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Relationships of the neutrophil–lymphocyte and CRP–albumin ratios with the duration of hospitalization and fatality in geriatric patients with COVID-19

Semih Kalyon[1], Fethi Gültop[2], Funda Şimşek[3] and Mine Adaş[4]

Abstract

Objective: The aim of this study was to determine the associations of the neutrophil–lymphocyte ratio (NLR) and C-reactive protein (CRP)–albumin ratio (CAR) with the duration of hospital stay and fatality rate in geriatric patients with coronavirus disease 2019 (COVID-19).

Methods: Patients older than 65 years with polymerase chain reaction-positive COVID-19 were included. Neutrophil, lymphocyte, CRP, albumin, and demographic data and the duration of hospitalization were recorded.

Results: The mean length of stay was 15 days. NLR and CAR were significantly higher in patients who died than in those who survived. The cutoffs predictive of mortality were 4.02 (area under the curve [AUC] = 0.717) for NLR and 23 for CAR (AUC = 0.781). The fatality rate among patients who required inpatient treatment was 33%.

Conclusion: NLR and CAR, which can be calculated inexpensively and quickly at the first admission to the hospital, are extremely useful for estimating the duration of hospitalization and risk of mortality in geriatric patients with COVID-19. Using these data, treatment can quickly be intensified when needed.

[1]Asst Prof. MD. Prof. Dr. Cemil Taşcıoğlu City Hospital, Internal Medicine Department, Istanbul, Turkey
[2]Asst Prof. MD. Prof. Dr. Cemil Taşcıoğlu City Hospital, Anesthesia and Reanimation Department, Istanbul, Turkey
[3]Assoc Prof. MD. Prof. Dr. Cemil Taşcıoğlu City Hospital, Infectious Diseases Department, Istanbul, Turkey
[4]Assoc Prof. MD. Prof. Dr. Cemil Taşcıoğlu City Hospital, Internal Medicine Department, Istanbul, Turkey

Corresponding author:
Semih Kalyon, Prof. Dr. Cemil Taşcıoğlu City Hospital, Darülaceze Street No. 27. Şişli-Istanbul 34384, Turkey.
Email: semihkalyon@hotmail.com

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Introduction

Severe acute respiratory syndrome (SARS) coronavirus 2 was first identified in Wuhan, China in December 2019. Because of its similarity to the SARS and Middle East respiratory syndrome coronaviruses, this zoonotic virus was named coronavirus disease 2019 (COVID-19). The incubation period varies between 2 and 14 days.[1] COVID-19 affects many systems such as the gastrointestinal system, urinary system, nervous system, and skin, but it manifests as cough and fever if the respiratory tract is involved. Since the spread of the infection in China, 200,840,180 people have been infected with this virus globally as of August 2021, and 4,265,903 patients have died.[2] There is no specific treatment that has been proven and standardized for the disease.

The neutrophil–lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) are parameters that can be easily calculated from the routine and inexpensive hemogram. Similarly, C-reactive protein (CRP) and albumin are acute-phase reactants that are frequently used in the evaluation of infection. The main purpose of this study was to determine the roles of NLR, PLR, and the CRP–albumin ratio (CAR) in predicting the clinical course of the disease, duration of hospitalization, and mortality in geriatric patients with polymerase chain reaction (PCR)-proven COVID-19 who required in-hospital treatment.

Materials and methods

In this retrospective, case-control study conducted in a single-center, patients who were diagnosed with COVID-19 according to clinical, imaging, and PCR data between March 18, 2020 and June 1, 2020 and hospitalized for treatment were screened. The demographic data and laboratory results of all patients included in the study were obtained by reviewing hospital records. NLR was calculated by dividing the number of neutrophils by the number of lymphocytes using data from the hemogram. PLR was determined by dividing the number of platelets by the number of lymphocytes, and CAR was obtained by dividing the CRP level (mg/L) by the albumin (g/dL) level. The study protocol was approved by the ethics committee of Prof. Dr. Cemil Taşcıoğlu City Hospital (date: June 2, 2020, approval number: 211). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Written informed consent form was obtained from all patients.

Statistical analyses

NCSS 2007 (NCSS, Kaysville, Utah, USA) was used for the statistical analyses. Descriptive statistical methods (mean,

standard deviation, median, frequency, percentage, minimum, maximum) were used to evaluate the study data. The normality of the data distribution was tested using the Shapiro–Wilk test and graphical analysis. The Mann–Whitney U test was used to compare quantitative variables that did not display a normal distribution between survivors and non-survivors. The Kruskal–Wallis and Dunn–Bonferroni tests were performed to compare quantitative variables that did not display a normal distribution between more than two groups of patients. Pearson's chi-squared test and Fisher's exact test were used to compare qualitative data. Diagnostic screening tests (sensitivity, specificity, positive predictive value, negative predictive value) and receiver operating characteristic (ROC) curve analysis were used to determine the predictive value of the parameters. The Youden index was used to determine the optimal cutoffs. Statistical significance was accepted as $P < 0.05$.

Results

Of the 639 patients at least 18 years old treated during the study period, 258 were at least 65 years old. Among these patients, 199 were PCR-positive for COVID-19 using pharyngeal swab samples. Of these patients, 175 patients for whom complete data were obtained at their first hospital admission were included in this study. The cohort consisted of 103 women (58.9%) and 72 men (41.1%). The ages of the subjects participating in the study ranged from 65 to 95 years (median, 73 years). The duration of hospitalization ranged from 2 to 61 days (median, 14 days). Concomitant diseases were recorded, and the coexisting diseases included diabetes (44%, n = 77), hypertension (77.1%, n = 135), hyperlipidemia (57.1%, n = 100), coronary artery disease (36%, n = 63), congestive heart failure (7.4%, n = 13), chronic renal failure (8%, n = 14), chronic lung disease (21.7%, n = 38), cirrhosis (1.7%, n = 3), thyroid diseases (6.3%, n = 11), collagen tissue disease (5.1%, n = 9), inflammatory bowel disease (1.7%, n = 3), cerebrovascular accident (13.1%, n = 23), and malignancy (6.9%, n = 12). Of the included patients, 33.1% (n = 58) died.

No differences in age and sex were observed between surviving and deceased patients. The length of hospitalization was significantly lower in surviving patients ($P = 0.023$). In addition, no difference in the rate of any comorbidity was observed between survivors and non-survivors (Table 1).

NLR, CRP, CAR, and creatinine and fasting blood glucose (FBG) levels were significantly higher in patients who died than in those who survived (all $P < 0.001$). Albumin levels were significantly lower in patients who died ($P = 0.003$). However, PLR and alanine aminotransferase (ALT) levels did not differ between surviving and deceased patients (Table 2).

The cutoff for CRP for predicting mortality was 81.4 mg/L (sensitivity, 69%; specificity, 74.4%; positive predictive value, 57.1; negative predictive value, 57.1). The area under the ROC curve for CRP was .775. The mortality rate was significantly higher in patients with CRP levels of $\geq$81.4 mg/L than in those with CRP levels of $<$81.4 mg/L ($P < 0.001$). The cutoff for albumin levels was 3.24 g/dL (sensitivity, 55.55%; specificity, 60.3%; positive predictive value, 55.5; negative predictive value, 70.8). Patients with albumin levels of $\leq$3.24 g/dL had a significantly higher risk of death ($P < 0.001$, Table 3).

The cutoff for the neutrophil count was 4.530×10^9/L (sensitivity, 72.4%; specificity, 61.5%; positive predictive value, 48.27;

Table 1. Demographic data of the patients.

		Survivors	Non-survivors	*P*
Age, years	*Median (Q1–Q3)*	72 (67–80)	75 (69–80)	[a]*0.214*
Sex, n (%)	Female	73 (62.4)	30 (51.7)	[b]*0.177*
	Male	44 (37.6)	28 (48.3)	
Hospital stay, days	*Median (Q1–Q3)*	12 (9–19)	16 (11–22)	[a]*0.023**
Comorbidities, n (%)	Diabetes mellitus	48 (41.0)	29 (50.0)	[b]*0.260*
	Hypertension	88 (75.2)	47 (81.0)	[b]*0.388*
	Hyperlipidemia	62 (53.0)	38 (65.5)	[b]*0.115*
	Coronary artery disease	41 (35.0)	22 (37.9)	[b]*0.708*
	Congestive heart failure	10 (8.5)	3 (5.2)	[c]*0.549*
	Chronic kidney failure	9 (7.7)	5 (8.6)	[c]*1.000*
	Chronic pulmonary diseases	23 (19.7)	15 (25.9)	[b]*0.349*
	Cirrhosis	2 (1.7)	1 (1.7)	[c]*1.000*
	Thyroid diseases	9 (7.7)	2 (3.4)	[c]*0.342*
	Collagen tissue diseases	5 (4.3)	4 (6.9)	[c]*0.481*
	Inflammatory bowel diseases	2 (1.7)	1 (1.7)	[c]*1.000*
	Cerebrovascular accident	14 (12.0)	9 (15.5)	[b]*0.635*
	Malignancy	6 (5.1)	6 (10.3)	[c]*0.215*

[a]Mann–Whitney U test, [b]Pearson's chi-squared test, [c]Fisher's exact test. *$P < 0.05$.

Table 2. Comparison of laboratory findings between survivors and non-survivors.

		PCR-positive patients		
		Survivors (n = 117)	Non-survivors (n = 58)	*P*
NLR	*Median (Q1–Q3)*	3.14 (2.2–4.9)	5.88 (3.5–12.3)	[a]***0.001****
PLR	*Median (Q1–Q3)*	151.5 (119.2–213.3)	187.7 (124.6–316.3)	[a]*0.073*
CRP (mg/L)	*Median (Q1–Q3)*	40.9 (0.5–312)	105.9 (3.6–513)	[a]***0.001****
Albumin (g/dL)	*Median (Q1–Q3)*	3.4 (0.1–4.7)	3.1 (0.1–4.3)	[a]***0.003****
CAR	*Median (Q1–Q3)*	11.9 (3.6–26.4)	39.4 (19.6–64.9)	[a]***0.001****
ALT (U/L)	*Median (Q1–Q3)*	20 (14–28)	22.5 (13–34)	[a]*0.279*
Creatinine (mg/dL)	*Median (Q1–Q3)*	0.92 (0.71–1.19)	1.32 (0.85–2)	[a]***0.001****
Glucose (mg/dL)	*Median (Q1–Q3)*	113 (98–140)	137 (115–203)	[a]***0.001****

[a]Mann–Whitney U test. **$P < 0.01$.

NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio; CRP, C-reactive protein; CAR, CRP–albumin ratio; ALT, alanine aminotransferase.

negative predictive value, 81.81. The area under the ROC curve was 73.5. The rate of death was significantly higher in patients with neutrophil counts of $\geq 4.53 \times 10^9$/L than in those with neutrophil counts of $< 4.53 \times 10^9$/L ($P < 0.001$, Table 3).

The cutoff for the lymphocyte count was 0.965×10^9/L (sensitivity, 68.4%; specificity, 55.2%; positive predictive value, 46.37; negative predictive value, 75.47). The area under the ROC curve was 59.50. The mortality was significantly higher in patients with lymphocyte counts of $\leq 0.965 \times 10^9$/L than in those with lymphocyte counts of $> 0.965 \times 10^9$/L ($P = 0.041$, Table 3).

The cutoff for NLR was 4.02 (sensitivity, 74.14%; sensitivity, 65.81%; positive predictive value, 51.8; negative predictive

Table 3. Diagnostic screening tests and ROC curve results for NLR, CAR, albumin, neutrophils, and lymphocytes

	Diagnostic scan					ROC curve		
	Cutoff	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the ROC curve	95% confidence interval	*P*
NLR	≥***4.02***	74.14	65.81	51.80	83.70	**0.717**	0.634–0.800	***0.001****
CAR	≥***23***	70.69	72.65	56.20	83.30	**0.781**	0.708–0.853	***0.001****
CRP (mg/L)	≥***81.4***	69.00	74.40	57.10	82.80	**0.775**	0.702–0.849	***0.001****
Albumin (g/dL)	≤***3.24***	76.10	60.30	55.50	79.40	**0.708**	0.635–0.774	***0.001****
Neutrophil ($\times 10^9$/L)	≥**4.530**	72.40	61.50	48.27	81.81	**0.735**	0.657–0.812	***0.001****
Lymphocyte ($\times 10^9$/L)	≤**0.965**	68.40	55.20	46.37	75.47	**0.595**	0.497–0.693	***0.041****

**P < 0.01.
NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio; CRP, C-reactive protein; CAR, CRP–albumin ratio; ROC, receiver operating characteristic.

Table 4. Comparison of NLR and CAR between survivors and non-survivors.

		Survivors n (%)	Non-survivors n (%)	*OR (95% CI)*	*P*
NLR	<4.02	77 (83.7)	15 (16.3)	5.518 (2.738–11.123)	[b]***0.001****
	≥4.02	40 (48.2)	43 (51.8)		
CAR	<23	85 (83.3)	17 (16.7)	6.406 (3.193–12.854)	[b]***0.001****
	≥23	32 (43.8)	41 (56.2)		

[b]Pearson's chi–squared test. **P < 0.01.
NLR, neutrophil–lymphocyte ratio, CAR, C-reactive protein–albumin ratio; OR, odds ratio; CI, confidence interval.

value, 83.7). The area under the ROC curve was 71.7% (standard error, 4.2%). The mortality rate was 5.518-fold higher (95% confidence interval [CI] = 2.783–11.123) in patients with an NLR of ≥4.02 than in those with an NLR of <4.02 ($P < 0.001$, Tables 3–4, Figure 1).

The cutoff for CAR was 23 (sensitivity, 70.69%; specificity, 72.65%; positive predictive value, 56.2; negative predictive value, 83.3). The area under the ROC curve 78.1% (standard error, 3.7%). The mortality rate was 6.406-fold higher in patients with a CAR of ≥23 than in those with a CAR of <23 ($P < 0.001$, Tables 3–4, Figure 2).

The accuracy of the lymphocyte count for predicting mortality was significantly lower than that of CRP levels, neutrophil counts, CAR, and NLR (all $P < 0.05$, Figure 3). Meanwhile, the accuracy of CRP levels, neutrophil counts, albumin levels, CAR, and NLR for predicting mortality was similar.

When the patients were divided into three groups by age (65–74, 75–84, ≥85), there were no significant differences among the groups regarding the sex distribution, duration of hospitalization, mortality rate, NLR, CAR, ALT level, and creatinine level. However, PLR significantly

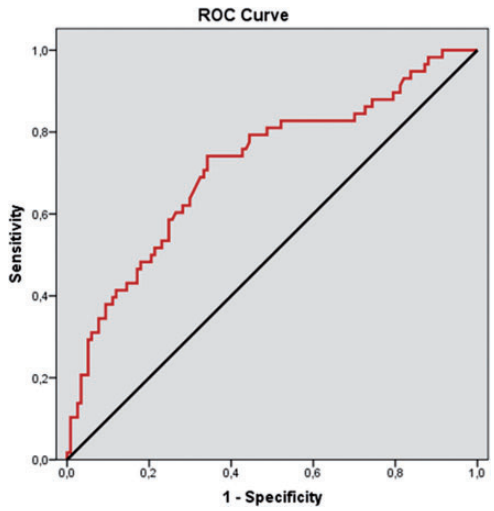

Figure 1. Receiver operating characteristic curve for the neutrophil–lymphocyte ratio.

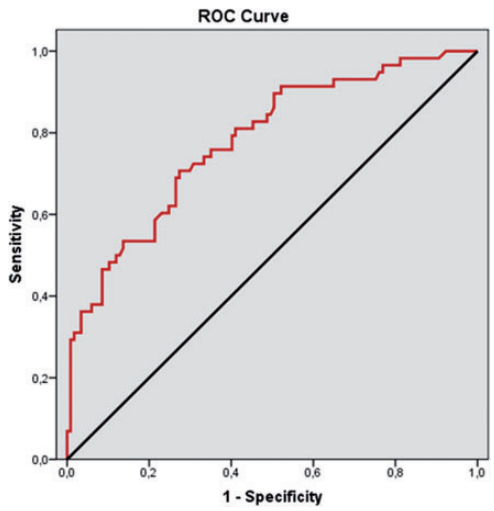

Figure 2. Receiver operating characteristic curve for the C-reactive protein–albumin ratio.

differed among the groups ($P = 0.041$). Specifically, PLR was significantly higher in patients aged ≥85 years than in those aged 75 to 84 years ($P = 0.035$). In addition, glucose levels significantly differed among the age groups ($P = 0.037$). In particular, glucose levels were significantly higher in patients aged ≥85 years than in those aged 75 to 84 years ($P = 0.031$, Table 5).

In a comparison of patient categorized into four groups using NLR and CAR, mortality rates were found to significantly differ among the groups ($P < 0.001$). The lowest mortality rate (10.3%) was observed in the NLR <4.02 and CAR <23 group, whereas the highest mortality rate (67.3%) was identified in the NLR ≥4.02 and CAR ≥23 group. Compared with the findings in the NLR <4.02 and CAR < 23 group, the risk of death was 4.357-fold higher in the NLR < 4.02 and CAR ≥23 group (odds ratio [OR] = 4.357, 95% CI = 1.374–13.818), 3.631-fold higher in the NLR ≥4.02 and CAR < 23 group (OR = 3.631, 95% CI = 1.239–10.640), and 17.973-fold higher in the NLR ≥4.02 and CAR ≥23 group (OR = 17.973, 95% CI = 6.719–48.081, Table 6).

Discussion

COVID-19 is currently the most important health problem globally, and it has been declared a pandemic associated with high mortality rates because of the lack of specific treatments. In previous studies, no difference was found in the rates of COVID-19 between the sexes, and the average patient age ranges 49 to 58 years.[3,4] In addition, studies have reported that COVID-19 progresses more seriously in older patients.[5,6] In our study, because the patients were selected from the geriatric age group, the mean age of our patients was 74 years.

Wang *et al*. reported that the mean hospital stay of patients with COVID-19 with a mean age of 56 years was 10 days.[7] The mean length of stay in our patients was 15 days. Our patients were hospitalized longer because our study population included older patients than other studies.

According to official Chinese reports, 2.5% of all patients with COVID-19 who received outpatient and inpatient treatment

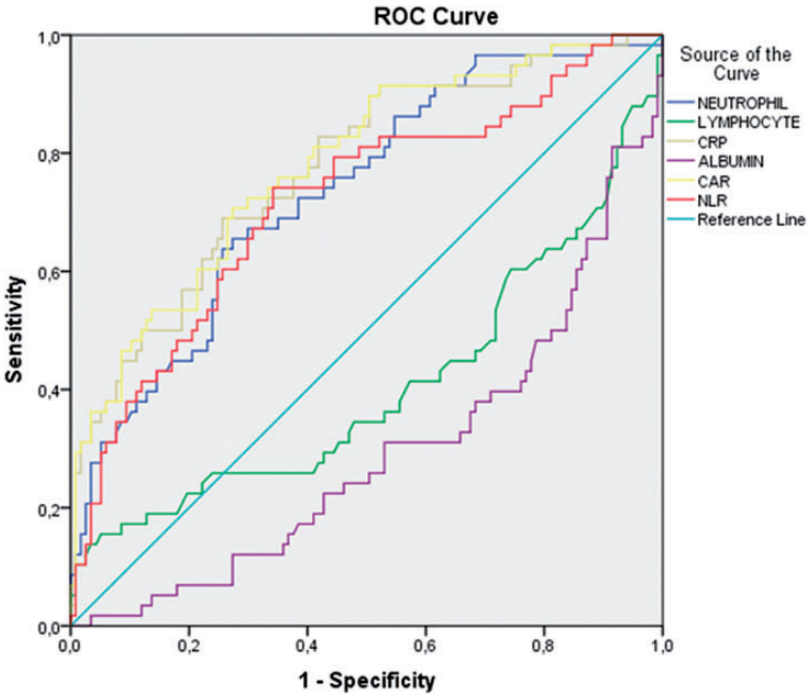

Figure 3. Receiver operating characteristic curves for the neutrophil count, lymphocyte count, C-reactive protein level, albumin level, C-reactive protein–albumin ratio, and neutrophil–lymphocyte ratio.

Table 5. Comparison of demographic and laboratory findings according to age.

		Age, years			
		65–74	75–84	≥85	*P*
Sex, n (%)	Female	53 (55.2)	33 (63.5)	17 (63.0)	[b]*0.557*
	Male	43 (44.8)	19 (36.5)	10 (37.0)	
Hospital stay, days	*Median (Q1–Q3)*	14 (10–19)	13 (9–20)	15 (12–21)	[d]*0.267*
Patients	Survivors	68 (70.8)	31 (59.6)	18 (66.7)	[b]*0.384*
	Non-survivors	28 (29.2)	21 (40.4)	9 (33.3)	
NLR	*Median (Q1–Q3)*	3.4 (2.3–6.9)	3.8 (2.3–6.4)	4.5 (3.2–6.9)	[d]*0.443*
PLR	*Median (Q1–Q3)*	151 (120.3–229.0)	149.9 (104.2–210.1)	185.5 (154.3–302.0)	[d]*0.041**
CAR	*Median (Q1–Q3)*	21 (6–40.1)	15.3 (4.4–36.1)	22.4 (6–38)	[d]*0.705*
ALT (U/L)	*Median (Q1–Q3)*	21.5 (16–32.5)	16 (10–28.5)	19 (13–31)	[d]*0.050**
Creatinine (mg/dL)	*Median (Q1–Q3)*	1.01 (0.7–1.48)	1.03 (0.81–1.44)	0.92 (0.61–1.19)	[d]*0.320*
Glucose (mg/dL)	*Median (Q1–Q3)*	125 (103–160.5)	117 (101–163.5)	109 (97–132)	[d]*0.037**

[b]Pearson's chi-squared test, [d]Kruskal–Wallis Test. *$P < 0.05$.

NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio; CAR, C-reactive protein–albumin ratio; ALT, alanine aminotransferase.

Table 6. Comparison of patient outcomes according to cutoffs for CAR and NLR.

	Survivors *n (%)*	Non-survivors *n (%)*	*OR (95% CI)*	*P value*
NLR < 4.02, CAR < 23	*61 (89.7)*	*7 (10.3)*	–	*0.001***
NLR < 4.02, CAR ≥ 23	*16 (66.7)*	*8 (33.3)*	*4.357 (1.374–13.818)*	
NLR ≥ 4.02, CAR < 23	*24 (70.6)*	*10 (29.4)*	*3.631 (1.239–10.640)*	
NLR ≥ 4.02, CAR ≥ 23	*16 (32.7)*	*33 (67.3)*	*17.973 (6.719–48.081)*	

[b]Pearson's chi-squared test. **$P < 0.01$.
NLR, neutrophil–lymphocyte ratio; CAR, C-reactive protein–albumin ratio; OR, odds ratio; CI, confidence interval.

died in China as of February 2020, whereas the rate in the WHO official statement in July 2020 was 4.6%.[2,8] Liu *et al*. stated in their study that 13% of inpatients with a mean age of 54 years died.[9] In two other studies, the fatality rate was 15% in patients with a mean age of 49 years and 20% in patients with a mean age of 71 years.[3,10] In our study involving patients aged 65 years and older, the fatality rate among geriatric patients who were hospitalized with the diagnosis of PCR-positive COVID-19 was 33%. This rate, which is higher than that in other studies, is attributable to the high mean age of the patients, as the fatality rate in patients aged 18 to 64 years who received inpatient treatment for PCR-positive COVID-19 in our hospital was 16%.

When the comorbid chronic diseases of our patients were examined, the most common diseases were hypertension, diabetes, and hyperlipidemia. However, the rates of comorbidity did not differ between survivors and non-survivors. The findings of higher blood glucose and creatinine levels in non-survivors may be attributable to the severe course of the infection and presence of acute organ damage.

In the course of viral infections, neutropenia and lymphopenia occur at various rates depending on the severity of the disease. NLR, which is calculated by dividing the number of neutrophils by the number of lymphocytes, was significantly higher in patients with increased disease severity and associated with poor prognosis in several previous studies.[4,9,11,12] Two previous studies reported NLRs for predicting in-hospital mortality among elderly patients of 7.1 and 7.7, respectively.[13,14] NLR was significantly higher in patients who died than in those who survived in this study ($P < 0.001$). NLR of ≥4.02 was associated with increased mortality.

In patients with COVID-19, platelet counts can be within normal levels or elevated in response to infection, and thrombocytopenia may also be observed because of the infection. The relationship between PLR and the severity of COVID-19 was previously examined in only one study. Although Qu *et al*. did not find a relationship between PLR at the time of hospital admission and the severity of COVID-19, they found a positive correlation between PLR and the severity of the disease in later periods of the disease.[5] The reason for this finding is that although the lymphocyte count is generally normal at the beginning of the infection, it tends to decrease in the later stages of the disease. Similar to previous findings, there was no significant difference in PLR levels between survivors and non-survivors in this study. Therefore, PLR at the time of hospital admission is not a useful parameter for predicting the duration of stay or mortality.

Both coronavirus infection and secondary bacterial infection can increase CRP levels. In addition, the presence of

malnutrition in patients with severe COVID-19 causes hypoalbuminemia. Because of these reasons, CAR is highly accurate for predicting the severity of COVID-19. Previous studies described the relationship between high CRP levels and disease severity,[6,12,15,16] as well as between low albumin levels and the poor prognosis of COVID-19.[6,10,12] CRP and albumin levels in our study were supported by prior findings. CRP levels were significantly higher and albumin levels were significantly lower in non-survivors ($P < 0.001$ and $P < 0.003$, respectively). Moreover, another study recorded the relationship between a high CAR and disease severity, whereas a second study (online ahead of print) reported the relationship between a high CAR and mortality in patients with hypertension. In the study reported by Karakoyun *et al.*, the CAR cutoff was 0.9, and ratios higher than 0.9 were associated with increased severity of COVID-19. In hypertensive patients as a specific group, CAR $\geq$20.75 was significantly related to in-hospital death.[17,18] However, no study in the literature evaluated COVID-19 specifically in geriatric patients, and no study analyzed the association of the CAR with mortality and the duration of hospital stay. Therefore, our study revealed for the first time that CAR at the time of admission was significantly higher in non-survivors than in survivors ($P < 0.001$). In particular, the cutoff of CAR was 23, and values of 23 and higher were associated with increased mortality. This result is similar to the results reported by Saylik *et al.*[18]

A previous study reported that CAR was superior to NLR in the prediction of mortality, but another study reported that NLR was superior to CAR in geriatric patients.[13,14] According to our results, CAR and NLR had similar predictive value. Both variables are useful for predicting mortality. In addition, our study demonstrated that simultaneous elevation of NLR and CAR was linked to a 17.9-fold higher risk of mortality.

When we classified the patients into three groups by age, no any age group-specific differences were identified. Therefore, all geriatric patients older than 65 years have a similar duration of hospitalization and a similar risk of death independent of age, although these findings are proportional to NLR and CAR.

NLR and CAR can be calculated quickly, easily, and inexpensively even at the first admission to any hospital. These variables are highly accurate for predicting the severity, mean length of stay, and fatality rates of patients with COVID-19. Therefore, immediately after admission, these variables can be calculated and used to predict the clinical course of geriatric patients with COVID-19. Using these variables, treatment can be intensified as needed early in the disease course.

The limitations of this study included its retrospective nature and limited number of patients at a single institution, which could limit the generalizability of these findings. In addition, patients who had recently received chemotherapy could not be excluded, and we could not evaluate the treatment protocols of patients.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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ORCID iD

Semih Kalyon https://orcid.org/0000-0003-4207-0800

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