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ORIGINAL ARTICLE

Platelet Indexes for Predicting Disease Severity and Prognosis in Elderly Patients with Coronavirus Disease-19

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SUMMARY

Background: **This study aimed to investigate the usefulness of platelet indices in predicting prognosis in coronavirus disease-19 (COVID-19).**
Methods: **Patients aged ≥ 65 years who presented to the emergency department with a positive polymerase chain reaction test were retrospectively analyzed.**
Results: **Significant differences were found in the mean values of platelet (PLT) and plateletcrit (PCT) parameters in those with severe disease, those who died, and those who required intensive care unit (ICU) admission. Mean PLT and PCT values were higher in patients with severe COVID-19 (p-values < 0.001, for both), those requiring ICU admission (p = 0.016; p = 0.006; respectively), and those who died (p = 0.015; p = 0.005, respectively). PLT and PCT were found to be statistically significant in predicting death [PLT (area under the curve (AUC): 0.598; p = 0.0145) and PCT (AUC: 0.617; p = 0.0034)], severity [PLT (AUC: 0.653; p = 0.0002) and PCT (AUC: 0.654; p = 0.0002)], and ICU admission [PLT (AUC: 0.598; p = 0.0235) and PCT (AUC: 0.605; p = 0.0148)].**
Conclusions: **PLT and PCT values were significantly higher in patients with high disease severity, those requiring ICU admission, and those who died. Furthermore, they were statistically significant in predicting disease severity, ICU admission, and death.**
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KEYWORDS

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INTRODUCTION

The outbreak of coronavirus disease-19 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 poses a major threat to public health worldwide [1]. Although COVID-19 affects people of all ages, it is considered to be more of a geriatric health concern because of the high COVID-19-associated mortality rate among the elderly with multiple comorbid diseases [2, 3].
The World Health Organization reported that approximately 80% of infected people had mild-to-moderate infections, 13.8% had serious infections, and 6.1% had

critical illness [4]. In addition, it was reported that approximately 26.1% - 32.0% of confirmed cases might turn into serious or critical cases, with a mortality rate of 4.3% - 11% [4-6].

Prognostic factors for COVID-19 have not yet been fully determined [7]. Biomarkers and certain clinical factors may help predict adverse outcomes observed in patients with COVID-19 [7]. Inflammation accompanied by an immune response frequently occurs in viral respiratory infections, and growing evidence suggests its importance in the progression of COVID-19 [8]. As the indicators of inflammation or immunity are common and easily obtainable, identifying risk factors associated with disease severity in the blood of patients with COVID-19 is vital for early intervention to improve the mortality rate [8].

Although neutrophils and lymphocytes are the primary cells associated with inflammation, the importance and role of platelets in inflammation has recently been emphasized [9]. Through the production and release of various cytokines and chemokines, platelets actively participate in the process of inflammation, atherogenesis, and thrombus formation [9]. Platelet indices are biological markers that provide information about the morphology and functions of platelets and can be obtained or calculated automatically using devices that measure complete blood count at lower costs [10]. Although certain platelet indices are included in routine hematological examinations, those considered to be relatively less important by clinicians have recently been found to be associated with the severity and prognosis of non-hematological diseases [10].

The present study aimed to investigate the usefulness of platelet indices in predicting disease severity, admission to ICU, and death in elderly patients with COVID-19.

MATERIALS AND METHODS

Data collection

Patients who applied to Mersin University Hospital Emergency Department between August 1st, 2020, and March 31st, 2021, were included in the study. Age, gender, complaints, vital signs, comorbid diseases, laboratory and radiological examination results, platelet indices, emergency service, and hospital outcome of the patients were recorded in the data form prepared in advance. Patients' data were analyzed retrospectively.

Inclusion criteria: Patients with (1) a positive COVID-19 polymerase chain reaction test at emergency room admission; (2) an age of ≥ 65 years; and (3) complete data were included in the study.

Exclusion criteria: (1) Patients with missing data; (2) patients who received blood product transfusion before emergency room admission; (3) patients who received radiotherapy, chemotherapy, or a bone marrow transplant one month prior to emergency room admission; and (4) patients with hematological diseases (rheumatological diseases, lymphoma, leukemia, and bone marrow diseases) were excluded from the study.

Platelet indices: Platelet (PLT) count, mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT) were measured and studied using the SYSMEX-XN-1000/23797 hemogram device. Reference ranges were determined as 150 - 400*10^3/µL for PLT, 7.4 - 10.4 fL for MPV, 9 - 17 fL for PDW, and value in % for PCT.

Severity status: Blood oxygen saturation ≤ 93%; respiratory failure; septic shock; multiple organ dysfunction; dyspnea; cases with a respiratory rate > 30/minute, PaO2/FiO2 ratio < 300, and/or lung infiltrates in > 50% of lung area within 24 - 48 hours were considered as severe cases [4].

The present study was conducted upon approval of the Mersin University Rectorate Clinical Research Ethics Committee (date: 26/05/2021; number: 2021/410).

Statistical analysis

The Shapiro-Wilk test was used to evaluate normality for continuous measurements. Intergroup differences for continuous variables were tested using Student's *t*-test; mean and standard deviation values were provided as descriptive statistics. Pearson's likelihood ratio and Fisher's exact and chi-squared tests were used for analyzing categorical variables; count and percentage values were provided as descriptive statistics. Receiver operating characteristic curve (ROC) analysis was used for determining the cutoff points for the continuous parameters for predicting death, severity, and intensive care status. Sensitivity, selectivity, positive predictive value (PPV), negative predictive value, likelihood ratio (LR) (+), LR (-), and area under the curve (AUC) values were provided as descriptive statistics. A value of $p < 0.05$ was considered statistically significant.

RESULTS

A total of 202 patients (111 women and 91 men) were included in the study (Figure 1); their mean age was 76.26 ± 7.33 years. The rates of mortality, patients with high disease severity, and ICU admission were 45%, 73.8%, and 33.2%, respectively. Chronic diseases were observed in 88.6% of the patients included in the study. There was no significant difference in the presence of chronic diseases in terms of ICU admission, COVID-19 disease severity, and death. An evaluation of the complaints at admission indicated that the rates of death ($p = 0.034$) and ICU admission ($p = 0.035$) were higher in patients who presented with complaints of deteriorated general condition. The rates of mortality and severe COVID-19 disease were higher and those of ICU admission were lower ($p < 0.001$) in patients who presented with shortness of breath. The rate of patients with

Table 1. Comparison of basic characteristics of patients in case of death, disease severity, and intensive care unit admission.

		No Death (n = 111) n (%)	Death (n = 91) n (%)	p	Non-severe (n = 53) n (%)	Severe (n = 149) n (%)	p	ICU (n = 135) n (%)	No ICU (n = 67) n (%)	p
Gender	Men	45 (40.5)	46 (50.5)	0.155	24 (45.3)	67 (45.0)	0.968	56 (41.5)	35 (52.2)	0.177
	Women	66 (59.5)	45 (49.5)		29 (54.7)	82 (55.0)		79 (58.5)	32 (47.8)	
Presence of chronic disease		98 (88.3)	88.3 (89.0)	0.872	48 (90.6)	131 (87.9)	0.788	121 (89,6)	58 (86.6)	0.682
Chronic disease	Diabetes mellitus	53 (47.7)	38 (41.8)	0.395	25 (47.2)	66 (44.3)	0.841	64 (47.4)	27 (40.3)	0.370
	Hypertension	74 (66.7)	61 (67.0)	0.956	37 (69.8)	98 (65.8)	0.714	93 (68.9)	42 (62.7)	0.428
	Heart failure	17 (15.3)	13 (14.3)	0.995	9 (17.0)	21 (14.1)	0.777	20 (14.8)	10 (14.9)	1.000
	Coronary artery disease	41 (36.9)	31 (34.1)	0.672	22 (41.5)	50 (33.6)	0.384	52 (38.5)	20 (29.9)	0.275
	Arrhythmia	4 (3.6)	6 (6.6)	0.351	3 (5.7)	7 (4.7)	0.724	6 (4.4)	4 (6.0)	0.733
	Chronic kidney disease	8 (7.2)	11 (12.1)	0.347	4 (7.5)	15 (10.1)	0.786	10 (7.4)	9 (13.4)	0.260
	Cerebral vascular disease	8 (7.2)	12 (13.2)	0.238	5 (9.4)	15 (10.1)	1.000	12 (8.9)	8 (11.9)	0.665
	Chronic obstructive pulmonary disease/asthma	13 (11.7)	13 (14.3)	0.740	5 (9.4)	21 (14.1)	0.528	16 (11.9)	10 (14.9)	0.696
	Cancer	4 (3.6)	3 (3.3)	1.000	2 (3.8)	5 (3.4)	1.000	5 (3.7)	2 (3.0)	1.000
Symptoms on admission	General condition disorder	15 (13.5)	24 (26.4)	0.034	6 (11.3)	33 (22.1)	0.130	20 (14.8)	19 (28.4)	0.035
	Dyspnea	47 (42.3)	66 (72.5)	< 0.001	13 (24.5)	100 (67.1)	< 0.001	62 (45.9)	51 (76.1)	< 0.001
	Fever	33 (29.7)	37 (40.7)	0.104	13 (24.5)	57 (38.3)	0.102	42 (31.1)	28 (41.8)	0.133
	Cough/sputum	35 (31.5)	39 (42.9)	0.096	13 (24.5)	61 (40.9)	0.050	47 (34.8)	27 (40.3)	0.446
	Fatigue/malaise	41 (36.9)	18 (19.8)	0.008	15 (28.3)	44 (29.5)	1.000	51 (37.8)	8 (11.9)	< 0.001

Abbrevations: ICU - intensive care unit.

severe COVID-19 was higher in patients who presented with cough/sputum complaints (p = 0.05) (Table 1). There were significant differences between the severity of the disease, death, and ICU admission, and the mean values of white blood cell, neutrophil, PLT, PCT, and C-reactive protein parameters. The mean values of these parameters were higher in patients with severe COVID-19 (all p-values < 0.001), patients admitted to ICU (p < 0.001; < 0.001; 0.016; 0.006; and < 0.001, respectively), and patients who died (p < 0.001; < 0.001; 0.015; 0.005, and < 0.001, respectively) (Table 2).

ROC analysis results of platelet indices for disease severity, ICU, and death

The ROC analysis on continuous measurements in cases that died found that only PLT (AUC: 0.598; p = 0.0145) and PCT (AUC: 0.617; p = 0.0034) were statistically significant for distinguishing between the deceased and the survivors based on the cutoff points. Based on the cutoff value, patients with a PLT value of > 193 and a PCT value of > 0.24 (Table 3, Figure 2A) had a higher risk of death. A comparison of the AUC values indicated that the difference between PLT and MPV (p = 0.045) and MPV and PCT (p = 0.043) in terms of AUC was statistically significant.

PLT (AUC: 0.653; p = 0.0002) and PCT (AUC: 0.654; p = 0.0002) were found to be statistically significant for distinguishing between severe and non-severe cases based on the cutoff points. It was observed that patients with a PLT of > 193 and a PCT of > 0.23 according to the cutoff value could have a high COVID-19 severity. PPV rates of PLT and PCT in terms of distinguishing

Table 2. Comparison of laboratory values in case of death, disease severity, and intensive care unit admission.

	WBC	Lymphocyte	Neutrophil	PLT	PDW	MPV	PCT	CRP	Troponin
No death (n = 111)	7.560 ± 4.010	1.124 ± 0.559	5.591 ± 3.005	208.55 ± 79.99	12.700 ± 2.410	10.80 ± 1.36	0.219 ± 0.079	94.755 ± 83.196	0.047 ± 0.131
Death (n = 91)	10.633 ± 5.337	1.014 ± 0.842	8.723 ± 4.324	237.80 ± 88.73	12.648 ± 2.509	10.72 ± 1.01	0.252 ± 0.086	170.109 ± 98.374	0.356 ± 2.121
p	< 0.001	0.268	< 0.001	0.015	0.884	0.632	0.005	< 0.001	0.173
Non-severe (n = 53)	6.355 ± 2.422	1.199 ± 0.574	4.551 ± 2.369	187.75 ± 59.926	12.728 ± 2.263	10.721 ± 0.910	0.199 ± 0.058	68.891 ± 66.579	0.057 ± 0.179
Severe (n = 149)	9.866 ± 5.211	1.030 ± 0.738	7.874 ± 4.063	233.81 ± 89.506	12.658 ± 2.520	10.778 ± 1.307	0.246 ± 0.088	149.840 ± 98.238	0.235 ± 1.671
p	< 0.001	0.133	< 0.001	< 0.001	0.858	0.769	< 0.001	< 0.001	0.462
No-ICU (n = 135)	7.881 ± 3.991	1.141 ± 0.761	6.140 ± 3.653	210.820 ± 77.737	12.671 ± 2.378	10.822 ± 1.291	0.222 ± 0.076	108.369 ± 84.773	0.042 ± 0.096
ICU (n = 67)	11.087 ± 5.787	0.940 ± 0.543	8.738 ± 4.038	243.700 ± 95.617	12.687 ± 2.607	10.644 ± 1.039	0.256 ± 0.093	168.747 ± 109.146	0.468 ± 2.440
p	< 0.001	0.055	< 0.001	0.016	0.966	0.327	0.006	< 0.001	0.158

Table 2. Comparison of laboratory values in case of death, disease severity, and intensive care unit admission (continued).

		HGB	RBC
No death (n = 111)		12.432 ±2.078	4.392 ± 0.630
Death (n = 91)		12.085 ± 2.029	4.322 ± 0.675
p		0.234	0.444
Non-severe (n = 53)		12.383 ± 2.188	4.345 ± 0.676
Severe (n = 149)		12.238 ± 2.016	4.366 ± 0.643
p		0.661	0.842
No-ICU (n = 135)		12.253 ± 1.984	4.339 ± 0.629
ICU (n = 67)		12.323 ± 2.215	4.403 ± 0.693
p		0.819	0.511

Abbreviations: HGB - hemoglobin, RBC count - red blood cell, WBC - white blood cell count, PLT - platelet, PDW - platelet distribution width, MPV - mean platelet volume, PCT - plateletcrit, CRP - C-reactive protein, ICU - intensive care unit.

Table 3. Diagnostic accuracy criteria of parameters and receiver operating characteristic (ROC) analysis results.

		Specificity (% 95 CI)	PPV	NPV	LR (+)	LR (-)
Death	PLT	52.25 (42.6 - 61.8)	52.25 (42.56 - 61.82)	63.74 (52.99 - 73.56)	1.33 (1.04 - 1.71)	0.69 (0.50 - 0.96)
	MPV	13.51 (7.8 - 21.3)	46.67 (39.21 - 54.24)	68.18 (45.13 - 86.08)	1.07 (0.97 - 1.17)	0.57 (0.24 - 1.34)
	PCT	76.58 (67.6 - 84.1)	60.00 (47.10 - 71.96)	62.04 (53.36 - 70.19)	1.83 (1.21 - 2.76)	0.75 (0.61 - 0.92)
	PDW	66.67 (57.1 - 75.3)	49.32 (37.41 - 61.28)	57.36 (48.36 - 66.03)	1.19 (0.82 - 1.71)	0.91 (0.73 - 1.12)
Severe	PLT	64.15 (49.8 - 76.9)	82.88 (74.57 - 89.36)	37.36 (27.44 - 48.13)	1.72 (1.18 - 2.52)	0.60 (0.45 - 0.79)
	MPV	84.91 (72.4 - 93.2)	81.40 (66.59 - 91.58)	28.30 (21.45 - 35.98)	1.56 (0.77 - 3.14)	0.90 (0.78 - 1.04)
	PCT	79.25 (65.9 - 89.1)	86.42 (76.99 - 93.01)	34.71 (26.29 - 43.90)	2.26 (1.30 - 3.94)	0.67 (0.55 - 0.82)
	PDW	71.70 (57.7 - 83.2)	79.45 (68.38 - 88.01)	29.46 (21.76 - 38.12)	1.38 (0.86 - 2.21)	0.85 (0.69 - 1.05)
ICU	PLT	51.85 (43.1 - 60.5)	40.37 (31.08 - 50.19)	75.27 (65.24 - 83.63)	1.36 (1.07 - 1.74)	0.66 (1.46 - 1.96)
	MPV	74.07 (65.8 - 81.2)	41.67 (29.07 - 55.12)	70.42 (62.19 - 77.78)	1.44 (0.94 - 2.19)	0.85 (0.69 - 1.04)
	PCT	48.15 (39.5 - 56.9)	40.68 (31.73 - 50.11)	77.38 (66.95 - 85.79)	1.38 (1.11 - 1.72)	0.59 (0.39 - 0.90)
	PDW	67.41 (58.8 - 75.2)	39.73 (28.46 - 51.86)	70.54 (61.88 - 78.24)	1.33 (0.92 - 1.92)	0.84 (0.66 - 1.07)

Table 3. Diagnostic accuracy criteria of parameters and receiver operating characteristic (ROC) analysis results (continued).

		Cutoff value	AUC (p)	Sensitivity (% 95 CI)
Death	PLT	> 193	0.598 (0.0145)	63.74 (53.0 - 73.6)
	MPV	≤ 12	0.509 (0.8332)	92.31 (84.8 - 96.8)
	PCT	> 0.24	0.617 (0.0034)	42.86 (32.5 - 53.7)
	PDW	≤ 11	0.515 (0.7163)	39.56 (29.5 - 50.4)
Severe	PLT	>193	0.653 (0.0002)	61.74 (53.4 - 69.6)
	MPV	≤ 9.8	0.515 (0.7468)	23.49 (16.9 - 31.1)
	PCT	> 0.23	0.654 (0.0002)	46.98 (38.8 - 55.3)
	PDW	≤ 11	0.525 (0.5857)	38.93 (31.1 - 47.2)
ICU	PLT	> 194	0.598 (0.0235)	65.67 (53.1 - 76.8)
	MPV	≤ 10.1	0.540 (0.3431)	37.31 (25.8 - 50.0)
	PCT	> 0.20	0.605 (0.0148)	71.64 (59.3 - 82.0)
	PDW	≤ 11	0.514 (0.7455)	43.28 (31.2 - 56.0)

PPV - positive predictive value, NPV - negative predictive value, LR - Likelihood Ratio, AUC - area under the curve, PLT - platelet, PDW - platelet distribution width, MPV - Mean Platelet Volume, PCT - Plateletcrit, ICU - Intensive Care Unit.

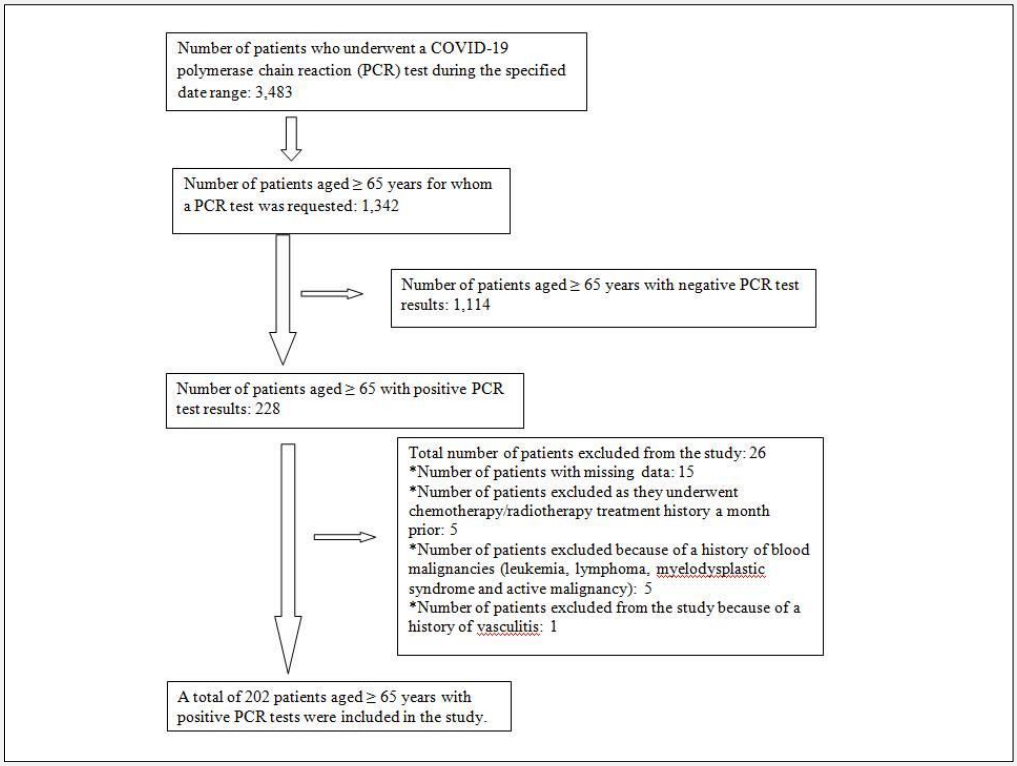

Figure 1. Flowchart representing patient selection.

Abbreviations: PCR - polymerase chain reaction.

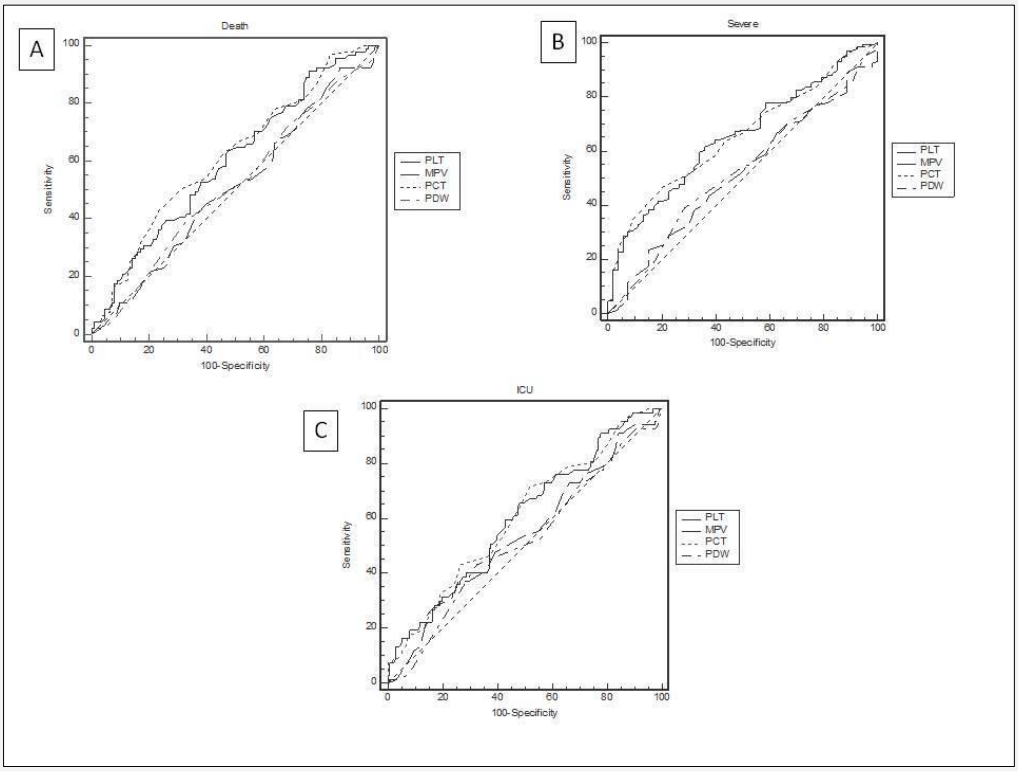

Figure 2. ROC analysis in predicting death (A), disease severity (B), and ICU admission (C).

Abbreviation: ICU - intensive care unit.

between severe and non-severe cases were over 80% at the cutoff value. The specificity at the cutoff value set for PCT was 79.25% (Table 3, Figure 2B). On comparison of these parameters in terms of AUC, the differences between PLT and MPV (p = 0.005), PLT and PDW (p = 0.011), MPV and PCT (p = 0.018), and MPV and PDW (p = 0.029) were statistically significant in terms of AUC.

PLT (AUC: 0.598; p = 0.0235) and PCT (AUC: 0.605; p = 0.0148) were statistically significant in predicting the ICU admission status based on the cutoff points specified for the parameters. It was observed that patients with PLT > 194 and PCT > 0.20 could be admitted to the ICU (Table 3, Figure 2C).

DISCUSSION

Standard laboratory markers for assessing hospital mortality, ICU admissions, or severity of COVID-19 have not yet been established. Dynamic changes in PLT parameters in patients with COVID-19 have been the focus of attention [11]. The elderly population with high mortality rates has been the most affected group during the COVID-19 pandemic [2]. The present study aimed to investigate the usefulness of PLT indices in predicting the severity of the disease, admission to the intensive care unit (ICU), and death in elderly patients with COVID-19. In the present study, the mortality, severity, and ICU admission rates were 45%, 73.8%, and 33.2%. There are numerous publications and conflicting data on hematological and hemostatic disorders in COVID-19, and certain data suggest an association with COVİD-19 disease progression, severity, and/or mortality [12].

PLT

PLT could predict death, disease severity, and ICU admission in COVID-19 patients based on the cutoff value. Some studies suggested a relationship between the PLT count, severity of COVID-19, and mortality rate, and reported different results. A study by Golwala et al. reported that the PLT count was lower in patients who died compared with that in those who survived [13]. A study by Ruan et al. reported that thrombocytopenia was not observed; however, the mean PLT number was higher in the deceased group [14]. A study by Yang et

al. showed that the PLT count in deceased cases was higher than that in survivors [15]. A study by Guclu et al. reported that thrombocytopenia was more likely to be seen in cases that did not survive, mean PLT count was higher in severe cases, and there was no correlation between PLT count and disease severity or mortality [16]. With regard to the severity of COVID-19, certain studies reported lower PLT values [17,18], whereas others observed higher values [15,16,19-21] in severe cases compared with that in non-severe cases. A study by Qu et al. found that the PLT count was lower in severe cases at hospital admission, but the peak PLT count was higher in the severe disease group during follow-up [22]. It was reported that different mechanisms played a role in both. The aforementioned differences between the studies were explained by the duration of the tests, the use of drugs that might cause thrombocytopenia, and the complex nature of thrombocytopenia induced by drugs or by the disease [16]. A study by Wang et al. on hospitalized patients with COVID-19 reported that there was no significant difference in the mean PLT count between patients admitted and not admitted to the ICU [23]. A study by Huang et al. found that the PLT count in patients admitted to the ICU was higher but not statistically significant [19]. Consistent with the aforementioned reports, Fan et al. found no association between the PLT count and ICU admission either at admission or during hospitalization [20]. In the present study, although the mean PLT number was within the normal range in our study; it was determined that the mean PLT levels were higher in patients who had serious illness, were hospitalized in the ICU, and died. It was determined that PLT could predict the severity of the disease, hospitalization in the ICU, and death status of the patients according to the cutoff values. The physiological response of elderly patients to the disease varies. Studies in which PLT counts were found to be higher indicated that the average ages of the patients who died were higher than those who survived. The fact that only elderly patients were included in our study may have led to high PLT counts. Further, increased PLT counts may be an indicator of cytokine storm. It was argued that various cytokines and stem cell factors could stimulate the production of megakaryocytes, and IL-6 could lead to increased PLT synthesis by directly stimulating thrombopoiesis. In addition, it was reported that endothelial damage that induces vWF release, which could interact with megakaryocytes through GPIbvWF signaling to increase PLT production, and thrombopoietin release, which stimulates lung megakaryocytes to produce PLT, might be other mechanisms that led to elevated PLT [12].

PCT

Studies conducted on patients admitted to the ICU found that the PCT values were significantly lower in patients who died [10,13,24]. A study by Zhang et al. on disease severity reported that there was no significant difference between patients with low and normal PCT values [24]. A study by Wang et al. on patients with moderate and severe COVID-19 found that PCT was not significant in determining the severity of the disease [4]. Unlike the data presented in the relevant literature, the present study found that the mean PCT levels in severe cases, ICU cases, and cases that died were higher and that PCT could predict the severity of the COVID-19 disease, ICU admission, and risk of mortality in patients based on the cutoff values. PCT is the percentage of PLT in the blood, which is a reflection of PLT number and PLT size, and shows a positive correlation with PLT [10,13,24]. PCT elevation has been interpreted as an expected situation for these reasons.

PDW-MPV

Contradicting results were reported in studies on MPV and PDW values with regard to disease severity and mortality. Studies on patients admitted to the ICU reported that patients with high MPV and PDW values were associated with a more severe disease and that PDW and MPV values were higher in deceased patients [13,24]. Another study conducted on patients admitted to ICU reported that elevated PDW was associated with an increase in the mortality rate [10]. A study by Guclu et al. on COVID-19 patients reported that there was no significant difference in the first MPV values in terms of mortality, and the following values were higher in cases that died. In addition, PDW was higher in patients who died [16]. The same study reported that there was no difference in PDW and MPV between the two groups in terms of disease severity [16]. The present study determined that MPV and PDW values did not differ in terms of death, disease severity, and ICU admission. Moreover, it found that the sensitivity of MPV in predicting death was high, and although the selectivity in terms of disease severity and the PPV value were high, the discrimination power based on AUC was weak and not statistically significant.

CONCLUSION

PLT and PCT values were significantly higher in severe cases, in cases admitted to the ICU, and in cases that died, and they could predict the severity of the disease, ICU admission, and death based on the cutoff value. There was no difference in MPV and PDW values between the groups. There is a need for more comprehensive studies on the utility of PLT and PCT values in predicting the prognosis of the disease in elderly patients with COVID-19.

Limitations

This study had several limitations. First, the data were collected from a single hospital and cannot be generalized to all other regions. Second, there may be errors in clinician documentation and data collection due to the retrospective nature of the study. Third, the lack of cy-

tokine and thrombopoietin levels constitutes a limitation.

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