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Original Research

The Neutrophil to Lymphocyte Ratio and In-Hospital All-Cause Mortality in Patients with COVID-19

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ABSTRACT

Objective: In December 2019, pneumonia associated with severe acute respiratory syndrome coronavirus 2 emerged in China, and has been spread worldwide eventuating the coronavirus disease 2019 (COVID-19) pandemic. As of June 27, 2020, 195,883 people have been diagnosed with COVID-19 in Turkey, among them 5082 are dead. Moreover, 9,999,606 people were infected worldwide. The neutrophil-to-lymphocyte ratio (NLR) has been reported as an inflammatory biomarker. This study aimed to evaluate the relationship between NLR on admission and in-hospital all-cause mortality in adult patients with COVID-19.

Methods: This retrospective cohort study included a total of 455 COVID-19 patients from Turkey. The diagnosis of COVID-19 was made according to the World Health Organization's interim guidance and confirmed by RNA detection of SARS-CoV-2. The NLR was calculated for each patient.

Results: The NLR on admission was found to be significantly higher in nonsurvivor COVID-19 patients than survivors (12.3 [0.8–137.3] vs. 3.2 [0.6–79.0], p<0.001). Forward stepwise logistic regression analysis was carried out to determine the independent predictors of in-hospital all-cause mortality of patients with COVID-19. The analysis demonstrated that age [odds ratio (OR)=1.203, 95% confidence interval (CI): 1.027–1.408, p=0.022], NLR (OR=1.261, 95% CI: 1.054–1.509, p=0.011), lactate dehydrogenase level (OR=1.013, 95% CI: 1.004–1.022, p=0.005), glomerular filtration rate (OR=0.920, 95% CI: 0.853–0.992, p=0.030), alanine transaminase level (OR=1.107, 95% CI: 1.011–1.212, p=0.028), and aspartate transaminase level on admission (OR=0.939, 95% CI: 0.888–0.993, p=0.027) were independent predictors of in-hospital all-cause mortality of patients with COVID-19. In the receiver operating characteristic curve analysis, the sensitivity and specificity of the NLR for predicting in-hospital all-cause mortality were found to be 92% and 53%, respectively, at the cut-off value of 3.

Conclusion: The NLR on admission predicts in-hospital all-cause mortality of patients with COVID-19.

Keywords: Coronavirus, lymphocyte, neutrophil

INTRODUCTION

In December 2019, pneumonia associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1) emerged in Wuhan, China, and has been spread worldwide eventuating the coronavirus disease 2019 (COVID-19) pandemic with emerging global concerns. New confirmed cases and deaths caused by COVID-19 are reported daily all over the world. As of June 27, 2020, 195,883 people have been diagnosed with COVID-19 in Turkey, among them 5082 are dead. Moreover, 9,999,606 people were infected worldwide. Risk stratification in such pandemics is extremely required. Early and effective predictors of clinical outcomes are urgently needed as there is no standardized treatment available currently.

The neutrophil-to-lymphocyte ratio (NLR), calculated by dividing absolute neutrophil count with absolute lymphocyte count, has been reported as an inflammatory biomarker that can be used as an indicator of systemic inflammation (2, 3). Prognostic value of the NLR in various diseases, such as community pneumonia (4, 5) and sepsis, have been reported in various studies (6). A recent

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study has exhibited that the NLR is independently associated with mortality in hospitalized COVID-19 patients (7). The present study aims to evaluate the impact of the NLR on in-hospital all-cause mortality in adult patients with COVID-19.

METHODS

Study Population and Design

This retrospective cohort study included a total of 455 adult COVID-19 patients from Turkey. The diagnosis of COVID-19 was made according to the World Health Organization's interim guidance and confirmed by RNA detection of SARS-CoV-2. All adult patients diagnosed with COVID-19 were screened, and those who died or discharged between March 10, 2019, and June 10, 2020, were enrolled in this study. Out of 455 patients, 145 were critically ill and were admitted to the intensive care unit. The study was conducted following the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Çukurova University (No: 99, 15 May 2020), as well as by the Ministry of Health. The need for written informed consent was waived due to the retrospective nature of the study.

Data Collection

Epidemiologic, demographic, clinical, laboratory, treatment, and outcome data were extracted from electronic medical records using admission numbers which were unique to each patient. In-hospital all-cause mortality outcomes were followed up till June 15, 2020.

Laboratory Procedures

RNA detection of SARS-CoV-2 in respiratory specimens was carried out by real-time polymerase chain reaction. The criteria for discharge were the absence of fever for at least 3 days, substantial improvement in both lungs detected by chest computed tomography, clinical remission of respiratory symptoms, and one negative sample of throat swab for SARS-CoV-2 RNA. Blood examinations included complete blood count and serum biochemical tests.

Statistical Analysis

Data analyses were performed using SPSS version 22.0 statistical software package (IBM SPSS Corp.; Armonk, NY, USA). The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. Continuous variables were expressed as mean±standard deviation or median (minimum-maximum). Categorical variables were expressed as number (percentage). The independent samples t-test or Mann–Whitney U-test was used to compare continuous variables based on whether statistical assumptions were fulfilled or not. The Chi-square test or Fisher's exact test was used to compare categorical variables based on whether statistical assumptions were fulfilled or not. All significant parameters in the univariate analysis were selected for the multivariable model, and a forward stepwise logistic regression analysis was used to determine the independent predictors of in-hospital mortality of COVID-19 patients. The odds ratio (OR) and 95% confidence interval (CI) of each independent variable were calculated. A receiver operating characteristic curve analysis was carried out to identify the optimal cut-off level of the NLR that predicts the in-hospital all-cause mortality. The area under the curve was calculated as a measure of the accuracy of the test. A two-tailed p-value of less than 0.05 was considered significant.

Main Points:

- This study evaluated the relationship between the neutrophil to lymphocyte ratio (NLR) on admission and in-hospital all-cause mortality in adult patients with the coronavirus disease 2019 (COVID-19).
- The NLR on admission was significantly higher in nonsurvivors COVID-19 patients than in survivors.
- Age, the NLR, lactate dehydrogenase level, glomerular filtration rate, alanine transaminase level, and aspartate transaminase level on admission were independent predictors of in-hospital all-cause mortality of patients with COVID-19.
- The sensitivity and specificity of the NLR for predicting in-hospital all-cause mortality were 92% and 53%, respectively, at the cut-off value of 3.

RESULTS

This retrospective cohort study enrolled a total of 455 hospitalized COVID-19 patients (217 males, median age: 56 [18–98] years). In the final analysis, 92 patients died during hospitalization, and 363 patients were discharged.

The most common comorbidity was found to be hypertension (37.4%), followed by diabetes mellitus (28.1%), and coronary artery disease (19.3%). The most common symptom found on admission was cough, followed by fever, and dyspnea. Leukocyte count, neutrophil count, mean platelet volume, red cell distribution width, the NLR, the platelet-to-lymphocyte ratio, C-reactive protein (CRP), procalcitonin, ferritin, lactate dehydrogenase, alanine transaminase, and aspartate transaminase levels on admission were found to be significantly higher in nonsurvivor COVID-19 patients than survivors. However, hemoglobin level, lymphocyte count, and glomerular filtration rate were significantly lower in the former. Table 1 shows the comparison of baseline characteristics of patients with COVID-19 according to in-hospital all-cause mortality.

Forward stepwise logistic regression analysis was carried out to determine the independent predictors of in-hospital all-cause mortality of patients with COVID-19. The analysis demonstrated the following factors as independent predictors: age (OR=1.203, 95% CI: 1.027–1.408, p=0.022), the NLR (OR=1.261, 95% CI: 1.054–1.509, p=0.011), lactate dehydrogenase level (OR=1.013, 95% CI: 1.004–1.022, p=0.005), glomerular filtration rate (OR=0.920, 95% CI: 0.853–0.992, p=0.030), alanine transaminase level (OR=1.107, 95% CI: 1.011–1.212, p=0.028), and aspartate transaminase level on admission (OR=0.939, 95% CI: 0.888–0.993, p=0.027) (Table 2).

The sensitivity and specificity of the NLR for predicting in-hospital all-cause mortality were found to be 92% and 53%, respectively, in the receiver operating characteristic curve analysis, at the cut-off value of 3, with the area under the curve being 0.842 (95% CI: 0.795–0.889, p<0.001) (Figure 1).

Table 1. Comparison of baseline characteristics of patients with COVID-19 according to in-hospital all-cause mortality

Variable	Total (n=455)	Survivor (n=363)	Nonsurvivor (n=92)	p
Demographic and Clinical Features				
Age (year)	56.0 (18.0–98.0)	52.0 (18.0–98.0)	71.0 (39.0–95.0)	<0.001
Gender, (male) n (%)	217 (47.7)	172 (47.4)	45 (48.9)	0.793
BMI (kg/m^2)	27.2 (18.4–49.1)	27.0 (18.4–49.1)	27.7 (18.7–47.8)	0.670
Current smoker, n (%)	101 (22.2)	77 (21.2)	24 (26.1)	0.315
ICU admission, n (%)	145 (31.9)	55 (15.2)	90 (97.8)	<0.001
Comorbidities				
DM, n (%)	128 (28.1)	90 (24.8)	38 (41.3)	0.002
HT, n (%)	170 (37.4)	113 (31.1)	57 (62.0)	<0.001
CAD, n (%)	88 (19.3)	53 (14.6)	35 (38.0)	<0.001
HF, n (%)	32 (7.0)	22 (6.1)	10 (10.9)	0.107
COPD, n (%)	45 (9.9)	28 (7.7)	17 (18.5)	0.002
Stroke, n (%)	14 (3.1)	9 (2.5)	5 (5.4)	0.171
Malignancy, n (%)	17 (3.7)	10 (2.8)	7 (7.6)	0.057
Symptoms				<0.001
Fever (temperature ≥37.3°C)	138 (30.3)	93 (25.6)	45 (48.9)	
Cough, n (%)	150 (33.0)	139 (38.3)	11 (12.0)	
Dyspnea, n (%)	51 (11.2)	24 (6.6)	27 (29.3)	
Fatigue, n (%)	21 (4.6)	16 (4.4)	5 (5.4)	
Headache, n (%)	6 (1.3)	6 (1.7)	0 (0.0)	
Loss of smell and taste, n (%)	18 (4.0)	17 (4.7)	1 (1.1)	
Other symptoms, n (%)	47 (10.3)	44 (12.1)	3 (3.3)	
Laboratory Findings				
Hemoglobin (g/dL)	12.5±1.2	12.8±2.0	11.1±2.3	<0.001
Leukocyte count, × 10^3/μL	7.8±4.5	7.0±3.4	11.5±6.1	<0.001
Platelet count, × 10^3/μL	216.0 (45.0–568.0)	217.0 (68.0–568.0)	215.0 (45.0–511.0)	0.711
Neutrophil count, × 10^3/μL	5.9±4.2	4.9±3.0	9.9±5.5	<0.001
Lymphocyte count, × 10^3/μL	1.4±1.0	1.5±0.9	1.0±1.3	<0.001
MPV (fL)	9.3 (6.5–13.3)	9.1 (6.5–12.3)	9.6 (7.4–13.3)	<0.001
RDW (%)	14.0±3.1	13.6±1.6	15.8±5.8	<0.001
MCV (fL)	85.9±7.3	85.6±7.2	87.0±7.9	0.126
NLR	3.7 (0.6–137.3)	3.2 (0.6–24.3)	12.1 (0.8–137.3)	<0.001
PLR	171.6 (21.5–1215.0)	164.7 (35.3–1215.0)	274.2 (21.5–1196.9)	<0.001
CRP (mg/L)	24.0 (0.1–437.0)	12.4 (0.1–356.0)	157.0 (1.8–437.0)	<0.001
Procalcitonin (ng/m)	0.12 (0.01–20.0)	0.10 (0.01–7.0)	1.3 (0.07–20.0)	<0.001

Table 1. Comparison of baseline characteristics of patients with COVID-19 according to in-hospital all-cause mortality (Continued)

Variable	Total (n=455)	Survivor (n=363)	Nonsurvivor (n=92)	p
Ferritin (ng/mL)	142.5 (5.8-25583.0)	117.5 (5.8-2000.0)	856.0 (69.5-25583.0)	<0.001
LDH (U/L)	284.5 (112.0-3970.0)	255.0 (117.0-1191.0)	484.5 (112.0-3970.0)	<0.001
GFR (mL/min per 1.73 m^2)	95.0 (4.0-139.0)	95.0 (4.0-138.0)	38.5 (5.0-139.0)	<0.001
ALT (U/L)	24.0 (10.0-627.0)	23.0 (10.0-270.0)	31.5 (10.0-627.0)	<0.001
AST (U/L)	30.0 (11.0-1983.0)	28.0 (11.0-397.0)	48.0 (20.0-1983.0)	<0.001
Imaging Features-				0.038
No features, n (%)	8 (1.8)	8 (2.2)	0 (0.0)	
Consolidation, n (%)	14 (3.1)	11 (3.0)	3 (3.3)	
Ground-glass opacity, n (%)	321 (70.5)	262 (72.2)	59 (64.1)	
Infiltration, n (%)	6 (1.3)	6 (1.7)	0 (0.0)	
Pleural effusion, n (%)	1 (0.2)	0 (0.0)	1 (1.1)	
Mixed features, n (%)	105 (23.1)	76 (20.9)	29 (31.5)	
Cause of Death				-
AKI, n (%)	4 (4.3)	-	4 (4.3)	-
ARDS, n (%)	7 (7.6)	-	7 (7.6)	-
MOF, n (%)	23 (25.0)	-	23 (25.0)	-
Sepsis, n (%)	51 (55.4)	-	51 (55.4)	-
Other, n (%)	7 (7.6)	-	7 (7.6)	-

Data are presented as number (%), mean±standard deviation or median (minimum-maximum).

p-value was calculated using the independent samples t-test or the Mann-Whitney U-test for continuous variables, and the Chi-square test or Fisher's exact test for categorical variables as appropriate. p-value<0.05 was considered significant.

AKI: acute kidney injury; ALT: alanine transaminase; ARDS: acute respiratory distress syndrome; AST: aspartate transaminase; BMI: body mass index; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; DM: diabetes mellitus; GFR: glomerular filtration rate; HF: heart failure; HT: hypertension; ICU: intensive care unit; LDH: lactate dehydrogenase; MCV: mean corpuscular volume; MOF: multiple organ failure; MPV: mean platelet volume; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; RDW: red cell distribution width.

DISCUSSION

The major findings of this study were the following independent predictors of in-hospital all-cause mortality of patients with COVID-19: age, the NLR, lactate dehydrogenase level on admission, and baseline glomerular filtration rate. The sensitivity and specificity of the NLR for predicting mortality were 92% and 53%, respectively, at the cut-off value of 3.

Recent studies have investigated the relationship between various baseline leukocyte counts and clinical outcomes in COVID-19 patients. Liu et al. (8) found that the NLR is a predictive factor for early-stage COVID-19 infection that may lead to a critical illness. Qin et al. (9) reported that patients with a severe form of the disease seem to have higher neutrophil count but lower lymphocyte count compared to patients with a nonsevere form of the disease, thus the NLR was found to be higher in the former. Similarly, Mo et al. (10) found that refractory patients had higher neutrophil counts as compared to general patients.

The NLR has been proposed as a novel and cost-effective inflammatory biomarker, considering both neutrophil and lymphocyte counts. High NLR results from the increased neutrophil count and decreased lymphocyte count. Inflammation may involve increased neutrophil release. Possible reasons for the COVID-19-associated lymphopenia may include a direct infection of lymphocytes by SARS-CoV-2, lymphocyte sequestration in the lung, cytokine-mediated lymphocyte trafficking, immune-mediated lymphocyte destruction, bone marrow, thymus suppression, or apoptosis. Dysregulated immune cell responses and consequently immunological abnormality play a remarkable role in the severity of viral infections (11). Previous studies have demonstrated that lymphopenia played a prominent role in severe acute respiratory syndrome coronavirus (SARS-CoV) infection, and lymphocyte counts could predict the severity and clinical outcomes (12). Immunological responses involving hematological changes of leukocytes were notably associated with the severity and clinical outcomes of the middle east re-

Table 2. Risk factors for in–hospital all–cause mortality in patients with COVID–19

	Univariate Analysis		Multivariate Analysis	
Variable	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Age (year)	1.090 (1.068–1.113)	<0.001	1.203 (1.027–1.408)	0.022
DM, n (%)	2.135 (1.323–3.445)	0.002		
HT, n (%)	3.603 (2.239–5.799)	<0.001		
CAD, n (%)	3.592 (2.153–5.992)	<0.001		
COPD, n (%)	2.712 (1.412–5.208)	0.003		
Hemoglobin (g/dL)	0.672 (0.597–0.756)	<0.001	–	–
Leukocyte count, × 10^3/μL	1.226 (1.160–1295)	<0.001	–	–
MPV (fL)	1.617 (1.298–2.016)	<0.001	–	–
RDW (%)	1.355 (1.202–1.526)	<0.001	–	–
NLR	1.213 (1.159–1.268)	<0.001	1.261 (1.054–1.509)	0.011
PLR	1.003 (1.002–1.004)	<0.001	–	–
Procalcitonin (ng/m)	1.119 (1.035–1.211)	0.005	–	–
Ferritin (ng/mL)	1.002 (1.001–1.003–)	<0.001	–	–
LDH (U/L)	1.007 (1.005–1.006)	<0.001	1.013 (1.004–1.022)	0.005
GFR (mL/min per 1.73 m^2)	0.960 (0.952–0.968)	<0.001	0.920 (0.853–0.992)	0.030
ALT (U/L)	1.007 (1.003–1.012)	0.002	1.107 (1.011–1.212)	0.028
AST (U/L)	1.014 (1.007–1.021)	<0.001	0.939 (0.888–0.993)	0.027

p–value<0.05 was considered significant.

ALT: alanine transaminase; AST: aspartate transaminase; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; GFR: glomerular filtration rate; HT: hypertension; LDH: lactate dehydrogenase; MPV: mean platelet volume; NLR: neutrophil–to–lymphocyte ratio; PLR: platelet–to–lymphocyte ratio; RDW: red cell distribution width.

spiratory syndrome coronavirus (MERS-CoV) disease (13). Lymphocytopenia was associated with poor prognosis in MERS-CoV infection (14). Similarly, recent studies on COVID-19 have shown that higher levels of inflammatory cytokines, chemokines, and NLR in infected patients were correlated with the severity of the disease suggesting the involvement of cytokine storm in disease severity (9, 15). These findings are consistent with the results of the present study. In this study, neutrophil count, CRP, and procalcitonin levels were found to be significantly higher in nonsurvivor COVID-19 patients than survivors. The possible reason for these findings would be patients with extremely dysregulated immune responses due to high viral burden are likely to get bacterial coinfections.

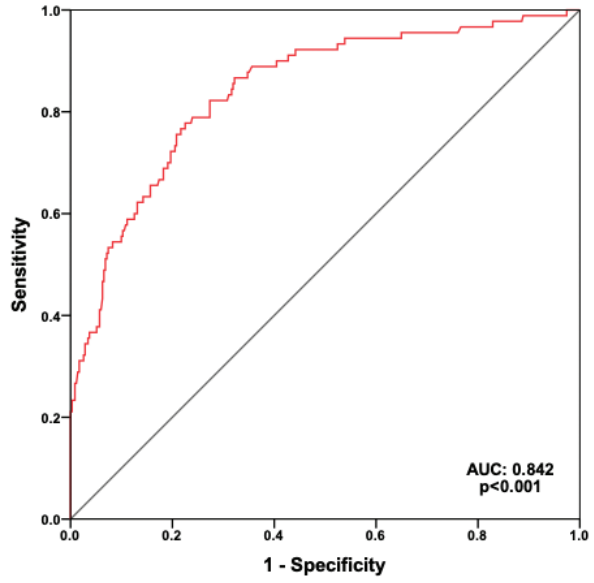
In the present study, out of the total 455 COVID-19 patients, 363 were discharged and 92 died during hospitalization. Zhou et al. (16) included a total of 191 patients in their study, of whom 137 were discharged and 54 died in hospital. Ruan et al. (17) included a total of 150 patients in their study, of whom 82 were discharged and 68 died. Wang et al. (18) and Zhang et al. (19) reported better clinical outcomes in their studies. This heterogeneity is probably due to the differences in the severity of illness of the enrolled patients. In this study, out of 455 patients, 145 were critically ill and were admitted to the intensive care unit.

The results of this study have several clinical implications. Physicians may identify high-risk COVID-19 patients at an early stage, assess admission to the intensive care unit for close monitoring, and modify treatments accordingly to reduce the in-hospital death as NLR could be quickly calculated based on a blood routine test on admission. Although treatment strategies were not investigated in this study, high-risk patients may be candidates to hydroxychloroquine, potent antibiotic and antiviral therapies, and corticosteroids.

Limitations of the Study

The present study has several limitations. First, because of its retrospective design, it might have a selection bias. Second, data regarding the time between the onset of illness and hospital admission could not be obtained. This might have influenced the findings that show the link between baseline NLR levels and mortality. Third, severity scores were not attainable. Thus, the relationship between NLR and disease severity could not be evaluated. Finally, as all subjects in this study were hospitalized Turk-

Figure 1. The receiver operating characteristic curve analysis of NLR for predicting in-hospital mortality in COVID-19 patients. AUC, area under the curve



ish patients diagnosed with COVID-19, the results of this study might not be directly applied to other ethnicities.

CONCLUSION

This retrospective cohort study, which was conducted among the Turkish population, revealed that NLR on admission is an independent risk factor for in-hospital all-cause mortality.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Çukurova University as well as by the Ministry of Health (No: 99, 15 May 2020).

Informed Consent: The need for written informed consent was waived due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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