ORIGINAL ARTICLE
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Usefulness of C-Reactive Protein for Evaluating Clinical Outcomes in Cirrhotic Patients with Bacteremia

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Background/Aims: The purpose of this study was to evaluate the value of initial C-reactive protein (CRP) as a predictor of clinical outcome and to investigate whether follow-up CRP measurement is useful for the prediction of the clinical outcome of bloodstream infections in patients with liver cirrhosis (LC), whose CRP production in response to infection may be attenuated.
Methods: A retrospective, observational study including 202 LC patients with *Escherichia coli* or *Klebsiella pneumoniae* bacteremia was conducted to assess the usefulness of serial CRP measurements in predicting clinical outcome in LC patients. The CRP ratio was defined as the ratio of the follow-up CRP level to the initial CRP level.
Results: The overall 30-day mortality rate of the study population was 23.8% (48/202). In the multivariate analysis, advanced age (≥ 70 years), healthcare-associated or nosocomial infections, model for end-stage liver disease (MELD) score of ≥ 30, and initial body temperature of < 37°C were significant factors associated with mortality (all $p < 0.05$). No association between initial CRP level and mortality was found. In a further analysis including 87 evaluable cases who had repeated CRP measurements at day 4 and/or 5, a CRP ratio of ≥ 0.7 was found to be a significant factor associated with mortality (odds ratio, 19.12; 95% confidence interval, 1.32 to 276.86; $p = 0.043$) after adjusting for other confounding variables.
Conclusions: Initial CRP level did not predict mortality of sepsis in LC patients. However, serial CRP measurements during the first week of antimicrobial therapy may be useful as a prognostic factor for mortality in LC patients. **(Korean J Intern Med 2011;26:195-200)**

Keywords: C-reactive protein; Bacteremia; Liver cirrhosis; Treatment outcome

INTRODUCTION

C-reactive protein (CRP) is an acute-phase protein synthesized primarily by the liver in response to tissue damage; the only determinant of the serum level is the rate of CRP production in the liver [1]. Because some biochemical markers of sepsis, such as CRP and procalcitonin, closely reflect the activity of infection, higher values or a less rapid decline in inflammatory variables could be expected in complex cases during the treatment of sepsis. CRP is one of the most frequently used clinical inflammatory markers that can be obtained routinely in every laboratory, making CRP useful in diagnosing infection and evaluating a patient's response to antimicrobial therapy.

Production of CRP in response to infection may be attenuated in patients with liver dysfunction; this may result in difficulties interpreting CRP levels in liver cirrhosis (LC) patients [2-4]. Additionally, the value of changes in CRP levels over time has not yet been

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Table 1. Demographic and clinical characteristics of the study population

Characteristic	Value (n = 202)
Age, median yr (range)	58 (28-81)
Gender	
Male	138 (68.3)
Female	64 (31.7)
Cause of liver cirrhosis	
Hepatitis B virus	134 (66.3)
Hepatitis C virus	26 (12.9)
Alcoholism	20 (9.9)
Cryptogenic	10 (5.0)
Others	12 (5.9)
Acquisition site of bacteremia	
Community-acquired	88 (43.6)
Healthcare-associated	72 (35.6)
Nosocomial	42 (20.8)
Primary site of infection	
Spontaneous bacterial peritonitis	82 (40.6)
Urinary tract infection	39 (19.3)
Unknown	27 (13.4)
Pancreaticobiliary tract infection	16 (7.9)
Liver abscess	13 (6.4)
Varix bleeding	9 (4.5)
Others	16 (7.9)
ESBL-producing organism	
No	187 (92.6)
Yes	15 (7.4)
Child-Pugh classification	
Child A	16 (7.9)
Child B	56 (27.7)
Child C	130 (64.4)

Values are presented as number (%) unless otherwise indicated.
ESBL, extended-spectrum beta-lactamase.

systemically investigated in patients with liver dysfunction. Several previous studies demonstrated that decreases in CRP levels precede clinical improvement, whereas the failure of CRP levels to fall suggests a poor outcome in bloodstream infection [5,6], community-acquired pneumonia [7,8], ventilator-associated pneumonia [9], and infective endocarditis [10]. However, few data are available regarding the usefulness of CRP measurement for evaluating clinical outcome in LC patients with bacteremia. The purpose of this study was to evaluate the value of initial CRP as a predictor of clinical outcome and to investigate whether follow-up CRP measurement is useful for predicting the clinical outcome of bloodstream infections in patients with LC.

METHODS

A retrospective, observational cohort study was conducted to evaluate the outcomes of cirrhotic patients with bacteremia and to assess the usefulness of serial CRP measurement for the prediction of clinical outcomes in patients with LC. The database at our Clinical Microbiology Laboratory and electronic medical records were reviewed to identify LC patients with *Escherichia coli* or *Klebsiella pneumoniae* bacteremia at the Samsung Medical Center (Seoul, Korea), a 1,950-bed tertiary care university hospital, from January 2003 to December 2007. Only patients aged ≥ 18 years with LC were included. Among the cirrhotic patients with bacteremia, only those who had initial and follow-up CRP levels recorded in their medical histories were included. The initial CRP level was defined as the level of CRP in the blood samples within 24 hours after blood culture samples were obtained. The day when the blood culture samples were obtained was designated as day 0. The follow-up CRP level was defined as the level of CRP in the blood samples at day 4 or 5; when both values were available, the lower level was adopted as the follow-up CRP level. To assess and apply the serial change in CRP level in the outcome analysis, we used the ratio of the follow-up CRP level to the initial CRP level (CRP ratio).

Bacteremia was classified as community-acquired, healthcare-associated, or nosocomial using previously described criteria [11]. The following variables were also recorded and included in the outcome analysis to control for potential confounding factors: age, gender, etiology of LC, type of bacteremia, infectious focus of bacteremia, Child-Turcotte-Pugh score [12], initial body temperature, initial white blood cell (WBC) count, sepsis-related organ failure assessment (SOFA) score [13], model for end-stage liver disease (MELD) score [14], Pitt bacteremia score [15], and adequacy of initial antibiotic treatment [16]. The primary outcome measure used was 30-day mortality. Because this study was observational, patient management and antimicrobial treatment regimens were chosen by the patients' physicians with no guidance or intervention from the study protocol or study investigators.

The Mann-Whitney *U* test was used to compare the

Table 2. Factors associated with 30-day mortality in cirrhotic patients with *Escherichia coli* or *Klebsiella pneumoniae* bacteremia

	Survivors (n = 154)	Non-survivors (n = 48)	*p* value
Advanced age (≥ 70 yr)	15 (9.7)	9 (18.8)	0.092
Male	102 (66.2)	36 (75)	0.26
Acquisition site of bacteremia			0.011
Community-acquired	75 (48.7)	13 (27.1)	
Healthcare-associated	53 (34.4)	19 (39.6)	
Nosocomial	26 (16.9)	16 (33.3)	
ESBL-producing organism	10 (6.5)	5 (10.4)	0.356
Child-Pugh classification			< 0.001
Child A or B	70 (45.5)	2 (4.2)	
Child C	84 (54.5)	46 (95.8)	
SOFA score	5 (0-17)	8 (4-13)	< 0.001
MELD score	18 (1-40)	31 (17-48)	< 0.001
Pitt bacteremia score	1 (0-5)	1.50 (0-9)	0.009
Inadequate initial antibiotics	11 (7.1)	9 (18.75)	0.027
Initial CRP, mg/dL	3.785 (0.09-27.77)	3.425 (0.61-19.82)	0.721
WBC, /mm^3	8,835 (1,100-31,650)	7,400 (620-69,290)	0.016
Body temperature, °C	38.6 (35.0-41.0)	37.9 (35.0-40.0)	< 0.001

Values are presented as number (%) or median (range).

ESBL, extended-spectrum beta-lactamase; SOFA, sepsis-related organ failure assessment score; MELD, model for end-stage liver disease; CRP, C-reactive protein; WBC, white blood cell.

median values, and the χ^2 or Fisher's exact test was used to compare categorical variables. Multivariate logistic regression analysis was performed to investigate whether initial CRP levels and the CRP ratio were associated with the 30-day mortality. To simplify the application of the rule, continuous variables were re-categorized into binary factors using the most discriminant cutoff point. All reported *p* values were 2-tailed, and *p* values < 0.05 were considered to indicate statistical significance. Data analysis was performed using commercially available software (PASW statistics version 17.0; SPSS Inc., Chicago, IL, USA).

RESULTS

In total, 202 cirrhotic patients with *E. coli* or *K. pneumoniae* bacteremia, whose initial CRP levels were available, were included. Demographic and clinical features of the study population are shown in Table 1. The most frequent cause of cirrhosis was hepatitis B virus (134 patients, 66.3%), and the most common focus of bacteremia was spontaneous bacterial peritonitis (82 patients, 40.6%). Of the 202 patients, 130 (64.4%) were classified as Child C according to the Child-Pugh classification.

The overall 30-day mortality rate was 23.8% (48/154). Factors associated with mortality were advanced age (≥ 70 years), healthcare-associated or nosocomial infections, Child class C, higher SOFA score, higher MELD score, higher Pitt bacteremia score, inappropriate initial antimicrobial therapy, lower WBC count, and lower body temperature (all $p < 0.05$) (Table 2). Among these variables, age ≥ 70 years (odds ratio [OR], 3.68; 95% confidence interval [CI], 1.04 to 13.02), healthcare-associated or nosocomial infections (OR, 4.18; 95% CI, 1.51 to 11.55), MELD score of ≥ 30 (OR, 7.48; 95% CI, 2.88 to 19.41), and initial body temperature of < 37°C (OR, 13.85; 95% CI, 3.81 to 50.34) were found to be significant factors associated with mortality in the multivariate analysis (all $p < 0.05$). No association was found between initial CRP level and mortality.

A further analysis including 87 evaluable cases who had repeated CRP measurements at day 4 and/or 5 was performed. Nine of these 87 patients (10.3%) died within

Table 3. Factors associated with 30-day mortality in cirrhotic patients with bacteremia who had repeated CRP measurements at day 4 and/or 5

	Survivors (n = 78)	Non-survivors (n = 9)	*p* value
Advanced age (≥ 70 yr)	9 (11.5)	4 (44.4)	0.026
Male	51 (65.4)	8 (88.9)	0.261
Acquisition site of bacteremia			
Community-acquired	37 (47.4)	2 (22.2)	0.178
Healthcare-associated	31 (39.7)	3 (33.3)	
Nosocomial	10 (12.8)	4 (44.4)	
ESBL-producing organism	6 (7.7)	3 (33.3)	0.048
Child-Pugh classification			0.170
Child A or B	38 (48.7)	2 (22.2)	
Child C	40 (51.3)	7 (77.8)	
SOFA score	5 (0-17)	8 (4-13)	0.018
MELD score	18 (1-40)	29 (17-45)	0.004
Pitt bacteremia score	1 (0-5)	1 (0-2)	0.863
Inadequate initial antibiotics	9 (11.5)	2 (22.2)	0.318
Initial CRP, mg/dL	5.64 (0.09-27.77)	2.59 (0.61-14.26)	0.691
CRP ratio[a] of ≥ 0.7	35 (44.9)	8 (88.9)	0.015
WBC, /mm^3	9,000 (1,100-21,240)	7,820 (1,800-28,540)	0.435
Body temperature, °C	38.6 (35.5-41.0)	38.3 (35-39.2)	0.233

Values are presented as number (%) or median (range).

CRP, C-reactive protein; ESBL, extended-spectrum beta-lactamase; SOFA, sepsis-related organ failure assessment score; MELD, model for end-stage liver disease; WBC, white blood cell.

[a] CRP ratio was defined as the ratio of the follow-up CRP level to the initial CRP level.

30 days. The CRP level decreased below 70% of the initial level in only one of the nine non-survivors, whereas 43 of the 78 survivors showed decreased CRP levels below 70% of the initial level at day 4 or 5 (11% vs. 55%; $p = 0.015$). Factors associated with mortality were advanced age (≥ 70 years), extended-spectrum beta-lactamase (ESBL)-producing organisms, higher SOFA score, higher MELD score, and CRP ratio of ≥ 0.7 (all $p < 0.05$) (Table 3). After adjustment for confounding variables, a CRP ratio of ≥ 0.7 was found to be a significant factor associated with mortality (OR, 19.12; 95% CI, 1.32 to 276.86; $p = 0.043$), along with age ≥ 70 years (OR, 39.31; 95% CI, 2.57 to 369.99; $p = 0.007$) and higher MELD score (OR, 1.20 [per 1-point increment]; 95% CI, 1.01 to 1.45; $p = 0.043$).

DISCUSSION

In the current study, we evaluated the usefulness of serial measurements of CRP levels after the initiation of antimicrobial therapy in cirrhotic patients with bacteremia who might have an attenuated CRP response to infection. Our data, which included patients with LC, showed that a decrease in CRP level after the initiation of antimicrobial therapy was significantly associated with a better outcome, although no association between initial CRP level and outcome was found. As previously reported by Povoa et al. [5] a decrease in CRP level, indicating resolution of the inflammatory process, is associated with a better outcome, whereas persistently elevated or increasing CRP levels, possibly denoting ongoing inflammation, are associated with further deterioration and a poor prognosis. Persistently elevated or increasing CRP levels, even in patients with severe liver dysfunction due to LC, can predict a poor outcome. Park et al. [2] demonstrated that CRP levels were increased even in LC patients with underlying liver dysfunction, despite the fact that the more severe the underlying liver dysfunction, the lower the CRP response to *E. coli* bacteremia. Based on the findings in these studies, serial CRP level measurements could be

useful as a marker of the resolution of sepsis and might help clinicians to make better decisions when reassessing patients who fail to improve, including LC patients with liver dysfunction.

Serial CRP measurements in patients with sepsis may be useful in the identification of patients with the highest risk for poor outcome. Earlier prediction of a poor outcome could result in prompt and more appropriate management of these patients. Similarly, the identification of patients in whom a favorable course of disease is expected might facilitate therapeutic management of these patients, which might include oral antibiotics, instead of intravenous antibiotics, or a shorter duration of therapy [10]. However, because predictive rules for prognosis serve only as a guide to clinical management, CRP levels cannot be used as a sole prognostic marker, and should instead be applied in combination with other clinical variables that may be associated with outcome. Not surprisingly, advanced age and severity of the underlying illness (MELD score) were also significant factors associated with mortality.

The CRP level was found to be an independent marker of severity in community-acquired pneumonia, and an elevated CRP, of ≥ 10 mg/dL, was not only associated with an increased 30-day mortality, but was also a marker for the development of complicated pneumonia in a previous study [7]. However, no association between the initial CRP level and the 30-day mortality was found in our study, including in LC patients with bacteremia, although monitoring of CRP levels after the initiation of antimicrobial therapy was useful for predicting the clinical outcome of the bacteremia. Instead, normal body temperature (< 37°C) was a significant factor associated with mortality in LC patients with bacteremia. Patients with severe liver dysfunction are likely to have a blunted inflammatory response. Consequently, these patients might have an attenuated CRP response and a febrile response to severe infection. This highlights the importance of host factors in determining the outcome of infection.

Our study has several limitations. First, this was a single-center, retrospective observational study, and our results have not been validated with a new data set. The criteria for performance of blood cultures were not standardized, and there was no specific guideline for the monitoring of CRP levels. Furthermore, because this study was retrospective in nature, the possibility that these limitations precluded accurate comparisons should be considered. Second, we used all-cause 30-day mortality, rather than infection-related mortality, as an outcome measure. We had difficulty determining whether these deaths were directly related to bacteremia because the majority of the patients also had underlying conditions that could shorten their life spans. Third, our study was performed at a single large institution, and the results may or may not be applicable to other hospital settings. Finally, due to the small sample size (78 vs. 9 cases) for comparison, the association between the CRP ratio and 30-day mortality might not be considered justified. Despite these shortcomings, we believe that CRP measurement may be useful for monitoring treatment response in LC patients with serious bacterial infections. To our knowledge, this is the first reported study to evaluate the usefulness of CRP level monitoring to predict the clinical course of LC patients with bacteremia who have liver dysfunction and reduced capacity of CRP production.

In conclusion, in LC patients with *E. coli* or *K. pneumoniae* bacteremia, initial CRP level did not predict prognosis; however, when patients survived over 4-5 days of antimicrobial therapy, a decrease in CRP level was associated with 30-day survival, whereas persistently elevated or increasing CRP levels were associated with further deterioration and a poor prognosis. Our data suggest that serial CRP measurements during the first week of antimicrobial therapy may be useful as a prognostic factor for mortality in patients with LC despite the blunted inflammatory response in such patients.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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