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Diagnostic and prognostic role of presepsin in patients with cirrhosis and bacterial infection

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Abstract

Objectives: Serum biomarkers have suboptimal accuracy for the early diagnosis of bacterial infection (BI) in cirrhosis. The aim of the study was to evaluate the diagnostic and prognostic accuracy of presepsin (PSP) in a cohort of hospitalized patients with cirrhosis.

Methods: All adult cirrhotics admitted between 03.2016 and 06.2019 were consecutively evaluated. PSP was measured using chemiluminescent enzyme immunoassay, and its accuracy was compared with that of common biomarkers.

Results: A total of 278 cirrhotic patients for a total of 448 hospitalizations were prospectively collected. Prevalence of BI at admission was 28.3%. Median (range) Log_{10}PSP in the whole cohort was 2.83 (2.48–3.19) ng/L, significantly higher in patients with BI than in patients without (p<0.001). For a cutoff value of 2.87 ng/L, Log_{10}PSP showed sensitivity, specificity and AUC-ROC of 0.66 (95% CI 0.57–0.74), 0.63 (95% CI 0.57–0.68) and 0.69 (95% CI 0.63–0.73), lower than that of C-reactive protein (p=0.002), but similar to procalcitonin (p=0.18) Patients with BI at hospitalization had higher probability of 28-day mortality (sub-hazard ratio [sHR] 2.65;95% CI 1.49–4.70; p=0.001). At multivariate Cox's regression analysis, Log_{10}PSP (sHR 2.4; 95% CI 1.22–4.82; p=0.01) together with age and severity of liver disease, was an independent predictor of short-term mortality.

Conclusions: PSP shows low diagnostic accuracy for BI in cirrhosis, but it is an independent predictor of short-term mortality. PSP may be a biomarker of systemic inflammation, commonly seen in end-stage liver disease.

Keywords: acute-on-chronic liver failure; c-reactive protein; liver transplantation; sepsis.

Introduction

The liver actively regulates immune and inflammatory pathways, through complex mechanisms involving tolerance against toxins and immunogenic responses [1, 2]. In cirrhosis, this homeostatic role is impaired, in view of a simultaneous reduction of immune-surveillance and an increase of systemic inflammation. Therefore, cirrhosis carries a high risk of bacterial infection (BI) and overwhelming systemic responses [3]. These events often determine worsening of portal-hypertension, impairment of hepatic and extra-hepatic organs dysfunction [3, 4], and ultimately an increase in mortality [5].

Early diagnosis of BI is often difficult in patients with cirrhosis because conventional criteria – as those used for systemic inflammatory response syndrome – have several limitations, especially among the sickest ones [6]. Similarly, the commonly adopted serum biomarkers have poor accuracy [7, 8]. Leucocytes might be qualitatively and quantitatively influenced by hypersplenism and cirrhosis-associated immune dysfunction (CAID), respectively [9]; C-reactive protein (CRP) might mirror the underlying chronic inflammatory state rather than an infection [10, 11]; procalcitonin (PCT) could be falsely increased in cases of renal dysfunction or in superimposed conditions, as acute-on-chronic liver failure (ACLF) [12, 13].

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Among recently proposed diagnostic biomarkers of BI, presepsin (PSP) is a 13 kDa N-terminal fragment, produced after formation and subsequent proteolysis of the complex between lipopolysaccharide and its binding protein [14]. In critically ill patients without cirrhosis, PSP has already showed a good diagnostic accuracy for sepsis and a satisfactory prognostic role [15–18]. Nevertheless, its role in cirrhosis is currently poorly understood, because of small sample size and different endpoints adopted in the available studies [19–21]. Therefore, the aims of our study were to prospectively measure PSP in a large cohort of hospitalized patients with cirrhosis, according to the severity of underlying liver disease; to evaluate its diagnostic role for BI; to compare its accuracy with that of commonly used biomarkers; and to explore a prognostic role in terms of short-term survival.

Materials and methods

This was a prospective, single-center, observational study performed at Padua University Hospital. This is a Tertiary Center Hospital actively involved in the management of severely ill patients with cirrhosis, with a well-known liver transplant program. The study was approved by the local Ethical Committee. All consecutive patients admitted at Multivisceral Transplant Unit between 01.03.2016 and 30.06.2019 were prospectively evaluated. Exclusion criteria were: 18<age>80 years; absence of definite diagnosis of cirrhosis, made on conventional histological, radiological and biochemical criteria; previous solid organ transplantation (including liver transplantation); hospital admission for ≤48 h; definite or highly suspected non-bacterial (e.g., fungal, parasitic, and viral) infection at time of hospitalization. Notably, patients with acute liver failure, acute liver injury or with flares of underlying chronic liver disease (e.g., autoimmune flare, hepatitis D superinfection, hepatitis B flare) were not enrolled.

For each patient, the following variables were evaluated at the time of hospital admission: age, gender, etiology of liver disease, diagnosis of hepatocellular carcinoma, previous hospital admissions; mean arterial pressure, PaO2, presence and grade of hepatic encephalopathy, ascites, acute kidney injury; ACLF was defined according to EASL-CLIF criteria [22]. Charlson comorbidiy index was obtained for each patient at time of admission.

Each patient underwent baseline measurement of blood biomarkers (leucocyte count, CRP, PSP); for patients with high suspicion of infection, PCT was also obtained. The Model for End Stage Liver Disease (MELD) and Child-Pugh scores were collected at admission for each patient, whereas disease-specific scores (e.g., CLIF-AD, CLIF-C ACLF) were calculated when appropriate [22].

BI was diagnosed using the commonly adopted criteria, described elsewhere [23]. Each BI was classified as hospital acquired, healthcare-associated and community-acquired according to epidemiological characteristics [24]. When available, bacterial strains were classified according to Gram stain.

PSP was measured in each patient at hospital admission. In detail, a blood sample was obtained at fasting and sent to the local Laboratory Medicine, where it was analyzed. The PSP concentration was determined using the PATHFAST™ analyzer (Mitsubishi Chemical Europe GmbH), with an analytical method based on the chemiluminescent enzyme immunoassay technique. Data from manufacturer: the measuring range was between 20 and 20.000 ng/L; the imprecision has been obtained by measuring for 20 non-consecutive days in duplicate 4 plasma samples that showed a mean value between 445 and 19.292 ng/L, with a coefficient of variation between 3.8 and 5.0%; the reference range was from 57 to 337 ng/L. Plasma PSP value was expressed in this study as its logarithmic transformation (log_{10}PSP). The outcome of each patient was prospectively evaluated in terms of 28-day survival since hospital admission, considering liver transplantation as a competing event. This study was conducted in accordance with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects.

Statistical analysis

Variables were reported as counts and percentages or median (range), as appropriate. The diagnostic accuracy of PSP, CRP, PCT, and leucocytes in predicting BI was assessed by the area under the curve (AUC) identified by the receiver operating characteristic (ROC) and estimated by a generalized linear mixed model with logit link function and a compound symmetry covariance matrix, to take into account the correlation of the data given by the repeated hospitalizations. AUCs were estimated with the 95% confidence interval (CI) obtained with the Wald method and compared by chi-square test. Threshold values were identified applying the Youden index. The sensitivity and specificity corresponding to the previously identified threshold value of PSP, CRP, PCT, and leucocytes were estimated with the 95% CI calculated with the binomial method. Probabilities of 28-day outcome were evaluated using the Fine and Gray approach considering liver transplantation as a competing event and estimated as cumulative incidence. Follow-up time was defined as the time from date of hospitalization to date of death, liver transplantation or end of follow-up, whichever came first. Risks were expressed as sub-hazard ratios (sHR) and 95% CIs. Potential predictors of mortality were identified with univariate Cox regression for competing risks considering the hospitalizations clustered within patients to take into account the correlation. The prognostic role of log_{10}PSP in terms of 28-day survival was investigated using a multivariate Cox's regression model, adjusted for confounders (age, presence of BI, AKI, severity of liver disease according to Child-Pugh, MELD, presence of ACLF, CRP).

The effect of Child-Pugh classes, BI, and their interaction on log_{10}PSP was investigated with a generalized linear model considering the Normal distribution, the clustering of the hospitalizations within patients and a compound symmetry covariance matrix. Difference between presence or absence of BI on log_{10}PSP was estimated with least squares and 95% CI for each Child-Pugh class. The same model was applied for evaluating the effect of AKI, BI and their interaction on log_{10}PSP. The significance level was set at the 5% bilateral value. Statistical analysis was performed with SAS 9.4 (SAS Institute Inc., Cary, NC, USA) for Windows.

Results

A total of 1,280 hospitalizations occurred in the study period, and 448 (35%) were considered (Supplementary Figure 1).

Characteristics of 278 patients enrolled are presented in Table 1. In detail, 70.9% were males and nearly half had alcohol related disease. All patients were admitted due to liver-related conditions, and no active, liver-unrelated inflammatory conditions occurred at time of hospitalization. BI was diagnosed at admission in about one third of patients (127/448, 28.3%), being the lower respiratory tract, urinary tract and blood the most common sources. Prevalence of hospital-acquired and culture-positive infections was 53.5 and 62.2%, respectively. Gram +ve strains were prevalent (54/79, 68.3%).

Patients with BI at admission had similar demographic characteristics than patients without, but they were sicker in terms of liver dysfunction (ACLF: 43.3 vs. 14.3%; p<0.001; median (range) Child-Pugh score: 11.0 (5.0–15.0) vs. 9.0 (5.0–15.0); median (range) MELD score: 22.2 (7.6–45.9) vs. 15.2 (6.0–50.5); each p<0.001; Table 2). Considering serum biomarkers, median (range) CRP (33.0 (2.0–276.0) vs. 9.7 (2.0–150.0) mg/L; p<0.001) and leucocytes (6.4 (0.4–31.5) vs. 5.2 (0.6–23.3)·10^9/L; p=<0.001) were significantly higher among patients with BI, whereas PCT was not (0.9 (0.0–50.0) vs. 0.4 (0.0–89.0) µg/L; p=0.61).

Table 1: Characteristics of enrolled patients and clinical features at hospitalization.

Patients	**n=278**
Male gender, n (%)	197 (70.9)
Age, years	57.4 (18–79.5)
Etiology of liver disease	
Alcohol	132 (47.5)
HCV	42 (15.1)
HBV	23 (8.2)
Mixed (Alcohol + virus)	19 (6.8)
Metabolic	22 (7.9)
Cholestatic/autoimmune	33 (11.9)
Other	7 (2.5)
Hepatocellular carcinoma, n (%)	69 (24.8)
Charlson comorbidity index	5 (2–13)
Hospitalizations	**n=448**
Length of hospitalization, days	6 (2–64)
Lab tests at admission	
Hemoglobin, g/L	98.0 (8.0–173.0)
INR	1.4 (1.0–8.1)
Creatinine, µmol/L	85.5 (26.0–783.0)
Bilirubin, µmol/L	50.9 (2.0–971.0)
Na^+, mEq/L	136.0 (26.5–150.0)
Albumin, g/L	30.0 (12.0–50.0)
Child-Pugh score	9.0 (5.0–15.0)
A/B/C	75/151/222
MELD score	17 (6.0–51.0)
MELD-Na score	21 (6.0–56.0)
CLIF-AD score[a]	50.9 (24.8–73.1)
CLIF-C ACLF score	46.8 (30.6–70.7)

[a]Only in patients with AD; only in patients with ACLF. AD, acute decompensation; ACLF, acute-on-chronic liver failure.

Presepsin

The median (range) value of plasma log_{10}PSP at hospitalization was 2.83 (2.48–3.19) ng/L in the whole cohort. Notably, males had higher median (range) values than females (2.85 (1.74–4.45) vs 2.78 (1.83–3.80) ng/L; p=0.025) and PSP was within the pre-defined values for the general population only in a minority of cases (121/448, 27%).

Patients with BI showed significantly higher median (range) log_{10}PSP values than patients without (3.05 (2.07–4.45) vs. 2.74 (1.74–4.30) ng/L; p<0.001). However, only 33% patients in the latter group had PSP serum levels within the pre-defined range.

Plasma log_{10}PSP was not significantly different across different types of infection (p=0.29) and after stratification for Gram stain (Gram –ve vs. Gram +ve: 3.09 (2.28–3.98) vs. 3.00 (2.07–4.45) ng/L; p=0.64).

In the whole cohort, log_{10}PSP rose according to severity of underlying liver disease (i.e., Child-Pugh classes; p<0.001), and presence of BI (p=0.003), even if there was no significant interaction between Child-Pugh classes and BI (p=0.25). When comparing patients with similar underlying liver dysfunction, log_{10}PSP was significantly different according to infectious status in those belonging to Child-Pugh A class (p<0.001), but not among Child-Pugh B and C patients (each p=0.06; Figure 1).

A total of 90 (20%) cases fulfilled criteria of AKI at the time of hospitalization. Presence of AKI and BI significantly influenced log_{10}PSP values (each p<0.001), but without a significant interaction between these two factors (p=0.42; Supplementary Figure 2).

Diagnostic accuracy of PSP for BI in cirrhosis

A log_{10}PSP cutoff value of 2.87 ng/L was able to retrieve the best diagnostic accuracy for BI in the whole cohort, displaying an AUC-ROC equal to 0.69 (95% CI 0.63–0.73), with a sensitivity and specificity equal to 0.66 (95% CI 0.57–0.74) and 0.63 (95% CI 0.57–0.68), respectively. The accuracy, sensitivity and specificity of CRP and leucocytes (WBC) were obtained using the same method (Supplementary Table 1). For a cutoff value of 27 mg/L, CRP displayed an AUC-ROC of 0.77 (95% CI 0.72–0.82), whereas leucocytes displayed an AUC-ROC equal to 0.59 (95% CI 0.53–0.65) using a cutoff value of 7.19·10^9/L. After

Table 2: Clinical features in the whole population according to BI.

	Bacterial infection n=127	No bacterial infection n=321	OR (95% CI)	p-Value
Male gender, n (%)	97 (76.3)	237 (73.8)	1.12 (0.66–1.86)	0.69
Age, years	58.0 (18.1–78.5)	57.3 (18.7–79.5)	1 (0.98–1.21)	0.98
Alcoholic liver disease	60 (47.2)	142 (44.2)	1.15 (0.74–1.79)	0.54
Child-Pugh score	**11.0 (5.0–15.0)**	**9.0 (5.0–15.0)**	**1.4 (1.26–1.53)**	**<0.001**
MELD score	**22.2 (7.6–45.9)**	**15.2 (6.0–50.5)**	**1.10 (1.06–1.13)**	**<0.001**
MELD Na^+ score	**25.4 (6.9–46.9)**	**18.7 (6.0–56.0)**	**1.09 (1.04–1.13)**	**<0.001**
ACLF, n (%)	**55 (43.3)**	**46 (14.3)**	**4.36 (2.7–7.00)**	**<0.001**
WBC, 10^9/L	**6.4 (0.4–31.5)**	**5.2 (0.6–23.3)**	**1.09 (1.04–1.14)**	**<0.001**
CRP, mg/L	**33.0 (2.0–276.0)**	**9.7 (2.0–150.0)**	**1.04 (1.03–1.05)**	**<0.001**
PCT, µg/L[a]	0.9 (0.0–50.0)	0.4 (0.0–89.0)	1.04 (0.89–1.23)	0.61
Log_{10}PSP, ng/L	**3.05 (2.07–4.45)**	**2.74 (1.74–4.30)**	**3.64 (2.25–5.87)**	**<0.001**

[a]Available in 254 cases. AD, acute decompensation; ACLF, acute-on-chronic liver failure; BI, bacterial infection; CRP, C-reactive protein; PCT, procalcitonin; PSP, presepsin; WBC, white blood cell count. Bold values are those with statistically significant p-value.

comparison of different biomarkers, the diagnostic accuracy of PSP was lower than that of CRP (p=0.002), but higher than that of WBC (p=0.006). A model including both PSP, CRP and WBC showed an AUC-ROC equal to 0.77, not significantly different than that of CRP alone (p=0.83; Figure 2).

Comparison of presepsin and procalcitonin

We have further analyzed a cohort of patients with the highest risk of BI at hospitalization (n=251), in whom PCT was also retrieved. After calculating sensitivity and specificity in this subset of patients (Supplementary Table 2), PSP, CRP and PCT displayed an AUC-ROC of 0.61 (95% CI 0.53–0.68), 0.68 (95% CI 0.61–0.75) and 0.65 (95% CI 0.58–0.75), respectively. The diagnostic accuracy of PSP was similar to that of CRP (p=0.052) and of PCT (p=0.18), but better than that of WBC (p<0.001). A model including all biomarkers showed an AUC-ROC equal to 0.69 (95% CI 0.62–0.75), with a better accuracy than that of PSP alone (p=00.03), but similar to that of PCT and CRP alone (p=00.32 and p=0.49, respectively, Figure 3).

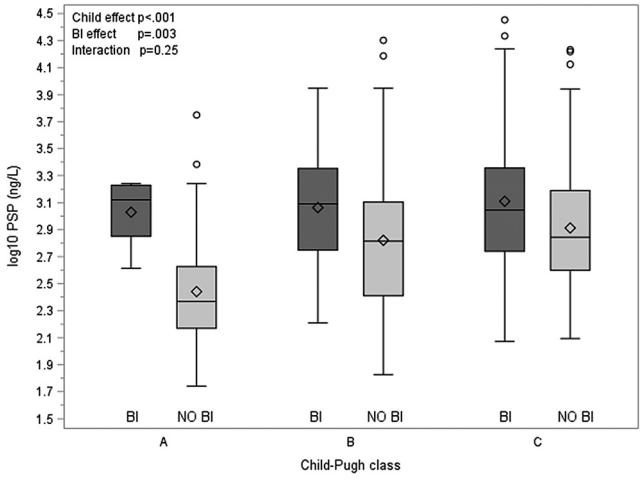

Figure 1: PSP values according to severity of underlying liver disease and bacterial infection.
BI, Bacterial infection; PSP, presepsin.

Prognostic role of Log_{10}PSP in patients with cirrhosis

All cases included in the study were followed-up until recording the final event (i.e., hospital discharge, liver

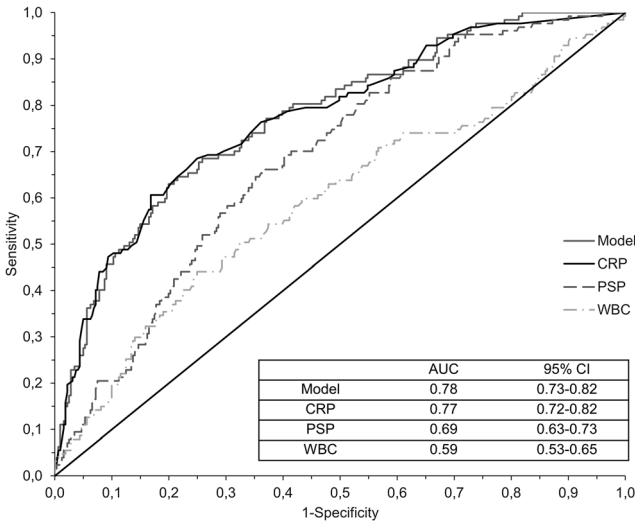

Figure 2: ROC curves for diagnostic accuracy of bacterial infection in cirrhosis.
Model curve refers to pooled diagnostic accuracy of CRP, PSP, WBC.
CRP, C-reactive protein; PSP, presepsin; WBC, white blood cell count.

transplantation, death) and/or for at least 28 days. Twenty-eight (10%) patients underwent LT during this period, whereas 58 (20.8%) died. All but one causes of death were liver-related, being end-stage liver disease and sepsis the commonest events (37 and 36%, respectively). At competing risks analysis, patients with BI at hospitalization had a significantly higher probability of 28-day mortality than patients without (sHR 2.65, 95% CI 1.49–4.70; p<0.001;Supplementary Figure 3).

At univariate Cox's regression analysis, age, log_{10}PSP, Child-Pugh score, MELD score, presence of ACLF at admission, BI, AKI and CRP were all predictors of 28-day mortality (Supplementary Table 3). At multivariate Cox's regression analysis, log_{10}PSP (sHR 2.44 95% CI 1.22–4.82; p=0.01), together with age (sHR 1.08; 95% CI 1.04–1.12; p<0.001), Child-Pugh score C (sHR 7.84; 95% CI 1.54–143.3; p=0.004) and presence of ACLF at any stage (sHR 2.75; 95% CI 1.28–5.8; p=0.014) were independent predictors of short-term mortality (Table 3). Notably, neither CRP nor AKI and BI at hospitalization was significantly associated with short-term mortality. In a multivariate Cox's regression model including MELD score as a significant predictor of short-term outcome (sHR 1.08; 95% 1.03–1.15; p=0.008), we confirmed that log_{10}PSP (SHR 1.96; 95% CI 1.01–3.81; p=0.046) was an independent predictor of 28-day mortality together with age (sHR 1.09; 95% CI 1.06–1.14; p<0.001, Supplementary Table 4).

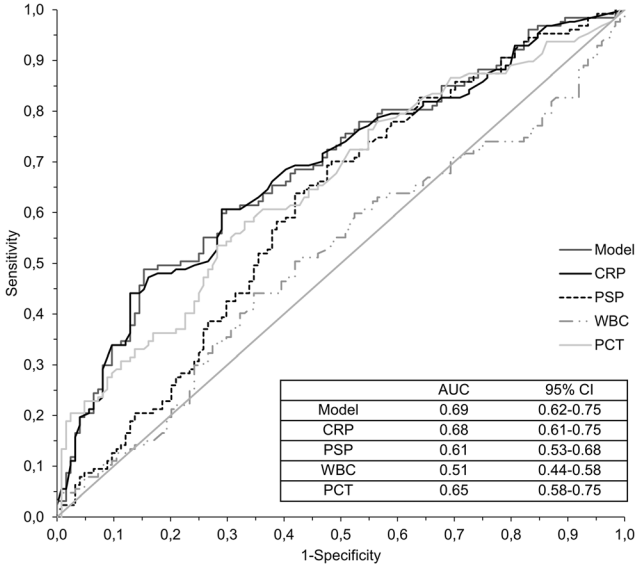

Figure 3: ROC curves for diagnostic accuracy of bacterial infection in cirrhosis, including only cases with available PCT serum levels. Model curve refers to pooled diagnostic accuracy of CRP, PSP, PCT, WBC. CRP, C-reactive protein; PCT, procalcitonin; PSP, presepsin; WBC, white blood cell count.

Table 3: Predictors of 28-day mortality in hospitalized patients with cirrhosis at Cox's regression multivariate analysis.

Parameter	p-Value	SHR	95% CI	
Age, years	**<0.001**	**1.08**	**1.04**	**1.12**
Log_{10}PSP, ng/L	**0.012**	**2.44**	**1.22**	**4.82**
Child-Pugh B	**0.004**	**1.91**	**0.31**	**36.55**
Child-Pugh C		**7.84**	**1.54**	**143.33**
ACLF	**0.014**	**2.75**	**1.28**	**5.87**
BI	0.71	1.14	0.60	2.12
AKI	0.87	0.94	0.45	1.99
CRP, mg/L	0.84	1.00	0.99	1.01

ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; CRP, C-reactive protein; PSP, presepsin. Bold values are those with statistically significant p-value.

Discussion

BI represents a common event in the natural history of cirrhosis, often associated with an impairment of hepatic and extra-hepatic organ(s) function. Our study confirmed the high prevalence of BI at hospitalization (28.3% of the whole cohort, 38.9% considering only patients admitted for AD or ACLF). Sources of infection were consistent with previous reports [23, 25], whereas we confirmed the rising epidemiological trend of Gram +ve strains among culture-positive infections [26].

An early diagnosis of BI is of utmost importance in patients with cirrhosis, in order to rapidly institute adequate antibiotic and supportive therapy. Therefore, the availability of new biomarkers or composite scores is urgently needed for such patients. The lipopolysaccharide and its receptor (CD14) have already been investigated as potential biomarkers of bacterial infection, with promising results [27, 28]. In this study, we have further explored this topic using a relatively new serum glyco-peptide, PSP, which is derived from the cleavage of lipopolysaccharide-CD14 complex.

In our cohort, the median (range) log_{10}PSP serum level was equal to 2.83 (2.48–3.19) ng/L, a value higher than that previously reported [19]. Notably, PSP was within the range established for the general population (57–337 ng/L) in a minority of cases (27%), and displayed a wide inter-individual variability. This was confirmed also in patients without infection, who showed a log_{10}PSP within the range previously established in 33% cases, and a log_{10}PSP>4 ng/Lin 5/321 (1.5%) hospitalizations, being significantly influenced by renal and liver dysfunction in this cohort. This might reflect the correlation between increased bacterial translocation, high serum values of lipopolysaccharide, CAID and liver dysfunction [9, 29]. Therefore, it was not surprising that PSP was significantly

different according to infection only in compensated patients (e.g., Child-Pugh A), but not in decompensated ones (Figure 1). We also confirmed that PSP might be influenced by renal dysfunction (Supplementary Figure 2), as previously shown in cohorts of patients without cirrhosis [30].

For a logarithmic cutoff value of 2.87 ng/L, diagnostic sensitivity, specificity, and accuracy of PSP for the early diagnosis of BI was equal to 0.66 (95% CI 0.57–0.74), 0.63 (95% CI 0.57–0.68), and 0.69 (95% CI 0.63–0.73), respectively. Papp et al. [19] for a PSP logarithmic cut-off value (2.94 ng/L, reported a diagnostic accuracy of 0.77 (95% CI 73–84), whereas Fischer et al. [20] using a higher cut-off (log_{10}PSP 3.16 ng/L), showed a diagnostic accuracy of 0.75 (95% CI 0.67–0.84). Patients' baseline characteristics (i.e., liver and renal dysfunction) and underlying clinical condition (i.e., prevalence of ACLF) between our cohort and previously published studies could explain these differences. Taken together, these data confirmed the suboptimal diagnostic accuracy of PSP in patients with cirrhosis, conversely from data obtained in non-cirrhotic patients. Indeed, a previous metanalysis on nine studies showed a PSP diagnostic sensitivity and specificity ranging from 71–100% and 62–98%, respectively [31]. The fact that CD14 acts as a co-receptor not only for LPS but also for other molecular triggers [32], and that lipopolysaccharide serum levels are over-expressed in patients with cirrhosis due to increased intestinal permeability [27], may explain this difference on diagnostic performance of PSP in cirrhosis.

Using a cut-off value of 27 mg/L, CRP was the serum biomarker having the best diagnostic accuracy in our study (p=0.002 vs. PSP). Moreover, a composite model, pooling together PSP, WBC and CRP did not perform better than CRP alone (Figure 2). For a cutoff value of 0.86 μg/L, PCT displayed a diagnostic accuracy of 0.65 (95% CI 0.58–0.75), not significantly better than that of PSP (p=0.18). It is noteworthy to mention that both biomarkers are commonly influenced by renal dysfunction and by persistent systemic inflammation, highly prevalent factors among decompensated cirrhosis and ACLF [12].

Summarizing our findings, this study confirmed that CRP remains the most reliable biomarker for the early diagnosis of BI in cirrhosis, even if without an optimal accuracy (AUC-ROC 0.77), whereas PSP has a disappointing performance. Moreover, considering only culture-positive infections, PSP values were not significantly different between Gram positive and negative strains. Several studies have clearly shown a benefit from the use of PCT-guided algorithms for the monitoring (i.e., antibiotic discontinuation) rather than for the diagnosis of infection, especially in severely ill patients [33]. Therefore, since PCT and PSP share similar characteristics in our cohort of patients, further studies investigating this topic would be of interest in the next future.

Regarding the short-term outcome, 20% patients died within 28 days. This was consistent with baseline characteristics of our cohort, in which 22.5% patients fulfilled criteria of ACLF. At competing risks analysis, patients with BI at admission had a higher probability of death than patients without (sHR 2.65, 95% CI 1.49–4.70; p<0.001; Supplementary Figure 3). Nevertheless, these patients were sicker at baseline, as shown by MELD score (22.2 (7.6–45.9) vs. 15.2 (6.0–50.5); p<0.001) and by prevalence of ACLF (43 vs. 14.3%; p<0.001). At multivariate Cox's regression model, age, log_{10}PSP (sHR 2.44; 95% CI 1.22–4.82; p=0.012), and severity of liver disease (according to Child-Pugh score, MELD score and presence of ACLF), were considered as independent predictors of death. On a clinical point of view, PSP may represent bacterial translocation and systemic inflammation, factors that correlate with the severity of underlying disease, in a similar way of lipopolysaccharide binding protein and interleukin-6 [9, 28]. Indeed, our data are consistent with that reported in cohorts of patients with and without cirrhosis, where prognostic value of PSP has been clearly demonstrated [20, 21, 34].

The strengths of our study are the prospective design, the evaluation of a new biomarker of systemic infection in a real-life cohort of hospitalized patients, using the same analytic method; moreover, this was the largest study evaluating both diagnostic and prognostic role of PSP in cirrhosis to date. Limitations could be the presence of a proportion of planned hospitalizations and the absence of PCT measurement in the whole cohort. Given that, subanalyses have been conducted on these topics. Furthermore, although we have hypothesized that PSP was a biomarker of systemic inflammation, we did not collect other molecules, as interleukin-1 and interleukin-6, which have been already investigated in patients with cirrhosis [35, 36], for a direct comparison.

In summary, this study demonstrated that PSP could be considered a sub-optimal biomarker for the early diagnosis of BI in hospitalized patients with cirrhosis, with a lower accuracy than CRP; however, it was an independent predictor of short-term mortality, mirroring the pro-inflammatory state which correlates with poor outcome in end-stage liver disease.

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Competing interests: Authors state no conflict of interest.

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: The study was approved by the local Ethical Committee.

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