels until day 7 (p = 0.016). The results of Lemos et al. study also showed that there was a significant decrease in D-dimer after enoxaparin administration (4,176 g/L to 1,469 g/L; p = 0.009).[11] Yu et al reported that a decrease in D-dimer levels in COVID-19 patients 19 shows a good prognosis.[14] The D-dimer reflects the presence of fibrin clot formation, cross-linking of blood clots by factor XIIIa and fibrinolysis. The significant increase in D-dimer in COVID-19 reflects pulmonary vascular bed thrombosis, fibrinolysis, viremia-induced coagulation activation, and cytokine storm, but superinfection and organ disruption may also be likely causes. Cut-off levels of D-dimer >1 g/ml indicate a high risk of poor prognosis. Elevated levels of D-dimer indicate the severity of COVID-19 infection and can be used as a prognostic predictor in critically ill cases.[15]

V. CONCLUSION

In this study, it was found that there was a significant relationship in the use of LMWH thromboprophylaxis to an increase in the PF ratio in COVID-19 patients (p=0.022), as well as a significant relationship in the use of LMWH thromboprophylaxis to the decrease in d-dimer levels in COVID-19 patients (p=0.016). Based on these results, we can consider LMWH as thromboprophylaxis in mild-moderate COVID-19 patients, thereby reducing mortality and length of hospital stay. Further research needs to be done with a longer observation time and a larger number of research subjects.

REFERENCES

[1]. Gennaro FD, Pizzol D, Marotta C, et al. Coronavirus disease (COVID-19) current status and future perspectives: a narrative review. Int. J. Environ. Res. Public Health 2020; 17: 2690.

[2]. Guo YR, Cao QD, Hong ZS, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status. Military Medical Research (2020) 7:11

[3]. Susilo A, Rumende M, Pitoyo CW, et al. Coronavirus Disease 2019: Review of Current Literatures. Jurnal Penyakit Dalam Indonesia. 2020; 7(1): 1-23.

[4]. Wiersinga WJ, Rhodes A, Cheng AC, et al. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19) A Review. JAMA. 2020;324(8):782-793.

[5]. Wang J, Yu H, Hua Q, et al. A descriptive study of random forest algorithm for predicting COVID-19 patient's outcome. PeerJ. 2020; 8: e9945.

[6]. Negri EM, Piloto BM, Morinaga LK. Heparin therapy improving hypoxia in COVID-19 patients – a case series. Front Physiol. 2020; 11: 573044.

[7]. Willim HA, Hardigaloeh AT, Supit AI, et al. Koagulopati pada coronavirus disease-2019 (COVID-19): tinjauan pustaka. Intisari Sains Medis. 2020; 11(3): 749-756.

[8]. Shi C, Wang C, Wang HX, et al. The potential of low molecular weight heparin to mitigate cytokine storm in severe COVID-19 patients: a retrospective cohort study. Clin Transl Sci. 2020; 13(6): 1087-1095.

[9]. Sadheghipour P, Bikdeli B. 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. JAMA. 2021; 325(16): 1620-1630.

[10]. Prediletto I, Antoni LD, Carbonara P, et al. Standardizing PaO2 for PaCO2 in P/F ratio predicts in-hospital mortality in acute respiratory failure due to Covid-19: a pilot prospective study. European Journal of Internal Medicine. 2021; 21; 1-7.

[11]. Lemos ACB, Santo DADE, Salvetti MC, et al. Therapeutic versus prophylactic anticoagulation for severe COVID-19: a randomized phase II clinical trial (HESACOVID). Thrombosis Research. 2020; 196: 359-366.

[12]. Gu YL, Wang DH, Chen C, et al. PaO_2/FiO_2 and IL-6 are risk factors of mortality for intensive care COVID-19 patients. Scientific Reports. 2021;11: 7334.

[13]. Zinellu A, Vito AD, Scano V, et al. The PaO_2/FiO_2 ratio on admission is independently associated with prolonged hospitalization in COVID-19 patients. The Journal of Infection in Developing Countries. 2021; 15(3): 353-359.

[14]. Yu B, Li X, Chen J, et al. Evaluation of variation in D-dimer levels among COVID-19 and bacterial pneumonia: a retrospective analysis. J Thromb Thrombolysis. 2020; 50(3): 548-557.

[15]. Wool GD, Miller JL. The impact of COVID-19 disease on platelets and coagulation. Pathobiology. 2021; 88: 15-27.