Original Article

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Serum Procalcitonin for Determining Prognosis in Cirrhotic Patients with Systemic Inflammatory Response Syndrome: A Preliminary Report

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ABSTRACT

Background & Aims: Systemic inflammatory response syndrome (SIRS) caused by overt or occult bacterial infection is often present in patients with advanced cirrhosis with an associated negative outcome. Procalcitonin (PCT), a calcitonin precursor, seems to be the most promising biomarker to diagnose sepsis and predict mortality in this population. We conducted a prospective observational study to evaluate the diagnostic and prognostic values of serial measurement of plasma PCT levels in cirrhotic patients presented with SIRS.

Methods: This study was conducted between March 2012 and January 2013 at a tertiary academic medical center. All patients were managed in accordance with standard care by a multidisciplinary team. Serum PCT level was measured by the electrochemiluminescence immunoassay (Elecsys BRAHMS PCT, Cobas, ROCHE) at baseline, 24 hours and 72 hours after admission. The clinical outcomes were the presence of infection and in-hospital mortality.

Results: Our preliminary data was taken from 29 cirrhotic patients with SIRS. The mean age was 60± 11.7 years, and 72% were male. Most patients had severe liver disease on admission, with a mean model of end-stage liver disease score of 21.8±8.5, 69% with Child-Pugh class C. Twenty-three patients (79%) with SIRS had obvious infection at the following sites: spontaneous bacterial peritonitis (44.8%), respiratory infections (10.3%), isolated bacteremia (6.9%), and others (17%). On admission the median PCT levels were significantly higher in patients with sepsis in comparison to patients with SIRS (4.5 vs. 1.28 ng/mL, $p = 0.046$). In patients with sepsis, the maximum values for PCT were noted at admission, and declined gradually. Eleven patients died during hospitalization (37.9%), 10 of whom had an obvious infection. The median PCT levels during the first 72 hours of admission were significantly higher in the non-survivor group compared with the survivor group. Conclusions: This study showed that PCT levels were of value in differentiating between sepsis and SIRS in cirrhotic patients, particularly at admission, this biomarker can help predict in-hospital mortality.

Key words: Systemic inflammatory response syndrome, SIRS, cirrhosis, procalcitonin

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INTRODUCTION

Systemic inflammatory response syndrome (SIRS) is often present in patients with advanced cirrhosis and portal hypertension, and might be associated with a negative outcome. Systemic inflammation can be caused by overt or occult bacterial infection. In cirrhotic patients inflammation has been shown to increase the risk of complications such as variceal bleeding, encephalopathy and acute-on chronic liver failure. However, the diagnosis of SIRS in cirrhotic patients is problematic because clinical signs and laboratory tests are nonspecific. In these patients, hyperdynamic circulation leads to tachycardia in the absence of infection, patients receiving beta-blockers have a reduced heart rate, hepatic encephalopathy course with tachypnea, and hypersplenism decreases leukocyte count. These factors decrease the value of SIRS criteria for detecting sepsis in cirrhotic subjects. In fact, SIRS is present in 10-30% of decompensated cirrhotic patients without infection, rendering SIRS an inaccurate marker of infection in the cirrhotic population.

Several biomarkers have been tested as potential diagnostic markers for sepsis. Procalcitonin (PCT), a calcitonin precursor, appears most promising. PCT is a rather specific marker for severe bacterial infection in patients presenting with suspected sepsis. This marker is also a useful tool to shorten the duration of antibiotic therapy in patients hospitalized with community-acquired pneumonia. Interestingly, several investigators have shown that the dynamics of plasma PCT levels were markedly different between patients who died of sepsis compared with those who survived. Although there is a large body of literature in favor of PCT in the general population, the clinical usefulness of this biomarker to diagnose infection and to be incorporated in the therapeutic algorithm of antibiotic therapy in cirrhotic patients should be investigated further. Importantly, previous studies have shown that patients with advanced liver failure present an attenuated production of acute-phase proteins in response to infection.

The primary objective of the present study was to determine the prognostic value of serial measurement of PCT level within 72 hours after admission in predicting in-hospital mortality and cirrhotic related complication in cirrhotic patients with SIRS. The secondary objective was to evaluate the diagnostic accuracy of PCT levels within 72 hours after admission in determining the presence of infection in cirrhotic patients presented with SIRS.

METHODS

This single-center prospective observational study was conducted between March 2012 and January 2013 at the Faculty of Medicine, Siriraj Hospital, Bangkok. All patients aged > 18 with a clinical and/or histological diagnosis of cirrhosis, admitted to the general medical wards or to the intensive care unit with the primary indication of SIRS were included. Exclusion criteria were (1) chronic renal failure (serum creatinine level >1.5 mg/dL at least 1 month); (2) admission for acute upper gastrointestinal bleeding; (3) treatment with immunosuppressive agents; and (4) early discharge or death within 72 hours after admission. The study was approved by the local Institutional Review Board, and complied with the Declarations of Helsinki. Each patient (or his/her next-of-kin if patient was unconscious) gave an informed consent to participate in the study.

All patients were managed following standard cares by a multidisciplinary team. During treatment the physicians in charge did not use PCT results for clinical decision making. Clinical, biochemical, and physiological data were collected daily by an independent research assistant. A number of organ failure scores were also quantified on admission and daily thereafter, including Child-Pugh score, model of end-stage liver disease score (MELD) and Sequential Organ Failure Assessment (SOFA) score. Grading of encephalopathy according to West Haven Criteria was calculated during admission. In all cases, a full set of specimen cultures was taken at the time of admission to the ward [peripheral blood, urine, and ascites]. All cultures were collected under strict aseptic technique. After screening for infection, broad spectrum parenteral antibiotics were prescribed in patients with suspected severe sepsis or septic shock, depending on the suspected source of infection and the results of microbiological cultures, when available. The antibiotic spectrum was narrowed, whenever possible, based on culture results obtained after admission. Patients were followed up until death or at least 28 days after admission to determine mortality and complications of cirrhosis (eg, gastrointestinal bleeding, hepatic encephalopathy, and acute renal failure).

All study patients had serum PCT levels measured at baseline, 24 hours and 72 hours after admission. Serum PCT level was measured by the

electrochemiluminescence immunoassay (Elecsys BRAHMS PCT, Cobas, ROCHE).

Definition of SIRS and sepsis

SIRS was assessed according to the recommendations of the American College of Chest Physicians/ Society of Critical Care Medicine Consensus Conference. Patients were considered to have SIRS if they fulfilled at least 2 of the following 4 criteria: (1) fever (>38˚C) or hypothermia (<36˚C), (2) tachycardia (>90/min), (3) tachypnea (>20/min), or (4) leucopenia (<4.0 $\times 10^9$/L), leukocytosis (>12.0 $\times 10^9$/L) or a leftward shift (>10% immature granulocytes). If SIRS was accompanied with bacterial infection as proven by cultures or on clinical grounds, a patient was defined as having sepsis. Patients were considered to have an infection if there was a known or suspected infection based on 1 or more of the followings: white blood cells in a normally sterile body fluid (eg, polymorphonuclear count >250/mm^3 in ascitic fluid); radiographic evidence of pneumonia associated with purulent sputum; or a syndrome associated with a high risk of infection (eg, ascending cholangitis). The final diagnosis of sepsis and septic shock was made (by the physicians who were previously involved in treatment of the patients) at a later stage from medical records for patient's summary discharge, and was blinded to PCT results. Patients had septic shock if they presented with sepsis-induced hypotension despite adequate fluid resuscitation, as well as organ dysfunction or perfusion abnormalities.

Statistical analysis

Continuous variables were summarized with means and standard deviations or median (range), while categorical variables were summarized with frequencies and percentages. Continuous data were analyzed using unpaired *t*-test if normally distributed, or the Wilcoxon rank sums test if non-normally distributed. The chi-squared test or Fisher's exact test was used for comparison of frequency data where appropriate. All statistical testing was done at the conventional 2-tailed α level of 0.05.

RESULTS

A total of 29 cirrhotic patients with SIRS were included in the study. Patient characteristics are summarized in Table 1 and Table 2. Most patients had severe liver disease (mean MELD score 21.8±8.5; 69% of Child-Pugh class C patients) and 48% were diagnosed with hepatocellular carcinoma (HCC) before admission.

Among patients with SIRS, 23 patients (79.3%) had an obvious infection and thus sepsis according to

Table 1. Demographic and baseline characteristics of 29 cirrhotic patients with SIRS.

Variables (n=29)	
Age (years) mean ± SD	60 ± 11.7
Male, n (%)	21 (72.4)
Cirrhotic characteristics	
Child A/B/C, n (%)	1 (3.4)/8 (27.6)/20 (69)
Diagnosis duration (month), median (max, min)	28 (256, 1)
Etiology, n (%)	
-CH-B	8 (27.6)
-CH-C	6 (20.7)
-Alcohol	9 (31.0)
-NAFLD	1 (3.4)
-Cryptogenic	5 (17.2)
Presence of HCC, n (%)	14 (48.3)
Presence of infectious sources, n (%)	23 (79.3)
Presence of shock, n (%)	10 (34.5)

Table 2. Baseline laboratory profiles and clinical scores of 29 cirrhotic patients with SIRS.

Variables	
Hemoglobin (g/L), mean ± SD	10.9 ± 1.6
WBC (cell/mm^3)*	5,640 (19,450, 50)
%Neutrophil, mean ± SD	73 ± 20.6
Platelet (cell/mm^3/1000)*	74 (190, 22)
Creatinine (mg/dL)*	1.3 (7.9, 0.6)
Total bilirubin (mg/dL)*	4.6 (36.4, 0.6)
ALT (U/L)*	48 (403, 16)
ALP (U/L)*	136 (503, 40)
Albumin (mg/dL), mean ± SD	2.5 ± 0.5
PT-INR, mean ± SD	1.66 ± 0.48
CTP score, mean ± SD	10.8 ± 2.2
MELD score, mean ± SD	21.8 ± 8.5
SOFA score*	6 (17, 1)

*median (max, min)

Table 3. Characteristics of admission of the cirrhotic patients with SIRS according to the presence or absence of infection.

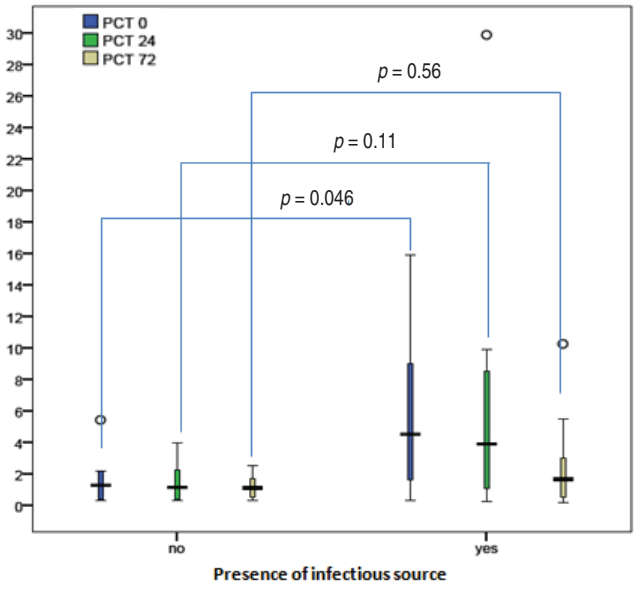
Variables	Presence of infectious source		*p*-value
	Yes (n=23)	No (n=6)	
Hemoglobin (g/L), mean ± SD	10.9 ± 1.6	11.3 ± 1.7	0.61
WBC (cell/mm^3)*	5,640 (19,450, 50)	6,040 (17,880, 3, 330)	0.32
%Neutrophil, mean ± SD	73.2 ± 21.4	72.5 ± 19.2	0.95
Platelet (cell/mm^3/1000)*	70 (177, 22)	144.5 (190, 32)	0.049
Creatinine (mg/dL)*	1.3 (7.9, 0.6)	1.2 (1.3, 0.9)	0.74
Total bilirubin (mg/dL)*	6.1 (36.4, 0.6)	3.3 (36.4, 1.0)	0.7
ALT (U/L)*	43 (403, 16)	53 (253, 35)	0.30
Albumin (mg/dL), mean ± SD	2.4 ± 0.5	2.9 ± 0.4	0.03
PT-INR, mean ± SD	1.79 ± 0.5	1.35 ± 0.3	0.026
CTP score, mean ± SD	11.4 ± 1.9	8.8 ± 2.3	0.042
MELD score, mean ± SD	22.9 ± 8.6	17.5 ± 7.9	0.18
SOFA score*	7 (17, 1)	4.5 (8, 2)	0.08

*median (max, min)

the definition. Patients were infected at the following sites: spontaneous bacterial peritonitis (n=13, 44.8%); respiratory infections (n=3, 10.3%); isolated bacteremia (n=2, 6.9%); urinary tract infections (n=1, 3.4%); and others, including cutaneous infections (n=1, 3.4%); infectious diarrhea (n=1, 3.4%); ascending cholangitis (n=1, 3.4%); and septic arthritis (n=1, 3.4%). As expected, patients with sepsis had significantly higher liver severity scores (Child-Pugh score 11.4±1.9 vs. 8.8±2.3, p = 0.042) on admission as compared to patients with SIRS, as shown in Table 3. Median platelet counts and serum albumin values were significantly lower in patients with the presence of infection. Median SOFA scores were higher in patients with infection, but the difference did not reach statistical significance (p = 0.08).

Measurement of PCT levels

To evaluate the usefulness of PCT in differentiating sepsis from SIRS, we collected plasma sample from each patients in the first 72 hours of admission. At admission, PCT levels were significantly higher in patients with sepsis in comparison to patients with SIRS (Figure 1). Median PCT levels were about 3 times higher in sepsis as compared to SIRS. In patients with sepsis, maximum values for PCT were reached on day 0 and declined gradually after the first 24 hours of admission. The difference in PCT levels between sepsis and SIRS patients was not maintained after day 1.



Variables	Presence of infectious source		*p*-value
	Yes (n = 23)	No (n=6)	
PCT 0 hr, median (max, min)	4.5 (59.2, 0.31)	1.28 (5.41, 0.27)	0.046
PCT 24 hr, median (max, min)	3.94 (29.86, 0.25)	1.10 (3.96, 0.32)	0.11
PCT 72 hr, median (max, min)	1.65 (10.24, 0.19)	1.08 (2.52, 031)	0.56

Figure 1. Plasma levels of PCT in the first 72 hours of admission in cirrhotic patients with SIRS according to the presence or absence of infection.

Table 4. Demographic and baseline characteristics of the survivor group and non-survivor group.

Variables	Survivor (n =18)	Non survivor (n=11)	*p*-value
Age (years) mean ± SD	61 ± 11.5	58 ± 12.2	0.53
Gender			1.0
- Male, n	13	8	
- Female, n	5	3	
Cirrhotic characteristic			
Diagnosis duration (months), median (max, min)	24.5 (108, 1)	38 (256, 8)	0.046
Etiology, n			0.76
- CH-B	5	3	
- CH-C	3	3	
- Alcohol	5	4	
- NAFLD	1	0	
- Cryptogenic	4	1	
Presence of HCC, n	6	8	0.07
Presence of infectious source, n	13	10	0.36
Presecne of shock, n	3	7	0.017

Table 5. Characteristics at admission of the cirrhotic patients with SIRS who died and those who survived.

Variables	Survivor (n = 18)	Non survivor (n=11)	*p*-value
Hemoglobin (g/L), mean ± SD	10.8 ± 1.8	11.2 ± 1.2	0.6
WBC (cell/mm^3)*	7,045 (19,450, 2,630)	4,470 (18,140, 50)	0.4
%Neutrophil, mean ± SD	73.3 ± 16.2	72.6 ± 17.3	0.9
Platelet (cell/mm^3)/1000)*	81.5 (190, 32)	77 (161, 22)	0.3
Creatinine (mg/dL), mean ± SD	1.1 ± 0.4	2.4 ± 2.0	0.02
Total bilirubin (mg/dL)*	3.6 (36.4, 1)	6.7 (36.4, 0.6)	0.7
ALT (U/L)*	45.5 (148, 20)	53 (403.16)	0.07
ALP (U/L)*	134 (389, 40)	209 (503, 61)	0.09
Albumin (mg/dL), mean ± SD	2.7 ± 0.4	2.4 ± 0.6	0.16
PT-INR, mean ± SD	1.49 ± 0.28	1.94 ± 0.62	0.014
CTP score, mean ± SD	101 ± 2.2	120 ± 19	0.032
MELD score, mean ± SD	18.8 ± 6.5	26.6 ± 9.5	0.015
SOFA score, mean ± SD	5.2 ± 2.5	11.0 ± 4.9	< 0.01

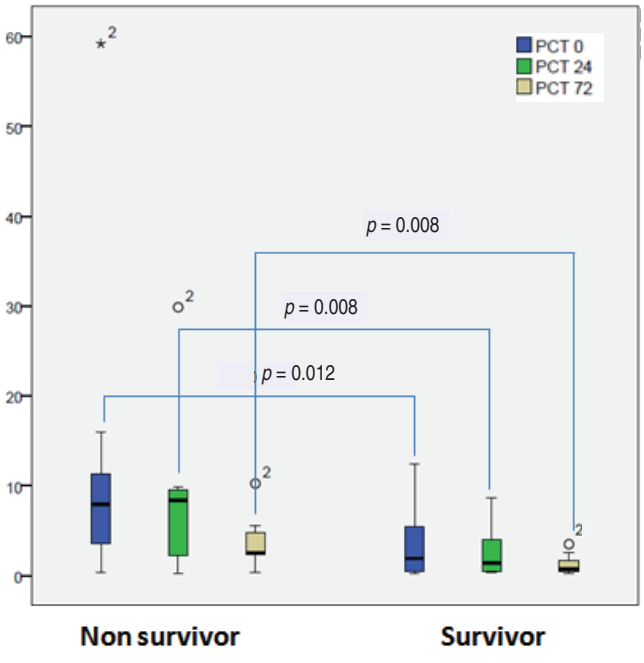
*Median (max, min).

Outcomes

Eleven patients died during hospitalization (37.9%). Ten patients had an obvious infection. Seven who died developed circulatory failure related to septic shock, while two developed respiratory failure related to hypoxic lung infection and required mechanical ventilation. Baseline characteristics of patients who died and those who survived are summarized in Table 4 and Table 5. The mean age, proportion of male gender and etiology of cirrhosis were not different between patients who died and those who survived (Table 4). Patients who died during hospitalization had higher Child-Pugh scores, MELD scores and SOFA scores than patients who survived (Table 5). The proportion of acute renal failure developed during hospitalization was significantly higher in patients who died.

Prognostic values of serial PCT measurement

To evaluate the usefulness of PCT in determining prognosis in cirrhotic patients with SIRS, we per-



Variables	Survivor (n = 18)	Non surivor (n-11)	*P*-value
PCT 0 hr, median (max, min)	1.85 (12.45, 0.27)	8.02 (59.20, 0.31)	0.012
PCT 24 hr, median (max, min)	1.28 (8.63, 0.32)	8.41 (29.86, 0.25)	0.008
PCT 72 hr, median (max, min)	0.72 (3.49, 0.19)	2.52 (10.24, 0.32)	0.008

Figure 2. Plasma levels of PCT in the first 72 hours of admission among cirrhotic patients with SIRS according to the status during hospitalization.

formed analysis outcomes over hospitalization and follow-up period of 30 days. Median PCT levels during the first 72 hours of admission were significantly higher in the non-survivor group compared with the survivor group (Figure 2). In patients who died during hospitalization, maximum value for PCT was reached in 24 hours and declined rapidly in 72 hours after admission.

DISCUSSION

Previous studies have evaluated the usefulness of PCT for early diagnosis of the bacterial infection, for shortening the antibiotic use and for predicting the prognosis in critically-ill patients. To our knowledge, this was the first study to prospectively validate the performance of PCT in discriminating sepsis from SIRS and in determining its prognostic value for predicting poor clinical outcome in cirrhotic patients with SIRS. In the present study, the mortality rate of cirrhotic patients presented with SIRS was 37.9%, comparable to the mortality of 31% reported by Cazzaniga and colleaques[6].

Many clinicians agree that a noninvasive and readily available biochemical parameter would be highly desirable to guide antibiotic therapy in cirrhotic patients with clinical suspicion of sepsis. PCT has been demonstrated to be more accurate for the diagnosis of bacterial sepsis than other routinely used inflammatory marker. Furthermore, slowly decreasing, persistently elevated, or increasing PCT levels are associated with poor outcomes in patients with severe infection. However, previous studies have shown that patients with advanced liver failure present an attenuated production of acute-phase proteins in response to infection. It is essential for prospective studies to determine the usefulness of PCT measurement in the assessment of probability of infection in cirrhotic patients with SIRS. In the present study, we found that the median PCT level on admission was different (4.5 vs. 1.28; p=0.046). This finding can be applied to early identification of bacterial infection and thus to early antibiotic therapy. However, a definite distinction between SIRS and sepsis in cirrhotic patients could not be made based on PCT levels, but rather requiring complete clinical and laboratory evaluation of the patient. Moreover, the validity of PCT measurement to diagnose a bacterial infection should be evaluated with sensitivity, specificity, and positive and negative predictive values, using the optimal cut-off points. On the basis of preliminary data from this small sample size, we could not analyze the accuracies of this biomarker at this moment. Subject enrollment is still ongoing for this study.

As expected, most of the patients in this study had severe liver disease, 69% of whom being Child-Pugh class C. The present study identified well-known prognostic factors of death related to the degree of liver failure (ie, Child-Pugh score and MELD score). This is in agreement with several published studies emphasizing that severe cirrhosis is an independent factor of mortality, particularly in cases of bacterial infections. The in-hospital mortality in this study was 38%, and almost all related to circulatory failure and septic shock. Interestingly, among the 18 survivors, 13 (72%) had sepsis and 3 (17%) developed circulatory failure related to septic shock. These findings suggest that not all infected patients with cirrhosis develop an intense

systemic inflammatory response to pathogens. Further studies are needed to investigate the immune response in such patients. The present study then has attempted to assess the degree of systemic inflammatory response by using the determinants of serum PCT over the first 72 hours of admission for predicting hospital-mortality in cirrhotic patients with SIRS. Not surprisingly, we found that serum PCT levels at admission, 24 hours and 72 hours of admission were significantly higher in the non-survivor group. Although the number of cases were small (11 non-survivors), an increased mortality was noted in cirrhotic patients with high levels of PCT over the first 72 hours of admission. PCT seems to be useful for predicting clinical relevant outcome in this population, but the sharp decline of this biomarker levels after day 1 in patients who died during hospitalization suggests that late sampling may easily lead to false-negative results.

A particular strength of this study is that PCT levels were not used for treatment decisions, as treating physicians were blinded to the test results to avoid bias. The eventual diagnosis of sepsis versus SIRS was made by the physicians who were involved in treatment of the patients, and this also helped avoid information bias. However, there were some limitations of the study. First, the small sample size in this preliminary study did not allow evaluating the role of PCT for predicting cirrhosis-related complications including upper gastrointestinal bleeding and hepatorenal syndrome. Second, because of the single-center setting, our results cannot easily be extrapolated to centers with different thresholds for initiation and discontinuation of empiric antibiotic therapy in cirrhotic patients with non-specific signs and symptoms compatible with early-onset sepsis.

Conclusions

This study showed that PCT levels are of value in differentiating between sepsis and SIRS in cirrhotic patients. Especially during the first 24 hours of admission, PCT levels can help to predict patient's mortality and to improve the clinical outcome. Although PCT is a likely useful biomarker for distinguishing sepsis from SIRS and for predicting a poor prognosis, PCT alone cannot replace clinical decision-making which requires integration of multiple clinical data.Acknowledgement: This study was supported by Siriraj Research Development Fund and the Gastroenterological Association of Thailand Fund.

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