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Can the blood urea nitrogen to serum albumin ratio predict a prolonged hospital stay in patients with acute cholecystitis?

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Abstract

Aim: The blood urea nitrogen to serum albumin ratio (BAR) is a biomarker of acute pulmonary embolism, pneumonia, critical illness, and prognostic mortality in geriatric patients. Hospital stay of patients with acute cholecystitis is prolonged according to the severity of the disease. We evaluated the predictive ability of BAR for prolonged hospital stay in acute cholecystitis.

Materials and Methods: This study was designed retrospectively and evaluated data collected at an emergency department from January 5, 2022, through April 5, 2022. Patients stayed in the hospital for eight days or longer were categorized as having a prolonged hospital stay, while those staying for seven days or less were considered to have an expected hospital stay. The receiver operating characteristic assessment was undertaken to establish the extent to which the investigated variables predicted prolonged hospital stay.

Results: The study was conducted over the data of 220 patients. The mean age (25th-75th percentile) was 59.0 (43.8-71.0) years, and 109 (50 %) patients were female. During the one-month follow-up, four (2 %) patients died. In total, 86 patients underwent surgery. The odds ratio for predicting prolonged hospital stay was found to be 4.88 [95% confidence interval (CI): 1.66-14.37, p=0.002] for BAR, 2.81 (95% CI: 1.36-5.78, p=0.004) for blood urea nitrogen, and 0.13 (95% CI: 0.04-0.38, p<0.001) for albumin.

Conclusion: The BAR calculated during the initial presentation to the emergency department can anticipate extended hospital stays in patients with acute cholecystitis.

Introduction

The gallbladder inflammation with or without stones is acute cholecystitis. Although it can occur at any age, it is most often seen between the fourth and eighth decades of life and more common in women. Mortality rate is about 1% [1]. Patients present with symptoms such as vomiting, fever, nausea, pain in the right upper quadrant, loss of appetite, tenderness, and chills. The history, physical examination, laboratory, and radiological imaging results should be evaluated together to make a diagnosis [2,3]. Ultrasonography is the most preferred imaging method with a sensitivity of 90-95%, and hepatobiliary scintigraphy is the gold standard diagnostic test. Surgical intervention may be required in treatment. Tokyo guidelines 2018 (TG18) classify severity of acute cholecystitis as grade 1, grade 2, and grade 3 [2]. Early treatment is important because late treatment can cause more complications and undesirable outcomes. Extended hospital stays are observed in cases of severe acute cholecystitis, leading to elevated expenses. Being able to forecast the duration of patients' hospitalization will provide valuable data of significance.

The blood urea nitrogen (BUN) value changes depending on dehydration status, protein uptake and degradation, renal perfusion, or neurohormonal effects. BUN has been shown to be associated with poor outcomes in heart failure, critical illness, pneumonia, and acute cholecystitis [4,5]. The relationship between the severity of acute cholecystitis and increased BUN values has also been reported in previous studies [6].

The albumin level is known to have a relationship with food intake and body immunity [7]. It has also been associated with mortality in patients with COVID-19 and pneumonia [8,9]. It has been suggested that a low albumin level can assist in early diagnosis and predict surgical intervention requirement in patients with acute cholecystitis [10].

It is known that a high BUN to serum albumin ratio (BAR) is an important prognostic biomarker of mortal-

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ity in patients with critical illness, pneumonia, acute pulmonary embolism and advanced age [11,12].

In the literature, prolonged hospitalization in patients with acute cholecystitis has mostly been evaluated in relation to surgical operations. In the recent analysis, we hypothesized that BAR could predict prolonged hospital stay in patients with acute cholecystitis.

Materials and Methods

This study was designed retrospectively and evaluated data collected at an emergency department (ED) from January 5, 2022, through April 5, 2022. Patients that presented to the ED with complaints such as weakness, vomiting, abdominal pain, nausea, fever, and postprandial digestive system disorders and received a diagnosis of acute cholecystitis were screened. The study included individuals over the age of 18 with a confirmed diagnosis of cholecystitis through clinical, radiological, and laboratory assessments. Participants with incomplete data were excluded from the analysis. Patient age, gender, BUN and albumin values, survival status, length of hospital stay, comorbidities, and C-reactive protein (CRP), neutrophil, white blood cell (WBC), basophil, monocyte, red blood cell count, lymphocyte, eosinophil, hemoglobin, hematocrit, mean cell volume, mean corpuscular hemoglobin, mean erythrocyte hemoglobin concentration, platelet count (PLT), plateletcrit, platelet distribution width, red cell distribution width, alanine aminotransferase, aspartate aminotransferase, creatinine, direct bilirubin, total bilirubin, and indirect bilirubin values were recorded. The TG18 classification was formulated as follows: Grade III (dysfunction in $\geq$1 of the following): Respiratory dysfunction (PaO_2/FiO_2 ratio <300), cardiovascular dysfunction (hypotension requiring dopamine $\geq$5 µg/kg per min or any dose of norepinephrine), neurological dysfunction (disturbance of consciousness), hepatic dysfunction: PT-INR >1.5), hematological dysfunction (platelet count <100,000/mm^3), renal dysfunction (oliguria or creatinine >2.0 mg/dL. Grade II: ($\geq$2 of the following conditions): Abnormal WBC count (>12,000/mm^3 or <4,000/mm^3), age $\geq$75 years, high fever ($\geq$39°C/102.2°F), hypoalbuminemia (<0.7 x upper limit of normal), hyperbilirubinemia (total bilirubin $\geq$5 mg/dL). Grade I: Does not meet the criteria of Grade III or Grade II acute cholangitis at initial diagnosis. All the patients were followed up for at least one day. The hospitalization durations of the patients were found from the clinic register office system. Patients stayed in the hospital for eight days or longer were categorized as having a prolonged hospital stay, while those staying for seven days or less were considered to have an expected hospital stay. BAR was computed by separating the initial BUN by the baseline albumin value. Data on 28-day mortality were achieved from the clinic registry system and the federal death notification system. The study was conducted following the principles of the Declaration of Helsinki, and ethical agreement was provided by the local committee. Due to the retrospective design of the study and the use of no personal data, consent was not obtained from the case and control groups within the knowledge of the ethics committee.

Statistical analysis

Open-source software (Jamovi, Sidney, Australia, https://www.jamovi.org, v. 1.6.21) was used for the analyses of the data. Whether quantitative variables were normally distributed was checked with the Shapiro–Wilk test. continuous variables as median [interquartile range (IQR)] values, and categorical variables were presented as percentages, and chi-square test was conducted for the comparison of variables. The study groups were compared with the Mann Whitney U test in the presence of quantitative variables having an abnormal distribution. The receiver operating characteristic (ROC) assessment was undertaken to establish the extent to which the investigated variables predicted prolonged hospital stay. The ideal cut-off values of the parameters were defined using the Youden index. The odds ratio values were calculated to determine and compare the parameters in terms of their predictive abilities. The statistical significance limit was accepted as $p<0.05$.

Results

A total of 236 patients were initially identified, but 16 were excluded due to missing data. As a result, the study was conducted over the data of 220 patients. The flowchart of the study is presented in Figure 1. The patients were two groups as those with a prolonged hospital stay (eight days and over) and those with an expected hospital stay (seven days and less). During the one-month follow-up, 4 (2 %) of the patients died. The median age (25^{th}-75^{th} percentile) was 59.0 (43.8-71.0) years. There were 109 (50 %) female patients. During the one-month follow-up, four (2%) patients died. In total, 86 patients underwent surgery. The most common comorbid disease was hypertension (n = 97,

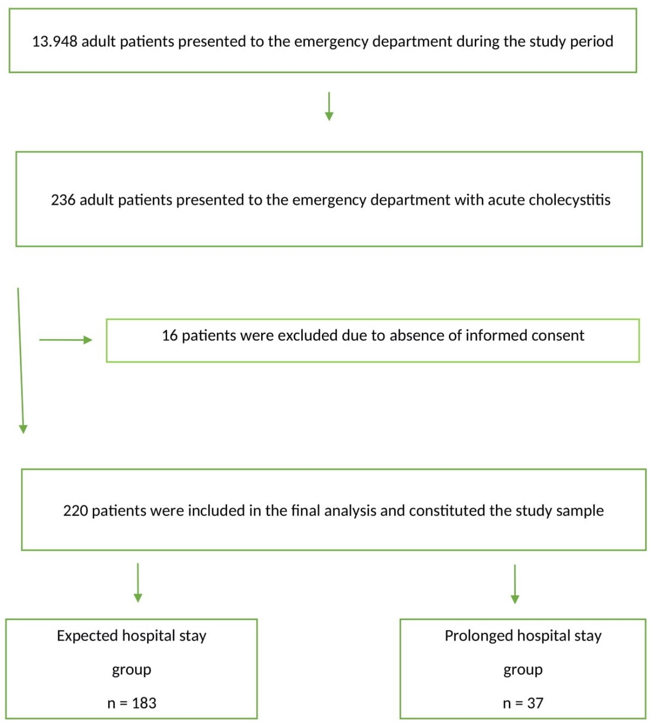

Figure 1. The flowchart of the study.

Table 1. Demographic data and comorbidities of the study groups.

	Total	Expected hospital stay	Prolonged hospital stay	p
	n = 220	n = 183	n = 37	
	(%, 25th-75th percentile)	(%, 25th-75th percentile)	(%, 25th-75th percentile)	
Age	59.0 (43.8-71.0)	58.0 (41.5-70.0)	65.0 (50.0-79.0)	**0.02**
Gender	111 (50.5%)	95 (51.9%)	16 (43.2%)	0.434
Hypertension	97 (44.1%)	75 (41.0%)	22 (59.5%)	0.06
Diabetes mellitus	47 (21.4%)	40 (21.9%)	7 (18.9%)	0.859
Chronic obstructive pulmonary disease	14 (6.4%)	13 (7.1%)	1 (2.7%)	0.528
Coronary artery disease	43 (19.5%)	34 (18.6%)	9 (24.3%)	0.564
Congestive heart failure	15 (6.8%)	8 (4.4%)	7 (18.9%)	**0.004**
Chronic kidney disease	7 (3.2%)	7 (3.8%)	0 (0.0%)	0.487
Cerebrovascular disease	16 (7.3%)	13 (7.1%)	3 (8.1%)	1.000
Mortality	4 (1.8%)	4 (2.2%)	0 (0.0%)	0.816
Surgery	86 (39.1%)	79 (43%)	7(18.9%)	**0.006**

Table 2. Baseline characteristics of the enrolled patients and their comparison between the study groups.

		Total	Expected hospital stay	Prolonged hospital stay	p
		n = 220	n = 183	n = 37	
		(%, 25th-75th percentile)	(%, 25th-75th percentile)	(%, 25th-75th percentile)	
White blood cell count (10^3/µl)		12.7 (10.0-16.5)	12.7 (10.1-16.6)	12.6 (10.0-15.5)	0.792
Neutrophil count (10^3/µl)		10.2 (7.6-13.7)	10.3 (7.6-13.6)	9.7 (8.2-13.8)	0.819
Monocyte count (10^3/µl)		0.7 (0.5-1.0)	0.7 (0.5-1.0)	0.7 (0.5-0.9)	0.464
Lymphocyte count (10^3/µl)		1.6 (1.0-2.2)	1.6 (1.0-2.3)	1.3 (0.7-1.7)	0.003
Eosinophil count (10^3/µl)		0.1 (0.0-0.1)	0.1 (0.0-0.1)	0.0 (0.0-0.1)	0.049
Basophil count (10^3/µl)		0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.615
Red blood cell count (10^3/µl)		4.6 (4.2-5.0)	4.6 (4.2-5.0)	4.7 (4.3-5.0)	0.790
Hemoglobin (G/Dl)		13.2 (12.1-14.3)	13.2 (12.1-14.3)	13.0 (12.1-14.2)	0.466
Hematocrit (%)		39.8 (36.9-43.5)	40.0 (36.9-43.5)	39.6 (38.2-43.0)	0.735
Mean corpuscular volume (Fl)		86.5 (83.7-90.0)	86.7 (83.7-90.3)	86.1 (83.9-88.9)	0.258
Mean corpuscular hemoglobin (G/Dl)		28.8 (27.5-29.8)	29.0 (27.7-29.9)	28.2 (26.8-29.6)	0.054
Mean corpuscular hemoglobin count (G/Dl)		33.0 (32.2-33.7)	33.2 (32.3-33.7)	32.9 (32.1-33.4)	0.184
Red cell distribution width (%)		13.7 (13.1-14.6)	13.6 (13.0-14.4)	14.2 (13.4-16.1)	0.006
Platelet count (10^3/µl)		253.5 (207.5-318.8)	257.0 (209.0-321.0)	239.0 (193.0-291.0)	0.122
Mean platelet volume (Fl)		9.5 (8.7-10.2)	9.4 (8.7-10.2)	9.6 (8.6-10.2)	0.521
Plateletcrit (%)		0.2 (0.2-0.3)	0.2 (0.2-0.3)	0.2 (0.2-0.3)	0.105
Platelet distribution width (Fl)		16.2 (15.9-16.5)	16.2 (15.9-16.4)	16.2 (16.0-16.7)	0.146
Alanine aminotransferase (Iu/L)		31.0 (17.0-96.0)	27.0 (16.0-76.0)	44.0 (26.0-164.0)	0.019
Albumin (G/Dl)		38.0 (3.47-4.20)	39.0 (3.50-4.25)	37.0 (3.30-3.85)	0.003
Aspartate aminotransferase (Iu/L)		33.0 (22.0-91.2)	31.0 (21.0-63.0)	56.0 (28.0-152.0)	0.027
C-reactive protein (Mg/Dl)		75.5 (12.0-156.8)	69.0 (11.0-148.0)	110.0 (26.0-201.0)	0.060
Blood urea nitrogen (g/l)		32.1 (23.5-42.3)	30.0 (23.5-38.5)	38.5 (27.8-66.3)	0.007
Creatinine (Mg/Dl)		0.8 (0.7-1.0)	0.8 (0.7-1.0)	1.1 (0.8-1.2)	0.004
Blood urea nitrogen-to-albumin ratio		8.3 (5.9-11.5)	0.8 (5.6-10.7)	10.4 (7.5-19.7)	0.003
Length of hospital stay (days)		4.0 (3.0-6.0)	4.0 (3.0-5.0)	9.0 (8.0-12.0)	0.001
Mortality	Absent	214 (98.2%)	177 (97.8%)	37 (100.0%)	0.810
	Present	4 (2%)	4 (2.2%)	0 (0.0%)	

44.1%), and there were 22 (59.5%) hypertensive patients in the prolonged hospital stay group. Diabetes mellitus was the second most common comorbidity seen at a rate of 21.4% (n = 47) among all the patients. The demographic data and comorbidities of the expected and prolonged hospital stay groups are shown in Table 1.

There was no significant difference between the expected and prolonged hospital stay groups in relation to the WBC and CRP values, which are inflammatory markers ($p = 0.827$ and 0.060, respectively). The total, direct, and indirect bilirubin values were significantly higher in the prolonged hospital stay group ($p < 0.001$ for all). The median hospital stay was 9 days (IQR: 8-12) for the prolonged hospital stay group and 4 (IQR: 3-5) days for the expected

Table 3. Tokyo severity grading of acute cholecystitis according to the study groups.

		Expected hospital stay	Prolonged hospital stay	Total
Tokyo Severity Grading	1	100 (93 %)	8 (7 %)	108
	2	37 (84 %)	7 (16 %)	44
	3	46 (68 %)	22 (32 %)	68
	Total	183 (83 %)	37 (17 %)	220

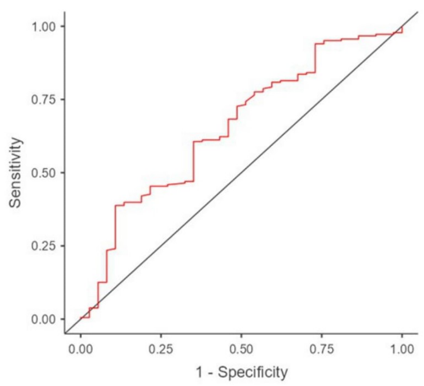

Figure 2. Receiver operating characteristic curve of the blood urea nitrogen-to-albumin ratio in predicting prolonged hospital stay in patients with acute cholecystitis.

hospital stay group.

The baseline characteristics of the enrolled patients and their comparison between the prolonged and expected hospital stay groups are shown in Table 2. According to the TG18 classification, the grade of acute cholecystitis was 3 in 31% of the patients. In the prolonged hospital stay group, grade 3 was most common (32%), followed by grade 2 (16%) and grade 1 (7%) (Table 3).

The ROC curve analysis revealed that a high BAR value had potential value in predicting prolonged hospital stay (Figure 2). The area under the ROC curve value of BAR was calculated as 0.650 ($p=0.003$). According to this analysis, when the cut-off value of BAR was taken as 6.54, it had a positive predictive value of 22.76%, specificity of 38.8%, sensitivity of 89.19%, and negative predictive value of 94.67% in predicting prolonged hospital stay. The odds ratio was calculated as 4.88 [95% confidence interval (CI): 1.66-14.37, $p = 0.002$] for BAR, 2.81 (95% CI: 1.36-5.78, $p=0.004$) for BUN, and 0.13 (95% CI: 0.04-0.38, $p<0.001$) for albumin. The BUN value was determined as 33.2 g/l in grade 1, 33.2 g/l in grade 2, and 30.0 g/l in grade 3.

Discussion

We evaluated 220 patients presenting to the ED with acute cholecystitis, who were hospitalized and followed up. We observed a significant relationship between the baseline BAR and longer hospital stay, with the BAR value being significantly higher in the prolonged hospital stay group than in the expected hospital stay group. Long-term hospital stay studies have been conducted in patients with acute cholecystitis usually after laparoscopy or different surgical procedures. To our knowledge, the study is the first to evaluate the relationship between BAR and prolonged hospital stay.

Anticipating poor outcomes in patients is essential for guiding treatment decisions and optimizing resource allocation. Therefore, researchers have attempted to predict poor outcomes with scoring and laboratory parameters in almost every clinical situation. BUN and albumin have been previously investigated in patients with acute cholecystitis. Er et al. showed that BUN could predict the severity of acute cholecystitis [6]. reported that albumin was lower in patients with acute cholecystitis (30.5 g/l) compared to the control group (38.1) [13]. Clinicians have also evaluated lengthy hospitalization in patients with acute cholecystitis for laparoscopy and post-surgical conditions [14,15]. However, we found only few studies evaluating the ability of baseline parameters to predict lengthy hospitalization in patients with acute cholecystitis.

BAR has been correlated with poor outcomes in ischemic stroke, heart failure, COVID-19, and acute gastrointestinal bleeding, and in the elderly [16,17]. Ryu et al. reported that BAR was positively associated with short term mortality in aspiration pneumonia [18]. In the study conducted with 801 patients, Han et al. found that BAR could predict mortality in sepsis [19]. These studies show that BAR is associated with poor patient outcomes. Since BAR is the ratio of the BUN and serum albumin values, an elevated in the BUN value and the depth of hypoalbuminemia affect this ratio. BUN has been found to be related to many conditions such as urea excretion and absorption balance, renal perfusion, protein uptake and catabolism, and hormonal influence. Albumin is negatively affected by both nutritional deficiency and inflammation. Furthermore, it has been reported that inflammation both causes organ dysfunction and is a potential factor in cardio-renal disorder [20]. Therefore, a decrease in the albumin value and an increase in the BUN value are expected in patients with cholecystitis.

Taking the ratio of parameters that can predict poor outcomes is a sensible method of achieving stronger results. However, there is a limitation when taking the ratio of BUN to albumin. While BUN is higher than normal in inflammatory diseases and critically ill patients, the decrease in albumin is limited [11,21]. In the current study, the mean BUN value was 32 g/l in the whole cohort and 38 g/l in the prolonged hospital stay group. However, an albumin value of prolonged hospital stay group did not decrease to a similar extent (from 38 g/L to 37 g/L). Therefore, this decrease did not contribute much to the BAR value, resulting in similar area under the curve (AUC) values for BUN and BAR (0.650 and 0.640, respectively).

Dundar et al. also found that BUN and BAR had similar performance in predicting in-hospital mortality [0.747 (0.701–0.793) and 0.793 (0.753–0.833), respectively] [17]. In order for the BAR parameter to have a more significant and stronger predictive ability, it should be further investigated in a larger number of patients or patient groups other than cholecystitis presenting with a greater decrease in albumin. Despite this limitation, we found that the odds ratio of BAR was higher than that of the BUN and albumin value alone in our study, suggesting that the increase in BAR increases the possibility of a prolonged hospital stay in patients with acute cholecystitis.

Er et al. evaluating 110 patients, showed that the BUN value were higher in cases classified as grade 3 compared to the remaining groups according to TG18 [6]. Liu et al. reported that among the patients that had undergone laparoscopic cholecystectomy, the BUN value was significantly advanced in those with cardiovascular disease [5]. In another study, it was reported that organ dysfunction requiring intensive care support may develop in grade 3 cholecystitis according to TG18 [2]. In a current study, unlike previous studies, the BUN value did not significantly differ according to disease severity, but it was significantly higher in the prolonged hospital stay group. It can be considered that the ability of a single parameter to predict prolonged hospital stay independently of the evaluator can assist clinicians in managing patients according to the density and capacity of hospitals.

In a study on the prediction of the severity of acute cholecystitis in the ED, Woo at el. determined that AUC value of albumin value [0.776 (95% CI:0.701– 0.840, p< 0.001) was higher than those of WBC count, neutrophil-to-lymphocyte ratio, platelet count, and neutrophil count [22]. Hayasaki et al. reported that the decrease in the albumin value could predict the long-term hospitalization of postoperative patients [23]. In another study, Lee et al. determined that the serum albumin values were significantly lower in severe acute cholecystitis [24]. In the current study, we similarly found that albumin could predict prolonged hospital stay. A logical explanation for this finding is that inflammation, one of main components of acute cholecystitis, reduces albumin. Therefore, albumin can be guiding for clinicians as a good predictor.

Our study has certain limitations. It was conducted in a single center over a limited period. Different results may be obtained during other months of the year or in studies involving a large number of patients. Second, it has a retrospective design, therefore the possibility of bias could not be eliminated.

Conclusion

In conclusion, the BAR calculated at the time of the initial emergency department presentation can predict prolonged hospital stays in cases of acute cholecystitis. BAR is a simple, significant, and useful parameter for clinicians to use hospital resources efficiently.

Authorship contributions

Surgical and Medical Practices: A.Ö., K.Ö., A.A., S.Ö. Concept: A.Ö., K.Ö., A.A., S.Ö.. Design: A.Ö., K.Ö., A.A., S.Ö., Data Collection or Processing: A.Ö., K.Ö., A.A., S.Ö. Analysis or Interpretation: A.Ö., K.Ö., A.A., S.Ö., Literature Search: A.Ö., K.Ö., A.A., S.Ö., Writing: A.Ö, S.Ö.

Ethical approval

This study received approval from the Ethics Committee of University of Health Sciences Turkey, Ümraniye Training and Research Hospital (Approval No: B.10.1.TKH.4.34.H.GP.0.01-77).

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