BENHA MEDICAL JOURNAL bmj

Print ISSN 1110-208X.

Online ISSN 2357-0016

Original article

Relationship Between Platelet Indices and Severity of COVID-19 Infection

Mahmoud H. Rizk, Mohamed A. El Assal, Fawzy M. Khalil,

El Mokhtar O. Ahmed, Mohamed A. Afifi

Internal Medicine Department, Faculty of Medicine Benha University, Egypt.

Corresponding to:
Dr. El Mokhtar O. Ahmed.
Internal Medicine Department, Faculty of Medicine Benha University, Egypt.
Email: mctrhmd@gmail.com

Received:
Accepted:

Abstract:

Background: Coronavirus disease of 2019 (COVID-19) has resulted in millions of cases worldwide. As the pandemic has progressed, the understanding of this disease has evolved. Both arterial and venous thrombosis are primarily caused by platelets, and platelet-virus interactions increase the risk of thrombosis by encouraging pro-inflammatory and procoagulant states during viral infection. Aim: To investigate the relationship between platelet indices such as platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), platelet large cell count (PLCC), and platelet large cell ratio (PLCR) and severity of illness in patients with COVID-19. **Methods:** A case-control study included 50 patients with COVID-19 infection and 50 healthy individuals (control group), patients were selected from outpatient clinic, internal medicine department, intermediate, and intensive care units at Benha University Hospital, Egypt. Platelet indices were recorded from both groups. **Results:** COVID-19 cases were significantly associated with higher MPV and PLCR, significantly lower PLT, PCT, PDW, and PLCC when compared to control group. Severity showed significant positive correlations with MPV, PLCR and significant negative correlations with PLT and PCT. While no significant correlations were found between severity with PDW or PLCC. Lower PLT, higher MPV and PLCR, were considered unfavourable risk predictors of COVID-19 severity. Lower PLT, higher MPV and PLCR were considered unfavourable risk predictors of COVID-19 mortality. **Conclusion:** Platelet indices like PLT, PCT, MPV, PDW, PLCC, and PLCR could be used as efficient diagnostic and prognostic biomarkers for COVID-19.

Key words: COVID-19, Platelet Indices, Platelet Count, Severity.

Introduction

Coronaviruses are positive single-stranded, enclosed, large RNA viruses that, in addition to humans, can infect a range of animals. Coronaviruses were named by their shape as spherical virions with a core-shell and surface projections resembling a solar corona. Coronaviruses are classified into four subfamilies: alpha, beta, gamma, and delta. Alpha and beta coronaviruses originated from mammals, primarily bats, whereas gamma and delta viruses are derived from pigs and birds [(1).] Coronaviruses have been proven to survive for days on different surfaces. Furthermore, hand washing is the cornerstone of virus prevention [(2)]. Masks, gowns, and gloves for contact isolation are also recommended. Because transmission across the ocular surface is conceivable, eye protection should be utilized [(3).] The first clinical manifestation of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) related diseases was COVID-19 pneumonia, followed by gastrointestinal symptoms and silent infections, particularly in young children. So far, observations indicate a mean incubation period of five days and a median incubation period of three days [(3).] In approximately 75% of patients, computed tomography shows that the infection has progressed to a severe condition with dyspnea and severe chest symptoms akin to pneumonia. The majority of instances of pneumonia appear in the second or third week following an asymptomatic illness [(4).] Antiviral medications (such as remdesivir), anti-SARS-CoV-2 monoclonal antibodies (such as bamlanivimab/etesevimab, casirivimab/imdevimab), anti-inflammatory medications (such as dexamethasone), and immunomodulators agents (such as baricitinib, tocilizumab) are currently available under Food and Drug Administration (FDA) [(5).] Platelet reactivity for various diseases is heavily reliant on biologically active markers such as CD36, CD41, CD42a, CD42b, and CD61. Some examples are active surface receptors and platelet secretory products. Platelets change the expression and signaling of these markers in various disease diagnosis and prognosis, opening up a vast area for research. Platelet activity is mostly connected with the start of coagulation cascades. Damage to a blood artery directs platelet action to the sub-endothelial surface, where it establishes hemostasis [(6).] Deep vein thrombosis, pulmonary embolism, and microthrombi in small and large arteries are all possibilities. These initial observations were accompanied by significantly higher amounts of D-dimer, a fibrin degradation product, in the plasma of patients with COVID-19 [(7).] These abnormally high amounts of D-dimers in plasma have been linked to severe COVID-19 infection and major thrombotic events [(8).] These findings made platelets and thrombus formation among the key research areas for COVID-19. RT-qPCR was used to find SARS-CoV-2 mRNA traces in isolated platelets, and electron microscopy was used to show virions within platelet sections [(9).] Platelets may be considered an innate immune response component since they can take up and eliminate viruses such as influenza or human immunodeficiency viruses (HIVs). However, angiotensin-converting enzyme 2 (ACE2) has been identified as the principal cell entrance receptor for SARS-CoV-2 (for example, in airway epithelial cells). ACE2 is expressed on the surfaces of many immune cells, including monocytes and macrophages, as well as respiratory and vascular endothelial cells. [(10).] Blood platelet count changes have been recorded in patients with acute COVID-19 infection. Severely sick individuals frequently have decreased PLT, although in patients with minor symptoms of other respiratory infections, such as influenza, modestly higher PLT have been reported [(11).] Patients with severe COVID-19 infection had a low PCT as well as an increase in MPV, PDW, and PLCR [(12).]

Subjects and methods

Study design: This case-control study included 50 patients with COVID-19 infection (10 mild cases, 10 moderate cases, 10 severe cases , 20 critical cases) and 50 healthy controls, patients were selected from outpatient clinic, internal medicine department, intermediate care and intensive care unit at Benha University Hospital June 2022 to February 2023 According to Living guidance for clinical management of COVID-19 WHO 23 November 2021 (CDC, 2020). The included cases were of both sexes and older than 18 years, they were RT-PCR positive. Patients with known hematological diseases or patients using drugs that may affect platelets function or count, pregnant women and alcoholics were excluded from this study. All studied cases were subjected to full history taking including history of vaccination, symptoms of COVID-19, any hematological disease and drug history that may affect PLT or function. General examination including vital signs and oxygen saturation, cardiopulmonary, abdominal and neurological examination was done. All participants were undergone laboratory investigations including platelet count and platelet indices. Imaging with chest x- ray and CT scan were also done for all patients.

Ethical Considerations

An approval from Research Ethics Committee in Benha Faculty of Medicine was obtained. An informed consent was obtained from each patient (or relatives) before enrollment in the study. {M.S.2.6.2022}

Sample size:

Sample size was calculated by Stata Corp. 2021. Stata Statistical Software: Release 17. College Station, TX: Stata Corp LLC., and published study with respect to platelet indices in COVID-19 infection cases compared to healthy control groups. (15)

Statistical Analysis

The collected data was analyzed using Statistical package for Social Science (IBM Corp. released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). The Student T Test was performed to determine the statistical significance of the difference between the means of the two research groups. To investigate the association between two qualitative variables, the Chi-Square test was performed. The strength of link between two quantitative variables was determined using correlation analysis. The receiver operating characteristic (ROC) curve was used for assessing the sensitivity and specificity of quantitative diagnostic measures. The optimal cut off point was determined by maximizing the area under curve (AUC) value. Risk variables were predicted using regression analysis. P-value is considered significant if <0.05 at confidence interval 95%.

Results

Table (1): The mean age of COVID-19 cases was 45.4 years, ranged from 19 to 72. 52% of them were males and 48% were females. No significant differences were found between COVID-19 patients and control group regarding risk factors or vaccination. Symptoms and laboratory parameters were described in Table 1 and 2. Among all studied cases, 66% were admitted to ICU, mean ICU stay was 7.97 days, ranged from 2 to 15 days. 10% of the patients died during the period of the study. COVID-19 cases were significantly associated with higher WBC count and neutrophil lymphocyte ratio (N/L) but significantly lower absolute lymphocytic count (ALC) when compared to control group. While no significant differences were found between cases and control group regarding haemoglobin (Hb) or absolute neutrophilic count (ANC).

Table (2) COVID-19 cases were significantly associated with higher MPV and PLCR, as well as lower PLT, PCT, PDW, and PLCC when compared to control group**.**

DOI: 10.21608/bmfj.2023.221152.1848

Table (1): Comparison of patients with COVID-19 and control groups regarding studied parameters.

		Patients n = 50	Control n = 50	*P*
Age (years)	**Mean ± SD.**	45.44 ± 15.84	45.24 ± 15.47	0.949
	Median (Range)	46.5 (19.0 – 72.0)	47.5 (20.0 – 69.0)	
Male	**N (%)**	26(52.0%)	29(58.0%)	0.546
Female	**N (%)**	24(48.0%)	21(42.0%)	
Medical occupation	**N (%)**	41(82.0%)	40(80.0%)	0.799
COVID vaccination	**N (%)**	45(90.0%)	47(94.0%)	0.715
DM	**N (%)**	11(22.0%)	9(18.0%)	0.617
HTN	**N (%)**	5(10.0%)	4(8.0%)	1.000
CKD	**N (%)**	5(10.0%)	1(2.0%)	0.204
Fever	**N (%)**	46(92.0%)		
Cough	**N (%)**	41(82.0%)		
Hypoxia	**N (%)**	29(58.0%)		
Sepsis	**N (%)**	17(34.0%)		
Thrombosis	**N (%)**	18(36.0%)		
Shock	**N (%)**	15(30.0%)		
DCL	**N (%)**	10(20.0%)		
ICU admission	**N (%)**	33 (66.0%)		
ICU stay	**Mean ± SE.**	7.97 ± 0.70		
	Median (Range)	7.0 (2.0 – 15.0)		
Alive	**N (%)**	45 (90.0%)		
Died	**N (%)**	5(10.0%)		

DM : Diabetes milites, HTN : Hypertension, DCL: Disturbed conscious level

Table (2): Comparison of CBC among COVID-19 and control groups**.**

		Patients n = 50	Control n = 50	P
Hemoglobin (g/dL)	**Mean ± SD.**	12.83 ± 0.96	13.05 ± 0.96	0.269
	Median (Range)	12.85 (11.0 – 14.30)	13.05 (11.3 – 15.60)	
WBC ($X10^9$/L)	**Mean ± SE.**	10.18 ± 0.49	8.44 ± 0.28	0.042*
	Median (Range)	9.80 (4.60 – 18.20)	9.05 (4.60 – 11.00)	
ALC ($X10^9$/L)	**Mean ± SE.**	0.88 ± 0.05	3.12 ± 0.11	<0.001*
	Median (Range)	0.90 (0.36 – 1.40)	3.05 (1.60 – 4.50)	
ANC ($X10^9$/L)	**Mean ± SE.**	7.15 ± 0.34	6.05 ± 0.17	0.187
	Median (Range)	6.0 (4.5 – 12.1)	4.8 (3.4 – 7.5)	
N/L	**Mean ± SE.**	10.43 ± 1.06	1.74 ± 0.09	<0.001*
	Median (Range)	7.56 (3.21 – 33.16)	1.60 (0.90 – 3.30)	
Platelets (PLT) ($X10^9$/L)	**Mean ± SD.**	238.11 ± 49.44	272.24 ± 68.07	0.005*
	Median (Range)	226.83(183.0 – 433.17)	254.33 (194.0 – 440.0)	
PCT	**Mean ± SD.**	0.26 ± 0.05	0.29 ± 0.06	0.002*
	Median (Range)	0.24 (0.20 – 0.47)	0.28 (0.22 – 0.47)	
MPV (fL)	**Mean ± SD.**	10.77 ± 1.83	9.65 ± 1.52	<0.001*
	Median (Range)	11 (8.5 – 13.4)	9.66 (7.46 – 12.69)	
PDW (%)	**Mean ± SD.**	14.69 ± 3.14	16.00 ± 3.01	0.036*
	Median (Range)	13.73 (11.44 – 27.08)	15.73 (12.13 – 27.08)	
PLCC	**Mean ± SD.**	71.18 ± 6.00	73.49 ± 6.17	0.040*
	Median (Range)	69.3 (65.7 – 87.4)	71.1 (67.4 – 89.7)	
PLCR (%)	**Mean ± SD.**	27.91 ± 6.02	25.07 ± 3.20	0.004*
	Median (Range)	27.24 (22.42 – 47.41)	24.83 (20.03 – 32.05)	

SD. Standard deviation, SE. Standard error, Range: Min. – Max. *:Significant ≤0.05; U, *Mann-Whitney test. WBC,* total leucocytic count; ALC, absolute lymphocytic count; ANC, absolute neutrophilic count; N/L, neutrophil lymphocyte ratio.

Table (3): Platelets showed gradual decrease in count and PCT associated with ascending COVID-19 severity, on the other hand, platelets showed gradual increase in MPV and PLCR associated with ascending COVID-19 severity. PDW and PLCC were not associated with COVID-19 severity.

Figure 1 :COVID-19 severity showed significant positive correlations with MPV (r=0.915, p<0.001), and PLCR (r=0.654, p<0.001); as well as significant negative correlations with PLT (r=-0.797, p<0.001), and PCT (r=-0.507, p<0.001). No significant correlations were found between severity of infection and PDW or PLCC (p>0.05 for each).

Table (3): Association between severity of COVID-19 with platelet count and indices.

		Severity of patients with COVID-19				P1	Mild vs.	Moderate vs	Severe vs
		Mild n=10	**Moderate n=10**	**Severe n=10**	**Critical n=20**				
Platelets (PLT) ($X10^9$/L)	**Mean ± SD.**	308.48±62.14	251.07±12.17	228.44±14.12	201.24±11.59	<0.001*	P2=0.017*	-	-
	Median (range)	284.6(254.3-433.2)	251.6(232.3-270.8)	226.8(208.0-248.8)	201.2(183.0-221.3)		P3=0.001* P4<0.001*	P5=0.343 P6=0.017*	- P7=0.189
PCT	**Mean ± SD.**	0.32±0.02	0.27±0.004	0.24±0.001	0.22±0.003	<0.001*	P2=0.029*	-	-
	Median (range)	0.30(0.28-0.47)	0.28(0.25-0.28)	0.24(0.24-0.25)	0.22(020-24)		P3<0.001* P4<0.001*	P5=0.146 P6=0.005*	- P7=0.243
MPV (fL)	**Mean ± SD.**	8.91±0.37	9.76±0.49	10.87±0.65	12.17±0.67	<0.001*	P2=0.107	-	-
	Median (range)	8.9(8.5-9.4)	9.8(9.1-10.7)	11.1(10.0-11.7)	12.1(11.2-13.4)		P3<0.001* P4<0.001*	P5=0.036* P6<0.001*	- P7=0.005*
PDW (%)	**Mean ± SD.**	12.90 ± 1.02	14.85 ± 1.26	15.43 ± 4.75	15.13 ± 3.37	0.242	P2=0.166	-	-
	Median (range)	12.85(11.44 – 14.52)	15.04(13.00 – 16.58)	13.66(12.13 – 27.08)	14.18(12.69 – 27.08)		P3=0.075 P4=0.069	P5=0.678 P6=0.814	- P7=0.060
PLCC	**Mean ± SD.**	70.34 ± 5.16	71.98 ± 7.83	70.34 ± 5.17	71.62 ± 6.12	0.885	P2=0.553	-	-
	Median (range)	69.28(65.69 – 83.40)	69.28(65.69 – 87.35)	69.34(65.69 – 83.40)	69.28(65.69 – 87.35)		P3=0.998 P4=0.593	P5=0.553 P6=0.880	- P7=0.593
PLCR (%)	**Mean ± SD.**	23.02±0.42	24.43±1.70	26.82±1.10	32.65±6.94	<0.001*	P2=0.424	-	-
	Median (range)	23.02(22.42-23.62)	24.04(22.42-27.24)	27.24(24.83-27.84)	29.04(27.84-47.41)		P3=0.033* P4<0.001*	P5=0.176 P6<0.001*	- P7<0.001*

SD. Standard deviation, Range: Min. – Max. *: Significant ≤0.05; PCT, Plateletcrit; MPV, Mean platelet volume; PDW, Platelet distribution width; PLCC, Platelet large cell count; PLCR, Platelet large cell ratio. P1, p value for comparison between all severity grades; P2, p value for comparison between mild versus moderate; P3, p value for comparison between mild versus severe; P4, p value for comparison between mild versus critical; P5, p value for comparison between moderate versus severe; P6, p value for comparison between moderate versus critical; P7, p value for comparison between severe versus critical.

DOI: 10.21608/bmfj.2023.221152.1848

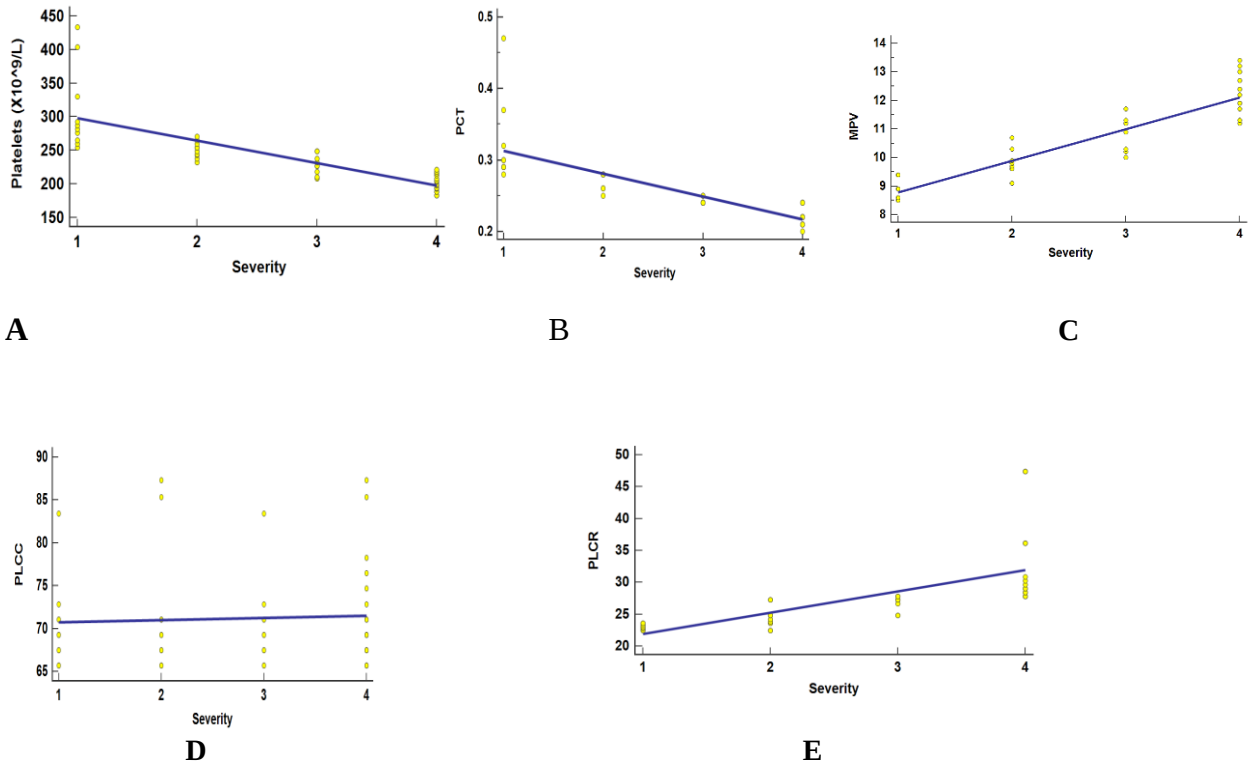

Figure (1): Correlation between severities with (A) platelet count, (B) PCT, (C) MPV, (D) PLCC, (E) PLCR among patients with covid-19. Severity 1, mild; 2, moderate; 3, severe and 4, critical.

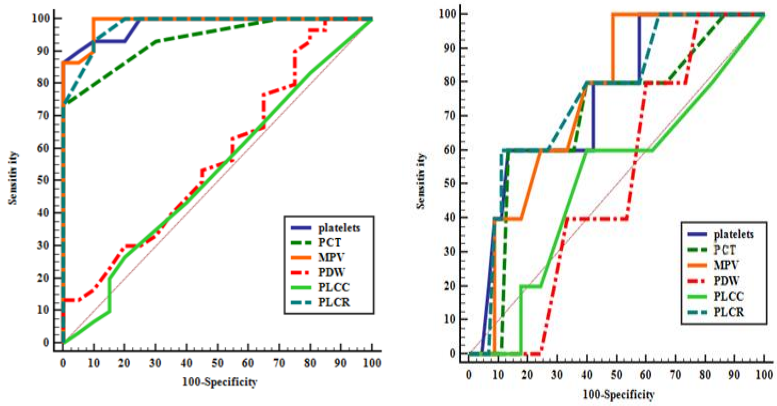

Figure (2) ROC for platelet indices for discrimination between (A) (severe + critical) versus (mild+ moderate), (B) non survivors (dead versus alive).ROC curve of platelet count and indices was conducted for prediction of COVID-19 severity and mortality. On prediction of severity, PLT, PCT, MPV and PLCR showed high accuracy AUC (AUC=0.982, 0.937, 0.988, 0.978 respectively), while PDW and PLCC showed low accuracy AUC (AUC=0.574, 0.526 respectively). On prediction of mortality, PLT, MPV, PLCR showed moderate accuracy AUC

(AUC=0.749, 0.751, 0.758 respectively). While PCT, PDW and PLCC showed low accuracy AUC (AUC=0.680, 0.507, 0.509 respectively).

Table 4 Regression analysis was conducted for prediction of COVID-19 susceptibility, severity and mortality using age, sex, occupation, vaccination, comorbidities, platelet count, indices, as covariates, by conducting both invariable and multivariable analyses. Lower ALC, PLT and PCT, however higher MPV and PLCR were considered unfavourable risk predictors of COVID-19 susceptibility. In addition, lower ALC and PLT, higher MPV and PLCR were considered unfavourable risk predictors of COVID-19 severity. Moreover, lower PLT and higher MPV and PLCR were considered poor risk predictors of COVID-19 mortality.

Table (4): Logistic Regression analysis for prediction of COVID diagnosis, severity and mortality.

	COVID diagnosis		COVID severity		prediction of mortality	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
	P	**P**	**P**	**P**	**P**	**P**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Age	0.949		0.446		0.479	
	1.001(0.976 – 1.026)		1.013(0.980 – 1.046)		1.022(0.961 – 1.087)	
Sex	0.547		0.260		0.707	
	1.275(0.579 – 2.807)		1.791(0.649 – 4.943)		0.697(0.106 – 4.578)	
Occupation	0.799		0.692		0.902	
	1.139(0.419 – 3.097)		0.770(0.212 – 2.797)		0.865(0.085 – 8.807)	
Vaccination	0.465		0.582		0.446	
	0.574(0.130 – 2.545)		1.694(0.260 – 2.060)		0.390(0.035 – 4.388)	
Any comorbidity	0.133		0.093		0.300	
	1.941(0.818 – 4.607)		0.399(0.137 – 1.165)		2.719(0.411 – 1.004)	
ALC	<0.001*	0.030*	<0.001*	0.025*	0.094	
	0.2750.167-0.453)	0.298(0.100-0.889)	0.002(0.000 – 0.021)	0.421(0.045-0.934)	0.045(0.001 – 1.703)	
Platelets (PLT)	0.010*	<0.001*	<0.001*	<0.001*	0.032*	0.017*
	0.989(0.981 – 0.997)	0.251(0.115 – 0.562)	0.844(0.787 – 0.905)	0.039(0.007-0.230)	0.968(0.929 – 0.990)	0.955(0.915 – 0.976)
PCT	0.002*	<0.001*	<0.001*	0.856	0.520	
	0.011(0.009 – 0.057)	0.056(0.015 – 0.162)	0.576(0.273-0.947)	0.998(0.998-1.003)	2.631(0.798-3.490)	
MPV	0.001*	<0.001*	<0.001*	<0.001*	0.033*	0.021*
	1.662(1.243 – 2.221)	1.964(1.731 – 2.400)	2.078(1.741 – 5.150)	1.368(1.183-1.582)	1.013(1.003 – 1.054)	1.243(1.193 – 1.430)
PDW	0.049*	0.116	0.159		0.618	
	0.856(0.733 – 0.999)	0.643(0.449 – 1.922)	1.133(0.952 – 1.349)		0.896(0.580 – 1.382)	
PLCC	0.066		0.708		0.645	
	0.937(0.875 – 1.004)		1.016(0.934 – 1.106)		0.957(0.794 – 1.153)	
PLCR	0.009*	0.012*	<0.001*	0.022*	0.041*	0.033*
	1.170(1.039 – 1.317)	1.495(1.093 - 2.045)	1.659(1.255 – 5.626)	1.985(1.976-2.004)	1.074(1.053 – 1.111)	1.482(1.192 – 1.1402)

OR, odds ratio; CI, confidence interval.

DOI: 10.21608/bmfj.2023.221152.1848

Discussion

COVID-19 is a potentially fatal infectious disease caused by SARS-CoV-2, which was discovered in the Chinese town of Wuhan in November 2019 [13]. Excessive cytokine release has been connected to COVD-19 and the cytokine storm it creates. As a result, it is normal to expect alterations in platelet indices. An automated haematology analyzer can provide platelet-related data such as PLT, PCT, MPV, PDW, PLCC, and PLCR. COVID-19 platelet indices can thus be utilized as simple diagnostic and prognostic tools [14]. In our study, COVID-19 cases were significantly connected with higher MPV and PLCR, while lower PLT, PCT, PDW, and PLCC when compared to the control group [15]. Current study revealed that PLT and PCT declined steadily with increasing COVID-19 severity, while the increase in MPV and PLCR was linked to increasing COVID-19 severity, whereas PDW and PLCC were not. There were also significant negative correlations between COVID-19 severity and PLT and PCT. However, no significant link was seen between severity and PDW or PLCC discovered that platelet count, size, and maturity are connected to an increase in critical illness and all-cause mortality in hospitalized COVID-19 patients. Platelets decreased in count with time and were connected to severity [16]. meta-analysis discovered that high serum levels of CRP, d-dimer, and ferritin were linked to a poor result in COVID-19 infection [17]. The current investigations discovered that COVID-19 severity predictors were PLT, MPV, and PLCR which showed excellent accuracy. PLT, MPV, and PLCR showed good accuracy AUC for non- surviving prediction, in contrast to PDW, and PLCC, which showed poor accuracy AUC. This was consistent with the findings of**,** who discovered that severe patients had much higher MPV and PLCR at hospital admission than non-severe patients [18]. Others discovered in a study that the non-survival group had much higher total WBC and neutrophil counts, but significantly lower lymphocyte and platelet counts, than the survival group at the time of admission [19].

Conclusion

Platelet indices including PCT, MPV, PDW, PLCC, and PLCR are straightforward, affordable, and readily accessible laboratory values from frequently used automated haematology analyzers. Compared to non-COVID-19 people, COVID-19 patients were shown to have different values for several metrics. As a result, these measures could be used as effective COVID-19 biomarkers. However, more researches involving large populations are required to fully establish the value of platelet indices in COVID-19.

Conflict of interest

None of the contributors declared any conflict of interest.

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To cite this article: Mahmoud H. Rizk, Mohamed A. El Assal, Fawzy M. Khalil, El Mokhtar O. Ahmed, Mohamed A. Afifi. Relationship Between Platelet Indices and Severity of COVID-19 Infection. BMFJ XXX, DOI: 10.21608/bmfj.2023.221152.1848.