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Endotoxin Activity Assay as a Novel Predictor of Disease Progression in Patients With Mild Cholangitis

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Abstract

Background/Aim: Acute cholangitis is a critical biliary infection that can swiftly evolve into sepsis and organ failure. Certain patients with mild acute cholangitis might advance to a more severe status. Identifying predictive factors for such exacerbation is of paramount importance. This study aimed to investigate whether the endotoxin activity assay (EAA) could serve as a predictive biomarker for the progression of mild acute cholangitis.

Patients and Methods: We conducted a retrospective observational study at Yokohama City University Hospital, enrolling 200 patients hospitalized with acute cholangitis between May 2011 and June 2015. Patients with initially mild acute cholangitis were stratified into two groups based on their severity on Day 1: the stable group (remaining mild) and the exacerbation group (progressing to moderate/severe cholangitis). Clinical parameters were analyzed to assess risk factors for exacerbation.

Results: Among 74 patients with mild acute cholangitis at admission, 33 (44.6%) progressed to moderate/severe cholangitis within 24 h. Multivariate logistic regression analysis identified chemotherapy within 28 days [odds ratio (OR)=3.440, 95% confidence interval (CI)=1.170-10.100, p=0.025], serum albumin levels (OR=0.303, 95%CI=0.094-0.975, p=0.045), and EAA ≥0.4 (OR=3.880, 95%CI=1.210-12.500, p=0.023) as independent predictors of disease exacerbation. A predictive equation was developed using the logistic regression model: log (P/1-P)=3.285-1.265×Alb (mg/dl) + 1.291 × (Chemotherapy within 28 days) +1.343 × (EAA ≥0.4) (P: the probability of exacerbation).

Conclusion: EAA was identified as the most significant factor for exacerbating mild acute cholangitis. The combination of EAA, albumin levels, and a history of chemotherapy within the past 28 days suggests the potential to predict the progression of mild acute cholangitis to a more severe form.

Keywords: Acute cholangitis, EAA, predictive risk factors.

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Introduction

Acute cholangitis is a potentially life-threatening biliary infection that results from bacterial invasion due to biliary obstruction. The condition can rapidly escalate to sepsis and multi-organ failure if left untreated (1). The Tokyo Guidelines (TG13, TG18) have provided standardized criteria for diagnosis and severity classification, categorizing cases as mild, moderate, or severe based on clinical and laboratory parameters (2, 3). The mortality rate among patients with acute cholangitis ranges from 2.7% to 10.0%; however, in those with severe cholangitis, it can increase to nearly 20.0% (3). While mild cases are often manageable with conservative therapy, some patients experience rapid disease progression, leading to increased morbidity and mortality.

Despite advances in risk stratification, predicting the deterioration of mild acute cholangitis remains challenging. The current severity classification relies on clinical judgment and laboratory markers, but these assessments may not adequately capture early signs of exacerbation (4). Identifying reliable biomarkers that predict progression to moderate or severe cholangitis is crucial for optimizing early therapeutic interventions, such as timely antibiotic administration, biliary drainage, and intensive care support.

Endotoxins, primarily lipopolysaccharides (LPS) from Gram-negative bacteria, play a central role in the pathophysiology of sepsis and severe biliary infections. These endotoxins trigger a systemic inflammatory response, leading to endothelial dysfunction, disseminated intravascular coagulation (DIC), and multiple organ failure (5). The Endotoxin Activity Assay (EAA) is a novel diagnostic tool that quantifies endotoxin-related neutrophil activation, offering a rapid and reliable method to assess bacterial endotoxemia (6). We demonstrated a correlation between high EAA levels and disease severity in acute cholangitis, suggesting that EAA could serve as an early predictor of worsening clinical status (7).

The aim of this study was to investigate potential predictive factors for exacerbation of mild acute cholangitis to moderate/severe cholangitis by evaluating clinical variables and biomarkers including EAA.

Patients and Methods

We conducted a retrospective observational study in the Department of Gastroenterological Surgery at Yokohama City University Hospital (Yokohama, Japan). This study protocol was approved by the Ethical Review Board of Yokohama City University Hospital (Yokohama, Japan) (approval number: 110512019), and informed consent was obtained from all patients. We enrolled 200 patients who were hospitalized for acute cholangitis at our department between May 2011 and June 2015 to this study. All patients underwent blood sampling, blood culture, and computed tomography (CT) examination upon admission, and the severity of cholangitis was assessed based on TG18 (3). Additionally, EAA, which indicates neutrophil activity, was measured using the remaining admission blood sample as we described before (7). DIC was diagnosed using the Japanese Association for Acute Medicine criteria (JAAM criteria), and organ dysfunction was evaluated using the sequential organ failure assessment score (SOFA score) (8-10). The initial treatment consisted of antimicrobial therapy, with piperacillin/tazobactam (PIPC/TAZ) as the first-line agent. In cases where resistant strains had been previously identified, carbapenems or other alternative antibiotics were administered. Stent replacement was considered if the initial treatment was ineffective regardless of whether a stent was present. If two months had passed since the previous stent placement, stent replacement was performed during hospitalization.

Patients with mild acute cholangitis on admission (Day 0) were stratified according to their severity of cholangitis on Day 1 into the following two groups: the Stable group (the severity on Day 1 was mild) and the Exacerbation group (the severity on Day 1 was moderate or severe). Clinical findings were retrospectively analyzed to evaluate the risk of progression to severe cholangitis in patients with mild cholangitis.

EAA. EAA was measured using residual blood from the admission blood test, following the manufacturer's instructions (Spectral Diagnostics, Toronto, ON, Canada). The method for EAA measurement was previously described (8).

Statistical analysis. All statistical analyses were conducted using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (11). All values are expressed as median and interquartile range or a number and percentage (%). The Mann-Whitney *U*-test was used to analyze the continuous variables, while the χ^2 test was used to analyze the categorical variables.

Univariate logistic regression analysis was conducted to assess the association between each independent variable and exacerbation. Variables with $p<0.1$ in the univariate analysis were considered potential predictors and included in the multivariable analysis. Multivariable logistic regression analysis with a stepwise selection method was applied to identify the most relevant predictors. Variables that remained significant ($p<0.1$) were included in the final model.

A predictive model for exacerbation was constructed using statistically significant factors identified in the multivariable logistic regression analysis. The performance of the final model was assessed using a receiver operating characteristic (ROC) curve analysis. The optimal cutoff value for predicting exacerbation was determined using Youden's Index.

Results

Patient characteristics. The patient demographic and clinical characteristics are presented in Table I. The cohort comprised 149 men and 51 women, with a median age of 73 years. A total of 136 patients (68.0%) had underlying malignancies, of whom 85 (42.5%) had undergone chemotherapy within the preceding 28 days. Biliary drainage stents were present in 120 patients (60.0%), whereas 100 patients (50.0%) had previously undergone choledochojejunostomy. Additionally, 15 patients (7.5%) had liver abscesses, and 89 patients (44.5%) underwent biliary drainage within 24 h of admission. Based on the Tokyo Guidelines 2018 (TG18), acute cholangitis severity was classified as mild in 74 patients (37.0%), moderate in 51 patients (25.5%), and severe in 75 patients (37.5%).

Table I. *Characteristics of patients.*

	n (%)
Age	73 (66-77)
Sex	
Male/Female	149/51
Cancer bearing	136 (68.0)
Chemotherapy within 28 days	85 (42.5)
Biliary drainage stent	120 (60.0)
Biliary drainage on Day 0	89 (44.5)
Biliary drainage during hospitalization	148 (74.0)
Choledochojejunostomy	100 (50.0)
Liver abscess	15 (7.5)
Sepsis grading (SSCG2016)	
Sepsis	141 (70.5)
Septic shock	2 (1.0)
Acute cholangitis severity grading (TG18)	
Mild	74 (37.0)
Moderate	51 (25.5)
Severe	75 (37.5)

TG18: Tokyo Guidelines 2018. SSCG2016: Surviving Sepsis Campaign Guidelines 2016.

The characteristics of the patients with mild acute cholangitis are shown in Table II. There were 50 men and 24 women, with a median age of 70 years. Forty-eight patients (64.9%) were cancer-bearing, 29 of whom (39.2%) had received chemotherapy with 28 days. Forty-six patients (62.2%) had a bile duct drainage stent, 40 patients (54.1%) were post-choledochojejunostomy, and five patients (2.5%) had liver abscess. Thirty-two patients (43.2%) underwent bile duct drainage within 24 h.

The patients with mild acute cholangitis on admission (Day0) were divided into two groups (the Stable group and the Exacerbation group) according to the severity of cholangitis on the day after admission (Day1) (Figure 1).

Comparison between the Stable Group and the Exacerbation Group. Table III shows the comparison between the Stable

Table II. *Characteristics of patients with mild cholangitis on admission.*

	n (%)
Age (years)	70 (62-74)
Sex	
Male/Female	50/24
Cancer bearing	48 (64.9)
Chemotherapy within 28 days	29 (39.2)
Biliary drainage stent	46 (62.2)
Choledochojejunostomy	40 (54.1)
Liver abscess	5 (2.5)
Vital signs	
Body temperature (˚C)	38.6 (38.0-39.0)
Systolic blood pressure (mmHg)	130 (113-146)
Diastolic blood pressure (mmHg)	77 (68-85)
Heart rate	97 (83-111)
Laboratory data on Day 0	
WBC (/μl)	7,400 (6,100-9,800)
CRP (mg/dl)	2.47 (0.89-6.22)
Procalcitonin (ng/ml)	0.35 (0.20-0.68)
Total bilirubin (mg/dl)	1.1 (0.7-1.7)
Albumin (mg/dl)	3.5 (3.2-3.8)
Creatinine (mg/dl)	0.71 (0.62-0.88)
Platelet (10^4/ml)	17.8 (13.3-24.8)
PT-INR	1.13 (1.04-1.19)
FDP-E (μg/ml)	133 (92-209)
JAAM-DIC score ≧4	5 (6.8)
EAA	0.29 (0.20-0.42)
≧0.4	21 (28.4)
Positive blood culture	18 (24.3)
SOFA score	1 (1-2)
Sepsis grading (SSCG2016)	
Sepsis	39 (52.7)
Biliary drainage on Day 0	32 (43.2)
Biliary drainage during hospitalization	57 (77.0)
Initial antibiotic therapy	
TAZ/PIPC/Carbapenem agents/Others	60/9/5
ICU admissions	5 (6.8)
Length of hospital stay	8 (5-14)
28-day mortality	5 (2.7)

WBC: White blood cell count; CRP: C-reactive protein; JAAM-DIC score: Japanese Association for Acute Medicine disseminated intravascular coagulation score; SIRS: systemic inflammatory response syndrome; SOFA score: sequential organ failure assessment score; TG18: Tokyo Guidelines 2018; SSCG2016: Surviving Sepsis Campaign Guidelines 2016; TAZ/PIPC: Piperacillin/Tazobactam.

Group (n=41) and the Exacerbation Group (n=33). Among patients aged 75 years or older, six cases (14.6%) were in the Stable group, whereas 11 cases (33.3%) were in the Exacerbation group, indicating a higher prevalence in the Exacerbation group (p=0.057). Chemotherapy within 28 days prior to admission was statistically more common in

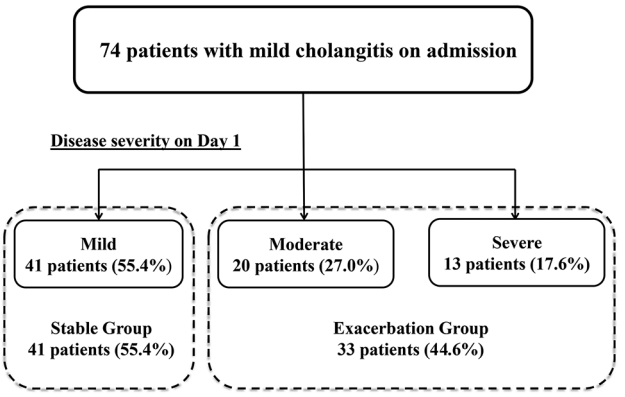

Figure 1. *Flowchart depicting patients with mild cholangitis at admission. They were categorized into two groups: the Stable group and the Exacerbation group, based on the severity of cholangitis on the day after admission (Day 1). The severity was classified according to the Tokyo Guidelines 2018 (TG18).*

the Exacerbation Group, with 18 patients (54.6%) having undergone chemotherapy, compared to 11 patients (26.8%) in the Stable Group (p=0.015). C-reactive protein (CRP) levels were significantly higher in the Exacerbation group than in the Stable group (1.55 *vs.* 4.6, p=0.006). Conversely, serum albumin (Alb) levels were significantly lower in the Exacerbation group compared to the Stable group (3.7 *vs.* 3.4, p=0.007). EAA levels were also significantly elevated in the Exacerbation group (0.24 *vs.* 0.35, p=0.001). Moreover, the number of patients with an EAA value of ≥0.4 was significantly higher in the Exacerbation group [7 cases (17.1%) in the Stable group *vs.* 14 cases (42.4%) in the Exacerbation group]. There were no significant differences between the two groups in terms of drainage timing or the choice of antimicrobial agents. Although the difference was not statistically significant, the number of intensive care unit (ICU) admissions was higher in the Exacerbation group (2.4% *vs.* 12.1%, p=0.099), and all 28-day mortality cases were observed exclusively in the Exacerbation group (0% *vs.* 6.06%, p=0.110).

Univariate and multivariate logistic regression analysis. Table IV presents the results of the logistic regression analysis identifying risk factors associated with the exacerbation of

Table III. *Characteristics of patients in two groups depending on severity of cholangitis on Day1.*

Variables	Stable Group (n=41)	Exacerbation Group (n=33)	*p*-Value
Age	70 (62-74)	69 (62-77)	0.542
≧75	6 (14.6%)	11 (33.3%)	0.057
Sex			
Male/Female	29/12	21/12	0.517
Cancer bearing	24 (58.5%)	24 (72.7%)	0.204
Chemotherapy within 28 days	11 (26.8%)	18 (54.6%)	0.015
Biliary drainage stent	24 (58.5%)	22 (66.7%)	0.473
Choledochojejunostomy	23 (56.1%)	17 (51.5%)	0.694
Liver abscess	2 (4.9%)	3 (9.1%)	0.473
Vital signs			
Body temperature (˚C)	38.5 (38.1-39.0)	38.6 (37.0-39.0)	0.781
Systolic blood pressure (mmHg)	132 (116-151)	119 (109-138)	0.069
Diastolic blood pressure (mmHg)	77 (67-85)	77 (68-84)	0.987
Heart rate	95 (81-108)	98 (83-114)	0.424
Laboratory data on Day 0			
WBC (/μl)	7,300 (6,200-9,600)	7,600 (6,000-9,800)	0.983
CRP (mg/dl)	1.55 (0.71-3.98)	4.6 (01.24-8.41)	0.006
Procalcitonin (ng/ml)	0.27 (0.18-0.55)	0.47 (0.26-0.69)	0.057
Total bilirubin (mg/dl)	1.0 (0.7-1.5)	1.3 (0.8-2.6)	0.195
Albumin (mg/dl)	3.7 (3.3-4.0)	3.4 (3.1-3.6)	0.007
Creatinine (mg/dl)	0.71 (0.62-0.88)	0.70 (0.63-0.88)	0.926
Platelet (10^4/ml)	17.9 (15.0-23.2)	17.4 (11.4-25.9)	0.507
PT-INR	1.10 (1.03-1.15)	1.14 (1.07-1.24)	0.108
FDP-E (μg/ml)	119 (87-209)	144 (120-208)	0.296
JAAM-DIC score ≧4	2 (4.9%)	3 (9.1%)	0.473
EAA	0.24 (0.15-0.32)	0.35 (0.28-0.46)	0.001
≧0.4	7 (17.1%)	14 (42.4%)	0.016
Positive blood culture	6 (14.6%)	12 (36.4%)	0.030
SOFA score	1 (1-2)	2 (1-3)	0.068
Sepsis grading (SSCG2016)			
Sepsis	19 (46.3%)	20 (60.6%)	0.249
Biliary drainage on Day 0	14 (34.2%)	17 (51.5%)	0.694
Biliary drainage during hospitalization	30 (73.2%)	27 (81.8%)	0.379
Initial antibiotic therapy			
TAZ/PIPC/Carbapenem agents/Others	35/3/3	25/6/2	0.401
ICU admissions during hospitalization	1 (2.4%)	4 (12.1%)	0.099
Length of hospital stay	8 (5-14)	8 (6-13)	0.631
28-day mortality	0 (0.0%)	2 (6.06%)	0.110

WBC: White blood cell count; CRP: C-reactive protein; JAAM-DIC score: Japanese Association for Acute Medicine disseminated intravascular coagulation score; SIRS: systemic inflammatory response syndrome; SOFA score: sequential organ failure assessment score; TG18: Tokyo Guidelines 2018; SSCG2016: Surviving Sepsis Campaign Guidelines 2016; TAZ/PIPC: Piperacillin/Tazobactam.

acute cholangitis. In the univariate analysis, several factors showed potential associations with disease progression. Advanced age (≥75 years) exhibited a trend towards significance [odds ratio (OR)=2.917, 95% confidence interval (CI)=0.943-9.020, *p*=0.063]. Serum albumin levels were significantly associated with a lower risk of cholangitis exacerbation (OR=0.303, 95%CI=0.106-0.865, *p*=0.026), while CRP levels correlated positively with worsening disease (OR=1.147, 95%CI=1.020-1.290, *p*=0.018). Additionally, recent chemotherapy within 28 days (OR=3.273, 95%CI=1.240-8.660, *p*=0.017), SOFA score (OR=1.533, 95%CI=1.000-2.340, *p*=0.048) and EAA ≥0.4 (OR=3.579, 95%CI=1.231-10.402, *p*=0.019) demonstrated associations with cholangitis progression.

Table IV. *Independent variables in multivariate logistic regression analyses associated with predictive factors for exacerbation of mild acute cholangitis.*

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% Confidence interval	*p*-Value	Odds ratio	95% Confidence interval	*p*-Value
Age ≥75	2.917	0.943-9.020	0.063			
Alb	0.303	0.106-0.865	0.026	0.303	0.094-0.975	0.045
CRP	1.147	1.020-1.290	0.018			
Procalcitonin	1.135	0.899-1.430	0.288			
Lac ≥2	1.550	0.498-4.850	0.448			
Liver abscess	1.950	0.306-12.400	0.480			
Chemotherapy within 28 days	3.273	1.240-8.660	0.017	3.440	1.170-10.100	0.025
DIC ≥4	1.950	0.306-12.400	0.480			
SOFA score	1.533	1.000-2.340	0.048			
EAA ≥0.4	3.579	1.231-10.402	0.019	3.880	1.210-12.500	0.023

In the multivariate analysis, serum albumin levels (OR=0.303, 95%CI=0.094-0.975, p=0.045), chemotherapy within 28 days (OR=3.440, 95%CI=1.170-10.100, p=0.025), and EAA ≥0.4 (OR=4.632, 95%CI=1.589-13.515, p=0.005) were identified as independent risk factors for the worsening of acute cholangitis.

Prediction model based on statistically significant factors. A predictive model for exacerbation was constructed using statistically significant factors identified in the multivariable logistic regression analysis. The final model included serum Alb, chemotherapy history within last 28 days, and EAA ≥0.4 at admission as independent predictors. A predictive equation was developed using the logistic regression model: log (P/1-P)=3.285-1.265×Alb (mg/dl) + 1.291 × (Chemotherapy within 28 days) +1.343 × (EAA ≥0.4) (P: the probability of exacerbation). Figure 2 illustrates the performance of the final model using the ROC curve, with the area under the curve (AUC) measured at 0.75. The optimal cutoff value for predicting exacerbation was determined using Youden's Index, establishing a threshold of 0.455, which resulted in a sensitivity of 69.7% and specificity of 68.3%.

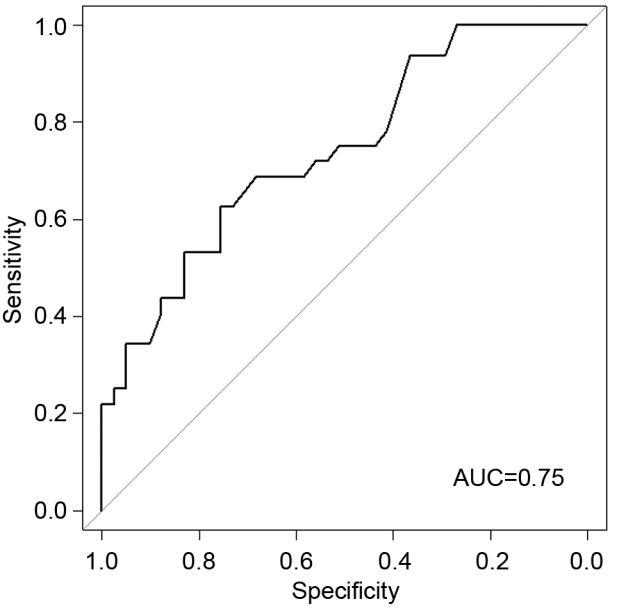

Figure 2. *The performance of the prognostic model was assessed by the ROC curve, with the area under the curve (AUC) measured at 0.75. The optimal cutoff value for predicting exacerbation was determined using Youden's Index, establishing a threshold of 0.455, which resulted in a sensitivity of 69.7% and specificity of 68.3%.*

Discussion

This study investigated potential predictors of disease progression in patients with mild acute cholangitis, with a particular focus on the EAA. Among 74 patients initially diagnosed with mild acute cholangitis, 44.6% progressed to moderate or severe cholangitis within 24 h. Multivariate logistic regression analysis identified three independent risk factors for exacerbation: recent chemotherapy within the past 28 days, lower serum albumin levels, and EAA ≥0.4. Notably, EAA was the most significant predictor of

worsening disease status, emphasizing its potential utility as an early biomarker.

To our knowledge, this study is the first to comprehensively evaluate EAA as a predictive biomarker for acute cholangitis progression. The key strengths of this study include its systematic assessment of a novel biomarker (EAA), its analysis of independent risk factors, and its potential implications for early risk stratification. The identification of EAA ≥0.4 as a strong predictor provides a new approach for clinical decision-making, allowing for timely intervention before severe complications arise. Additionally, the study reinforces the importance of considering albumin levels and recent chemotherapy history in predicting disease progression.

Previous studies have explored various clinical and laboratory markers for assessing cholangitis severity, including the Tokyo Guidelines (TG18) criteria and inflammatory biomarkers such as CRP and procalcitonin (3, 12-15). However, these conventional markers may not fully capture the early pathophysiological changes leading to disease progression. Endotoxins, primarily derived from Gram-negative bacterial infections, have been implicated in the development of sepsis and multi-organ failure (16-18). However, endotoxin levels are not included in the TG18 severity assessment criteria, as no correlation has been observed between endotoxin levels and the severity of acute cholangitis (3).

The utility of EAA as a biomarker has been demonstrated in other critical conditions, including sepsis and systemic inflammatory response syndrome (7, 19-21). We previously reported that EAA levels at admission were significantly correlated with the severity of cholangitis and were also associated with the positive rate of blood cultures (7). By increasing the number of cases to more than twice the original, similar results were obtained in the present analysis (Data not shown). Our study extends these findings by demonstrating that EAA can serve as an early predictor of worsening acute cholangitis, supplementing traditional severity assessments.

The association between elevated EAA levels and cholangitis progression highlights the critical role of endotoxemia in disease exacerbation. A higher EAA value reflects increased neutrophil activation in response to endotoxins, which may indicate a heightened inflammatory state preceding overt clinical deterioration. The predictive value of serum albumin levels suggests that nutritional status and systemic inflammation play a role in disease severity (22). Albumin is a well-established marker of systemic illness and has been linked to worse outcomes in infectious diseases (23). Similarly, the impact of recent chemotherapy suggests that immunosuppression and gut translocation of endotoxins may contribute to a higher risk of disease progression. These findings collectively underscore the need for closer monitoring and early therapeutic intervention in patients with mild acute cholangitis who present these risk factors.

Despite its strengths, this study has several limitations. First, the study was conducted retrospectively at a single institution, which may limit generalizability to other clinical settings. Second, although EAA was identified as a significant predictor, its widespread implementation in routine clinical practice requires further validation through prospective multicenter studies. Additionally, we did not evaluate dynamic changes in EAA over time, which could provide further insights into its role in disease monitoring.

Conclusion

This study demonstrates that EAA is a valuable predictor of disease progression in patients with mild acute cholangitis. Patients with EAA ≥ 0.4, lower serum albumin levels, and a history of recent chemotherapy are at higher risk of worsening cholangitis. These findings suggest that incorporating EAA into routine risk assessment may enhance early identification of high-risk patients, facilitating timely interventions such as intensified antibiotic therapy, early biliary drainage, and close clinical monitoring. Future prospective studies are warranted to further validate these findings and refine risk stratification strategies in acute cholangitis management.

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Authors' Contributions

IE, RM, and KM conceptualized the study. KM, KG, SA, YS, and TK collected the clinical data. KM, KM, and YH designed the statistical analysis plan and performed the statistical analyses. KM, KM, and YH contributed to the interpretation of the results. KM and KM prepared the initial manuscript draft. IE and RM supervised the study. All Authors reviewed the manuscript draft, provided critical revisions for intellectual content, and approved the final version for publication.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in relation to this study.

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