



## Interleukin-6 as an early diagnostic marker for bacterial sepsis in patients with liver cirrhosis<sup>☆</sup>



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### ABSTRACT

**Objective:** Liver cirrhosis is associated with frequent bacterial infections that increase the mortality rate. However, the early diagnosis and treatment of these infections are often difficult. In this retrospective-prospective observational study, the serum levels of interleukin-6 (IL-6) and procalcitonin (PCT) were measured in 233 cirrhotic patients to evaluate the early diagnostic and prognostic values of IL-6 and PCT for cirrhotic patients.

**Methods:** Cirrhotic patients admitted to the Liver Research Center of the First Affiliated Hospital of Fujian Medical University between 1 October 2012 and 30 June 2014 were enrolled. They showed no evidence of infection on admission, and all had first onset of fever and met the systemic inflammatory response syndrome criteria 72 hours after admission. The serum IL-6 and PCT levels were determined on admission, at the onset of fever (0 hour) and 24 and 48 hours after fever onset.

**Results:** A total of 233 cirrhotic patients, including 183 men and 50 women, with a median age of 56 (46–65) years were enrolled. A training group of 159 patients was retrospectively enrolled from 1 October 2012 to 31 December 2013, and a validation group of 74 patients was prospectively enrolled from 1 January 2014 to 30 June 2014. Among these patients, 134 were diagnosed with bacterial sepsis, 96 of whom were in the training group and 38 of whom were in the validation group; infections were ultimately ruled out in 99 patients: 63 training patients and 36 validation patients. At 0 hour, the IL-6 and PCT levels as well as the proportion of neutrophils were much higher in septic patients than in nonseptic ones. The IL-6 level and proportion of neutrophils peaked upon the onset of fever, 24 hours before the PCT levels and white blood cell count, and then sharply declined. The area under the receiver operating characteristic curve of IL-6 for diagnosing sepsis was largest at the onset of fever (area under the receiver operating characteristic curve, 0.983; 95% confidence interval, 0.967–0.999). The threshold of IL-6 for diagnosis was 135 pg/mL, with a sensitivity of 94.8% and a specificity of 93.7%. These diagnostic values were also confirmed in the validation group, with a sensitivity of 97.4% and specificity of 80.6%. Eleven (11.5%) patients died, and 85 (88.5%) patients recovered in the sepsis group of training patients after a 4-week follow-up. The IL-6 level was significantly higher in the nonsurvival group than that in the survival group (1813.00 vs 472.10 pg/mL,  $P = .004$ ) at the onset of sepsis. The cutoff value for predicting prognosis was 1105 pg/mL, with a sensitivity of 81.8% and a specificity of 76.5%.

**Conclusions:** The serum IL-6 levels increased earlier than the PCT in septic cirrhotic patients. The direct measurement of the serum IL-6 level can help to rapidly detect bacterial infection, thus allowing for early therapeutic decisions and prognostic predictions.

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**Abbreviations:** T, body temperature; R, respiratory rate; HR, heart rate; BP, blood pressure; IL-6, interleukin-6; CRP, C-reactive protein; PCT, procalcitonin; SIRS, systemic inflammatory response syndrome; WBC, white blood cell count; N%, proportion of neutrophils; HCV, hepatitis C virus; HBV, hepatitis B virus; DM, diabetes mellitus.

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## 1. Introduction

Patients with advanced cirrhosis are prone to bacterial infections, with a prevalence of 30% on admission or during hospitalization [1]. Such infections have become the leading cause of death in these patients [2]. The in-hospital mortality rate of patients with cirrhosis who have septic shock exceeds 70%, which is much higher than the rate of the patients without cirrhosis [3,4]. Antibiotics should be intravenously administered immediately after sepsis is diagnosed. Any delay in the initiation of appropriate antibiotics in patients with severe sepsis is

associated with an increase in the mortality rate [5–7]. However, the early diagnosis of sepsis is extremely difficult, especially in patients with cirrhosis.

In the noncirrhotic population, 2 acute-phase serum proteins, serum C-reactive protein (CRP) and procalcitonin (PCT), have been widely used as diagnostic markers of infection [8]. Several studies have demonstrated that the CRP levels negatively correlated with the extent of liver failure [9,10]. C-reactive protein has been shown to be less diagnostic in the cirrhotic population [11]. Procalcitonin has been shown to react faster with an inflammatory stimulus than CRP [12]. It is mainly produced by the liver; thus, liver dysfunction interferes with the synthesis of PCT [13]. The diagnostic accuracy of PCT in cirrhotic patients remains controversial [11].

Interleukin-6 (IL-6) is produced during bacterial infections and is involved in the initiation of the acute-phase response in humans [14]. The level of IL-6 also increases earlier than that of PCT [12]. The level of PCT increases for 6 to 8 hours after exposure to bacterial products and reaches a plateau 12 hours thereafter [15,16]. Bacterial infection can be detected earlier by directly measuring the serum level of IL-6 compared to that of other acute-phase proteins, which are secreted in response to proinflammatory cytokines. Several studies have affirmed the diagnostic value of IL-6 in septic patients in the general population [17–19]. Byl et al [20] found that IL-6 level was elevated with deterioration of cirrhosis due to infection. Wang et al [21] also reported that the IL-6 levels significantly increased from the baseline levels in cirrhotic patients with hospital-acquired infections. Therefore, IL-6 may be a promising early diagnostic marker of bacterial sepsis in patients with cirrhosis. However, the best threshold for IL-6 and its role in the routine diagnosis of bacterial infection in cirrhotic patients remain undetermined because of the limited number of patients.

In this cohort study, we focused on cirrhotic patients who suffered from bacterial sepsis during hospitalization by analyzing the levels of IL-6 and PCT as well as the white blood cell count (WBC) and proportion of neutrophils (N%) to evaluate the rapid diagnostic and predictive values of serum IL-6 for cirrhotic patients with bacterial sepsis.

## 2. Methods

### 2.1. Patients

This work was a retrospective-prospective cohort study conducted from 1 October 2012 to 30 June 2014. Cirrhotic patients hospitalized at the Liver Research Center of the First Affiliated Hospital of Fujian Medical University were analyzed in this study. Patients were hospitalized because of gastrointestinal bleeding, hepatic encephalopathy, hepatorenal syndrome, massive ascites, a recent deterioration of liver function, or hepatocellular carcinoma. Because determining the accurate time of bacterial sepsis was difficult when the infections developed in the community, which would preclude the assessment of initial data, only patients who showed no signs of infection on admission but developed a fever and the met systemic inflammatory response syndrome (SIRS) criteria during hospitalization were included in this research. Patients showing any signs of infection within 72 hours after admission and those with alcoholic hepatitis were excluded from this study because the baseline IL-6 levels were elevated in these patients [22].

The training cohort was enrolled from 1 October 2012 to 31 December 2013, and the validation cohort was prospectively enrolled from 1 January to 30 June 2014. The same parameters were collected in both groups.

### 2.2. Diagnosis of sepsis

Systemic inflammatory response syndrome was diagnosed when 2 or more of the following criteria were met [23]: (1) body temperature greater than 38°C or less than 36°C; (2) tachycardia greater than 90 beats per minute; (3) hyperventilation: respiratory rate greater than 20 beats per minute or arterial hypocapnia less than 32 mm Hg;

(4) WBC greater than 12000/mm<sup>3</sup> or less than 4000/mm<sup>3</sup> or immature forms greater than 10%.

Infection was diagnosed based on the following criteria [23]: (1) clinical symptoms of infection, such as fever, hypotension, abdominal pain, diarrhea, cough, expectoration, and frequent, urgent, or painful urination; (2) pathogenic bacterial growth in blood cultures or in normally sterile sites (eg, ascites, urine); (3) radiography or computed tomography test of chest, urine sediment, or ascitic fluid cell count was positive; (4) for patients with negative cultures, infection was clinically and/or radiologically confirmed as well as based on the response to antibiotic treatment.

Infection was excluded based on the following evidence: (1) no clinical symptoms of infections; (2) radiography or computed tomography test of chest, urine sediment and culture, ascitic fluid cell count and cultures, and blood culture were all negative; (3) fever stopped spontaneously without antibiotic therapy, or patients did not respond to antibiotic therapy.

Sepsis was diagnosis based on the presence of SIRS and infections.

### 2.3. Data collection

The patient's vital signs, including the highest body temperature (T), lowest blood pressure (BP), and highest heart (HR) and respiratory rates (R), were recorded on admission and upon the onset of fever (0 hour) as well as 24 and 48 hours after the onset of fever. Routine blood tests and microbiological culture were performed at the same time point. The outcome (survival or death) was assessed after a 4-week follow-up. Serum samples from all cirrhotic patients were collected on admission and stored at –80°C to measure the baseline PCT and IL-6 levels.

### 2.4. Bacterial culture and measurements of plasma PCT and IL-6 levels

Blood cultures were obtained from separate venipuncture sites in at least 2 collection bottles. All cultures were incubated at 35.8°C in an appropriate atmosphere and observed for 7 days. The IL-6 and PCT levels were determined with a commercially available electrochemiluminescence analyzer (ECL, Roche E601, Switzerland).

### 2.5. Cost-effectiveness analysis

The cost-effectiveness of different biomarkers for the diagnosis of sepsis was evaluated in the training group. The effectiveness was determined based on the sensitivity for diagnosis, and the cost depended on the expense of the tests. According to the prices paid in China, the cost was \$8.6 (¥54) for IL-6 detection, \$38.5 (¥240) for PCT detection, and \$4.8 (¥30) for a routine blood test.

### 2.6. Statistical analysis

The data are expressed as median values with interquartile ranges. A Mann-Whitney test or Student *t* test was used to compare groups. The significance of the difference in proportions was tested with the  $\chi^2$  statistic. The diagnostic accuracy is expressed as the area under the receiver operating characteristic curve (AUC), which was derived from a logistic regression analysis. Statistical significance was achieved if  $P < .05$  with a 2-tailed tests. All data were analyzed with SPSS (Chicago, IL) 13.0.

### 2.7. Ethics

The study protocol was approved by the Institutional Ethics Committee of the First Affiliated Hospital of Fujian Medical University and complied with the Declaration of Helsinki. Written informed consent for the use of stored serum samples was obtained from all patients.

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