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Diagnostic performance of procalcitonin for bacterial infection in severe alcoholic hepatitis compared with C-reactive protein

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Abstract

Background Severe alcoholic hepatitis is a catastrophic disease with a mortality rate of up to 35–50% at 30 days. Bacterial infection is an important prognostic factor in patients with severe alcoholic hepatitis, but it is difficult to detect the presence of infection immediately. Procalcitonin (PCT) is a well-known inflammatory marker that can detect bacterial infections in various diseases early. Therefore, we aimed to evaluate the diagnostic accuracy of PCT for bacterial infection in severe alcoholic hepatitis.

Methods We prospectively enrolled patients with severe alcoholic hepatitis, defined as modified Maddrey's Discriminant Function ≥ 32, from 10 medical centers. At admission, we performed an initial evaluation including physical examination, laboratory test, radiology, blood and urine culture, PCT, and C-reactive protein (CRP). We compared the receiver operating characteristic (ROC) curves of PCT and CRP for bacterial infection, systemic inflammatory response syndrome (SIRS), and sepsis among total patients.

Results A total of 108 patients with severe alcoholic hepatitis were enrolled. The number of bacterial infections, SIRS, and sepsis were 31 (28.7%), 41 (38.0%), and 19 (17.6%), respectively. The patients with bacterial infection had significantly higher MELD scores (24.0 vs. 15.0), PCT levels (1.5 vs. 0.4 ng/mL), and CRP levels (4.9 vs. 2.5 mg/dL) compared to those without bacterial infection. The area under the ROC curve (AUROC) of PCT vs. CRP for bacterial infection was 0.752 and 0.655, respectively ($P=0.113$). The AUROC of PCT vs. CRP for SIRS was 0.699 and 0.662, respectively ($P=0.490$). The AUROC of PCT vs. CRP for sepsis was 0.780 and 0.630, respectively ($P=0.027$).

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†Nae-Yun Heo and Yang-Hyun Baek denote shared supervision and shared contribution as co-corresponding author.

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Conclusions Among patients with severe alcoholic hepatitis, PCT showed a trend of superior diagnostic performance in the early detection of bacterial infection and sepsis compared to CRP. Although PCT might have better potential to diagnose sepsis in the setting of severe alcoholic hepatitis, it is necessary to find more reliable diagnostic markers.

Keywords Alcoholic hepatitis, Bacterial infection, Sepsis, Procalcitonin, C-reactive protein

Introduction

Alcohol consumption has catastrophic consequences, with an estimated 3 million deaths (5.3% of all deaths) globally in 2016 attributed to harmful alcohol use, including 607,000 deaths from alcohol-attributable liver diseases [1]. Alcoholic liver disease encompasses a spectrum of conditions, including steatosis, steatohepatitis, fibrosis, and cirrhosis. Patients with underlying alcoholic liver disease who continue heavy drinking may develop sudden-onset jaundice, ascites, encephalopathy, and other signs of liver failure, known as alcoholic hepatitis. According to prospective studies, the patients of alcoholic hepatitis with modified discriminant function ≥ 32 showed a poor prognosis as high mortality in a month as 35-50%. Therefore, this condition is defined as severe alcoholic hepatitis [2–4]. Steroid therapy is currently the only effective medical treatment that reduces 28-day mortality based on clinical trials and meta-analyses in severe hepatitis [5, 6]. Meanwhile, alcohol-induced derangement of the immune system triggers an extended inflammatory response, resulting in immune exhaustion and dysregulated compensatory anti-inflammatory pathway [7]. Therefore, patients with severe alcoholic hepatitis are susceptible to bacterial infections, with a known prevalence of 26–37% [8]. Steroid therapy induces immune suppression, making severe infection or sepsis a contraindication. Therefore, it is crucial to identify evidence of infection upon admission.

However, patients with severe alcoholic hepatitis often exhibit clinical symptoms such as fever, abdominal pain, and leukocytosis, making it challenging to differentiate between infectious and non-infectious conditions. Culture is a specific diagnostic tool for bacterial infection, but it requires several days to obtain results. Therefore, clinicians frequently rely on early inflammatory biomarkers like C-reactive protein (CRP) to detect sepsis in alcoholic hepatitis. While CRP is a useful acute phase protein that reflects the severity of inflammation, its levels can increase not only in infectious conditions but also in non-infectious conditions.

Procalcitonin (PCT) is a precursor of calcitonin, and its concentration significantly increases in severe bacterial and fungal infections. However, it only shows a slight elevation in non-infectious inflammation, trauma, and malignancy, which makes it a valuable diagnostic biomarker for acute severe infections [9, 10]. However, there are limited studies that have investigated the comparative diagnostic capacity of PCT and CRP in severe alcoholic hepatitis. Therefore, our intention is to compare the effectiveness of PCT and CRP in detecting bacterial infections in severe alcoholic hepatitis through a prospectively enrolled multicenter clinical trial.

Methods

Study subjects

Prospective enrollment of patients with severe alcoholic hepatitis was conducted at 10 university hospitals in South Korea between June 2020 and July 2022. The inclusion criteria were as follows: age ≥ 19 years, chronic alcohol intake (≥ 60 g/day in males and ≥ 40 g/day in females) for the past three months, abnormal liver function profiles (total bilirubin ≥ 5 mg/dL, AST 40–500 U/L, ALT < 200 U/L, AST/ALT > 2), and a modified Maddrey's discriminant function score ≥ 32. Patients with any of the following exclusion criteria were not included: persistent jaundice lasting over 3 months, recent abstinence from drinking for ≥ 2 months, viral hepatitis infection (HAV, HBV, HCV), autoimmune hepatitis, toxic hepatitis, drug-induced liver injury, malignancy, acute pancreatitis, gastrointestinal bleeding, and acute cholangitis. Informed consent was obtained from each patient included in the study, and the study protocol was approved by the institutional review board at all participating sites. This study was registered in the Clinical Research Information Service as KCT0004627 (Registration Date: 2020-01-14).

Calculation of the number of study subjects

Based on previous studies comparing the diagnostic accuracy of PCT and CRP for bacterial infection in various diseases, it was assumed that the AUROC of PCT and CRP for bacterial infection was 0.90 and 0.75, respectively [11–14]. With a significance level of 0.05, a statistical power of 0.80, and an expected ratio of infected to non-infected subjects of 1:2, the total sample size was calculated to be 108 [15].

Measurement of PCT and CRP

Serum PCT was measured using various methods according to the hospital, including electro-chemiluminescence immunoassay (COBAS e411, e602, e801 system, Roche), time-resolved amplified cryptate emission (Kryptor Compact PLUS), enzyme-linked fluorescent assay (VIDAS), or chemiluminescence immunoassay

(ADVIA Centaur XPT Immunoassay System, Siemens Healthcare Diagnostics).

Serum CRP was measured using different methods depending on the hospital, including latex agglutination turbidimetric immunoassay (Hitachi 7600, 7170), latex particle immunoturbidimetric method (AU5800 Chemistry Analyzer, Beckman Coulter AU-5800), particle-enhanced immunoturbidimetric assay (COBAS e602, e702, e703 system), latex-enhanced Immunoturbidimetric assay (ADVIA Chemistry XPT), immunoturbidimetric test (AU5800 clinical chemistry analyzer, Beckman Coulter), and highly sensitive near infrared particle immunoassay rate methodology (Beckman Coulter). Refer to Supplementary Table 1 for specific details at each hospital.

Definition of events

Bacterial infection was defined as the presence of an identified pathogen in cultures obtained from blood, urine, sputum, ascitic fluid, pus, or cerebral spinal fluid. Additionally, clinical diagnosis of bacterial infection, such as spontaneous bacterial peritonitis, pneumonia, urinary tract infection, or meningitis, was also considered even if no pathogen was identified in cultures. That is to say, spontaneous bacterial peritonitis was diagnosed when the absolute neutrophil count in ascites was $>250/mm^3$, pneumonia when there were radiologic findings of pneumonia on chest X-ray or computed tomography, urinary tract infection as pyuria with dysuria or costovertebral angle tenderness, and meningitis as the relevant cerebrospinal fluid finding.

Systemic inflammatory response syndrome (SIRS) was defined by the presence of at least two of the following conditions: ① Fever (>38℃) or hypothermia (<36℃), ② Tachypnea (>20/min), ③ Tachycardia (>90/min), and ④ Leukocytosis (WBC>12,000/mm^3) or leukopenia (WBC<4,000/mm^3) or band form>10%. Sepsis was defined as the presence of SIRS in combination with bacterial infection [16]. We utilized the definition of sepsis based on the proposal from a consensus meeting by the American College of Chest Physicians and Society of Critical Care Medicine in 1991 [16]. Although more recent definitions such as Sequential Organ Failure Assessment (SOFA) or quick Sequential Organ Failure Assessment (qSOFA) are used to evaluate the severity of organ failure effectively, we chose the former definition because it was meaningful to assess the diagnostic capacity of inflammatory biomarkers in discriminating bacterial infection among patients with severe alcoholic hepatitis, as they often develop SIRS. According to the protocol of the study, serum PCT, CRP, and other baseline laboratory examination were evaluated during initial assessment at admission. Also, the evaluation of bacterial infection such as radiology or culture was performed within 3 days after admission.

Endpoints

The primary endpoint of this study was to evaluate and compare the diagnostic capacity of PCT and CRP in detecting bacterial infection among patients with severe alcoholic hepatitis.

The secondary endpoints of this study were to compare the diagnostic capacity of PCT and CRP in detecting SIRS among patients with severe alcoholic hepatitis, and to compare the diagnostic capacity of PCT and CRP in detecting sepsis among the patients with severe alcoholic hepatitis and among those with SIRS.

Statistical analysis

The continuous variables between infected and non-infected group were compared using the Student's t-test in normal distribution or Mann-Whitney U test in non-normal distribution.

Receiver-operating characteristics (ROC) curves were constructed to analyze the diagnostic capacity of PCT and CRP levels for the event (bacterial infection, SIRS, and sepsis) among patients with severe alcoholic hepatitis. The area under the ROC curve (AUROC) was calculated for both PCT and CRP levels, and optimal cut-off values for each event were determined.

The statistical analyses were performed using the R program (version 4.1.1), and a p-value less than 0.05 was considered statistically significant.

Results

Baseline characteristics

During the study period, a total of 108 subjects with severe alcoholic hepatitis were enrolled. The number of bacterial infections, SIRS, and sepsis were 31 (28.7%), 41 (38.0%), and 19 (17.6%), respectively. They were divided into two groups based on the presence or absence of bacterial infection: Group 1 (alcoholic hepatitis with infection, $n=31$) and Group 2 (alcoholic hepatitis without infection, $n=77$).

There were no significant difference between the two groups in terms of age, height, body weight, and body temperature. Additionally, the level of white blood cell count, hemoglobin, AST, ALT, GGT, total bilirubin, and PT INR were similar between the two groups. However, Group 1 showed significantly lower level of albumin and higher level of blood urea nitrogen (BUN) and creatinine compared to Group 2. Furthermore, Group 1 had significantly higher MELD score, PCT level, and CRP level compared to Group 2. Group 1 had more patients with SIRS compared to Group 2 (Table 1).

Table 1 Baseline characteristics of the patients with severe alcoholic hepatitis according to infection

	Group 1 Infected patients (*n* = 31)	Group 2 Non-infected patients (*n* = 77)	*P*-value
Male (%)	21 (67.7%)	58 (75.3%)	0.572
Age (years)*	45.9 ± 7.3	48.2 ± 9.1	0.211
Height (cm)*	169.3 ± 7.5	169.6 ± 7.9	0.875
Body weight (kg)*	66.1 ± 13.1	67.8 ± 12.5	0.520
Body temperature (℃)†	36.5 (36.2–37.5)	36.7 (36.5–37.2)	0.337
WBC (/mm^3)†	11,570 (8,560 – 22,060)	11,250 (6,740 – 16,790)	0.289
Hb (g/dL)†	9.5 (7.6–11.4)	10.6 (9.6–11.6)	0.062
AST (U/L)†	149 (98–215)	126 (87–217)	0.608
ALT (U/L)†	36 (27–62)	39 (23–62)	0.957
GGT (U/L)†	186 (87–534)	237 (113–432)	0.992
Total bilirubin (mg/dL)†	13.8 (9.5–22.2)	17.4 (12.3–25.7)	0.106
Albumin (g/dL)†	2.4 (2.1–2.7)	2.7 (2.5–2.9)	0.003
INR†	1.8 (1.7–2.4)	1.9 (1.6–2.1)	0.613
BUN (mg/dL)†	25.9 (11.0–62.0)	14.0 (7.5–20.2)	0.001
Creatinine (mg/dL)†	1.9 (0.7–3.4)	0.8 (0.6–1.3)	0.003
MELD score†	24.0 (14.5–31.0)	15.0 (12.0–21.0)	0.019
Procalcitonin (ng/mL)†	1.5 (0.4–4.1)	0.4 (0.2–0.7)	< 0.001
C-reactive protein (mg/dL)†	4.9 (1.8–8.6)	2.5 (0.9–4.7)	0.012
SIRS	20 (64.5%)	21 (27.3%)	0.001
Sepsis	19 (61.3%)	0 (0%)	< 0.001

WBC, white blood cell; Hb, hemoglobin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; INR, international normalized ratio; MELD, model of end-stage liver disease, SIRS, systemic inflammatory response syndrome

*mean ± standard deviation

†median (interquartile range)

Table 2 Cause of the bacterial infection or sepsis among the patients with severe alcoholic hepatitis at admission

	Bacterial infection (*n* = 31)	Sepsis (*n* = 19)
Pneumonia	7 (22.6%)	4 (21.1%)
Bacteremia	5 (16.1%)	3 (15.8%)
Urinary tract infection	5 (16.1%)	2 (10.5%)
Clostridioides difficile-associated diarrhea	3 (9.7%)	3 (15.8%)
Colitis	2 (6.5%)	2 (10.5%)
Acute pyelonephritis	1 (3.2%)	
Cellulitis	1 (3.2%)	
Cholecystitis	1 (3.2%)	1 (5.3%)
Spontaneous bacterial peritonitis	1 (3.2%)	1 (5.3%)
Spontaneous bacterial empyema	1 (3.2%)	1 (5.3%)
Pneumonia *plus* enteritis	1 (3.2%)	
Pneumonia *plus* urinary tract infection	1 (3.2%)	1 (5.3%)
Pneumonia *plus* soft tissue infection	1 (3.2%)	1 (5.3%)
Urinary tract infection *plus* peritonitis *plus* bacteremia	1 (3.2%)	

Table 3 Identified bacteria in the bacterial infection or sepsis among the patients with severe alcoholic hepatitis at admission

	Bacterial infection (*n* = 31)	Sepsis (*n* = 19)
No growth	12 (38.7%)	7 (36.8%)
Escherichia coli	5 (16.1%)	2 (10.5%)
Enterococcus	3 (9.7%)	3 (15.8%)
Clostridioides difficile	3 (9.7%)	3 (15.8%)
Staphylococcus	3 (9.7%)	1 (5.3%)
Acinetobacter	1 (3.2%)	1 (5.3%)
Streptococcus agalactiae	1 (3.2%)	
Campylobacter	1 (3.2%)	
Klebsiella pneumonia + *Aspergillus*	1 (3.2%)	1 (5.3%)
Escherichia coli + *Acinetobacter*	1 (3.2%)	1 (5.3%)

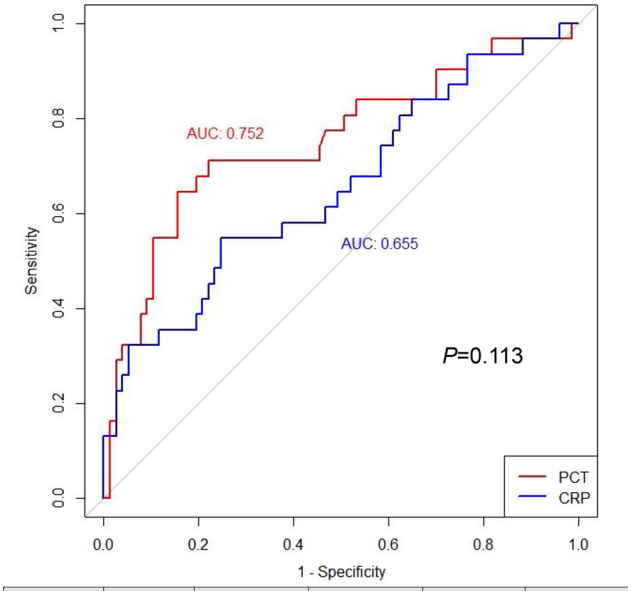
Clinical outcome in severe alcoholic hepatitis at admission

The causes of bacterial infection were pneumonia, bacteremia, urinary tract infection, *Clostridioides difficile*-associated diarrhea, colitis, acute pyelonephritis, cellulitis, cholecystitis, spontaneous bacterial peritonitis, spontaneous bacterial empyema, and several multi-organ infections (Table 2). Out of 31 patients with bacterial infection, 19 patients had identified pathogens in their cultures. The major pathogens included *Escherichia coli*, *Enterococcus*, *Clostridioides difficile*, *and Staphylococcus* (Table 3).

The causes of sepsis were pneumonia, bacteremia, *Clostridioides difficile*-associated diarrhea, colitis, urinary tract infection, cholecystitis, spontaneous bacterial peritonitis, spontaneous bacterial empyema, and several multi-organ infections (Table 2). Out of 19 patients with sepsis, 12 patients had identified pathogens in their cultures. The major pathogens included *Enterococcus*, *Clostridioides difficile*, *and Escherichia coli* (Table 3).

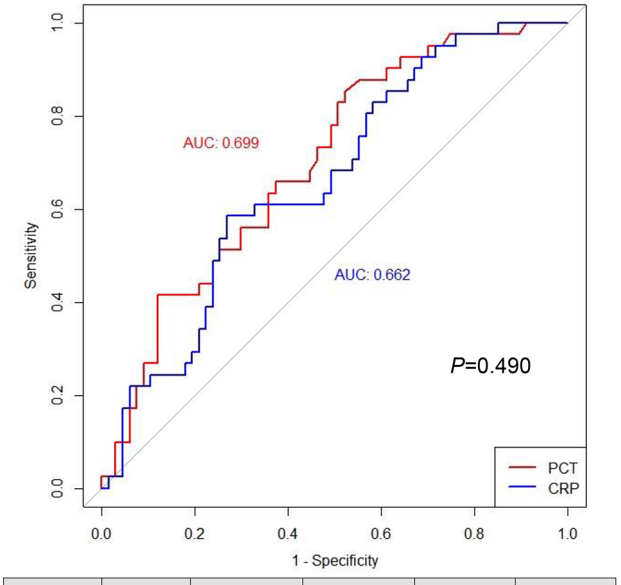
Comparison of diagnostic capacity of PCT comparing CRP in severe alcoholic hepatitis

The AUROC for bacterial infection in patients with severe alcoholic hepatitis was higher for PCT compared to CRP, but the difference was not statistically significant (0.752 and 0.655, respectively; $P=0.113$). The cut-off value for PCT was 1.07 ng/mL, while for CRP it was 4.81 mg/dL (Fig. 1). Regarding SIRS in patients with severe alcoholic hepatitis, the AUROC values for PCT and CRP were comparable (0.699 and 0.662, respectively; $P=0.490$), and the corresponding cut-off values were 0.30 ng/mL for PCT and 4.46 mg/dL for CRP (Fig. 2). In the case of sepsis among patients with severe alcoholic hepatitis, the AUROC for PCT was significantly higher than that of CRP (0.780 and 0.630, respectively; $P=0.027$). The cut-off values for PCT and CRP in this setting were 0.95 ng/mL and 1.40 mg/dL, respectively (Fig. 3). In the case of sepsis among 41 patients with severe alcoholic hepatitis accompanying SIRS, the AUROC for PCT was



	Cut-off	Sensitivity	Specificity	PPV	NPV
PCT	1.07	0.645	0.844	0.625	0.855
CRP	4.81	0.548	0.753	0.472	0.806

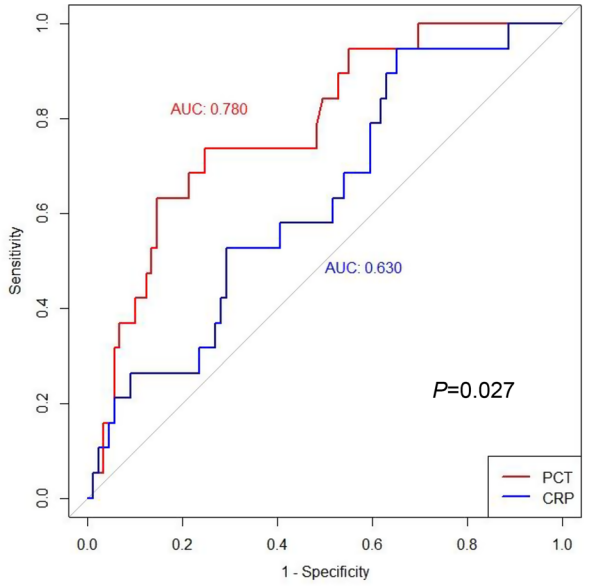
Fig. 1 Diagnostic accuracy of procalcitonin and C-reactive protein for bacterial infection in severe alcoholic hepatitis



	Cut-off	Sensitivity	Specificity	PPV	NPV
PCT	0.30	0.854	0.478	0.500	0.842
CRP	4.46	0.585	0.731	0.571	0.742

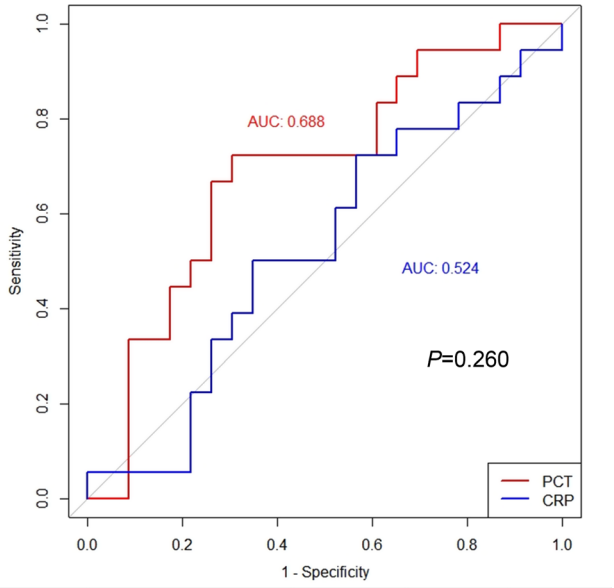
Fig. 2 Diagnostic accuracy of procalcitonin and C-reactive protein for systemic inflammatory response syndrome in severe alcoholic hepatitis

significantly higher than that of CRP (0.688 and 0.524, respectively; $P=0.260$). The cut-off values for PCT and CRP in this setting were 0.95 ng/mL and 1.32 mg/dL, respectively (Fig. 4). Sensitivity, specificity, positive



	Cut-off	Sensitivity	Specificity	PPV	NPV
PCT	0.95	0.737	0.753	0.389	0.931
CRP	1.40	0.947	0.348	0.237	0.969

Fig. 3 Diagnostic accuracy of procalcitonin and C-reactive protein for sepsis in severe alcoholic hepatitis*



	Cut-off	Sensitivity	Specificity	PPV	NPV
PCT	0.95	0.722	0.696	0.650	0.762
CRP	1.32	0.944	0.217	0.486	0.833

Fig. 4 Diagnostic accuracy of procalcitonin and C-reactive protein for sepsis in severe alcoholic hepatitis accompanying systemic inflammatory response syndrome*

predictive value, and negative predictive value of PCT and CRP for each event such as bacterial infection, SIRS, and sepsis among severe alcoholic hepatitis were described in Figs. 1, 2, 3 and 4.

Discussion

This study demonstrated that serum levels of both PCT and CRP were significantly higher in the group with bacterial infection compared to the non-infected group among patients with severe alcoholic hepatitis (modified Maddrey's Discriminant Function was ≥32). Additionally, serum PCT exhibited a superior ability in diagnosing bacterial infection when compared to serum CRP. Especially, serum PCT showed better and moderately accurate diagnostic performance for sepsis compared with serum CRP with statistically significant difference. On the other hand, when focusing on patients with severe alcoholic hepatitis and SIRS, serum PCT displayed a limited diagnostic capacity for sepsis, and serum CRP did not have discrimination for it at all.

Infection is not only a major complication of severe alcoholic hepatitis but also one of the leading causes of mortality in this context. In the STOPAH trial, the largest trial conducted on severe alcoholic hepatitis to date, infections accounted for 24% of all deaths [6]. The susceptibility to infection in alcoholic hepatitis stems from immune dysfunction associated with chronic liver disease and immune-suppressive treatments [8]. Although steroid therapy has shown improved short-term survival in severe alcoholic hepatitis, severe infection or sepsis is considered as a contraindication. Even among responders to steroids, the presence of infection is associated with poor survival rates comparable to those of non-responders [17]. Therefore, early detection of infection and prompt initiation of antibiotic treatment are crucial components of the management of severe alcoholic hepatitis.

However, diagnosing infection in severe alcoholic hepatitis based on clinical manifestations alone is challenging, as patients may exhibit fever, tachycardia, tachypnea, and leukocytosis regardless of infection. Therefore, physicians often rely on biomarkers of infection during the initial evaluation of severe alcoholic hepatitis, with CRP and PCT being representative examples.

CRP is an acute-phase protein primarily produced by hepatocytes in response to the stimulation of interleukin (IL)-6 during the acute phase response. It is elevated in various inflammatory conditions, including not only infection but also rheumatoid diseases, cardiovascular diseases, trauma, and advanced cancer [18].

PCT is a precursor of calcitonin consisting of 116 amino acids, and its levels rapidly increase in the presence of severe bacterial infection or sepsis. While PCT is normally produced in the thyroid, infection can trigger its massive production from other sites such as the liver, lung, kidney, adipocytes, and muscle [19]. Studies have shown that PCT levels increase following endotoxin injection in healthy individuals, with peak levels coinciding with tumor necrosis factor (TNF)-α and IL-6 peaks. This suggests that pro-inflammatory cytokines induced by bacterial infection can stimulate PCT production [20]. Although PCT levels can also rise in non-infectious conditions like trauma, burns, and pancreatitis, research by Rau et al. demonstrated that while CRP levels were elevated in both infected and sterile pancreatic necrosis as well as interstitial edematous pancreatitis in acute pancreatitis, PCT levels were elevated only in infected pancreatic necrosis [21]. This finding suggests that PCT may be a more useful biomarker in distinguishing bacterial infection from non-infectious inflammatory conditions compared to CRP.

In our study, we observed that PCT demonstrated better diagnostic performance for bacterial infection among patients with severe alcoholic hepatitis compared to CRP (AUROC: 0.752 vs. 0.655). This trend was particularly evident when diagnosing sepsis in patients with severe alcoholic hepatitis (AUROC: 0.780 vs. 0.630). These findings align with previous studies that have compared PCT and CRP in the diagnosis of sepsis in intensive care unit (ICU) settings. For example, Luzzani et al. reported an AUROC of 0.925 for PCT compared to 0.677 for CRP when differentiating septic (sepsis, severe sepsis, or septic shock) from non-septic (SIRS) subjects among 800 patient days in 70 ICU patients [11]. Meynaar et al. found that PCT had the highest discriminatory power for distinguishing sepsis from SIRS among four inflammatory biomarkers such as PCT, CRP, IL-6, and lipopolysaccharide binding protein in 76 critically ill patients, with AUROCs of 0.95 and 0.75 for PCT and CRP, respectively [12]. Similarly, Rey et al. reported an AUROC of 0.912 for PCT compared to 0.750 for CRP in diagnosing septic conditions versus non-septic (SIRS) conditions among 359 patient day episodes in 95 pediatric ICU patients [13]. Collectively, these ICU studies consistently demonstrate that PCT exhibits significantly better diagnostic performance for septic conditions compared to CRP.

However, there is limited data available comparing PCT with CRP in the diagnosis of bacterial infection or sepsis specifically in acute or chronic liver disease. One study by Viallon et al. investigated the potential role of PCT and pro-inflammatory cytokines in diagnosing spontaneous bacterial peritonitis in cirrhotic patients. The results of this study demonstrated that PCT had the best diagnostic performance with an AUROC of 0.98 at a cut-off value of 0.76 ng/mL, outperforming CRP, TNF-α, and IL-6 (with AUROCs of 0.79, 0.81, and 0.72, respectively) [22]. Another study by Elefsiniotis et al. reported that serum PCT levels were higher in the decompensated cirrhosis group with bacterial infection compared

to acute alcoholic hepatitis with a cirrhotic background but without infection (9.80±16.80 ng/mL vs. 0.40±0.30 ng/mL, $P=0.001$) [23]. Kumar et al. compared PCT and CRP in diagnosing sepsis among 40 patients with alcoholic hepatitis and SIRS. The study showed comparable results for both biomarkers in detecting sepsis among alcoholic hepatitis patients, with an AUROC of 0.81 for PCT and 0.83 for CRP. It's important to note that in this study, the severity of alcoholic hepatitis was not defined according to modified Maddrey's Discriminant Function [14]. In another study related to severe alcoholic hepatitis, Michelena et al. presented that PCT showed good diagnostic performance to discriminate those with infection-associated SIRS (sepsis) from those with SIRS without infection among all patients with SIRS compared with CRP (AUROC: 0.766, $P<0.001$), but CRP did not (AUROC: 0.648, $P=0.044$) [24].

The relatively low AUROC values of PCT and CRP in the diagnosis of infection in our study could be attributed to the inclusion of hidden infected patients in the non-infected group among patients with severe alcoholic hepatitis. It is known that severe alcoholic hepatitis can render patients susceptible to bacterial translocation from the large intestine. This condition can lead to overt spontaneous bacterial peritonitis or bacteremia of gastrointestinal origin. However, there may also be cases of hidden local inflammation caused by bacteria, which are not easily detectable. As a result, the discriminatory power of biomarkers for infection may be compromised, leading to lower diagnostic effectiveness.

Another intriguing finding is that CRP did not demonstrate diagnostic utility in detecting sepsis among patients with severe alcoholic hepatitis and SIRS (AUROC: 0.524). This is similar to the result of the study of Michelena et al. in which CRP did not showed significant diagnostic performance to detect sepsis among all the patients with severe alcoholic hepatitis with SIIRS [24]. However, this contrasts with the results of similar studies conducted in ICU settings, where CRP showed discriminatory performance among patients with SIRS. Additionally, it contradicts the findings of Kumar et al., who studied subjects with alcoholic hepatitis and SIRS in which the severity of alcoholic hepatitis was not mentioned. This finding suggests that CRP levels may increase in the context of "severe alcoholic hepatitis", leading to SIRS, even in the absence of sepsis, to as high level as in cases of SIRS with sepsis. CRP may serve as a biomarker for inflammation rather than being specific to infection in this condition.

Although diagnostic accuracy of PCT was not excellent to detect bacterial infection, high specificity and negative predictive value was as high as 84.4% and 85.5%, respectively. This finding may be helpful to clinicians treating patients with severe alcoholic hepatitis with low PCT levels and no definite clinical clues of a bacterial infection. In this case, steroid therapy could be initiated based on the low possibility of a bacterial infection. In contrast, steroids should be prudently administered to patients with severe alcoholic hepatitis and high PCT values. In terms of clinical settings, PCT levels may be a more useful tool for treatment decisions than CRP levels.

This study has several limitations. Firstly, there is a possibility that some unrecognized patients with infection or sepsis were included in the non-infected group because not all infected patients had positive blood culture results due to intermittent bacteremia. However, we defined bacterial infection not only based on identified bloodstream infection but also on clinical diagnosis of representative infections. By using these extended criteria, we aimed to reduce the chance of missing infection cases. Secondly, this study enrolled the patients with alcoholic hepatitis based on drinking history and clinical findings, but not on pathologic evidence. The related study showed that 20% of the patient suspicious of alcoholic hepatitis might be proven to have other diagnosis after liver biopsy [25]. According to a recommendation from an academic consortia [26], definite alcoholic hepatitis was defined as clinically diagnosed and biopsy proven, probable alcoholic hepatitis as clinically diagnosed alcoholic hepatitis without confounding factors, and possible alcoholic hepatitis as clinically diagnosed but with potential confounding factors. We think that our study subjects could be included in the category of probable alcoholic hepatitis clinically diagnosed without confounding factors because the investigators excluded the other differential diagnosis. Thirdly, we used the older definition of sepsis based on bacterial infection combined with SIRS instead of newer Sepsis-3 definition based on several organ failures. Sepsis-3 criteria showed better predictive performance for in-hospital mortality in the patients suspicious of sepsis compared with SIRS criteria. Although we chose the SIRS criteria due to specific condition of severe alcoholic hepatitis in which there are frequent inflammation without bacterial infection, it is necessary to evaluate the diagnostic performance of PCT according to updated sepsis criteria forward. Fourthly, there may be variability in biomarker measurements among laboratories in different hospitals. However, the coefficient of variance for these biomarkers was acceptable (<30%) based on nationwide proficiency testing in Korea. Lastly, we did not gather the dynamic changes in PCT and CRP during hospitalization. Therefore, one spot investigation of these inflammatory biomarkers might be insufficient to catch the clue of bacterial infection.

In conclusion, the diagnostic capacity of serum PCT in discriminating bacterial infection and sepsis in severe alcoholic hepatitis is superior to serum CRP. PCT was found to be a limited diagnostic tool for detecting sepsis

among patients with severe alcoholic hepatitis and SIRS, and CRP did not demonstrate discriminatory capacity.

Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUROC	Area under the receiver operating characteristic
CRP	C-reactive protein
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
MELD	Model of end-stage liver disease
PCT	Procalcitonin
qSOFA	Quick sequential organ failure assessment
ROC	Receiver operating characteristic
SIRS	Systemic inflammatory response syndrome
SOFA	Sequential organ failure assessment

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-024-03519-x.

Supplementary Material 1

Supplementary Material 2

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Author contributions
Study design was performed by Nae-Yun Heo, Yang-Hyun Baek, and Kyung Ran Jun. Data collection was performed by Min Kyu Kang, Yu Rim Lee, Soo Young Park, Kwang Il Seo, Sang Soo Lee, Byung Seok Kim, Jeong Eun Song, Jun Sik Yoon, Young Mi Hong, Ki Tae Yoon, Woo Jin Chung, Seung Ha Park, Eunju Kim, Jung Gil Park, Yang-Hyun Baek, and Nae-Yun Heo. Analysis and interpretation of data were performed by Nae-Yun Heo, Yang-Hyun Baek, Min Kyu Kang, and Yu Rim Lee. Drafting of a manuscript was performed by Nae-Yun Heo and Yang-Hyun Baek. All authors read and approved the final manuscript.

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Data availability
The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate
This study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This study protocol was approved by Institutional review boards of all ten participating medical centers; Inje University Haeundae Paik Hospital (Inje University Haeundae Paik Hospital Institutional Review Board), Inje University Busan Paik Hospital (Inje University Busan Paik Hospital Institutional Review Board), Dong-A University Hospital (Dong-A University Hospital Institutional Review Board), Pusan National University Yangsan Hospital (Pusan National University Yangsan Hospital Institutional Review Board), Kosin University Gospel Hospital (Kosin University Gospel Hospital Institutional Review Board), Gyeongsang National University Changwon Hospital (Gyeongsang National University Changwon Hospital Institutional Review Board), Daegu Catholic University Medical Center (Daegu Catholic University Medical Center Institutional Review Board), Kyungpook National University Hospital/Kyungpook National University Chilgok Hospital (Kyungpook National University Hospital Institutional Review Board), Keimyung University Dongsan Hospital (Keimyung University Dongsan Hosptial Institutional Review Board), Yeungnam University Medical Center (Yeungnam University Hospital Institutional Review Board).

Consent for publication
Not applicable.

Informed consent
was obtained from all individual participants included in the study.

Competing interests
The authors declare no competing interests.

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