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# Association of abnormal coagulation parameters with adverse clinical outcomes among patients with moderate to severe SARS-CoV-2 infection

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**ABSTRACT**

**Introduction**: This study aimed to determine the association between thrombophilia and adverse clinical outcomes among hospitalized patients with moderate to severe COVID-19 in a tertiary COVID-19 referral hospital.

**Materials and Methods**: This is a cross-sectional study among adult patients hospitalized with moderate to severe COVID-19. Demographic, clinical characteristics, laboratory parameters, and clinical outcomes (in-hospital mortality, disease progression, thrombosis, and composite outcomes) were obtained. Multiple logistics regression was used to determine the association between abnormal coagulation parameters and the development of adverse outcomes.

**Results:** The most frequent coagulation abnormalities were elevated D-dimer (79.3%), abnormal platelet count (35.5%), and

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Email Address: gtzamora@up.edu.ph
Date received: October 23, 2024
Date revised: October 23, 2024
Date accepted: January 26, 2025
DOI: https://doi.org/10.54645/2025181TXV-14

**KEYWORDS**

thrombophilia, antiphospholipid, COVID-19, thrombosis, Philippines

low fibrinogen (100%). A total of 81 (36.2%) participants developed the primary composite outcome (in-hospital mortality, disease progression, thrombosis, disseminated intravascular coagulation, or shock). 11 patients developed venous thrombosis, and eight patients had arterial thrombosis. The most common coagulation abnormality among those with thrombosis was an elevated D-dimer (89.5%) at >500 ug/L. Elevated D-dimer was associated with a 12.05-times increased risk of any composite outcome ($p$ = 0.002). Leukocytosis was associated with 3.47-times increased odds of any composite outcome (p<0.001), 3.55-times increased odds of thrombosis (p=0.029), and 8.21-times increased odds of in-hospital mortality (p<0.001). Abnormal platelet count was associated with 2.61-times increased odds of in-hospital mortality (p=0.033).

**Conclusions:** There was a significant association between abnormal platelet count, elevated D-dimer level, leukocytosis, and positive ACL IgM with adverse clinical outcomes. This suggests the utility of these coagulation parameters in monitoring patients with severe COVID-19.

## INTRODUCTION

The coronavirus disease 2019 (COVID-19) has affected millions worldwide and in the Philippines. Recent data showed that the mortality rate in the Philippines was 899 per million population. Several local studies in the Philippines also showed a mortality rate of 15.1% to 18.2% among hospitalized patients with moderate to severe COVID-19 disease (Malundo et al. 2022a; Malundo et al. 2022b; Punzalan et al. 2023). Most of the deaths were observed among patients with severe COVID-19. Among the various presentations of COVID-19 include thrombophilia, with patients developing COVID-associated coagulopathy (CAC), which is associated with high mortality (Gerber and Chaturvedi 2021). Although associated with elevated D-dimer levels, this COVID-19 coagulopathy may be distinct from classic disseminated intravascular coagulation because it is associated with elevated fibrinogen levels, only modest prolongation of prothrombin time and partial thromboplastin time (PTT), and abnormal bleeding is unusual (Helms et al. 2020; Spiezia et al. 2020; Tang et al. 2020b). Lupus anticoagulants are commonly reported in patients with COVID-19 presenting with prolonged partial thromboplastin time (PTT), with rates as high as 91% (Bowles et al. 2020). In addition, thrombocytopenia is not as prominent in COVID-19 as other viral illnesses, such as dengue infection, but lower platelet counts may be associated with more severe disease (Fan et al. 2020; Punzalan et al. 2023).

These coagulation abnormalities seen among patients with COVID-19 may be considered prognostic factors (Liu et al. 2020). COVID-19 patients with coagulation abnormalities had worse survival than those without. The levels of these coagulation parameters may change in patients with varying illness severities. Hence, early assessment and monitoring of coagulation parameters may be used in predicting COVID-19 severity and death and target more aggressive treatments and improve outcomes among these patients (Esmaeel et al. 2022; Teimury et al. 2022). Currently, the screening for antiphospholipid antibody syndrome (APS) includes checking the presence of anticardiolipin IgG and IgM and phospholipid-binding proteins such as B2-glycoprotein IgG and IgM, using solid-phase immunoassays (Linnemann Christina 2019). Lupus anticoagulants were also tested. However, using an anticoagulant such as heparin, currently included in the guidelines for managing moderate to severe COVID-19, may interfere with the results.

This study aimed to determine the association between thrombophilia and adverse clinical outcomes among patients with moderate to severe COVID-19 admitted at the University of the Philippines - Philippine General Hospital (UP-PGH), a tertiary COVID-19 referral hospital in the country, from July 2020 to December 2020. Specifically, the aims were to describe the coagulation and antiphospholipid antibody profile of the patients and determine their association with the adverse clinical outcomes of in-hospital mortality, disease progression, or development of any arterial or venous thrombosis any time during hospitalization, or a composite of these three outcomes.

## MATERIALS AND METHODS

### Study Design and Setting

This cross-sectional study was conducted at the UP-PGH from July 2020 to December 2020. UP-PGH is a tertiary university hospital and a COVID-19 referral center in the National Capital Region (NCR).

### Participants

We recruited and followed hospitalized patients aged 18 years and above, with moderate to severe RT-PCR-positive COVID-19 disease from admission until discharge or death. We excluded patients over 80 years old and those pregnant or with known malignancy or thrombophilia. The patients or their legally authorized representatives signed an informed consent before participating, ensuring the confidentiality and privacy of all collected information. The University of the Philippines Manila Research Ethics Board approved the conduct of the study (UPMREB 2020-353-01). The study followed the National Ethical Guidelines for Research Involving Human Participants 2022.

### Definitions

Thrombophilia or an abnormal coagulation profile was defined using several laboratory parameters, all analyzed in the study to determine its association with clinical outcomes. Abnormal coagulation profile includes INR value of more than 1.5, PTT >1.5 times elevated (compared to mid-normal value) or >45 seconds, fibrinogen level <1.5 g/L, platelet count <150,000/$mm^3$ or more than >450,000/mm3, D-dimer level >500 ug/L, and the presence of antiphospholipid (APL) antibodies: anticardiolipin (aCL) antibody of IgG and/or IgM isotype and antibeta2 glycoprotein I antibody of IgG and/or IgM isotype (Barbhaiya et al. 2023; Cidade et al. 2022; Pagana and Pagana 2014).

To grade the severity, we used the Philippine COVID-19 Living Recommendations. Those presenting with clinical (cough, fever, and tachypnea) and/or radiographic evidence of pneumonia but without respiratory distress or difficulty breathing, respiratory rate <30 breaths/minute, or peripheral oxygen saturation (SpO2) ⩾ 94% on room air were classified to have moderate COVID-19. In addition, it includes symptomatic patients who were not diagnosed with pneumonia but have risk factors for progression, including diabetes mellitus, hypertension, cardiovascular disease, asthma, chronic obstructive pulmonary disease (COPD), and immunocompromising conditions like human immunodeficiency virus (HIV) infection, prolonged steroid use, and active cancer. Individuals with pneumonia with any of the following conditions were classified as having severe COVID-19: respiratory distress signs, SpO2 <94% on room air, respiratory rate ⩾30 breaths per minute, or requirement for oxygen supplementation. Patients with impending respiratory failure requiring high flow oxygen or ventilatory support, ARDS, sepsis, or septic shock, deteriorating sensorium, multi-organ failure, and thrombosis already have critical COVID-19.

**Data Collection**
The following clinical data were gathered: patient demographics and clinical parameters (age, sex, comorbidities, temperature, vital signs) during admission. Blood was drawn upon consent to be included in the study, within three days of admission, for complete blood count, platelet count, lipid profile, albumin, D-dimer, PT and PTT, fibrinogen, and the antiphospholipid panel (anticardiolipin IgM and IgG, and B2 glycoprotein IgM and IgG). No repeat testing was done for all blood tests done in this study. The patients were monitored daily for disease progression or mortality during their whole admission period. All data were stored and managed electronically using the Research Electronic Data Capture (REDCap) application.

**Outcomes**
Patients were monitored for the development of the outcomes while admitted. The primary outcome of the study was a composite of in-hospital mortality, disease progression, or development of thrombosis or overt DIC based on the International Society of Thrombosis and Hemostasis scoring for overt disseminated intravascular coagulation during admission (Iba et al. 2019).

**Statistical analysis**
The sample size requirements were computed to ensure the attainment of all objectives by selecting a large enough sample size to describe the phenomenon of interest sufficiently. The confidence level for all computations was set at 95%. The sample size to determine the proportion of patients with abnormal coagulation profiles and the primary composite outcome were computed based on estimating the proportion formula. Data from related COVID-19 studies were used to estimate the proportion related to each parameter being investigated. The sample size needed to determine the association of abnormal coagulation profiles with the primary composite outcome was computed using the test for two proportions and two means. Adjusting for 10% non-response, the final sample size used in the study was 222.

Descriptive statistics were used to summarize the data collected. Mean and standard deviation were used for quantitative variables, while proportions and frequencies were used for qualitative ones. An independent t-test was done to compare the differences in each clinical and laboratory parameter between those who developed the primary composite outcome versus those who did not develop the primary composite outcome. For categorical variables, the Z-test was used. We compared the coagulation profile of patients with moderate and severe COVID-19 disease using Fisher's exact test. Statistical analyses were performed in STATA. Multiple logistic regressions were used to determine the association between the abnormal coagulation parameters described above and the development of adverse outcomes. An adjustment was done to account for confounding variables particularly age, with diabetes, with heart disease, d dimer (500/1000), WBC, platelet, hemoglobin, use of enoxaparin, presence of any thrombophilia, and antiphospholipid antibodies. Hypothesis testing was done at a 5% significance level (two-tailed). Estimates were reported at a 95% confidence level.

## RESULTS

**Characteristics of the study participants**
A total of 224 patients were included in our study; 162/224 (72%) had severe COVID-19, while 62/224 (28%) had a moderate disease. There were 45/224 (20.2%) patients who died from the disease. The mean age of enrolled patients is 54.54 ± 14.01 (SD) years. Most of the patients were male (140/224, 63%) and had known comorbidities (172/224, 77%), with hypertension (128/224, 57%) and diabetes mellitus (75/224, 34%) being the most common. There were 194 patients who were on prophylactic anticoagulant low-molecular-weight heparin and enoxaparin. Among those given enoxaparin, 55 were on antiplatelets (25 on aspirin, 24 on aspirin and clopidogrel, six on clopidogrel), and three were given other anticoagulants (one each given heparin, warfarin, or apixaban) during their hospitalization. There were 30 patients who did not receive anticoagulants; six were maintained on antiplatelets.

The coagulation profile of the participants classified by COVID-19 severity is shown in **Table 1**. In order of frequency, the specific abnormalities were low fibrinogen (100%), elevated D-dimer >500 ug/L (165/224, 79%), abnormal platelet count (77/224, 36%), and abnormal PT (5/224, 3%) and PTT (6/224, 3%). Notably, fibrinogen levels were only taken in 61 participants, all low (<1.5 g/L). At least one kind of antiphospholipid antibody was seen in 37 patients (17%) while seven patients (3%) had two or more APLs. Anticardiolipin IgM and IgG were more frequent than beta-2 glycoprotein IgM and IgG. There was at least one coagulation abnormality in 196/224 or 88% of our patients, and these abnormalities were similarly present in both moderate and severe cases of COVID-19.

**Table 1:** Distribution of participants by COVID-19 severity and coagulation profile

| | All Patients | Moderate Disease | Severe Disease | p-value |
|---|---|---|---|---|
| INR >1.5 | 5/175 (2.9%) | - | 5/175 (2.9%) | 0.33** |
| Prolonged PTT (>45 seconds) | 6/191 (3.1%) | 2/53 (3.8%) | 4/138 (2.9%) | 0.66** |
| Fibrinogen <1.5g/L | 61/61 (100.0%) | 12/12 (100.0%) | 49/49 (100.0%) | - |
| Platelet <150,000 or >450,000 | 77/217 (35.5%) | 23/59 (39.0%) | 54/158 (34.2%) | 0.51 |
| D-dimer >500 ug/L | 165/208 (79.3%) | 47/61 (77.0%) | 118/147 (80.3%) | 0.60 |
| Presence of at least 1 kind of antiphospholipid antibody, any level (low positive AND positive)* | 37/222 (16.7%) | 9/61 (14.8%) | 28/161 (17.4%) | 0.64 |
| Anticardiolipin IgG<br>10-40 weak positive<br>>40 positive | <br>12/222 (5.4%)<br>2/222 (0.9%) | <br>3/61 (4.9%)<br>- | <br>9/161 (5.6%)<br>2/161 (1.2%) | <br>1.00** |
| Anticardiolipin IgM<br>10-40 weak positive<br>>40 positive | <br>12/222 (5.4%)<br>5/222 (2.2%) | <br>4/61 (6.6%)<br>- | <br>8/161 (5.0%)<br>5/161 (3.1%) | <br>0.44** |
| Beta-2 glycoprotein IgG<br>7-10 weak positive<br>>10 positive | <br>1/222 (0.4%)<br>3/222 (1.4%) | <br>-<br>1/61 (1.6%) | <br>1/161 (0.6%)<br>2/161 (1.2%) | <br>1.00** |

| | | | | |
|---|---|---|---|---|
| Beta-2 glycoprotein IgM<br>7-10 weak positive<br>>10 positive | <br>5/221 (2.3%)<br>4/221 (1.8%) | <br>1/61 (1.6%)<br>- | <br>4/160 (2.5%)<br>4/160 (2.5%) | 0.72** |
| Presence of 2 or more APL, any level (low positive and positive) | 7/222 (3.2%) | - | 7/161 (4.4%) | 0.19** |
| More than 1 of the above abnormalities or thrombophilias (APL at any level) | 122/224 (54.5%) | 32/62 (51.6%) | 90/162 (55.6%) | 0.60 |
| Presence of any thrombophilia | 196/224 (87.5%) | 54/62 (87.1%) | 142/162 (87.6%) | 0.91 |

**Abbreviations**: INR: international normalized ratio; PTT: partial thromboplastin time; IgG: Immunoglobulin G; IgM: Immunoglobulin M; APL: antiphospholipid
*Antiphospholipid antibodies (APL)- anticardiolipin IgM or IgG, beta2 glycoprotein IgM or IgG
**Fisher's exact test

**Patient outcomes**

The most common adverse outcomes were the need for invasive ventilation (59/224, 26%), in-hospital mortality (45/224, 20%), and shock (41/224, 18%). Less than 10% of patients developed thrombosis (11/224), deterioration in kidney function needing renal replacement therapy (9/224), or disseminated intravascular coagulation (DIC) (2/224). **Table 2** shows the distribution of participants by outcomes. There were significantly more patients with severe COVID-19 who died (p=0.006) or developed shock (p=0.039), venous thrombosis (p=0.037), or needed invasive ventilation.

**Table 2:** Distribution of participants by outcomes (N=224)

| Adverse Outcomes | Total | Moderate Disease (n=62) | Severe Disease (n=162) | p-value |
|---|---|---|---|---|
| Shock | 41 (18.3%) | 6 (9.7%) | 35 (21.6%) | 0.04 |
| DIC | 2 (0.9%) | - | 2 (1.2%) | 1.00* |
| Need for invasive ventilation | 59 (26.5%) | 4 (6.4%) | 55 (34.2%) | <0.001* |
| In-hospital mortality | 45 (20%) | 5 (8.1%) | 40 (24.7%) | 0.006* |
| Development of any thrombosis | 19 (8.5%) | 4 (6.4%) | 15 (9.3%) | 0.60* |
| Development of venous thrombosis | 11 (4.5%) | 0 | 11 (6.8%)[a] | 0.04* |
| Need for renal replacement therapy | 9 (4%) | 0 | 9 (5.6%) | 0.07* |
| Development of arterial thrombosis | 8 (3.6%) | 4 (6.4%)[b] | 4 (2.5%)[c] | 0.22* |
| Composite outcome | 81 (36.2%) | 12 (19.4%) | 69 (42.6%) | 0.001 |

**Abbreviation**: DIC: Disseminated intravascular coagulation
[a] all were acute pulmonary embolism
[b] 2 acute ischemic stroke, 1 acute hemorrhagic stroke and 1 acute limb ischemia
[c] 2 acute myocardial infarction, 1 acute ischemic stroke and 1 acute hemorrhagic stroke
*Fisher's exact test

All 11 patients who developed venous thrombosis manifested with acute pulmonary embolism documented via computed tomography pulmonary angiogram. Those who developed arterial thrombosis (n=8) presented with acute ischemic stroke (n=2), acute hemorrhagic stroke (n=1), acute limb ischemia (n=1) in patients categorized as having moderate COVID-19 and acute myocardial infarction (n=2), acute ischemic stroke (n=1) and acute hemorrhagic stroke (n=1) among those with severe COVID-19. Nine patients with thrombosis died (47%). The most common coagulation abnormality among those with thrombosis was an elevated D-dimer; 17/19 patients (90%) had D-dimer >500 ug/L, and 5 of them with values more than 5000 ug/L.

A total of 81 (36%) participants developed the primary composite outcome (in-hospital mortality, disease progression, thrombosis, DIC, or shock), which was significantly more frequent among those with severe COVID-19. Their clinical profile was generally like those who did not develop the primary composite outcome. However, those who developed the composite outcome had significantly lower hemoglobin ($p$ = 0.03) and platelet count ($p$ <0.0001), and higher WBC count ($p$ <0.0001), prothrombin time ($p$ = 0.0055), D-dimer ($p$ <0.0001), and proportion with positive anticardiolipin IgG ($p$ = 0.043) and with any thrombophilia ($p$ = 0.003). **Table 3** summarizes the comparison between the two groups regarding clinical and laboratory profiles.

**Table 3:** Comparison of clinical and laboratory profiles between those with and without the primary composite outcome

| | Without primary composite outcome (n=143) | With primary composite outcome (n=81) | p-value |
|---|---|---|---|
| ***Clinical Profile*** | | | |
| Mean age (±SD) | 54.00 (±14.16) | 55.50 (±13.79) | 0.44 |
| Male sex | 89 (62.2%) | 51 (63.0%) | 0.91 |
| With comorbidities | 108 (75.5%) | 64 (79.0%) | 0.55 |
| Diabetes | 45 (31.5%) | 30 (37.0%) | 0.46 |
| Hypertension | 83 (58.0%) | 45 (55.6%) | 0.78 |
| Heart disease | 17 (11.9%) | 11 (13.6%) | 0.83 |
| Chronic Liver Disease | 1 (0.7%) | 1 (1.2%) | 1.00* |
| CKD | 12 (8.4%) | 11 (13.6%) | 0.22 |
| COPD | 1 (0.7%) | 1 (1.2%) | 1.00* |
| Asthma | 12 (8.4%) | 6 (7.4%) | 0.80 |
| Active tuberculosis | 4 (2.8%) | 1 (1.2%) | 0.66* |

| | | | |
|---|---|---|---|
| HIV | - | - | - |
| Cancer | 1 (0.7%) | - | 1.00* |
| Neurologic disease | 6 (4.2%) | 3 (3.7%) | 1.00* |
| Others | 24 (16.8%) | 18 (22.2%) | 0.32 |
| ***Laboratory Profile*** | | | |
| Hemoglobin (±SD) | 125.56 (±23.50) | 117.74 (±28.67) | 0.03 |
| WBC (±SD) | 9.45 (±4.04) | 14.72 (±9.12) | <0.0001 |
| Platelet (±SD) | 357.40 (±154.82) | 251.36 (±157.30) | <0.0001 |
| INR (±SD) | 1.08 (±0.12) | 1.17 (±0.26) | 0.006 |
| PT result (±SD) | 13.67 (±1.54) | 14.71 (±3.34) | 0.006 |
| PT INR > 1.5 | - | 5 (6.2%) | 0.006** |
| Prolonged PTT | 30.43 (±4.95) | 32.59 (±14.08) | 0.13 |
| PTT > 45 secs | 2 (1.4%) | 4 (4.9%) | 0.19* |
| Fibrinogen (±SD) | 567.58 (±202.52) | 522.43 (±198.77) | 0.41 |
| Fibrinogen < 1.5 | 40 (28.0%) | 21 (25.9%) | 0.74 |
| D-dimer (±SD) | 1.89 (±2.87) | 5.60 (±6.02) | <0.0001 |
| D-Dimer > 500 | 93 (65.0%) | 72 (88.9%) | <0.0001 |
| Anti-cardiolipin IgM | 9 (6.3%) | 5 (6.2%) | 0.97 |
| Anti-cardiolipin IgG | 7 (4.9%) | 10 (12.4%) | 0.04 |
| Beta2 glycoprotein IgM | 2 (1.4%) | 2 (2.5%) | 0.56 |
| Beta2 glycoprotein IgG | 5 (3.5%) | 4 (4.9%) | 0.598 |
| Any one of antiphospholipids | 21 (14.9%) | 16 (19.8%) | 0.35 |
| Presence of any thrombophilia | 118 (82.5%) | 78 (96.3%) | 0.003 |

**Abbreviations**: CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disorder; HIV: human immunodeficiency virus; PT: prothrombin time; PTT: partial thromboplastin; INR: international normalized ratio; IgG: Immunoglobulin G; IgM: Immunoglobulin M
*Fisher's exact test

**Factors associated with adverse clinical outcomes**

**Table 4** shows the results of multiple logistic regression analysis. After adjusting for confounding variables, our study showed that an elevated D-dimer (>500µg/L) was associated with 12.05-times increased odds of any composite outcome (95% CI: 2.46, 59.09, $p$ = 0.002). Moreover, leukocytosis was associated with 3.47-times increased odds of any composite outcome (95% CI: 1.77, 6.81; p < 0.001), 3.55-times increased odds of any thrombosis (95% CI: 1.14, 11.10; p = 0.03), and 8.21-times increased odds of in-hospital mortality (95% CI: 3.24, 20.80; p < 0.001). Lastly, thrombocytopenia (<150) or thrombocytosis (>450) was associated with 2.61-times increased odds of in-hospital mortality (95% CI: 1.08, 6.32; p = 0.03).

## DISCUSSION

Our study was conducted in a tertiary government COVID-19 referral center in the Philippines, with most patients with severe disease. The mortality rate was 20%, comparable to other studies in published local literature (Malundo et al. 2022a; Malundo et al. 2022b; Punzalan et al. 2023; Salamat et al. 2021). This study found elevated D-dimer, low fibrinogen, abnormal platelet count, and prolonged PTT among COVID-19 patients. These findings were similar to several local and international reports (Len et al. 2022; Punzalan et al. 2023; Salamat et al. 2021) on coagulation abnormalities among patients with severe COVID. These coagulation abnormalities may be related to impaired hematopoiesis (Wang et al. 2021), endothelial dysfunction leading to the accumulation of coagulation factors (Otifi and Adiga 2022), and the pro-inflammatory and hypercoagulable state (Fara et al. 2020) observed in COVID-19. This study was the first to determine the presence of antiphospholipid antibodies (APLs) among patients with moderate to severe COVID-19 in the Philippines. It also demonstrated a significant association between positive ACL IgM and thrombosis. APLs abnormally target phospholipid proteins and may arise transiently in patients with critical illness and various infections and lead to a hypercoagulable state (Uthman and Gharavi 2002). We observed a frequency of 37 (21%) patients with at least one APL antibody; this is lower compared to the pooled prevalence of 47% (n = 1,159) by Taha et al. (Taha and Samavati 2021). In the latter study, hospitalized patients with COVID-19 had testing for APLs and found the lupus anticoagulant (LACs) most frequent (pooled prevalence of 51%). In contrast, our study could not check for LACs since most patients were immediately started on an anticoagulant on admission.

This was part of the institution's COVID-19 protocol for patients with moderate-severe COVID-19 disease since lower mortality rates had been reported in patients who received prophylactic anticoagulation (Tang et al. 2020a). This benefit was attributed not only to the prevention of venous thromboembolism (VTE) and resolution of pulmonary microthromboses (Luo et al. 2020) but also to the anti-inflammatory properties of heparin potentially leading to a decrease in lung inflammation and fibrosis (Poterucha et al. 2017). Among our study participants, 194 (87%) patients were started on anticoagulants on admission; however, 8% still developed thrombosis, including venous (5%) and arterial (4%) thrombosis. These values are lower compared to the meta-analysis of Jimenez et al. (Jiménez et al. 2021), with a pooled sample of 18,093 patients, which showed a 17%, 12%, and 7% estimated pooled incidence of VTE, deep venous thrombosis (DVT), and pulmonary embolism (PE), respectively, among hospitalized patients with COVID-19.

All 11 patients in our study participants who developed venous thrombosis manifested with acute pulmonary embolism, akin to a review (Klok et al. 2020) of 184 patients with COVID-19 receiving at least standard doses of thromboprophylaxis which showed VTE in 27% with the most commonly seen thrombotic complication being pulmonary embolism (81%). A hypercoagulable state develops during the acute (pneumonia) phase of COVID-19 when T- and B-cells decrease while inflammatory cytokines and D-dimer levels increase (Li et al. 2020; Lin et al. 2020). Hypercoagulability may be due to the virus activating the coagulation cascade through various mechanisms or may be part of disseminated intravascular coagulation (DIC). Neutrophil extracellular traps (NETs) may also account for the interrelationship between inflammation and thrombosis (Yang et al. 2017).

**Table 4:** Risk Factors for Composite Outcomes, Any Thrombosis, and In-hospital Mortality, by Multiple Logistic Analysis.

| VARIABLE | COMPOSITE OUTCOME | | | ANY THROMBOSIS | | | IN-HOSPITAL MORTALITY | | |
|---|---|---|---|---|---|---|---|---|---|
| | aOR | 95% CI | p-value | aOR | 95% CI | p-value | aOR | 95% CI | p-value |
| Age >55 | 1.05 | 0.53, 2.10 | 0.89 | 1.49 | 0.48, 4.63 | 0.49 | 0.69 | 0.28, 1.66 | 0.41 |
| Diabetes | 1.11 | 0.53, 2.35 | 0.78 | 2.61 | 0.79, 8.60 | 0.11 | 2.24 | 0.88, 5.72 | 0.09 |
| Heart disease | 1.17 | 0.43, 3.15 | 0.76 | 1.94 | 0.44, 8.45 | 0.38 | 1.73 | 0.50, 5.89 | 0.38 |
| D-Dimer >500 ug/L | 12.05 | 2.46, 59.09 | 0.002* | 2.92 | 0.34, 25.37 | 0.33 | - | - | - |
| WBC | 3.47 | 1.77, 6.81 | <0.001* | 3.55 | 1.14, 11.10 | 0.03* | 8.21 | 3.24, 20.80 | <0.001* |
| Platelet <150 or >450 | 2.15 | 1.07, 4.32 | 0.03* | 1.20 | 0.39, 3.71 | 0.75 | 2.61 | 1.08, 6.32 | 0.03* |
| Hemoglobin | 0.78 | 0.38, 1.58 | 0.48 | 0.39 | 0.12, 1.22 | 0.11 | 1.03 | 0.42, 2.55 | 0.95 |
| Use of anticoagulant (enoxaparin) | 2.22 | 0.77, 6.43 | 0.14 | 0.63 | 0.13, 2.98 | 0.56 | 2.80 | 0.61, 12.71 | 0.18 |
| Presence of any thrombophilia | | | | | | | | | |
| Anti-cardiolipin IgM | 1.03 | 0.25, 4.23 | 0.96 | 0.43 | 0.02, 7.37 | 0.56 | 0.15 | 0.01, 2.21 | 0.17 |
| Anti-cardiolipin IgG | 2.00 | 0.57, 7.10 | 0.28 | 3.25 | 0.72, 14.75 | 0.13 | 0.96 | 0.21, 4.32 | 0.96 |
| Beta2 glycoprotein IgM | 1.47 | 0.13, 16.26 | 0.75 | 5.73 | 0.26, 128.64 | 0.27 | 3.31 | 0.15, 70.88 | 0.44 |
| Beta2 glycoprotein IgG | 1.63 | 0.30, 8.90 | 0.57 | 0.86 | 0.07, 10.63 | 0.90 | 1.62 | 0.21, 12.27 | 0.64a |

**Abbreviations**: aOR: adjusted odds ratio; CI: confidence interval; WBC: white blood cells; IgG: Immunoglobulin G; IgM: Immunoglobulin M
*significant association

Patients who developed VTE in the study of Cui et al. (Cui et al. 2020) had older age, longer PTT, and high D-dimer levels. In Cui's study, a cut-off value of 1600 ug/L for D-dimer was predictive of VTE with a sensitivity and specificity of 85.0% and 88.5%, respectively. In our study, 89% of those who developed thrombosis had a D-dimer level >500 ug/L. However, multivariate analysis did not show a significant association between D-dimer >500 ug/L and thrombosis.

We found a significant association between anticardiolipin IgM and thrombosis and between thrombosis and in-hospital mortality. Arterial thrombosis, 3 (1%) of which were acute ischemic stroke, was seen in 8 of our patients, concordant with the 1.2% pooled incidence seen in the systematic review of 135 patients by Ying-Kiat et al. (Tan et al. 2020). This study had a mortality rate and reported the presence of APLs: anticardiolipin IgM at 20% (2/10), B2GP IgM at 10% (1/10), and IgG at 38.5% (5/13). Burn et al. (Burn et al. 2022) likewise reported that thrombosis was associated with excess mortality in their European cohort, emphasizing the importance of reducing thrombosis occurrence.

Approximately 36% of our study participants developed the primary composite outcome (in-hospital mortality, disease progression, thrombosis, or DIC), reflecting severe disease in the most studied population. Our study reported that abnormal platelet levels were associated with 2.61-times increased odds of in-hospital mortality. Abnormal platelet count was significantly associated with the need for invasive ventilation and mortality. These findings are similar to those of Yuan et al. (Yuan et al. 2022), whose multicenter retrospective study of 2209 patients showed 127 (5.7%) with thrombocytopenia, and these patients showed a significantly higher rate of respiratory failure (41.9% vs. controls at 22.6%, p=0.020), and all-cause mortality (hazard ratio 3.08 (2.26-4.18), p<0.001). In addition to these outcomes, Yuan's cohorts showed increased ICU admission and DIC frequency.

This study observed that an elevated D-dimer (>500µg/L) was associated with 12.05-times increased odds of any composite outcome (in-hospital mortality, disease progression, or development of thrombosis or overt DIC during admission). This result agreed with numerous previous studies that showed an elevated D-dimer on admission correlated with disease severity and effectively predicted in-hospital mortality in patients with COVID-19 (Li et al. 2021; Poudel et al. 2021; Yao et al. 2020; Zhang et al. 2020). Different cut-offs were used in previous studies for elevated D-dimer, ranging from >500µg/L to >2000µg/L. The sensitivity and specificity of D-dimer for predicting in-hospital mortality increased with higher cut-off values. A previous study with a cut-off value of >500µg/L reported sensitivity of 88.2% and specificity of 71.3% (Yao et al. 2020). On the other hand, another study with a cut-off value of 2000 µg/L recorded a sensitivity of 92.3% and a specificity of 83.3% (Zhang et al. 2020). Elevated D-dimer is the most frequently reported laboratory parameter abnormalities in patients with COVID-19 coagulopathy (Asakura and Ogawa 2021). D-dimer is produced in the blood from degradation of stabilized fibrin polymer by plasmin. Previous studies showed that elevated D-dimer levels are associated with coagulopathy severity (Asakura and Ogawa 2021; Lehmann et al. 2021; Nemec et al. 2022).

Our study also showed that leukocytosis was associated with 3.47-times increased odds of any composite outcome, 3.55-times increased odds of any thrombosis, and 8.21-times increased odds of in-hospital mortality. Our results agreed with a previous study conducted in the Philippines that showed that WBC $>10\times10^9$/L is a predictor of mortality among COVID-19 patients (Malundo et al. 2022b). Several studies in other countries also demonstrated that elevated WBC is an independent predictor of mortality, particularly increased neutrophil count (Keski 2021; Lalani et al. 2022; Zhao et al. 2020). COVID-19 patients with higher WBC and neutrophil count had significantly shorter survival than those with normal WBC levels (Keski 2021). WBC ≥12.0 g/L was associated with an increased odds of pulmonary embolism (PE) (OR 21.4 [4.0-397.9], $p = .004$). This previous study also reported that D-dimer and WBC levels were more accurate than Wells' score in predicting the diagnosis of PE (Galland et al. 2021). Leukocytes express tissue factor and produce proinflammatory and procoagulant molecules that can promote thrombus formation. Activation of leukocytes can induce platelet activation and adhesion, activation of the intrinsic and extrinsic coagulation pathways (Swystun and Liaw 2016). Emigration of leukocytes promote endothelial damage that also contribute to venous thrombosis (Stewart et al. 1974). These processes promote increased systemic thrombogenicity (Swystun and Liaw 2016). This may explain the increased risk of thrombosis among COVID-19 patients with elevated WBC levels.

This study had several limitations. Lupus anticoagulants were not tested due to the immediate initiation of anticoagulants among hospitalized patients with moderate to severe COVID-19 in our institution, without contraindications. Non-clinically evident thrombosis may have been missed because imaging procedures were only done for patients who were symptomatic and with a high index of suspicion for thrombosis. Only one measurement of APLs was done, and we could not determine if the antibodies were transient or persistent. Not all patients were tested for complete coagulation parameters since some, e.g., fibrinogen, was not part of the institution's COVID protocol and was subject to the attending physician's discretion.

## CONCLUSIONS

This study showed a high prevalence of abnormal coagulation profiles among hospitalized patients with moderate to severe COVID-19 disease. The most frequent were low fibrinogen, elevated D-dimer, and abnormal platelet count. We demonstrated the association of abnormal platelet count, elevated D-dimer, elevated leukocytes, and anticardiolipin IgM with adverse clinical outcomes, including thrombosis and in-hospital mortality. Our findings suggest that thrombophilia present on admission may predict the development of adverse clinical outcomes. Among the antiphospholipid antibodies, the presence of anticardiolipin IgM on admission may predict the development of thrombosis. These identified clinical profiles and laboratory parameters can be used to identify patients who will need more intensive monitoring and treatment for complications of COVID-19 disease. The findings of this study can also guide clinicians in our setting in optimizing thromboprophylaxis based on individual risk factors, disease severity, and coagulation profiles.

## ACKNOWLEDGMENT

The authors wish to acknowledge the University of the Philippines (UP) Manila COVID-19 Research Initiative, UP-PGH Medical Research Laboratory and the UP National Institutes of Health.

## CONFLICT OF INTEREST

This work was funded by the Department of Science and Technology Philippine Council for Health Research and Development.a

All the authors have nothing to disclose in terms of other financial or non-financial interests related directly or indirectly to the work submitted for publication.

## CONTRIBUTIONS OF INDIVIDUAL AUTHORS

All authors approved the manuscript.

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