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Original Article

Predictive role of neutrophil-to-lymphocyte ratio (NLR) in the progression of COVID-19 patients in intensive care unit

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ABSTRACT

Aims: The aim of this study was to evaluate the neutrophil-to-lymphocyte ratio (NLR) as a predictive marker for the prognosis of COVID-19 patients, in order to provide an easy, accessible, and cost-effective way to measure inflammation.

Methods: A total of 365 patients, aged over 18 years and admitted to the intensive care unit (ICU) between 01.08.2020 and 31.03.2021 with a positive RT-PCR test for COVID-19, were included. This was a single-center, retrospective study. Demographic data and laboratory results of the patients at the time of the first admission and ICU admission were analyzed. The relationship between NLR values at initial presentation and ICU admission with patient prognosis was statistically investigated.

Results: In our study, we found that NLR and d-NLR values at the time of initial hospital admission and ICU admission had a predictive role in forecasting 30-day mortality in COVID-19 patients admitted to the ICU. An NLR cutoff value of>0.48 at first presentation predicted mortality with a sensitivity of 72.2% and a specificity of 46.0%. An NLR cutoff value of 11.7 at ICU admission predicted mortality with a sensitivity of 64.7% and a specificity of 60.9%. Additionally, procalcitonin, CRP, IL-6, D-Dimer, and ferritin levels at both initial admission and ICU admission were found to have a predictive role in mortality.

Conclusion: The NLR is a predictive marker for mortality in ICU patients. The lower sensitivity and specificity values compared to those in the literature are attributed to differences in the age, comorbidities, and clinical severity of the patient population included in this study.

Keywords: COVID-19, neutrophil-to-lymphocyte ratio, mortality, intensive care, prognosis

INTRODUCTION

In December 2019, pneumonia cases caused by a novel coronavirus leading to acute respiratory distress syndrome were reported in humans in Wuhan, Hubei Province, China. Due to the increasing number of cases, the World Health Organization declared a pandemic in March 2020.[1,2] One of the major issues arising from the pandemic was the significant strain placed on national healthcare systems worldwide and the increased number of patients requiring intensive care unit (ICU) support within a very limited timeframe. Many hospitals made adjustments to inpatient services and ICUs due to the increased hospital admissions caused by the pandemic.[3-5] The importance of the effective use of resources in ICUs became even more critical as hospitals received patient admissions exceeding their capacities.[6,7] Early diagnosis and treatment in critically ill patients can impact disease prognosis and reduce mortality rates.[8] Particularly, hyperinflammatory response and cytokine storm, associated with elevated levels of inflammatory markers, has been shown to significantly increase mortality.[6]

The neutrophil-to-lymphocyte ratio (NLR) is used as a marker of systemic inflammation. The inflammatory response stimulates the release of inflammatory cytokines such as TNF-alpha and IL-6, leading to an increase in neutrophil levels. Proinflammatory mediators such as catecholamines and cortisol bind to the lymphocyte surface, initiating lymphocytic apoptosis, which results in lymphopenia.[6,9] In addition to being an indicator of inflammation, NLR

has been studied in various fields to determine its potential associations.[10,11] The clinical course of COVID-19 correlates with the inflammatory response, and NLR, reflecting changes in both neutrophil and lymphocyte counts, is considered a reliable inflammatory marker.[12]

This study aims to investigate the effect of NLR values on the prognosis and length of ICU stay in patients admitted to the ICU. Additionally, other inflammatory markers that influence the prognosis of COVID-19 were also analyzed.

METHODS

The study protocol was approved by the Clinical Researches Ethics Committee of University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital (Date: 08.03.2021, Decision No: 106/12). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This was a single-center, retrospective study conducted between 01.08.2020 and 31.03.2021 at the COVID-19 ICU of University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital. The study included patients aged 18 years and older, who were admitted to the ICU for the first time with a positive SARS-CoV-2 RT-PCR result.

Patients with a history of previous hospitalization in different hospitals, those under 18 years of age, patients with a negative SARS-CoV-2 RT-PCR test result or no PCR test result, patients with respiratory distress due to non-COVID-19 causes, patients with long-standing COVID-19-like symptoms who tested positive for SARS-CoV-2 RT-PCR during hospitalization with a different diagnosis, and patients with repeated ICU admissions were excluded. In the case of repeated ICU admissions, only the first admission data were included in the study.

Demographic and clinical data of the patients were obtained through analysis of the hospital's electronic automation system and ICU monitoring forms. Laboratory parameters during the first hospital admission and the first ICU admission were included in the study. The parameters evaluated included leukocyte count, neutrophil count, lymphocyte count, ferritin, D-Dimer, procalcitonin (PCT), CRP, BNP, IL-6, NLR, and derived neutrophil-to-lymphocyte ratio (d-NLR) [d-NLR is calculated by dividing the difference between the total leukocyte count and the neutrophil count by the neutrophil count].

The onset dates of symptoms and signs, age, gender, comorbidities, dates of first hospital admission and ICU admission, ICU and hospital length of stay, SOFA and APACHE scores were recorded. Mortality was assessed based on the patiaent's status on the 30th day of ICU admission.

Statistical Analysis

Data analysis was performed using SPSS (Statistical Package for Social Sciences, Chicago, IL, USA) version 22.0. Descriptive statistics for continuous variables were presented as mean±standard deviation and median (minimum-maximum), while categorical variables were presented as frequency and percentage. The distribution of continuous variables was evaluated for normality using the Shapiro-Wilk test. When parametric conditions were met, the differences between two groups for continuous variables were assessed using the Independent t-test, and when parametric conditions were not met, the Mann-Whitney U test was used. For comparisons involving more than two groups, continuous variables were evaluated using the Kruskal-Wallis test. In cases where significant differences were found, pairwise analysis was performed to identify the source of the differences. For categorical variables, the chi-square test or Fisher's exact test was used. Survival analysis was conducted using Kaplan-Meier analysis and the Log-Rank test. Regression analysis was performed to evaluate factors affecting mortality. In the ROC analysis, predictive factors for mortality were assessed, and cut-off values were determined. Sensitivity and specificity values corresponding to the identified cut-off values were calculated. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 365 patients were included in the study. The mean age of the patients was 69.94 (12.57). Of the patients, 153 (41.9%) were female and 212 (58.1%) were male (Table 1).

Mortality occurred in 199 patients (54.5%) within 30 days (Table 1). The mean age of survivors was 66.82 (13.33), and the mean age of deceased patients was 72.41 (11.38). The mean age of deceased patients was significantly higher than that of survivors ($p<0.001$). The gender distribution between deceased and surviving patients was similar ($p=0.913$) (Table 2).

The time from symptom onset to hospital admission was 3.27 (3.21) days for deceased patients and 4.42 (3.97) days for survivors ($p=0.003$). The time from symptom onset to ICU admission was similar for both groups ($p=0.053$) (Table 2).

The length of ICU stay and total hospital stay were significantly longer in survivors ($p<0.001$) (Table 2).

The APACHE II and SOFA scores were significantly higher in deceased patients compared to survivors ($p<0.001$) (Table 2).

There was no significant difference between deceased and surviving patients in terms of the prevalence of hypertension ($p=0.074$), diabetes mellitus ($p=0.776$), pulmonary diseases ($p=0.685$), and rheumatologic diseases ($p=0.965$). However, the prevalence of cardiac diseases ($p=0.003$), neurological diseases ($p=0.011$), kidney diseases ($p=0.015$), and malignancies ($p=0.025$) were significantly higher in deceased patients (Table 2).

There was no significant difference between deceased and surviving patients regarding the presenting symptoms ($p>0.05$). The prevalence of myalgia and loss of taste and smell was significantly higher in survivors than in deceased patients ($p=0.040$, $p=0.026$) (Table 2).

The NLR value at the time of first admission and ICU admission was significantly higher in deceased patients compared to survivors ($p=0.001$ and $p<0.001$, respectively). The d-NLR value calculated at first admission and ICU

Table 1. Demographic data and basic characteristics of all patients

Variable	
Age (years)	69.94±12.57
Gender	
Female	153 (41.9%)
Male	212 (58.1%)
Comorbidities	
Hypertension	227 (67.2%)
Diabetes mellitus	139 (38.1%)
Cardiac disease	119 (32.6%)
Pulmonary disease	76 (20.8%)
Neurological disease	49 (13.4%)
Kidney disease	32 (8.8%)
Malignancy	25 (6.8%)
Rheumatological disease	20 (5.5%)
Presenting symptoms	
Dyspnea	198 (54.2%)
Cough	137 (37.5%)
Fever	114 (31.2%)
Fatigue	95(26.0%)
Myalgia	53 (14.5%)
Nausea-vomiting	33 (19.0%)
Loss of appetite	27 (7.4%)
Headache	24 (6.6%)
Sputum production	22 (6.0%)
Loss of taste-smell	10 (2.7%)
Chest pain	7 (1.9%)
Time from symptom onset to presentation (days)	3.79±3.62
Time from symptom onset to ICU admission (days)	7.89±5.02
ICU length of stay (days)	9 (1-56)
Hospital length of stay (days)	14 (0-79)
SOFA score	3 (1-15)
APACHE II score	17 (6-53)
Mortality	199 (54.5%)

The data are presented as mean±standard deviation, median (minimum-maximum), and number (%). Abbreviations: ICU: Intencive care unit, SOFA: Sequential organ failure assessment, APACHE: Acute physiology and chronic health evaluation

Table 2. Distribution of demographic data and basic characteristics in deceased and surviving patients

	Deceased (n=166)	Survived (n=199)	p
Age (years)	66.82±13.33	72.41±11.38	<0.001*
Gender			
Female	70 (42.2%)	83 (41.7%)	0.913**
Male	96 (57.8%)	116 (58.3%)	
Comorbidities			
Hypertension	95 (57.1%)	132 (66.3%)	0.074**
Diabetes mellitus	60 (37.3%)	79 (38.7%)	0.776**
Cardiac disease	41 (24.7%)	78 (39.2%)	0.003**
Pulmonary disease	33 (19.9%)	43 (21.6%)	0.685**
Neurological disease	14 (8.4%)	35(17.6%)	0.011**
Kidney disease	8 (4.8%)	24 (12.1%)	0.015**
Malignancy	6(3.6%)	19 (9.5%)	0.025**
Rheumatological disease	9 (5.4%)	11 (5.5%)	0.965**
Presenting symptoms			
Dyspnea	85 (51.2%)	113 (56.8%)	0.287**
Cough	63 (38.0%)	74 (37.2%)	0.880**
Fever	45 (27.1%)	69 (34.7%)	0.120**
Fatigue	38 (23.6%)	57 (27.9%)	0.348**
Myalgia	31(18.7%)	22 (11.1%)	0.040**
Nausea-vomiting	12 (7.2%)	21 (10.6%)	0.270**
Loss of appetite	12 (7.2%)	15 (7.5%)	0.911**
Headache	8 (4.8%)	16 (8.0%)	0.216**
Sputum production	8 (4.8%)	14 (7.0%)	0.376**
Loss of taste-smell	8 (4.8%)	2 (1.0%)	0.026**
Chest pain	2 (1.2%)	5 (2.52%)	0.332**
Time from symptom onset to presentation (days)	4.42±3.97	3.27±3.21	0.003*
Time from symptom onset to ICU admission (days)	11.22±28.81	6.99±4.49	0.053*
ICU length of stay (days)	12 (1-52)	7 (1-56)	<0.001***
Hospital length of stay (days)	19 (0-79)	11 (1-41)	<0.001***
SOFA score	2 (1-13)	4(2-15)	<0.001***
APACHE II score	13 (6-29)	19 (8-53)	<0.001***

The data are presented as mean±standard deviation, median (minimum-maximum), and number (%); *Independent Simple T test, ** Chi-square test, *** Mann-Whitney U test, Abbreviations: ICU: Intencive care unit, SOFA: Sequential organ failure assessment, APACHE: Acute physiology and chronic health evaluation

admission was also significantly higher in deceased patients compared to survivors (p<0.001 and p=0.017, respectively) (Table 3).

Procalcitonin, CRP, and BNP levels at first admission and ICU admission were significantly higher in deceased patients compared to survivors (p<0.001) (Table 3).

The D-Dimer values measured at first admission and ICU admission were significantly higher in deceased patients compared to survivors (p=0.002 and p<0.001, respectively). IL-6 levels measured at first admission and ICU admission were also significantly higher in deceased patients compared to survivors (p<0.001). There was no significant difference in ferritin levels at first admission, but levels at ICU admission were significantly higher in deceased patients (p=0.251 and p=0.001, respectively) (Table 3).

In ROC analysis, the role of laboratory test results at first admission and ICU admission in predicting mortality was analyzed. Elevated procalcitonin (AUC=0.679, p<0.001), elevated NLR (AUC=0.604, p=0.001), elevated d-NLR (AUC=0.579, p=0.009), elevated D-Dimer (AUC=0.607, p=0.001), elevated CRP (AUC=0.619, p<0.001), and elevated IL-6 (AUC=0.750, p<0.001) all had significant predictive value for mortality. Elevated WBC and ferritin levels at ICU admission also had predictive value for mortality (<0.05) (Table 4, Figure 1, Figure 2).

For NLR at first admission, the cut-off value of >4.38 predicted 30-day mortality with 72.2% sensitivity and 46.0% specificity. For NLR at ICU admission, the cut-off value of 11.17 predicted mortality with 64.7% sensitivity and 60.9% specificity (Table 5). Table 5 shows the cut-off values, sensitivity, and specificity for tests predicting mortality at first admission and ICU admission.

In univariate analysis of risk factors associated with mortality, advanced age was found to be a significant risk factor for increased mortality (OR: 1.03, p<0.001). Gender (OR: 0.97, p=0.913), history of diabetes mellitus (OR: 1.06,

Table 3. Laboratory tests at initial admission and ICU admission in deceased and surviving patients

	Initial admission			ICU admission		
	Deceased	**Survived**	**p**	**Deceased**	**Survived**	***p**
Procalcitonin (µg/L)	0.1 (0.0-0.3)	0.2 (0.1-.7)	<0.001	0.1 (0-0.3)	0.5 (0.2-1.8)	<0.001
Aspartate transaminase (U/L)	34.5 (24.0-50.0)	33.0 (23.0-54.0)	0.753	32.0 (22.0-45.0)	41.0 (29.0-58.0)	<0.001
Alanine transaminase (U/L)	23.5 (16.0-40.0)	20.0 (14.0-32.5)	0.017	27.5 (17.0-48.0)	24.0 (16.0-39.0)	0.274
Laktat dehidrogenaz (U/L)	329.0 (235.0-439.0)	368.5 (275.0-516.0)	0.015	375.5 (296.0-470.0)	540.0 (419.0-681.0)	<0.001
Creatinine kinase (U/L)	102.5 (56.0-217.0)	137.0 (70.0-321.0)	0.022	71.0 (39.5-143.5)	135.0 (71.0-416.0)	<0.001
Creatinine kinase-MB (U/L)	19.0 (15.2-26.0)	21.5 (15.0-29.9)	0.125	22.0 (16.5-28.8)	29.0 (22.0-44.0)	<0.001
White blood cell ($\times10^3$/µL)	6.4 (4.9-8.2)	6.6 (4.94-9.3)	0.290	7.5 (5.8-9.9)	8.8 (6.2-12.7)	0.009
Platelet ($\times10^3$/µL)	195.5 (162.0-259.0)	184.0 (143.0-232.0)	0.016	247.5(198.0-317.0	201.0 (149.0-270.0)	<0.001
Neutrophil ($\times10^3$/µL)	4.8 (3.4-6.4)	5.0 (3.5-7.7)	0.141	6.4 (4.7-8.76)	7.9 (5.3-11.6)	0.001
Lymphocyte ($\times10^3$/µL)	0.9 (0.7-1.3)	0.8 (0.5-1.1)	0.005	0.6 (0.4-1.0)	0.5 (0.3-0.7)	<0.001
NLR	4.8 (2.8-8.4)	6.0 (3.8-11.1)	0.001	9.2 (5.6-15.3)	14.3 (8.3-24.9)	<0.001
d-NLR	3.3 (1.9-5.2)	3.8 (2.4-5.8)	<0.001	5.9 (4.0-9.5)	8.24 (5.5-13.5)	0.017
PLR	206.4 (147.2-289.3)	214.7 (141.2-326.7)	0.622	384.5 (239.0-371.0)	371.0 (239.2-560.7)	0.556
Ferritin (µg/L)	453.5 (229.0-894.0)	549.5 (232.0-1030.0)	0.251	574.0 (314.0-1004.0)	853.0 (485.0-1483.0)	<0.001
PaO_2/FiO_2	164.8 (128.8-207.8)	155.5 (121.4-204.0)	0.261	113.1 (87.7-153.3)	86.9 (63.6-120.0)	<0.001
Troponin (ng/ml)	0.1 (0.1-0.11)	0.1 (0.1-0.13)	0.018	0.1 (0.1-0.1)	0.1 (0.1-0.3)	<0.001
BNP (ng/L)	359.6 (120.5-906.7)	822.1 (288.4-3807.0)	<0.001	508.2 (271.8-1250.0)	1791.0 (517.0-5607.0)	<0.001
Fibrinojen (mg/dl)	543.0 (451.0-635.0)	529.0 (428.0-647.0)	0.333	554.5 (454.0-645.0)	562.0 (460-650.0)	0.383
D-Dimer (µg/l)	0.7 (0.4-1.2)	0.9 (0.5-2.0)	0.002	0.9 (0.5-1.7)	1.4 (0.8-3.0)	<0.001
C-reactive protein (mg/L)	85.5 (42.7-135.6)	115.0 (60.9-206.4)	<0.001	64.5 (35.8-128.3)	134.5 (77.0-201.0)	<0.001
Interleukin-6 (pg/ml)	17.2 (11.8-50.6)	56.9 (28.8-93.7)	<0.001	17.9 (10.9-43.40)	45.9 (23.4-81.2)	<0.001

Mann Whitney U Test. The data are presented as median and IQR (interquartile range, 25th-75th percentiles). Abbreviations: NLR: Neutrophil-to-lymphocyte ratio, d-NLR: Derived neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, PaO_2: Arterial oxygen partial pressure, FiO_2: Fractional inspired oxygen, BNP: Brain natriuretic peptide

Table 4. Predictive value of test results at initial admission and ICU admission for predicting mortality

	Parameter	**AUC**	**SE**	**95 CI%**		**p**
				Minimum	**Maximum**	
Initial admission	Procalcitonin	0.679	0.029	0.622	0.735	<0.001
	White blood count	0.531	0.030	0.472	0.590	0.305
	NLR	0.604	0.030	0.545	0.662	0.001
	d-NLR	0.579	0.009	0.555	0.670	<0.001
	Ferritin	0.536	0.036	0.466	0.607	0.317
	PaO_2/FiO_2	0.463	0.035	0.394	0.532	0.299
	Fibrinojen	0.472	0.033	0.408	0.537	0.401
	D-Dimer	0.607	0.030	0.548	0.666	0.001
	C-reaktive protein	0.619	0.033	0.555	0.683	<0.001
	Interleukin-6	0.750	0.045	0.662	0.838	<0.001
ICU admission	Procalcitonin	0.771	0.025	0.722	0.820	<0.001
	White blood count	0.588	0.030	0.530	0.647	0.004
	NLR	0.662	0.028	0.606	0.717	<0.001
	d-NLR	0.652	0.029	0.595	0.708	<0.001
	Ferritin	0.602	0.030	0.543	0.661	0.001
	PaO_2/FiO_2	0.327	0.028	0.271	0.383	<0.001
	Fibrinojen	0.531	0.030	0.472	0.591	0.306
	D-Dimer	0.647	0.029	0.591	0.704	<0.001
	C-reactive protein	0.701	0.027	0.647	0.755	<0.001
	Interleukin-6	0.706	0.033	0.642	0.770	<0.001
	SOFA	0.756	0.025	0.707	0.805	<0.001
	APACHE II	0.851	0.020	0.811	0.890	<0.001

Abbreviations: AUC: Area under the curve, S.E: Standard error, CI: Confidence ınterval, NLR: Neutrophil-to-lymphocyte ratio, d-NLR: Derived neutrophil-to-lymphocyte ratio, ICU: Intencive care unit, PaO_2: Arterial oxygen partial pressure, FiO_2: Fractional inspired oxygen, SOFA: Sequential organ failure assessment, APACHE: Acute physiology and chronic health evaluation

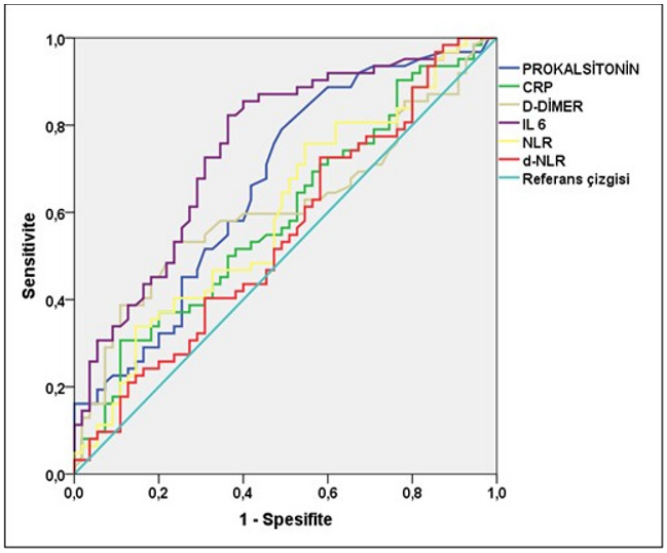

Figure 1. ROC analysis of initial assessment laboratory results and mortality
ROC: Receiver operating characteristic, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, d-NLR: Derived neutrophil-to-lymphocyte ratio

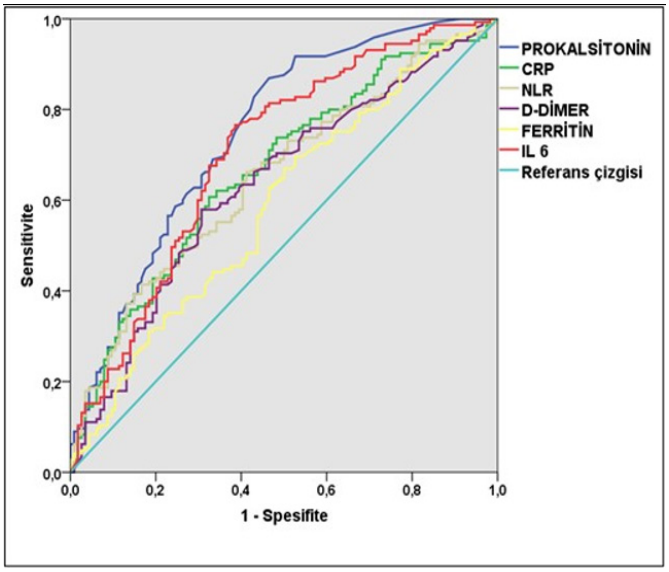

Figure 2. ROC analysis of ICU admission laboratory results and mortality
ROC: Receiver operating characteristic, ICU: Intencive care unit, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio

p=0.776), history of hypertension (OR: 1.46, p=0.078), history of pulmonary diseases (OR: 1.10, p=0.693), and history of rheumatologic diseases (OR: 0.96, p=0.934) were not significant risk factors for increased mortality. History of cardiac diseases (OR: 2.13, p=0.001) and renal diseases (OR: 2.55, p=0.027) were identified as risk factors associated with increased mortality (Table 6).

Table 6. Mortality-related risk factors

	OR	95 CI%		p
		Mimimum	Maximum	
Age	1.03	1.01	1.05	<0.001
Gender	0.97	0.64	1.48	0.913
Diabetes mellitus	1.06	0.69	1.62	0.776
Hypertension	1.46	0.95	2.24	0.078
Cardiac disease	2.13	1.34	3.37	0.001
Pulmonary disease	1.10	0.66	1.84	0.693
Rheumatologic disease	0.96	0.38	2.38	0.934
Renal disease	2.55	1.11	5.84	0.027
Neurological disease	2.31	1.20	4.74	0.012
Malignancy	2.81	1.09	7.22	0.031

Abbreviations: OR: Odds ratio, CI: Confidence interval

In the univariate analysis of mortality-related risk factors, NLR, d-NLR, and IL-6 levels at first admission, and NLR and CRP levels at ICU admission were identified as significant independent risk factors for mortality (Table 7).

For patients with NLR values>4.38 at first admission, the survival rate during hospitalization was significantly lower (p<0.001). For patients with NLR values >4.38 at ICU admission, the survival rate during hospitalization was also significantly lower (p<0.001). For patients with d-NLR values >3.03 at first admission, the survival rate during hospitalization was significantly lower (p<0.001). For patients with d-NLR values >5.64 at ICU admission, the 30-day survival rate during hospitalization was significantly lower (p<0.001) (Table 5).

Table 5. Cut-off values for laboratory results with diagnostic value in predicting mortality and their sensitivity and specificity levels

Time	Parameter	Cut-off	AUC	p	Sensitivity (%)	Specificity (%)
Initial admission	Procalcitonin	0.12	0.670	<0.001	82.9%	47.4%
	NLR	4.38	0.604	0.001	72.2%	46.0%
	d-NLR	3.03	0.579	0.009	67.2%	49.0%
	D-dimer	0.93	0.607	0.001	53.6%	68.6%
	C-reactive protein	143	0.619	<0.001	42.1%	78.9%
	Interleukin-6	23.2	0.750	<0.001	82.5%	63.2%
ICU admission	Procalcitonin	0.13	0.771	<0.001	88.7%	54.7%
	White blood cell	9.6	0.588	0.004	45.1%	73.9%
	NLR	11.17	0.662	<0.001	64.7%	60.9%
	d-NLR	5.64	0.652	<0.001	78.4%	49.1%
	Ferritin	575	0.602	0.001	67.3%	50.3%
	D-dimer	1.95	0.647	<0.001	58.7%	67.1%
	C-reactive protein	76	0.701	<0.001	74.4%	57.8%
	Interleukin-6	23.5	0.750	<0.001	76.0%	61.4%

Abbreviations: AUC: Area under the curve, NLR: Neutrophil-to-lymphocyte ratio, d-NLR: Derived neutrophil-to-lymphocyte ratio

Table 7. Univariate analysis of the relationship between initial assessment and ICU admission tests and mortality

	Parameter	OR	95 CI%		p
			Minimum	Maximum	
Initial admission	Procalcitonin	1.83	1.26	2.67	0.002
	White blood cell	1.04	0.99	1.10	0.105
	NLR	1.04	1.01	1.08	0.009
	d-NLR	3.06	1.65	5.67	0.000
	Ferritin	1.00	1.00	1.00	0.208
	Fibrinojen	0.99	0.99	1.00	0.345
	D-dimer	1.10	1.01	1.20	0.021
	C-reactive protein	1.00	1.00	1.00	<0.001
	Interleukin-6	1.02	1.00	1.03	0.001
ICU admission	Procalcitonin	1.11	1.02	1.20	0.013
	White blood cell	1.05	1.00	1.10	0.021
	NLR	1.04	1.02	1.06	<0.001
	d-NLR	2.02	1.24	3.30	0.005
	Ferritin	1.00	1.00	1.00	0.013
	Fibrinojen	1.00	0.99	1.00	0.328
	D-dimer	0.99	0.99	1.00	0.514
	C-reactive protein	1.00	1.00	1.01	<0.001
	Interleukin-6	1.00	1.00	1.00	0.035

Abbreviations: OR: Odds ratio, CI: Confidence interval, NLR: Neutrophil-to-lymphocyte ratio, d-NLR: Derived neutrophil-to-lymphocyte ratio, ICU: Intencive care unit

DISCUSSION

In our study, which investigated the relationship between NLR and mortality in patients admitted to the ICU with COVID-19 infection, we found that deceased patients had higher NLR, procalcitonin, CRP, IL-6, D-Dimer, and BNP levels. We also observed that deceased patients had a higher mean age, as well as higher APACHE II and SOFA scores. Additionally, in the multivariate analysis of risk factors associated with mortality, NLR, d-NLR, and IL-6 levels at the time of initial hospital admission, and NLR and CRP levels at ICU admission, were found to be significant independent risk factors for mortality.

The literature suggests that different NLR values have a predictive role in mortality and patient prognosis.[13-15] NLR values may vary due to systemic inflammatory conditions such as race, socioeconomic status, smoking, obesity, diabetes, age, cardiovascular diseases, and cancer.[16] In a study by Meng et al.[17], higher NLR values were found in males and patients over the age of 65. We believe that differences in NLR values across studies may be due to variations in clinical severity of the disease, as well as different characteristics of the included patients, such as age, gender, and comorbidities. In our study, NLR values at both initial hospital admission and ICU admission were consistent with the literature and were found to be risk factors for mortality. Furthermore, although the neutrophil count at initial admission was not associated with mortality, lymphocyte levels at both initial admission and ICU admission were significantly associated with mortality. An increase in systemic inflammatory response due to COVID-19 is believed to play a role in these findings. While an increase in neutrophil levels is observed due to heightened inflammatory responses, lymphocyte levels decrease due to apoptosis. The use of NLR, a combined parameter of neutrophils and lymphocytes, has been shown to be a more effective and reliable indicator of systemic inflammation.[18] Therefore, we believe that using NLR values rather than just neutrophil and/or lymphocyte counts may be more effective.

Studies in the literature have reported hospital mortality rates in COVID-19 patients ranging from 18.8% to 49.6%. Additionally, mortality rates have been reported to be over 60% in older and critically ill patients.[13,19] In our study, the mortality rate was found to be 54.5%. We believe that the higher mortality rate in our study can be attributed to the fact that our study only included ICU patients and the mean age of deceased patients was above 60 years.

Viral infections respond primarily through T lymphocytes and cytotoxic lymphocytes, such as natural killer cells. In patients with low lymphocyte counts, viral infections may progress more rapidly. SARS-CoV-2 directly reduces lymphocyte levels through ACE-2 receptors present on lymphocytes. Despite an increase in neutrophil counts, studies have shown that their phagocytic ability is partially impaired. The decrease in T lymphocytes and the increase in neutrophils may increase the risk of bacterial infections. Secondary bacterial infections may contribute to the deterioration of the disease. NLR, PCT, and CRP are parameters that can be used to assess the severity of bacterial infections.[13,14,17] In accordance with the literature, we observed lower lymphocyte counts and higher neutrophil, CRP, and PCT levels in deceased patients. When comparing the results of initial admission and ICU admission, neutrophil levels increased in both groups, while lymphocyte levels decreased. In deceased patients, higher PCT and CRP levels

were observed. This finding may be explained by an increase in inflammatory response due to the progression of COVID-19, as well as secondary bacterial infections.

Ferritin, an acute-phase reactant, is known to be prognostic in acute infections and tissue damage. It is also used in the prognosis of COVID-19 patients. In a study by Chen et al.[13], ferritin levels in deceased patients were found to be twice as high as in surviving patients. Tural et al.[20] also reported that ferritin levels were associated with mortality. In our study, ferritin levels at the time of hospital admission were similar in both surviving and deceased patients. However, in line with the literature, ferritin levels at ICU admission were significantly higher in deceased patients. Therefore, we believe that ferritin could be a valuable parameter for assessing patient prognosis in COVID-19 patients in the ICU.

One of the important causes of mortality in COVID-19 patients is the cytokine storm caused by the excessive release of proinflammatory cytokines such as IL-6.[21,22] Chen et al.[13] reported that IL-6 levels were higher in deceased patients compared to survivors. In our study, in accordance with the literature, we found higher IL-6 levels in deceased patients at hospital admission. Additionally, we observed that IL-6 levels at hospital admission were associated with mortality. The lack of a difference in IL-6 levels at ICU admission could be due to the already severe clinical condition of ICU patients.

D-Dimer and BNP levels also have prognostic significance in COVID-19 patients regarding mortality and the clinical course of the disease. Elevated D-Dimer and BNP levels have been reported as predictive factors for mortality.[23,24] In line with the literature, we observed higher D-Dimer and BNP levels in deceased patients. We believe that D-Dimer and BNP levels are valuable indicators for assessing patient prognosis.

Limitations

The limitations of our study include that it is a retrospective study, and therefore only data recorded in the files were analyzed. Additionally, due to the presence of multiple comorbidities and medications in patients in the ICU, the impact of these factors on the evaluated parameters could not be clearly assessed.

CONCLUSION

In our study, we found that NLR and d-NLR values at the time of initial hospital admission and ICU admission had a predictive role in forecasting 30-day mortality in COVID-19 patients admitted to the ICU. Additionally, procalcitonin, CRP, IL-6, D-Dimer, and ferritin levels at both initial admission and ICU admission were found to have a predictive role in mortality.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study protocol was approved by the Clinical Researches Ethics Committee of University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital (Date: 08.03.2021, Decision No: 106/12).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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