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The Role of Inflammatory Parameters in the Prognosis of Patients with COVID-19

COVID-19 Hastalarında Enflamatuvar Parametrelerin Prognostik Rolü

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ABSTRACT

Background: The prognostic significance of inflammatory parameters in patients with Coronavirus disease-2019 (COVID-19) has been investigated.

Materials and Methods: Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio, C-reactive protein (CRP) albumin ratio (CAR), systemic inflammation index (SII), CRP-lymphocyte ratio (CRP/L), neutrophil to lymphocyte, platelet ratio (NLPR), red cell volume distribution width index (RDW-SD), and procalcitonin were evaluated in relation to admission to intensive care unit (ICU) and mortality in 419 patients with moderate-to-severe COVID-19.

Results: NLR, CAR, CRP/L, NLPR, RDW-SD and procalcitonin levels were higher both in those who needed ICU compared to those who did not (p=0.001, 0.005, 0.002, 0.001, 0.001 and 0.001; respectively), and in those who died compared to the survival group (p=0.001, 0.024, 0.009, 0.001, 0.001 and 0.001; respectively). SII was higher only in those who needed ICU (p=0.001). NLR (0.610, p=0.002), CAR (0.602, p=0.005), SII (0.573, p=0.043), CRP/L (0.593, p=0.010), and NLPR (0.618, p=0.001) were statistically significant for admission to ICU; and NLR (0.637, p=0.006), CAR (0.613, p=0.024), CRP/L (0.605, p=0.035) and NLPR (0.660, p=0.001) were statistically significant for mortality in the evaluation of area under curve in ROC analysis. RDW-SD was an independent risk factor for both ICU admission [odds ratio (OR): 1.194, p=0.024] and mortality (OR: 1.263, p=0.002), and procalcitonin was an independent risk factor for ICU admission (OR: 1.492, p=0.034) in multivariate analysis.

Conclusion: NLR, CAR, CRP/L, NLPR, RDW-SD and procalcitonin were determined as prognostic parameters in terms of both the need for ICU and mortality in patients with COVID-19. SII was a prognostic parameter only for the need for ICU.

Keywords: COVID-19, inflammatory index, intensive care unit, lymphocytes, mortality

ÖZ

Amaç: Koronavirüs hastalığı-2019 (COVID-19) hastalarında enflamatuvar parametrelerin prognostik önemi araştırılmıştır.

Gereç ve Yöntemler: Dört yüz on dokuz orta-ağır COVID-19 hastasında, nötrofil lenfosit oranı (NLR), platelet lenfosit oranı, C-reaktif protein (CRP) albümin oranı (CAR), sistemik enflamasyon indeks (SII), CRP lenfosit oranı (CRP/L), nötrofil-lenfosit, platelet oranı (NLPR), kırmızı hücre volüm dağılım genişliği (RDW-SD) ve prokalsitoninin yoğun bakım ünitesine (YBÜ) giriş ve mortalite ile ilişkisi değerlendirilmiştir.

Bulgular: NLR, CAR, CRP/L, NLPR, RDW-SD, prokalsitonin hem YBÜ'ye girenlerde girmeyenlere göre artış (sırasıyla p=0,001, 0,005, 0,002, 0,001, 0,001 ve 0,001), hem de ölenlerde survival grubuna göre artış (sırasıyla p=0,001, 0,024, 0,009, 0,001, 0,001 ve 0,001) saptandı. SII sadece yoğun bakıma girenlerde artış saptandı (p=0,001). ROC analizinde eğri altındaki alan değerlendirmesinde, YBÜ'ye giriş için NLR (0,610, p=0,002), CAR (0,602, p=0,005), SII (0,573, p=0,043), CRP/L (0,593, p=0,010), NLPR (0,618, p=0,001); mortalite için NLR (0.637, p=0,006), CAR (0,613, p=0,024), CRP/L (0,605, p=0,035), NLPR (0,660, p=0,001) saptandı. Multivaryant analizde, RDW-SD hem YBÜ girişi [olasılık oranı (OO): 1,194, p=0,024] hem de mortalite için (OO: 1,263, p=0,002), prokalsitonin de YBÜ'ye giriş için (OO: 1,492, p=0,034) bağımsız risk faktörü olarak saptanmıştır.

Sonuç: NLR, CAR, CRP/L, NLPR, RDW-SD ve prokalsitonin COVID-19 hastalarında hem YBÜ hem de mortalite için prognostik önemli olabilecek parametreler olarak değerlendirilmiştir. SII ise sadece YBÜ için prognostik önemi olabileceği saptanmıştır.

Anahtar Kelimeler: COVID-19, enflamatuvar indeks, yoğun bakım, lenfosit, mortalite

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Introduction

The Coronavirus disease-2019 (COVID-19) epidemic has affected the whole world, causing approximately 300 million confirmed cases and 5.5 million deaths from December 2019 to January 2022 (1). Its clinical spectrum ranges from asymptomatic and mild to critical illness including acute respiratory distress syndrome (ARDS), multi-organ failure and death (2). The severe clinical condition elicited by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) is due to ARDS, macrophage activation, cytokine storm, endothelial dysfunction and coagulopathy caused by immune system dysfunction and hyperinflammation (3).

Whole blood parameters, white blood cell and sub-parameters including neutrophils, lymphocytes, monocytes, eosinophils and basophils are inexpensive and easily accessible biomarkers of systemic inflammation. Neutrophils usually increase and lymphocytes decrease in the progression of inflammatory diseases (4). Platelets play a key role in hemostasis. It also plays a role in host defense in infection and is an effector and modulator of immune cells (5). While whole blood parameters and other inflammation parameters have roles alone in demonstrating systemic inflammation, parameters resulting from their ratio to each other can also be used.

Parameters such as neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), systemic inflammation index (SII), monocyte to lymphocyte ratio, derived NLR (dNLR), mean platelet volume to platelet ratio (MPR), lymphocyte to monocyte ratio (LMR), C-reactive protein (CRP) albumin ratio (CAR), CRP lymphocyte ratio (CRP/L), neutrophil to lymphocyte, platelet ratio (NLPR), systemic inflammation response index (SIRI) and aggregate index of systemic inflammation (AISI) have been studied in many inflammatory diseases and cancers and also the role of them in the diagnosis, prognosis and follow-up of patients with COVID-19 has also been studied (6,7,8,9,10).

The aim of this study was to investigate the role of different inflammatory parameters (including NLR, PLR, CAR, SII, NLPR, CRP/L, procalcitonin) in predicting intensive care unit (ICU) admission and mortality in hospitalized patients with moderate and severe COVID-19.

Material and Methods

Hospitalized patients with moderate-to-severe COVID-19 pneumonia were included in this retrospective, single-center study. 419 patients, over 18 years old, who were hospitalized in University of Health Sciences Türkiye, İstanbul Sultan 2. Abdülhamid Han Training and Research Hospital, İstanbul, Türkiye between March 15, 2020 and September 30, 2020 were included in the study. Informed consent was waived because of the retrospective nature of the study. This study was approved by the Ethics Committee of the Ümraniye Training and Research Hospital (date: November 19, 2020, no: 346). Patients with malignancy, immunosuppression, mild COVID-19 disease [patients with real-time reverse transcriptase polymerase chain reaction (RT-PCR) positive but no lung involvement], those younger than 18 years of age, and outpatient COVID-19 patients were not included in this study. Patients who needed ICU less than 5 days after hospitalization were excluded from the study. SARS-CoV-2 was founded by RT-PCR using a COVID-19 Nucleic Acid Detection Kit according to the manufacturer's recommendation (Bioeksen Ltd., Türkiye). Lung involvement was detected by chest X-ray and, if necessary, by thorax computed tomography.

Moderate and severe disease definitions were determined according to the World Health Organization (WHO) weight classification and the COVID-19 guidelines of the Turkish Ministry of Health (11,12). Severe COVID-19 was defined in the presence of oxygen saturation (SpO_2) <90% in room air, bilateral diffuse lung involvement, tachypnea >30/min, no need for invasive mechanical ventilation, and not presenting with ARDS, sepsis, or septic shock. Moderate COVID-19 was determined as mild lung involvement and absence of severe COVID-19 findings. Three hundred nine (73.7%) of the patients included in this study were moderate cases and 110 (26.3%) were severe cases. All patients were treated with favipiravir in accordance with the Turkish national COVID-19 guidelines. Oxygen support was given to patients with SpO_2 <90% in room air. Antibiotic treatment was given to patients with suspected or proven secondary bacterial infection. Steroid therapy was given to patients with worsening hypoxemia and increased lung involvement, and patients who developed macrophage activation syndrome were treated with anti-IL6 (tocilizumab) therapy according to the WHO and Türkiye national COVID-19 guidelines (11,12). Patients with septic shock, hypotension persisting despite fluid support and requiring vasopressor therapy, ARDS, and the need for non-invasive and invasive mechanical ventilation were admitted to the ICU.

Patients were classified as non-survivor and survivor; and needing ICU and not needing ICU. Patients' age, gender, hematocrit (HCT), white cell cells (WBC), mean corpuscular volume (MCV), red cell volume distribution width index (RDW-SD), platelet, neutrophil, lymphocyte, CRP, procalcitonin, D-dimer, albumin, and ferritin were compared between these groups. Different inflammatory parameters calculated from the parameters measured in whole blood were also compared between the groups. The calculation of these inflammatory parameters is as follows;

NLR (neutrophil/lymphocyte), PLR (platelet/lymphocyte), CAR (CRP/albumin), SII [(neutrophilxplatelet)/lymphocyte], CRP/L (CRP/lymphocyte), NLPR (neutrophil/[lymphocytex platelet]).

Statistical Analysis

Descriptive analyzes (frequency distributions, percentage, mean, median and interquartile range) were used as statistical methods in the analysis of the data in the study. Normality of the data was ensured by Kolmogorov-Smirnov test. The t-test was used for those with normal distribution, and the Mann-Whitney U test was used for continuous variables. Logistic regression analysis was used to calculate influencing factors, ROC curve analysis was used for cut-off point, and sensitivity analysis was used for sensitivity. The results were evaluated at the 95% confidence interval (CI), at the $p<0.05$ significance level. In the analysis of the data, PSPP (PSPP is free software; you can redistribute it and/or modify it under the terms of the GNU General Public License as published by the Free Software Foundation; either version 3 of the License, or (at your option any later version) and Microsoft Excel computer programs were used.

Results

The study included 419 hospitalized patients with moderate and severe COVID-19. One hundred sixty-six (39.62%) of the patients were female and 253 (60.38%) were male. The median age of the patients was calculated as 59 years (range; 19-98). Eighty-seven (20.76%) patients needed ICU and 41 (9.80%) patients died. The patients were compared by dividing them into groups as those who needed ICU and those who did not, and those who died and survived. The parameters and factors affecting mortality and ICU admission were tried to be determined.

Comparison of Patient Groups with and without ICU Admission

There was a statistically significant difference between the ages of patients with ICU admission and no ICU admission [66 (37-98) vs. 57 (19-96) years; respectively, p=0.001]. Fifty-four (62.07%) of the 87 patients admitted to the ICU were male and 33 (37.93%) were female. There was no statistical difference between the groups in terms of gender (p=0.72). Similarly, there was no statistically significant difference between the two groups for WBC, Hb, HCT, platelet and D-dimer levels (p=0.081, 0.118, 0.055, 0.156 and 0.120, respectively). MCV was higher in the ICU admission group than in the no ICU admission group [86.4 (63.6-96.4) fL vs. 85.65 (8.4-102.9) fL; respectively, p=0.019]. RDW-SD was significantly higher in the ICU admission group [13.5 (11.8-25.3)] than in the no ICU admission group [13.1 (11.4-36.1)] (p=0.001). The number of neutrophils was higher in the ICU admission group than in the no ICU admission group [5.2 (1.94-41.18) x 10^3/μL vs. 4.42 (1.48-18.35) x 10^3/μL; respectively, p=0.008]. The lymphocyte count was significantly lower in the ICU admission group compared to the no ICU admission group [1.09 (0.23-3.1) x 10^3/μL vs. 1.14 [0.36-229] x 10^3/μL; respectively, p=0.031). Albumin was statistically lower in the ICU admission group than in the no ICU admission group [32 (22-44) g/L vs 35 (21-47) g/L; respectively, p=0.001]. CRP was 83.8 (6.3-311.9) mg/L in the ICU admission group and 62.1 (2-270.4) mg/L in the no ICU admission group, and the difference between the groups was statistically significant (p=0.004). Similarly, ferritin was significantly higher in the ICU admission group compared to the no ICU admission group [671.72 (41.94-3152.33) ng/mL vs. 388.21 (5.39-3406.07) ng/mL; respectively, p=0.001]. Procalcitonin was 0.18 (0.01-9.42) ng/mL in the ICU admission group and 0.05 (0-9.41) ng/mL in the no ICU admission group, the difference was statistically significant (p=0.001) (Table 1).

NLR was significantly higher in the ICU admission group compared to the no ICU admission group [4.63 (1.31-31.87) vs. 3.66 (0.02-21.8); respectively, p=0.001] in the evaluation of inflammation parameters. CAR [2.49 (0.18-14.18) vs. 1.88 (0.05-8.18); respectively, p=0.005], SII [860.57 (193.17-5931.03) vs. 702.35 (6.29-7280); respectively, p=0.020], CRP/ L [81.93 (7.29-1300.87) vs. 51.68 (0.32-521.91); respectively, p=0.002] and NLPR [0.03 (0.01-0.23) vs. 0.02 (0-0.44); respectively, p=0.001], were significantly higher in ICU admission group than the no ICU admission group. There was no statistically significant difference between the two groups in terms of PLR (p=0.313) (Table 1).

ROC curve analysis was performed to evaluate the prediction of ICU admission in patients with COVID-19. Sensitivity, specificity and area under the ROC curve (AUC) for NLR were 61%, 51% and 0.610, respectively at a cut-off (4.5); and sensitivity, specificity and AUC for CAR were 61%, 49% and 0.602, respectively at a cut-off (2.5). Similarly, sensitivity, specificity and AUC for SII were 56%, 53% and 0.573, respectively at a cut-off (800); and 55%, 56% and 0.593 for CRP/L, respectively at a cut-off (60); and 64%, 52% and 0.618 for NLPR, respectively at a cut-off (0.026) (Table 2 and Figure 1A). In Univariate regression analysis, there was statistically significant relationship between, RDW-SD (OR: 1.242, p=0.008), procalcitonin (OR: 1.579, p=0.011), NLR (OR: 1.104, p=0.000), CAR (OR: 1.202, p=0.001), SII (OR: 1.000, p=0.011), CRP/L (OR: 1.004, p=0.002), NLPR (OR: 2.393, p=0.000) and the need for admission to ICU but not for PLR (OR: 1.001, p=0.165). RDW-SD (OR: 1.194, p=0.024) and procalcitonin (OR: 1.492, p=0.034) were defined as

Table 1. Characteristics of patients with COVID-19 by ICU admission status

	ICU admission (n=87)	No ICU admission (n=332)	p
Age	66 (37-98)	57 (19-96)	**0.001**
Gender Male Female	 54 (62.07%) 33 (37.93%)	 199 (59.94%) 133 (40.06%)	 0.72
WBC (10^3/μL)	6.83 (3.32-45.6)	6.15 (2.26-20.22)	0.081
Hb (g/dL)	13.2 (9.1-15.9)	13.5 (9.5-43.7)	0.118
HCT (%)	38.9 (21.1-50.3)	40.15 (15.9-51.9)	0.055
MCV (fL)	86.4 (63.6-96.4)	85.65 (8.4-102.9)	**0.019**
RDW-SD	13.5 (11.8-25.3)	13.1 (11.4-36.1)	**0.001**
Platelets (10^3/μL)	176 (38-463)	195 (12.7-633)	0.156
Neutrophil (10^3/μL)	5.2 (1.94-41.18)	4.42 (1.48-18.35)	**0.008**
Lymphocyte (10^3/μL)	1.09 (0.23-3.1)	1.14 (0.36-229)	**0.031**
CRP (mg/L)	83.8 (6.3-311.9)	62.1 (2-270.4)	**0.004**
D-dimer (μg/mL)	0.51 (0.01-8.66)	0.4 (0.01-702)	0.120
Albumin (g/L)	32 (22-44)	35 (21-47)	**0.001**
Ferritin (ng/mL)	671.72 (41.94-3152.33)	388.21 (5.39-3406.07)	**0.001**
Procalcitonin (ng/mL)	0.18 (0.01-9.42)	0.05 (0-9.41)	**0.001**
NLR	4.63 (1.31-31.87)	3.66 (0.02-21.8)	**0.001**
PLR	166.21 (43.68-629.17)	165.6 (1.15-794.03)	0.313
CAR	2.49 (0.18-14.18)	1.88 (0.05-8.18)	**0.005**
SII	860.57 (193.17-5931.03)	702.35 (6.29-7280)	**0.020**
CRP/L	81.93 (7.29-1300.87)	51.68 (0.32-521.91)	**0.002**
NLPR	0.03 (0.01-0.23)	0.02 (0-0.44)	**0.001**

Data are median (IQR); n (%). WBC: White blood cell, Hb: Hemoglobin concentration, HCT: Hematocrit value, MCV: Mean corpuscular volume, RDW-SD: Red cell volume distribution width index, CRP: C-reactive protein, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, CAR: C-reactive protein to albumin ratio, SII: Systemic inflammation index, CRP/L: C-reactive protein to lymphocyte ratio, NLPR: Neutrophil to lymphocyte x platelet ratio, COVID-19: Coronavirus disease-2019, ICU: Intensive care unit

independent risk factors in predicting admission to ICU in multivariate analysis (Table 3).

Comparison of Non-survivor and Survivor Patient Groups

There was a statistically significant difference between the ages of the patients in the non-survivor and survivor groups [72 (55-98) vs. 57.5 (19-96) years; respectively, p=0.001]. Twenty-nine (70.73%) of the 41 patients who died were male and 12 (29.27%) were female, and there was no statistical difference between the groups in terms of gender (p=0.154). Similarly, there was no significant difference between the two groups for WBC, Hb, HCT and D-dimer levels (p=0.110, 0.113, 0.087 and 0.077, respectively). MCV was significantly higher in the non-survivor group than in the survivor group [87 (63.6-96.4) fL vs. 85.7 (8.4-102.9) fL; respectively, p=0.030]. RDW-SD was significantly higher in the non-survivor group [14 (11.8-25.3)] compared to the survivor group [13.1 (11.4-36.1) (p=0.001)]. Platelet count [167 (38-411) x 10^3/μL vs. 193.5 (12.7-633) x 10^3/μL; respectively, p=0.039], neutrophil count [5.38 (2.24-41.18) x 10^3/μL vs. 4.53 (1.48-18.35) x 10^3/μL; respectively, p=0.025], CRP [96.8 (6.3-299.2) mg/L vs. 64.8 (2-311.9) mg/L; respectively, p=0.016], ferritin [716.32 (86.46-3064.63) ng/mL vs. 390.56 (5.39-3406.07) ng/mL; respectively, p=0.008] and procalcitonin [0.25 (0.01-7.12) ng/mL vs. 0.06 (0-9.42) ng/mL; respectively, p=0.001] were significantly higher in the non-survivor group than in the survivor group. Lymphocyte count [0.96 (0.23-3.1) x 10^3/μL vs. 1.15 (0.36-229) x 10^3/μL; respectively, p=0.019] and albumin [31 (23-43) g/L vs. 35 (21-47) g/L; respectively, p=0.008] were significantly lower in the non-survivor group compared to the survivor group (Table 4).

NLR was significantly higher in the non-survivor group compared to the survivor group [6.32 (1.72-31.87) vs. 3.76 (0.02-21.8); respectively, p=0.001] in the evaluation of inflammation parameters. Similarly, CAR [2.48 (0.18-10.98) vs. 1.94 (0.05-14.18); respectively, p=0.024], CRP/L [86.58 (7.29-1300.87) vs. 55.35 (0.32-521.91); respectively,

p=0.009] and NLPR [0.03 (0.01-0.23) vs. 0.02 (0-0.44); respectively, p=0.001] were significantly higher in the non-survivor group compared to the survivor group. There was no significant difference between the two groups in terms of PLR and SII (p=0.501, 0.064; respectively) (Table 4).

ROC curve analysis was performed to evaluate predicting mortality in patients with COVID-19. Sensitivity, specificity and AUC for NLR were 60%, 59% and 0.637, respectively at a cut-off (4.5); and 59%, 49% and 0.613 for CAR, respectively at a cut-off (2.5). The sensitivity, specificity and AUC for CRP/L were 54%, 63% and 0.605, respectively at a cut-off (60); and 63%, 61% and 0.660 for NLPR, respectively at a cut-off (0.026) (Table 2 and Figure 1B).

Table 2. ROC curve analysis for the ICU admission and mortality of different inflammation parameters in patients with COVID-19

ICU admission							
	AUC	**Cut-off**	**Sensitivity**	**Specificity**	**p**	**95% CI lower**	**95% CI upper**
NLR	0.610	4.5	61%	51%	**0.002**	0.542	0.677
PLR	0.530	-	-	-	0.398	0.459	0.602
CAR	0.602	2.5	61%	49%	**0.005**	0.535	0.669
SII	0.573	800	56%	53%	**0.043**	0.502	0.643
CRP/L	0.593	60	55%	56%	**0.010**	0.527	0.659
NLPR	0.618	0.026	64%	52%	**0.001**	0.554	0.682
Mortality							
	AUC	**Cut-off**	**Sensitivity**	**Specificity**	**p**	**95% CI lower**	**95% CI upper**
NLR	0.637	4.5	60%	59%	**0.006**	0.537	0.736
PLR	0.521	-	-	-	0.671	0.416	0.627
CAR	0.613	2.5	59%	49%	**0.024**	0.518	0.708
SII	0.575	-	-	-	0.136	0.472	0.677
CRP/L	0.605	60	54%	63%	**0.035**	0.514	0.697
NLPR	0.660	0.026	63%	61%	**0.001**	0.569	0.752

CI: Confidence interval, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, CAR: C-reactive protein to albumin ratio, SII: Systemic inflammation index, CRP/L: C-reactive protein to lymphocyte ratio, NLPR: Neutrophil to lymphocyte x platelet ratio, COVID-19: Coronavirus disease-2019, ICU: Intensive care unit, AUC: Area under curve

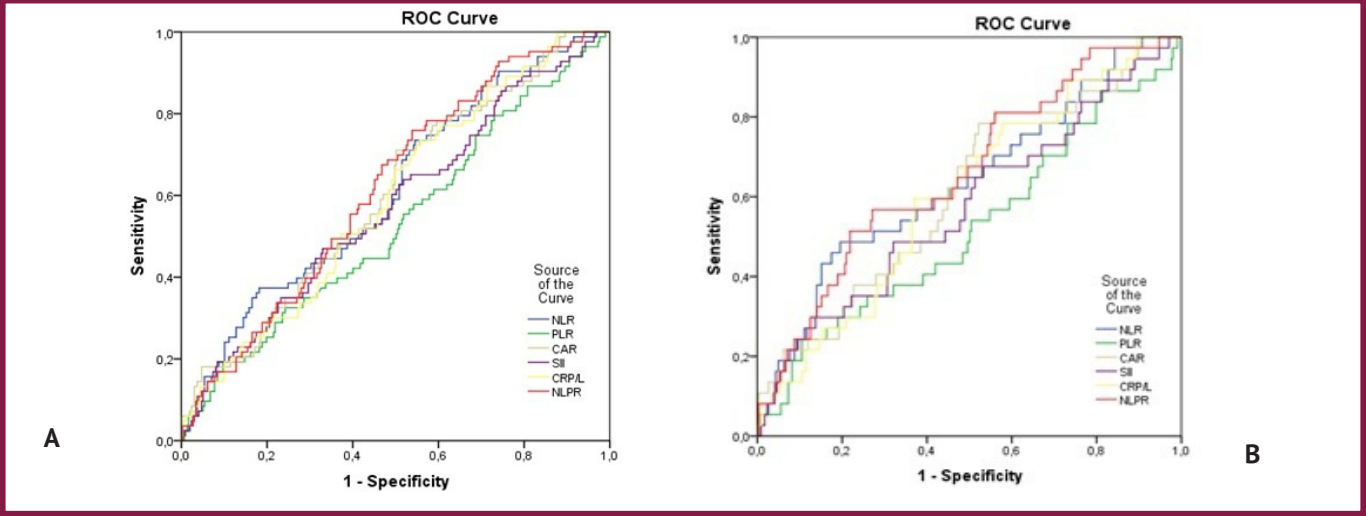

Figure 1. The ROC curve results for the (A) ICU admission and (B) mortality of NLR, PLR, CAR, SII, CRP/L and NLPR

NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, CAR: C-reactive protein to albumin ratio; SII: Systemic inflammation index, CRP/L: C-reactive protein to lymphocyte ratio, NLPR: Neutrophil to lymphocyte, platelet ratio

Table 3. Univariate and multivariate logistic regression with ICU admission and mortality in patients with COVID-19

	Univariate logistic regression							
	ICU admission				Mortality			
	OR	95% CI lower	95% CI upper	p	OR	95% CI lower	95% CI upper	p
RDW-SD	1.242	1.059	1.456	**0.008**	1.310	1.093	1.570	**0.003**
Procalcitonin (ng/mL)	1.579	1.113	2.241	**0.011**	1.400	1.088	1.803	**0.009**
NLR	1.104	1.047	1.165	**0.000**	1.128	1.060	1.200	**0.000**
PLR	1.001	0.999	1.004	0.165	1.002	0.999	1.004	0.239
CAR	1.202	1.076	1.343	**0.001**	1.221	1.063	1.403	**0.005**
SII	1.000	1.000	1.000	**0.011**	1.000	1.000	1.001	**0.017**
CRP/L	1.004	1.001	1.006	**0.002**	1.004	1.001	1.007	**0.007**
NLPR	2.393	1.858	3.083	**0.000**	1.128	1.060	1.200	**0.000**
	Multivariate logistic regression							
	ICU admission				Mortality			
	OR	95% CI lower	95% CI upper	p	OR	95% CI lower	95% CI upper	p
RDW-SD	1.194	1.024	1.392	**0.024**	1.263	1.089	1.464	**0.002**
Procalcitonin (ng/mL)	1.492	1.031	2.160	**0.034**	-	-	-	-

ICU: Intensive care unit, OR: Odds ratio, CI: Confidence interval, RDW-SD: Red cell volume distribution width index, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, CAR: C-reactive protein to albumin ratio, SII: Systemic inflammation index, CRP/L: C-reactive protein to lymphocyte ratio; NLPR: Neutrophil to lymphocyte x platelet ratio, COVID-19: Coronavirus disease-2019

Table 4. Characteristics of patients with COVID-19 by survival status

	Non-survivor (n=41)	Survivor (n=378)	p
Age	72 (55-98)	57.5 (19-96)	**0.001**
Gender Male Female	 29 (70.73%) 12 (29.27%)	 224 (59.26%) 154 (40.74%)	 0.154
WBC (10^3/µL)	7.03 (3.68-45.67)	6.22 (2.26-20.22)	0.110
Hb (g/dL)	13 (9.1-15.7)	13.5 (9.5-43.7)	0.113
HCT (%)	38.7 (28.1-50.3)	40 (15.9-51.9)	0.087
MCV (fL)	87 (63.6-96.4)	85.7 (8.4-102.9)	**0.030**
RDW-SD (%)	14 (11.8-25.3)	13.1 (11.4-36.1)	**0.001**
Platelets (10^3/µL)	167 (38-411)	193.5 (12.7-633)	**0.039**
Neutrophil (10^3/µL)	5.38 (2.24-41.18)	4.53 (1.48-18.35)	**0.025**
Lymphocyte (10^3/µL)	0.96 (0.23-3.1)	1.15 (0.36-229)	**0.019**
CRP (mg/L)	96.8 (6.3-299.2)	64.8 (2-311.9)	**0.016**
D-dimer (µg/mL)	0.52 (0.01-8.66)	0.41 (0.01-702)	0.077
Albumin (g/L)	31 (23-43)	35 (21-47)	**0.008**
Ferritin (ng/mL)	716.32 (86.46-3064.63)	390.56 (5.39-3406.07)	**0.008**
Procalcitonin (ng/mL)	0.25 (0.01-7.12)	0.06 (0-9.42)	**0.001**
NLR	6.32 (1.72-31.87)	3.76 (0.02-21.8)	**0.001**
PLR	166.21 (43.68-629.17)	165.6 (1.15-794.03)	0.501
CAR	2.48 (0.18-10.98)	1.94 (0.05-14.18)	**0.024**
SII	1025.45 (193.17-5797.09)	716.03 (6.29-7280)	0.064
CRP/L	86.58 (7.29-1300.87)	55.35 (0.32-521.91)	**0.009**
NLPR	0.03 (0.01-0.23)	0.02 (0-0.44)	**0.001**

Data are median (IQR); n (%). WBC: White blood cell, Hb: Hemoglobin concentration, HCT: Hematocrit value, MCV: Mean corpuscular volume, RDW-SD: Red cell volume distribution width index, CRP: C-reactive protein, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, CAR: C-reactive protein to albumin ratio, SII: Systemic inflammation index, CRP/L: C-reactive protein to lymphocyte ratio, NLPR: Neutrophil to lymphocyte x platelet ratio, COVID-19: Coronavirus disease-2019

In univariate regression analysis, there was a statistically significant relationship between, RDW-SD (OR: 1.310, p=0.003), procalcitonin (OR: 1.400, p=0.009), NLR (OR: 1.128, p=0.000), CAR (OR: 1.221, p=0.005), SII (OR: 1.000, p=0.017), CRP/L (OR: 1.004, p=0.007), NLPR (OR: 1.128, p=0.000) and mortality but not for PLR (OR: 1.002, p=0.239). RDW-SD (OR: 1.263, p=0.002) was defined as an independent risk factor in predicting mortality in multivariate analysis (Table 3).

Discussion

COVID-19 that affects the whole world has a clinical spectrum ranging from asymptomatic disease to critical cases. ARDS, severe pneumonia and multiorgan failure which may require admission to the ICU and result in death may be seen in severe cases (13). The incidence of ARDS and severe disease was 14.8% and 18.1%, respectively, and the fatality rate was 4.3% in the meta-analysis by Sun et al. (14). This demonstrates the importance of parameters that can predict poor outcome in patients with COVID-19. It is known that indices calculated by whole blood parameters alone or by their ratios to each other can be used to show systemic inflammation in COVID-19 and many cancers (9). This study was aimed to evaluate the value of inflammation parameters in predicting ICU admission and mortality in patients with COVID-19.

Higher WBC and neutrophil levels and lower lymphocyte and platelet levels were associated with mortality in the meta-analysis of Taylor et al. (15). High CRP levels were associated with the severity of the disease in another meta-analysis by Meng et al. (16). In this study, similar to the literature, high neutrophil and CRP levels, low lymphocyte levels were associated with ICU admission and mortality in patients with COVID-19. On the other hand, platelet was associated only with mortality. In contrast, there was no association between WBC and prognosis.

Many diseases affect the morphology and functions of red blood cells. Viral infections can affect red blood cells, changing their size, firmness and distribution width. This change was also detected in patients with COVID-19 and was associated with the severity of the disease (17). RDW-SD and MCV were associated with mortality, while Hb and HCT were not in the study of Pluta et al. (18) including 70 patients who were admitted to the ICU with COVID-19. Similarly, in this study, Hb and HCT were ineffective for prognosis, while MCV and RDW-SD were associated with both mortality and ICU admission. In addition, RDW-SD was shown to be an independent risk factor for both mortality (OR: 1.194, p=0.024) and admission to ICU (OR: 1.263, p=0.002) in the multivariate analysis.

It was stated that high D-dimer and low albumin levels were associated with mortality in a meta-analysis by Wu et al. (19). Low albumin was associated with both ICU admission and mortality in our study. On the other hand, D-dimer was high in the evaluation of both groups, but there was no statistically significant difference.

In our study, the need for ICU and mortality risk were higher when NLR >4.5, CAR >2.5, CRP/L >60, NLPR >0.026. When SII was >800, there was a statistically significant increase in those admitted to the ICU, but there was no correlation between it and mortality. There was no relationship between both ICU admission and mortality and PLR. In addition, NLR, CAR, SII, CRP/L and NLPR were associated with both ICU admission and mortality in the univariate analysis. ROC analysis was performed for more detailed information, and AUC was 0.610, 0.602, 0.573, 0.593 and 0.618 at admission to ICU for NLR, CAR, SII, CRP/L and NLPR, respectively. The AUC was 0.637, 0.613, 0.605 and 0.660, respectively, when NLR, CAR, CRP/L, and NLPR were evaluated for mortality. According to these results, NLPR had the highest sensitivity (cut-off >0.026, 64% in ICU admission, 63% in mortality) and CRP/L had the highest specificity (cut-off >60, 56% in ICU admission, 63% in mortality).

Similarly, SII was higher in patients who admitted to ICU compared to those who did not in the study by Nalbant et al. (20). In ROC analysis, when SII was ≥813.6, AUC was 0.689, sensitivity was 70.8% and specificity was 66% (20). NLR and CAR were higher in the mortality group than in the survival group in the study by Acehan et al. (21). CAR was an independent risk factor for mortality. AISI, NLPR, SII, and SIRI were associated with admission to ICU in the study by Hamad et al. (22). Similar to this study, NLRP sensitivity was the highest index (cut-off >0.0195, 61.3%) (22).

Acar et al. (23) studied LCRP, which is the opposite of CRP/L, and it was associated with mortality in patients with COVID-19 (cut-off <1, AUC: 0.817, sensitivity 100%, specificity 86.8%). In this study, procalcitonin levels were associated with both ICU admission and mortality. It was an independent risk factor for ICU admission (OR: 1.492, 95% CI: 1.031-2.160) in the multivariate analysis. Similar to our study, Tong-Minh et al. (24) showed correlation between procalcitonin levels and mortality and procalcitonin was an independent risk factor for mortality (OR: 2.11, 95% CI: 1.36-3.61) in multivariate analysis.

Study Limitations

The limitations of the study are that it cannot be generalized to the population without being supported by prospective studies, since it was single-centered and retrospective. Patients with malignancy and immunosuppression that may affect hematological

parameters such as lymphocytes and neutrophils were not included in the study, but other potential causes that could affect these parameters were not evaluated in this study.

Conclusion

NLR, CAR, NLPR, and CRP/L were associated with both ICU admission and mortality in patients with COVID-19. SII was associated with only admission to the ICU. In addition, it was evaluated that high procalcitonin levels may be an independent risk factor for admission to ICU, and RDW-SD may be an independent risk factor for both mortality and admission to ICU. Using algorithms that can be developed with these measured parameters, it may be possible to predict the prognosis of COVID-19 patients and to decide on anti-inflammatory treatment for the severe course of the disease.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of the Ümraniye Training and Research Hospital (date: November 19, 2020, no: 346).

Informed Consent: Informed consent was waived because of the retrospective nature of the study.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.C., T.Ç., E.S., Ö.A., Concept: K.C., T.Ç., E.S., Ö.A., Design: K.C., T.Ç., E.S., Ö.A., Data Collection or Processing: K.C., T.Ç., E.S., Ö.A., Analysis or Interpretation: K.C., T.Ç., E.S., Ö.A., Literature Search: K.C., T.Ç., E.S., Ö.A., Writing: K.C., T.Ç., E.S., Ö.A.

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