RESEARCH ARTICLE

# Increased hs-CRP and Sepsis Influence the Occurrence of Thrombocytopenia in Severe and Critically Ill COVID-19 Patients Receiving Anticoagulants

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## Abstract

**BACKGROUND:** Despites its benefits, as one of COVID-19 principal treatments, anticoagulant raises a significant concern regarding the anticoagulant-related thrombocytopenia. However, up to date, there is lack of study examining anticoagulant-induced thrombocytopenia during COVID-19, hence this study was conducted to determine the factors inducing anticoagulant-induced thrombocytopenia in COVID-19 patients.

**METHODS:** An observational cross-sectional study of 106 anticoagulant-treated COVID-19 subjects was conducted. Blood serum was drawn from subjects, then platelets, prothrombin time (PT), activated partial thromboplastin (aPPT), international ratio (INR), D-dimer, ferritin, fibrinogen, and high-sensitivity C-reactive protein (hs-CRP), were measured. For thrombocytopenia risk assessment, the 4T score was calculated. To assess the risk of thrombocytopenia. Statistical analysis using Chi-square and Mann-Whitney U test were performed and followed by multivariate analysis to examine the correlation among the thrombocytopenia risk factors.

**RESULTS:** Significant differences were identified in the length of stay (LOS) ($p$=0.04), disease severity ($p$=0.021), sepsis ($p$=0.006), hs-CRP ($p$=0.003), and mortality rate ($p$=0.028) between thrombocytopenia and non-thrombocytopenia groups. A multivariate analysis through linear and logistic regression disclosed an increase in hs-CRP (OR=-0.29; $p$=0.045) and sepsis (OR=4.32; $p$=0.03) that precipitate the thrombocytopenia events.

**CONCLUSION:** In severe and critically ill COVID-19 patients, the occurrence of thrombocytopenia was followed by an increase in inflammatory parameters such as D-dimer, fibrinogen, ferritin, hs-CRP and prolonged coagulation. The increase in hs-CRP and sepsis may raise the risk of thrombocytopenia, especially in severe and crtically ill cases of COVID-19.

**KEYWORDS:** COVID-19, anticoagulant, thrombocytopenia, inflammation, infectious disease

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## Introduction

Coronavirus Disease-19 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV2) has initiated big health issues around the world.(1-3) The clinical manifestations of COVID-19 disease are differs, but the severe cases especially need thorough attention since patients rarely came with symptoms in the early days of infection, hence it his harder to be distinguished.(1)

Cytokines play a role in the pathogenesis of viral sepsis in COVID-19. *In vitro* observations showed that infected cells had slow secretion of cytokines and chemokines in the early phase of COVID-19 infection. Furthermore, pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α will get more abundant during critical phase.(1,4-6)

Hypoxia in patients with moderate to severe COVID-19 triggers endothelial dysfunction and hypercoagulation. Pro-inflammatory cytokines provide a stimulus for platelet production, activation, and aggregation. IL-6 and TNF-α elevate platelet aggregation by increasing tissue factor expression and decreasing tissue plasminogen activity so that fibrinolysis is diminished. Complement component in the form of membrane attack complex (MAC) initiates cell lysis that contributes to coagulopathy that leads to microthrombus and formation of von Willebrand factor (VWF).(7-12)

Numerous results of studies examining COVID-19 hypercoagulation recommend anticoagulation for therapy. Clinical observations of COVID-19 patients disclosed an increase in D-dimer and other coagulation markers on days 7-14 of treatment. Therefore, the Anticoagulation Forum (ACF) and the American College of Chest Physicians (ACCP) release several recommendations that suggest the use of anticoagulants to reduce mortality in COVID-19 patients.(13-15)

One of the hematological manifestations of COVID-19 is thrombocytopenia, a marker of inflammation or a predictor of mortality. COVID-19 patients with elevated D-dimers present ongoing inflammation which leads to poor outcomes. The hypercoagulable condition due to COVID-19 requires anticoagulation.(3) However, thrombocytopenia itself is statistically more common in severe COVID-19 patients with high mortality.(16,17) The incidence of thrombocytopenia per se is also influenced by the use of anticoagulants. One of the commonly used anticoagulants is heparin.(18) In hospitalized patients, heparin-induced thrombocytopenia (HIT) occurs to approximately 0.5-1% for unfractionated heparin (UFH) and 0.1-0.5% for low molecular weight heparin (LMWH). This event can occur in 5-14 days with an increased risk of hemorrhage.(19,20) In Indonesia, there is lack of study examining anticoagulant-induced thrombocytopenia during COVID-19 pandemic and the factors influencing it remains unknown. Therefore, this study was conducted to determine the incidence of thrombocytopenia in COVID-19 patients after receiving anticoagulant therapy and its association with coagulation and inflammatory markers.

## Methods

### Study Design and Subjects Recruitment

This was a cross-sectional study involving moderate to critically ill COVID-19 subjects that were hospitalized in the isolation room at RSUD Dr. Soetomo, Surabaya, between January and September 2021. The diagnosis and criteria of severity of COVID-19 was made referring to the guidelines of World Health Organization (WHO) and the Indonesian Ministry of Health. Clinical characteristics of COVID-19 were divided according to the severity of the disease, namely severe (severe and critcally ill cases) and non-severe (moderate cases). The subject was confirmed for COVID-19 after positive oropharyngeal swab results.(21) Thrombocytopenia was characterized by a decline of platelet count to <150,000/μL.(22) Inclusion criteria of subjects were as follows: high risk of thromboembolism with respiratory rate >24 times per min, <90% decreased oxygen saturation, elevated C-reactive protein (CRP), rising D-dimer and fibrinogen; and low risk of thromboembolism with D-dimer result of >0.5 μg/mL. Subjects who had abnormal baseline platelet count, oncohematologic disease, severe COVID-19 with thrombopenia at initial diagnosis, previously received anticoagulant therapy and chemotherapy were excluded from the study. This study was approved by the Ethical Committee of Dr. Soetomo General/Teaching Hospital Surabaya (No. 0572/LOE/301.4.2/IX/2021).

### Laboratory Assessment

Prothrombin time (PT), activated partial thromboplastin (aPPT), international ratio (INR), D-dimer, ferritin, fibrinogen, and high-sensitivity CRP (hs-CRP), were measured. PT, aPTT, and fibrinogen were examined by Sysmex 2500i (Sysmex Corporation, Kobe, Japan) with photo-optical method; D-dimer was examined by Sysmex 2500i (Sysmex Corporation) with latex enhanced turbidimetric test; platelets were examined using Sysmex XN-1000 Hematology Analyzer (Sysmex Corporation); ferritin was examined using Completed Assay SNIBE Immunology (Snibe Diagnostic, Shenzhen, China) with the chemiluminescent (CLIA) method; and hs-CRP was examined using Completed Assay SNIBE Immunology (Snibe Diagnostic) with photometry method. Meanwhile for INR calculation was based on the formula: $INR = PT_{test}/PT_{normal}$, with $PT_{test}$ was obtained from the PT examination of study subject and $PT_{normal}$ was the geometric mean of the PT of a reference sample group as calculated by Sysmex 2500i (Sysmex Corporation).

For thrombocytopenia risk assessment, the 4T score, which included platelet count, timing of anticoagulant, incidence of thrombosis, and exclusion of other causes of thrombocytopenia, was counted.(22,23) Thrombocytopenia event during 5-14 days after anticoagulant treatment was then evaluated. Data were collected by consecutive sampling on eligible subjects. Meanwhile, for the demographic data of subjects, including gender, age, type of anticoagulant therapy given, duration of anticoagulant therapy, hospital length of stay, as well as the comorbidities were obtained from subjects' medical record.

**Statistical Analysis**

Statistical analysis was performed using SPSS version 24.0 software (IBM Corporation, Armonk, NY, USA). Statistical significance was assessed by means of Chi-square for dichotomous variables, or by means of the two independent sample using the Mann-Whitney U test for continuous variable depending on whether the data are normally distributed or not. Multivariate analysis was also performed to determine the correlation among factors causing anticoagulant-induced thrombocytopenia in COVID-19 subjects. A $p$-value<0.05 was considered as significant.

## Results

**Subjects Characteristics based on Thrombocytopenia Event**

Total of 128 confirmed COVID-19 subjects were recruited, however only 106 subjects were given anticoagulant therapy since the other 22 subjects were excluded for having D-dimer <500 µg/dL. In accordance with the criteria for using anticoagulant, the types of anticoagulants given to patients were unfractionated heparin (heparin), low molecular weight heparin (fondaparinux and enoxaparin), and direct oral anticoagulant (rivaroxaban). More than half of the subjects received heparin therapy (55.66%), and the others received fondaparinux (23.58%), enoxaparin (16.04%), and rivaroxaban (4.72%) (Figure 1). Among eligible subjects, only 20 thrombocytopenia events were recorded.

The characteristics of subjects were then grouped according to the incidence of thrombocytopenia (Table 1). There was no significant difference of age and the duration of anticoagulant therapy treatment between subjects with thrombocytopenia and subjects without thrombocytopenia event. However, there was a significant difference in the length of stay (LOS) between the two groups ($p$=0.040), and longer duration was found in thrombocytopenia group. There was also a significant difference in the severity of COVID-19 disease between thrombocytopenia and non-thrombocytopenia groups ($p$=0.021) and 4T score ($p$=0.000). In the thrombocytopenia group, 85% of the subjects were characterized into severe and critically ill. There was also no significant difference in anticoagulant therapy used for the thrombocytopenia and non-thrombocytopenia subjects.

In thrombocytopenia group, the most frequent comorbid were diabetes mellitus (DM), sepsis, and hypertension (50%, 40%, and 35%, respectively). Meanwhile for the non-thrombocytopenia group, the most frequent comorbid were hypertension, DM, and liver diseases (57%, 49%, and 30%, respectively). Although other comorbidities showed no significant difference between the two groups, but there was a significant difference of sepsis $p$=0.006), since septic subjects tended to experience thrombocytopenia (40%). There was also significant difference of mortality cases between thrombocytopenia and non- thrombocytopenia group ($p$=0.028).

**Subjects Characteristics based on Bleeding Event**

Beside analysis based on the incidence of thrombocytopenia, an analysis based on the bleeding event was also performed (Table 2). A total of 16 subjects experienced bleeding, in which 13 cases of bleeding occurred in severe cases of COVID-19 (severe and critically ill) after the administration of anticoagulants. There was no significant difference of age and LOS between subjects with bleeding occurrence and subjects without bleeding occurrence. There was significant difference in the duration of anticoagulant administration between the two groups ($p$=0.013), even though there was no significant difference between the types of anticoagulants. The results also showed that no significant difference was found for the severity of COVID-19 in the two groups.

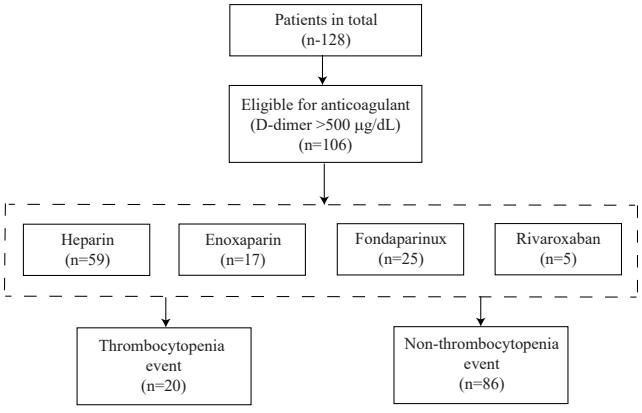


**Figure 1. Subjects' classification based on the anticoagulant given and the thrombocytopenia event.**

**Table 1. The characteristics of subjects based on the incidence of thrombocytopenia.**

| Characteristics | Thrombocytopenia Event (n=20) | Non-thrombocytopenia Event (n=86) | *p*-value |
|---|---|---|---|
| Gender, n (%) | | | |
| Male | 8 (40%) | 34 (40%) | - |
| Female | 12 (60%) | 52 (60%) | |
| Age (years old), mean±SD | 57.00±14.62 | 54.67±11.87 | 0.450 |
| Duration for anticoagulant (days), median (min-max) | 10 (2-22) | 8 (3-23) | 0.740 |
| Length of stay (LOS) (days), median (min-max) | 20.5 (8-6) | 17 (3-55) | 0.040# |
| Severity COVID-19, n (%) | | | |
| Severe and critically ill | 17 (85%) | 48 (56%) | 0.021* |
| Non-severe | 3 (15%) | 38 (44%) | |
| Anticoagulant, n (%) | | | |
| Heparin | 10 (50%) | 59 (69%) | 0.218 |
| Fondaparinux | 4 (20%) | 21 (24%) | |
| Enoxaparin | 6 (30%) | 11 (13%) | |
| Rivaroxaban | 0 (0%) | 5 (6%) | |
| 4T score, median (min-max) | 5 (4-7) | 2 (2-5) | 0.000 |
| Comorbidities, n (%) | | | |
| DM | 10 (50%) | 42 (49%) | 0.930 |
| Obesity | 0 (0%) | 5 (6%) | 0.180 |
| Hypertension | 7 (35%) | 49 (57%) | 0.076 |
| Renal diseases | 5 (25%) | 13 (15%) | 0.325 |
| Heart diseases | 4 (20%) | 11 (13%) | 0.476 |
| Liver diseases | 4 (20%) | 26 (30%) | 0.422 |
| HIV | 2 (10%) | 1 (1%) | 0.092 |
| Sepsis | 8 (40%) | 10 (12%) | 0.006* |
| Laboratory parameters after anticoagulant therapy, median (min-max) | | | |
| D-dimer (µg/L) | 1330 (540-15340) | 1750 (160-35200) | 0.364 |
| Platelet (/µL) | 205 (152-406) | 238 (151-737) | 0.123 |
| PT (s) | 12.6 (9.8-14.3) | 13.0 (9.6-31.8) | 0.253 |
| aPPT (s) | 29.9 (23.4-33.1) | 27.8 (19.5-47.7) | 0.488 |
| INR (ratio) | 0.9 (0.9-1.1) | 0.9 (0.8-5.0) | 0.786 |
| Fibrinogen (mg/dL) | 614.9 (117.0-832.0) | 502.0 (190.7-3980.0) | 0.980 |
| Ferritin (mg/dL) | 2016.0 (582.3-5508.8) | 1215.6 (53.9-4000) | 0.066 |
| hs-CRP (mg/dL) | 15.1 (3.3-28.4) | 5.6 (0.1-33.02) | 0.003# |
| Death, n (%) | 5 (25%) | 16 (19%) | 0.028* |

*Significant if *p*-value<0.05, tested with from Chi-Square; #Significant if *p*-value<0.05, tested with Man-Whitney U test.

In subjects with bleeding occurrence, the most frequent comorbidities were DM (50%) and followed by hypertension and sepsis (each 43.8%). While in non-bleeding group, the most frequent comorbidities were hypertension (54.4%) and DM (48.9%). There were significant differences for obesity and sepsis in bleeding and non-bleeding groups ($p$=0.019, $p$=0.006, respectively). After the anticoagulant administration, subjects that having bleeding event showing more sepsis cases (43.8%) compared to non-bleeding subjects (12.22%). Mortality rate between two groups also shown to be differ significantly, with higher rate of mortality in subjects with bleeding event (37.5% *vs*. 16.7%; $p$=0.029).

### Cut-off Point Prediction for Thrombocytopenia

The laboratory examination after the therapy showed that D-dimer, platelets, and PT of the thrombocytopenia group were lower than the non-thrombocytopenia group, while aPPT, INR, fibrinogen, ferritin and hs-CRP were shown to be higher. Even so, no significant difference was found beside hs-CRP level ($p$=0.003), which showed that the

**Table 2. The characteristics of subjects based on the incidence of bleeding after using anticoagulant therapy.**

| Characteristics | Bleeding Event (n=16) | Non-bleeding Event (n=90) | *p*-value |
|---|---|---|---|
| Gender, n (%) | | | |
| Male | 6 (37.5%) | 36 (40%) | - |
| Female | 10 (62.5%) | 54 (60%) | |
| Age (years old), mean±SD | 56.14±10.65 | 53.48±11.59 | 0.557 |
| Duration for anticoagulant (days), median (min-max) | 4 (2-12) | 8 (3-23) | 0.013# |
| Length of stay (LOS) (days), median (min-max) | 20 (7-69) | 16 (6-43) | 0.429 |
| Severity COVID-19, n (%) | | | |
| Severe and critically ill | 13 (81.3%) | 52 (57.8%) | 0.134 |
| Non-severe | 3 (18.8%) | 38 (42.2%) | |
| Anticoagulant, n (%) | | | |
| Heparin | 10 (62.5%) | 49 (54.4%) | 0.558 |
| Fondaparinux | 3 (18.8%) | 21 (24.4%) | |
| Enoxaparin | 3 (18.8%) | 14 (15.6%) | |
| Rivaroxaban | 0 (0%) | 5 (5.6%) | |
| Comorbidities, n (%) | | | |
| DM | 8 (50%) | 44 (48.9%) | 1.000 |
| Obesity | 0 (0%) | 5 (5.6%) | 0.019* |
| Hypertension | 7 (43.8%) | 49 (54.454.4%) | 0.605 |
| Renal diseases | 5 (31.3%) | 13 (14.4%) | 0.142 |
| Heart diseases | 1 (6.3%) | 14 (15.6%) | 0.552 |
| Liver diseases | 4 (25%) | 26 (28.9%) | 1.000 |
| HIV | 2 (12.5%) | 1 (1.10%) | 0.060 |
| Sepsis | 7 (43.8%) | 11 (12.2%) | 0.006* |
| Laboratory parameters after anticoagulant therapy, median (min-max) | | | |
| D-dimer (µg/L) | 1050 (540-3330) | 1300 (190-9810) | 0.517 |
| Platelet (/µL) | 282 (152-514) | 225 (151-737) | 0.591 |
| PT (s) | 13.1 (9.8-14.8) | 12.6 (9.6-31.8) | 0.594 |
| aPPT (s) | 31.6 (25.3-33.3) | 26.3 (19.5-47.7) | 0.168 |
| INR (ratio) | 0.9 (0.9-2.4) | 0.9 (0.8-5.0) | 0.676 |
| Fibrinogen (mg/dL) | 502.0 (190.7-844.9) | 590.4 (117.0-3980.0) | 0.379 |
| Ferritin (mg/dL) | 1605.0 (1102.0-4000.0) | 1215.6 (53.9-5508.0) | 0.160 |
| hs-CRP (mg/dL) | 8.6 (0.1-17.9) | 7.3 (0.1-33.2) | 0.475 |
| Death, n (%) | 6 (37.5%) | 15 (16.7%) | 0.029* |

*Significant if *p*-value<0.05, tested with from Chi-Square; #Significant if *p*-value<0.05, tested with Man-Whitney U test.

hs-CRP was significantly higher in the thrombocytopenia group (15.1 mg/dL *vs.* 5.6 mg/dL) (Table 1). Meanwhile for the analysis based on the bleeding event, no laboratory parameters showed significant difference between the bleeding group and non-bleeding group (Table 2).

Based on the result of this study, as much as 23% of severe and critically ill subjects experienced thrombocytopenia after 5-14 days of anticoagulant treatment. Hence, the cut-off value of anticoagulation parameters in COVID-19 subjects needed to be considered. Moreover, in severe and critically ill cases, anticoagulation alone was not able to prevent the progression of inflammation that occurs in COVID-19 cases. The cut-off value of laboratory parameters was obtained to predict the incidence of thrombocytopenia and beleeding event, especially for current the study population. A cut-off value of D-dimer = 1350 µg/L, which mean that D-dimer level higher than that could initiate the thrombocytopenia and bleeding event in COVID-19 subjects. Meanwhile the cut-off value for platelets = 208.5 /µL, PT = 12.3 s, aPPT = 29.75 s, INR = 0.96, fibrinogen = 608.95 mg/dL, ferritin = 1810.5 mg/dL, and hs-CRP = 11.65 mg/dL (Table 3).

In addition, a multivariate analysis through linear and logistic regression was performed for parameters that showed significant results in the bivariate analysis. The results showed significant increases in hs-CRP (OR=-0.29; *p*=0.045) and sepsis (OR=4.32; *p*=0.03) that might cause the occurrence of thrombocytopenia in severe and critically ill COVID-19 subjects receiving anticoagulants (Table 4).

## Discussion

COVID-19 has been known to cause hypercoagulopathy through various pathomechanisms. Therefore, the guidelines for the management of COVID-19 patients recommend the use of anticoagulant, including heparin. The use of heparin as thrombophylaxis or therapy is often performed during the treatment of COVID-19 patients. As the immune system also plays the main role in COVID-19 treatment, a concern on the anticoagulant-induced thrombocytopenia or HIT has been raised.(24) Thrombocytopenia due to anticoagulant itself is caused by the initiation of the formation of immunogloblin G (IgG) against the platelet factor (PF4)-heparin complex. This complex will activate platelets, endothelial cells, monocytes, and pro-coagulant substances. When HIT occurred, antibody attaches to the PF4-heparin complex, and it also binds to the FcγRIIa receptor which then secretes the thrombus-causing particles. Thrombin is produced regarding the platelet consumption due to clearance in spleen or the platelet-fibrin thrombin complex. Fondaparinux also has a mechanism that can induce IgG PF4 in causing thrombopenia.(20,24,25)

According to its pathogenesis, the coronavirus itself is capable of infecting bone marrow cells causing impaired hematopoiesis. Coronavirus enters bone marrow cells and platelets via the cluster of differentiation (CD)-13 receptor, stimulates growth inhibition and bone marrow apoptosis leading to ineffective hematopoiesis and thrombocytopenia. Additionally, it is assumed that COVID-19 patients who experience cytokine storms have impaired hematopoietic progenitor cells, thereby reducing the production of platelets and other blood cells.(4)

HIT usually occurs after an exposure to heparin for 5-14 days. This condition varies, depending on the clinical setting and the type of heparin, either UFH or LMWH. Adult patients receiving heparin therapy for medical indications are more susceptible to developing thrombocytopenia than the pediatric population. A meta-analysis study shows that the incidence of thrombocytopenia in UFH was 1.5% *vs.* LMWH 1.2%.(22) The prevalence of anticoagulant-induced thrombocytopenia, UFH, reached around 22 per 1000 cases, while with LMWH, it was only 5 per 1000 cases.(20) Meanwhile, the role of DOAC has not yet been studied.(22) Literature review of several articles report the incidence of heparin induced thrombocytopenia (HIT) in COVID-19. A study finds that out of 6 patients treated with UFH, 3 patients experienced HIT (50%). On the other hand, another study reports 5 case series of COVID-19 patients from 439 patients followed in a cohort. From 25 days of observations there were around 12% of patients experiencing HIT, while its incidence in non-covid cases was only about 3%.(26) In our study, 20 of 106 patients given anticoagulant experienced thrombocytopenia.

Because of the high risk of thrombosis in COVID-19 cases, heparin prophylaxis is recommended for hospitalized COVID-19 patients. HIT usually occurs about 5-14 days after heparin exposure. Platelet in patients with HIT counted around 50,000-70,000/uL. Patients with HIT rarely develop severe thrombocytopenia unless severe thrombosis or consumptive coagulopathy is present. The 4T score helps in screening for HIT in patients experiencing thrombocytopenia. 4T score <=3 can reliably exclude the likelihood of HIT.(27) In our study, the median value

**Table 3. Cut-off point prediction thrombocytopenia event from laboratory parameters.**

| Laboratory Results | Cut-off | Thrombocytopenia Event | | Bleeding Event | |
|---|---|---|---|---|---|
| | | Sensitivity | Specificity | Sensitivity | Specificity |
| D-dimer (µg/L) | 1350 | 66.7% | 75.0% | 40.0% | 53.3% |
| Platelet (/µL) | 208.5 | 33.3% | 33.3% | 66.7% | 31.5% |
| Prothrombin time (s) | 12.3 | 66.7% | 50.0% | 80.0% | 53.3% |
| aPTT (s) | 29.75 | 50.0% | 50.0% | 40.0% | 46.7% |
| INR | 0.96 | 50.0% | 50.0% | 40.0% | 40.0% |
| Fibrinogen (mg/dL) | 608.9 | 66.7% | 75.0% | 20.0% | 53.8% |
| Ferritin (mg/dL) | 1810.5 | 66.7% | 75.0% | 60.0% | 66.7% |
| hs-CRP (mg/dL) | 11.65 | 66.7% | 75.0% | 40.0% | 53.3% |

**Table 4. Multivariate analysis factor and laboratorial parameter that induced thrombocytopenia event.**

| Parameters | *p*-value Bivariate | Odds Ratio (OR) | 95% CI | *p*-value Multivariate |
|---|---|---|---|---|
| Hypertension | 0.187* | 0.45 | (0.12-1.65) | 0.230 |
| Sepsis | 0.027* | 4.32 | (1.15-16.21) | 0.030[#] |
| **Parameters** | ***p*-value Bivariate** | **Odds Ratio (OR)** | **Std. Error** | ***p*-value Multivariate** |
| Fibrinogen (mg/dL) | 0.142* | 0.16 | 94.38 | 0.273 |
| hs-CRP (mg/dL) | 0.011* | -0.29 | 2776.57 | 0.045[$] |

*If *p*-value<0.25, parameter was included in the multivariate analysis with regression log and regression linear; [#]Significant if *p*-value<0.05, tested with regression log analysis; [$]Significant if *p*-value<0.05, tested with regression linear analysis.

of pre-heparin thrombocytopenia was 164,000 while the post-heparin thrombocyte was 86,000. Compared to other groups, HIT occurred more frequently in the UFH group, although statistically insignificant.

A study evaluating 180 days of death in COVID-19 patients reveals that the length of stay of patients with low platelets is shorter than them in non-thrombocytopenia. The study population involved 167 patients, most of them were in severe and critically ill category. Decreased platelet count is somehow closely linked to poor respiratory function and oxygenation index. Consequently, 86.6% of deaths in this population occurred during 90 days.(16)

A cohort study assessing LMWH and UFH exposure in COVID-19 patients found no difference in mortality between the two groups ($p$=0.6571). Besides, there was no difference in mortality in patients receiving prophylactic doses and heparin therapy.(24) However, COVID-19 patients who developed thrombocytopenia had a significantly high mortality, not only at day 28 but also day 90 and 180.(16)

Our study disclosed higher mortality and length of stay in thrombocytopenia patients. It is consistent with the literature explaining that platelets interact with viral pathogens via receptors which recognize microbial antigens, protease-activated receptor 4 (PAR4), and glycoprotein IIIa (GPIIIa). All of them induce platelet activation, inflammation, lung damage and death.(16)

The elevation of inflammatory markers is discovered in severe and critically ill COVID-19 patients. It is usually recognized by increased CRP, IL-6, procalcitonin and ferritin. Despite the viral-related sepsis, high levels of procalcitonin are equivalent to five times the risk of severe COVID-19. High levels of CRP were also associated with acute respiratory distress syndrome (ARDS), cardiac injury, and death ($p$=0.042).(28) On the other hand, patients with thrombocytopenia are very likely to develop septic shock which also results in death.(16) The results of this study indicate that several inflammatory parameters such as D-dimer, PT, fibrinogen, ferritin, and incidence of sepsis support the event of thrombocytopenia and mortality outcomes.

The data collected in this study were obtained from secondary sources which is patients' medical record, and including only a few numbers of severe and critically ill COVID-19 patients with thrombocytopenia. In this study, the only inflammatory markers evaluated was hs-CRP, therefore it is necessary to examine other parameters as well. However, hopefully this study will upraise the ideas for supplementary research focusing on the correlation of inflammatory markers with anticoagulant-induced thrombocytopenia in COVID-19 patients. Further study to examine and create a score for initiating anticoagulants and the risk of thrombocytopenia and bleeding events is important to be conducted.

## Conclusion

In severe and critically ill COVID-19 patients, the occurrence of thrombocytopenia is followed by an increase in inflammatory parameters such as D-dimer, fibrinogen, ferritin, hs-CRP and prolonged coagulation. Increased hs-CRP and sepsis might be the factors that influence the thrombocytopenia in severe and critically ill COVID-19 patients receiving anticoagulants.

## Authors Contribution

AAP and SUYB were involved in planning and supervising the work, MS, PNAA and MN performed the measurements,

PZR, CW and KNW processed the experimental data, performed the analysis, drafted the manuscript and designed the figure. CW and KNW performed the calculations and statistical analysis. AAP and SUYB aided in interpreting the results and worked on the manuscript. All authors discussed the results and commented on the manuscript.

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