Serum Procalcitonin in Patients with Acute Liver Failure

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ABSTRACT

Background Procalcitonin (PCT) is a known diagnostic marker of bacterial infection. There are no previous reports of PCT concerning acute liver failure (ALF). We evaluated the clinical value of serum PCT levels in patients with ALF.

Methods Forty-four patients with acute hepatitis (19 men and 25 women; median age, 40 years; range, 20–79 years) were retrospectively enrolled from January 2001 and June 2015. PCT levels were measured by saved serum samples obtained within 3 days after admission. ALF was defined as prothrombin time (PT) < 40% regardless of hepatic encephalopathy.

Results Serum PCT levels were significantly higher in the patients with ALF (n = 16) than in those with non-ALF (n = 28) [0.25 (0.13–2.66) ng/mL vs. 0.165 (0.03–1.08), P = 0.00967]. Creatinine, total bilirubin, and direct bilirubin were positively correlated, and PT was negatively correlated with PCT. Receiver operating characteristic curve analysis showed an area under the curve of 0.74 for detecting ALF. With a PCT cut-off value of 0.5 ng/mL, the presence of ALF could be demonstrated with low sensitivity (37.5%) and high specificity (96.5%) with high positive (85.7%) and negative (72.9%) predictive value. Multivariate analysis showed that PCT was an independent factor associated with the presence of ALF. The cumulative survival rate was also significantly lower in patients with PCT ≥ 0.5 ng/mL (P = 0.0314), but it was not an independent prognostic factor.

Conclusion Serum PCT level was significantly higher in patients with ALF.

Key words acute hepatitis; acute liver failure; fulminant hepatitis; procalcitonin

Acute liver failure (ALF), especially fulminant hepatitis is a severe liver disorder with high mortality.[1] Despite advances in intensive care, the mortality rate remains high.[2] Liver transplantation (LT) is regarded as the standard therapy for patients with ALF, and the cumulative survival rates at 1, 5, and 10 years after LT in Japan were 79%, 74%, and 73%, respectively.[3] For early prediction of disease severity, it is critically important for patients to receive LT. Scoring systems using multiple factors [age; duration from onset to hepatic encephalopathy; creatinine (Cre), bilirubin, and cholinesterase levels; platelet counts; prothrombin time (PT); arterial blood pH; and liver atrophy] have been reported to be useful for predicting the severity and prognosis of ALF.[4–9] Moreover, factor V levels, interleukin-10, tumor necrosis factor-α, serum Gc-globulin, and M30 have also been identified to predict the prognosis of ALF as single prognostic factors.[10–13]

Procalcitonin (PCT), the prototype of a hormokine mediator, is released from all cell types throughout the body by microbial infections and is regarded as a reliable marker of sepsis.[14, 15] Serum PCT levels have also been shown to be higher in cirrhotic patients with bacterial infection than in those without infection.[16–20] However, no previous reports have evaluated PCT as a biomarker of ALF. This study aimed to evaluate the clinical value of serum PCT levels in patients with ALF.

SUBJECTS AND METHODS

Subjects

Between January 2001 and June 2015, a total of 85 consecutive hospitalized patients with acute hepatitis in the Department of Gastroenterology, Tottori Univeristy Hospital in Yonago were retrospectively evaluated. In this study, we defined acute hepatitis as ALT of more than 1.5 times the upper normal limit (using 19IU/L for female and 30IU/L for male) without underlying chronic liver disease.[21, 22] Chronic liver disease including cirrhosis

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Abbreviations: AFP, alpha-fetoprotein; AIH, autoimmune hepatitis; ALF, acute liver failure; ALP, alkaline phosphatase; ALT, alanine aminotransferase; anti-HBc, antibody to hepatitis core antigen; AST, aminotransferase; BT, bacterial translocation; Cre, creatinine; CRP, C-reactive protein; CMV, cytomegalovirus; DILI, drug-induced liver injury; DLBCL, diffuse large B cell lymphoma; EBV, Epstein-Barr virus; GGT, gamma-glutamyl transpeptidase; HAV, hepatitis A virus; HBeAg, hepatitis B envelop antigen; HbsAg, hepatitis B surface antigen; HBV, hepatitis B viral; HCV, hepatitis C virus; HE, hepatic encephalopathy; HEV, hepatitis E virus; HGF, hepatocyte growth factor; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; LT, liver transplantation; PCT, procalcitonin; PT, prothrombin time; ROC, receiver operating characteristic; SBP, spontaneous bacterial peritonitis

was diagnosed according to clinical, biochemical, and/or imaging findings. Patients with underlying chronic liver disease, a history of alcoholism (ethanol consumption more than 40 g/day and longer than 25 years), and drug-induced liver injury (DILI) were excluded from the study. All patients whose serum samples within 3 days after admission were unavailable were excluded from the study. A total of 44 patients (19 men and 25 women; median age, 40 years; range, 20–79 years) were enrolled.

Definitions and examined items

In Japan, ALF is defined as percent PT < 40% regardless of hepatic encephalopathy (HE), and it is divided into "ALF without HE" and "ALF with HE".[23] In this study, all the HE were diagnosed after admission. All the patients underwent blood biochemical examinations including Cre, total and direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), alpha-fetoprotein (AFP), PT, and C-reactive protein (CRP) within 24 h after hospitalization. All the patients were also tested for immunoglobulin M (IgM) and G (IgG) antibody against hepatitis A virus (HAV), hepatitis B surface antigen (HBsAg), hepatitis B envelop antigen (HBeAg), IgM antibody to hepatitis core antigen (IgM anti-HBc), hepatitis B viral (HBV) DNA, hepatitis C virus (HCV) antibody, HCV-RNA, and immunoglobulin A (IgA) antibodies to hepatitis E virus (HEV) using routine commercially available enzyme immune assays. IgM and IgG antibodies against Epstein-Barr virus (EBV), herpes simplex virus, cytomegalovirus (CMV) were assayed. In all the patients, systemic and focal bacterial infection was checked by 2 sets of blood culture, urine test, ultrasonography and computed tomography. Serum PCT levels were measured with an Electro Chemi Luminescence Immuno Assay (BRAHMS PCT; Roche Diagnostics, Tokyo, Japan) in their saved sera obtained within 3 days after admission.

Ethical Considerations

The study protocol was approved by the Institutional Review Board of our institute (No.1512A098) under the guidelines of the 1975 Declaration of Helsinki.

Statistical analysis

Data are expressed as median (range). Statistical analyses for significant differences among the groups were performed using Mann-Whitney's *U* test or the Kruskal-Wallis test. Correlations were calculated using Pearson's product-moment correlation coefficient. Receiver operating characteristic (ROC) curve analysis was also used in order to determine the sensitivity and specificity of the serum PCT values for the detecting ALF in the study population. Univariate and multivariate analyses were performed using the multiple logistic regression analysis method. The cumulative survival rate was calculated by the Kaplan-Meier method and significant differences between the two groups were calculated using the log-rank test. All statistical analyses were performed using StatFlex (Windows ver. 6.0; Artech, Osaka, Japan). Statistical significance was set at $P < 0.05$.

RESULTS

Patient background

Baseline characteristics of the patients are presented in Table 1. Twenty-nine patients (66%) underwent liver biopsy. The etiology of acute hepatitis included HBV infection ($n = 9$), HCV infection ($n = 3$), CMV infection

Table 1. Characteristics of 44 patients with acute hepatitis

Male/Female	19:25		
Age (years)	40 (20–79)		
Etiology			
Viral infection	18 (40.9%)		
HBV	9		
HCV	3		
CMV	3		
EBV	3		
Autoimmune hepatitis	7 (15.9%)		
Others*	8 (18.2%)		
Indeterminate	11 (25%)		
Acute liver failure	16 (36.4%)		
with HE	6 (13.6%)		
without HE	10 (22.7%)		
Laboratory values			
AST	1025	(47–20490)	IU/L
ALT	884	(51–14510)	IU/L
ALP	503	(122–2706)	IU/L
GGT	186	(27–994)	IU/L
Total bilirubin	3.85	(0.6–40.5)	IU/L
D/T ratio	0.55	(0.11–0.73)	
PT	59.4	(5–116)	%
IgG	1603	(836–3690)	mg/dL
Creatinine	0.7	(0.41–6.68)	mg/dL
CRP	0.35	(0.04–20.11)	mg/dL
AFP	4.9	(0.1–191.6)	ng/mL
PCT	0.2	(0.03–2.66)	ng/mL

*Other etiologies include Syphilis, Chlamydia, Mycoplasma, and diffuse large B cell lymphoma. Data are expressed as median (range).

AFP, alpha-fetoprotein; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; CMV, cytomegalovirus; D/T ratio, direct and total bilirubin ratio; EBV, Epstein-Barr virus; GGT, gamma-glutamyl transpeptidase; HBV, hepatitis B virus; HCV, hepatitis C virus; HE, hepatic encephalopathy; Ig, immunoglobulin; PCT, procalcitonin; PT, percent prothrombin time.

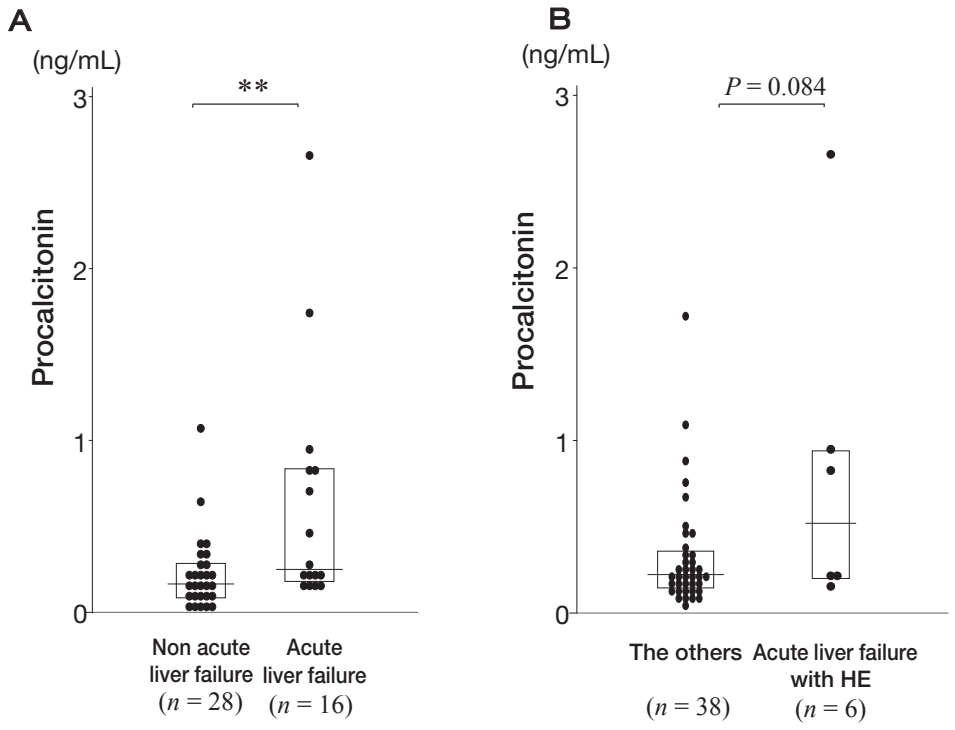

Fig. 1. Differences in serum PCT levels in acute hepatitis. **A**: The serum PCT levels were significantly higher in patients with ALF (n = 16) than in those with non-ALF (n = 28) [0.25 (0.132.66) vs. 0.165 (0.03–1.08) ng/mL, P = 0.009]. **P < 0.01. **B**: relatively higher in ALF with HE (n = 6) than the others (n = 38) [0.52 (0.13–2.66) vs. 0.19 (0.03–1.73) ng/mL, P = 0.084]. ALF, acute liver failure; HE, hepatic encephalopathy; PCT, procalcitonine.

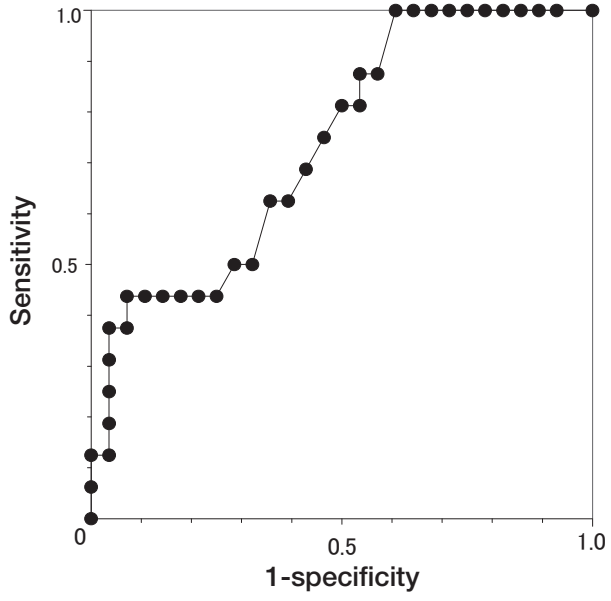

Fig. 2. The ROC curve of serum PCT levels for detecting ALF. The AUROC for serum PCT was 0.74 for detecting ALF in the cases of acute hepatitis on admission. ALF, acute liver failure; AUROC, area under the receiver operator characteristic; PCT, procalcitonine; ROC, receiver operating characteristic.

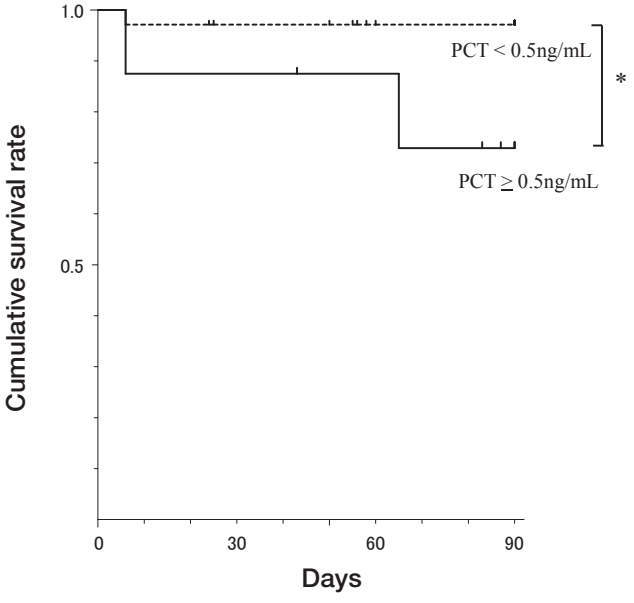

Fig. 3. Cumulative survival rate with a PCT cut-off level of 0.5 ng/mL. The cumulative survival rate was significantly lower in the patients with PCT ≥ 0.5 ng/mL (P = 0.031). *P < 0.05. PCT, procalcitonine.

(n = 3), EBV infection (n = 3), autoimmune hepatitis (n = 7), other etiology (n = 8) and indeterminate (n = 11). Ten patients had ALF without HE and six patients had ALF with HE. Four patients of "ALF with HE" died (one by suicide) during the study period. One patient with HE was not ALF since the HE was considered to be induced by a disorder in the urea cycle. The main etiology of ALF was HBV (43.8%). None of the patients were diagnosed with a systemic or focal bacterial infection. There were no cases of spontaneous bacterial peritonitis (SBP). Six patients received artificial liver support using hemodialysis, and 10 patients underwent plasma exchange in addition to conventional supportive treatment. Subsequently, three patients died of hepatic failure and one patient unfortunately committed suicide after recovery. No patient received liver transplantation because of no available donor organs. There were no missing data or outliers in obtained serum PCT.

Table 2. Correlations between serum PCT levels and clinical/biochemical parameters

Patients (n = 44)	r	(95% CI)	P value
Age (year)	0.1711	(–0.133–0.445)	0.267
AST	0.171	(–0.133–0.445)	0.268
ALT	0.157	(–0.146–0.434)	0.307
ALP	–0.130	(–0.411–0.173)	0.399
GGT	–0.161	(–0.437–0.143)	0.297
Total bilirubin	0.454	(0.182–0.663)	0.002
Direct bilirubin	0.541	(0.288–0.724)	< 0.001
D/T ratio	0.225	(–0.081–0.492)	0.146
PT	–0.3930	(–0.618–0.109)	0.008
IgG	–0.1164	(–0.406–0.194)	0.463
Creatinine	0.8078	(0.672–0.891)	< 0.001
CRP	0.2528	(–0.051–0.514)	0.102
AFP	0.1936	(–0.160–0.503)	0.280

AFP, alpha-fetoprotein; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CRP, C-reactive protein; D/T ratio, direct and total bilirubin ratio; GGT, gamma-glutamyl transpeptidase; Ig, immunoglobulin; PCT, procalcitonin; PT, percent prothrombin activity.

Analysis of serum procalcitonin levels

Serum PCT levels were significantly higher in the patients with ALF (n = 16) than in those with non-ALF (n = 28) [0.25 (0.13–2.66) vs. 0.165 (0.03–1.08) ng/mL, P = 0.00967] (Fig. 1A), and relatively higher in ALF with HE than the others [0.52 (0.13–2.66) vs. 0.19 (0.03–1.73) ng/mL, P = 0.084] (Fig. 1B). Creatinine, total bilirubin, and direct bilirubin were positively and PT was negatively correlated with PCT. (Table 2). The area under the ROC (AUROC) was 0.74 for detecting ALF on admission (Fig. 2). The cutoff value of 0.5 ng/mL for PCT showed a low sensitivity (37.5%) and a higher specificity (96.5%) for detecting ALF on admission. The positive predictive value (PPV) and negative predictive value (NPV) were 85.7% and 72.9%, respectively. We compared the clinical parameters between patients with low PCT (< 0.5 ng/mL) and those with high PCT (≥ 0.5 ng/mL). The prevalence of HE was significantly higher in the high PCT group than in the low PCT group. On the other hand, the serum GGT and PT levels were significantly lower in the high PCT group than in the low PCT group (Table 3). It is not surprising that the number of patients complicated with HE was greater in ALF group. The levels of serum AST [589 (47–3016) vs. 1925 (154–24090), P = 0.0011], ALT [639.5 (51–3612) vs. 2782 (141–14510), P = 0.0004], total bilirubin [1.8 (4.3–5.8) vs. 10 (1.4–40.5), P = 0.0002], D/T ratio [0.39 (0.11–0.69) vs. 0.65 (0.3–0.73),

Table 3. Comparison of background between patients with low PCT and high PCT levels

		PCT (ng/mL)		P value
		< 0.5 (n = 36)	≥ 0.5 (n = 8)	
Gender (male:female)		16:20	3:5	0.720
Age (year)		38 (20–79)	48 (22–71)	0.692
Etiology (viral:non-viral)		16:20	2:6	0.312
Hepatic encephalopathy (yes:no)		33:3	4:4	0.004
AST	(IU/L)	1030 (47–24090)	929 (254–15604)	0.503
ALT	(IU/L)	985 (51–9598)	676 (217–14510)	0.715
ALP	(IU/L)	521 (122–2706)	466 (275–617)	0.196
GGT	(IU/L)	189 (38–994)	94 (27–266)	0.037
Total bilirubin	(mg/dL)	3.05 (0.6–29.7)	7.15 (0.9–40.5)	0.385
D/T ratio		0.57 (0.11–0.73)	0.58 (0.27–0.71)	0.673
PT	(%)	69 (12–116)	28 (5–24)	0.011
Creatinine	(mg/dL)	0.69 (0.41–2.23)	0.74 (0.51–6.68)	0.308
CRP	(mg/dL)	0.88 (0.04–20.11)	2.6 (0.23–14.66)	0.139
AFP	(ng/dL)	4.9 (0.1–83.4)	6.15 (0.7–191.6)	0.585

Data are expressed as median (range). AFP, alpha-fetoprotein; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; D/T ratio, direct and total bilirubin ratio; GGT, gamma-glutamyl transpeptidase; PCT, procalcitonin; PT, percent prothrombin activity.

Table 4. Differences between non-ALF and ALF

		Non-ALF (n = 28)	ALF (n = 16)	P value
Gender (male:female)		12:16	7:9	0.956
Age (year)		39 (20–79)	40 (22–71)	0.877
Etiology (viral:non-viral)		11:17	7:9	1.000
Hepatic encephalopathy (yes:no)		1:27	5:11	0.010
AST	(IU/L)	589 (47–3016)	1925 (154–24090)	0.001
ALT	(IU/L)	639.5 (51–3612)	2782 (141–14510)	< 0.001
ALP	(IU/L)	546 (122–2706)	465.5 (275–617)	0.089
GGT	(IU/L)	189 (38–994)	162.5 (27–613)	0.193
Total bilirubin	(mg/dL)	1.8 (4.3–5.8)	10 (1.4–40.5)	< 0.001
D/T ratio		0.39 (0.11–0.69)	0.65 (0.3–0.73)	0.013
Creatinine	(mg/dL)	0.66 (0.41–1.17)	0.82 (0.41–6.68)	0.022
CRP	(mg/dL)	0.89 (0.06–20.11)	1.3 (0.04–5.93)	0.450
AFP	(ng/dL)	28.5 (0.1–56.7)	6.15 (0.7–191.6)	0.290
PCT	(ng/dL)	0.165 (0.03–1.08)	0.22 (0.13–2.66)	0.008

Data are expressed as median (range). ALF, acute liver failure; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; D/T ratio, direct and total bilirubin ratio; CRP, C-reactive protein; AFP, alpha-fetoprotein; PCT, procalcitonin.

Table 5. Multivariate analysis for detecting ALF on admission

		Odds ratio	95% CI	P value
PCT	(ng/dL)	52.15	(1.08–2525.65)	0.046
AST >1000	(IU/L)	1.50	(0.09–24.21)	0.775
ALT >1000	(IU/L)	5.97	(0.35–101.39)	0.217
Total bilirubin	(mg/dL)	1.08	(0.92–1.27)	0.363
D/T ratio		6.37	(0.01–4256.02)	0.577
Creatinine	(mg/dL)	27.43	(0.41–1855.89)	0.124

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; D/T ratio, direct and total bilirubin ratio; PCT, procalcitonin.

P = 0.0132], Cre [0.66 (0.41–1.17) vs. 0.82 (0.41–6.68), P = 0.022], and serum PCT [0.165 (0.03–1.08) vs. 0.22 (0.13–2.66), P = 0.0082], showed significant differences between non-ALF and ALF patients (Table 4). Multiple logistic regression analysis revealed PCT to be an independent factor for detecting ALF on admission (Table 5). In this multiple regression analysis, HE was excluded because it was not the factor on admission. The cumulative survival rate was significantly lower in patients with PCT ≥ 0.5 ng/mL than in those with PCT < 0.5 ng/mL (P = 0.0314) (Fig. 3). However, multivariate analysis did not demonstrate PCT as an independent prognostic factor.

DISCUSSION

This study provided two novel findings. First, serum PCT levels in patients with ALF were significantly higher than those in non-ALF patients. Second, this is the first report to demonstrate that the serum PCT level was independently associated with ALF.

To our knowledge, only two reports have thus far evaluated serum PCT in acute hepatitis. Elefsiniotis et al.[24] evaluated serum PCT levels in a small sample (n = 13) of patients with acute icteric viral hepatitis (including 4 patients with acute exacerbation of chronic viral hepatitis), and indicated no remarkable elevation (0.37 ± 0.22 ng/mL) as compared with a group of decompensated cirrhosis with culture-proven bacterial infection (9.8 ± 16.8 ng/mL). Another report was a case presentation of acute Q-fever granulomatous hepatitis.[25] The hepatitis was induced by bacterial (*Coxiella brunetii*) infection and treated by antibiotics; the authors concluded that the serum PCT level was useful for monitoring the treatment of bacterial hepatitis. In both these reports, serum PCT levels were not evaluated in ALF cases. On the other hand, some reports have evaluated serum PCT levels in cirrhotic patients with chronic liver failure.[16–20] In these reports, the serum PCT levels were mainly evaluated for detecting bacterial infection in cirrhosis, such as SBP induced by bacterial translocation (BT). No study has thus far evaluated the clinical significance of serum PCT in

ALF. The present study showed that serum PCT levels in ALF patients were significantly higher than those in non-ALF patients.

There were some patients with elevated CRP, however, none of the patients was diagnosed with focal and systemic bacterial infection. There are only small number of reports mentioned about the relationship between hepatitis and CRP. Wigmore SJ et al.[26] indicated that the serum CRP concentration in patients with fulminant hepatic failure on the day of admission was high [6 (2.2–8.6) mg/dL], and they thought it may have been stimulated by pro-inflammatory cytokines. Atono Y et al.[27] also reported that CRP was markedly increased in the acute phase of acute hepatitis type A (1.34 ± 2.18mg/dL) and B (0.88 ± 0.78mg/dL). According to these reports, to some extent, serum CRP levels might be affected by acute hepatitis. Considering our four patients with higher CRP (≥ 5), their final diagnoses were autoimmune hepatitis (AIH) (CRP 5.93mg/dL), diffuse large B cell lymphoma (DLBCL) (CRP 7.06mg/dL) and two unknowns (CRP 14.7 and 20.1mg/dL). In the AIH case, the CRP gradually decreased from 5.93 to 1.83 mg/dL at two weeks of admission, and in DLBCL case, it also decreased gradually from 7.06 to 0.4 mg/dL at three weeks of admission. Probably, these CRP levels might be affected by these backgrounds. On the other hand, one of the two patients with unknown cause was administered antibiotics empirically, and the CRP level decreased from 14.7 to 2.4mg/dL at fourth day of admission. The other patient with unknown cause was not administered any antibiotics, and the CRP decreased from 20.1 to 2.8 mg/dL at fourth day of admission. These two cases demonstrated a similar clinical course in CRP levels regardless of antibiotics. There were no remarkable inflammatory backgrounds such as autoimmune diseases in these cases. The dynamics of CRP in acute hepatitis with unknown causes has still been remained unclear.

In the absence of bacterial infection, serum PCT levels were also reported to be elevated in cases of surgery, trauma, cardiogenic shock, severe pancreatitis, severe renal and liver dysfunction (Child-Pugh C), and multiple organ failure.[28]

In this study, we found the strong positive correlation between PCT and Cre. PCT has been reported to predict the acute kidney injury complicated with infection or acute pancreatitis.[29, 30] The reason may be due to the plasma disappearance rate prolongation of PCT in renal dysfunction.[31] Renal dysfunction is also reported frequently complicated with ALF.[32] However, no previous reports demonstrated the relation between PCT and renal dysfunction in ALF.

Although the mechanism for the PCT elevation in ALF remains unknown, subsequent endotoxemia and systemic inflammation may also play important roles in PCT elevation. BT may be involved in high serum PCT levels in ALF.[33] Further study with a larger number of patients is needed to clarify these observations.

We selected serum PCT level of 0.5 ng/mL as an optimal cut-off level for detecting ALF. This cut-off value showed high specificity but low sensitivity. Although the cut-off value of 0.5 ng/mL is used for diagnosing sepsis,[28] an optimal cut-off value for ALF needs to be validated by further studies.

This is the first report to evaluate PCT in ALF. However, this study is a retrospective study with a relatively small number of cases. Therefore, we could not demonstrate PCT as a distinct predictive and prognostic biomarker for ALF with HE. To evaluate PCT as a predictive and prognostic marker for ALF with HE, our findings should be validated in a larger sample size with a prospective cohort.

In conclusion, serum PCT level was significantly higher in patients with ALF following acute hepatitis. PCT is expected to be an early predictive biomarker in acute hepatitis.

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The authors declare no conflict of interest.

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