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Research article

Age, comorbidities, c-reactive protein and procalcitonin as predictors of severity in confirmed COVID-19 patients in the Philippines

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ABSTRACT

Background: The Coronavirus Disease 2019 (COVID-19) pandemic has been affecting people globally, and the Philippines is one of the countries greatly struck by the virus. The continued rise of new positive cases has drawn attention to the urgent need for healthcare management to cope with this challenge. Severity prediction could help improve medical decision-making and optimise the patient's treatment plan with a good clinical outcome. This study aimed to identify the determinants of COVID-19 disease severity.

Methods: Demographic characteristics and laboratory findings were collected from electronic medical records and paper forms of all confirmed COVID-19 cases reported by the University of Perpetual Help DALTA Medical Center between the September 1, 2020 and the October 31, 2021. We performed statistical analyses and interpretation of data to compare severe and non-severe groups.

Results: 5,396 confirmed cases were examined. Most of the severe cases were elderly, male, had blood type A, and with comorbidities. Cycle threshold (Ct) values were lower in the severe group. Most patients had higher-than-normal levels of all blood parameters except platelet, white blood cell (WBC), neutrophil, and lymphocyte counts. Age, sex, ABO blood groups, comorbidities, open reading frame 1 ab (ORF1ab) and nucleocapsid (N) gene Ct values, ferritin, C-reactive protein (CRP), procalcitonin (PCT), D-dimer, white blood cell (WBC) count, neutrophil count, and lymphocyte count were significantly associated with disease severity. In multivariate analysis, age groups >60 and 30–59 years, presence of comorbidities, CRP level >5 ng/mL, and PCT >0.05 ng/mL were identified as disease severity predictors.

Conclusions: Based on our results, age, comorbidities, CRP, and PCT level may be utilised as primary assessment factors for possible hospital admission and close monitoring upon testing. Early detection of these risk factors may provide strategic interventions that help reduce mortality, hospital admissions, and more expensive and extensive treatments.

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1. Introduction

Initially known as 2019-nCoV and later renamed as COVID-19 or the Coronavirus Disease 2019, it was a respiratory illness caused by a novel coronavirus known as the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The first confirmed case of COVID-19, like its predecessor SARS, was initially reported towards the end of 2019 in China, originating from clustered cases of pneumonia of unknown origin. Most of the first patients were stall owners, market staff, and frequent visitors having direct and indirect contact with the Huanan seafood and animal market in Wuhan City, Hubei Province [1].

Nearly 662 million cases have been reported globally since the 15th of January 2023, with a mortality toll of about 6.7 million or 1% of the affected population. Approximately 2.9 million (43%) of all fatalities were recorded in the region of the Americas, while over two million (31%) and over 800,000 (12%) occurred in areas of Europe and Southeast Asia, respectively [2]. The Western Pacific Region, with more than 30 member countries, had reported a total of 111,125,686 cases, with the Philippines accounting for more than 3% of the total, with more than four million recorded cases and greater than 65,000 fatalities [3]. The National Capital Region (NCR) accounts for a quarter of all recorded deaths, followed by Regions IV-A (CALABARZON) and III (Central Luzon). The vaccination rollout was still lagging, with 67.47 per 100 population fully vaccinated against COVID-19 and 19.48 per 100 population administered with a booster shot [4]. Meanwhile, in the neighbouring Southeast Asian country of Thailand, 33,792 deaths have been recorded by far, with 77.25 per 100 population fully vaccinated against COVID-19 and 38.22 per 100 population boosted, based on the updated WHO Coronavirus (COVID-19) Dashboard.

Even though older adults with underlying conditions seemed more vulnerable to severe disease and mortality [5], several near-death infections developed in healthy individuals with no health issues [6]; as a result, there were several critical yet unresolved concerns, such as why disease severity varied and why some people had more serious diseases. This suggested that there may be missing links behind this disparity.

This research was expected to address the scarcity of available statistical data that associates several demographic and clinical blood parameters with the degree of severity of COVID-19 infection, which may explain the aggregated number of confirmed cases classified as critical and severe, moderate, mild, and asymptomatic.

2. Methods

2.1. Study design and setting

Between the September 1, 2020, and the October 31, 2021, the retrospective secondary data analysis of confirmed COVID-19 cases was conducted using electronic medical records and case investigation forms. Anonymised data that contain medical information were obtained from the Hospital Information System (HIS), Laboratory Information System (LIS), and Molecular Information System (MIS), while disease severity classifications were extracted from individual case investigation forms.

2.2. Participants and eligibility criteria

The researcher identified all confirmed COVID-19 cases reported by the University of Perpetual Help DALTA Medical Center in the Philippines between September 1, 2020, and October 31, 2021. A confirmed case referred to a person with positive SARS-CoV-2 Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) regardless of clinical signs and symptoms. The Molecular Diagnostic Laboratory of the same hospital carried out all RT-PCR tests. Cases without disease severity classifications indicated, discrepant personal identifiers, and duplicate cases were not considered for analysis in this study. In compliance with the Data Privacy Act of 2012, datasets were anonymised to protect the privacy and confidentiality of the reported cases.

2.3. Data collection

Demographic characteristics and laboratory findings of all eligible cases were retrieved from existing medical records between February and April 2022 upon the approval of the hospital's Executive Board and Data Privacy Officer. The researcher handled the data in a spreadsheet before starting the analysis. Demographic data such as age and sex, which were taken during the initial hospital admission and/or testing, were extracted from existing records in the Hospital Information System. Cycle threshold (Ct) values were generated after the SARS-CoV-2 RT-PCR test using MA-6000 thermal cycler coupled with Sansure Biotech Novel Coronavirus (2019-nCoV) Nucleic Diagnostic Kit that has two target genes, namely open reading frame 1 ab (ORF1ab) and nucleocapsid (N). This information was stored in the Molecular Information System (MIS). Laboratory Information System (LIS) was responsible for storing hematologic examinations. ABO blood group was tested using conventional forward and reverse typing. The photometric method was applied using COBAS C311 for clinical chemistry assays such as lactate dehydrogenase (LDH) and C-reactive protein (CRP), and DT-100 by Tcoag for coagulation assays like prothrombin time (PT) and activated partial thromboplastin time (APTT). The immunoassays such as ferritin, procalcitonin (PCT), and D-dimer were measured in biomérieux VIDAS. Sysmex XN-550 measured white blood cell (WBC) and differential counts (neutrophils and lymphocytes) through flow cytometry and platelet count using impedance with hydrodynamic focusing. The standard cut-off values for those laboratory testing were applied to the dataset to classify the patient into a group following routine clinical practice before the analysis.

We divided COVID-19 disease severity into two (2) groups: severe and non-severe. Severe included those who were classified as: (I) severe (severe pneumonia with RR $>$ 30 breaths/minute and SpO_2 $<$92%); (II) critical (manifestation of acute respiratory distress

syndrome, sepsis, and/or septic shock). Non-severe cases included: (I) asymptomatic (did not develop symptoms); (II) mild (presented with typical signs and symptoms such as fever, sore throat, cough, anosmia, ageusia, without pneumonia); (III) moderate (non-severe pneumonia with a respiratory rate of 21–30 breaths per minute and oxygen saturation greater than 92%). These stratified classifications were based on the manifestations of clinical signs and symptoms, diagnostic imaging criteria, vital statistics, and laboratory test results as presented in the guidelines adopted by the Department of Health Philippines in its nationally circulated Department Memorandum No. 2020-0381 (or Interim Guidelines on the COVID-19 Disease Severity Classification Management) issued on the July 21, 2020 [7,8,9]. A total of 5,815 confirmed COVID-19 cases were reported. A thorough review of missing outcome data and identifiers resulted in 5,396 cases analyzed for risk factor analysis (Fig. 1).

2.4. Statistical analysis

The collected data were summarised and presented using suitable tables and graphs. Considering this study's large amount of data, the Kolmogorov-Smirnov test for normality was first applied to the dataset before analysis. Continuous normally distributed variables were presented as mean and standard deviation (SD), while nonnormal variables were presented as median and interquartile range. Categorical variables were presented as numbers and percentages. Independent variables were assessed using the *t*-test for continuous variables and a chi-square (χ^2) test or Fisher's exact for categorical variables as appropriate. A binary logistic regression followed this to assess the statistical significance between individual independent and dependent variables. Lastly, ordinal logistic regression was used to identify significant predictors among significant factors with a p-value <0.05. Logistic regression models were conducted to determine the association between predictor and dependent variables. The dependent variable (disease severity classification) was classified as severe and non-severe (reference category). A p-value <0.05 was considered statistically significant. We conducted statistical analyses using SPSS software version 22.

2.5. Ethical approval

This study did not involve any human participants. The study was ethically approved and exempted by The Research Ethics Review Committee for Research Involving Human Participants, Group I, Chulalongkorn University (COA No. 060/65) and the Institutional Ethics Review Board of the University of Perpetual Help System (UPHS-IERB SP 2022-01).

3. Results

3.1. Disease severity classification and characteristics of confirmed COVID-19 cases

Between September 2020 and October 2021, 5,815 confirmed the Molecular Diagnostic Laboratory of the University of Perpetual Help DALTA Medical Center in the Philippines through SARS-CoV-2 RT-PCR testing reported COVID-19 cases. Of these patients, 5,396 recorded cases were considered for analysis, while the remaining 419 were omitted due to duplications from repeat testing and discrepancies in personal identifiers. Since the nature of this study involved analysis of all available medical records, all 5,396 cases were analyzed, and the researcher came up with the following numbers per disease severity classification: 777 "severe" cases and 4,619 "non-severe" cases.

All baseline demographic characteristics and laboratory findings are listed in Table 1. Most severe COVID-19 cases were 60 or more, with a median age of 62. Generally, non-severe cases were observably younger, with a median age of 37 years, than those inflicted with severe COVID-19. Male patients represented marginally over 50% of all recorded cases, and the majority identified with

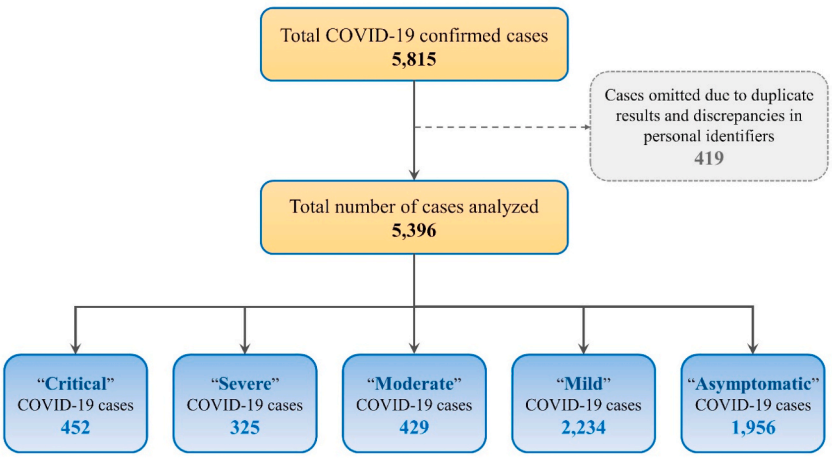

Fig. 1. Flowchart of the study population.

Table 1
Demographic characteristics and laboratory findings of confirmed COVID-19 cases stratified by disease severity.

Factors	Disease Severity, *n* (%)			*p*-value
	Total	Severe	Non-Severe	
DEMOGRAPHIC CHARACTERISTICS				
Age (in years) ($n = 5,396$)				
≥60	1,063 (19.7)	439 (56.5)	624 (13.5)	<0.001[a]
30 - 59	3,017 (55.9)	324 (41.7)	2,693 (58.3)	
<30	1,316 (24.4)	14 (1.8)	1,302 (28.2)	
Total	5,396 (100)	777 (100)	4,619 (100)	
Median (IQR)	40 (30–55)	62 (51–71)	37 (28–50)	
Sex ($n = 5,396$)				
Male	2,710 (50.2)	417 (53.7)	2,293 (49.6)	0.038[a]
Female	2,686 (49.8)	360 (46.3)	2,326 (50.4)	
Total	5,396 (100)	777 (100)	4,619 (100)	
CLINICAL FEATURES				
ABO Blood Groups ($n = 2,045$)				
A	895 (43.8)	528 (68.0)	367 (29.0)	<0.001[a]
B	459 (22.4)	120 (15.4)	339 (26.7)	
O	612 (29.9)	115 (14.8)	497 (39.2)	
AB	79 (3.9)	14 (1.8)	65 (5.1)	
Total	2,045 (100)	777 (100)	1,268 (100)	
Comorbidities ($n = 5,396$)				
Presence	2,625 (48.6)	747 (96.1)	1,878 (40.7)	<0.001[a]
Absence	2,771 (51.4)	30 (3.9)	2,741 (59.3)	
Total	5,396 (100)	777 (100)	4,619 (100)	
Ct value, median (IQR)				
ORF1ab gene (n = 5,136)	27.64 (20.16–34.70)	25.31 (20.32–32.03)	28.22 (20.13–35.01)	<0.001[c]
N gene (n = 5,359)	27.63 (19.06–33.75)	25.00 (19.10–31.87)	28.28 (19.10–31.86)	<0.001[c]
INFLAMMATORY MARKERS				
Lactate Dehydrogenase (U/L) ($n = 942$)				
>225	878 (93.2)	728 (95.4)	150 (83.8)	<0.001[b]
135 - 225	61 (6.5)	33 (4.3)	28 (15.6)	
<135	3 (0.3)	2 (0.3)	1 (0.6)	
Total	942 (100)	763 (100)	179 (100)	
Median (IQR)	599 (392–859)	655 (452–898)	425 (265–625)	
Ferritin (ng/mL) ($n = 942$)				
>435	774 (82.2)	648 (84.9)	126 (70.4)	<0.001[b]
10 - 435	168 (17.8)	115 (15.1)	53 (29.6)	
Total	942 (100)	763 (100)	179 (100)	
Median	656.32	684.65	525.62	
(IQR)	(458.89–956.65)	(485.25-1,005.65)	(400.25–750.26)	
C-Reactive Protein (ng/mL) ($n = 941$)				
≥5	869 (92.3)	719 (94.4)	150 (83.8)	<0.001[b]
<5	72 (7.7)	43 (5.6)	29 (16.2)	
Total	941 (100)	762 (100)	179 (100)	
Median	22.86	28.53	11.35	
(IQR)	(10.20–99.80)	(10.34–105.29)	(6.32–20.56)	
Procalcitonin (ng/mL) ($n = 942$)				
≥0.05	715 (75.9)	565 (74.0)	150 (84.3)	0.004[b]
<0.05	227 (24.1)	199 (26.0)	28 (15.7)	
Total	942 (100)	764 (100)	178 (100)	
Median	2.50	2.35	6.06	
(IQR)	(0.56–12.31)	(0.40–10.52)	(0.73–15.24)	
COAGULATION MARKERS				
Platelet Count ($x10^9/L$) ($n = 1,665$)				
>400	86 (5.2)	31 (4.0)	55 (6.2)	0.127[a]
150 - 400	1,540 (92.5)	728 (93.7)	812 (91.4)	
<150	39 (2.3)	18 (2.3)	21 (2.4)	
Total	1,665 (100)	777 (100)	888 (100)	
Median (IQR)	234 (199–300)	236 (199–311)	232 (199–290)	
Prothrombin Time (seconds) ($n = 1,149$)				
>13.5	898 (78.2)	592 (76.5)	306 (81.6)	0.049[a]
11.0–13.5	251 (21.8)	182 (23.5)	69 (18.4)	
Total	1,149 (100)	774 (100)	375 (100)	
Median	14.9	14.7	15.2	
(IQR)	(13.2–15.7)	(13.6–15.9)	(14.2–15.6)	

(*continued on next page*)

Table 1 (*continued*)

Factors	Disease Severity, *n* (%)			*p*-value
	Total	Severe	Non-Severe	
Activated Partial Thromboplastin Time (seconds) ($n = 1,149$)				
>35.0	695 (60.5)	466 (60.2)	229 (61.1)	0.961[a]
21.0–35.0	451 (39.3)	306 (39.5)	145 (38.7)	
<21.0	3 (0.2)	2 (0.3)	1 (0.2)	
Total	1,149 (100)	774 (100)	375 (100)	
Median	35.70	36.0	35.6	
(IQR)	(33.3–37.5)	(33.3–38.3)	(33.5–36.9)	
D-dimer (ng/mL) ($n = 940$)				
≥500	767 (81.6)	632 (82.8)	135 (76.3)	0.042[b]
<500	173 (18.4)	131 (17.2)	42 (23.7)	
Total	940 (100)	763 (100)	177 (100)	
Median	769.80	799.85	654.30	
(IQR)	(562.31-1,154.80)	(572.41-1,254.30)	(500.25–865.25)	
INFECTION MARKERS				
White Blood Cell Count ($x10^9$/L) ($n = 1,665$)				
>10.0	291 (17.5)	157 (20.2)	134 (15.1)	0.013[a]
4.5–10.0	1,262 (75.8)	575 (74.0)	687 (77.4)	
<4.5	112 (6.7)	45 (5.8)	67 (7.5)	
Total	1,665 (100)	777 (100)	888 (100)	
Median (IQR)	7.90 (6.14–9.50)	7.90 (6.42–9.70)	7.90 (5.80–9.40)	
Neutrophil Count ($x10^9$/L) ($n = 1,665$)				
>0.70	433 (26.0)	236 (30.4)	197 (22.2)	0.001[a]
0.50–0.70	1,157 (69.5)	511 (65.8)	646 (72.7)	
<0.50	75 (4.5)	30 (3.8)	45 (5.1)	
Total	1,665 (100)	777 (100)	888 (100)	
Median (IQR)	0.62 (0.58–0.71)	0.65 (0.58–0.75)	0.62 (0.58–0.69)	
Lymphocyte Count ($x10^9$/L) ($n = 1,665$)				
>0.40	67 (4.0)	28 (3.6)	39 (4.4)	0.002[a]
0.20–0.40	1,089 (65.4)	479 (61.7)	610 (68.7)	
<0.20	509 (30.6)	270 (34.7)	239 (26.9)	
Total	1,665 (100)	777 (100)	888 (100)	
Median (IQR)	0.24 (0.18–0.28)	0.22 (0.16–0.28)	0.24 (0.19–0.29)	

[a] χ^2 test.
[b] Fisher's exact test.
[c] *t*-test.

severe infection. In contrast, females accounted for 49.8% of all cases and were the majority of the non-severe group.

Blood type-A accounted for 68% of severe cases, while the majority (39.2%) of the non-severe were type-O. Overall, most of the recorded cases, regardless of severity, were of type A(43.8%), followed by type O (29.9%), type B (22.4%), and AB(3.9%). For this study, comorbidities were limited to the presence of one or more or the total absence of the following pre-existing conditions: chronic lung disease, cardiovascular disease (CVD), cancer, chronic kidney disease (CKD), diabetes mellitus, and hypertension (HPN). 96.1% (747/777) of severe cases had one or more of these pre-existing conditions before being infected with COVID-19, while the majority of the non-severe COVID-19 cases, 59.3% (2,741/4,619) were not suffering from any of these conditions.

The open reading frame 1 ab (ORF1ab) and nucleocapsid (N) genes of SARS-CoV-2 were the only genes incorporated in this study due to the limitation of the testing kit available in the laboratory. Cycle threshold (Ct) values less than or equal to 40 on either gene were diagnostic for COVID-19. The Ct value is inversely proportional to the quantity of viral RNA copies identified in positive samples. The more viral RNA there is, the lower the Ct value. A lower median Ct value for the ORF1ab gene was recorded in severe cases at 25.31 (IQR: 20.32, 32.03) compared to non-severe cases at 28.22 (IQR: 20.13, 35.01). A similar trend was observed with the N gene wherein a lower Ct value of 25.00 (IQR: 19.10, 31.87) was observed from the severe group against the non-severe group with 28.28 (IQR: 19.10, 31.86).

Lactate Dehydrogenase (LDH) levels were divided into low (<135 U/L), normal (135–225 U/L), and high (>225 U/L). Most severe COVID-19 cases had elevated LDH with a median level of 655 U/L. Although to a lesser degree, most non-severe cases also had higher-than-normal LDH with a median level of 425 U/L. Similarly, ferritin levels were classified as low (<10 ng/mL), normal (10–435 ng/mL), and high (>435 ng/mL). Higher than normal levels of ferritin were evident in both severe) and non-severe groups. This was in addition to the higher median ferritin of 684.65 ng/mL recorded in severe COVID-19 cases compared to 525.62 ng/mL in the opposite group. C-Reactive Protein (CRP) levels were classified into normal (<5 ng/mL) and high (≥5 ng/mL). Severe cases had more than double the median CRP level of 28.53 ng/mL than the non-severe group at 11.35 ng/mL, with both tallying more than 80% of cases in their respective groups with abnormally high CRP levels. While a similar trend of severe cases recording higher median values of the biomarkers than their non-severe counterpart was noted in the previous inflammatory markers, a different outcome was observed with procalcitonin. PCT levels were grouped into normal (<0.50 ng/mL) and high (≥0.50 ng/mL). Non-severe COVID-19 cases had a considerably higher PCT median value of 6.06 ng/mL, while the severe group recorded 2.35 ng/mL (0.40, 10.52). This showed a

Table 2
Binary logistic regression analysis of demographic characteristics and laboratory findings of confirmed COVID-19 cases stratified by disease severity.

Factors	Disease Severity, *n* (%)			p-value	OR (95% CI)
	Total	Severe	Non-Severe		
DEMOGRAPHIC CHARACTERISTICS					
Age (in years) (n = 5,396)					
≥60	1,063 (19.7)	439 (56.5)	624 (13.5)	<0.001*	65.43 (38.11–112.34)
30 - 59	3,017 (55.9)	324 (41.7)	2,693 (58.3)	<0.001*	11.19 (6.53–19.18)
<30	1,316 (24.4)	14 (1.8)	1,302 (28.2)		1.00
Sex (n = 5,396)					
Male	2,710 (50.2)	417 (53.7)	2,293 (49.6)	0.038*	1.18 (1.01–1.37)
Female	2,686 (49.8)	360 (46.3)	2,326 (50.4)		1.00
CLINICAL FEATURES					
ABO Blood Groups (n = 2,045)					
A	895 (43.8)	528 (68.0)	367 (29.0)	<0.001*	6.68 (3.69–12.08)
B	459 (22.4)	120 (15.4)	339 (26.7)	0.113	1.64 (0.89–3.04)
O	612 (29.9)	115 (14.8)	497 (39.2)	0.818	1.07 (0.58–1.98)
AB	79 (3.9)	14 (1.8)	65 (5.1)		1.00
Comorbidities (n = 5,396)					
Presence	2,625 (48.6)	747 (96.1)	1,878 (40.7)	<0.001*	36.34 (25.11–52.60)
Absence	2,771 (51.4)	30 (3.9)	2,741 (59.3)		1.00
Ct value, median (IQR)					
ORF1ab gene	27.64 (20.16–34.70)	25.31 (20.32–32.03)	28.22 (20.13–35.01)	<0.001*	0.98 (0.97–0.99)
N gene	27.63 (19.06–33.75)	25.00 (19.10–31.87)	28.28 (19.10–31.86)	<0.001*	0.98 (0.97–0.99)
INFLAMMATORY MARKERS					
Lactate Dehydrogenase (U/L) (n = 942)					
>225	878 (93.2)	728 (95.4)	150 (83.8)	0.470	2.43 (0.22–26.93)
135 - 225	61 (6.5)	33 (4.3)	28 (15.6)	0.670	1.70 (0.15–19.72)
<135	3 (0.3)	2 (0.3)	1 (0.6)		1.00
Ferritin (ng/mL) (n = 942)					
>435	774 (82.2)	648 (84.9)	126 (70.4)	<0.001*	2.37 (1.63–3.46)
10 - 435	168 (17.8)	115 (15.1)	53 (29.6)		1.00
C-Reactive Protein (ng/mL) (n = 941)					
≥5	869 (92.3)	719 (94.4)	150 (83.8)	<0.001*	3.23 (1.96–5.34)
<5	72 (7.7)	43 (5.6)	29 (16.2)		1.00
Procalcitonin (ng/mL) (n = 942)					
≥0.05	715 (75.9)	565 (74.0)	150 (84.3)	0.004*	0.53 (0.34–0.82)
<0.05	227 (24.1)	199 (26.0)	28 (15.7)		1.00
COAGULATION MARKERS					
Platelet Count (x10^9/L) (n = 1,665)					
>400	86 (5.2)	31 (4.0)	55 (6.2)	0.285	0.66 (0.31–1.42)
150 - 400	1,540 (92.5)	728 (93.7)	812 (91.4)	0.890	1.05 (0.55–1.98)
<150	39 (2.3)	18 (2.3)	21 (2.4)		1.00
Prothrombin Time (seconds) (n = 1,149)					
>13.5	898 (78.2)	592 (76.5)	306 (81.6)	0.050	0.73 (0.54–1.00)
11.0–13.5	251 (21.8)	182 (23.5)	69 (18.4)		1.00
Activated Partial Thromboplastin Time (seconds) (n = 1,149)					
>35.0	695 (60.5)	466 (60.2)	229 (61.1)	0.989	1.02 (0.09–11.28)
21.0–35.0	451 (39.3)	306 (39.5)	145 (38.7)	0.965	1.06 (0.09–11.73)
<21.0	3 (0.2)	2 (0.3)	1 (0.2)		1.00
D-dimer (ng/mL) (n = 940)					
≥500	767 (81.6)	632 (82.8)	135 (76.3)	0.043*	1.50 (1.01–2.23)
<500	173 (18.4)	131 (17.2)	42 (23.7)		1.00
INFECTION MARKERS					
White Blood Cell Count (x10^9/L) (n = 1,665)					
>10.0	291 (17.5)	157 (20.2)	134 (15.1)	0.014*	1.74 (1.12–2.72)
4.5–10.0	1,262 (75.8)	575 (74.0)	687 (77.4)	0.273	1.25 (0.84–1.85)
<4.5	112 (6.7)	45 (5.8)	67 (7.5)		1.00
Neutrophil Count (x10^9/L) (n = 1,665)					
>0.70	433 (26.0)	236 (30.4)	197 (22.2)	0.021*	1.80 (1.09–2.96)
0.50–0.70	1,157 (69.5)	511 (65.8)	646 (72.7)	0.482	1.19 (0.74–1.91)
<0.50	75 (4.5)	30 (3.8)	45 (5.1)		1.00
Lymphocyte Count (x10^9/L) (n = 1,665)					
>0.40	67 (4.0)	28 (3.6)	39 (4.4)	0.085	0.64 (0.38–1.06)
0.20–0.40	1,089 (65.4)	479 (61.7)	610 (68.7)	0.001*	0.70 (0.56–0.86)
<0.20	509 (30.6)	270 (34.7)	239 (26.9)		1.00

reversed trend wherein a higher median value was observed in the non-severe than the severe group. This was in addition to the fact that there were more non-severe (84.3%) than severe (74.1%) cases that exhibited PCT levels of >0.50 ng/mL.

Platelet count was identified as low (<150 × 10^9/L), normal (150-400 × 10^9/L), and high (>400 × 10^9/L). More than 90% of cases in both severe and non-severe groups had normal platelet counts. A median platelet count of 236 × 10^9/L and 232 × 10^9/L were obtained from the severe and non-severe groups. Prothrombin Time (PT) was grouped into low (<11 s), normal (11.0–13.5 s), and high (>13.5 s). 76.5% and 81.6% of severe and non-severe COVID-19 had PT longer than 13.5 s, while no recorded cases of PT fell to less than 11 s. A longer median PT of 15.2 s was observed from the non-severe cohort against 14.7 s from the severe group. Activated Partial Thromboplastin Time (APTT) was classified as low (<21 s), normal (21–35 s), and high (>35 s). Similarly, most severe and non-severe COVID-19 cases had high APTT levels. The severe group had a median APTT of 36.0 s (IQR: 33.3, 38.3), while the non-severe group recorded 35.6 s. D-dimer levels were separated into normal (<500 ng/mL) and high (≥500 ng/mL). More than 75% of cases in both groups had blood D-dimer levels of ≥500 ng/mL. Severe cases had a higher median D-dimer of 799.85 ng/mL compared to the 654.30 ng/mL (IQR: 500.25, 865.25) non-severe group.

Table 3
Multivariate analysis of factors significantly associated with disease severity among confirmed COVID-19 cases.

Independent Variables	β	SE (β)	p-value	OR (95% CI)
DEMOGRAPHIC CHARACTERISTICS				
Age (in years)				
≥60	4.071	0.620	<0.001*	58.62 (17.40–197.49)
30 - 59	1.939	0.488	<0.001*	6.95 (2.67–18.09)
<30				1.00
Sex				
Male	0.539	0.278	0.052	1.72 (1.00–2.95)
Female				1.00
CLINICAL FEATURES				
ABO Blood Groups				
A	1.499	0.771	0.052	4.48 (0.99–20.30)
B	0.423	0.790	0.592	1.53 (0.33–7.18)
O	−0.17	0.789	0.983	0.98 (0.21–4.62)
AB				1.00
Comorbidities				
Presence	3.391	0.350	<0.001*	29.68 (14.95–58.94)
Absence				1.00
Ct value				
ORF1ab gene	0.073	0.101	0.473	1.08 (0.88–1.31)
N gene	−0.089	0.099	0.366	0.92 (0.75–1.11)
INFLAMMATORY MARKERS				
Ferritin (ng/mL)				
>435	0.401	0.379	0.290	1.49 (0.71–3.14)
10–435				1.00
C-Reactive Protein (ng/mL)				
≥5	2.073	0.497	<0.001*	7.95 (3.00–21.06)
<5				1.00
Procalcitonin (ng/mL)				
≥0.05	−2.545	0.480	<0.001*	0.08 (0.03–0.20)
<0.05				1.00
COAGULATION MARKERS				
D-dimer (ng/mL)				
≥500	0.111	0.379	0.770	1.12 (0.53–2.35)
<500				1.00
INFECTION MARKERS				
White Blood Cell Count (x10^9/L)				
>10.0	−0.434	0.673	0.519	0.65 (0.17–2.42)
4.5–10.0	0.402	0.643	0.532	1.49 (0.42–5.27)
<4.5				1.00
Neutrophil Count (x10^9/L)				
>0.70	−0.378	1.466	0.796	0.69 (0.04–12.11)
0.50–0.70	0.046	1.365	0.973	1.05 (0.07–15.21)
<0.50				1.00
Lymphocyte Count (x10^9/L)				
>0.40	−0.082	1.593	0.959	0.92 (0.04–20.88)
0.20–0.40	0.033	0.535	0.950	1.03 (0.36–2.95)
<0.20				1.00

White blood cell (WBC) count was identified as low (<4.5 × 10^9/L), normal (4.5-10.0 × 10^9/L), and high (>10 × 10^9/L). More than 70% of cases in both severe and non-severe groups had a normal WBC count, with similar median values of 7.90 × 10^9/L. There were 5% more cases with higher-than-normal WBC count in the severe than non-severe group. Likewise, the neutrophil count was divided into low (<0.50), normal (0.50–0.70), and high (>0.70), with the majority of both severe and non-severe cases having a normal neutrophil count. A little higher median count of 0.65 × 10^9/L was observed with the severe group as opposed to the latter with 0.62 × 10^9/L. Lymphocyte count was grouped into low (<0.20), normal (0.20–0.40), and high (>0.40). Normal lymphocyte count was predominant in both groups, accounting for more than 60% of cases in both cohorts. A reversed trend from the neutrophil count was observed in the median lymphocyte count, with the non-severe COVID-19 cases charting 0.24 × 10^9/L, a figure higher than the severe group at 0.22 × 10^9/L.

Univariate analysis in Table 1 showed that age groups ($p < 0.001$), sex ($p = 0.038$), ABO blood groups ($p < 0.001$), comorbidities ($p < 0.001$), ORF1ab gene ($p < 0.001$), N gene ($p < 0.001$), LDH ($p < 0.001$), ferritin ($p < 0.001$), CRP ($p < 0.001$), PCT ($p = 0.004$), PT ($p = 0.049$), D-dimer ($p = 0.042$), WBC count ($p = 0.013$), neutrophil count ($p = 0.001$), and lymphocyte count ($p = 0.002$) were, when taken individually, were significantly associated with COVID-19 disease severity. On the other hand, factors such as platelet count ($p = 0.127$) and APTT ($p = 0.961$) were not statistically significant.

3.2. Determinants of disease severity with binary and multivariate logistic regression

Factor analysis was performed using binary logistic regression to determine which factors are significantly associated with disease severity. The binary logistic regression revealed age groups, sex, ABO blood groups, comorbidities, ORF1ab and N genes, ferritin, CRP, PCT, D-dimer, WBC count, neutrophil count, and lymphocyte count were significant factors related to disease severity (Table 2).

The odds ratio for age ≥60 years was 65.43 [95% CI (38.11–112.34], meaning older patients were 65.43 times more likely to acquire severe COVID-19 than those less than 30 years of age. Similarly, those aged 30 to 59 years had 11.19 [95% CI (16.53–19.18)] times more likely to have severe COVID-19 than the younger cohort of patients. Male patients were 1.18 [95% CI (1.01–1.37)] times more likely to acquire severe COVID-19 than their female counterparts. A significant association was also found in blood group A with an odds ratio of 6.68 [95% CI (3.69–12.08)]. Those whose blood group was type-A were 6.68 times more likely to acquire critical COVID-19 than type-AB individuals. The presence of comorbidities has also been linked to disease severity. With an odds ratio of 36.34 [95% CI (25.11–52.60)], patients who had one or more pre-existing conditions or comorbidities like chronic lung disease, CKD, CVD, cancer, HPN, and DM had 36.34 times higher likelihood of acquiring critical COVID-19 than those who were not suffering from such conditions.

The inflammatory marker ferritin was found to be significantly associated with disease severity. A blood ferritin level of >435 ng/mL had an odds ratio of 2.37 [95% CI (1.63–3.46)], which translated to a 2.37 times higher likelihood of acquiring severe COVID-19 than those whose blood ferritin level was normal. CRP, with higher-than-normal levels of ≥5 ng/mL, resulted in an odds ratio of 3.23 [95% CI (1.96–5.34)], meaning those who had high blood CRP were 3.23 times more likely to get infected with several COVID-19 than those who had normal levels. With an odds ratio of 0.53 [95% CI (0.34–0.82)], patients who had PCT levels of ≥0.05 ng/mL were 47 times less likely to acquire severe COVID-19 than those whose blood PCT was <0.05 ng/mL.

Among the coagulation markers, only D-dimer was found to be significantly associated. Blood D-dimer level of ≥500 ng/mL resulted in an odds ratio of 1.50 [95% CI (1.01–2.23)], meaning those who had high blood D-dimer levels were 1.50 times more likely to be infected with severe COVID-19 than those with normal levels.

With an odds ratio of 1.74 [95% CI (1.12–2.72)], those with high WBC counts were 1.74 times more likely to contract severe COVID-19 than those with low levels. Similarly, those with a high neutrophil count of >0.70 × 10^9/L had an odds ratio of 1.80 [95% CI (1.09–2.96)], which means that they had 1.80 times higher likelihood of acquiring severe COVID-19 than their low counterpart. Those with normal lymphocyte count of 0.20-0.40 × 10^9/L were also found to be significant and resulted in an odds ratio of 0.70 [95% CI (0.56–0.86)]. This means that those who had normal lymphocyte count had a 30% reduction in chances of acquiring severe COVID-19 than those with low lymphocyte count.

To further determine which among the factors that were significantly associated with disease severity contributed significantly to disease severity, factor analysis was performed using multivariate logistic regression where disease severity was taken as the dependent variable and the predictors, or independent variables, were those factors found to be significantly associated with disease severity, as shown in Table 2. The multivariate logistic regression revealed that age groups >60 years and 30–59 years, presence of comorbidities, CRP ≥5 ng/mL, and PCT ≥0.05 ng/mL were significant predictors of COVID-19 disease severity (Table 3).

The odds ratio for age >60 years was 58.62 [95% CI (17.40–197.49)], meaning that older patients were 58.62 times more likely to acquire severe COVID-19 than those who were aged less than 30 years. Similarly, those aged 30 to 59 years had 6.95 [95% CI (2.67–18.09)] times more likely to have severe COVID-19 than the younger cohort of patients. The presence of comorbidities has also been linked to disease severity. With an odds ratio of 29.68 [95% CI (14.95–58.94)], patients who had one or more comorbidities like chronic lung disease, CKD, CVD, cancer, HPN, and DM had 29.68 times higher likelihood of acquiring severe COVID-19 than those who were not suffering from such conditions. The inflammatory marker CRP, with higher-than-normal levels of ≥5 ng/mL, resulted in an odds ratio of 7.95 [95% CI (3.00–21.06)], meaning those who had high CRP levels were 7.95 times more likely to get infected with severe COVID-19 than those who had normal CRP of below 5 ng/mL. A high PCT level of ≥0.05 ng/mL resulted in an odds ratio of 0.08 [95% CI (0.03–0.20)] was another significant inflammatory marker. This means that those whose blood PCT levels were 0.05 ng/mL and higher were 20 times less likely to acquire severe COVID-19 than those with PCT below 0.05 ng/mL.

4. Discussion

4.1. Highlights of the study

In this study, we observed that most severe patients were older, predominantly male, with blood type A, had one or more comorbidities, lower median Ct values in both ORF1ab and N genes, and higher-than-normal LDH, ferritin, CRP, PCT, PT, APTT, and D-dimer, while maintaining normal levels of complete blood count components such as WBC count and its subsets neutrophils and lymphocytes. Non-severe group, on the other hand, had an observable lower median age, composed of more females than males, were predominantly type O, had no known comorbidities, and higher median Ct values in both ORF1ab and N genes, all while maintaining the same trend as the critical and severe for other blood biomarkers.

Binary logistic regression was utilised to individually assess the association of these demographic and clinical factors with the degree of severity of COVID-19 infection. This revealed age (in years), sex, ABO blood groups, comorbidities, Ct values of ORF1ab and N genes, ferritin, CRP, PCT, D-dimer, WBC count, neutrophil count, and lymphocyte count were significantly associated with disease severity. To further analyse these significant factors, multivariate analysis was done to collectively investigate their possible association and predictability of COVID-19 disease severity. This had shown that age, particularly >60 and 30–59 years, presence of comorbidities, high CRP level of ≥5 ng/mL, and high PCT level of ≥0.05 ng/mL were significant predictors of the degree of severity of COVID-19 infection.

4.2. Previous research findings related to the study

Previous studies around the globe have identified the relationship between many demographic characteristics and clinical laboratory findings with several outcome measures such as survival and non-survival, severe and non-severe, ICU admission and fatalities, and to some extent mild, moderate, severe, and critical groups. Although similarities have been identified, several factors vary across different cohorts, timelines, and geographical locations.

This study confirmed that, much like the rest of the world, age was a significantly associated factor with COVID-19 disease severity in the Philippines, meaning elderly individuals had a higher likelihood of acquiring severe forms of COVID-19 than younger individuals [10,11,12,13,14,15,16]. Much like other Asian territories, males were found to be more susceptible to COVID-19 than females. They had higher chances of acquiring more severe forms leading to ICU admission and, ultimately, death [. The distribution of infections mirrored the current Philippine population with a little more males than females and the worldwide statistics wherein almost two-thirds of all infections were aged 25 to 64 years [15,24]. For this study, sex was not a significant predictive factor contributing to the degree of severity. Although some had elaborated on the occurrence of females being less susceptible to severe forms of COVID-19 than males through a phenomenon wherein females' reduced vulnerability to viral infections may be caused by their X chromosomes (females have two, while males only have one) as well as sex chromosomes that serve critical roles in both adaptive and innate immunity [25].

Blood type O was the most common among ABO blood groups in the Philippines, followed by A, B, and AB. Pooled datasets from China and the US showed how the majority of the recorded infections were also typed A and was then identified as a risk factor. At the same time, type-O was referred to as a protective factor with significantly lower death prevalence [26,27,28,29]. Type-A accounting for most severe cases was consistent with the case-control analysis of single-nucleotide polymorphisms (SNPs) of chromosome 9, the ABO blood group gene, of almost 4,000 patients from Spain and Italy. In addition, this finding about the said blood group was congruent with the studies conducted in Turkey, Sweden, France, and Cyprus [30]. It is interesting that countries heavily impacted by COVID-19 fatalities, such as Italy, the US, Brazil, and Spain, all had a proportion of type-O individuals that were less than 40% of the population, while nations with lower COVID-19 death rates, such as Saudi Arabia, Egypt, and Singapore, all had a proportion of the same type higher than 40% [31,32]. Guillon et al. explored the suppressing activity of ABO antibodies against the natural SARS-CoV-2 receptors. The S protein synthesised by A-positive-infected cells overlaps A histo-blood group epitopes in vitro; hence anti-A natural antibody may prevent S protein and ACE2 adhesion. Blood type-O individuals may create anti-A and anti-B natural antibodies, which may impede viral cell adhesion and explain their lower infection risk [33,34]. In our study, type-A was a significant factor contributing to disease severity. It was observed to be predominant in those who contracted severe COVID-19, while a congruent finding for the number of non-severe cases seemed to affirm type-O as a protective factor.

Several hypotheses have been proposed to explain why comorbidities related to the body's most vital organs, like the heart and blood vessels, brain, and kidneys, were associated with increased disease severity and death. For example, the heart and kidneys were determined to have the highest levels of ACE2, a discovered functional host-cell receptor for SARS-CoV-2 [35]. This study found this data consistent with the fact that those who had identified themselves with one or more pre-existing conditions suffered from severe COVID-19. At the same time, there was a greater percentage of those with no comorbidities among the non-severe cases. Also, the higher percentage of individuals aged 60 years and up who acquired severe COVID-19, coupled with a great majority of the severe group having one or more comorbidities, can support the findings of a higher mortality rate in previous studies [15].

The Ct value is inversely proportional to the quantity of viral RNA copies identified in positive samples. The more viral RNA there is, the lower the Ct value [36]. A lower median Ct value (meaning highest viral load) found in the severe group for both ORF1ab and N genes was a similar finding from a previous study wherein Ct values were considerably lower in individuals who reported one or more respiratory symptoms and higher in those who reported the absence of symptoms at the time of collection [37], as the majority of the severe confirmed COVID-19 cases in this study presented with one or more comorbidities.

Cytokine storm was a phenomenon linked to the increased levels of ferritin, CRP, and other inflammatory blood biomarkers [38,

39], as well as ARDS, a phenomenon that identified patients in critical COVID-19 state [40], further worsening to ICU support and ultimately death [41]. Ferritin, an iron storage protein whose median level was higher in severe than non-severe patients, was remarkably high among patients who died of COVID-19 and had a longer duration of hospital stay in a previous study [42], deducing it as a contributor to cytokine storm phenomenon as well as more severe forms of the disease [43]. This was in addition to the fact that CRP, a common marker of severe infections and inflammations [44] and an important player in host resistance to pathogenic microorganisms, had been pointed out by previous clinical studies to be associated with lesions in the respiratory system among patients identified with more severe forms of the disease [45]. Additionally, a previous study showed how elevated PCT levels increased the chances of admission to the ICU and death among patients from a facility in Kuwait. This finding was quite different in this study, wherein higher levels of blood PCT were more evident in the non-severe group [46]. This was consistent with findings from a study done in Croatia wherein lower levels of CRP, PCT, and ferritin were evident in survivors [15]. Hospitalised severe COVID-19 patients in Bangladesh recorded increased biomarkers levels [47]. At the same time, LDH was mentioned to have also been increased from a study in Pakistan [22], which remarkably mirrored the difference in median values of LDH between the two groups. In our study, elevated levels of these blood biomarkers were seen in most cases of severe and even non-severe COVID-19, of which CRP and PCT were found to be significant predictors of COVID-19 disease severity.

A previous study revealed that levels of APTT, PT, and D-dimer varied considerably between severity levels, with critically ill individuals having greater levels [14,17,22,48]. This finding was consistent with this study. Platelet was not significantly associated with disease severity in this study, a finding similar to a cohort in Pakistan [22]. Severe cases with slightly higher median platelet count than non-severe cases were similar to a cohort from the same country where thrombocytopenia was observed with increased disease severity [16] but different from a cohort in Wuhan where lower platelet counts were more frequent in the severe than non-severe group [49]. What strengthened the variety of results depending on the sampling population and geographic location was a finding from a study in Kuwait where more than half of the patients had lower-than-normal PT [17]. In contrast, this study found the majority of recorded cases in both groups to be higher than normal. The same study from Kuwait and another from China had over half of the patients with high D-dimer [17,48] and severely ill individual having considerably greater levels of D-dimer [47]. This finding which also appeared in this study with more than 80% of recorded cases exhibiting above normal blood D-dimer levels [14]. D-dimer was a culprit for altered coagulation patterns among patients identified with COVID-19 infection [50] as well as those who had died [51] and were admitted to the ICU or identified as having critical and severe COVID-19 infections [52,53] and death as the worst clinical outcome [54]. Like a study conducted by Taj et al. APTT was found to be prolonged in severe cases but appeared to be the same case for non-severe cases in this study. It has been said the degree of coagulopathy as well as the presence of conditions that affect the normal coagulation process in the body, greatly affect the manifestation and variability of both PT and APTT [22].

WBC count finding for this study was similar to the research carried out in Kuwait [17] and during the beginning of the pandemic across 31 provinces in China [23] wherein a great majority had normal WBC count [49]. This was quite different to what was expected as the clinical management guidelines for COVID-19 in the Philippines alert clinicians of decreased levels of WBC, and the findings from a unit of hospitalised patients in Bangladesh and Pakistan wherein increased levels of WBC [16] and neutrophil count was observed [47]. Neutrophil and lymphocyte counts had contrasting findings to some articles that linked severe COVID-19 to an increased neutrophil count [46] and the issued clinical management guidance of the Department of Health Philippines wherein decreased levels of lymphocytes (termed as lymphocytopenia) was to be observed, as was with several provinces in China [11,49]. Additionally, our study results differ from research conducted in Pakistan, wherein decreased lymphocytes and increased neutrophils were noted and attributed to increased inflammation and suppression of the immune system [22].

4.3. Significant findings of the study

With a significant death toll worldwide and the continuously evolving viral phenotype, COVID-19 still has no end. The frequent resurge in cases had been re-occurring in the Philippines, which may be attributed to the constantly changing induction process that the virus undergoes. This study aimed to stratify several identified cases and analyse some of the most common demographic characteristics and blood parameters that may influence the degree of severity of COVID-19 infection. Regardless of the previous similar studies conducted across several countries [11,15,16,17,21,24], those findings were less likely to be consistent, partly due to geographical and ethnic differences as well as the variation in sample size. To the best of our knowledge, this work represents the first large-scale analysis of factors affecting COVID-19 severity in the Philippines. In addition to the advantage of using a larger sample size, this study has also integrated several routine blood tests that are commonly done in the hospital as part of the standard care of COVID-19 patients [7,8], thereby increasing the feasibility of implementing this research's findings in the real clinical settings.

The Philippines has a relatively young population with a high-density concentration in cities and nearby provinces which were included in the setting of this study. These factors may contribute to a diverse age population, with more than 50% of the recorded COVID-19 cases being aged 30–59 years, followed by those younger than 30 years of age. This study showed a relatively younger median age of all cases at just 40 years, significantly lower than those in Egypt at 48 years [11] and across China at 50 years [55] and an even lower median age of 37 years for those who get infected with non-severe COVID-19.

The majority of non-severe COVID-19 cases were not suffering from any comorbidity. This pattern was similar to the ABO blood groups in which non-severe cases were predominantly blood type-O. On the other hand, more than 90% of severe cases had one or more comorbidities, with an observable ABO blood group pattern showing blood type-A being predominant in this group. Some may argue that this phenomenon could account for type-O being more resistant to COVID-19 because of the absence of comorbidities and type-A being more susceptible to COVID-19 due to one or more comorbidity. This may also be one reason hospitals were congested during the surge in cases because those who identify themselves as apparently healthy individuals were rushed for emergency

treatment when symptoms of moderate pneumonia surfaced.

CRP and PCT, both of which were inflammatory markers, were found to be significant factors even after multivariate analysis. These blood biomarkers, which were previously cited for having been associated with lung lesions among patients with more severe forms of the disease [45] and higher chances of ICU admission, should be given particular attention. Since it doesn't take a long while for this test to be done in a clinical laboratory, this should be adapted as a screening biomarker alongside blood typing and identifying age as well as pertinent medical history and point for prioritisation in the current vaccination rollouts. Therefore, special attention should be given to these populations at risk to reduce the burden of care and the possible mortality risk. Certain measures should be imposed to limit possible viral induction in the elderly population, those who have pre-existing medical conditions, and those who have been identified to have higher-than-normal blood CRP and PCT levels. However, we observed that association between the PCT level and COVID-19 severity in this study, that a high PCT level correlating with a reduced risk of disease severity unexpectedly contradicts the previous findings and the role of this parameter in typical clinical practice. This inconsistency may be affected by existing clinical conditions in some patients of the non-severe group, particularly bacterial co-infection [56]. Generally, the PCT parameter appears to be more sensitive to bacterial infection than viral infection or non-infectious inflammatory diseases, that serum PCT level was found markedly elevated in the patients who infected with bacteria while remained relatively low in those who infected with virus [57,58]. PCT is usually produced within two to 4 h of response to an inflammatory stimulus (infection and injury), reaches its peak within 24 to 48 h, and then starts to rapidly decline with effective treatment or in case of non-bacterial infections and other non-infectious conditions [59,60]. The elevated PCT level can be detectable for a week in patients with inadequate bacterial infection control in relation to the severity [61]. In our study, the PCT level was analyzed at only one timepoint of diagnosis. Hence, it could be possible that non-severe patients with high PCT may have sought medical intervention sooner during their PCT peaks, while patients in severe group may have sought medical treatment later when worse symptoms have developed, thus missing the timing of PCT peak. On the other hand, an inverse association between PCT level and COVID-19 severity detected in this study could also be true, which explained by the suppressive effect of the virus on this parameter. Previous studies have demonstrated that PCT synthesis could be inhibited during viral infection, possibly by the activity of interferon (IFN)-gamma whose concentration also increases along with this condition [62,63]. Therefore, the usefulness of this parameter as a predictor of COVID-19 severity needs to be further verified by ruling out the possible influence of the underlying conditions.

Overall, the current study provided a set of factors to help predict the severity of confirmed COVID-19 patients in the Philippines at the first admission. Typically, following its COVID-19 guidelines, these blood biomarkers have already been used for assessing a patient's condition instead of clinical signs and symptoms, allowing the effective implementation of these identified predictors in the actual clinical settings. Nevertheless, their use in clinical applications could be limited due to the changes of the viral genome and the coverage of vaccines in the Philippines from the time of conducting this research until the present time. The emergence of new virus variants that differ in their genotype and phenotype from the first SARS-CoV-2 detected in this study, particularly the Omicron and its subvariants, can cause changes in their pathogenicity and transmissibility [64], which may in turn led to different clinical outcomes in COVID-19 patients. As the Omicron strains appear to be more transmissible and less pathogenic that the majority of the Omicron-infected cases tended to exhibit less severe or milder clinical manifestation than those infected with other variants, therefore a high-severity group would be narrowed down to the patient's characteristics of old age and having comorbidities [65,66]. Additionally, the introduction of COVID-19 vaccines to the Philippines during the time period of data collected [67] could have an impact on the immune characteristics of patients across different age groups [68]. The severity of COVID-19 infection was shown to be reduced in vaccinated elderly individuals [69], while in this study the older age was a significant factor associated with increased severity. However, the vaccine immunity in this vulnerable group seems to be transient and gradually declines over time [70]. Besides, no major changes in blood parameters involved in this present study or the risk of hematological abnormalities following COVID-19 vaccination was currently observed [71,72], supporting the possible utility of these factors in vaccinated cases.

4.4. Potential limitations of the study

The present study has a few drawbacks. The study only represented select localities in the Philippines, not the entirety of the population at risk. Only conventional PCR test results warranted the inclusion of a confirmed case and not alternative diagnostic techniques such as rapid antigen testing, nucleic acid amplification test, and cartridge-based PCR. There was also the possibility of bias because of the self-reporting nature of the patient's pertinent clinical data, such as comorbidities upon admission and history taking. Even if interviews were conducted to confirm the details presented in the paper forms, potential loss of data due to omissions was possible. Due to the study's cross-sectional nature, causal inferences cannot be established, in addition to the non-consideration of the impact of SARS-CoV-2 variants given the limited conduct of whole genome sequencing (WGS) in the Philippines. The missing of some blood parameter data was especially evident in the non-severe case group, particularly the mild and asymptomatic cases, due to the limitations imposed by the clinical management guidelines issued by the Department of Health Philippines in managing confirmed COVID-19 cases. Therefore, further studies were recommended to explore more about the roles of those blood biomarkers and other pertinent clinical data such as systolic and diastolic blood pressure, heart rate, and oxygen saturation level [11]. In addition, the possible contribution of viral mutations and COVID-19 vaccination to the disease severity have not been taken into account in this study, partly due to the unavailability of genomic sequencing for COVID-19 variants detection as well as the low vaccine acceptance rate in the Philippines during the time of data collection [73]. Taking these factors into account would warrant further studies, of which the results can be implemented in clinical settings.

5. Conclusion

Since it doesn't take long for these pertinent medical history and laboratory findings to be done, the identified risk factors should be considered during patient history taking, triaging, priority in admission and testing, and vaccination rollout efforts. To reduce the burden of care and the possible mortality risk, special attention should be given to these populations at risk. Certain measures should be imposed to limit possible viral induction in the elderly population, those who have pre-existing medical conditions, and those who have been identified to have higher-than-normal blood CRP and PCT levels.

Author contribution statement

Marjonel L. Acedera: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Wandee Sirichokchatchawan; Sirikalaya Brimson: Analyzed and interpreted the data; Wrote the paper.

Anchalee Prasansuklab: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

The data used to support the findings of this study are included within the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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