ORIGINAL ARTICLE

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The Effect of Uric Acid/Albumin Ratio on Prognosis of Patients Followed Up with COVID-19 Diagnosis

Ürik Asit/Albümin Oranının COVID-19 Tanısı ile Takip Edilen Hastaların Prognozuna Etkisi

Başak ÇAKIR GÜNEY[1], İrfan KÜÇÜK[2], Bünyamin GÜNEY[3], Nurgül TÜKEL[1], Zeliha SERİNDAĞ[1], Yeşim ÖNAL TAŞTAN[1], Ahmet Emre KALAMAN[1], Mustafa KAPLAN[4]

[1]*Sultan 2. Abdulhamid Han Training and Research Hospital, Clinic of Internal Medicine, İstanbul, Türkiye*
[2]*University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar Training and Research Hospital, Clinic of Gastroenterology, İstanbul, Türkiye*
[3]*İstanbul Training and Research Hospital, Clinic of Medical Oncology, İstanbul, Türkiye*
[4]*Sultan 2. Abdulhamid Han Training and Research Hospital, Clinic of Gastroenterology, İstanbul, Türkiye*

ABSTRACT

Aim: The aim of this study was to investigate the effect of the uric acid to albumin ratio (UAR) on prognosis in Coronavirus Disease 2019 (COVID-19) patients followed up in the intensive care unit (ICU) and wards.

Materials and Methods: A single center, retrospective study was organized to observe the UAR values of 204 COVID-19 patients (>18 years of age) hospitalized at the Sultan 2. Abdulhamid Han Training and Research Hospital between May 1, 2020 and April 1, 2022. Patients were divided into two groups according to UAR, as low and high UAR groups, using Receiver Operating Characteristic curve analysis to determine the optimal cut-off value for UAR. The cut-off value was determined as 1.63. Demographic clinical characteristics and laboratory parameters of the participants during their hospitalization were retrospectively obtained from the hospital's electronic medical records.

Results: Patients with high UAR (≥1.63) required longer ICU hospitalization (14.5% vs. 51%, p<0.001) and showed higher in-hospital mortality (0.05% vs. 43.5%, p<0.001).

Conclusion: In this study, we have concluded that UAR is a useful tool independent of other parameters in predicting in-hospital mortality in patients with COVID-19 followed in ICU and wards.

Keywords: UAR, COVID-19, prognosis, mortality

ÖZ

Amaç: Bu çalışmada, yoğun bakım ünitesinde (YBÜ) ve servislerde takip edilen Koronavirüs Hastalığı 2019 (COVID-19) hastalarında asit albümin oranının (UAR) prognoz üzerine etkisinin araştırılması amaçlandı.

Gereç ve Yöntem: 2. Abdülhamid Han Eğitim ve Araştırma Hastanesi'nde 1 Mayıs 2020 1 Nisan 2022 tarihleri arasında yatan 204 COVID-19 hastasının (>18 yaş) UAR değerlerini gözlemlemek için tek merkezli, retrospektif bir çalışma düzenlendi. Hastalar, UAR için optimal kesme değerini belirlemek üzere Alıcı İşletim Özelliği eğrisi analizi kullanılarak UAR'ye göre düşük ve yüksek UAR grupları olmak üzere iki gruba ayrılmıştır. Kesme değeri 1,63 olarak belirlendi. Katılımcıların hastanede yattıkları süre boyunca demografik klinik özellikleri ve laboratuvar parametreleri hastanenin elektronik tıbbi kayıtlarından retrospektif olarak elde edilmiştir.

Bulgular: Yüksek UAR (≥1,63) olan hastalar daha uzun süreli YBÜ yatış gerektirmiş (%14,5'e karşı %51, p<0,001) ve daha yüksek hastane içi mortalite (%0,05'e karşı %43,5, p<0,001) göstermiştir.

Address for Correspondence: Başak ÇAKIR GÜNEY MD, Sultan 2. Abdulhamid Han Training and Research Hospital, Clinic of Internal Medicine, İstanbul, Türkiye
E-mail: dr.bskckr@gmail.com **ORCID ID:** orcid.org/0000-0003-2389-2833
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Sonuç: Bu çalışmada, YBÜ ve servislerde takip edilen COVID-19 tanılı hastalarda, diğer parametrelerden bağımsız olarak, UAR'nin hastane içi mortaliteyi öngörmek için yararlı bir araç olduğu sonucuna varılmıştır.

Anahtar Kelimeler: UAR, COVID-19, prognoz, mortalite

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) emerged in China in December 2019 and was accepted by the World Health Organization as a pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) on March 11, 2020, and has caused the death of millions of people since its emergence[1,2]. While most of the COVID-19 patients recover without any complications, a significant number of patients face serious complications and death. Patients with COVID-19 present with a variety of symptoms as well as different prognoses, including recovery, intensive care unit (ICU) admission, and death. While only fever and cough can be seen in mild cases, critical cases can be seen in various presentation such as Acute Respiratory Distress Syndrome (ARDS), sepsis or septic shock. Early detection of high-risk patients likely to develop critical illness is essential to allocate limited resources to treat the disease[3].

It is known that immunosuppression, malignancy, diabetes, and hypertension (HT) adversely affect the prognosis in COVID-19 patients and cause high mortality[4]. A severe and uncontrolled immune inflammatory response is an effective predictor of disease severity and poor prognosis. Many different serological markers have been identified as the indicators of inflammatory response. In previous studies, C-reactive protein (CRP), erythrocyte sedimentation rate (erythrocyte sedimentation rate), ferritin, proinflammatory cytokines in addition to lactate dehydrogenase (LDH), D-dimer, and high-sensitivity cardiac troponin I were determined to be predictors of serious morbidity and mortality[5-7]. Albumin is an important molecule in the body's defense mechanisms, which plays a role in antiinflammation, antiapoptosis and protection of the body from oxidative stress[8,9]. Low albumin level was also found to be significant in predicting disease severity and mortality in previous studies[10-13].

Uric acid (UA) is a catabolic product of purine from RNA and DNA as a metabolic index, it is less affected by other factors than drugs and high purine diet. Previous studies have shown that UA is closely related to the activation of the immune system and scavenging of free oxygen radicals[14-16]. High UA levels can be detected in chronic diseases such as HT, diabetes, chronic kidney disease, obesity, and gout. In addition, hyperuricemia was found to be associated with increased mortality in these diseases[17,18]. It has been reported that kidney and gastrointestinal involvement rates are high in COVID-19 patients. Since the kidneys and intestines are both targets of SARS-CoV2 and primary sites of UA excretion, serum UA concentrations have been shown to be lower in patients with COVID-19 disease. Hypouricemia has also been found to be strongly associated with poor prognosis and mortality[19-23]. However, it is known that hyperuricemia is associated with hypoxia and systemic inflammation in respiratory tract diseases, and some studies have found that both hyperuricemia and hypouricemia are associated with increased mortality[3,24].

In recent studies, systemic immune inflammatory indices such as neutrophil lymphocyte ratio (NLR), derived neutrophil to lymphocyte ratio, platelet lymphocyte ratio (PLR), monocyte lymphocyte ratio and systemic inflammatory index (SII) have been shown to be useful in predicting disease severity and mortality in COVID-19[25-27]. Uric acid to albumin ratio (UAR) is an index that has been shown to predict prognosis in many diseases such as acute renal failure, pneumonia, and acute coronary diseases, and unlike these diseases, there is no study conducted in COVID-19 patients. In this study, we planned to investigate the effect of UAR on prognosis in COVID-19 patients followed in ICU and other wards[28-30].

MATERIALS AND METHODS

Patient Selection

COVID-19 patients (>18 years old), hospitalized at the Sultan 2. Abdulhamid Han Training and Research Hospital in the internal medicine clinic between May 1, 2020 and April 1, 2022 were the main focus of this single-center, retrospective study. COVID-19 diagnoses were made by a positive result from a real-time reverse transcriptase (RT) polymerase chain reaction (PCR) assay of nasal and pharyngeal swab specimens. Patients who had negative RT-PCR results or patients using drugs to decrease serum UA level and patients under 18 years old were excluded from the study. Ethics committee approval for the study was obtained from the University of Health Sciences Türkiye, Hamidiye Clinical Research Ethics Committee (decision no: E-46418926-050.99-133138, date: 31.05.2022).

Statistical Analysis

The power analysis of the study was performed with G*Power 3.1.9.4. When the effect size d: 0.5, α err prob: 0.04, Power (1-β error prob): 0.964, the total sample size was found to be 204. For the study, 364 patients who were followed up with a diagnosis of COVID-19 were screened and patients with undesirable UA levels during hospitalization were excluded from the study. When the number of 204 patients identified

after power analysis was reached, data collection was terminated through the system. The patients were divided into two groups according to UAR as the low and high UAR groups.

The demographic, clinical characteristics and laboratory parameters of the participants during their hospitalization were retrospectively obtained from the hospital's electronic medical records. The duration of follow up in the ICU, the treatments they received, and the duration and doses of these treatments were recorded.

Laboratory Analysis

Blood samples were obtained on the first day of the Sultan 2. Abdulhamid Han Education and Research Hospital admission. Immediately after sampling, complete blood count parameters were determined by a hematology analyzer (ABX Pentra DX 120). Serum UA and albumin levels were measured using a Roche Diagnostics Cobas 8000 c502 analyzer (Roche Holding AG, Basel, Switzerland). Serum albumin level was determined using the bromocresol green method.

ICU Evaluation Criteria

The patients were admitted to the ICU according to the following criteria: 1) Meeting criteria for ARDS or needs O^2 >6 liters per minute to maintain SpO^2 >92% (or rapid escalation of oxygen requirement), 2) Respiratory rate>30 per minute, 3) Systolic blood pressure <90 mmHg, mean arterial pressure <65 mmHg, tachycardia and other signs of shock, 4) Arterial blood gas with pH <7.3 or partial CO^2 pressure >50 mmHg or above patient's baseline, lactate >2 mmol/liter, 5) Concerning clinical appearance (cyanosis fast breathing, grunting, chest indrawing, inability to drink, lethargy, convulsions, mottled or cool skin). The decision of ICU admission was based on the criteria by Brigham and Women's Hospital COVID-19 guidelines which were updated on December 20, 2020[31].

RESULTS

The primary outcome was defined as all cause in-hospital mortality in this study. The secondary outcome was defined as ICU admission.

Continuous variables were presented as mean (standard deviation) or median (interquartile range), or median interquartile range (25^{th} to 75^{th}) according to data distribution, and as absolute number (and percentage) for categorical variables; the distribution was tested with the Shapiro-Wilk test. ROC curve was used to determine the optimal cut-off value (by Youden index) for UAR. Differences between patient outcomes were studied with t-test for independent groups or with the Mann-Whitney U test if non-parametric analysis was required.The evaluation of differences between groups of categorical data was carried out with the chi-square statistics. In order to calculate the probability of mortality for patients admitted to the ICU, binary logistic regression analysis was used. Stepwise binary logistic regression was employed, where variables with p<0.05 were included in the multivariable model. The effect on mortality (survival) over time was investigated with the Kaplan-Meiere (Log-Rank-Mante Cox) and Cox Regression in the Statistical Analysis field. All confidence intervals were established at 95%; two-tailed significance level was established to be <0.05. Statistical data analysis was performed using the R v4.01(Vienna; Austria) with "rms" "hmisc" "epi" "survival" "ggfortify" packages.

Two hundred and four patients with COVID-19 (PCR positive) who were followed in hospital were included in the study. ROC curve analysis was made to determine optimal cut-off value for UAR. According to the ROC analysis, optimal cut-off with highest Youden index was found as 1.63 (Figure 1). Sensitivity of this cut-off value for in-hospital mortality was 86%, while specificity was 71%. Patients were divided into two groups as low UAR and high UAR regarding this cut-off value. Comparison of baseline characteristics, laboratory parameters and duration of hospitalization for these two groups were given in Table 1. The first group (UAR <1.63) included 119 patients, while the higher UAR group (≥1.63) included 85 patients. Although the mean age for the general population was 63±16.3 years, the mean age was 57.4±15.9 years in the low UAR group, and 70.9±13.2 in the high UAR group (p<0.001). Variables including the presence of HT, diabetes mellitus (DM),

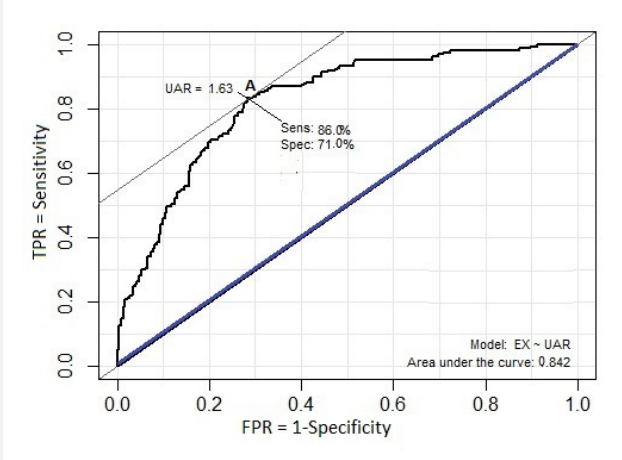

Figure 1. ROC curve of UAR for predicting in-hospital mortality

Navy blue line: a diagnostic test with the lowest discriminatory ability, which is no better than chance, area under the curve (AUC) =0.5, black line: a test with good discriminatory ability (AUC =0.842 x-axis: coordinate points with 1 - specificity y-axis: sensitivity as the all cut-off values measured from the test results, A: Youden Index cut-off point (reference) value, UAR: Uric acid albumin ratio, FPR: False positive rate, TPR: True positive rate

chronic heart failure, coronary artery disease, and male gender were comparable between the low and high UAR groups (p=0.71, p=0.64, p=0.73, p=0.22, and p=0.08, respectively), whereas chronic obstructive pulmonary disease and chronic renal disease frequencies were found to be higher in the high UAR group (p=0.02 and p<0.001, respectively), while glomerular filtration rate (GFR) was lower in the high UAR group (80.60±21 vs. 58.5±24, p<0.001). Inflammatory laboratory markers including CRP, ferritin, D-dimer, white blood cell count (WBC), UA, creatinine, aspartate aminotransferase (AST) and LDH levels were found to be higher in the high UAR group (p<0.001, p=0.002, p=0.002, p=0.002, p<0.001, p<0.001, p=0.003, and p<0.001, respectively). Albumin, GFR, lymphocyte count, and hemoglobin level demonstrated lower levels in the high UAR group (p<0.001, p<0.001, p=0.007, and p<0.001 respectively). Patients with high UAR required more ICU admission (14.5% vs. 51%, p<0.001) and demonstrated higher in-hospital mortality (0.05% vs. 43.5%, p<0.001). There was a significant difference in mortality between the two groups. We predicted that the difference in age and renal failure rate between the two groups significantly affected mortality.

Univariable logistic regression analysis to predict in-hospital mortality is present in Table 2. The parameters included in univariable logistic regression analysis were as follows: UA level, albumin level, UAR, age, creatinine level, CRP, AST, LDH, ferritin, hemoglobin, D-dimer levels, and leucocyte count. Among these variables, UA, albumin, CRP, AST, LDH, D-Dimer, ferritin, hemoglobin levels, UAR, age and leucocyte count were related to in-hospital mortality in univariable logistic regression analysis (p<0.001 for all).

Table 1. Comparison of basal characteristics, laboratory parameters and hospitalization duration between the high UAR and low UAR groups

Variable	All patient	Low UAR group (n=119)	High UAR group (n=85)	p-value
Age (mean ± SD)	63±16.3	57.4±15.9	70.9±13.2	p<0.001*
Gender (male) (n, %)	125 (61.2%)	67 (56.3%)	58 (68.2%)	0.08**
Hypertension (n, %)	29 (14.2%)	16 (13.4%)	13 (15.3%)	0.71**
DM (n, %)	14 (6.9%)	9 (7.6%)	5 (5.9%)	0.64**
COPD (n, %)	7 (3.4%)	1 (0.8%)	6 (7.1%)	0.02**
CRF (n, %)	35 (17.2%)	6 (5%)	29 (34.1%)	p<0.001**
CAD (n, %)	14 (6.9%)	6 (5%)	8 (9.4%)	0.22**
CHF (n, %)	4 (2%)	2 (1.7%)	2 (2.4%)	0.73**
Uric acid (mg/dL) (mean ± SD)	5.9±3.3	4.5±0.9	7.8±4.3	p<0.001*
Albumin (g/L) (mean ± SD)	3.3±0.7	3.6±0.6	2.8±0.6	p<0.001*
Hospitalization (mean ± SD)	10±6.9	10.1±6.4	11.7±7.6	0.10*
Creatinine (mg/dL) (mean ± SD)	1.2±0.9	1±0.3	1.5±1.3	p<0.001*
GFR (mL/dL/1.73 m^2) (mean ± SD)	71.5±25	80.6±21	58.5±24	p<0.001*
AST (U/L) (mean ± SD)	79.1±182	54±73	114±268	0.03*
LDH (U/L) (mean ± SD)	763±755	591±353	944±1017	p<0.001*
CRP (mg/dL) (mean ± SD)	109±89	81±80	149±88	p<0.001*
Ferritin (ng/mL) (mean ± SD)	1546±4400	714±2020	2739±6280	0.002*
D-dimer (µg/L) (mean ± SD)	2827±5190	2100±4600	3870±5745	0.002*
WBC (mm^3) (mean ± SD)	6380±4470	5470±3190	7700±6180	0.002*
Lymphocyte (mm^3) (mean ± SD)	1040±660	1150±590	880±740	0.007*
Hemoglobin (g/dL) (mean ± SD)	11.1±2.1	11.7±2.1	10.3±1.9	p<0.00**
Platelet ($10^3/mm^3$) (mean ± SD)	193±101	200±101	183±101	0.25*
ICU admission (n, %)	61 (30.3%)	17 (14.5%)	44 (51%)	p<0.001**
In-hospital mortality (n, %)	43 (21%)	6 (0.05%)	37 (43.5%)	p<0.001**

UAR: Uric acid to albumin ratio, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, CRF: Chronic renal failure, CAD: Coronary artery disease, CHF: Chronic heart failure, GFR: Glomerular filtration rate, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, CRP: C-reactive protein, WBC: White blood cell, ICU: Intensive care unit, *Student's t-test, **Chi-square test

Table 2. Univariable and multivariable logistic regression analysis (modeling to binary) to predict in-hospital mortality

	Univariable			Multivariable		
Variable	**Odds ratio**	**Confidence interval**	**p-value***	**Odds ratio**	**Confidence interval**	**p-value***
UAR	4.650	2.660-8.150	<0.001	3.300	1.570-6.981	0.002
Age	1.700	1.050.1.100	<0.001	1.120	1.040-1.200	0.003
Creatinine (mg/dL)	1.030	0.700.1.500	0.88	-	-	-
CRP (mg/dL)	1.009	1.004-1.010	<0.001	1.001	0.990-1.011	0.81
AST (U/L)	1.008	1.003-1.01	<0.001	1.003	0.99-1.011	0.61
LDH (U/L)	1.003	1.002-1.004	<0.001	1.004	1.002-1.006	0.81
WBC (mm^3)	1.002	1.001-1.003	<0.001	1.002	1.001-1.002	0.03
D-dimer (µg/L)	1.002	1.001-1.003	<0.001	1.001	0.999-1.002	0.07
Ferritin (ng/mL)	1.002	1.001-1.003	<0.001	1.000	0.999-1.001	0.27
Hemoglobin (g/dL)	0.590	0.480-0.720	<0.001	0.686	0.471-1.001	0.06

UAR: Uric acid albumin ratio, CRP: C-reactive protein, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, WBC: White blood cell, *Univariable and Multivariable logistic regression analysis

In Table 2, multivariate logistic regression analysis to predict in-hospital mortality was given. The variables UAR, age, AST, LDH, CRP, ferritin, D-dimer, WBC, ferritin, and hemoglobin were included in the analysis. Among these variables, UAR, older age and WBC count independently predicted the in-hospital mortality (p=0.002, p=0.003, and p=0.03, respectively). The distribution of UAR levels for survivor (n=161) and non- survivor (n=43) was given in Box/Violin Plot (Figure 2). Wider distribution of UAR with a higher mean level was observed with this plot. The effect of UAR (reference: <1.63) on mortality over time (survival) was statistically significant (Kaplan-Meiere; 96.086±8.273 versus 17.065±1.623; Log-Rank (Mantel-Cox) p<0.0001; Figure 3). The mortality rate of patients with high UAR values over time was 3.164 times higher than the other patients [Cox Regression; Exp (b)= 3.164 (1.883-5.317); p<0.0001].

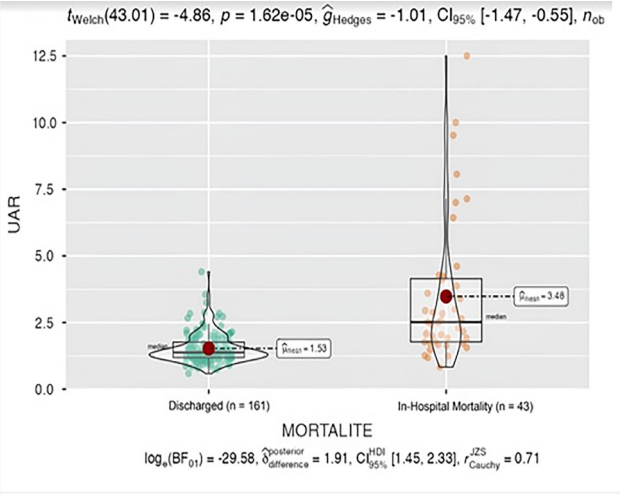

Figure 2. Box and Violin plot of UAR for discharged and in-hospital mortality. The median and mean values of patients who were discharged are close to each other, with the median and quartiles also being relatively close. The majority of the data are distributed between the median and the mean. In contrast, in patients with in-hospital mortality, the UAR value increases, the distribution is more elongated with extreme values emerge. It is seen that there is a statistical difference between the UAR levels of the discharged and in-hospital mortality

UAR: Uric acid albumin ratio, CI: Confidence interval

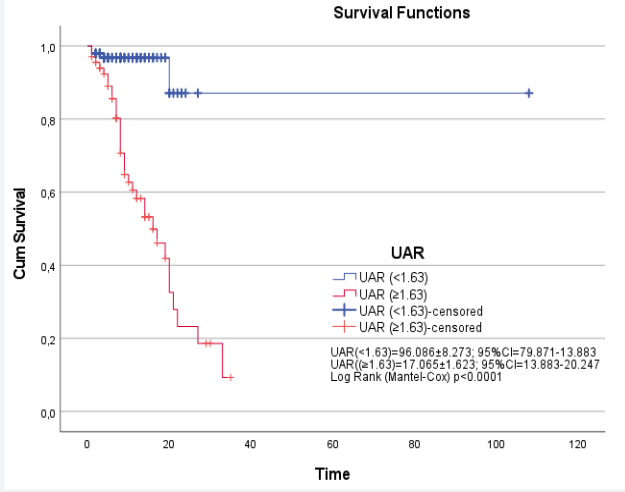

Figure 3. Kaplan-Meier curves to assess the association between UAR and mortality over time

UAR: Uric acid albumin ratio

DISCUSSION

Since its emergence, COVID-19 has emerged with a pandemic that has arisen with a wide spectrum ranging from mild symptoms such as cough and fever to pneumonia, severe respiratory distress, need for care, and it still continues[1-3]. The course of COVID-19 in this wide range varies according to the basal characteristics of the patient (gender, age, HT, DM etc.). Moreover, COVID-19 affects the respiratory, urinary and gastrointestinal systems at different levels in patients, and it affects the blood values of the patients, especially the inflammation markers, at different levels. This shows the course of the disease and is a predictor for the course of the disease[4-6].

One of these parameters is albumin, and some studies have shown that low albumin levels are associated with high mortality[10-13]. It has been shown in previous studies that albumin is decreased in malnutrition and as a negative acute phase reactant secondary to inflammation, and hypoalbuminemia has been shown to be associated with mortality even in the general population[32,33]. Hypoalbuminemia may be due to the presence of a systemic inflammatory condition and malnutrition in COVID-19. It is known that due to increased capillary permeability due to inflammation, serum albumin may be extravasated into the interstitial space and the volume distribution of albumin increases[34,35].

In a study conducted by Shoji et al.[36] in 2024, it was shown that the risk of serious disease was higher in diabetic patients infected with COVID-19 due to hypoalbuminemia, as assessed by the blood albumin level at the time of diagnosis.

Another parameter affected by COVID-19 is UA. In previous studies, hypouricemia has been shown as a poor prognostic factor in patients with intra-abdominal sepsis[37], radiation pneumonitis[38] and COVID-19[19-23]. It remains unclear whether the poor outcomes, particularly in COVID-19 patients, are due in part to a lack of antioxidants. Hyperuricemia has also been found to be associated with a variety of diseases, including coronary heart disease [39], HT[40], kidney failure[41], and exacerbations of chronic obstructive pulmonary disease[42]. This may be due to the direct pathophysiological effects of high UA concentrations, such as increased oxidative stress, inflammation, endothelial dysfunction, activation of the renin angiotensin aldosterone system, and insulin resistance[43]. In addition, there are studies showing that both hypouricemia and hyperuricemia increase mortality in COVID-19 patients[3,24]. Although hypouricemia and hyperuricemia are thought to be related to the increase in mortality in COVID-19 patients due to the reasons mentioned above, these reasons are open to discussion.

UAR has been shown to predict mortality in various diseases, alongside indices such as NLR, PLR, C-reactive protein albumin ratio (CAR), and SII[25-27]. In studies, it has been shown that it is a better predictor of mortality than CAR in some patient groups such as non-ST-elevation myocardial infarction[30].

In a study conducted by Ertan et al.[44] in 2024, it was shown that the UAR associated with 28-day mortality in patients with acute kidney injury developing in the ICU was important in showing mortality with 39.3% sensitivity and 84.1% specificity.

This study evaluated UAR as a predictor of mortality in COVID-19 patients. Patients were divided into the low and high UAR groups based on a ROC analysis, determining the cut-off value. Results showed that patients with high UAR were associated with more ICU admissions. UAR independently predicted in-hospital mortality. These findings suggest that UAR may be a valuable, accessible parameter for risk stratification in ICU and ward patients with COVID-19. Future studies with larger datasets are needed to validate these findings.

Study Limitations

Firstly, the retrospective nature of this single center study is one of its limitations. Secondly, this study had a relatively small number of patients. Thirdly, we only analyzed serum concentrations of UA and albumin on admission and did not have access to follow up measurements over time. Another limitation is that, unlike other biomarkers, there is no consensus on the standard cut-off values of UAR. Therefore, future studies including larger data sets are needed to test the results of our study.

CONCLUSION

UAR is a useful ratio that can be easily calculated with routine blood tests. In this study, we showed that UAR could independently predict hospital mortality in patients diagnosed with COVID-19, followed in the ICU and onwards.

Ethics

Ethics Committee Approval: Ethics committee approval for the study was obtained from the University of Health Sciences Türkiye, Hamidiye Clinical Research Ethics Committee (decision no.: E-46418926-050.99-133138, date: 31.05.2022).

Informed Consent: The main focus of this single-center, retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.Ç.G., N.T., Z.S., Y.Ö.T., A.E.K., M.K., Concept: B.Ç.G., N.T., Z.S., Y.Ö.T., A.E.K., M.K., Design: B.Ç.G., İ.K., M.K., Data Collection or Processing: B.Ç.G., N.T., Z.S., Y.Ö.T., A.E.K., M.K., Analysis or Interpretation: İ.K., Literature Search: B.Ç.G., İ.K., B.G., N.K., Z.S., Writing: B.Ç.G., İ.K., B.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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