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Association between platelet indices and the severity of the disease and mortality in patients with COVID-19

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Abstract. – OBJECTIVE: The aim of the study was to determine the association between platelet indices and disease severity, and outcomes of the patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in a secondary hospital.

PATIENTS AND METHODS: 722 hospitalized patients who had positive rRT-PCR for SARS-CoV-2 and/or typical findings of COVID-19 at chest computed tomography (CT) were enrolled in this study. Initial platelet count (PLT) and indices, including mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), MPV/PCT, MPV/PLT, PDW/PLT, PDW/PCT on admission and the third day of hospitalization, and their relationship with disease severity and outcomes were evaluated retrospectively.

RESULTS: The mean age of the patients was 57.2±15.6 years (range: 16-94) and male/female ratio was 1.22. 81.9% of the patients had moderate and 11.8% had severe disease. 1.8% of the patients had thrombocytopenia at admission. The patients transferred to the intensive care unit (ICU) had significantly lower baseline lymphocyte counts, PLT, PCT, and 3rd day lymphocyte counts when compared with the patients in wards. ICU patients also had higher baseline CRP, LDH, ferritin, MPV/PCT, MPV/PLT, PDW/PLT, PDW/PCT ratios, and 3rd day PDW, CRP, LDH, and ferritin levels than the patients in wards. Mortality was associated with lower baseline lymphocyte counts, PLT, PCT, 3rd day lymphocyte counts and PCT. Higher baseline CRP, LDH, ferritin, MPV/PCT, PDW/PLT, PDW/PCT and 3rd day CRP, LDH, ferritin, procalcitonin, PDW, MPV/PCT, PDW/PLT, and PDW/PCT ratios were also associated with poor prognosis.

CONCLUSIONS: Platelet count and ratios were significantly associated with mortality in patients with COVID-19.

Key Words:
COVID-19, MPV, Platelet, Outcome, Adults.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak rapidly spread from Wuhan, China to all over the world in December 2019. It has a variety of clinical manifestations, ranging from asymptomatic infection to severe life-threatening disease. Cytokine storm, acute respiratory distress syndrome and thrombotic complications are major causes of morbidity and mortality in patients with COVID-19 disease.

Platelets play a crucial role in coagulation, hemostasis, thrombosis, immunomodulatory processes, and inflammation. The interaction between pathogens and platelets causes alterations in platelet function (platelet activation and/or apoptosis)[1,2]. Viruses, such as human immunodeficiency virus (HIV), hepatitis C virus (HCV), Ebola, Dengue virus (DV), and influenza virus can directly activate platelets[3,4]. Platelets respond to viruses as both limiting viral proliferation, or complicating inflammation and disease pathogenesis[2,4], such as activated platelets stimulate the coagulation cascade leading to lung injury in influenza[5,6].

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Zhang et al[3] demonstrated that platelets are hyperactivated in COVID-19 patients and SARS-CoV-2-activated platelets *via* the interaction of Spike protein and platelet ACE2 potentiate the pro-thrombotic state and inflammatory response in these patients. Also, the other studies[1,3,7,8] have reported aggregation, adhesion, infiltration, and inflammatory response of platelets contributing to lung injury and microvascular thrombosis in SARS-CoV-2-associated pneumonia. The thrombotic microangiopathy, especially in the lungs, but also in the heart, kidneys and liver have been demonstrated in autopsies of COVID-19 patients[9]. Gu et al[10] stated in their review about thrombocytopathy, endotheliopathy and thromboinflammation in COVID-19 patients that platelet activation and apoptosis are important contributors with the other mechanisms, including hypoxia, inflammation, immune system activation, endothelial activation aand dysfunction in COVID-19 pathogenesis.

It has been proposed that platelets and indices, such as mean platelet volume (MPV), may be used as a prognostic marker in sepsis, critical illnesses[11-14], and also in COVID-19 disease[15-17]. Thus, the aim of this study was to determine the association between platelets and indices, and identify significant prognostic markers which can predict severity and mortality of the disease in the early stage.

Patients and Methods

A total of 722 hospitalized patients who had positive rRT-PCR for SARS-CoV-2 and/or typical findings of COVID-19 at chest computed tomography (CT) between March 31 and May 30, 2020 and September 1 and January 31, 2021 were enrolled in this retrospective observational study.

Demographics, comorbidities, symptoms and signs on admission, initial laboratory tests, PCR results, and outcomes (ICU requirement, discharge, and mortality) were extracted retrospectively from electronic medical records. The pregnants, patients younger than 18 years old and the patients with missing data (n=119) were excluded from the study.

Oropharyngeal and nasopharyngeal swab samples were taken from all of the patients were transferred to laboratory authorized by the Ministry of Health Public Health Office. rRT-PCR tests for SARS-CoV-2 were performed by using Biospeedy COVID-19 RT-qPCR Detection Kits (Bioksen, Istanbul, Turkey). All of the patients had baseline complete blood count, biochemical tests, C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), D-dimer on admission and 3rd day of hospitalization.

Platelet count (PLT), MPV, PDW, and PCT were automatically determined by using an automated blood cell analyzer (Mindray, BC-6800, Mindray Biomedical Electronics, Nanchang, Shenzhen, China). MPV/PCT, MPV/PLT, PDW/PLT, and PDW/PCT ratios were calculated.

Diagnosis of COVID-19 disease was based on the WHO guidance[18] and the New Coronavirus Pneumonia Prevention and Control Program (fifth edition) published by the National Health Commission of China[19]. According to clinical features on admission, the patients were classified as mild, moderate, severe and critical cases. Mild patients refer to patients with no radiographic evidence of pneumonia and moderate patients were the patients with fever, respiratory symptoms, and radiographic evidence of pneumonia. The patients who had respiratory distress ($\geq$ 30 breaths), $\leq$ 93% oxygen saturation at rest, ratio of partial pressure of arterial oxygen to fractional concentration of oxygen inspired air $\leq$ 300 mm Hg or and/or lung infiltrates >50% within 24-48 hours defined as having severe disease. If the patients had complications, such as respiratory failure, requirement of mechanical ventilation support, septic shock, and multiple organ failure were defined as critical cases[19].

All of the patients had chest CT on admission. Multiple ground-glass opacities and consalidations were considered typical for COVID-19. CT findings were classified as; 0: Normal, 1: Mild (ground-glass opacity and consolidation, lesions can be single or multiple and may de located in both lung lobes), 2: Moderate (large lesions in more than one lobe in both lungs, various sizes of consolidation and fibrosis), 3: Severe (lesions are diffuse in both lungs and different density, white lung sign due to involvement of large areas of lung, thickening of interlobular pleura and bilateral pleura, and pleural effusion)[20].

The patients who clinically decompensated (tachypnea respiratory rate >30/min, dyspnea, refractory hypoxemia, hypotension) and had decreased oxygen saturation rate (<90%) despite treatment, oxygen support, and prone positioning were transferred to ICU.

The criteria for discharge were absence of fever at least 3 days, clinical remission of respiratory and other symptoms[21].

The study protocol was approved by the Istinye University Hospital Ethics Committee (No:

2/2021.K-19). This study was performed in accordance with the declaration of Helsinki. Written informed consent were taken from patients and first degree relatives for the patients with critical disease before treatment.

Statistical Analysis

Statistical analysis was performed using SPSS 15.0 software (SPSS Inc., Chicago, IL, U.S.A.). Results were expressed as numbers and percentages for categorical variables and mean ± SD, minimum, and maximum for numerical variables. The Chi-square test was used for the comparison of rates in independent groups. As the numerical variables did not meet the normal distribution, comparisons of two independent groups were made by using the Mann Whitney U test. The analysis of the relationship between ordinal and numerical variables was conducted by using Spearman correlation analysis since parametric test conditions were not met. Determining factors were analyzed by the logistic regression analysis forward method. Cutoff analyzes were made with receiver operating characteristics (ROC) curve analysis. *p*-values of <0.05 were considered statistically significant.

Results

The mean age of 722 patients was 57.2±15.6 (range: 16-94 years), and male: female ratio was 1.22. The median duration of hospitalization was 6.4±4.8 days. The total number of cases in Turkey was 163,942 (peak 5138 case/day) in the first wave and 2,207,330 (peak 6593 case/day) in the second wave.

Overall, 59.8% of the patients had at least one underlying comorbidity. The most common comorbidity was HT, followed by DM, asthma, and chronic obstructive pulmonary disease (COPD). The most common symptoms on admission were cough (50.3%), fever (33%), and dyspnea (33%). 74% of the patients had positive RT-PCR. 81.9% of the patients had moderate and 11.8% had severe disease. The clinical and demographic characteristics of the patients are shown in Table I.

5.6% of the patients (n=41) who transferred to the intensive care unit (ICU) were older (mean age: 63.3±12.3, median 66 *vs.* 56 years, p =0.007), 68.3% were male and had predominantly HT (58.5%). DM was significantly more common in ICU patients (43.9% *vs.* 15.9%, p<0.001). ICU patients had more fever and dyspnea at admission when compared with the patients in wards (p<0.001). Male predominance was observed in both of the patient groups (68.3% in ICU and 54.3% in wards, p=0.08).

The severity of disease, the distribution, and the stage of the CT findings were significantly different between the patients in ICU and those in wards (p<0.001, p=0.041, p=0.011, respectively). 80.5% of the patients in ICU had severe disease, 61% of those patients had severe CT, and all of them had bilateral CT findings. 95.1% of the patients in ICU and 72.7% of the patients in wards had positive RT-PCR (p<0.001).

1.93% (n=14) of the patients had PLT <100x10^3 µL, 16.6% (n=120) had PLT between 100-150x10^3 µL, and 19.2% (n=139) had lymphopenia at admission. Baseline laboratory findings, MPV/PCT, MPV/PLT, PDW/PLT, and PDW/PCT ratios are shown in Table I, and comparisons with the 3rd day of hospitalization are shown in Table II.

There was a weak and a medium positive correlation between the severity of the disease, stage of CT, CRP, LDH, ferritin, D-dimer values at admission and 3rd day of hospitalization, MPV/PCT, PDW/PLT, and PDW/PCT ratios, and a statistically significant negative relationship with PLT and lymphocyte count. A weak and medium positive correlation was observed between the distribution of CT findings, baseline MPV, PDW, CRP, LDH, ferritin, and D-dimer levels, and 3rd day CRP, LDH, and ferritin values, whereas statistically significant negative relationship with lymphocyte counts, 3rd day MPV/PCT, MPV/PLT, PDW/PLT, and PDW/PCT ratios.

The patients in ICU had significantly lower lymphocyte counts, PLT, PCT and 3rd day lymphocyte counts when compared with the patients in wards. ICU patients also had higher baseline CRP, LDH, ferritin, MPV/PCT, MPV/PLT, PDW/PLT, PDW/PCT ratios, and 3rd day PDW, CRP, LDH, and ferritin levels than the patients in wards (Table II).

The combination of hydroxychloroquine and azithromycin treatment was given to 36% of patients (n=260) in the first wave of the outbreak, whereas 62.1% (n=449) of the patients received favipiravir monotherapy in the second wave. Low molecular weight heparin (LMWH), as Enoxaparin and methylprednisolone 40-80 mg/day intravenously were given to all of the patients (n=462) in the second wave. Forty patients were given tocilizumab (Actemra®, Roche, Chugai Pharma Manufacturing Co. Ltd, Utsunomiya-city, Japan) 1 × 200-400 mg and six patients received conva-

Table I. The demographics, clinical characteristics and laboratory findings of the patients at admission.

Age (years; mean ± SD)	7.2 ± 15.6
Gender (male/female)	1.22 (398/324)
Duration of disease (days; mean ± SD)	6.4 ± 4.8
Concomitant chronic diseases n, (%)	
Hypertension	323 (44.7%)
Diabetes mellitus	126 (17.5%)
COPD	110 (15.2%)
Cardiovascular disease	68 (9.4%)
Chronic renal disease	17 (2.4%)
Cerebrovascular disease	6 (0.8%)
Others (Behçet disease, Celiac disease, ulcerative colitis, epilepsy, rheumatoid arthritis)	30 (4.2%)
Signs and symptoms n, (%)	
Fever (temperature ≥ 37.3°C)	238 (33%)
Fatigue	159 (22%)
Sore throat	22 (3%)
Cough	63 (50.3%)
Dyspnea	238 (33%)
Nausea/vomiting	48 (6.6%)
Diarrhea	16 (2.2%)
Myalgia	60 (8.3%)
Headache	38 (5.3%)
Anosmia and ageusia	14 (1.9%)
Back pain	6 (0.8%)
Chest CT imaging n, (%)	
Mild	231 (35%)
Moderate	311 (47.1%)
Severe	118 (17.9%)
Lesion distribution n, (%)	
Unilateral	86 (13%)
Bilateral	533 (86.8%)
RT-PCR n, (%)	
Positive	531 (74%)
Negative	187 (26%)
Severity of disease n, (%)	
Mild	46 (6.4%)
Moderate	591 (81.9%)
Severe	85 (11.8%)
Laboratory findings	
Hemoglobin (110-160 g/L)	13.2 ± 1.6 (7.6-18.3)
White blood cell count (4-10 × 10^3 µL)	7272.8 ± 3592.1 (58-36700)
Lymphocyte count (0.8-4 × 10^3 µL)	1367.7 ± 673.3 (0-5670)
Platelet count (100-300 × 10^3 µL)	223.4 ± 87.8 (21-774)
MPV (f/L)	9.5 ± 1.0 (7-14.4)
PCT (%)	2.4 ± 45.2 (0.003-0.870)
PDW	16.1 ± 0.4 (14.9-17.3)
MPV/PCT	55.8 ± 129.6 (0.01-3466.7)
MPV/PLT	0.05 ± 0.03 (0.01-0.48)
PDW/PLT	0.08 ± 0.04 (0.02-0.8)
PDW/PCT	94.5 ± 202.0 (0.01-5400)
ALT (0-41 IU/L)	32.3 ± 29.1 (3-318)
AST (0-50 IU/L)	33.6 ± 30.2 (10-492)
Urea (10-50 mg/dl)	36.1 ± 20.7 (8-190)
Creatinin (0.7-1.2 mg/dl)	1.03 ± 3.55 (0.01-2.91)
CRP (0-5 mg/L)	58.9 ± 68.6 (0-342.2)
LDH (135-225 IU/L)	269.8 ± 103.7 (20-956)
Ferritin (30-400 mcg/L)	406.5 ± 38.8 (5-2639)
D-dimer (0-500 µg/ml)	878.6 ± 1315.9 (1-21900)
Procalcitonin (0-0.12 ng/ml)	0.30 ± 0.69 (0.01-5.11)
Outcome	
Discharge n, (%)	666 (92.2%)
Intensive care unit n, (%)	41 (5.7%)
Discharge from hospital with oxygen concentrators n, (%)	10 (1.38%)
Rehospitalization n, (%)	9 (1.24%)
Death n, (%)	30 (4.2%)

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CRP = C-reactive protein; LDH = Lactate dehydrogenase; COPD = Chronic obstructive pulmonary disease; RT-PCR = Reverse-transcription polymerase chain reaction; MPV = Mean platelet volume; PDW = Platelet distribution width; PCT = Plateletcrit; PLT=Platelet. $p < 0.05$ is statistically significant.

Table II. Comparison of laboratory findings at admission and 3rd day among patients with mild-moderate disease and critically ill patients.

	Patients in wards (n = 681) Median (IQR)	Patients in ICU (n = 41) Median (IQR)	p
Lymphocyte (×10³ µL)			
Initial	1.290 (920-1.740)	780 (520-1.175)	< 0.001
3rd day	1.330 (942.5-1.837)	665 (477.5-907.5)	< 0.001
Platelet (×10³ µL)			
Initial	207 (166.5-262.5)	173 (139.5-243.5)	0.006
3rd day	240 (185-317.8)	221 (161.5-300.3)	0.281
MPV (f/L)			
Initial	9.4 (8.75-10.1)	9.4 (8.75-10.4)	0.613
3rd day	9.4 (8.7-10.1)	9.1 (8.5-10.1)	0.648
PDW			
Initial	16.1 (15.9-16.4)	16.3 (16-16.5)	0.079
3rd day	16 (15.9-16.4)	16.2 (16-16.6)	0.034
PCT (%)			
Initial	0.20 (0.16-0.25)	0.17 (0.13-0.2)	0.004
3rd day	0.23 (0.18-0.29)	0.21 (0.16-0.25)	0.109
MPV/PCT			
Initial	47.4 (37.6-60.7)	57.3 (44.1-70.9)	0.002
3rd day	41.3 (31.5-54)	45.5 (36.8-61.8)	0.131
MPV/PLT			
Initial	0.05 (0.03-0.06)	0.05 (0.04-0.07)	0.011
3rd day	0.04 (0.03-0.05)	0.04 (0.03-0.06)	0.365
PDW/PLT			
Initial	0.08 (0.06-0.1)	0.09 (0.07-0.12)	0.005
3rd day	0.07 (0.05-0.09)	0.07 (0.05-0.08)	0.229
PDW/PCT			
Initial	81.4 (65.2-102.8	100.6 (74.8-122.6)	0.003
3rd day	70.8 (55.8-90.1)	78.2 (63.9-)	0.078
CRP (0-5 mg/L)			
Initial	26.6 (10.8-72)	96.9 (35-172.7)	< 0.001
3rd day	30 (11.5-73.8)	80.3 (39-152.6)	< 0.001
LDH (135-225 IU/L)			
Initial	245 (197-307)	332 (250.5-411)	< 0.001
3rd day	263 (214-325)	404 (314-509)	< 0.001
Ferritin (30-400 mcg/L)			
Initial	268.5 (131.9-521.8)	599.9 (316.3-834.9)	< 0.001
3rd day	352 (163.1-687.5)	642.2 (452.6-1.207)	< 0.001
D-dimer (0-500 µg/ml)			
Initial	568 (400-950)	680.5 (435.3-1.005)	0.291
3rd day	602 (390.5-949.5)	627 (460-849)	0.894
Procalcitonin (0-0.12 ng/ml)			
Initial	0.1 (0.06-0.21)	0.15 (0.09-0.35)	0.05
3rd day	0.09 (0.05-0.15)	0.11 (0.07-0.15)	0.190

CRP = C-reactive protein; LDH = Lactate dehydrogenase; MPV = Mean platelet volume; PDW = Platelet distribution width; PCT= Plateletcrit; PLT = Platelet. p 0.05 is statistically significant.

lescent plasma. Only two patients received pulse methylprednisolone 250 mg/day for three consecutive days.

The overall mortality rate was 3.7 and 42.8% in our ICU. NIV was required in 75.6% of the patients in the ICU, whereas 36.5% of the patients underwent IMV. Respiratory failure was the most common complication, followed by cardiac arrest in ICU. The median time from hospitalization to death was 6.04±4.08 days and was not significantly different from survivors. None of the patients survived among patients who underwent IMV. Older age, DM, dyspnea at admission, and the need for IMV were associated with poor prognosis (p<0.001, p=0.005, p<0.001, and p<0.001, respectively).

When the impact of laboratory findings on mortality was examined, it was observed that

Table III. The relationship between platelet indices and mortality.

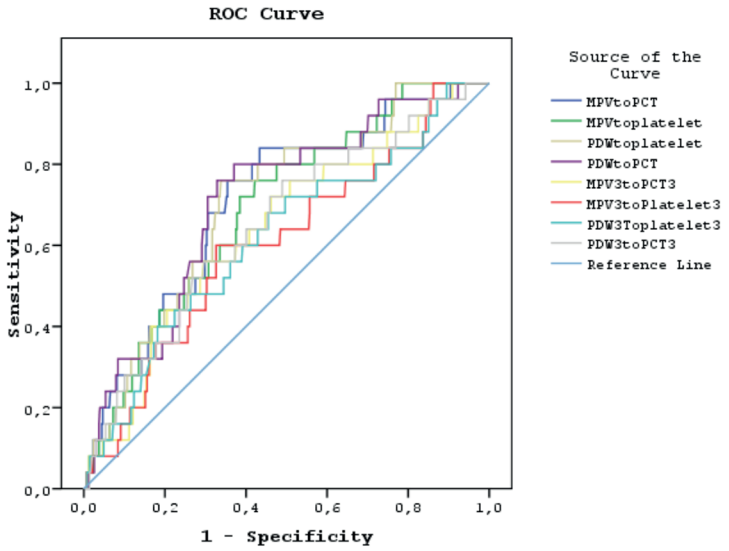
	Survivors (n = 692) Median (IQR)	Non-survivor (n = 30) Median (IQR)	p
Lymphocyte (×10³ µL)			
Initial	1.290 (910-1.740)	840 (550-1.123)	< 0.001
3rd day	1.330 (930-1.830)	600 (475-715)	< 0.001
Platelet (×10³ µL)			
Initial	208 (167-263)	158 (131.8-193.8)	< 0.001
3rd day	240 (185-318)	200 (161-280.5)	0.060
MPV (f/L)			
Initial	9.4 (8.7-10.1)	9.4 (8.88-10.53)	0.430
3rd day	9.4 (8.6-10.1)	9.6 (8.7-10.05)	0.579
PDW			
Initial	16.1 (15.9-16.4)	16.2 (16-16.5)	0.317
3rd day	16.1 (15.9-16.4)	16.3 (16.05-16.7	0.007
PCT (%)			
Initial	0.20 (0.16-0.25)	0.15 (0.12-0.18)	< 0.001
3rd day	0.23 (0.18-0.29)	0.19 (0.14-0.24)	0.017
MPV/PCT			
Initial	47.4 (37.6-60.3)	64.9 (52.6-79.4)	< 0.001
3rd day	41.4 (31.5-54)	50.5 (39.5-61.9)	0.018
MPV/PLT			
Initial	0.05 (0.03-0.06)	0.06 (0.05-0.08)	< 0.001
3rd day	0.04 (0.03-0.05)	0.05 (0.03-0.06)	0.074
PDW/PLT			
Initial	0.08 (0.06-0.10)	0.10 (0.08-0.12)	< 0.001
3rd day	0.07 (0.05-0.09)	0.08 (0.06-0.10)	0.044
PDW/PCT			
Initial	81.4 (65.1-102.5)	105.9 (90.3-133.6)	< 0.001
3rd day	0.7 (55.8-89.6)	88 (68.7-116.4)	0.011
CRP (0-5 mg/L)			
Initial	26.8 (11-72.8)	94.4 (54.1-221)	< 0.001
3rd day	30.9 (11.9-75.1)	85 (45.6-252.4)	< 0.001
LDH (135-225 IU/L)			
Initial	245 (197-308)	317 (266-354)	< 0.001
3rd day	264 (216-331)	426 (344-555)	< 0.001
Ferritin (30-400 mcg/L)			
Initial	273 (137.9-531)	632.5 (282.9-821.9)	< 0.001
3rd day	369 (162.9-713.5)	565 (347-1.021)	0.007
D-dimer (0-500 µg/ml)			
Initial	569 (404.5-943)	700 (419-1.485)	0.211
3rd day	600 (390-930)	794 (470-1.380)	0.234
Procalcitonin (0-0.12 ng/ml)			
Initial	0.11 (0.07-0.21)	0.13 (0.09-0.56)	0.124
3rd day	0.09 (0.05-0.15)	0.11 (0.07-0.18)	0.049

CRP = C-reactive protein; LDH = Lactate dehydrogenase; MPV = Mean platelet volume; PDW = Platelet distribution width; PCT= Plateletcrit; PLT = Platelet. $p < 0.05$ is statistically significant.

non-survivors had significantly lower baseline and 3rd day lymphocyte counts, PLT, and PCT than the survivors. Non-survivors had significantly higher baseline CRP, LDH, ferritin, MPV/PCT, MPV/PLT, PDW/PLT, PDW/PCT, and 3rd day CRP, LDH, ferritin, procalcitonin, PDW, MPV/PCT, PDW/PLT, and PDW/PCT ratios than the survivors (Table III). ROC curves analysis for the platelet indices ratios is shown in Figure 1.

Discussion

Wool and Miller[22] proposed possible mechanisms of thrombocytopenia in COVID-19 as platelet activation by increased thrombin generation and consumptive coagulopathy[23], direct viral-platelet interaction and subsequent clearance by reticuloendothelial system[2], platelet clearance due to increased endothelial damage or platelet



	AUC	SE	*p*	Asymptotic 95% Confidence Interval	
MPV/PCT	**0.710**	**0.051**	**0.000**	**0.611**	**0.810**
MPV/platelet	0.691	0.049	0.001	0.595	0.788
PDW/Platelet	**0.708**	**0.049**	**0.000**	**0.612**	**0.803**
PDW/PCT	**0.712**	**0.051**	**0.000**	**0.612**	**0.811**
MPV3/PCT3	0.641	0.056	0.018	0.531	0.751
MPV3/Platelet3	0.606	0.059	0.074	0.492	0.721
PDW3/Platelet3	0.620	0.059	0.044	0.503	0.736
PDW3/PCT3	0.650	0.057	0.011	0.539	0.762

Figure 1. Receiver operating characteristics (ROC) curves analysis for platelet indices ratios at admission and 3rd day of hospitalization. MPV = Mean platelet volume; PDW = Platelet distribution width; PCT = Plateletcrit.

autoantibody formation[23], bone marrow or megakaryocyte suppression[23] due to inflammatory response, direct viral infection or reduced thrombopoietin. Lefrancais et al[24] showed in mice by direct visualizing the lung microcirculation that the lung is a reservoir for hematopoietic progenitor cells, and megakaryocytes circulate through the lungs and release platelets dynamically. Megakaryocytes have been demonstrated also in the human pulmonary circulation[25]. Thus, extensive alveolar and interstitial inflammation of lungs in COVID-19 may contribute to thrombocytopenia.

Thrombocytopenia has been reported in 5-41.7% of the patients with COVID-19, and is typically mild (a platelet count of <150 × 10^9 cells per L)[17,23,26-28]. It has been stated[17,26-31] that low PLT is associated with increased risk of severe disease, admission to ICU, progression to acute respiratory distress syndrome, need for mechanical ventilation and mortality in patients with COVID-19. Liu et al[17] reported that not only low PLT at admission, but also dynamic changes of PLT were related with mortality in hospitalized patients. An increment of per 50 × 10^9/L in platelets was associated with a 40% decrease in mortality[17]. ICU patients and non-survivors had significantly lower PLT at admission, but no difference was observed in 3rd day PLT between these patients in this study.

The changes in platelet size due to platelet activation during inflammation and thrombosis have been reported in autoimmune disorders, sepsis, cardiovascular disease, atherosclerosis, venous thromboembolism, malignancy associated thrombosis, and chronic lung diseases[32,33]. Inflammatory cytokines, including IL-6, IL-1, and TNF-α have been shown[33] to stimulate the release of large platelets from the bone marrow by activated thrombopoiesis. An increased platelet turnover, as in sepsis is associated with increased platelet size and immature platelet fractions[32,34]. The decrease in PLT in the first days is accompanied by an increase in MPV in patients with sepsis[34].

Hottz et al[8] reported that increased platelet activation and platelet-monocyte aggregate formation are observed in severe COVID-19 patients who requiring ICU and IMV, but not in patients with mild disease. MPV reflects average size of circulating platelets, and PDW specifies distribution of different sizes of platelets, indicative of platelet function and activation. MPV is inversely proportional to PLT[23], which means increased PLT and decreased MPV in acute phase of inflammation.

Liu et al[17] demonstrated that COVID-19 patients with thrombocytopenia had a statistically significantly larger MPV than COVID-19 patients without thrombocytopenia (median 10.3 fL *vs.* 9.9 fL, respectively). In our study, statistically significant difference was observed in MPV values between the patient with PLT <100x10^3 µL, patients with PLT between 100-150x10^3 µL and those without thrombocytopenia (median 10.55 fL, range: 7-13.5, median:10 fL, range: 7.3-14.4, and median: 9.3 fL, range: 7.2-12.4, respectively) at admission.

Guclu et al[16] reported that non-survivors had lower PLT and, higher MPV and PDW than survivors both at admission and 3rd day of sepsis, but this difference was not statistically significant. They stated that increased number of young platelets are more active than older platelets, may explain the increase in MPV and PDW.

Zang et al[3] reported that severe and critically severe COVID-19 patients presented with decreased PLT and PCT, and increased MPV and PDW when compared with healthy donors, non-COVID-19 patients, and mild and moderate COVID-19 patients. Similarly, our patients in ICU had significantly lower baseline PLT, PCT, and additionally higher baseline MPV/PCT, MPV/PLT, PDW/PLT, PDW/PCT ratios than the others. Comer et al[35] reported that increased MPV is associated with disease severity in COVID-19 during hospitalization and ICU admission. Ozder[36] observed higher MPV values among diabetic patients with COVID-19 than non-diabetic COVID-19 patients and healthy controls. In contrast, no significant difference was obtained in MPV levels at baseline and 3rd day in this study.

Sayed et al[37] reported that MPV/PCT was the most sensitive ratio (sensitivity=94.7%) in children with sepsis. PLT and PCT were significantly lower and MPV, MPV/PLT, MPV/PCT, PDW/PLT, PDW/PCT ratios were significantly higher in non-survivor than survivors in their study. Golwala et al[38] stated that MPV/PCT, PDW/PLT and MPV/PLT were better predictors of mortality than PLT or PCT at admission in pediatric patients with sepsis. In our opinion, MPV/PCT, MPV/PLT, PDW/PLT, PDW/PCT ratios were also important other than MPV and PLT alone in mortality risk assessment in patients with COVID-19.

It has been proposed[13,39] that the MPV/PLT ratio is a predictive prognostic factor in critically ill patients, conducted in heterogeneous ICU patients. Similarly, Zong et al[15] reported increased MPV/PLT associated with disease progression in patients with COVID-19. In contrast with the study conducted by Bg et al[40], non-survivors had significantly higher baseline MPV/PLT ratio in our study.

Zong et al[15] also demonstrated a significant positive correlation between MPV/PLT and CT involvement. We also observed significant correlation between 3rd day MPV/PLT and CT involvement.

He et al[41] reported that mortality was significantly associated with low PLT, high PDW and MPV at admission. In this study, the patients in ICU and non-survivors had higher PDW levels only on the 3rd day of hospitalization.

As it has been proposed that MPV was observed to be significantly higher in non-survivors after the third day of admission and subsequent increasing values after the 3rd day might be useful as prognostic marker in patients with pneumonia[11], critically ill patients[12] and patients with sepsis[14], in our opinion not only PLT or MPV level alone, but also platelet indices and ratios should be checked regularly to predict the risk of mortality in patients with COVID-19.

Limitations of the study were being a single-center retrospective study with a small number of patients and inability to perform advanced examinations to identify abnormal platelet functions.

Conclusions

In conclusion, platelets and indices routinely measured within complete blood count and can be used as simple and cost-effective prognostic markers in critically ill patients. Their use in clinical practice is limited. Thus, further, larger studies are needed on the effect of platelet indices and ratios on the severity and prognosis of the COVID-19 disease.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Informed Consent

Informed consent was obtained from all individuals included in this study. Ethical approval: Research involving human subjects complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as revised in 2013), and has been approved by the Istinye University ethics committee (No: 2/2021.K-19).

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