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ORIGINAL ARTICLE

Could serum thrombocyte/lymphocyte (TLR), neutrophil/lymphocyte (NLR) and neutro-phil/albumin (NAR) ratios be indicators of hospitalization and mortality in COVID-19?

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ABSTRACT

Background and Objectives: Neutrophil / lymphocyte (NLR) and thrombocyte / lymphocyte ratios (TLR) are also a guiding factors in the prognostic evaluation of infectious diseases. Another parameter to determine inflammation and prognosis is albumin. This study was aimed to determine whether TLR, NLR and neutrophil / albumin ratios (NAR) are effective in predicting the severity and course of Corona Virus Disease-2019 (COVID-19).

Materials and Methods: In this retrospective and cross-sectional study, a total of 1597 patients who were admitted to our hospital between 15.03.2020- 1.06.2020, diagnosed with COVID-19 were evaluated.

Results: In the estimation of the decision for hospitalization, TLR, NLR and NAR AUROC values were 0.596, 0.634, 0.602 for cutoff values 123.7, 2.3 and 839.5, respectively. In predicting mortality, TLR, NLR and NAR AURO sample size can be specified C values were 0.674, 0.821, 0.787 for cutoff values 168.1, 5.2 and 1303.4, respectively ($p < 0.001$ for all).

Conclusion: In our study, it was determined that TLR, NLR and NAR are independent predictors in making the decision of hospitalization and in determining the prognosis in patients who are decided to be hospitalized.

Keywords: COVID-19; Neutrophil/lymphocyte ratio (NLR); Thrombocyte/lymphocyte ratio; Neutrophil/albumin (NAR); Prognosis; Hospitalization

INTRODUCTION

The world stepped into 2020 with an epidemic that is first detected in the center of Wuhan, China. The virus that causes Corona Virus Disease- 2019 (COVID-19) by isolation of the agent in January was defined as severe acute respiratory syndrome Corona virus 2 (SARS-CoV-2) (1). Then, an increasing number of cases were followed in other countries around the world. It was officially declared as a pandemic by the World Health Organization on March 11, 2020, with the death toll rising above 4000 people and was

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identified as COVID-19. The pandemic still continues despite the measures taken in all countries. On February 06, 2021, the number of cases confirmed through polymerase chain reaction (PCR) reached 14,790,123, death to 2,285,048, and the number of coun-tries or regions where cases were seen reached 223 (2).

While the clinical course of the disease is mild in 80% of the cases, severe illness is observed in 10-14% and 5% observed to undergo critical conditions. It has been reported that the risk factors in severe disease are comorbidities such as age, diabetes mellitus, hypertension and obesity (3). Hospitalization duration and mortality rate increase significantly in cases with severe disease. It is known that presentation of symptoms is not precise and uniform such as fever, cough, weakness and shortness of breath, and laboratory findings may be also normal in the early stages of the disease. In this disease, where effective treatment for the agent has not been found yet and vaccination can be applied differently in each country, early detection of patients with a high probability of developing critical illness can help to prevent worsening conditions through providing appropriate care and using the existing capacity more effectively within the health system (3, 4).

Regarding white blood cells, it is known that neutrophil / lymphocyte ratio (NLR) and thrombocyte / lymphocyte ratio (TLR) are also a guiding factors in the prognostic evaluation of cancer, cardiovascular diseases and infectious or non-infectious diseases (5-7). Another parameter to de-termine inflammation and prognosis is albumin. Albumin is the most abundant protein in plasma that regulates plasma osmotic pressure and interacts with endogenous and exogenous molecules. It is a molecule whose low levels are associated with mortality in inpatients (8). Neutrophil / albumin ratio (NAR) can be a new marker indicating systemic inflammation and mortality which can be calculated using hemogram parameters. This is an easy method to predict mortality in patients with COVID-19 (9).

This study was aimed to determine whether TLR, NLR and NAR are effective in predicting the severity and course of COVID-19 during the follow up.

MATERIALS AND METHODS

In this single center, retrospective and cross-sectional study, patients who were admitted to our hospital between 15.03.2020- 1.06.2020, diagnosed with COVID-19 were evaluated. In this study, patients whose PCR results were positive, who presented to the emergency department with symptoms associated with COVID-19 (such as fever, cough, shortness of breath, weakness, diarrhea) with an image compatible with COVID-19 in thorax computed tomography (CT) were included (Fig. 1. Patients' flowchart).

Ethics approval and consent to participate. Ethical committee approval was received (Approval date and number: 27.4.2020-2252; Istanbul Training and Research Hospital) and the patients gave informed consent before the beginning of the study. The experimental procedures were based on the Declaration of Helsinki and relevant institutional regulations. An informed consent was also obtained as written forms from all of our patients to publish.

Selection for hospitalization. Patients with fever (>38 Celsius), muscle/joint pains, cough and sore throat, with tachypnea (≥30/minute) or an oxygen saturation level of ≤93% in room air or bilateral diffuse pneumonia findings on chest X-ray or thorax CT were admitted.

Patients under the age of 18 and those who were decided to be admitted to the intensive care unit because of respiratory failure at the time of admission to the hospital were excluded from the study.

Demographic data such as age and gender, comorbidities such as diabetes mellitus, hypertension, coronary artery disease, chronic renal failure, chronic lung disease, malignancy, nasopharyngeal swab PCR results, thorax CT findings at initial diagnosis, basal laboratory parameters (CBC; complete blood count, CRP; C-reactive protein, CK; creatinine kinase, LDH; lactate dehydrogen-ase, D-dimer, AST; aspartate aminotransferase, ALT; alanine aminotransferase, total protein, albumin, urea, creatinine) were recorded.

Ethical committee approval was received (Approval date and number: 27.4.2020-2252; Istanbul Training and Research Hospital).

Statistical analysis. SPSS 22 (IBM Corp) program was used for statistical analysis. Visual methods (histogram and probability charts) and Kolmogorov-Smirnov test were used for normal distribution of variables, Mann-Whitney U test for quantitative

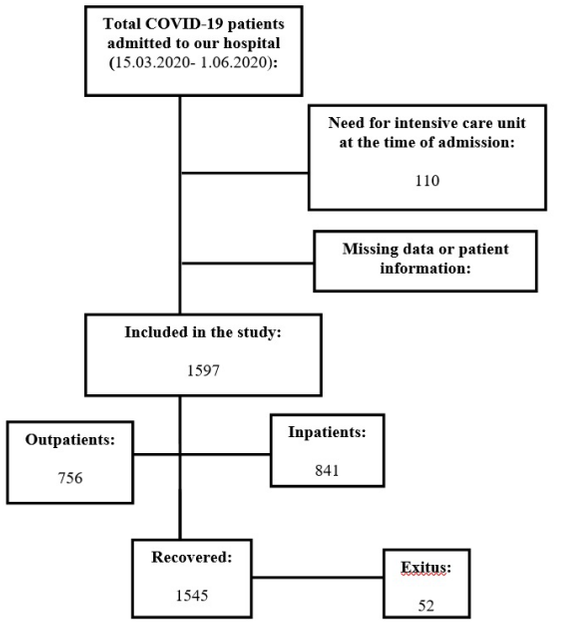


Fig. 1. Patients' flowchart

variables, Pearson Chi-Square or Fisher exact tests were used for qualitative variables. Statistically, results with a p value of less than 0.05 were considered significant.

By determining the area under the receiver operating characteristic curve (AUROC) and the TLR, NLR and NAR parameters, significant cutoff values for hospitalization indication and mortality prediction, sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) were investigated.

RESULTS

A total of 1597 SARS CoV-2 PCR positive cases with an age range between 18 and 91 years were included in the study; 52.7% of the cases were hospitalized. Any of comorbidities were detected in 35.5% of all patients. The most common comorbid diseases were hypertension (19.3%), diabetes mellitus (15%) and coronary artery disease (5.7%), respectively. Pulmonary involvement compatible with COVID-19 was detected in 68.7% of the patients. Clinical and laboratory data of patients who were followed up and treated as outpatient or inpatient are presented in Table 1. Comorbidi-ties, pneumonia and mortality rates were found to be higher in inpatients. The rates of TLR, NLR and NAR were significantly higher in outpatients, and also in patients with a fatal course compared to those who recovered (Table 1 and Table 2).

In the estimation of the decision for hospitalization, TLR, NLR and NAR AUROC values were 0.596, 0.634, 0.602 for cutoff values 123.7, 2.3 and 839.5, respectively ($p < 0.001$ for all) (Fig. 2a, 2b, 2c).

In predicting mortality, TLR, NLR and NAR AUROC values were 0.674, 0.821, 0.787 for cutoff values 168.1, 5.2 and 1303.4, respectively ($p < 0.001$ for all) (Fig. 3a, 3b, 3c). The cutoff values for which the sum of sensitivity and specificity of these three ratios in hospitalization decision and mortality prediction is maximum and the sensitivity, specificity, NPV and PPV values for these values are shown in Table 3.

DISCUSSION

As there are currently no standard treatment for COVID-19, clinicians are looking for a reliable prognostic marker that can differentiate patients with COVID-19 at risk of developing more severe forms of the disease (10). NLR and TLR are used in the prognostic evaluation of infectious or non-infectious diseases with various inflammation (5-7). Inflammation plays an important role in the pathophysiology of COVID-19 (11). In patients with severe COVID-19, increased leukocytosis, neutrophilia, lymphopenia and thrombocytopenia are observed compared to those without severe disease. The virus is thought to cause lymphopenia by infecting T cells via angiotensin converting enzyme -2 (ACE-2) receptors and CD147-spike proteins. It has been reported that these patients are more likely to develop acute respiratory distress syndrome (ARDS) and need inten-sive care unit follow up (3, 12-17).

Reports on the use of NLR or TLR in predicting prognosis in patients with SARS-CoV-2 infection have been published (18-19). Both NLR and TLR indirectly reflect a patient's inflammatory status (11, 12). In addition, NAR is a new marker proposed to predict systemic inflammation, as well as mortality (9).

In this study, COVID-19 patients who were inpatient or who were followed up in the intensive care unit had higher NLR, TLR, and NAR values than outpatients. In ROC analysis for the decision of hospitalization of NLR, TLR and NAR, AUROC values were 0.596, 0.634, 0.602, respectively; while they were 0.674, 0.821, 0.787 for mortality prediction,

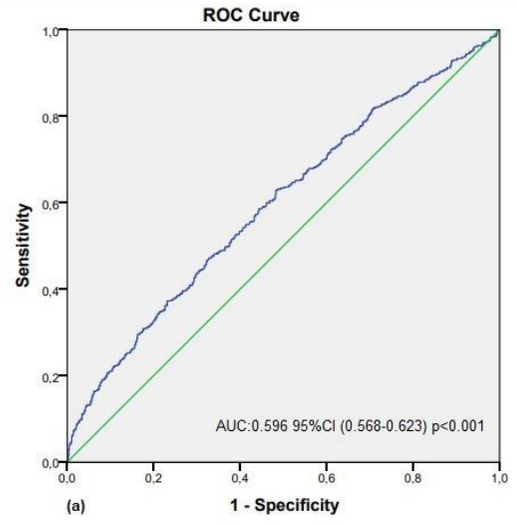
Table 1. Evaluation of clinical status and laboratory findings in outpatients and inpatients

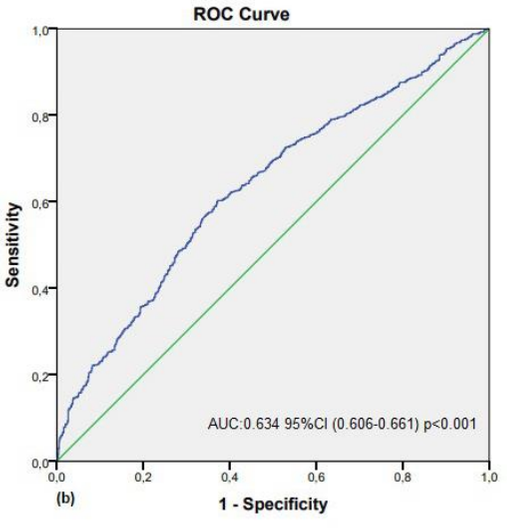
	Outpatients (n=756) n (%)	Inpatients (n=841) n (%)	p
Gender			
Male	463 (51.7)	433 (48.3)	<0.001
Female	293 (48.3)	408 (58.2)	
Age, median, (range)	35 (26-46)	55 (43-64)	<0.001
Comorbidity			
Chronic obstructive pulmonary disease	6 (0.8)	23 (2.7)	0.004
Asthma	17 (2.2)	47 (5.6)	0.001
Congestive heart failure	3 (0.4)	23 (2.7)	<0.001
Coronary artery disease	16 (2.1)	75 (8.9)	<0.001
Hypertension	36 (4.8)	273 (32.5)	<0.001
Diabetes mellitus	38 (5)	202 (24)	<0.001
Chronic renal failure	1 (0.1)	28 (3.3)	<0.001
Malignancy	3 (0.4)	41 (4.9)	<0.001
Cerebrovascular accident	0	8 (1)	0.008
Rheumatological disease	4 (0.5)	22 (2.6)	0.001
Pneumonia	372 (49.2)	725 (86.2)	<0.001
Mortality	7 (0.9)	45 (5.4)	<0.001
Laboratory values			
Leukocyte ($\times10^3$ cell/uL)	6.1 (4.9-7.5)	6.1 (4.7-7.7)	0.89
Neutrophil ($\times10^3$ cell/uL)	3.5 (2.6-4.6)	3.9 (2.8-5.5)	<0.001
Lymphocyte ($\times10^3$ cell/uL)	1.7 (1.3-2.3)	1.4 (0.9-1.9)	<0.001
Hemoglobin (g/dL)	14.4 (13.2-15.5)	13.5 (12.3-14.8)	<0.001
Thrombocyte ($\times10^3$ cell/uL)	217 (179-254)	207 (166-257)	0.04
C reactive protein (mg/L)	10 (4.7-24.3)	45 (16-119)	<0.001
Aspartate aminotransferase (U/L)	25 (20-33)	29 (22-41)	<0.001
Alanine aminotransferase (U/L)	24 (17-38)	24 (16-36)	0.76
Lactate dehydrogenase(U/L)	201 (170-261)	244 (194-318)	<0.001
Albumin (g/dL)	4.7 (4.4-5)	4.2 (3.8-4.6)	<0.001
Procalcitonin (mg/dl)	0.04 (0.3-0.11)	0.05 (0.03-0.12)	0.48
Thrombocyte/lymphocyte	122.7 (94-167.5)	141.5 (106.6-202.2)	<0.001
Neutrophil/lymphocyte	1.9 (1.4-3)	2.7 (1.7-4.4)	<0.001
Neutrophil/albumin	744 (577.9-1024.5)	921 (654.7-1361.8)	<0.001

Table 2. Clinical status and laboratory parameters in recovered and fatal cases

	Recovered cases n=1545	Fatal cases n=52	Total n=1597	p
Gender M/F	867/678	29/23	896/701	
Age*	45 (32-56)	67 (54-79)	46 (32-57)	<0.001
Comorbidity n (%)	530 (34.3)	37 (71.2)	567 (35.5)	<0.001
Pneumonia n (%)	1047 (67.8)	50 (96.2)	1097 (68.7)	<0.001
Laboratory values				
Thrombocyte/lymphocyte	131.1 (99.4-182.1)	186.4 (130.9-327.5)	132.3 (100.5-184.1)	<0.001
Neutrophil/lymphocyte	2.2 (1.5-3.6)	6.5 (3.1-12.8)	2.31 (1.5-3.7)	<0.001
Neutrophil/albumin	865.2 (629.5-1251.7)	1776.5 (1117.9-2651.9)	887.7 (640.8-1310.2)	<0.001

*median (range)





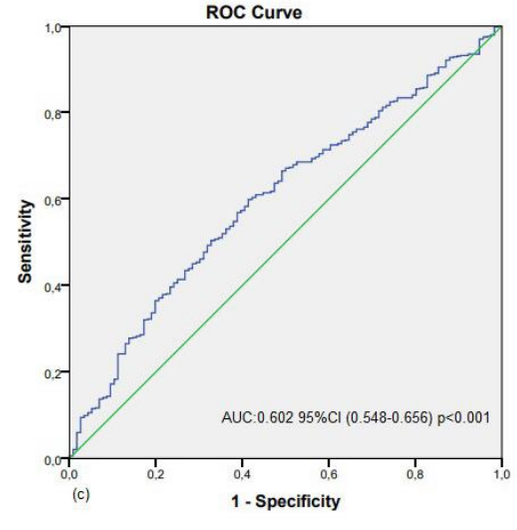
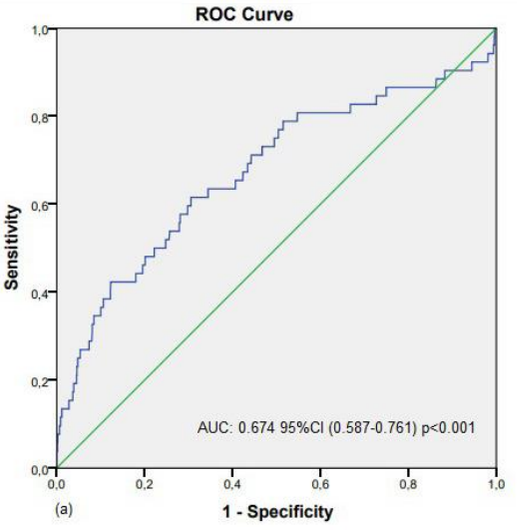
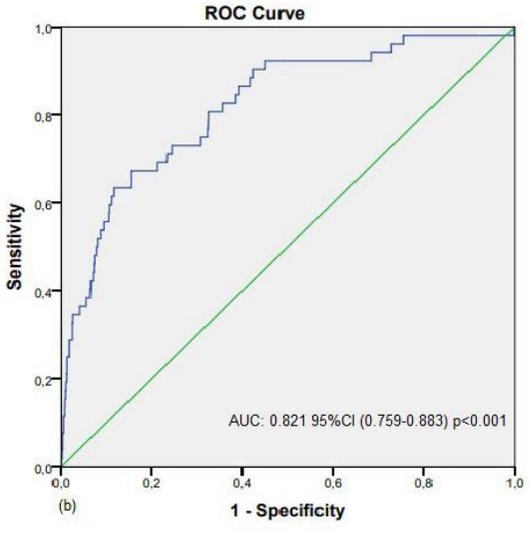


Fig. 2. ROC Curve for hospitalization decision: (a) Thrombocyte / lymphocyte, (b) neutrophil / lymphocyte and (c) neutrophil / albumin ratios





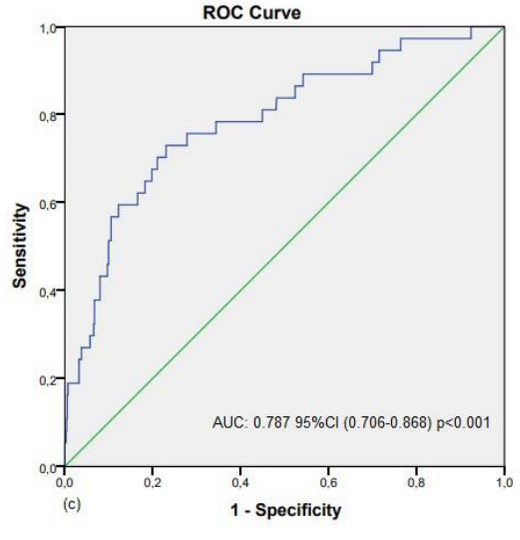


Fig. 3. ROC Curve for mortality: (a) Thrombocyte / lymphocyte, (b) neutrophil / lymphocyte and (c) neutrophil / albumin ratios

Table 3. Evaluation of thrombocyte/lymphocyte, neutrophil / lymphocyte and neutrophil / albu-min ratios in predicting hospitalization decision and mortality

	cutoff	Sensitivity % (95% Cl)	Specificity % (95% Cl)	PPV % (95% Cl)	NPV % (95% Cl)
Thrombocyte/lymphocyte*	123.7	63 (59.7-66.3)	51.5 (47.8-55.1)	59.1 (56.9-61.2)	55.6 (52.8-58.3)
Neutrophil / lymphocyte*	2.3	60.3 (56.9-63.6)	62.7 (58.7-65.8)	52.7 (50.2-55.1)	64 (61.5-66.4)
Neutrophil / albumin*	839.5	56,9 (52.9-60.8)	61.2 (51.7-70.1)	88.9 (86.3-91)	20.6 (18-23.6)
Thrombocyte/lymphocyte§	168.1	61.5 (47-74.7)	69.4 (67.1-71.7)	6.3 (5.1-7.9)	98.2 (97.4-98.7)
Neutrophil / lymphocyte§	5.20	63.5 (49-76.4)	88.2 (86.4-89.7)	15.3 (2.35-18.7)	98.6 (98-99)
Neutrophil / albumin§	1303.4	73 (55.9-86.2)	77 (73.7-80)	14.1 (11.5-17.3)	98.2 (97-98.9)

* Hospitalization decision, § mortality; PPV: Positive predictive value, NPV: Negative predictive value

respectively. This study shows that NLR, TLR and NAR can be used for the decision of hospitalization and especially for the prediction of severe disease.

NLR, which can be easily calculated from a complete blood count through dividing the absolute neutrophil count by the absolute number of lymphocytes, is a more sensitive indicator in other viral and bacterial infections compared to neutrophil and lymphocyte levels alone (18, 20-23). In this study, with the ROC analysis, it was determined that NLR showed an important performance both in making the hospitalization decision of the patients and in predicting the inpatient mortality. In predicting mortality in inpatients, the specificity for NLR cutoff value of 5.2 was 88.2% and NPV was 98.6%. This result supports that NLR is a powerful predictor that can be used in predicting mortality in COVID-19 inpatients. Yang et al. (19) found the AUROC value for NLR to be 0.841 to determine severe COVID-19 cases. They determined the highest sensitivity and specificity values for the optimal cut-off point 3.3 as 84% and 63.6%, respectively. It was emphasized that patients with an NLR value greater than 3.3 should be followed up more closely. Yan et al. (24) found the AUROC value as 0.945 in the inpatient mortality for NLR. For the optimal cutoff value of 11.75 and above, the sensitivity was 97.5% and the specificity 78.1% in predicting mortality. These studies support that NLR can be used as an independent biomarker in predicting poor clinical outcome. Our results are also in line with these studies.

Platelets are cells that play a role in hemostasis, coagulation, maintenance of vascular integrity, angiogenesis, innate immune response and inflammatory response in the human body. The production of megakaryocytes may increase in case of inflammation due to various cytokines (25, 26). The correlation of TLR with mortality and disease severity in bacterial pneumonia has been shown (27, 28). In this study, sensitivity was 63% and specificity was 61.5% at TLR cutoff value of 123.7. For the decision of hospitalization, this ratio increased up to 168.1 in patients in need of intensive care. At this point, sensitivity was 61.5% and specificity was 69.4%. Qu R et al. found that TLR correlated with the duration of hospitality. In these studies, sensitivity and specificity were reported as 100% and 86% at TLR cutoff value of 126.7 in the ROC analysis, respectively (29). In a similar study, Uyar et al. (30) reported sensitivity and specificity as 56.7% and 81.8% for the prediction of severe disease at TLR cutoff value of 221.

Albumin is the largest and most abundant protein in plasma. In the case of stress and inflammation, intracellular albumin entry increases and serum albumin levels may decrease. Albumin is also a negative acute phase reactant and its serum level is inversely proportional to the magnitude of the systemic inflammatory response. Low albumin levels are associated with the risk of mortality in hospitalized patients (8, 31-34). In severe viral infections, the number of neutrophils in peripheral blood increases significantly. Increasing neutrophil counts cause cytokine-chemokine storm and ultimately lung damage and ARDS (35). Like other five markers, NAR is recommended to be used as a prognosis predictor in different disease groups (36, 37). However, studies on the use of NAR as a prognosis biomarker for COVID-19 are very few. In one of these studies, Varim et al. (9) found sensitivity 71.1% and specificity 71.7% at AUROC values of 0.736 and 201.5 for NAR in predicting mortality. In this study, sensitivity at the cutoff value of NAR 839.5 was 56.9% and specificity was 61.2%

in the prediction of hospitalization, while sensitivity was 73% and specificity was 77% at the cutoff value of 1303.4 in mortality prediction.

Our study has also some limitations. This study was a single center, retrospective observational study. NLR, TLR, NAR measurements are affected by comorbidities and drugs used. Because they are affected by the acute phase increase and vary with more than one factor such as bone marrow capacity or response during viral infections, more significant results may not have been revealed. Therefore, it would be appropriate to confirm our findings with multi-center prospective studies.

CONCLUSION

In conclusion, in our study, it was determined that TLR, NLR and NAR are independent predictors in making the decision of hospitalization and in determining the prognosis in patients who are decided to be hospitalized. For this reason, high TLR, NLR and NAR values indicate that it can be used to monitor COVID-19 patients more closely and to determine the need for intensive care.

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We respectfully remember all the colleagues we lost in the COVID-19 fight.

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