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ORIGINAL RESEARCH

Factors Affecting Duration of Hospital Stay in Deceased COVID-19 Patients

Ercan Kurtipek[1], Mehmet Mermer[1], Bilgenur Yıldırım[1], Mehmet Akif Yazar[2], Mustafa Duran[3], Faysal Duksal[4]

[1]Department of Chest Diseases, University of Health Sciences, Konya City Hospital, Karatay, Konya, Turkey; [2]Department of Anesthesiology and Reanimation, University of Health Sciences, Konya City Hospital, Karatay, Konya, Turkey; [3]Department of Cardiology, University of Health Sciences, Konya City Hospital, Karatay, Konya, Turkey; [4]Department of Chest Diseases, University of Health Sciences, Konya Beyhekim Training and Research Hospital, Selcuklu, Konya, Turkey

Correspondence: Ercan Kurtipek, Department of Chest Diseases, University of Health Sciences, Konya City Hospital, Karatay, Konya, Turkey, Email kurtipek14@hotmail.com

Objective: Extensive research has been conducted to identify the predictive criteria for COVID-19 disease. White blood cell, C-reactive protein, CRP/albumin ratio, neutrophil-to-lymphocyte ratio and ferritin are among the indicators of increased inflammatory response; hence, they could be used to determine the prognosis of COVID-19 cases. Within the scope of this study, we aimed to elucidate the predictivity of NLR, CAR and other laboratory parameters on the duration of hospital stay and mortality in patients with COVID-19.

Materials and Method: The data of 1516 COVID-19 patients who were hospitalized in our institution have been analyzed retrospectively. Patients were divided into two groups those who deceased within the first 10 days of hospitalization (Group I, ≤10 days) and those who deceased in the later period (Group II, >10 days). Age, gender, time to mortality after hospitalization, neutrophil count, CRP, neutrophil-to-lymphocyte ratio (NLR), CRP/albumin ratio (CAR), and D-dimer values were obtained from blood samples taken during hospitalization.

Results: NLR and CAR values were significantly higher in those who died in the first 10 days compared to the other group ($p<0.02$ and $p<0.001$, respectively). In addition, WBC, neutrophil, CRP and D-dimer levels were statistically significantly higher than the other group ($p<0.05$). Logistic regression analysis results for NLR and CAR were significant. The cut-off values were calculated (5.74 and 4.27, respectively) for both parameters. Among the most common comorbid diseases were hypertension (HT) in 41%, coronary artery disease (CAD) in 41.7%, asthma-chronic obstructive pulmonary disease (COPD) in 36.7%, diabetes mellitus (DM) in 36.1%.

Conclusion: NLR and CAR may have a decisive influence in determining the length of stay in hospital for patients who die in hospital due to COVID-19. In addition, it is recommended that COVID-19 cases with diabetes be followed closely.

Keywords: COVID-19, neutrophil-to-lymphocyte ratio, CRP/albumin ratio, hospital mortality, predictive value

Introduction

The World Health Organization (WHO) China Office confirmed the existence of pneumonia, acute respiratory failure cases and deaths of unknown cause, clustered around a fish and livestock market since the beginning of December 2019 in Wuhan city of Hubei province, China, on December 31, 2019.[1] The causative agent was named the first novel coronavirus "2019-nCoV" by WHO and then severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) on February 11, 2020. On January 12, the genetic sequence of the virus was identified.[2] As a result, WHO declared COVID-19 an "International public health emergency" on 30 January and announced as a pandemic on March 11, with a high incidence of COVID-19 cases in 113 countries.[1,3]

Although it was more contagious than the SARS-CoV virus, the probability of mortality was lower. Coronaviruses are more common in the respiratory system, but SARS-CoV-2 can also affect the heart, gastrointestinal system, liver, kidney and central nervous system and cause multiorgan failure.[4] As of September 24, 2021, a total of 232,522,770 people in the

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world have been diagnosed with COVID-19 and 4,748,124 patients were deceased. In Turkey, as of the same date, 6,960,297 people were diagnosed and 62.524 patients deceased.

While most of the cases of COVID-19 have a mild disease; moderate-to-severe cases of COVID-19 show very rapid progression, and progress to acute respiratory failure, multiorgan failure, disseminated intravascular coagulopathy (DIC), septic shock and even death.[3] However, some COVID-19 cases also terminate with mortality despite being hospitalized and receiving serious treatment. Recognizing, cases with severe clinical presentation in advance is important for initiating appropriate treatment in the early period. Extensive research has been conducted to identify the predictive criteria. However, no study has been conducted on CRP/albumin ratio (CAR), neutrophil-to-lymphocyte ratio (NLR), and their relation to the length of hospital stay and time to mortality.[4] In such severe cases, a very rapid inflammatory response was observed. White blood cell, C-reactive protein, CRP/albumin ratio, neutrophil-to-lymphocyte ratio and ferritin are among the indicators of increased inflammatory response; hence, they could be used to determine the prognosis of COVID-19 cases.[5] Elevated NLR and CAR have been identified in previous inflammatory diseases.[6,7]

Within the scope of this study, we aimed to elucidate the predictivity of NLR, CAR and other laboratory parameters on the duration of hospital stay and mortality in patients with COVID-19.

Materials and Methods

The data of 1516 COVID-19 patients who were hospitalized in our institution between January 01, 2020 and February 28, 2021 have been analyzed retrospectively. The study was approved by the University of Health Sciences Hamidiye Clinical Research Ethics Committee on December 15, 2022. Our institution has been designated as a pandemic hospital by the Ministry of Health and no patients other than COVID-19 were admitted. As this is a retrospective study, the Committee do not need any patient consent forms. As all of the patients in our study died during their hospital stay due to COVID-19 and the data obtained were done by file scanning, patient consent was not obtained in this retrospective study.

The demographic characteristics and comorbidities of all patients were obtained from electronic hospital database. Patients with hematological malignancies were not included in the study as it may affect the NLR result. Age, gender, time to mortality after hospitalization, neutrophil count, CRP, neutrophil-to-lymphocyte ratio (NLR), CRP/albumin ratio (CAR), and D-dimer values were obtained from blood samples taken during hospitalization. Because blood was taken from the patients during their first hospitalization (prior to the use of corticosteroid), corticosteroids had no effect on NLR results. The NLR ratio was obtained by dividing the neutrophil level with the lymphocyte level. The CAR ratio was obtained by dividing the CRP level with the albumin level.

All hospitalized patients were treated according to the COVID-19 Treatment Guideline of the Turkish Ministry of Health, which can be reached at https://covid19.saglik.gov.tr/TR-66301/covid-19-rehberi.html. The guideline was updated in regular intervals, and our study was fulfilled in accordance with the changing procedures. In order to determine the factors affecting the duration of hospitalization, patients were divided into two groups as those who deceased within the first 10 days of hospitalization (Group I, ≤10 days) and those who deceased in the later period (Group II, >10 days). Severe cases were admitted to the intensive care unit (ICU), and more stable patients were hospitalized in service rooms. COVID-19 diagnosis was confirmed by real-time reverse transcriptase polymerase chain reaction (RT-PCR) test in addition to clinical features and computerized thoracic tomography (CT) findings.

Biochemical and hematological parameters were processed via blood samples taken from the patients during routine ICU and hospital ward follow-ups. CRP and albumin levels were analyzed via Roche COBAS 600, Diagnostic, Germany, R.D.G, using an original kit (Roche). Complete blood count parameters were analyzed with a Sysmex XN-1000 hematology analyzer (Kobe, Japan) and D-dimer levels were processed with Sysmex CS-2500 device.

Statistical Analysis

Statistical analyses were performed via Statistical Package for the Social Sciences 20.0 software (SPSS Inc., IL, USA). Student's *t*-test was used for pairwise comparison, and Mann–Whitney *U*-test was used in non-normal distribution. The median, interquartile range (IQR) was used to display continuous variables. The categorical variables were displayed as numbers and percentages (%). ROC analysis was performed to estimate mortality. Univariable and multivariable logistic

regression analyses were performed to predict survival of less than 10 days. The Backward logistic regression method was utilized.

ROC analysis was also performed to investigate the positive predictive power of NLR and CAR in the first 10 days. Sensitivity and specificity values were calculated. $P<0.05$ was considered statistically significant.

Result

Data from 1.516 patients have been analyzed within the scope of this research. A majority of the individuals (n=959, 63.3%) had deceased 10 days after hospitalization while 557 (36.7%) subjects had died after the first 10-day period. The mean age of the study group was 73.56 years (ranging between 18 and 101 years). The age distribution within the groups was as follows: Group I: 73.3 years and Group II: 74.0 years.

The mortality rate was higher in male patients (n=895, 59%) compared to females in both groups, but this finding was not significant ($p=0.587$). The average survival was 9.94 days from the time of admission.

Among the most common comorbid diseases were hypertension (HT) in 41%, coronary artery disease (cad) in 41.7%, asthma-chronic obstructive pulmonary disease (COPD) in 36.7%, diabetes Mellitus (DM) in 36.1%, cerebrovascular diseases in 9.5%, chronic renal failure (CRF) in 8.0% and malignancies in 5.9% study population. In addition, there was a significant difference in the diabetic individuals who were deceased within the first 10 days compared to the people with diabetes in Group II ($p=0.047$) (Table 1). Although there was no a significant difference in cases accompanied by airway diseases such as asthma and COPD, the p-value was very close to significance.

NLR and CAR values were significantly higher in Group I compared to Group II ($p<0.02$ and $p<0.001$, respectively). In addition, WBC, neutrophil, CRP and D-dimer levels were also significantly higher in Group I ($p<0.05$) (Table 2). The significant difference, as indicated in Table 2, between the statistically significant infection parameters of two groups, made us think that we should carefully monitor these markers in in-hospital death within the first 10 days.

Univariate logistic regression analysis revealed a significant relationship between Group I and WBC, neutrophil count, albumin, D-dimer, CRP, and DM (OR=0.96, 0.95, 1.05, 0.97, 1.00, and 0.80, respectively) (Table 3). Thus, multivariate logistic regression analysis showed that CRP and albumin were independent predictors of death in the first 10 days (Table 4).

As NLR and CAR values showed significant differences in the comparison analyses between the two groups, the diagnostic predictiveness of both parameters for COVID-19 was evaluated by ROC analyses. Logistic regression analysis was applied for NLR and CAR. The "area under the ROC Curve (AUC)" value obtained for NLR and CAR was

Table 1 Comparison of Demographic and Clinical Characteristics of All Cases Included in the Study

	All Patients N=1516	**Group 1, N=959 (63.3%)**	**Group 2, N=557 (36.7%)**	***P* value**
Age, mean	73.6	73.3	74.0	0.761
Gender (M/F)	895/621	565 (63.1%)/394 (63.5%)	330 (36.9%)/227 (36.6%)	0.587
Comorbidities				
DM	547 (36.1%)	364 (66.5%)	183 (33.5%)	0.047
Asthma/COPD	556 (36.7%)	368 (66.2%)	188 (33.8%)	0.072
CAD	632 (41.7%)	416 (65.8%)	216 (34.2%)	0.080
Malignity	89 (5.9%)	63 (70.8%)	26 (29.2%)	0.129
CVD	143 (9.5%)	97 (67.8%)	46 (32.2%)	0.237
HT	1066 (70.4%)	442 (70.9%)	624 (70.0%)	0.670
CRF	121 (8.0%)	52 (7.3%)	69 (8.3%)	0.660

Abbreviations: HT, hypertension; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; CVD, cerebrovascular diseases; CRF, chronic renal failure.

Table 2 Laboratory Results of All Cases Upon Admission to the Intensive Care Unit and in Hospital

	Group 1		Group 2		
	Mean ± SD	**Median (Min–max)**	**Mean ± SD**	**Median (Min–max)**	**P value**
WBC	11.82 ± 8.91	9.95 (0.19–183.48)	10 ± 5.39	8.84 (0.34–52.3)	<0.001
Neutrophil	9.95 ± 6.25	8.53 (0.14–46.19)	8.39 ± 4.96	7.24 (0.28–31.06)	<0.001
Lymphocyte	1.26 ± 6.04	0.83 (0.04–172.84)	1.03 ± 1.18	0.81 (0–20.09)	0.547
Platelet	217.85 ± 99.84	203 (17–748)	223.21 ± 89.06	211 (13–793)	0.141
NLR	14.79 ± 15.18	10.14 (0.02–161.4)	13.56 ± 13.83	9.21 (0.47–87.21)	0.023
CAR	4.31 ± 3.03	3.87 (0.07–17.82)	3.64 ± 2.69	3.25 (0.07–17.68)	<0.001
Albumin	31.53 ± 5.43	32.1 (7.56–47.6)	32.86 ± 4.8	33.2 (16.58–47.12)	<0.001
CRP	129.13 ± 84.12	120 (3.11–448)	113.73 ± 80.23	104 (3.11–465)	<0.001
D-Dimer	4.9 ± 8.4	1.7 (0.2–36.8)	3.4 ± 6.7	1.3 (0.2–36.5)	<0.001

Note: $p<0.05$ is statistically significant.
Abbreviations: NLR, neutrophil-to-lymphocyte ratio; CAR, CRP/albumin ratio; CRP, C-reactive protein. Continuous variables are presented as median values; IQR, interquartile ranges and nominal variables as frequencies.

Table 3 Relationship Between First 10 Days of Death and Other Variables Using Univariate Logistic Regression Analysis

	OR	**95% CI**	***P* value**
WBC	0.96	0.94, 0.97	<0.001
Platelet	1.00	1.00, 1.00	0.32
Lymphocyte	0.98	0.89, 1.01	0.49
Neutrophil	0.95	0.93, 0.97	<0.001
Albumin	1.05	1.03, 1.08	<0.001
D-Dimer	0.97	0.96, 0.99	0.001
Ferritin	1.00	1.00, 1.00	0.076
CRP	1.00	1.00, 1.00	<0.001
DM	0.80	0.64, 1.00	0.047
HT	0.94	0.75, 1.18	0.59
COPD/Asthma	0.82	0.66, 1.02	0.072
CRF	1.06	0.72, 1.55	0.76
CAD	0.83	0.67, 1.02	0.080
Malignity	0.70	0.43, 1.10	0.13
CVD	0.80	0.55, 1.15	0.24

Abbreviations: WBC, white blood cell; CRP, C-reactive protein; DM, diabetes mellitus, HT, hypertension; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; CAD, coronary artery disease; CVD, cerebrovascular diseases.

Table 4 Relationship Between First 10 Days of Death and Other Variables Using Multivariate Logistic Regression Analysis

Variable	OR	95% CI	*P*
CRP	1.00	0.99, 1.00	0.003
Albumin	1.06	1.02, 1.10	0.002

statistically significant. NLR and CAR variables were subject to univariate logistic regression and odds ratios (ORs) were calculated with a 95% confidence interval (Figure 1 and Table 5).

When the "cut-off" values for both parameters and the sensitivity and specificity values of these "cut-off" values were examined; ≥5.74 for NLR and ≥4.27 CAR were found to express better diagnostic predictivity for COVID-19 compared to other parameters (sensitivity= 33%, Specificity 74% for NLR; sensitivity 67%, specificity 45% for CAR).

Discussion

This research was the first of its kind as it was the only study to analyze deceased COVID-19 patients and categorize them according to the period from hospitalization to death. More than one-third of all patients who died due to COVID-19 had CAD, asthma/COPD, DM as comorbid diseases while malignancies and CVD were less associated. Djaharuddin et al evaluated comorbid diseases affecting mortality in COVID-19 patients, and showed that comorbid diseases such as hypertension, diabetes, and cardiovascular diseases significantly affected mortality.[8] In our study, hypertension was the dominant comorbidity in patients who were deceased due to COVID-19. In addition, there was a significant difference in diabetic individuals who died within the first 10 days compared to the diabetic patients in Group II indicating that COVID-19 cases accompanied by diabetes need to be followed more closely. Another study conducted in the USA showed that hospitalization was higher in COVID-19 patients with diabetes.[9] Asthma and COPD should also be monitored cautiously as respiratory distress plays a major role in mortality.[10] In addition, there are studies in which some risk scores are used to estimate the critical illness and death rate.[11] In the current study, we have elaborated that higher NLR, CAR WBC and CRP values predicted mortality earlier than other parameters. In a previous article evaluating only COVID-19 cases hospitalized in intensive care, the majority of deaths were at older age and in male gender, in line with our study. They admitted that >70 years of age was defined as the high-risk group, similar to our results.[12] In previous studies, the neutrophil/lymphocyte ratio (NLR) has been demonstrated as an important marker both

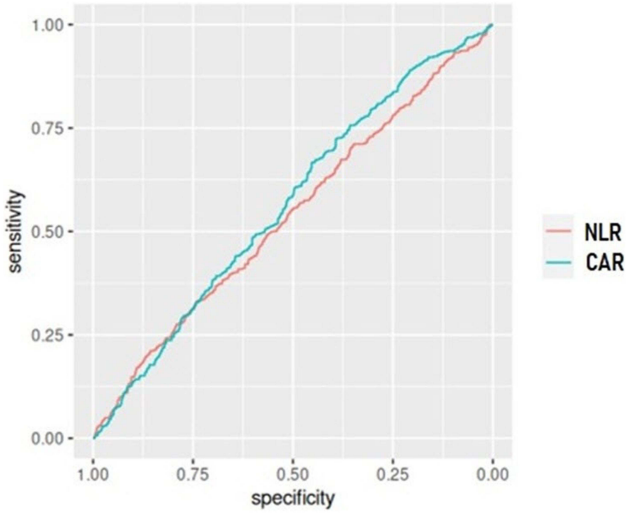

Figure 1 ROC analysis of NLR and CAR values for predicting COVID-19.

Table 5 AUX and Sensitivity/Specificity Values for NLR and CAR

Predictor	Optimal Cut-off	Direction	AUC	Sensitivity	Specificity
NLR	5.74	≤	0.54	0.33	0.74
CAR	4.27	≤	0.56	0.67	0.45

in mortality and in the severity of the disease.[13] NLR is an easily available, inexpensive parameter that provides insight for the cellular immune and systemic inflammatory response. It has been shown that NLR was beneficial especially in cases of severe pneumonia in the progression to "cytokine storm" and acute respiratory distress syndrome (ARDS) caused by the overstimulated immune system.[14,15] The clinician should keep in mind that, NLR may be an early indicator of clinical deterioration and hence monitor patients more closely.[16] CRP has been found to be high in the vast majority of COVID-19 patients and associated with the severity of the disease.[17] In a retrospective study conducted in China, it was suggested that CRP level at admission might be important in defining the severity of the disease.[18] In another study by Zhang et al, it was shown that high CRP levels at the time of hospitalization were an independent risk factor for mortality in COVID-19 patients.[19] On the other hand, CRP may be positioned as an early marker for mortality. In our study, the time of death was earlier in patients with high CRP, than in other groups.

CAR is a recently identified inflammatory marker. It is valuable in the study of mortality in intensive care patients.[20] COVID-19 has a heterogeneous spectrum among individuals ranging from mild cases to severe respiratory failure and mortality. At this stage, the importance of CAR is far more valuable as it could be achieved even with limited medical resources. CAR could be utilized as a prognostic biomarker to differentiate COVID-19 patients who may develop very severe illnesses and predict mortality. In our study, we have found that in patients with elevated CAR, the time of death was earlier.

The results of logistic regression analysis for NLR and CAR have shown that both parameters were valuable for predicting early or late time of death in patients hospitalized with a diagnosis of COVID-19. To the best of our knowledge, our research is significant with respect to emphasizing the predictivity of NLR and CAR from hospitalization time to mortality.

In a study conducted by Zang et al, significantly higher D-dimer levels were found in COVID-19 cases who died, compared to those who survived. In parallel with this, in our study, D-dimer levels were significantly higher in Group I.[21]

In addition, there are studies showing that low albumin was also correlated with the severity of the disease in COVID-19 cases.[22] Therefore, it is important to monitor albumin levels in order to have an idea about the clinical course of the patients.

The main limitation of our study could be attributed to being a single-center study. More prospective studies with larger sample sizes must confirm the relationship between in-hospital death and the NLR and CAR ratio in COVID-19 patients.

Conclusion

NLR and CAR may have a decisive influence in determining the length of stay in hospital for patients who die in hospital due to COVID-19. In addition, it is recommended that COVID-19 cases with diabetes be followed closely.

Abbreviations

AUC, area under the curve; CAD, coronary artery disease; CAR, CRP/albumin ratio; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; CRP, C-reactive protein; CT, computerized thoracic tomography; CVD, cardiovascular diseases; DIC, disseminated intravascular coagulopathy; DM, diabetes mellitus; HT, hypertension; ICU, intensive care unit; IQR, interquartile range; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; ROC, receiver operating characteristics; RT-PCR, real-time reverse transcriptase polymerase chain reaction; SARS CoV-2, severe acute respiratory syndrome coronavirus-2; SPSS, statistical package for the social sciences; WBC, white blood cells; WHO, World Health Organization.

Ethical Declaration

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted by our institution, and informed consent has been obtained from all participants.

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The authors declare that they have no competing interests in this work.

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