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## Observational Study

## Predictive value of presepsin and acylcarnitines for severity and biliary drainage in acute cholangitis

Han-Yu Zhang, Hong-Li Xiao, Guo-Xing Wang, Zhao-Qing Lu, Miao-Rong Xie, Chun-Sheng Li

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Bacteremia, which is a major cause of mortality in patients with acute cholangitis, induces hyperactive immune response and mitochondrial dysfunction. Presepsin is responsible for pathogen recognition by innate immunity. Acylcarnitines are established mitochondrial biomarkers.

**AIM**

To clarify the early predictive value of presepsin and acylcarnitines as biomarkers of severity of acute cholangitis and the need for biliary drainage.

**METHODS**

Of 280 patients with acute cholangitis were included and the severity was stratified according to the Tokyo Guidelines 2018. Blood presepsin and plasma acylcarnitines were tested at enrollment by chemiluminescent enzyme immunoassay and ultra-high-performance liquid chromatography-mass spectrometry, respectively.

**RESULTS**

The concentrations of presepsin, procalcitonin, short- and medium-chain acylcarnitines increased, while long-chain acylcarnitines decreased with the severity of acute cholangitis. The areas under the receiver operating characteristic curves (AUC) of presepsin for diagnosing moderate/severe and severe cholangitis (0.823 and 0.801, respectively) were greater than those of conventional markers. The combination of presepsin, direct bilirubin, alanine aminotransferase, temperature, and butyryl-L-carnitine showed good predictive ability for biliary drainage (AUC: 0.723). Presepsin, procalcitonin, acetyl-L-carnitine, hydroxydodecenoyl-L-carnitine, and temperature were independent predictors of bloodstream infection. After adjusting for severity classification, acetyl-L-carnitine was the only acylcarnitine independently associated with 28-d mortality (hazard ratio 14.396;  $P <$

0.001) (AUC: 0.880). Presepsin concentration showed positive correlation with direct bilirubin or acetyl-L-carnitine.

### CONCLUSION

Presepsin could serve as a specific biomarker to predict the severity of acute cholangitis and need for biliary drainage. Acetyl-L-carnitine is a potential prognostic factor for patients with acute cholangitis. Innate immune response was associated with mitochondrial metabolic dysfunction in acute cholangitis.

**Key Words:** Acute cholangitis; Severity; Biliary drainage; Presepsin; Acylcarnitines

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**Core Tip:** Acute cholangitis leads to sepsis and organ dysfunction because of biliary obstruction. Identification of predictive biomarkers for patients who require emergent biliary drainage and patients who may progress to systemic bloodstream infection at an early stage of the disease is a key imperative. Our study suggests that presepsin and acetyl-L-carnitine may serve as biomarkers to predict the severity of acute cholangitis and the need for biliary drainage. Innate immune response was associated with mitochondrial metabolic dysfunction.

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## INTRODUCTION

Acute cholangitis refers to bacterial infection of the extra-hepatic biliary tract which typically occurs in association with bile duct obstruction caused by choledocholithiasis, malignant stricture, or primary sclerosing cholangitis. Approximately 20% to 71% of patients with acute cholangitis progress to bacteremia or sepsis, which may lead to life-threatening organ failure and death[1,2]. Early biliary drainage to remove biliary obstruction is one of the main emergency treatments for acute cholangitis. Therefore, the identification of predictive biomarkers for patients who require emergent biliary drainage and patients who maybe progress to systemic bloodstream infection at an early stage of the disease is a key imperative.

Bacteremia induces hyperactive immune response and mitochondrial dysfunction which alter metabolism[3]. Presepsin, a soluble leukocyte differentiation antigen 14 (CD14) subtype, is responsible for pathogen recognition by innate immunity[4]. Presepsin is a biomarker of systemic inflammation that can facilitate early diagnosis, risk-stratification, and prognostic assessment of patients with sepsis[5-7]. Carnitine is responsible for mitochondrial transport and  $\beta$  oxidation of fatty acids. L-carnitine and acylcarnitines are established mitochondrial biomarkers[8]. Preclinical and recent clinical studies have demonstrated the association of plasma carnitine or acylcarnitines with organ dysfunction and poor survival in sepsis[9-11]. However, it is unknown whether presepsin or specific acylcarnitine species can reflect severity of acute cholangitis and the timing of biliary drainage. Therefore, this study aimed to evaluate the value of presepsin as well as specific acylcarnitines as predictors of severity, bloodstream infection, biliary drainage and prognosis in patients with acute cholangitis.

## MATERIALS AND METHODS

### Study design

A prospective observational study was conducted to clarify the predictive value of presepsin and acylcarnitines for severity and biliary drainage in patients with acute cholangitis. The primary outcomes were the abilities of presepsin and acylcarnitines to predict severe acute cholangitis compared with procalcitonin. The secondary outcomes included the value of presepsin and acylcarnitines to predict emergency biliary drainage, positive bloodstream infection, and prognosis of acute cholangitis. This study complied with the principles of the Declaration of Helsinki. The Beijing Friendship Hospital Ethics Committee approved the study protocol (No. 2018-P2-063-01). Patients were enrolled after providing written informed consent.

### Study participants

This was a single-center study conducted at the emergency department and emergency intensive care unit of Beijing Friendship Hospital, a National Clinical Research Center of Digestive Diseases. Between May 2019 and July 2021, consecutive adult patients who fulfilled the acute cholangitis criteria based on the Tokyo Guidelines 2018 (TG18) for acute cholangitis were enrolled[12]. The severity was stratified as mild, moderate, and severe according to TG18[12]. The exclusion criteria were as follows: (1) Patients with chronic kidney or liver disease who may have increased presepsin or acylcarnitine levels at baseline[13]; (2) HIV infection; (3) pregnant and lactating women; (4) patients with abdominal trauma or history of abdominal surgery in the past seven days; (5) incomplete data about the main study indices (presepsin, acylcarnitines, or blood culture results); and (6) patients who declined to participate.

### Data collection

We recorded demographic data, comorbidities, clinical and laboratory data, severity grading of acute cholangitis and biliary drainage data within 48 h after admission. Disease severity was assessed using the sequential organ failure assessment (SOFA) scores. The criteria for implementing biliary drainage were based on the American Society for Gastrointestinal Endoscopy (ASGE) guidelines for the management of cholangitis[14]. Blood samples of all patients and bile samples of patients who were subjected to endoscopic or percutaneous biliary drainage were cultured for aerobic and anaerobic bacteria. Pathogens in blood samples were identified by blood culture and metagenomic next generation sequencing (mNGS). Data for 28-d mortality were collected during follow-up.

### Sample collection and processing

Blood samples (5 mL) were collected immediately after admission and stored at 4 °C. 200 µL of these blood samples were extracted to detect presepsin concentration. The remaining blood samples were centrifuged for 10 min at 4500 g and the plasma sample was then stored at -80 °C within 24 h. For acylcarnitines detection, 50 µL plasma sample was drawn into a 2 mL centrifuge tube and mixed with 140 µL methanol and 10 µL internal standard (NSK-B-1) and further centrifuged for 5 minutes at 12000 g. 100 µL supernatant was transferred into 200 µL inner liner before analyses. For mNGS detection, 3 mL blood sample was drawn from patients and centrifuged at 4000 g for 10 min within 8 h after collection. DNA was extracted from plasma using a TIANamp Micro DNA Kit (Tiangen Biotech, Beijing, China, No. DP316) according to the manufacturer's operating manual. The extracted DNA specimens were used for the construction of DNA libraries.

### Measurements of presepsin

A chemiluminescent enzyme immunoassay was used to test presepsin concentration by a PATHFAST analyzer (Mitsubishi Chemical Medience Corporation, Tokyo, Japan). The detection range was 20 pg/mL to 200000 pg/mL. Information regarding conventional inflammatory biomarkers procalcitonin, C-reactive protein (CRP) and other indicators were obtained from the clinical laboratory data.

### Determination of acylcarnitines

Plasma acylcarnitines at enrollment were determined by an ultra-high-performance liquid chromatography-mass system (UHPLC-MS, [Supplementary file 1](#)) using a Waters XEVO TQ-S Micro triple quadrupole mass spectrometer (Waters Corp, United States). The length of carbon chains was used to define short-chain ( $C \leq 5$ ), medium-chain ( $C6-10$ ) and long-chain acylcarnitines ( $C \geq 12$ ) ([Supplementary Table 1](#)).

### Next-generation sequencing

mNGS testing of the blood samples was performed and analyzed by BGI-Shenzhen, as previously reported[15]. Briefly, the extracted DNA was fragmented to 300 bp. DNA libraries were constructed by end-repair, adapter ligation and PCR amplification using the PMseq™ high throughput gene detection kit for infectious pathogens (combined probe anchored polymerization sequencing method, BGI-Shenzhen, China, No. RM0438), according to the manufacturer's instructions ([Supplementary file 2](#)). Using bioinformatics analysis methods and pathogenic microorganism database, the types of pathogenic microorganisms obtained by sequencing were analyzed, and the detection results of each sample were obtained.

### Statistical analyses

Factoring a two-sided  $\alpha = 0.05$ ,  $\beta = 0.2$ , and assuming 50% of patients with mild acute cholangitis[16], it was determined that 268 patients were required for enrollment, *i.e.*, 134 with mild and moderate acute cholangitis and 134 with severe acute cholangitis. This study enrolled 387 patients to account for patients lost to follow-up and patients with incomplete data collection. Continuous variables with non-normal distribution were presented as median (25<sup>th</sup> to 75<sup>th</sup> percentile) and compared by Mann-Whitney *U* test or Kruskal-Wallis test. Comparisons between categorical variables were analyzed by Pearson  $\chi^2$  test. Significant biomarkers and clinical variables associated with severity, biliary drainage, bloodstream

infection, and 28-d mortality were identified by multivariate logistic regression models. The area under the receiver operating characteristic (ROC) curves were applied to examine the predictive accuracy of presepsin, acylcarnitines, and procalcitonin for severity and biliary drainage. The optimal cutoff levels determined by ROC curves and Youden index were used to dichotomize presepsin, acylcarnitines, procalcitonin, and other independent predictors. The area under the curve (AUC) comparisons were performed using MedCalc Version 13 software (Mariakerke, Belgium). Kaplan-Meier survival curves were established, and between-group differences in 28-d survival were assessed using the log-rank test. The Cox proportional hazard model was used to calculate the hazard ratio (HR) for 28-d mortality. Spearman rank correlation was performed for the correlation analysis. Two-sided *P* values < 0.05 were considered indicative of statistical significance. SPSS 25.0 software (SPSS, Chicago, IL, United States) was used for statistical analyses.

## RESULTS

### **Characteristics of the study population**

From May 2019 through July 2021, 387 patients with acute cholangitis were admitted to the emergency department or EICU. Data from 107 patients were not analyzed because 29 patients did not meet the inclusion criteria, 38 patients refused consent, 35 patients had incomplete main records, and 5 patients were lost to follow-up (Supplementary Figure 1). The remaining 280 patients were enrolled in this study and assigned to the mild group (*n* = 65), moderate group (*n* = 84), and severe group (*n* = 131) based on the TG18 criteria. The age, proportion of patients with biliary drainage, levels of temperature, white blood cell (WBC) count, total bilirubin, direct bilirubin and SOFA score, and 28-d mortality increased with the severity of acute cholangitis, and the differences among the three groups were significant (*P* < 0.05 for all) (Table 1).

### **Performance of presepsin to predict the severity of acute cholangitis compared with procalcitonin, CRP, or acylcarnitine**

Compared with the mild group, presepsin, procalcitonin, and CRP levels were significantly higher in patients with moderate and severe acute cholangitis (*P* < 0.001, Table 2). Plasma short chain and medium chain acylcarnitines (C0, C2–C6, C8) increased, while long chain acylcarnitines (C12–C14, C18, C20, C22) decreased with the severity of acute cholangitis (*P* < 0.05, Table 2). Multivariate logistic regression showed that increased levels of presepsin, WBC, total bilirubin, temperature, and age, and decreased level of tetradecadienyl-L-carnitine (C14:2), but not procalcitonin and CRP levels, were independent predictors of moderate and severe patients, compared with mild patients (Table 3). The AUC of presepsin for predicting moderate/severe cholangitis was 0.823 (sensitivity 0.75; specificity 0.78; cutoff value 1519 pg/mL), which was higher than that of WBC (0.734; *P* = 0.0189), total bilirubin (0.677; *P* = 0.0004), temperature (0.598; *P* < 0.0001), age (0.635; *P* = 0.0002), and C14:2 (0.678; *P* = 0.0012) (Figure 1A). Compared with mild/moderate patients, presepsin, procalcitonin and valeryl-L-carnitine (C5) were independently associated with severe cholangitis (Table 3). The AUC of presepsin (0.801; sensitivity 0.82; specificity 0.66; cutoff value 1680 pg/mL) for severe cholangitis was significantly higher than that of procalcitonin (0.696, *P* = 0.0028) and C5 (0.664, *P* = 0.0008) (Figure 1B).

### **Performance of presepsin and acylcarnitines to predict biliary drainage**

One hundred and seventy-six of 280 patients underwent biliary drainage. Compared with patients without biliary drainage, patients with biliary drainage had significantly increased temperature, levels of presepsin, total bilirubin, direct bilirubin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (*P* < 0.05 for all), rather than procalcitonin (*P* = 0.199) and CRP (*P* = 0.410) levels. On multivariate logistic regression, high presepsin (OR 2.312, *P* = 0.004), direct bilirubin (OR 1.902, *P* = 0.027), ALT (OR 1.878, *P* = 0.022) and temperature (OR 2.108, *P* = 0.006), and low plasma butyryl-L-carnitine (C4) (OR 3.326, *P* = 0.001) were identified as independent predictors of biliary drainage (Table 4). The AUC of a combination of these five predictors was 0.723, which was significantly greater compared with presepsin (0.604, *P* = 0.0001), direct bilirubin (0.600, *P* < 0.0001), ALT (0.579, *P* < 0.0001), temperature (0.599, *P* = 0.0001), and C4 (0.574, *P* < 0.0001) alone (Figure 1C). In the model composed of these five factors (Table 4), a cutoff score of 3 was associated with 79.6% sensitivity, 54.8% specificity, 63.8% PPV, and 72.9% NPV for predicting biliary drainage (LR + 1.76 and LR– 0.37) (Figure 1D).

### **The concentrations of presepsin, acylcarnitines, and procalcitonin in patients with positive and negative blood infection**

As a substitute for the severity of acute cholangitis, blood infection was identified by blood culture and blood mNGS. Compared to patients with no blood infection (*n* = 188), patients with blood infection (*n* = 92) were more likely to require biliary drainage, and had significantly higher temperature, WBC, and SOFA scores (*P* < 0.05 for all, Supplementary Table 2). The proportion of male patients in the blood infection group was significantly lower than that in the group without blood infection. The positive

**Table 1 Clinical characteristics according to severity grading of acute cholangitis**

Variables	All cases (n = 280)	Mild (n = 65)	Moderate (n = 84)	Severe (n = 131)	P value
Demographic data, age (yr)	74 (66, 84)	69 (63, 81)	79.5 (69, 87)	74 (66, 84)	0.001
Male, n (%)	166 (59.3)	34 (52.3)	53 (63.1)	79 (60.3)	0.392
Comorbidities, n (%)					
CHD	78 (27.9)	19 (29.2)	22 (26.2)	37(28.2)	0.911
Heart failure	23 (8.2)	3 (4.6)	5 (6.0)	15 (11.5)	0.173
Hypertension	87 (31.1)	16 (24.6)	32 (38.1)	39 (29.8)	0.192
CVD	33 (11.8)	4 (6.2)	10 (11.9)	19 (14.5)	0.233
COPD	10 (3.6)	1 (1.5)	2 (2.4)	7 (5.3)	0.313
Diabetes mellitus	64 (22.9)	11 (16.9)	18 (21.4)	35 (26.7)	0.286
Biliary drainage, n (%)					
No	104 (37.1)	34 (52.3)	27 (32.1)	43 (35.0)	0.015
ERCP/PTCD	176 (62.9)	31 (47.7)	57 (67.9)	88 (67.2)	
Infection data					
Temperature (°C)	37.5 (36.7, 38.5)	37.2 (36.5, 38.0)	37.5 (36.6, 38.6)	37.8 (36.8, 38.5)	0.044
WBC count ( $\times 10^9/L$ )	10.73 (7.37, 14.83)	8.10 (6.47, 10.22)	13.00 (8.61, 16.56)	11.35 (7.89, 15.71)	< 0.001
Liver function					
TBIL ( $\mu\text{mol/L}$ )	98.69 (62.63, 142.32)	69.26 (48.02, 103.37)	114.40 (77.04, 164.67)	103.99 (74.30, 139.53)	< 0.001
DBIL ( $\mu\text{mol/L}$ )	70.29 (42.68, 98.75)	43.20 (26.53, 75.64)	78.90 (58.09, 110.40)	72.07 (44.85, 96.29)	< 0.001
ALT (U/L)	148.00 (80.00, 287.50)	166.00 (63.50, 386.50)	145.00 (84.62, 300.00)	148.00 (77.00, 240.00)	0.626
AST (U/L)	138.05 (82.50, 286.10)	129.50 (69.60, 346.20)	138.80 (96.10, 299.10)	137.85 (72.03, 266.53)	0.744
SOFA score	2 (1, 4)	1 (1, 2)	1 (1, 2)	4 (3, 5)	< 0.001
28-d mortality, n (%)	9 (3.2)	0 (0.0)	0 (0.0)	9 (6.9)	0.005

Data expressed as median ( $P_{25}$ ,  $P_{75}$ ) or n (%). CHD: Coronary heart disease; CVD: Cerebral vascular disease; COPD: Chronic obstructive pulmonary disease; ERCP: Endoscopic retrograde cholangiopancreatography; PTCD: Percutaneous transhepatic biliary drainage; WBC: White blood cell; TBIL: Total bilirubin; DBIL: Direct bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; SOFA: Sequential organ failure assessment.

rates of blood culture, blood mNGS, and bile culture were 29.3% (82/280), 66.7% (14/21), and 76.7% (135/176), respectively. The most common bacteria identified were *Escherichia coli*, *Klebsiella pneumoniae* and *Enterococcus faecium*. Blood infection positivity was associated with significantly higher level of presepsin ( $P = 0.001$ ), procalcitonin ( $P < 0.001$ ), acetyl-L-carnitine (C2,  $P = 0.009$ ), propionyl-L-carnitine (C3,  $P = 0.035$ ), hexanoyl-L-carnitine (C6,  $P = 0.036$ ), and hydroxydodecenoyl-L-carnitine (C12:1 OH,  $P = 0.018$ ).

### Ability of presepsin, acylcarnitines, and procalcitonin to identify bloodstream infection in acute cholangitis

We dichotomized presepsin, procalcitonin, C2, C3, C6, and C12:1 OH using the optimal cutoff value. After adjusting for sex, severity grading, and SOFA score, presepsin (OR 3.466,  $P = 0.018$ ), procalcitonin (OR 4.054,  $P < 0.001$ ), C2 (OR 3.716,  $P = 0.005$ ), C12:1 OH (OR 3.611,  $P = 0.002$ ), and temperature (OR 1.671,  $P = 0.003$ ) were found to be independent predictors for bloodstream infection (Table 5). The AUC of presepsin for diagnosing blood infection was 0.610 (sensitivity 0.91; specificity 0.32; cut-off 1147.5 pg/mL), but there was no significant difference between presepsin and procalcitonin (AUC: 0.679), C2 (AUC: 0.599), C12:1 OH (AUC: 0.603), and temperature (AUC: 0.639) in this respect (Supplementary Table 3).

### Prognostic value of presepsin, acylcarnitines, and procalcitonin for 28-d mortality

The 28-d mortality rate in this study was 3.2%. The characteristics of survivors and non-survivors are illustrated in Supplementary Table 4. Compared with patients who survived, those who died within 28 d had significantly increased presepsin ( $P = 0.004$ ), C2 ( $P = 0.001$ ), and C12:1 OH ( $P = 0.004$ ) (Figure 2A-C), but not increased procalcitonin ( $P = 0.591$ ) and CRP ( $P = 0.141$ ). The AUC of presepsin (0.839), C2

Table 2 Biomarkers according to severity grading of acute cholangitis

Biomarkers	All cases (n = 280)	Mild (n = 65)	Moderate (n = 84)	Severe (n = 131)	P value
Presepsin (pg/mL)	1864.00 (1169.75, 2765.75)	1053.00 (576.50, 1505.50)	1634.00 (1103.00, 2325.75)	2536.00 (1812.00, 3730.00)	< 0.001
Procalcitonin (ng/mL)	11.32 (2.10, 40.53)	3.57 (0.64, 10.87)	10.70 (1.48, 31.00)	27.43 (4.76, 54.32)	< 0.001
CRP (mg/L)	83.71 (44.23, 153.29)	48.02 (17.00, 103.48)	80.76 (48.39, 143.91)	107.00 (61.18, 174.12)	< 0.001
Acylcarnitines (μmol/L)					
C0	28.54 (19.60, 38.65)	25.39 (18.72, 32.47)	29.65 (19.96, 38.38)	30.00 (21.19, 40.64)	0.042
C2	9.64 (6.16, 14.01)	8.35 (5.23, 12.29)	9.44 (6.67, 12.53)	10.32 (6.43, 15.30)	0.016
C3	0.38 (0.26, 0.60)	0.31 (0.21, 0.43)	0.35 (0.26, 0.53)	0.46 (0.29, 0.71)	< 0.001
C4	0.09 (0.06, 0.16)	0.08 (0.06, 0.12)	0.09 (0.05, 0.13)	0.10 (0.07, 0.19)	0.003
C5	0.11 (0.07, 0.18)	0.08 (0.06, 0.18)	0.09 (0.06, 0.14)	0.14 (0.08, 0.24)	< 0.001
C6	0.11 (0.07, 0.15)	0.08 (0.06, 0.14)	0.10 (0.06, 0.13)	0.13 (0.08, 0.20)	< 0.001
C8	0.13 (0.10, 0.22)	0.12 (0.08, 0.19)	0.13 (0.10, 0.20)	0.14 (0.11, 0.23)	0.037
C12	0.09 (0.04, 0.18)	0.14 (0.07, 0.28)	0.09 (0.04, 0.17)	0.08 (0.03, 0.13)	< 0.001
C12:1	0.05 (0.03, 0.08)	0.06 (0.04, 0.10)	0.05 (0.03, 0.09)	0.04 (0.02, 0.07)	0.001
C12DC	0.0005 (0.0004, 0.0008)	0.0006 (0.0005, 0.0009)	0.0005 (0.0004, 0.0009)	0.0004 (0.0003, 0.0007)	0.041
C13	0.03 (0.02, 0.07)	0.04 (0.03, 0.07)	0.03 (0.02, 0.08)	0.02 (0.01, 0.05)	0.008
C14	0.02 (0.01, 0.03)	0.03 (0.02, 0.04)	0.02 (0.01, 0.03)	0.02 (0.01, 0.03)	0.001
C14:1	0.09 (0.04, 0.16)	0.16 (0.07, 0.31)	0.09 (0.05, 0.13)	0.06 (0.03, 0.11)	< 0.001
C14:2	0.07 (0.03, 0.14)	0.12 (0.05, 0.22)	0.06 (0.03, 0.13)	0.05 (0.02, 0.10)	< 0.001
C16	0.10 (0.06, 0.15)	0.12 (0.08, 0.17)	0.10 (0.06, 0.14)	0.09 (0.05, 0.13)	0.003
C16:1	0.06 (0.03, 0.12)	0.10 (0.05, 0.16)	0.05 (0.03, 0.10)	0.05 (0.02, 0.12)	0.003
C16:2	0.02 (0.002, 0.06)	0.04 (0.01, 0.09)	0.01 (0.002, 0.05)	0.02 (0.002, 0.05)	0.006
C18:2	0.13 (0.07, 0.21)	0.16 (0.09, 0.24)	0.12 (0.07, 0.18)	0.11 (0.05, 0.22)	0.014
C18 OH	0.0004 (0.0002, 0.0009)	0.004 (0.003, 0.0013)	0.0006 (0.0002, 0.0010)	0.0004 (0.0002, 0.0007)	0.035
C20	0.0010 (0.0004, 0.0018)	0.0013 (0.0009, 0.0029)	0.0013 (0.0005, 0.0020)	0.0007 (0.0003, 0.0014)	0.001
C20:4	0.0013 (0.0007, 0.0023)	0.0018 (0.0009, 0.0021)	0.0018 (0.0008, 0.0037)	0.0012 (0.0005, 0.0020)	0.024
C22	0.0009 (0.0003, 0.0015)	0.0011 (0.0006, 0.0023)	0.0010 (0.0003, 0.0018)	0.0006 (0.0002, 0.0014)	0.009

Data expressed as median ( $P_{25}$ ,  $P_{75}$ ). CRP: C-reactive protein; C0: DL-Carnitine; C2: Acetyl-L-carnitine; C3: Propionyl-L-carnitine; C4: Butyryl-L-carnitine; C5: Valeryl-L-carnitine; C6: Hexenoyl-L-carnitine; C8: Octanoyl-L-carnitine; C12: Dodecanoyl-L-carnitine; C12:1: Dodecenoyl-L-carnitine; C12DC: Dodecanedioyl-L-carnitine; C13: Tridecanoyl-L-carnitine; C14: Tetradecanoyl-L-carnitine; C14:1: Tetradecenoyl-L-carnitine; C14:2: Tetradecadienyl-L-carnitine; C16: Hexadecanoyl-L-carnitine; C16:1: Hexadecenoyl-L-carnitine; C16:2: Hexadecadienyl-L-carnitine; C18:2: Octadecadienyl-L-carnitine; C18OH: Hydroxyoctadecanoyl-L-carnitine; C20: Icosyl-L-carnitine; C20:4: Arachidonoyl-L-carnitine; C22: Behenoyl-L-carnitine.

(0.880), and C12:1 OH (0.822) for 28-d mortality was similar to that of SOFA score (0.848,  $P > 0.05$  for all) (Figure 2D and Supplementary Table 5). After adjusting for severity of acute cholangitis by multivariate Cox proportional hazard models, high C2 ( $P = 0.004$ ) was the only independent predictor of 28-d mortality, rather than the levels of presepsin ( $P = 0.732$ ), C12:1 OH ( $P = 0.899$ ), and SOFA score ( $P = 0.133$ ) (Supplementary Table 6). Based on ROC curves for 28-d mortality and Youden index, a cutoff value of 17.07 μmol/L was used to dichotomize C2. Patients with high C2 Level had significantly higher 28-d mortality compared to those with low C2 Level (HR 14.396; 95%CI: 3.599-57.576;  $P < 0.001$ ; Figure 2E).

### Correlation of presepsin with acylcarnitines

Increased level of presepsin ( $r = 0.424$ ,  $P < 0.001$ ), procalcitonin ( $r = 0.357$ ,  $P < 0.001$ ), and C2 ( $r = 0.208$ ,  $P < 0.001$ ) showed a significant association with SOFA score. We confirmed that presepsin, but not procalcitonin, showed a significant positive correlation with total bilirubin ( $r = 0.290$ ,  $P < 0.001$ ), direct bilirubin ( $r = 0.304$ ,  $P < 0.001$ ), and C2 ( $r = 0.270$ ,  $P < 0.001$ ) (Supplementary Table 7).

**Table 3 Clinical variables and biomarkers associated with severity of acute cholangitis (multivariate logistic regression models)**

Variables	Mild vs moderate/severe		Mild/moderate vs severe	
	OR (95%CI)	P value	OR (95%CI)	P value
Presepsin (pg/mL)	1.001 (1.000-1.002)	< 0.001	1.000 (1.000-1.001)	< 0.001
Procalcitonin (ng/mL)	1.018 (0.995-1.041)	0.134	1.021 (1.008-1.035)	0.001
WBC ( $\times 10^9/L$ )	1.149 (1.050-1.258)	0.003	0.990 (0.945-1.037)	0.676
CRP (mg/L)	1.001 (0.995-1.008)	0.642	1.003 (0.999-1.008)	0.104
TBIL( $\mu\text{mol/L}$ )	1.008 (1.003-1.013)	0.003	0.999 (0.996-1.002)	0.504
Temperature ( $^{\circ}\text{C}$ )	1.540 (1.046-2.267)	0.029	1.118 (0.859-1.456)	0.407
Age (yr)	1.051 (1.018-1.085)	0.002	1.000 (0.977-1.022)	0.973
C14:2 ( $\mu\text{mol/L}$ )	0.036 (0.002-0.663)	0.025	-	-
C5 ( $\mu\text{mol/L}$ )	-	-	11.490(2.213-59.656)	0.004

WBC: White blood cell; CRP: C-reactive protein; TBIL: Total bilirubin; C14:2: Tetradecadienyl-L-carnitine; C5: Valeryl-L-carnitine; OR: Odds ratio; CI: Confidence interval.

**Table 4 A model for predicting biliary drainage in acute cholangitis multivariate logistic regression models**

Variables	B	SE	Wald	df	OR	95%CI	P value	Score
Presepsin > 1868 (pg/mL)	0.838	0.291	8.308	1	2.312	1.308-4.087	0.004	1
C4 $\leq$ 0.1803 ( $\mu\text{mol/L}$ )	1.202	0.347	12.017	1	3.326	1.686-6.561	0.001	1
DBIL > 51.18 ( $\mu\text{mol/L}$ )	0.643	0.290	4.912	1	1.902	1.077-3.358	0.027	1
ALT > 159 (U/L)	0.630	0.275	5.254	1	1.878	1.096-3.219	0.022	1
Temperature $\geq$ 37.3 ( $^{\circ}\text{C}$ )	0.746	0.270	7.602	1	2.108	1.241-3.581	0.006	1

C4: Butyryl-L-carnitine; DBIL: Direct bilirubin; ALT: Alanine aminotransferase; OR: Odds ratio; CI: Confidence interval.

## DISCUSSION

The immunologic profile and mitochondrial function of patients with acute cholangitis are similar to those of septic patients. Thus, in this prospective study, we explored the value of presepsin and carnitine metabolites as biomarkers to predict severity, emergency biliary drainage, and prognosis of patients with acute cholangitis. Our results indicated that the ability of presepsin level to predict moderate/severe and severe cholangitis was superior to that of procalcitonin level. High presepsin, direct bilirubin, ALT, temperature, and low C4 were independent predictors of urgent biliary drainage, and the combination of these five predictors significantly improved the predictive accuracy. As a substitute for severity of acute cholangitis, blood infection was found to be independently associated with the biomarkers of presepsin, procalcitonin, C2, and C12:1 OH. High C2 was identified as the only independent predictor of 28-d mortality. Additionally, the positive correlation between presepsin and C2 reflected the association between innate immune response and mitochondrial fatty acid  $\beta$ -oxidation (FAO) impairment during the progression of acute cholangitis.

CD14 are expressed on the surface of innate immune cells and play a role in the activation of innate immune response after recognition of bacteria[4,17]. Presepsin (soluble CD14) has been confirmed as a marker of host response in sepsis patients. Increased presepsin was demonstrated to be associated with organ dysfunction, positive blood culture and mortality in sepsis[4]. This result was consistent with our finding wherein presepsin level was found to identify severe acute cholangitis and bloodstream infection. Animal model of acute obstructive cholangitis demonstrated infiltration of macrophages and neutrophils into the liver sinusoids and around the bile duct leading to coagulopathy[18]. The study of Guicciardi *et al*[19] revealed that macrophages contributed to the pathogenesis of sclerosing cholangitis. These findings suggested the activation of innate immune response in acute cholangitis. In addition, a recent study showed that the conventional septic biomarker procalcitonin which was produced by C cells of the thyroid gland predicted severe but not moderate/severe acute cholangitis with better accuracy than WBC and CRP[16]. Furthermore, our finding demonstrated the superior ability of presepsin to predict severe or moderate/severe cholangitis compared to procalcitonin and other

Table 5 Variables associated with bloodstream infection multivariate logistic regression models

Variables	B	SE	Wald	df	OR	95%CI	P value
Presepsin (High vs low <sup>1</sup> )	1.243	0.524	5.617	1	3.466	1.240-9.689	0.018
Procalcitonin (High vs low <sup>2</sup> )	1.400	0.401	12.208	1	4.054	1.849-8.889	< 0.001
C2 (High vs low <sup>3</sup> )	1.313	0.464	7.998	1	3.716	1.496-9.229	0.005
C3 (High vs low <sup>4</sup> )	0.319	0.400	0.636	1	1.376	0.628-3.015	0.425
C6 (High vs low <sup>5</sup> )	-0.450	0.436	1.065	1	0.638	0.271-1.499	0.302
C12:1 OH (High vs low <sup>6</sup> )	1.284	0.410	9.829	1	3.611	1.618-8.058	0.002
Sex	0.282	0.356	0.628	1	1.326	0.660-2.667	0.428
Temperature (°C)	0.513	0.174	8.714	1	1.671	1.188-2.350	0.003
Severity grading	-0.071	0.285	0.062	1	0.932	0.533-1.628	0.804
SOFA score	-0.062	0.081	0.587	1	0.940	0.802-1.101	0.444

<sup>1</sup>Presepsin (high vs low): > 1147.5 pg/mL vs ≤ 1147.5 pg/mL.

<sup>2</sup>Procalcitonin (high vs low): > 10.83 ng/mL vs ≤ 10.83 ng/mL.

<sup>3</sup>C2 (high vs low): > 14.59 μmol/L vs ≤ 14.59 μmol/L.

<sup>4</sup>C3 (high vs low): > 0.53 μmol/L vs ≤ 0.53 μmol/L.

<sup>5</sup>C6 (high vs low): > 0.12 μmol/L vs ≤ 0.12 μmol/L.

<sup>6</sup>C12:1 OH (high vs low): > 0.02 μmol/L vs ≤ 0.02 μmol/L.

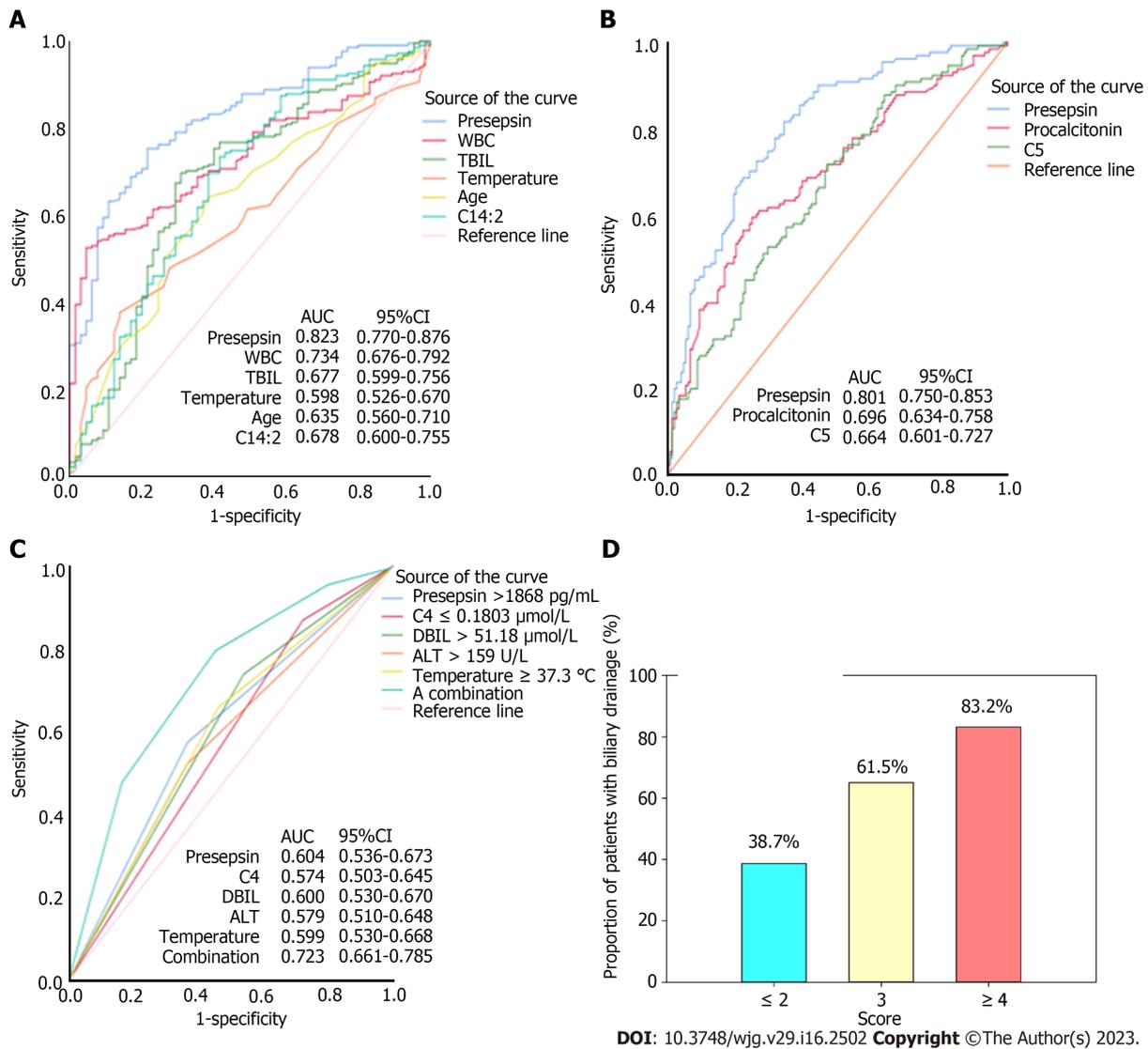
C2: Acetyl-L-carnitine; C3: Propionyl-L-carnitine; C6: Hexanoyl-L-carnitine; C12:1 OH: Hydroxydodecenoyl-L-carnitine; SOFA: Sequential organ failure assessment; OR: Odds ratio; CI: Confidence interval.

markers. The AUC of presepsin was higher than that of other markers in predicting any severity of acute cholangitis. As a surrogate of severe acute cholangitis, predictors for positive bloodstream infection were explored. The most commonly identified bacteria in our study were *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterococcus faecium*, which is consistent with the findings reported by An *et al*[20]. Similar to the study by Umefune *et al*[16] on the association between procalcitonin and positive blood culture in acute cholangitis, the current study found that presepsin, procalcitonin, C2, and C12:1 OH were independent predictors of positive blood infection.

Additionally, to facilitate early identification of patients who require emergency biliary drainage, we established a predictive model consisting of five factors including presepsin, direct bilirubin, ALT, temperature, and butyryl-L-carnitine (C4). Previous studies suggested that procalcitonin might be a decision-supporting biomarker for urgent biliary decompression even in cases that are not categorized as severe based on TG13[21,22]. However, there was no evidence in this study that procalcitonin, rather than presepsin, could independently predict biliary drainage. The results indicated superior ability of presepsin to reflect the degree of biliary obstruction compared to procalcitonin.

Acylcarnitines are recognized for facilitating FAO for energy production in mitochondria[23]. The blood concentrations of acylcarnitines, which represent a group of mitochondrial-derived metabolites, reflect disorders of long-chain FAO[24]. The production of acetylcarnitine (C2) represents metabolic flexibility in buffering the metabolic status between glucose oxidation and fat oxidation states[25]. Elevation in plasma concentration of C2 is a signal of metabolic inflexibility[8]. Mitochondrial metabolic dysfunction has been implicated as one of the potential causes of organ dysfunction in sepsis[26]. Metabolic flexibility was shown to be an important characteristic of patients with sepsis for survival [27]. Plasma C2 Level was shown to be associated with multiple organ dysfunction, extubation, and freedom from vasopressors, or mortality in patients with sepsis[10,11]. In several studies, plasma short chain and medium chain acylcarnitines (C2, C3, C4, C5, C6, C8, C10) were significantly increased in the non-survivors[11,28-30] and only C2 was associated with all of these indices and 28-d mortality in sepsis [12]. Similar to previous studies, our findings showed that concentrations of short- and medium-chain acylcarnitines increased with the severity and C2 was the only acylcarnitine implicated in 28-d mortality. Increased plasma C2 Level may indicate metabolic inflexibility of nonsurvivors with acute cholangitis. Inconsistent with the absence of long chain acetylcarnitine in sepsis studies, we found that concentrations of long chain acylcarnitines decreased with the severity of acute cholangitis, which might be due to impairment of long-chain FAO with disease progression.

Interestingly, in the current study, reduced butyryl-L-carnitine (C4) was found to be an independent predictor of biliary drainage. Butyrate, a short chain fatty acid, is produced in the bowel by bacterial fermentation of dietary fiber. C4, a butyrate ester of carnitine, is known to help maintain intestinal health and prevent intestinal inflammation[31]. C4 combined with presepsin, direct bilirubin, ALT, and temperature showed better predictive accuracy for emergency biliary drainage. The total score of this model was 5, and 83.2% of patients with score > 4 required biliary drainage (Figure 1D). Moreover, the

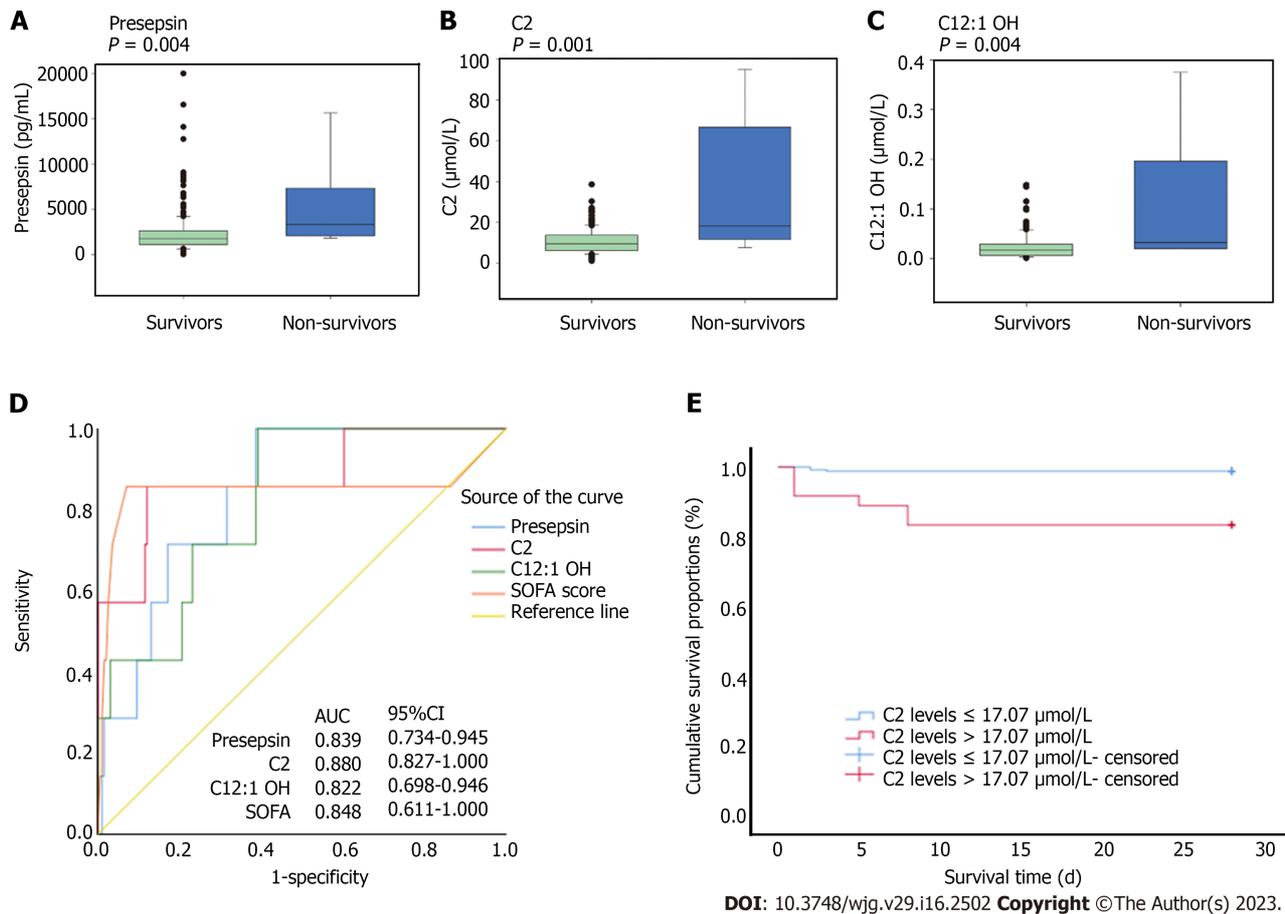


**Figure 1 Receiver operating characteristic curves for biomarkers and clinical parameters for predicting the severity of acute cholangitis and the need for biliary drainage.** A: Mild vs moderate/severe acute cholangitis; B: Mild/moderate vs severe acute cholangitis; C: No biliary drainage vs biliary drainage in acute cholangitis; D: Correlation between the score of biliary drainage prediction model and the proportion of patients with biliary drainage. WBC: White blood cell; TBIL: Total bilirubin; C14:2: Tetradecadienyl-L-carnitine; C5: Valeryl-L-carnitine; C4: Butyryl-L-carnitine; ALT: Alanine aminotransferase.

association between C4 and SOFA score, presepsin, and procalcitonin (Supplementary Table 7) may be explained by the compensatory mechanism of intestinal health on intestinal inflammation in acute cholangitis. Furthermore, the association between C2 and inflammation, as well as the hepatic host response to bacteria leading to the accumulation of long-chain acylcarnitines and defective FAO[32], may explain why C2 and hydroxydodecenoyl-L-carnitine (C12:1 OH) were identified as independent predictors of bloodstream infection in acute cholangitis.

The association between innate immunity and FAO may explain the positive correlation between presepsin and acylcarnitine. Recent evidence suggested that metabolic reprogramming including FAO was a prerequisite for the activation of macrophages and monocytes[33,34]. A study by Zhu *et al*[35] found that the rewiring of metabolic and mitochondrial bioenergetics by monocytes activated, deactivated and resolved acute inflammation in turn. During deactivation, the characteristics of lipid metabolic rewiring included increased acylcarnitines levels. The function of immunocytes depends on specific metabolic programs in mitochondria, including post-translational modifications (*e.g.*, acetylation). In their *in vitro* and *in vivo* studies, Chi *et al*[36] found that histone deacetylase 3 couples mitochondria to deacetylate the FAO enzyme HADHA for NLRP3 inflammasome activation in macrophages.

Some limitations of this study should be considered. First, we did not analyze the dynamic changes in presepsin and acylcarnitines levels over time throughout the disease course. Second, the association of presepsin or acylcarnitines with chronic liver or kidney dysfunction was not assessed in this study. Third, due to the low mortality, a larger sample size was required to verify biomarkers that were associated with death. Fourth, blood mNGS was required for larger population size to improve the



**Figure 2 Association of prepsin and acylcarnitines with 28-d survival in acute cholangitis.** A-C: 28-d survival showed significant correlation with prepsin (A), acetyl-L-carnitin (C2; B), and hydroxydodecenoyl-L-carnitine (C12:1 OH; C); D: Receiver operating characteristic curves of prepsin, C2, C12:1 OH and sequential organ failure assessment score for predicting 28-d mortality in patients with acute cholangitis; E: Kaplan–Meier survival curves showed that patients with C2 Levels > 17.07  $\mu\text{mol/L}$  had a lower probability of survival at 28 d (log-rank = 25.01;  $P < 0.001$ ) compared to patients with lower levels in acute cholangitis. C2: Acetyl-L-carnitine; C12:1 OH: Hydroxydodecenoyl-L-carnitine; SOFA: Sequential organ failure assessment; AUC: Area under the curve.

detection rate of positive bloodstream infection.

## CONCLUSION

Our study identified prepsin as a specific biomarker to predict the severity and emergency biliary drainage of acute cholangitis compared to procalcitonin and other clinical parameters. Acetyl-L-carnitine might be a promising biomarker for predicting mortality in patients with acute cholangitis. Our findings clarify the association between innate immune responses and mitochondrial FAO impairment in acute cholangitis.

## ARTICLE HIGHLIGHTS

### Research background

Acute cholangitis is potentially lethal when accompanied by sepsis because of biliary obstruction. It is necessary to identify predictive biomarkers for patients who require emergent biliary drainage and patients who may progress to systemic bloodstream infection at an early stage of the disease.

### Research motivation

Bacteremia induces hyperactive immune response and mitochondrial dysfunction. Prepsin is responsible for pathogen recognition by innate immunity. Acylcarnitines are established mitochondrial biomarkers. However, it is unknown whether prepsin or specific acylcarnitine species can reflect the severity of acute cholangitis and the timing of biliary drainage.

### Research objectives

To clarify the early predictive value of presepsin and acylcarnitines for severity and biliary drainage of acute cholangitis.

### Research methods

In this prospective observational study, 280 patients with acute cholangitis were included from May 2019 to July 2021. The severity was stratified as mild, moderate, and severe according to the Tokyo Guidelines 2018. Blood presepsin and plasma acylcarnitines were tested at enrollment by chemiluminescent enzyme immunoassay and ultra-high-performance liquid chromatography-mass spectrometry, respectively. Patients were followed-up for 28 d.

### Research results

The concentrations of presepsin, procalcitonin, short- and medium-chain acylcarnitines increased, while long-chain acylcarnitines decreased with the severity of acute cholangitis. The areas under the receiver operating characteristic curves (AUC) of presepsin for diagnosing moderate/severe and severe cholangitis (0.823 and 0.801, respectively) were greater than those of conventional markers. The AUC of a combination of presepsin, direct bilirubin, alanine aminotransferase, temperature, and butyryl-L-carnitine for predicting biliary drainage was 0.723. Presepsin, procalcitonin, acetyl-L-carnitine, hydroxy-dodecenoyl-L-carnitine, and temperature were independent predictors of bloodstream infection. After adjusting for severity classification, acetyl-L-carnitine was the only acylcarnitine independently associated with 28-d mortality (hazard ratio 14.396;  $P < 0.001$ ) (AUC: 0.880). Presepsin concentration showed positive correlation with direct bilirubin and acetyl-L-carnitine.

### Research conclusions

Presepsin may serve as a specific biomarker to predict the severity and biliary drainage of acute cholangitis. Acetyl-L-carnitine might be a promising prognostic factor for patients with acute cholangitis. Innate immune response was associated with mitochondrial metabolic dysfunction in acute cholangitis.

### Research perspectives

Prospective observational study reports the predictive value of presepsin and acylcarnitines for severity and biliary drainage of acute cholangitis. Future research should focus on the association between acylcarnitines and the changes of intestinal microflora and bacterial translocation in acute cholangitis.

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## FOOTNOTES

**Author contributions:** Li CS and Xie MR contributed to the study conception and design; Zhang HY, Xiao HL, Wang GX, Lu ZQ participated in the material preparation and data collection. Zhang HY, Xiao HL and Wang GX performed the analyses. Xiao HL drafted the initial manuscript and revised the article; all authors read and approved the final manuscript; Zhang HY, Xiao HL and Wang GX contributed equally and share first authorship.

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**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** There are no conflicts of interest to report.

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