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**ORIGINAL PAPER**

# Prognostic significance of C-reactive protein/albumin and neutrophil/lymphocyte ratios in patients with COVID-19

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**ABSTRACT**

**Introduction and aim.** COVID-19 causes an uncontrolled and generalized inflammatory response of the host immune system. Early recognition of the disease and early prediction of the clinical course are of great importance. The aim of this study was to evaluate the predictive role of the C-reactive protein/albumin ratio (CAR) and the neutrophil/lymphocyte ratio (NLR) for mortality in patients hospitalized with the diagnosis of COVID-19.

**Material and methods.** The patients, who were hospitalized for COVID-19 and whose CRP, albumin, neutrophil, and lymphocyte levels were documented within the first 24 hours after admission, were analyzed retrospectively. Patients were divided into survivors and non-survivors; the groups were compared. Univariate and multivariate Cox regression models were developed to evaluate the CAR and the NLR as risk factors for mortality in COVID-19 patients.

**Results.** One hundred and thirty patients were included in this study. The mean age of the survivor group (n=114) was 60±16 and 52% were male. The mean age of the non-survivor group (n=16) was 75±13 and 56% were male. In the non-survivor group, the CAR detected at the time of admission to the hospital was significantly higher compared to patients in the survivor group (p=0.026).

**Conclusion.** As a result, the CAR, the NLR and LDH are independent risk factor indicators of mortality in hospitalized patients.

**Keywords**. COVID-19, C-reactive protein/albumin, neutrophil/lymphocyte

## Introduction

The COVID-19 pandemic, caused by the SARS-CoV-2 virus that emerged in 2019, has spread globally and continues to be associated with mortality and morbidity despite vaccination.[1] The spectrum of disease caused by the coronavirus in humans can range from asymptomatic forms to severe viral pneumonia with severe acute respiratory failure, multi-organ dysfunction caused by sepsis and septic shock, and death.[2,3] While microbiological and radiological examinations are used for the diagnosis of COVID-19 infection, biochemical and hematological tests are used to grade disease risk and for disease follow-up and treatment.[4,5]

Biochemical and hematological alterations play important roles in the pathophysiology of COVID-19 infection and indicate the level of systemic inflammatory

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response. It has been stated that laboratory tests will be useful in the diagnosis of tissue and organ damage related to infection, identification of patients with low risk of severe disease, identification of patients with poor prognoses, and monitoring the course of the disease.[6] Complete blood count parameters are common, easy, and quick to measure and have been shown to be a prognostic marker in various disorders such as heart disease, tumors, sepsis, pneumonia and acute respiratory distress syndrome.[7,8] The value of the neutrophil/lymphocyte ratio (NLR), obtained by dividing the neutrophil count by the lymphocyte count, from hematological parameters, in the diagnosis and prognosis of COVID-19, has been demonstrated in many studies.[9-15]

The CRP/albumin ratio (CAR) represents a fraction of a positive acute phase inflammatory reactant versus a negative acute phase reactant and has the potential to simultaneously indicate the patient's inflammatory response and nutritional status.[16] In recent years, it has been shown that the CAR can be used as a prognostic biomarker in inflammatory disease, cancer and cardiovascular disease.[17,18] A recent study has shown that increased CRP levels and decreased albumin levels in COVID-19 patients may be associated with disease severity and mortality.[19] Biochemical and hematological biomarkers can play a crucial role in providing valuable insights into the severity and prognosis of COVID-19, guiding the determination of treatment strategies, and contributing to the clinical management of patients. In the current literature, there is a limited number of studies focusing on the clinical implications of such biochemical and hematological markers, and conflicting findings exist among the results of these studies.

## Aim

The aim of this study is to show the prognostic significance of the CAR and the NLR detected at admission in patients diagnosed with COVID-19.

## Material and methods

For this single-center, retrospective observational study, 130 patients who were hospitalized due to COVID-19 and were found to have a positive SARS-CoV-2 RT-PCR test between January and April 2021 were included.

Patients younger than 18 years of age, pregnant women, patients with negative or no SARS-CoV-2 RT-PCR test results, patients with respiratory distress due to a cause other than COVID-19, and patients with a positive SARS-CoV-2 RT-PCR test result while hospitalized with different diagnoses were excluded from the study. Additionally, patients with known hematological abnormalities and other inflammatory diseases were not included in the study (Fig. 1). The study was approved by the Internal Review Board (2021/170) of our center and was performed under the ethical standards of the Declaration of Helsinki.

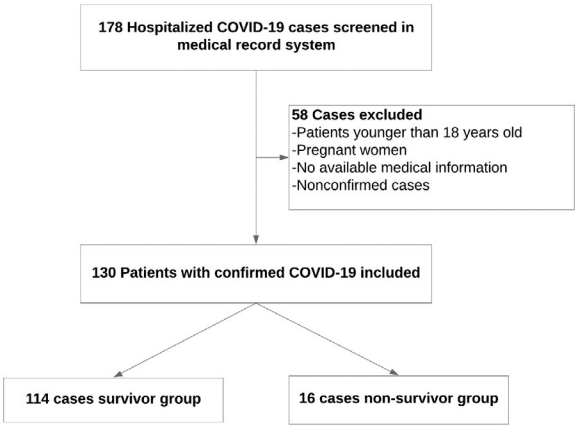


**Fig. 1.** Flowchart of the patient selection process

According to the WHO guideline (WHO interim guidance), the definitive diagnosis of COVID-19 is based on real-time reverse transcription-PCR (RT-PCR) testing. In our study, SARS-CoV-2 RNA was detected by the real-time RT-PCR method as determined in the Ministry of Health Public Health Microbiology Reference Laboratory. The current treatment guidelines prepared by the Ministry of Health were applied in the treatment of the patients.

### *Data collection and laboratory analyzes*

The patients' demographic characteristics and clinical information were collected from the hospital's electronic information system. The existing diseases and diagnoses of the patients detected at the time of hospitalization were differentiated according to the 19 types of diagnosis groups in the Charlson Comorbidity Index (CCI) score system, and the sum of the scores corresponding to these diagnostic groups was determined as the CCI score. For each patient their individual data was entered, and the index was calculated online. The pulmonary involvement rate was evaluated by accessing the thorax computed tomography reports of the patients from the hospital registry system. The pulmonary infiltration rate was classified as either below 50% or above 50%. Laboratory results for each patient were recorded in the first 24 hours of hospitalization. Laboratory analyses were performed using a Mindray BC-6800 hematology analyzer (Mindray, Shenzhen, China) for hematological parameters and a Beckman AU5800 instrument (Beckman Coulter, Ireland Inc.) for biochemical parameters. Serum biochemical measurements were performed in the hospital clinical laboratory using routine automated techniques. Among the laboratory tests creatinine, Na, K, Ca, Mg, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), neutrophil, lymphocyte, platelet, ferritin, D-Dimer, fi-

brinogen, platelet crit (PCT), C-reactive protein (CRP) and $HBA_1C$ results were recorded. The NLR was calculated by dividing the neutrophil count by the lymphocyte count, and the CAR was calculated by dividing the CRP level by the albumin level.

Patient groups were categorized into two distinct cohorts for comprehensive comparative analysis: Patient groups were compared as non-survivors and survivors. The primary focus of our investigation revolved around the critical endpoint of mortality, with a keen interest in unraveling the factors contributing to survival and those associated with unfortunate outcomes.

### *Statistical analysis*

Data analysis was done using the SPSS (Statistical Package for the Social Sciences, Chicago, IL, USA) 22.0 program. Descriptive statistics were presented as mean ± standard deviation and median (IQR) for continuous variables, and as numbers and percentages for categorical variables. The distribution of continuous variables was evaluated and in cases where parametric conditions were met, the difference of continuous variables between the two groups was evaluated with the independent sample t-test, and the Mann Whitney U test. If parametric conditions were not met, the chi-square test or Fisher's exact test was used in the analysis of categorical variables. Log rank analyses were performed, and Kaplan-Meier survival plots were used. A univariate Cox regression analysis was used to determine hazard ratios for parameters. Then, a multivariate Cox regression analysis was performed using the Backward LR method with parameters having a p value of >0.2 to construct the final model. According to the model, proportional hazard ratios were used to evaluate the potential independent effects of the parameters after adjustment for oxygen saturation ($SpO_2$), age, and CCI. The CAR, which was found to be an independent risk factor for mortality, was analyzed via ROC curve analysis and the optimum cut-off value was determined by the Youden Index. Sensitivity and specificity values corresponding to the determined cut-off value were presented. A $p<0.05$ level was considered significant.

## Results

The demographic, clinical and laboratory parameters of the 130 patients included in this study are shown in Table 1. The non-survivor group was older compared to the survivor group ($p<0.001$). While more than 50% pulmonary involvement was observed in 22% of the patients in the survivor group, it was observed in 31% of the patients in the non-survivor group. CCI score was higher and oxygen saturation was lower in the non-survivor group compared to the survivor group (p=0.004 and p=0.012, respectively). There was no difference between the groups in terms of length of hospital stay. PCT and creatinine levels were higher in the non-survivor group than in the survivor group ($p<0.001$ and p=0.007, respectively). In addition, CRP levels were higher in the non-survivor group, but albumin levels were lower, and so the CAR rate was also higher (p=0.022, p=0.048 and p=0.026, respectively). There was no difference between the groups in other laboratory parameters (Table 1).

**Table 1.** Demographic and clinical characteristics of patient survivors and non-survivors*

| | Survivor (n=114) | Non-survivor (n=16) | *p* |
|---|---|---|---|
| Age (years) | 60±16 | 75±13 | <0.001 |
| CCI | 3±2 | 5±2 | 0.004 |
| $SpO_2$ on admission, (%) | 93±5.2 | 90±3.5 | 0.012 |
| Hospital length of stay, (days) | 11±6 | 18±14 | 0.099 |
| **Laboratory** | | | |
| WBC, (/mm$^3$×10$^3$) | 7.3±4.3 | 6.4±3.1 | 0.960 |
| Hemoglobin, (g/dL) | 12.4±2 | 11.6±2.4 | 0.136 |
| Neutrophil, (/mm$^3$ ×10$^3$) | 4.6 (3.3) | 5.6 (4.6) | 0.319 |
| Lymphocyte, (/mm$^3$ ×10$^3$) | 1.1±0.5 | 1.1±0.7 | 0.565 |
| NLR | 4.18 (5) | 4.57 (7) | 0.549 |
| PLT, (/mm$^3$ ×10$^3$) | 191.2±84.2 | 186.3±91.9 | 0.526 |
| MPV, (fL) | 10±1.3 | 10.2±1.3 | 0.409 |
| PCT, (%) | 0.12 (0.14) | 0.54 (2.8) | <0.001 |
| Glucose, (mg/dL) | 158±79 | 144±60 | 0.461 |
| AST, (U/L) | 27 (18) | 35 (69) | 0.127 |
| ALT, (U/L) | 21 (17) | 29 (41) | 0.093 |
| Creatinine, (mg/dL) | 0.8 (0.4) | 1.3 (1) | 0.007 |
| Sodium, (mEq/L) | 136±4 | 138±6 | 0.076 |
| Potassium, (mEq/L) | 4.1±0.5 | 3.9±0.5 | 0.061 |
| Magnesium, (mg/dL) | 2.0±0.3 | 1.9±0.4 | 0.447 |
| Calcium, (mg/dL) | 9.1±0.5 | 9.1±0.5 | 0.650 |
| HbA1c, (%) | 7.6±1.5 | 7.2±0.3 | 0.607 |
| Ferritin, (ng/mL) | 283 (340) | 415 (1535) | 0.130 |
| LDH, (U/L) | 270±102 | 427±384 | 0.124 |
| CRP, (mg/L) | 42 (92) | 104 (86) | 0.022 |
| Albumin, (g/dL) | 3.7±0.6 | 3.4±0.7 | 0.048 |
| CAR | 13.16 (27) | 39.05 | 0.026 |
| D-dimer, (ng/mL) | 0.68 (1) | 0.98 (2) | 0.065 |
| Fibrinogen, (mg/dL) | 469±147 | 519±174 | 0.224 |

* Values are given as mean ± SD; others given as median (IQR), CCI – Charlson comorbidity index, $SpO_2$ – oxygen saturation, WBC – white blood cell, NLR – neutrophil/lymphocyte ratio, PLT – platelets, MPV – mean platelet volume, PCT – platelet crit, LDH – lactate dehydrogenase, CRP – C-reactive protein, CAR – CRP/albumin ratio

Independent risk factors were evaluated with univariate and multivariate Cox regression analyses. The NLR, the CAR and LDH were found to be statistically significant independent risk factors of mortality. (NLR: HR:1.041 [95%CI:1.014–1.070], p=0.003; LDH: HR:1.003 [95%CI:1.000–1.005], p=0.031; CAR: HR:1.02 [95%CI:1.001–1.039], p=0.041) (Table 2).

The ROC of the CAR for the prediction of COVID-19 mortality is shown in Figure 2. A CAR of >17.7 was defined as the optimal cut-off point for determining COVID-19 mortality, exhibiting 75% sensitivity and 57% specificity. The area under the curve of

the CAR for the prediction of COVID-19 mortality was 0.672 (95%CI: 0.543-0.801; p = 0.026).

**Table 2.** Univariate and multivariate cox regression analyses for death of COVID-19

| Variables | Univariate Analyses | | | | Multivariate Analyses | | | |
|---|---|---|---|---|---|---|---|---|
| | *p* value | HR | 95% CI for HR | | *p* value | HR | 95% CI for HR | |
| | | | Lower | Higher | | | Lower | Higher |
| Gender | 0.919 | 0.947 | 0.33 | 2.715 | | | | |
| CCI | 0.176 | 1.156 | 0.937 | 1.427 | 0.906 | 0.983 | 0.733 | 1.317 |
| Age | 0.073 | 1.038 | 0.997 | 1.082 | 0.324 | 1.024 | 0.977 | 1.074 |
| PI | 0.28 | 1.908 | 0.591 | 6.161 | | | | |
| D-dimer | 0.453 | 1.115 | 0.839 | 1.482 | | | | |
| Fibrinogen | 0.334 | 1.001 | 0.998 | 1.004 | | | | |
| WBC | 0.968 | 1.000 | 1.000 | 1.000 | | | | |
| PLT | 0.904 | 1.000 | 1.000 | 1.000 | | | | |
| MPV | 0.253 | 1.231 | 0.862 | 1.757 | | | | |
| PCT | 0.197 | 1.075 | 0.963 | 1.201 | | | | |
| Hemoglobin | 0.459 | 0.908 | 0.704 | 1.172 | | | | |
| NLR | 0.003 | 1.036 | 1.012 | 1.061 | 0.003 | 1.041 | 1.014 | 1.070 |
| AST | 0.862 | 1.000 | 0.998 | 1.002 | | | | |
| ALT | 0.932 | 1.000 | 0.996 | 1.005 | | | | |
| Creatinine | 0.993 | 0.999 | 0.758 | 1.317 | | | | |
| Sodium | 0.108 | 1.087 | 0.982 | 1.202 | | | | |
| Magnesium | 0.864 | 1.122 | 0.299 | 4.207 | | | | |
| Calcium | 0.263 | 0.505 | 0.153 | 1.671 | | | | |
| Potassium | 0.921 | 0.954 | 0.377 | 2.414 | | | | |
| LDH | 0.008 | 1.002 | 1.001 | 1.004 | 0.031 | 1.003 | 1.000 | 1.005 |
| Ferritin | 0.057 | 1.000 | 1.000 | 1.001 | | | | |
| HbA1c | 0.611 | 0.724 | 0.209 | 2.51 | | | | |
| $SpO_2$ | 0.02 | 0.902 | 0.828 | 0.984 | 0.663 | 0.972 | 0.854 | 1.106 |
| CAR | 0.001 | 1.025 | 1.010 | 1.041 | 0.041 | 1.02 | 1.001 | 1.039 |

* CCI – Charlson comorbidity index, PI – pulmonary involvement, WBC – white blood cell, PLT – platelets, MPV – mean platelet volume, PCT – platelet crit, NLR – neutrophil/lymphocyte ratio, LDH – lactate dehydrogenase, $SpO_2$ – oxygen saturation, CRP – C-reactive protein, CAR – CRP/albumin ratio

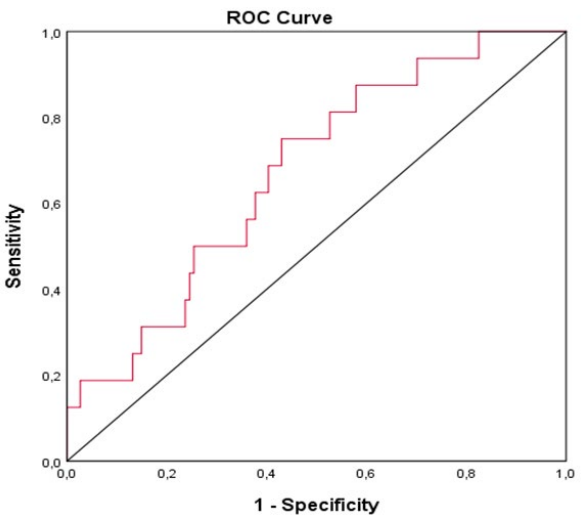


**Fig. 2.** Receiver operating characteristic curves for CAR for the mortality of COVID-19

A total of 16 patients died during hospitalization. All these patients had a CAR ≥17.7. Figure 3 show the Kaplan-Meier survival curve for the CAR according to this cut-off value. Patients with a CAR above the cut-off value had significantly higher mortality rates than those with a CAR below the cut-off value (log-rank test=4.972; p=0.026) (Fig. 3).

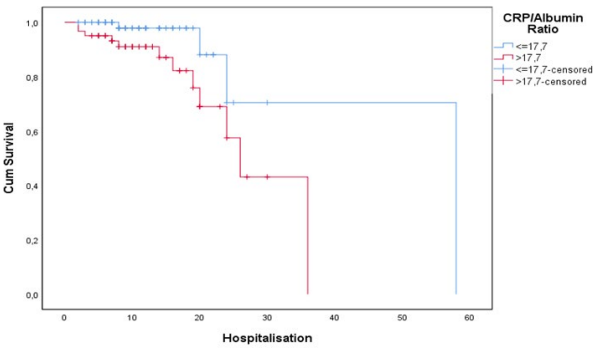


**Fig. 3.** The Kaplan-Meier survival curve for C-reactive protein/albumin ratio (CAR)

## Discussion

In this study, we aimed to show the prognostic importance of the NLR, and the CAR detected at admission in patients diagnosed with COVID-19. The main results of our study are as follows. i) The CAR was observed to be higher in the non-survivor group than in the survivor group. ii) Multivariate analyses demonstrated that the NLR and the CAR are independent risk factors of mortality in COVID-19 patients. iii) A CAR of >17.7 was defined as the optimal cut-off point for determining COVID-19 mortality.

Since its emergence from Wuhan in 2019, COVID-19 has become a serious pandemic. Early detection of patients with poor prognoses is important. The systemic inflammatory response is responsible for the clinical course of the COVID-19, and one of the important causes of mortality is the cytokine storm caused by the excessive release of proinflammatory cytokines.[20]

The NLR, calculated by dividing the neutrophil count by the lymphocyte count, is one of the important markers of immune damage and inflammation, whose use has increased rapidly in recent years. Increase in the NLR is a risk factor for mortality in malignancy, acute coronary syndrome, intracerebral hemorrhage, polymyositis and dermatomyositis.[13] Numerous studies have investigated the impact of NLR on mortality in COVID-19 patients.[11,12,14]

The inflammatory response may cause an increase in neutrophil levels by stimulating the release of inflammatory cytokines such as TNF alpha and IL-6. Proinflammatory mediators such as catecholamines and cortisol can bind to the lymphocyte surface and initiate

lymphocytic apoptosis, leading to lymphopenia.[10] The NLR is considered a more reliable inflammatory marker because it reflects changes in both neutrophil and lymphocyte counts in conditions that correlate with the inflammatory response to a disease, such as COVID-19. Yang et al. demonstrated that the NLR is an independent biomarker to indicate poor clinical outcomes in COVID-19 patients.[15] Aksu et al. showed that the NLR values are inflammatory markers that can be used to show pulmonary involvement and disease severity in COVID-19 patients.[9] A meta-analysis by Sarkar et al. showed that the NLR is an independent predictor of disease severity and mortality in COVID-19.[14] In our study, the NLR was found to be an independent predictor of mortality, in line with previous studies.

CRP, a positive acute phase reactant, is known to increase in response to infections, inflammation and tissue damage.[21] It has been shown that CRP levels are high in COVID-19 patients and the magnitude of the increase correlates with the severity of the disease.[22] It is known that albumin, a negative acute phase reactant and the basic protein in the blood, synthesized by the liver, tends to decrease in response to acute conditions such as inflammation, trauma, surgery and burns.[23] A meta-analysis of 11 studies showed that hypoalbuminemia is associated with the severity of COVID-19.[24] In a study including 188 patients, it was revealed that the CAR levels are superior to the fibrinogen/albumin ratio (FAR) and the NLR in predicting disease severity in COVID-19 patients.[25] In a recent study, the CAR was shown to be an independent predictor of disease severity in hospitalized patients with COVID-19.[26] In a study of hypertensive patients with COVID-19, the CAR levels were shown to be an independent predictor of in-hospital mortality.[27] In a retrospective study of 2309 COVID-19 patients, the findings revealed that a high CAR rate was associated with respiratory impairment, the need for oxygen therapy and ventilation, bacteremia, and thrombosis. Moreover, four different prognostic categories of CAR ratios were identified and shown to be associated with 30-day survival.[28] In a study conducted to predict 30-day mortality in patients admitted to the emergency department due to COVID-19, it was shown that the BUN/albumin ratio and CAR ratio predicted 30-day mortality.[29] On the other hand, in a retrospective study of 75 COVID-19 patients, the CAR rate was identified as an indicator of disease severity, but its relationship with mortality was not demonstrated.[30] In our study, the CAR was found to be higher in the non-survivor group compared to the survivor group, and the CAR was found to be an independent risk factor of mortality.

Our findings are potentially clinically relevant for treatment options and follow-up for COVID-19 patients. Since it is more effective to start treatment in the early stages of the disease in COVID-19, earlier detection of high-risk COVID-19 patients using the NLR and the CAR values may be very important and effective in reducing mortality.

Our study does have some limitations. The number of patients is relatively small, and the analysis was retrospective. It is important to acknowledge the limitation of a relatively small sample size, particularly considering the global scale of the epidemic during the study period. The challenges posed by the sample size might impact the generalizability of the findings, and caution should be exercised in extrapolating these results to broader populations. It is important to acknowledge the limitation of a relatively small sample size, particularly considering the global scale of the epidemic during the study period. The challenges posed by the sample size might impact the generalizability of the findings, and caution should be exercised in extrapolating these results to broader populations. The NLR was measured only at the time of admission to hospital and follow-up NLR values were not determined. Some of the parameters are also affected by conditions such as body mass index, physical activity, smoking and alcohol consumption.[31]

## Conclusion

In conclusion, both the CAR and NLR values, regarded as crucial indicators of the inflammatory response, offer valuable insights for clinicians in determining the disease trajectory. The ease and rapidity with which CAR and NLR can be measured in blood make them valuable tools for evaluating the prognosis of COVID-19 patients. However, it's essential to note that the AUC value for CAR ratio was found to be low for an ideal predictor in clinical decision-making. Therefore, we advocate for a cautious interpretation of the AUC, proposing its incorporation as supplementary information rather than a standalone determinant. Larger randomized controlled trials hold the potential to provide more conclusive evidence on the association between NLR and CAR values and in-hospital mortality among patients with COVID-19.

## Declarations

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***Author contributions***

Conceptualization, H.B.P.; Methodology, M.A.; Software, M.A.; Validation, H.B.P., M.A. and A.E.; Formal Analysis, T.A.; Investigation, M.B.; Resources, F.B.Ç.; Data Curation, H.B.P.; Writing – Original Draft Preparation, Z.P.; Writing – Review & Editing, Z.P.; Visualization, H.B.P.; Supervision, A.E.; Project Administration, M.B.

***Conflicts of interest***

There is no conflict of interest between authors of this manuscript.

***Data availability***

Data available on request from the authors.

***Ethics approval***

This manuscript have been approved by the Internal Review Board of RTEÜ Hospital (2021/170).

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