Original Paper

Serum Procalcitonin Correlates with Renal Function in Hepatitis B Virus-Related Acute-on-Chronic Liver Failure

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Key Words

Acute-on-chronic liver failure • Procalcitonin • Creatinine • Glomerular filtration rate

Abstract

Background/Aims: To investigate the relationship between elevated serum procalcitonin (PCT) and renal function in hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF). **Methods:** HBV-ACLF patients (n = 201) presenting to the State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, Zhejiang University, from January 2013 to November 2016 were categorized into three groups according to serum PCT levels: (i) normal group (n = 74) had PCT of ≤ 0.5 ng/mL; (ii) elevated group (n = 85) had PCT in the range 0.5–1.0 ng/mL; and (iii) highly elevated group (n = 42) had PCT of > 1.0 ng/mL. Thirty-five cases received standard care after admission. Serum PCT levels and renal function were determined during a two-week follow-up. **Results:** Significant increases in serum creatinine (Cr) were recorded in male and female patients in the elevated group and highly elevated group compared with the normal group ($P < 0.05$). In addition, serum Cr levels in male and female patients were significantly higher in the highly elevated group than in the elevated group ($P < 0.05$). The glomerular filtration rate (GFR) was significantly lower in the highly elevated group ($P < 0.05$) and this group had the highest risk of altered Cr (45.9% in males; 80% in females) and abnormal GFR (37.5%). Serum PCT levels correlated significantly with all renal function parameters including homocysteine (Hcy), GFR, Cr, blood urea nitrogen, uric acid, and cystatin C at baseline and during treatment. Univariate and multivariate analyses indicated that serum PCT was a strong predictor of renal dysfunction. **Conclusion:** Serum PCT is closely related to renal dysfunction in HBV-ACLF.

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Introduction

Patients with hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF) show significantly higher 28-day mortality than patients with non-HBV-ACLF [1]. Renal dysfunction is known as an independent predictor of mortality in HBV-ACLF [2]. Therefore, the identification of factors associated with renal dysfunction may contribute to determining the prognosis of HBV-ACLF patients.

High levels of serum procalcitonin (PCT), a calcitonin precursor hormone, have been found in patients with bacterial infections [3, 4]. Furthermore, elevated serum PCT levels have been reported to show pro-inflammatory effects and increase mortality rates in a sepsis model [5], while these effects are prevented via the inhibition of PCT expression [6]. Interestingly, serum PCT is also elevated in HBV-ACLF patients [7]. However, little is known about the correlation between serum PCT and renal dysfunction in HBV-ACLF patients. In this study, serum PCT was measured in HBV-ACLF patients to evaluate the association between serum PCT and renal function in these patients.

Materials and Methods

Patients

HBV-ACLF patients presenting to the State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, Zhejiang University, were analyzed from January 2013 to November 2016. ACLF patients aged ≥ 18 years with chronic HBV infection were included in this study. HBV infection was defined as detectable hepatitis B surface antigen (HBsAg) and HBV DNA for at least 6 months. HBV-ACLF is defined as an acute hepatic insult manifesting as jaundice (serum bilirubin ≥ 5 mg/dL) complicated by coagulopathy (international normalized ratio [INR] ≥ 1.5 or prothrombin activity $< 40\%$) within 4 weeks and clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed HBV-related chronic liver disease/cirrhosis, in association with a high 28-day mortality rate [1]. The exclusion criteria were as follows: patients co-infected with other hepatitis viruses (e.g. HAV, HCV, HDV and HEV) and/or human immunodeficiency virus; patients with a history of excessive alcohol consumption (> 40 g/day); patients with a history of liver allograft or malignancy such as hepatocellular carcinoma; and patients with signs of bacterial infection. Bacterial infection was diagnosed as described previously [7].

Grouping

HBV-ACLF patients ($n = 201$) were categorized into three groups according to serum PCT levels: (i) normal group ($n = 74$) with PCT of ≤ 0.5 ng/mL; (ii) elevated group ($n = 85$) with PCT in the range 0.5–1.0 ng/mL; and (iii) highly elevated group ($n = 42$) with PCT of > 1.0 ng/mL. Thirty-five cases received standard care after admission. Serum PCT and renal function parameters were determined during a two-week follow-up.

Bacterial culture and measurement of serum PCT

Peripheral blood samples for culture were obtained from separate venipuncture sites at admission and during treatment. All samples were incubated at 35.8 °C in an appropriate atmosphere. Serum PCT concentrations were determined through an automated immunofluorescence assay using a Kryptor analyzer (Brahms, Hennigsdorf, Germany).

Data collection

We reviewed the medical records of all patients participating in this study using data obtained exclusively from our hospital's electronic medical records and verification was provided independently by two of the authors. All of the biochemical and serological markers were detected at The First Affiliated Hospital of Zhejiang Medical University, including liver serological tests [i.e. alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TB)], hematological tests (i.e., INR), routine blood

examinations [i.e., white blood cell count, and percentage of neutrophils], as well as renal function tests [i.e., serum creatinine [Cr], glomerular filtration rate [GFR], cystatin C (CYC), blood urea nitrogen (BUN), and uric acid (UA)]. These studies were performed using standard methods in a clinical setting. The Model for End-Stage Liver Disease (MELD) score was calculated as follows: $9.6 \times \log_e [\text{creatinine (mg/dL)}] + 3.8 + \log_e [\text{bilirubin (mg/dL)}] + 11.2 \times \log_e (\text{INR}) + 6.43 \times (\text{etiology: 0 if cholestatic or alcoholic, 1 otherwise})$ [8].

Statistical analysis

All data were analyzed in SPSS 17.0 (Chicago, IL). Continuous variables are presented as means $\pm$ standard deviation, and categorical variables are presented as median values with interquartile ranges. Inter-group comparisons were performed using Student's *t*-test. Associations between dichotomic or linear variables were assessed by logistic or linear regression models, respectively. Multivariate models were obtained by stepwise forward selection, using $P > 0.1$ for removal from the model. Differences between two categorical variables were assessed by chi-square tests. The diagnostic accuracy was expressed as the area under the receiver operating characteristic curve (AUC) derived from logistic regression analysis. $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

HBV-ACLF patients ($n = 201$; 166 males; 35 females; age 47 years) and 61 healthy subjects (23 males; 38 females; age 47 years) were included in this study. There were no significant differences among age and hepatic function parameters such as ALT, AST, alkaline phosphatase, cholinesterase, total protein, gamma-glutamyl transpeptidase, or INR among the three HBV-ACLF patient groups ($P > 0.05$). No statistically significant differences were observed in TB and albumin (ALB) values between the normal group and the elevated group ($P > 0.05$). TB and ALB values were significantly lower in the highly elevated group than in the normal group and elevated group (both $P < 0.05$, Table 1). Compared with healthy subjects, serum PCT was significantly up-regulated in HBV-ACLF patients (0.1 ± 0.1 ng/mL versus 0.9 ± 1.3 ng/mL, $P < 0.001$, Fig. 1A).

HBV-ACLF patients with higher serum PCT showed more severe renal dysfunction

There was a significant increase in serum Cr levels of male and female patients in the elevated group and highly elevated group compared with those in the normal group ($P < 0.05$). In addition, serum Cr was significantly higher in male and female patients in the highly elevated group than in the elevated group ($P < 0.05$). A significant decrease in GFR was noted in the three groups, especially the highly elevated group ($P < 0.05$). Other renal function parameters including Hcy, BUN, and UA differed among these three groups (Table 1).

Serum PCT was higher in HBV-ACLF patients with higher MELD score

We classified ACLF patients into three groups according to their MELD score (ACLF1, ACLF2, and ACLF3, Table 2) and compared serum PCT levels among these groups. A significant increase in serum PCT was noted in ACLF3 compared with ACLF1 and ACLF2 ($P < 0.05$). No statistically significant difference was observed between ACLF1 and ACLF2 (Fig. 1B).

Serum PCT was higher in HBV-ACLF patients with renal dysfunction

To further investigate the relationship between PCT elevation and renal dysfunction, a stratified analysis was performed according to GFR (< 60 mL/min versus ≥ 60 mL/min) and serum Cr (≤ 104 $\mu\text{mol/L}$ versus > 104 $\mu\text{mol/L}$ in males; ≤ 84 $\mu\text{mol/L}$ versus > 84 $\mu\text{mol/L}$ in females). Among the patients, 33 (16.42%) had abnormal Cr levels including 24 males with levels of 216.63 ± 117.22 $\mu\text{mol/L}$ and 9 females with levels of 100.30 ± 24.08 $\mu\text{mol/L}$. In addition, 25 patients (19 males, 6 females) had decreased GFR at a mean level of 37.19 ± 16.41

Table 1. Baseline characteristics of the patients. PCT = procalcitonin; Cr = creatinine; BUN = blood urea nitrogen; UA = uric acid; GFR = glomerular filtration rate; CYC = cystatin C; HCY = homocysteine; WBC = white blood cell count; N% = percentage of neutrophils; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; CHE = cholinesterase; TBA = total bile acid; TP = total protein; GGT = gamma-glutamyl transpeptidase; TB = total bilirubin; ALB = albumin; INR = international normalized ratio; P1: elevated group versus normal group; P2: highly elevated group versus elevated group; P3: highly elevated group versus normal group; $P < 0.05$ was considered as significant; NA = not applicable

Parameters	Normal Group	Elevated Group	Highly elevated Group	Total	P1	P2	P3
Sex (male)	54	75	37	166	NA	NA	NA
Sex (female)	20	10	5	35	NA	NA	NA
Age (years)	45 (38–57)	45 (36–55.5)	52 (41–59.25)	47 (38–57)	0.906	0.107	0.129
PCT (ng/mL)	0.34 ± 0.11	0.7 ± 0.15	2.28 ± 2.38	0.9 ± 1.3	< 0.001	< 0.001	< 0.001
Cr ($\mu\text{mol/L}$, male)	62.4 ± 13.0	83.7 ± 65.8	134.5 ± 99.7	88.1 ± 69.8	0.008	0.007	< 0.001
Cr ($\mu\text{mol/L}$, female)	52.7 ± 17.99	68.3 ± 20.8	108.0 ± 35.47	65.1 ± 28.4	0.042	0.016	< 0.001
BUN (mmol/L)	3.94 ± 1.68	6.07 ± 7.77	10.43 ± 8.28	6.2 ± 6.79	0.016	0.006	< 0.001
UA ($\mu\text{mol/L}$)	152.7 ± 94.43	181.1 ± 105.78	267.62 ± 182.2	188.73 ± 128.73	0.078	0.006	< 0.001
GFR (mL/min)	117.36 ± 32.28	104.18 ± 28.57	73.27 ± 34.42	102.86 ± 34.96	0.007	< 0.001	< 0.001
CYC (mg/L)	0.98 ± 0.38	1.12 ± 0.69	1.81 ± 1.24	1.21 ± 0.81	0.143	0.002	< 0.001
Hcy ($\mu\text{mol/L}$)	13.61 ± 5.83	17 ± 11.06	22.38 ± 12.84	16.8 ± 10.31	0.036	0.034	0.001
WBC ($\times 10^9/\text{L}$)	6.71 ± 3.35	6.76 ± 2.42	8.81 ± 4.6	7.17 ± 3.4	0.911	0.009	0.012
N%	65.57 ± 10.51	65.13 ± 10.97	71.44 ± 13.91	66.62 ± 11.7	0.8	0.006	0.012
ALT (U/L)	446.96 ± 658.62	463.46 ± 654.7	371.81 ± 669.57	438.24 ± 656.9	0.875	0.463	0.558
AST (U/L)	347.2 ± 564.03	325.5 ± 461.49	246.57 ± 304.36	316.98 ± 475.36	0.79	0.317	0.287
ALP	141.46 ± 43.46	135.42 ± 35.33	141.6 ± 45.62	138.94 ± 40.61	0.343	0.403	0.987
CHE	3548.3 ± 1365.2	3468 ± 1358.3	3252.2 ± 1482.3	3452.8 ± 1384.4	0.712	0.421	0.284
TBA	188.8 ± 72.59	187.68 ± 68.76	165.32 ± 68.26	183.51 ± 70.37	0.921	0.089	0.093
TP	323.11 ± 154.3	333.3 ± 140.98	382.1 ± 184.59	339.72 ± 156.59	0.666	0.136	0.068
GGT (U/L)	104.82 ± 104.91	82.15 ± 51.31	83.17 ± 77.77	90.71 ± 80.5	0.094	0.93	0.246
TB	59.88 ± 9.23	59.6 ± 6.84	55.43 ± 7.06	58.83 ± 8	0.825	0.002	0.008
ALB (g/L)	32.24 ± 4.3	32.54 ± 4.08	30.82 ± 3.93	32.07 ± 4.17	0.65	0.026	0.086
INR	2.26 ± 0.98	2.32 ± 1.19	2.29 ± 0.82	2.29 ± 1.04	0.7	0.88	0.842

Fig. 1. Serum PCT in different groups according to MELD score. (A) Serum PCT was higher in ACLF patients than in healthy subjects (0.9 ± 1.3 ng/mL versus 0.1 ± 0.1 ng/mL, $P < 0.001$). (B) Serum PCT was higher in HBV-ACLF patients with higher MELD score, NS: no significance.

mL/min. Patients with a GFR below the cutoff value that is generally accepted as relevant for clinical decision-making showed substantially higher serum PCT levels compared with patients with a GFR of > 60 mL/min ($P < 0.001$, Fig. 2A). Patients with Cr levels above the cutoff value also had significantly higher serum PCT levels than patients with normal Cr levels (males, $P < 0.001$; females $P = 0.0378$, Fig. 2B-C).

Table 2. ACLF groups based on MELD score. MELD = Model for End-stage Liver Disease; N = patient number

Groups	ACLF1	ACLF2	ACLF3	Total
MELD range	20–29	30–39	≥ 40	
MELD score	27.0 ± 2.2	34.0 ± 2.7	50.9 ± 13.1	35.0 ± 9.7
N	54	113	34	201
PCT (ng/mL)	0.58 ± 0.70	0.76 ± 0.46	1.88 ± 2.76	0.9 ± 1.3

Fig. 2. Serum PCT increased in ACLF patients with renal dysfunction and decreased after treatment. (A) Serum PCT levels in patients with a GFR of < 60 mL/min were substantially higher than in patients with a GFR of ≥ 60 mL/min. (B, C) Patients with abnormal serum Cr levels (> 104 $\mu\text{mol/L}$ in males; > 84 $\mu\text{mol/L}$ in females) had significantly higher serum PCT levels than the normal control. (D) Serum PCT was down-regulated after 2 weeks' treatment. $P < 0.05$ is statistically significant, NS: no significance.

Serum PCT correlated with renal function parameters in HBV-ACLF patients at baseline and during treatment

Serum PCT levels correlated closely with the baseline renal function parameters including Hcy, GFR, Cr, BUN, UA and CYC (Table 3). Moreover, serum PCT and renal function were determined in the two weeks of follow-up in 35 patients (8 in the normal group, 15 in the elevated group, and 12 in the highly elevated group) who received standard care after admission. Our data showed that serum PCT was down-regulated (Fig. 2D), and also that it correlated with renal function parameters after 2 weeks of treatment (Table 4).

Table 3. Correlation between PCT and renal function parameters at baseline. Hcy = homocysteine; GFR = glomerular filtration rate; Cr = creatinine; BUN = blood urea nitrogen; UA = uric acid; CYC = cystatin C

Parameters	Slope	P value	95% CI for slope
Hcy	1.996	0.0073	0.5561 to 3.435
GFR	-10.87	< 0.0001	-14.29 to -7.458
Cr (male)	21.13	< 0.0001	14.28 to 27.98
Cr (female)	35.97	0.0001	19.26 to 52.67
BUN	1.8	< 0.0001	1.119 to 2.480
UA	39.98	< 0.0001	27.42 to 52.54
CYC	0.2385	< 0.0001	0.1582 to 0.3189

Serum PCT was a risk factor for abnormal Cr and decreased GFR

Since PCT showed a significant correlation with renal function parameters, we performed univariate and multivariate logistic regression analyses to identify the potential causal factors responsible for abnormal serum Cr levels (males > 104 $\mu\text{mol/L}$; females > 84 $\mu\text{mol/L}$) or decreased GFR (< 60 mL/min) in patients with HBV-ACLF. In both univariate and multivariate analyses, PCT was a risk factor for abnormal Cr and lower GFR in HBV-ACLF patients (Table 5).

High serum PCT predicted a high risk of abnormal Cr and lower GFR in HBV-ACLF patients

Among males, the risk of reaching the Cr threshold ($> 104 \mu\text{mol/L}$) was significantly higher in the highly elevated group than in the normal group (45.9% versus 1.9%, $P < 0.001$) or elevated group (45.9% versus 8%, $P < 0.001$). There was no statistically significant difference between the normal group and elevated group (1.9% versus 8%, $P = 0.26$). Similarly, the risk among the female patients was higher in the highly elevated group than in the normal group (80% versus 10%, $P = 0.002$). Furthermore, the risk of GFR of $< 60 \text{ mL/min}$ was significantly higher in the highly elevated group than in the normal group (37.5% versus 4.1%, $P < 0.001$) and the elevated group (37.5% versus 9.4%, $P < 0.001$); however, no statistically significant difference was noticed between the normal group and elevated group (4.1% versus 9.4%; $P = 0.31$, Table 6).

PCT cutoff values for evaluating renal dysfunction in HBV-ACLF patients

The most effective PCT cutoff value for evaluating Cr in HBV-ACLF patients was 0.925 ng/mL in males (AUC = 0.899; sensitivity 87.0%; specificity 80.4%) and 0.735 ng/mL in females (AUC = 0.840; sensitivity 77.8%; specificity 88.5%). Additionally, the PCT cutoff value for abnormal GFR in HBV-ACLF patients was 0.965 ng/mL (AUC = 0.810; sensitivity 68%; specificity 85%; Fig. 3).

Discussion

HBV-ACLF is a common clinical entity of HBV-associated end-stage liver disease in China [9] and frequently progresses to renal dysfunction and even death [10]. It is therefore essential to predict the risk factors associated with survival in HBV-ACLF patients at admission. Renal dysfunction is a critical complication in HBV-ACLF patients [2]; thus, it is important to identify the factors associated with renal function to obtain a prognosis in HBV-ACLF.

Table 4. Correlation between PCT and renal function parameters during treatment. GFR = glomerular filtration rate; Cr = creatinine; BUN = blood urea nitrogen; UA = uric acid; CYC = cystatin C

Parameters	Baseline		1 week		2 weeks	
	r ²	P value	r ²	P value	r ²	P value
GFR	0.4763	< 0.0001	0.2608	0.0017	0.3164	0.001
Cr	0.5324	< 0.0001	0.3146	0.0005	0.3644	0.0003
BUN	0.8252	< 0.0001	0.2684	0.0014	0.563	< 0.0001
UA	0.5582	< 0.0001	0.2584	0.0018	0.1441	0.0352
CYC	0.7934	< 0.0001	0.2911	0.0017	0.4841	< 0.0001

Table 5. Logistic regression analysis of clinical parameters to discriminate between high Cr (male $> 104 \mu\text{mol/L}$, female $> 84 \mu\text{mol/L}$) and low GFR ($< 60 \text{ mL/min}$) in HBV-ACLF patients. Univariate and multivariate logistic regression analysis to assess factors associated with high serum Cr and low GFR in HBV-ACLF patients. A stepwise forward multivariate analysis including Age, PCT, TP, ALB, TBIL, WBC, and N% was conducted with a probability of entry of $P < 0.05$ and probability of removal of $P > 0.1$. $P < 0.05$ was statistically significant. PCT = procalcitonin; TP = total protein; ALB = albumin; TB = total bilirubin; WBC = white blood cell count; and N% = percentage of neutrophils

Parameters	Cr (male)		Cr (female)		GFR	
	Coefficient	P value	Coefficient	P value	Coefficient	P value
Univariate analysis						
Age	0.061	0.001	0.148	0.023	0.067	< 0.001
PCT	1.383	< 0.001	2.576	0.018	1.142	0.001
TP	-0.068	0.019	-0.022	0.681	-0.045	0.097
ALB	-0.164	0.006	-0.151	0.138	-0.215	< 0.001
TBIL	0.005	< 0.001	-0.002	0.38	0.002	0.088
WBC	0.149	0.007	0.169	0.186	0.149	0.005
N%	0.073	0.002	0.098	0.053	0.058	0.009
Multivariate analysis						
Age	0.075	0.003	2.171	0.05	0.078	0.002
PCT	1.348	< 0.001	0.143	0.057	1.072	< 0.001
ALB	-0.239	0.005			-0.239	0.002
TBIL	0.009	< 0.001			0.004	0.016
Constant	-3.219	0.226			-1.325	0.593

Table 6. The risks of abnormal Cr and GFR gradually increased from normal group to elevated group and highly elevated group. Chi-square tests were computed to assess the risk of Cr increasing in HBV-ACLF patients with higher serum PCT levels (male). ^m = male; ^f = female; ^a = normal group; ^b = elevated group; ^c = highly elevated group; ^d = highly elevated group: normal group. Cr = creatinine, GFR = glomerular filtration rate

Parameters	Normal group	Elevated group	Highly elevated group	Total
Cr > 104 $\mu\text{mol/L}^{\text{m}}$	1 (1.9%)	6 (8.0%)	17 (45.9%)	24 (14.5%)
Cr $\leq$ 104 $\mu\text{mol/L}^{\text{m}}$	53 (98.1%)	69 (92.0%)	20 (54.1%)	142 (85.5%)
total	54 (100%)	75 (100%)	37 (100%)	166 (100%)
χ^2	1.27 ^a	21.862 ^b	26.903 ^c	39.13
P	0.26	< 0.001	< 0.001	< 0.001
Cr > 84 $\mu\text{mol/L}^{\text{f}}$	2 (10%)	3 (30%)	4 (80%)	9 (25.7%)
Cr $\leq$ 84 $\mu\text{mol/L}^{\text{f}}$	18 (90%)	7 (70%)	1 (20%)	25 (74.3%)
total	20 (100%)	10 (100%)	4 (100%)	34 (100%)
χ^2	1.813 ^a	3.506 ^b	9.547 ^c	9.394
P	0.178	0.061	0.002	< 0.001
GFR < 60 mL/min	3 (4.1%)	7 (9.4%)	15 (37.5%)	25 (13.1%)
GFR $\geq$ 60 mL/min	71 (95.9%)	78 (90.6%)	25 (62.5%)	174 (86.9%)
total	74 (100%)	85 (100%)	40 (100%)	199 (100%)
χ^2	1.03 ^a	14.293 ^b	19.401 ^c	23.207
P	0.31	< 0.001	< 0.001	< 0.001

As a prohormone of calcitonin, PCT is produced by the C-cells in the thyroid gland. Circulating levels of PCT in healthy subjects are usually undetectable [11]. However, serum PCT concentrations are significantly up-regulated in patients with inflammation [12].

HBV-ACLF patients usually have elevated serum PCT levels even in the absence of infection [7]; however, the influence of elevated serum PCT on HBV-ACLF progression is not clear. Therefore, we focused on the correlation between serum PCT and renal function in HBV-ACLF patients. Renal dysfunction is a common complication in patients with HBV-ACLF, especially in those with marked circulatory dysfunction [13]. Consistent with a previous report [14], our data showed that the baseline level of serum PCT was 1.8-fold higher than the upper limit (0.5 ng/mL). In addition, serum Cr was significantly higher and GFR was lower in HBV-ACLF patients with elevated serum PCT levels compared with controls. Furthermore, the other renal function parameters indicated that renal function had deteriorated alongside the elevation in serum PCT. Moreover, our study demonstrated a profound correlation between serum PCT and all renal function parameters in HBV-ACLF patients both at baseline and during treatment.

Elevated serum PCT was found to be associated with a higher mortality rate in a septic model [15], while immunoneutralization of PCT protected rats from lethal endotoxemia [6, 16]. Thus, elevated serum PCT levels were associated with the progression of sepsis. In our

Fig. 3. ROC curve was used to calculate the AUC of individual PCT levels to discriminate between abnormal Cr and GFR. The most effective PCT cutoff value for Cr in HBV-ACLF patients was 0.925 ng/mL in males (AUC = 0.899, sensitivity 87.0%, specificity 80.4%) and 0.735 ng/mL in females (AUC = 0.840, sensitivity 77.8%, specificity 88.5%). For diagnosing abnormal GFR in HBV-ACLF patients, the value was 0.965 ng/mL (AUC = 0.810, sensitivity 68%, specificity 85%).

study, univariate and multivariate logistic analyses revealed that serum PCT concentration was a determinant of high serum Cr levels and low GFR, which indicated that elevated serum PCT might be one of the risk factors of renal injury in HBV-ACLF patients, just like tumour necrosis factor- α , interleukin-6, and interleukin-1 [17]. Furthermore, among the patients with elevated serum PCT (> 0.5 ng/mL), most showed particularly high serum Cr levels and low GFR. Chi-square tests demonstrated that patients with elevated serum PCT were at higher risk of reaching the threshold serum Cr and GFR values.

Serum PCT rapidly increases in animal models after exposure to bacterial components and cytokines such as lipopolysaccharides (LPS), tumor necrosis factor- α (TNF- α), and IL-6 [18], and our previous study proved that hepatic macrophages are the cell source of hepatic PCT in acute liver failure [19]. The inhibition of PCT expression reduces the cytokine storm and rescues a mouse sepsis model [6, 16]. Systemic inflammation and immune system dysregulation are thought to integrate with the main physiopathological pathway involved in the natural history of HBV-ACLF [14]. Moreover, endotoxemia contributes to the activation of the innate immune system in liver failure [20]. This may explain the increase in serum PCT levels following endotoxemia and activation of the immune system in HBV-ACLF, in which serum LPS induces proinflammatory cytokines that stimulate the release of PCT, which in turn triggers the production of cytokines and causes a positive loop between PCT secretion and activation of the immune system [21]. Moreover, researchers have revealed that serum PCT levels reflect the inflammatory state and circulatory failure in HBV-ACLF patients [22]. Similarly, in this study, most patients with higher serum PCT levels showed elevated CYC levels and decreased GFR, which reflected the degree of circulatory failure.

This study had some limitations. First, it was a retrospective study from a single center. In addition, a clinical association study cannot prove a causal relationship [23]. Therefore, the suggested link between serum PCT and renal function in HBV-ACLF remains unproven. Despite these drawbacks, it is clear that serum PCT is associated with renal function in HBV-ACLF. Immunoneutralization of PCT will likely be a therapeutic approach for HBV-ACLF if the physiological effects can be clarified [24-26].

Conclusion

In conclusion, we demonstrated significant correlations between serum PCT and renal function parameters in HBV-ACLF patients. Elevated PCT is an alarming sign of renal dysfunction in patients with HBV-ACLF. Future studies are needed to evaluate the therapeutic value of serum PCT clearance in the progression of HBV-ACLF.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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