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Coagulation and Platelet Profiles of COVID-19 Patients Admitted to a COVID Referral Center from March 2020 to December 2022

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ABSTRACT

Objective. This study aimed to determine the demographic profiles of admitted COVID-19 patients, the association of coagulation and platelet tests on COVID-19 severity and compare the coagulation and platelet profile across the spectrum of the disease in terms of severity among adult COVID-19 patients admitted to the Philippine General Hospital from March 2020 to December 2022.

Methodology. Medical records of a sample of adult COVID-19 patients admitted to the emergency room of the Philippine General Hospital from March 2020 to December 2022 were reviewed. The demographics, initial COVID-19 diagnosis and initial coagulation and platelet test results were gathered and tabulated. Comparison of the initial coagulation and initial platelet results were made per disease category.

Results. Three hundred eighty-five (385) patients were included; 194 were males, and 191 were females. The mean age of all patients was 56.18 years old. There was a total of 30 patients classified as mild and 105 patients are under moderate category. 141 patients were classified as severe, whereas 109 patients were classified as critical. Platelet count test and Activated Partial Thromboplastin Time (APTT) were mostly normal in all disease categories. Prothrombin time was normal in a majority of patients from the mild and severe categories. INR and D-dimer were all elevated mostly in all disease categories.

Conclusion. Platelet counts and APTT were mostly normal in all disease categories. Prothrombin time and D-dimer had a significant association with disease severity. Platelet count, APTT and INR did not show significant association with disease severity. Prothrombin time, APTT, INR and D-dimer means had significant differences versus disease categories.

Key words: coagulation, platelet test, activated partial thromboplastin time, APTT, COVID-19, disease severity

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INTRODUCTION

COVID-19 had been an emerging global pandemic since 2020. According to the World Health Organization (WHO), the pandemic caused over 768 million confirmed cases including more than 6.9 million deaths all over the world.[1] In the Philippines, there were more than 4 million total cases with more than 66 thousand recorded deaths since the pandemic started.[2]

Even if the WHO ended the COVID-19 global pandemic response,[3] it still constantly affected every nation because COVID-19 cases had been detected and some countries had increasing cases. Since COVID-19 cases have been continuously recorded and detected, the burden of the management and prevention of the spread of the disease is still a problem for those countries that are affected.

Coronavirus disease 2019 (COVID-19) was caused by SARS-CoV-2, similarly known as Acute Respiratory Syndrome Coronavirus 2, a novel beta coronavirus.[4] The disease could cause clinical features that vary from mild to fatal illness. The most common symptoms were nonspecific and include fever, cough, myalgia, core throat, headache, chills, nausea, vomiting, diarrhea, ageusia, and conjunctival congestion.[5] Protocols were made for risk stratification and management intervention as well as

isolation and quarantine rules to prevent overwhelming numbers of patients in health facilities and hospitals. Asymptomatic and mild symptoms required home isolation. For those with worse symptoms such as shortness of breath, tachypnea, and any signs of respiratory distress, hospitalization was advised.[6]

COVID-19 posed a global threat because it was not only a respiratory infection but a disease that affected multiple organ systems such as cardiovascular, gastrointestinal, neurological, immune, and hematopoietic systems. It also mostly affects hemostasis.[7] According to Abd El-Lateef AE et al., the most common hematological complication of COVID-19 was coagulopathy. Although the exact pathogenesis of coagulopathy of COVID-19 had not been properly explained, many factors were contributory such as cytokine storm, neutrophil activation, impaired endothelial function, platelet activation, tissue factor expression and coagulation induction.[8] According to Wool et al, the SARS-COV-2 virus did not have an intrinsic procoagulant effect. The coagulopathy could be a byproduct of profound COVID-19 inflammatory response and endothelial activation/change.[9]

The most important biomarkers indicating poor prognosis in COVID-19 patients were coagulopathy and abnormal coagulation parameters. The occurrence of coagulation dysfunction was seen in severe and critically ill patients. There was also an increased occurrence of intravascular disseminated coagulopathy in patients with COVID-19.[4] Arterial and venous thrombotic complications were seen in ICU patients. There was an increased level of D-dimer and fibrinogen degradation products in patients with severe COVID-19 infection than the milder forms. Those patients with severe COVID-19 have also lower platelet counts compared to those with milder disease.[10] Since coagulopathy in patients with critical and fatal disease was common, coagulation parameters should be thoroughly discussed for risk classification and predicting prognosis.[11] Moreover, blood coagulation and platelet profiles should be done for COVID-19 patients for improvement of management and health outcomes.[4] Finally, there have been no studies about coagulation and platelet profiles for COVID-19 patients here in the Philippines to date. This study aims to provide an initial report on the relationship between coagulation and platelet profiles of COVID-19 patients in a COVID-referral center.

METHODOLOGY

The study employed a cross-sectional study design on the initial coagulation and platelet profiles of adult COVID-19 patients. Data sampling was done in this study based on the objectives. To determine the demographic profile of COVID-19 patients, a minimum sample size of 385 patients was computed with respect to sex with an expected proportion of 50% for the sex male, an error of 5% and a significance level of 0.05. A list of all COVID-19 patient case numbers admitted from March 2020 to December 2022 was gathered from the Health Information Management Division from the Medical Records. Random sampling was performed using a pseudo-random number-generating function in Microsoft Excel. Sampling was performed until the set sample size (N=385) was reached.

A list of all admitted COVID-19 patients from March 2020 to December 2022 was requested from the Health Information Management Division of the Medical Records. Random sampling using a random number-generating function from Microsoft Excel was made to select a minimum of 385 patients that were included in the study. Code numbers were assigned by the principal investigator to the records of patients who fulfilled the inclusion criteria. The clinical data was retrieved via the Radish platform while the coagulation and platelet results were reviewed in the OpenMRS platform.

Study population

All patients were 19 years old and above with or without co-morbidities; had been initially seen at the emergency room and subsequently admitted at the Philippine General Hospital; and diagnosed as COVID-19 by RT PCR positive with or without co-morbidities, were included.

Patients who were pregnant, who had missing data, or whose results were not continuous variables (e.g., INR <1, D-dimer >20) were not included in the study.

COVID-19 risk classification

The criteria for risk classification followed Department of Health (DOH) guidelines.[6]

- **Mild COVID-19** was classified as having an acute onset of fever and cough or any three (3) or more of the following: fever, cough, coryza, sore throat, diarrhea, anorexia/nausea/vomiting, loss of sense of smell or taste, general body weakness/malaise/fatigue, myalgia, headache with no pneumonia or desaturation.
- **Moderate COVID-19** is classified as pneumonia* but with no difficulty of breathing or shortness of breath, RR of less than 30 breaths/minute, $Sp0_2$ saturation of >94% at room air, or without pneumonia but with risk factors for progression: elderly (60 years old and above) and/or without co-morbidities.
- **Severe COVID-19** was classified as pneumonia* and any one of the following: signs of respiratory distress, $Sp0_2$ saturation of <94% at room air, respiratory rate of >30 breaths/minute, requiring oxygen supplementation.
- **Critical COVID-19** was as with pneumonia and any of the following: impending respiratory failure requiring high flow oxygen, non-invasive or invasive ventilation, acute respiratory distress syndrome, sepsis or shock, deteriorating sensorium, multi-organ failure, thrombosis.

Note: Pneumonia was diagnosed as evidence of lower respiratory disease during clinical assessment (e.g., cough, fever, plus crackles) and/or imaging such as chest x-ray, ultrasound or CT scan

Data analysis

Data gathered were encoded in Microsoft Excel 2019. Analysis was done using STATA 14.0. Descriptive statistics were employed in describing the socio-demographic and clinical characteristics of the patients. The mean was calculated for all continuous variables and proportions were calculated for all categorical variables. Pearson chi-square test was done to determine the association of the variables. Shapiro Wilk test was employed to test

Table 1. Demographic profile (age and sex) of all samples included in the study

Variable	Mean/Percentages n=385
Age (in years)	56.18
Sex	
Male	194 (50.39%)
Female	191 (49.61%)

Table 2. Demographic and clinical profiles of all samples across disease severity

Variable	Mild (n=30)	Moderate (n=105)	Severe (n=141)	Critical (n=109)
Age (in years)	46.73 ± 2.84	52.42 ± 1.66	57.10 ± 1.39	61.20 ± 1.43
Sex				
Male	(53.33%, 16)	(50.50%, 53)	(54.60%, 77)	(44.00%, 48)
Female	(46.67%, 14)	(49.50%, 52)	(45.40%, 64)	(56.00%, 61)
Co-morbidity				
Without co-morbidity (121, 31.43%)	14 (46.67%)	35 (33.33%)	41 (29.08%)	31 (28.44%)
With co-morbidity (264, 68.57%)	16 (53.33%)	70 (66.67%)	100 (70.92%)	78 (71.56%)
Any	6 (37.5%)	25 (35.71%)	38 (38.00%)	24 (30.77%)
Hypertension and Diabetes	2 (12.5%)	18 (25.71%)	28 (28.00%)	22 (28.21%)
Hypertension only	6 (37.5%)	20 (28.57%)	25 (25.00%)	19 (24.36%)
Diabetes only	1 (6.25%)	2 (2.86%)	7 (7.00%)	10 (12.82%)
Bronchial asthma only	1 (6.25%)	5 (7.14%)	2 (2.00%)	3 (3.85%)

if the data in each variable were normally distributed. If normally distributed, the means of the coagulation and platelet variables were compared across the categories of disease severity using One-way ANOVA. A post hoc test was performed. If the distribution was not normal, Kruskall-Wallis test was employed for comparison across disease severity.

Ethical considerations

This study was approved by the UPM Research Ethics Board committee (UPM REB Code 2023-0509-01). The study was done following the National Ethical Guidelines for Health-Related Research (NEGHHR). Patient information and all information regarding the identity of the patients were concealed ensuring patient privacy and confidentiality at all times.

Since this study involved a review of medical records, informed consent for the study was deemed unnecessary and impractical. A waiver of informed consent was requested and approved by the UPMREB panel since the study presented no more than minimal risk by the provisions (provision 11.2) stipulated in the 2017 National Ethical Guidelines for Health and Health-related Research.[12]

RESULTS

A total of 385 patients were included; 194 were males, and 191 were females. The mean age of all patients was 56.18 years old (Table 1). There was a total of 30 patients classified as mild. There were 105 patients under the moderate category. One hundred forty-one (141) patients were classified as severe, whereas 109 patients were classified as critical.

The mean age of patients in mild, moderate, severe, and critical COVID-19 patients was 46.73 years, 52.42 years, 57.10 years and 61.20 years, respectively (Table 2). The mean age was highest among patients with critical COVID-19 disease. The majority of the disease severity has the same sexual distribution as having more males than females except for those with critical COVID-19 (females>males). The proportion of patients with co-morbidities (68.57%) was higher than those without co-morbidities (31.34%). This was also observed across all disease categories. Those patients with critical COVID-19 had the highest percentage of patients with co-morbidities. The most common co-morbidities were hypertension and diabetes.

In the mild category, a majority of patients had normal platelet count (76.67%), normal prothrombin time (55.23%) and normal activated partial thromboplastin time (93.33%). INR (66.67%) and D-dimer (62.33%) were increased in a majority of mild COVID-19 patients. In the moderate category, most patients had normal platelet count (67.61%), and normal activated partial thromboplastin time (85.71%). There was an increased proportion of patients with prolonged prothrombin time (55.23%), increased INR (80%) and increased D-dimer (87.62%) in a majority of moderate COVID-19 patients. In the severe category, most patients had normal platelet count (75.23%), normal prothrombin time (50.46%), and normal activated partial thromboplastin time (88.07%). Moreover, there was a higher proportion of patients with increased INR and increased D-dimer in the critical category. Using the Pearson Chi-square test, there was a significant association between prothrombin time and d-dimer levels and the disease severity (p-values <0.05). There was no significant difference between platelet count, activated partial thromboplastin time, INR and disease severity (Table 3).

One of the objectives of the study was to compare the coagulation and platelet variables among the different COVID-19 disease categories. To compute this, the study used Kruskall-Wallis test to determine which among the mean of the variables had a significant difference with at least one pair of COVID-19 disease categories. Prothrombin time activated partial thromboplastin time, INR and D-dimer had a p <0.05 hence those variables had at least one pair of disease severity with a significant difference. To identify which pair of disease severity had significant differences, the study used the Dunn test. In the Dunn test, for the prothrombin time, there is a significant difference in the mean prothrombin time of mild vs moderate, mild versus critical and moderate versus severe category. In the activated partial thromboplastin time, no disease pairing had a significant difference. In the INR variable, there was a significance difference in the mild versus moderate, mild versus critical and moderate versus severe pairing categories. In the D-dimer variable, almost all the pairings have significant differences except moderate vs severe.

DISCUSSION

We described the demographic and clinical profiles as well as the coagulation and platelet profiles of patients with mild, moderate, severe and critical COVID-19 patients.

Table 3. Coagulation and platelet profiles of patients across disease severity

Variable	COVID-19 disease severity				
	Mild (n=30)	Moderate (n=105)	Severe (n=141)	Critical (n=109)	*p*
Platelet count					
Below normal (<150 x 10^9/L)	5 (16.67%)	19 (18.10%)	20 (14.18%)	14 (12.84%)	0.832
Normal (150-450 x 10^9/L)	23 (76.67%)	71 (67.61%)	104 (73.76%)	82 (75.23%)	
Above normal (>450 x 10^9/L)	2 (6.66%)	15 (14.29%)	17 (12.06%)	13 (11.93%)	
Prothrombin time					
Normal (≤11-4-13.9 sec)	24 (80.00%)	47 (44.76%)	85 (60.28%)	54 (49.54%)	**0.002**
Prolonged (>13.9 sec)	6 (20.00%)	58 (55.23%)	56 (39.72%)	55 (50.46%)	
APTT					
Normal (25-35 sec or less)	28 (93.33%)	90 (85.71%)	124 (87.94%)	96 (88.07%)	0.731
Prolonged (>35 sec)	2 (6.67%)	15 (14.29%)	17 (12.06%)	13 (11.93%)	
INR					
Normal (1 or less)	10 (33.33%)	21 (20.00%)	41 (29.08%)	26 (23.85%)	0.290
Increased (>1)	20 (66.67%)	84 (80.00%)	100 (70.92%)	83 (76.15%)	
D-dimer					
Normal (0-0.50 ug/mL)	11 (36.67%)	13 (12.38%)	6 (4.26%)	3 (2.75%)	**<0.001**
Increased (>0.50 ug/mL)	19 (63.33%)	92 (87.62%)	135 (95.74%)	106 (97.25%)	

Table 4. Kruskall-Wallis and Dunn Test on platelet and coagulation variables and disease severity

Variable	Kruskall-Wallis test (*p*)	Dunn test					
		Mild vs moderate	Mild vs severe	Mild vs critical	Moderate vs severe	Moderate vs critical	Severe vs critical
Platelet count	0.4382	-	-	-	-	-	-
Prothrombin time	0.0005	0.0012	0.2246	0.0085	0.0104	1.0000	0.1317
APTT	0.0306	0.1326	0.1545	1.0000	1.0000	0.0862	0.0950
INR	0.0009	0.0014	0.1959	0.0089	0.0189	1.0000	0.1723
D-dimer	0.0001	0.0003	0.0008	0.0000	1.0000	0.0073	0.0005

There was a total of 385 patients included in the study with a mean age of 56.18 years old. This was consistent with other studies, where the mean age is 53 years old or between (40-64 years old).[13] Most of the patients in this study were males, similar to other studies regarding COVID-19. A study by Ibrahim et al., attributed the X chromosome in women to play an essential role in innate and adaptive immunity, hence fewer women succumbed to COVID-19 than men. The study also reported that the majority of patients with COVID-19 had co-morbidities during the time of their admission.[14] Those in the critical category had the highest percentage of patients with co-morbidities. This was also a trend seen in other studies due to the increased susceptibility of patients with co-morbidities with COVID-19 severe infection. Among the co-morbidities, hypertension and diabetes were the most common co-morbidities which were seen also in other studies.[15]

Most of the patients exhibited normal platelet counts in all disease categories. This was also seen in the study by Abd El-Lateef et al., wherein the average platelet count was within normal limits. This could be due to the presence of lung inflammation that can increase the secretion of thrombopoietin which stimulates platelet production in COVID-19 patients.[8] There was no significant difference in the mean platelet count among the COVID-19 categories (mild, moderate, severe, critical). Other studies showed that lower platelet counts are seen in patients with more severe disease.[16]

The majority of patients with COVID-19 in this study had normal prothrombin and activated partial thromboplastin time. This was also seen in the study by Liao et al., where most of their patients had normal PT and APTT during the time of admission.[11] This may be attributed to hyper-coagulability occurring at the early stage of COVID-19. However, other studies showed elevated PT, APTT as well as INR at the time of admission.[4]

Most patients had increased INR across all categories which may be due to the activation of molecular pathways induced by SARS-CoV-2 infection which caused intrinsic and extrinsic coagulation cascades leading to increased APTT and INR.[8]

Another finding in the study was that D-dimer was elevated in all disease categories. This could be seen also in the study by Liao et al., showing non-survivors have increasing D-dimer and fibrin degradation products.[11] In the early stages of COVID-19 disease, damage to the endothelium caused by the SARS-CoV virus could lead to hypercoagulation with subsequent release of thrombin in the absence of fibrinolysis hence increasing the level of D-dimer.[8]

The investigators found that there was a significant association between prothrombin time, D-dimer and disease severity. Moreover, the means of prothrombin time, activated partial thromboplastin time, INR, and D-dimer had significant differences versus the disease category. And among the variables, D-dimer showed a significant difference in most of the categories compared. Other blood parameters in a similar study showed significant differences in the disease comparison were neutrophil count, lymphocyte count, neutrophil to lymphocyte ratio, fibrin degradation products, C-reactive protein, and lactate dehydrogenase and white blood cell count, IL-10, and serum ferritin.[11]

Our study had some limitations. Aside from the number of cases included, only the initial laboratory results for

the coagulation and platelet profiles of patients were analyzed. Blood parameters were not taken at different stages of the disease to see the dynamic changes in blood coagulation.

CONCLUSION AND RECOMMENDATIONS

In conclusion, the study population had a mean age of 56 years old. The majority were men and had co-morbidities during the time of COVID-19 admission. Platelet counts and APTT were within normal limits across all disease severity. The PT results were mostly normal in mild and severe cases, however, prolonged in those with moderate and critical categories. INR and D-dimer are increased in all disease categories. The prothrombin time and d-dimer had a significant association with disease severity. The means of prothrombin time, APTT, INR and d-dimer all have significant differences versus disease severity.

In future studies regarding coagulation, it is recommended to investigate the association of coagulation and platelet variables with survivorship and disease outcome. Additional coagulation parameters such as fibrinogen and other inflammatory biomarkers may complete the picture. Coagulation parameters measured at different disease stages or with treatment effect (before, during and after treatment) to see coagulation patterns would yield useful information.

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STATEMENT OF AUTHORSHIP

The authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

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