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The value of albumin-related ratios in predicting disease severity and mortality in acute cholangitis

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ABSTRACT

Aims: Acute cholangitis is a potentially fatal bacterial illness that poses a significant risk to patients if not promptly addressed, despite the progress made in the field of diagnosis and treatment. Multiple laboratory and clinical data are employed in assessing the severity and fatality rates associated with acute cholangitis. This study aimed to assess the predictive utility of the ratio between elevated laboratory results and albumin levels in determining the severity of disease and mortality rates in patients with cholangitis.

Methods: The study comprised a cohort of 471 individuals diagnosed with acute cholangitis, alongside a control group of 150 individuals without acute cholangitis. The patients' information was acquired by conducting a retrospective search of the computerized database. The study collected data on the age, gender, routine laboratory parameters, concomitant disorders, etiology of cholangitis, and outcomes (discharge or death) of all patients. The patients were categorized into three grades, namely grade 1, grade 2, and grade 3, based on the severity of cholangitis, using the Tokyo 2018 standards as a reference.

Results: The study comprised a sample size of 621 people. Out of the whole sample size, 53.1% (330 individuals) were identified as male. The study observed a broad range of ages (23-98) with a median age of 67 years, which was found to be greater in the cholangitis group. Among the patients in the cholangitis group, a mortality rate of 6.8% (32 individuals) was observed. A notable disparity was seen in all laboratory parameters between the two groups. The cholangitis group had greater levels of albumin-related ratios, and there was a positive correlation observed between all ratios and the severity of the condition. In deceased individuals, there were greater rates observed for variables other than the γ-glutamyl transferase/albumin ratio (GAR). The results of both univariate and multivariate regression analyses demonstrated a significant correlation between the ratios of direct bilirubin to albumin (DBAR), international normalized ratio to albumin (IAR), neutrophil to albumin (NAR), and mortality. Additionally, the study revealed that the mortality and severity of cholangitis could be predicted by all the albumin-related ratios examined, particularly the INR/albumin ratio (IAR), as indicated by the ROC analysis.

Conclusion: It is posited that the utilization of albumin-related ratios, obtainable through routine laboratory testing, may serve as an effective means to assess the severity of acute cholangitis and predict mortality rates associated with the condition. Immediate biliary drainage is recommended for patients with elevated ratios.

Keywords: Acute cholangitis, albumin-related ratios, severity, mortality

INTRODUCTION

Acute cholangitis refers to a bacterial infection that affects the biliary system, presenting a spectrum of severity that may range from moderate symptoms like jaundice, stomach discomfort, and fever to potentially life-threatening complications such as septic shock.[1] It continues to be a common clinical presentation worldwide. Previously associated with fatality rates above 50%, despite improvements in diagnosis and treatment, acute cholangitis remains a significant and potentially life-threatening condition in the absence of intervention.[2,3] A bile and biliary tract blockage that results in systemic inflammation is the cause of acute cholangitis, also defined as ascending cholangitis. Stones, pancreatic and biliary cancers, stents, and strictures may induce biliary tract obstruction.[3,4] The most common cause of acute cholangitis is choledocholithiasis.[5] Again, it has been reported that 1% to 5% of this picture develops following endoscopic retrograde cholangiopancreatography (ERCP).[6] An obstruction in the biliary tract leads to impaired bile flow to the small intestine and causes bile stasis. This bile stasis causes the proliferation of bacteria that either enter the biliary tract from the intestine or reach the biliary

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tract via the portal venous system.[7] The key elements of treatment in acute cholangitis are antimicrobial therapy and biliary decompression.[2,5] Early intervention is crucial in the management of grade 3 cholangitis in order to minimize the risk of catastrophic consequences.[2] However, cholangitis occurs for a wide variety of reasons and with different severity, and many factors may influence survival in patients with acute cholangitis.[8]

Although the severity of cholangitis has been assessed using a variety of criteria up to this point, a systematic method was not established until the Tokyo guidelines were released. The Tokyo Guidelines were produced in 2007 and were the first published set of diagnostic criteria backed by clinical, laboratory, and imaging research. Imaging results showing blockage as well as observations related to cholestasis and systemic inflammation were taken into account while formulating these criteria. Furthermore, using laboratory data such as white blood cells (WBC), c-reactive protein (CRP), international normalized ratio (INR), and albumin, a system evaluating the severity of the condition was devised using the Tokyo standard.[2]

WBC, neutrophils, and CRP increase in the presence of an infection. When the biliary tract is obstructed, bilirubin and glutamyl transferase (GGT) levels increase. On the other hand, albumin levels, which is a negative acute-phase reactant, decrease in the presence of inflammation.[9] In this study, we investigated the predictive value of the ratio of increased laboratory parameters to albumin in terms of the severity of cholangitis and mortality. Many studies have been conducted on the clinic, diagnosis, and treatment of cholangitis. With this study, we would like to contribute to the accumulation of knowledge in this field.

METHODS

The study was carried out with the permission of Batman Training and Research Hospital Scientific Researches Ethics Committee (Date: 24.01.2023, Decision No: 336). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study included 471 patients who underwent ERCP with the diagnosis of cholangitis at Batman Dünya Hospital between January 2010 and December 2022, and as a control group, 150 patients who underwent ERCP for biliary stent revision and did not have a cholangitis clinic in the same period. Information about the patients was obtained through a retrospective search of the electronic database. Age, gender, routine laboratory parameters, comorbid diseases, etiology of cholangitis, and discharge or death of all patients were recorded. Urea/albumin (UAR), INR/albumin (IAR), GGT/albumin (GAR), neutrophil/albumin (NAR), CRP/albumin (CAR), and direct bilirubin/albumin (DBAR) ratios were calculated by formulating in the SPSS program. In the Tokyo guideline, acute cholangitis is classified as grade 1, grade 2, and grade 3, and early bile drainage is recommended as the severity increases. In the present study, the Tokyo 2018 guideline was taken as a reference. Therefore, patients were grouped into grade 1, 2, and 3 according to the severity of cholangitis.

All patients older than 18 years of age, male and female, of both sexes, diagnosed with acute cholangitis and with routine laboratory parameters, were included in the study. Exclusion criteria were the absence of routine laboratory parameters, the presence of concomitant pancreatitis, a focus of infection other than cholangitis, the presence of any acute or chronic disease that would prolong the INR value other than cholangitis, and/or a history of drug use. Patients who had elevated WBC and CRP levels without cholangitis findings and underwent stent revision were excluded from the control group.

Statistical Analysis

The patient data obtained during the investigation were analyzed using the IBM Statistical Package for the Social Sciences (SPSS 25.0-IBM, NY, USA) software for Windows version 25.0. Descriptive statistics were provided in the form of frequency and percentage for categorical data, and median, minimum, and maximum for continuous data. The data's adherence to the Gaussian distribution was assessed using the Kolmogorov-Smirnov test. Intergroup comparisons were conducted using the Mann-Whitney U-Test for two groups, the Kruskal-Wallis H-Test for more than two groups, and the Chi-Square or Fisher's Exact Test for comparing categorical variables. A logistic regression analysis was employed to ascertain whether the escalation in rates constituted a risk factor for mortality. A receiver operating characteristic (ROC) analysis was conducted to evaluate the discriminatory potential of the ratio values in relation to disease severity and survival. Subsequently, a ROC curve was generated to visually represent the results. Spearman's correlation analysis was employed to assess the association between ratio values and disease severity. Statistical significance was attributed to the results when the p-value was below the threshold of 0.05.

RESULTS

A total of 621 participants, including 471 with cholangitis and 150 in the control group, were included in the study. Of these, 53.1% (330) were male. There was a wide age distribution (23-98), with a median age of 67 years. In the cholangitis group, 6.8% (32) of patients died. The distribution of demographic and clinical findings among the participants is given in **Table 1**. No statistically significant relationship is found between the groups in terms of gender distribution (p>0.05). There was a

statistically significant difference between the two groups in terms of age distribution (p<0.05). The mean age of the cholangitis group was higher than the mean age of the individuals in the control group. There was a statistically significant difference between the two groups in all laboratory parameters (p<0.05).

The results of the analyses evaluating whether there was a difference between albumin-related ratios according to the severity of cholangitis in the patients included in the study are shown in **Table 2**. A statistically significant difference was found between the groups in terms of ratios (p<0.001).

Table 1. Distribution of demographic and clinical findings of the patients

Characteristics (N=621)	Total (N=621) n (%) or Median (Min-Max)	Control (n=150) n (%) or Median (Min-Max)	Cholangitis (n=471) n (%) or Median (Min-Max)	p-value
Gender				0.147
Male	330 (53.1)	72 (48)	258 (54.8)	
Female	291 (46.9)	78 (52)	213 (45.2)	
Age, year	67 (23-98)	61 (23-87)	69 (26-98)	<0.001
Cholangitis Severity				NA
Control	150 (24.2)	150 (100)	NA	
Grade 1 (Mild)	200 (32.2)	NA	200 (42.5)	
Grade 2 (Moderate)	112 (18)	NA	112 (23.8)	
Grade 3 (Severe)	159 (25.6)	NA	159 (33.7)	
Cholangitis Source				
Hospital related	NA	NA	183 (38.9)	
Community-sourced	NA	NA	288 (66.1)	
Cholangitis Etiology				<0.001
Benign	500 (80.5)	141 (94)	359 (76.2)	
Malignant	121 (19.5)	9 (6)	112 (23.8)	
Comorbidity				0.001
Yes	536 (86.3)	117 (78)	419 (89)	
No	85 (13.7)	33 (22)	52 (11)	
Latest Status				<0.001
Alive	589 (94.8)	150 (100)	439 (93.2)	
Deceased	32 (5.2)	0 (0)	32 (6.8)	
Lab				
Glucose (mg/dl)	113 (25-795)	99 (65-321)	117 (25-795)	<0.001
Urea (mg/dl)	36 (10-232)	30 (10-73)	39 (12-232)	<0.001
Creatinine (mg/dl)	0.89 (0.36-5.90)	0.76 (0.48-1.90)	0.95 (0.36-5.90)	<0.001
AST (U/L)	99 (7-2235)	25 (7-728)	122 (7-2235)	<0.001
ALT (U/L)	108 (5-1359)	31.5 (5-899)	134 (6-1359)	<0.001
GGT (U/L)	340 (9-2374)	77 (9-1514)	419 (16-2374)	<0.001
ALP (U/L)	246 (21-2066)	120 (21-867)	287 (45-2066)	<0.001
Total Protein (g/dl)	6.60 (3.69-9.10)	6.90 (4.80-8.60)	6.50 (3.69-9.10)	<0.001
Albumin (g/dl)	3.90 (1.90-5.00)	4.30 (3.20-5.00)	3.70 (1.90-4.90)	<0.001
Total Bilirubin (mg/dl)	3.60 (0.20-30.36)	0.80 (0.2-17.76)	4.40 (0.40-30.36)	<0.001
Direct Bilirubin (mg/dl)	2.50 (0.07-23.23)	0.30 (0.07-15.11)	3.10 (0.1-23.23)	<0.001
INR	1.14 (0.89-3.13)	1.02 (0.89-2.20)	1.2 (0.90-3.13)	<0.001
WBC (µl)	9820 (2310-54770)	6870 (3550-9920)	11850 (2310-54770)	<0.001
Neutrophil (µl)	7730 (1560-50150)	4010 (1800-7510)	10000 (1560-50150)	<0.001
Lymphocyte (µl)	1100 (90-9970)	1860 (960-3900)	800 (90-9970)	<0.001
Hemoglobin (g/dl)	12.7 (7.1-17.6)	13.1 (9.4-16.0)	12.6 (7.1-17.6)	0.001
PLT (µl)	230 (20-723)	273.50 (65-512)	216 (20-723)	<0.001
CRP (mg/L)	62.30 (0.8-400.80)	3.20 (0.80-9.75)	91.00 (3.00-400.80)	<0.001
UAR	9.25(2.10-110.53)	7.17 (2.10-18.72)	10.54 (2.55-110.53)	<0.001
GAR	93.80 (2.08-629.45)	19.70 (2.08-344.09)	114.73 (4-629.45)	<0.001
DBAR	0.66 (0.02-9.16)	0.06 (0.02-3.46)	0.86 (0.02-9.16)	<0.001
IAR	3.00 (1.86-15.81)	2.37 (1.86-4.49)	3.28 (1.88-15.81)	<0.001
NAR	2.08 (0.42-20.90)	0.97 (0.42-1.72)	2.73 (0.43-20.90)	<0.001
CAR	16.68 (0.16-200.64)	0.83 (0.16-2.73)	24.18 (0.64-200.63)	<0.001

UAR: Urea/albumin ratio, GAR: GGT/albumin ratio, DBAR: Direct Bilirubin/albumin ratio, IAR: INR/albumin ratio, NAR: Neutrophil/albumin ratio, CAR: CRP/albumin ratio

Table 2. Distribution of rates according to cholangitis severity

	Control	Cholangitis Severity			p
		Grade 1 Median (Min-Max)	Grade 2 Median (Min-Max)	Grade 3 Median (Min-Max)	
UAR	7.17 (2.10-18.72)	8.31 (2.71-29.38)	11.02 (2.55-42.29)	17.09 (4.13-110.53)	<0.001
GAR	19.70 (2.08-344.09)	114.88 (4-629.45)	137.77 (4.65-560.24)	94.57 (9.46-558.33)	<0.001
DBAR	0.06 (0.02-3.46)	0.55 (0.002-9.16)	1.09 (0.14-6.85)	1.10 (0.14-9.13)	<0.001
IAR	2.37 (1.86-4.49)	2.82 (1.88-6.32)	3.22 (2.17-5.86)	4.50 (2.22-15.81)	<0.001
NAR	0.97 (0.42-1.72)	1.90 (0.58-8.24)	3.43 (0.43-11.03)	3.86 (0.64-20.9)	<0.001
CAR	0.83 (0.16-2.73)	15.08 (0.73-23.5)	23.99 (0.64-93.08)	45.17 (0.80-200.63)	<0.001

UAR: Urea/albumin ratio, GAR: GGT/albumin ratio, DBAR: Direct Bilirubin/albumin ratio, IAR: INR/albumin ratio, NAR: Neutrophil/albumin ratio, CAR: CRP/albumin ratio

The analysis, which evaluated the relationship between the rates of patients and disease severity, is presented in Table 3. It is seen that there is a positive linear relationship between ratios and disease severity. A low-level positive correlation was found for GAR, a moderate level for UAR, DBAR, and IAR, and a strong positive correlation for NAR and CAR.

Table 3. Correlation analysis results between ratios and disease severity

	UAR	GAR	DBAR	IAR	NAR	CAR
Spearman's Correlation						
Severity						
r	.517**	.356**	.628**	.696**	.706**	.749**
p	0.000	0.000	0.000	0.000	0.000	0.000
N	621	621	621	621	621	621

UAR: Urea/albumin ratio, GAR: GGT/albumin ratio, DBAR: Direct Bilirubin/albumin ratio, IAR: INR/albumin ratio, NAR: Neutrophil/albumin ratio, CAR: CRP/albumin ratio

The analysis comparing albumin-related ratios between discharged and exited patients is shown in Table 4. It was found that there was a statistically significant difference between the groups for UAR, DBAR, IAR, NAR, and CAR (p<0.001), but not for GAR (p = 0.344).

Table 4. Distribution of ratios by outcome variable

	Alive	Exitus	p
	Median (Min.- Maks.)	Median (Min.- Maks.)	
UAR	10.00 (2.55-110.53)	25.66 (4.17-86.98)	<0.001
GAR	117.50 (4.00-629.45)	105.06 (15.65-558.33)	0.344
DBAR	0.82 (0.24-9.16)	2.48 (0.24-9.13)	<0.001
IAR	3.23 (1.88-9.90)	5.48 (2.80-15.81)	<0.001
NAR	2.66 (0.43-13.76)	5.31 (0.63-20.90)	<0.001
CAR	23.40 (0.64-200.63)	43.64 (4.51-142.61)	0.001

UAR: Urea/albumin ratio, GAR: GGT/albumin ratio, DBAR: Direct Bilirubin/albumin ratio, IAR: INR/albumin ratio, NAR: Neutrophil/albumin ratio, CAR: CRP/albumin ratio

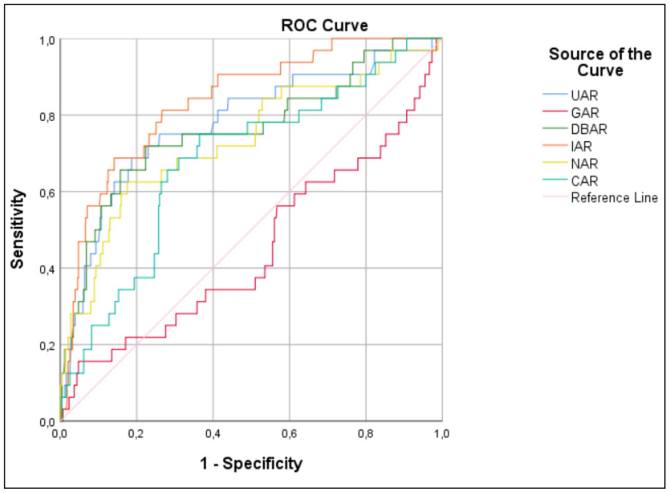
The results of the analysis evaluating whether high rates are a risk factor for mortality in patients with cholangitis are shown in Table 5. It was determined that high UAR, DBAR, IAR, NAR, and CAR were risk factors for mortality in univariate analysis. When the parameters that showed a significant difference in univariate analysis were re-evaluated in multivariate analysis, it was determined that a 1-unit increase in DBAR, IAR, and NAR increased mortality by 1.36, 1.45, and 1.16 times, respectively (p<0.05).

Table 5. Univariate and multivariate analysis of rates as mortality risk factors

	Univariate			Multivariate		
	Odds ratio	95% CI	p	Odds ratio	95% CI	p
UAR	1.053	1.032-1.075	<0.001	1.019	0.994-1.045	0.141
GAR	1.000	0.997-1.004	0.897			
DBAR	1.660	1.396-1.975	<0.001	1.363	1.108-1.676	0.003
IAR	1.785	1.487-2.143	<0.001	1.458	1.123-1.892	0.005
NAR	1.353	1.213-1.510	<0.001	1.165	1.008-1.345	0.038
CAR	1.017	1.007-1.027	0.001	0.897	0.972-1.002	0.095

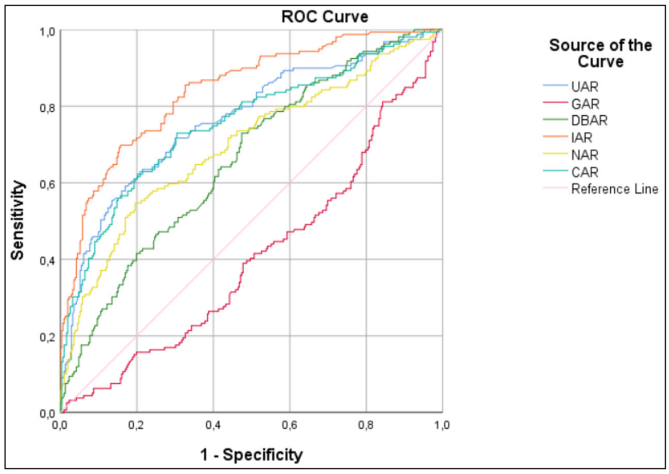
UAR: Urea/albumin ratio, GAR: GGT/albumin ratio, DBAR: Direct Bilirubin/albumin ratio, IAR: INR/albumin ratio, NAR: Neutrophil/albumin ratio, CAR: CRP/albumin ratio

The results of the ROC analysis performed to examine the differential effect of the ratios according to the mortality status of the patients are shown in Graphic 1. The area under the curve shows the statistical significance of the discrimination ability of the diagnostic test. In the present study, the highest value was found for IAR (84%), and an IAR >3.89 predicts mortality at a good level.



Graphic 1. ROC Analysis of Ratios by Mortality. UAR: Urea/albumin ratio, GAR: GGT/albumin ratio, DBAR: Direct Bilirubin/albumin ratio, IAR: INR/albumin ratio, NAR: Neutrophil/albumin ratio, CAR: CRP/albumin ratio

The results of the ROC analysis performed to examine the differential effect of the ratios according to severe cholangitis are shown in **Graphic 2**. The highest area under the curve was found for IAR (84%), and an IAR >3.46 was a good predictor of severe cholangitis.



Graphic 2. ROC Analysis of Ratios by Severe Cholangitis. UAR: Urea/albumin ratio, GAR: GGT/albumin ratio, DBAR: Direct Bilirubin/albumin ratio, IAR: INR/albumin ratio, NAR: Neutrophil/albumin ratio, CAR: CRP/albumin ratio

DISCUSSION

Acute cholangitis is a potentially fatal bacterial illness that poses a significant risk to patient health if not promptly addressed, notwithstanding the progress made in the field of diagnosis and treatment.[2] Biliary blockage can arise from several benign and malignant etiologies, encompassing pancreatic and biliary cancers, biliary stents, biliary strictures, and notably, the presence of stones.[3] Numerous research investigations have been undertaken to ascertain the extent of severity and fatality associated with cholangitis.[10-14] The Tokyo Guideline is extensively employed in the management of acute cholangitis. The Tokyo guidelines classify acute cholangitis into three grades: grade 1, grade 2, and grade 3. As the severity of the condition escalates, the guidelines advocate early biliary drainage.[2]

In the assessment of acute cholangitis, laboratory indicators such as bilirubin, alkaline phosphotase (ALP), gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) are employed to detect cholestasis-related elevations. These parameters are utilized alongside systemic inflammation markers including fever, elevated white blood cell count, and C-reactive protein (CRP) levels. Furthermore, the grading of cholangitis severity also takes into account elevated levels of bilirubin, decreased levels of albumin, increased white blood cell count, and indications of systemic organ failure. Patients diagnosed with acute cholangitis are deemed to have hepatic failure if their International Normalized Ratio (INR) exceeds 1.5. Similarly, renal failure is established if the patient's creatinine levels surpass 2 mg/dl. The individuals in question are classified as having severe cholangitis.[2] Individuals diagnosed with acute cholangitis who do not undergo biliary drainage will experience elevated levels of systemic inflammatory markers and cholestasis measures, irrespective of the plasma half-life. Furthermore, there is an elevated probability of experiencing organ failure. This study aimed to assess the ability of laboratory parameter ratios, including CRP, direct bilirubin, GGT, neutrophils, urea, and INR, to predict disease severity and death in patients with cholangitis. These laboratory parameters are known to increase in individuals with cholangitis, while albumin, a negative acute phase reactant, is expected to decrease.

The rates pertaining to albumin have been investigated in various pathological conditions. The association between disease activation and the CRP/albumin ratio was demonstrated in a study including individuals diagnosed with inflammatory bowel disease.[15] In a study conducted by Behera et al.[16] it was discovered that there exists an association between the ratio of C-reactive protein (CRP) to albumin and the prognosis of patients with acute pancreatitis. In their study, Şahiner et al.[17] investigated the relationship between mean platelet volume/albumin (MAR) and the severity of cholangitis. Their findings revealed a significant link between the severity of cholangitis and MAR. The findings of our investigation indicate a notable correlation between the CRP to albumin ratio (CAR) and both illness severity and fatality rates. Similarly, a significant association was identified between the urea-to-albumin ratio (UAR) and both the disease severity and mortality rate. In the literature, UAR was evaluated as a promising marker for predicting 28-day mortality in a study supporting our finding.[18] Despite the identification of a statistically significant association between GAR and the severity of acute cholangitis, our correlation analysis revealed a poor link between these variables. There was no statistically significant link seen between the variable of interest, GAR, and the outcome measure of mortality.

While there is a lack of existing literature examining the specific relationship between the DBAR and the severity and mortality of acute cholangitis, there is data suggesting that the bilirubin/albumin ratio is correlated with mortality in patients admitted to intensive care units.[19] Similarly, IAR and NAR have not been studied in acute cholangitis. According to a study conducted by Çekmen et al.[20] it was shown that NAR has potential utility in the diagnostic assessment of acute appendicitis. The present investigation revealed a notable association between the three ratios and both the severity of acute

cholangitis and death. Furthermore, regression analysis demonstrated that DBAR, IAR, and NAR were associated with a 1.36-fold, 1.45-fold, and 1.16-fold increase in mortality, respectively.

In the current investigation, a ROC analysis was conducted to assess the varying impact of the ratios on mortality and severe cholangitis. The results revealed that the IAR exhibited the highest area under the curve (AUC), indicating its superior predictive ability. Specifically, an IAR value greater than 3.89 was associated with mortality, while a value exceeding 3.46 was indicative of severe cholangitis, both at a satisfactory level of accuracy.

Despite certain limitations, such as its retrospective nature and the absence of healthy volunteers in the control group, the current investigation is believed to possess notable merits. These include a substantial sample size and the novel assessment of various albumin-related parameters in the context of acute cholangitis. As a result, these strengths are expected to make a valuable contribution to the existing body of literature.

CONCLUSION

Upon comprehensive examination of the present study data in conjunction with existing research, it is our contention that the utilization of albumin-related ratios derived from fundamental laboratory tests (namely UAR, DBAR, IAR, and NAR in the context of the present study) is warranted to assess the severity of acute cholangitis and predict mortality rates associated with this condition. Immediate biliary drainage should be administered to patients with elevated ratios.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Batman Training and Research Hospital Scientific Researches Ethics Committee (Date: 24.01.2023, Decision No: 336).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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