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Association between Haemostatic Parameters and Clinical Severity in COVID-19: A Single-Centre Experience in East Coast Malaysia

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Abstract

COVID-19 is primarily seen as a respiratory infection, but recent research suggests it should be considered a systemic disease. This is due to its effects on the hematopoietic and haemostasis systems, leading to systemic imbalances and coagulation dysfunction, which have been observed in severely ill COVID-19 patients and fatalities. This study aims to determine the association between haemostatic parameters and the clinical severity of COVID-19 infection at Hospital Pakar Universiti Sains Malaysia (USM). A retrospective study was carried out in the Haematology laboratory by analyzing data retrieved from the Laboratory Information System from July 2021 to July 2022. The study included 34 COVID-19 patients over 18 years of age, categorized into severe and non-severe groups. Demographic data and haematology parameters such as Prothrombin time, activated partial thromboplastin time, fibrinogen and D-dimer were collected. Fisher's Exact Test was used to analyze the association between demographic variables and the clinical severity of COVID-19, while the independent t-test and Mann-Whitney U test were employed to compare haemostatic parameters with clinical severity. The results showed that males (64.7%) and individuals aged 60 years and older (74.2%) were the most affected population at Hospital Pakar USM, with diabetic mellitus (64.5%) and hypertension (77.4%) being the most common comorbidities. There were marked increase in haemostatic parameters in the severe group of COVID-19, suggesting a direct relationship with clinical severity. However, no significant association was found between demographic data and haemostatic parameters with clinical severity of COVID-19. This study highlights the importance of haemostatic parameters concerning COVID-19 severity for better prognosis evaluation, management, and treatment.

Keywords

COVID-19, prothrombin time, activated partial thromboplastin time, fibrinogen, D-dimer

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Introduction

Since 2019, the world has been battling COVID-19, a deadly infectious disease caused by the novel coronavirus SARS-CoV-2.[1] This virus spreads primarily through respiratory droplets during close contact. When an infected individual coughs, sneezes, or speaks, the virus is released in their respiratory secretions. If these droplets are inhaled or come into contact with another person's mucous membranes, they can become infected. Although contaminated surfaces are not considered the main route of transmission, infection can still occur if someone touches their eyes, nose, or mouth after their hands have been exposed to these droplets or after touching contaminated surfaces.[2]

Although COVID-19 primarily affects the respiratory system, recent research suggests it should be viewed as a systemic disease since it impacts multiple body systems, including the immune, cardiovascular, gastrointestinal, neurological, and hematopoietic systems.[3-5] While acute respiratory issues like respiratory failure, acute respiratory distress syndrome (ARDS), and pneumonia are the most reported complications, the virus also affects the hematopoietic and haemostasis systems, leading to coagulation dysfunction. This imbalance has been observed in severely ill COVID-19 patients and has been linked to COVID-19 mortality.[6]

Most reports and published studies have focused on a single test of haemostatic parameters, with prothrombin time (PT) and activated partial thromboplastin time (aPTT) being the most reported in relation to COVID-19 severity. However, the significant role of thrombosis as a clinical outcome of COVID-19 suggests that the coagulation system is involved in the disease's pathogenesis. Only a few studies have noted that patients with severe COVID-19 tend to have lower antithrombin levels and higher levels of fibrinogen, D-dimer and fibrin degradation products. Additionally, a single test result is not enough to predict thrombosis due to its multifactorial nature.[7]

It was previously reported that, changes in haemostatic abnormalities can help predict the severity and prognosis of COVID-19. These changes include elevated D-dimer levels, increased fibrinogen concentrations, prolonged PT, aPTT and Thrombin Times (TT).[8] To date, such a study has not yet been conducted in Malaysia. Therefore, this study aims to determine the association between haemostatic parameters and the clinical severity of COVID-19 infection.

Material and Methods

Study design and sample selection

This retrospective study examines existing outcomes (illnesses) by analyzing patients' medical histories to identify risk factors.[9] The reference population for this study consisted of all COVID-19 patients admitted to Hospital Pakar Universiti Sains Malaysia (USM) between July 2021 and July 2022. The inclusion criteria consisted of patients aged 18 years and older, those with a confirmed positive COVID-19 diagnosis via RT-PCR, and patients who had a Disseminated Intravascular Coagulation (DIC) profile test ordered including PT, aPTT, fibrinogen level, and D-Dimer on day 1 admission. Exclusion criteria included patients without a DIC profile test, patients with a pre-existing coagulation disorder, pregnant women, and patients undergoing treatment that could affect the coagulation profile such as aspirin or warfarin.

Data collection

Demographic data such as age, gender, and underlying comorbidities were obtained from patients' physical medical records, with the tracing conducted by Unit Rekod, Hospital Pakar USM. Haematology parameters such as PT, aPTT, fibrinogen level, and D-Dimer were retrieved from the Laboratory Information System (LIS). All data were compiled using Microsoft Excel 2013 prior to analysis. Patients were categorized into five clinical stages (stages I, II, III, IV, and V) according to the Ministry of Health Malaysia (MOH) guidelines

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and were further divided into two groups based on disease severity: the severe group and the non-severe group [10]. The severe group included patients in stages IV and V, while the non-severe group included those in stages I, II, and III.

Statistical analysis

All data collected were analyzed using the Statistical Package for the Social Sciences (SPSS), version 26.0 (IBM SPSS Statistics, Armonk,NY). Subjects were categorized into two groups based on COVID-19 severity. Descriptive analyses were performed on categorical variables and expressed as frequencies and percentages. These variables were also compared using Fisher's Exact Test to determine the association between demographic data and COVID-19 severity. Meanwhile, comparisons between haemostatic parameters and COVID-19 severity were analyzed using an independent t-test for normally distributed variables and the Mann-Whitney U-test for variables with a skewed distribution. A p-value of <0.05 was considered statistically significant at a 95% confidence level.

Results

Association between demographic data with COVID-19 severity

A total of 34 COVID-19 patients were included in the study, with 8.8% (n=3) classified in the non-severe group and 91.2% (n=31) in the severe group. The patients' ages ranged from 28 to 81 years, with a mean age of 63.18 ± 13.84 years. Most of the patients (74.2%) were over 60 years old. However, no significant association was found between age and COVID-19 severity (p=0.415). Males constituted most of the study population, with 64.7% (n=22) males and 35.3% (n=12) females. Among the severe cases, 64.5% (n=20) were male, and 35.5% (n=11) were female. In the non-severe cases, 66.7% (n=2) were male, and 33.3% (n=1) were female. There was no significant association between gender and COVID-19 severity (p = 0.950). Among the 31 severe cases, 64.5% (n=20) of patients had diabetes mellitus (DM), while 66.7% (n=2) of the non-severe cases were diabetic. Hypertension (HPT) was present in 77.4% (n=24) of severe cases and 66.7% (n=2) of non-severe cases. For cardiovascular disease (CVD), 12.9% (n=4) of the severe cases had CVD, whereas no CVD was observed in the non-severe group. The analysis showed no significant association between the presence of DM, HPT, or CVD and the severity of COVID-19 (p = 0.950). The clinical characteristics of the study subjects by COVID-19 severity are detailed in Table 1.

Association between haemostatic parameters with COVID-19 severity

Haemostatic parameters include PT, aPTT, and D-dimer levels were analyzed using the Mann-Whitney U test, while Fibrinogen levels were analyzed using an independent t-test. The reference ranges used in this study were obtained from the Coagulation Section and presented in Table 2 below. The median (IQR) PT was 16.60 (6.0) in the severe group and 14.40 (0) in the non-severe group. For aPTT, the median (IQR) values were 49.30 (23.6) in the severe group and 38.00 (0) in the non-severe group. The D-dimer median (IQR) was 4.80 (6.1) in the severe group and 1.91 (0) in the non-severe group. Lastly, the mean ± SD fibrinogen level was 4.27 ± 1.81 in the severe group and 3.78 ± 1.24 in the non-severe group. The p-values for all these parameters were greater than 0.05, indicating no significant association between these haemostatic parameters and COVID-19 severity (Table 2).

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Table 1: Clinical characteristics of study subjects according to COVID-19 severity

Demographic data	All cases (n=34)	Disease severity of COVID-19		Statistical parameter*
		Non-severe cases (n=3)	Severe cases (n=31)	
Age, years (mean ± SD)	63.18±13.842	-	-	0.415
Age group (years)				
• 19-29	1	0	1	-
• 30-39	3	1	2	-
• 40-49	1	0	1	-
• 50-59	4	0	4	-
• >60	25	2	23	-
Gender				
Male	22	2	20	0.950
Female	12	1	11	
Comorbidities				
Diabetic Mellitus (DM)	22/34 (64.7%)	2/3 (66.7%)	20/31 (64.5%)	0.950
Hypertension (HPT)	26/34 (76.5%)	2/3 (66.7%)	24/31 (77.4%)	0.950
Cardiovascular Disease (CVD)	4/34 (11.8%)	0/3 (0%)	4/31 (12.9%)	0.950

*Tests analysed using Fisher-exact test

Table 2: Comparison for Haemostatic parameter between COVID-19 severity

Haemostatic parameters	Non severe Median (IQR)	Severe Median (IQR)	P-value	References range
PT (s)	14.40(0)	16.60(6.0)	0.331	12.61 - 15.72
aPTT (s)	38.00(0)	49.30(23.6)	0.379	30.0 - 45.8
Fibrinogen level (g/L) *	3.78±1.24	4.27±1.81	0.519	2.32 – 4.44
D-dimer (µg/mL)	1.91(0)	4.80(6.1)	0.145	<0.45

*Test done with independent t-test (results is represented in mean±SD)
Others were using the Mann-Whitney U-test

Discussion

COVID-19 infection is known to impair coagulation and is associated with a high incidence of venous and arterial thrombotic complications, including atypical thrombotic events.[11] Although in this study we did not assess clinical haemostatic outcomes such as bleeding, thrombosis, or disseminated intravascular coagulation (DIC). Instead, the aim was to determine the association between laboratory-based haemostatic parameters and the clinical severity of COVID-19 in patients admitted to Hospital Pakar USM. A total of 34 patients were recruited, with males comprising 64.7% of the sample. The mean age of the

patients was 63 years. These findings were similar to another study which reported that males and individuals over 60 were more commonly affected by COVID-19.[12] Meanwhile, the mean age in a study by Zhou et al. was slightly higher at 66.10 years.[13] This discrepancy may be due to differences in population age distribution between the reported study locations, as which was conducted in China (Zhou et al.), whereas our study took place in Kelantan, Malaysia.

It was previously reported that gender is a risk factor for mortality in COVID-19 patients, with men experiencing higher mortality rates than women.[14] Epidemiological data worldwide also suggested that men have higher morbidity and mortality rates compared to women.[15,16] Several factors may contribute to this difference, including gender-based immunological variations driven by sex hormones and the X chromosome, as well as higher expression of angiotensin-converting enzyme-2 (ACE2), which acts as a coronavirus receptor, in males than in females.[17,18] Additionally, lifestyle factors such as higher rates of drinking and smoking among men may also play a significant role in this disparity.[19] Lastly, studies have shown that women tend to perceive the COVID-19 pandemic with a greater sense of responsibility than men. Men, on the other hand, are less likely to adhere to recommendations such as staying at home, washing hands frequently, or wearing face masks.[20,21]

This study also found that the most common comorbidities among the patients were diabetes mellitus (DM) and hypertension (HPT), affecting 64.5% and 77.4% of the participants, respectively. Although the statistical analysis did not show a significant association between these comorbidities and disease severity, the high prevalence is notable. Similar findings were observed in another study where diabetes mellitus (17.1%) and hypertension (14.5%) were the most prevalent comorbidities, with diabetes mellitus being significantly linked to increased disease severity.[22]

In this study, haemostatic parameters did not show significant associations with COVID-19 severity. However, within the severe group, we observed markedly elevated levels of PT, aPTT, and D-dimer. Fibrinogen levels varied, with both normal and abnormal readings in the severe COVID-19 cases. It has been reported that the coagulation parameters in severe COVID-19 cases such as aPTT, D-dimer, and fibrinogen levels were increased.[23] Additionally, several studies have documented significant elevations in haemostatic parameters like PT in severe COVID-19 cases compared to non-severe cases.[24-26] Although severe COVID-19 can lead to prolongation of PT and aPTT, these increases are not as pronounced as those observed in cases of bacterial sepsis and DIC.[20]

D-dimer levels have been the focus of numerous COVID-19 studies. A meta-analysis found that 37.2% of COVID-19 patients had elevated D-dimer levels.[27] Consistent with these findings, our study also recorded increased D-dimer levels in the severe COVID-19 group. A previous study on COVID-19 patients found that 50 out of 115 patients (43.5%) had elevated D-dimer levels (>0.55 mg/L). Among the 28 critically ill patients, 17 (60.7%) had levels exceeding 0.55 mg/L, with 14 cases showing values more than twice the normal reference range.[12] Many researchers have suggested that D-dimer could be a valuable early indicator for enhancing the management of COVID-19 patients.[27,28]

Similar observations were made regarding fibrinogen levels in our study, where fibrinogen was found to be slightly higher in the severe group (4.27±1.81) compared to the non-severe group (3.78±1.24). Previous study has analyzed the coagulation function in 303 COVID-19 patients and found a correlation between high fibrinogen levels and disease severity.[29] Our findings align with this, showing notable increases in haemostatic parameters, although these differences did not reach statistical significance.

The lack of statistically significant associations in our study contrasts with several published reports. This discrepancy may be due to several factors. First, the small sample size (n=34), particularly the very limited number of non-severe cases (n=3), reduced the statistical power to detect meaningful differences. Second, only the earliest available laboratory results were analysed, which may not reflect the peak haemostatic abnormalities that develop later in the disease course. Third, population differences including genetic, demographic, and healthcare related factors may also contribute to the variation in findings. Lastly, the retrospective nature of the study limited control over confounding variables such as timing of sample collection and treatment interventions. Although this study did not assess longitudinal changes, the observed elevations in haemostatic parameters among severe cases suggest a potential trend toward coagulation activation in more severe disease. However, due to the lack of statistical significance, these findings should be interpreted with caution.

This study has several limitations. The small sample size with only 34 COVID-19 cases (3 non-severe and 31 severe) and single-centre design limit the generalizability of the findings. Additionally, the absence of clinical haemostatic outcomes such as bleeding or thrombosis restricts the ability to draw conclusions about the clinical implications of the laboratory findings. Future studies with larger, multicentre cohorts and integrated clinical and laboratory data are needed to validate these observations and better understand the role of haemostatic markers in COVID-19 severity.

Conclusion

Although the associations between demographic characteristics, haemostatic parameters, and COVID-19 severity did not reach statistical significance, the distribution of data demonstrated an upward trend in haematological parameters, consistent with observations reported in previous studies. Therefore, this study underscores the importance of monitoring haemostatic parameters in relation to COVID-19 severity to improve prognosis, management, and treatment.

List of Abbreviations

aPTT	activated partial thromboplastin time
COVID-19	Coronavirus disease
CVD	Cardiovascular disease
DIC	Disseminated Intravascular Coagulation
DM	Diabetes mellitus
HPT	Hypertension
IQR	Interquartile range
PT	Prothrombin time

Declaration of Competing Interests

The authors declare that they have no competing interests.

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