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Are presepsin and resistin better markers for bacterial infection in patients with decompensated liver cirrhosis?

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ABSTRACT

Background: Bacterial infections impair prognosis in patients with cirrhosis. Presepsin and, more recently, resistin are promising markers of infection and sepsis in patients without cirrhosis.
Aims: The aim of our study was to assess the performance of presepsin and resistin as early markers of infection compared with C reactive protein (CRP) and procalcitonin (PCT), and their prognostic relevance in patients with decompensated cirrhosis.
Methods: One hundred and fourteen consecutive patients with decompensated cirrhosis were enrolled and followed-up for 28 days. Diagnostic performances of CRP, PCT, presepsin and resistin were assessed.
Results: Fifty-three (46.5%) patients had bacterial infections of which 30 (56%) had sepsis. Presepsin and resistin had similar performance as CRP and PCT for the diagnosis of infection (best cut-off of 1444 pg/ml and 20 ng/ml, respectively) and sepsis. Presepsin (HR = 5.5; 95%CI: 2.36–13.21, $p < 0.0001$) and the ≥500 pg/ml increase of presepsin at 48 h (HR = 9.24; 95%CI: 3.66–23.27, $p < 0.008$) were independently associated with 28-day mortality.
Conclusions: Presepsin and resistin have similar diagnostic performances to CRP and PCT for bacterial infection in decompensated cirrhosis. Presepsin and Δ presepsin ≥500 pg/ml have also a prognostic relevance for 28-day mortality.

1. Introduction

Bacterial infections occur in up to 25% of cirrhotic patients hospitalized for decompensation [1]. The inflammatory response triggered by the infectious agent may lead to organ failures that are associated with an increased mortality of up to 38% in the first month and 63% in the first year [2].

Until microbiological confirmation, the clinical suspicion of bacterial infection is mainly based on the clinical context and on early inflammatory biomarkers, such as C-reactive protein (CRP) or procalcitonin (PCT), which have moderate sensitivity and specificity in patients with cirrhosis [3].

PCT, a peptide from the superfamily of calcitonin, is an essential tool for the diagnosis of sepsis and the monitoring of response to antimicrobial therapy [4]. However, because its small molecular weight, PCT is filtered through the basal glomerular membrane, thus serum levels may be elevated in kidney failure even in the absence of infection. This may also happen in case of acute kidney injury (AKI), a frequent complication of cirrhosis, especially in the context of bacterial infections [5].

Some studies consider CRP to be the best early biomarker of infection in patients with cirrhosis [6]. However, because of the different cut-off values suggested in the literature in decompensated stages, it is sometimes difficult to use CRP for diagnosis of infection as compared to non-cirrhotic patients [6].

On the other hand, CRP is synthesized by the liver along with other acute phase proteins. Thus, in advanced liver disease its value may remain low even in the presence of bacterial infection [7].

Moreover, uninfected patients with decompensated cirrhosis may have false elevations of CRP due to the systemic inflamma-

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tion that characterizes advanced liver disease, leading to a decrease in the ability of CRP to detect bacterial infections in these circumstances [8].

Cluster of differentiation 14 (CD14) is a multifunctional glycoprotein expressed on the surface of macrophages and neutrophils. It is the specific receptor for the complex formed by Gram-negative bacterial lipopolysaccharide (LPS) and lipopolysaccharide binding protein (LBP). CD14-LPS-LBP complex released into circulation is cleaved by inflammatory serum proteases and the resulting N-terminal fraction protein has been called presepsin [9].

In non-cirrhotic population, presepsin had a 0.89 accuracy for the early diagnosis of severe bacterial infections [10].

In a recent study, presepsin proved similar performances to PCT but superior to CRP in the diagnosis of severe bacterial infections in patients with cirrhosis [11].

Even in the absence of bacterial infections, baseline presepsin levels are higher in patients with decompensated cirrhosis as compared to those in patients with compensated disease. Moreover, in these patients, serum levels of ≥600 pg/ml could predict 3-month liver-related mortality [12].

Secreted by adipocytes and macrophages, resistin, was first described as an insulin resistance modulating hormone in patients with type 2 diabetes and obesity. Recently, a new proinflammatory role was described by enhancing the neutrophil response to LPS stimulation. High serum concentrations of resistin were reported in severe sepsis and septic shock [13,14].

Moreover, in liver cirrhosis, resistin seems to correlate positively with the stage of the disease, and negatively with survival [15]. To our knowledge, there are no publications regarding the role of resistin as a marker of infection in cirrhotic patients.

Thus, the aims of our study were to investigate the ability of both presepsin and resistin to predict early bacterial infection and sepsis in patients with decompensated cirrhosis as compared to CRP and PCT, and to evaluate the prognostic relevance of these markers for 28-day mortality.

2. Materials and methods

All consecutive cirrhotic patients admitted to the emergency department in a tertiary health care center in Cluj-Napoca, Romania and hospitalized for decompensated cirrhosis, between January 2017 and January 2018, were enrolled in the study, after signing the informed consent. The study was approved by the Ethical Committee of our institution (182/2017).

Decompensation was defined as one of the following: de novo or worsening ascites, portal hypertension related bleeding, overt hepatic encephalopathy (grades 2–4 in West Haven scale), AKI (increase in serum creatinine (sCr) levels ≥0.3 mg/dl within 48 h; or a percentage increase sCr ≥50% from baseline which is known, or presumed, to have occurred within the prior 7 days) or jaundice (total serum bilirubin >3 mg/dl) [16,17].

A complete screening for infection was done at admission: total white blood cell count (WBC), chest radiograph, blood cultures, urine sediment and culture, ascitic fluid neutrophil count and ascitic fluid culture.

All patients were treated according to the existing guidelines for the management of portal hypertension-related bleeding (fluid resuscitation, vasoactive drugs, endoscopic band ligation, antibiotics and beta-blockers after controlling the bleeding), ascites (sodium restriction and diuretics if no renal dysfunction or spontaneous bacterial peritonitis) or encephalopathy (treatment of the precipitant factor, lactulose to ensure two bowel movements per day and rifaximin 1200 mg/day). The antibiotic, if needed, was chosen according to the type of infection, either empirically or specifically for any identified bacteria. In case of spontaneous bacterial peritonitis, albumin was also associated to antibiotic therapy.

Ten milliliter of venous blood on clot activator tube was drawn from patients and centrifuged for 15 min at 5000 RPM. In the first six hours after centrifugation, CRP (Thermo Fisher Scientific, ELISA kit, 981,933) and PCT (Artron, One Step Rapid Diagnostic Test kit) levels were determined from the supernatant obtained. Presepsin levels were measured at admission from 5 ml of integral blood drawn on sodium citrate tubes using the Pathfast equipment as recommended by the manufacturer (Mitsubishi Chemical Medience Corporation).

Two ml of serum from enrolled patients was stored at −80 °C and serum resistin levels (BioVendor, Human resistin ELISA kit RD 191,016,100) were also measured as recommended by the manufacturer.

2.1. Definitions

The diagnosis of infections were the following:

i) Spontaneous bacterial peritonitis (SBP) and spontaneous empyema (SE): polymorphonuclear cell count in ascitic and pleural fluid >250 mm^3;
ii) Spontaneous bacteraemia (SB): positive blood cultures without an overt cause of bacteraemia;
iii) Urinary tract infections (UTI): more than 10 leukocytes per high-power field in urine and positive urine culture or uncountable (>500) leucocytes per field even without positive cultures;
iv) Respiratory and other types of infections were defined according to conventional criteria [18].
v) For each patient, the Child–Pugh, MELD-Na, SOFA (Sequential Organ Failure Assesment Score), CLIF-SOFA (Chronic Liver Failure- Sequential Organ Failure Assesment), CLIF-OF (Chronic Liver Failure-Organ Failure) scores and ACLF (Acute on Chronic Liver Failure) grade were calculated in the first 24 h after admission.

We defined sepsis as a SOFA score ≥2 associated with a qSOFA ≥2 at admission.

Baseline SOFA score was presumed to be 0 [17].

Patients with decompensated cirrhosis were evaluated at admission for the presence of ACLF. ACLF was further categorized as

A ACLF grade 1: (a) single kidney failure or (b) single liver, coagulation, circulatory or lungs failure associated with serum creatinine between 1.5 and 2 mg/dl and/or hepatic encephalopathy grades 1 or 2 or (c) single cerebral failure with serum creatinine between 1.5 and 2 mg/dl;
B ACLF grade 2: two organ failures, whatever the combination is;
C ACLF grade 3: three or more organ failures.

The definitions of organ failures were as follows:

1 Liver failure was defined by a serum bilirubin level ≥12 mg/dl;
2 Renal failure was defined by a serum creatinine level ≥2 mg/dl or the use of renal replacement therapy;
3 Cerebral failure was defined by grade 3 or 4 hepatic encephalopathy according to the West Haven classification.
4 Coagulation failure was defined by an INR >2.5;
5 Circulatory failure was defined by the use of vasoconstrictors (norepinephrine, epinephrine, dopamine, dobutamine or terlipressin) to increase arterial pressure;
6 Respiratory failure was defined by a PaO2 to FiO2 ratio of ≤200 or by a SpO2 to FiO2 ratio ≤214 [19].

Twenty-eight-day mortality was considered as endpoint for the prognostic assessment.

Table 1
Demographic data of study population.

Mean ± SD or n (%)	Total (n = 114)	Patients without infection (n = 61)	Patients with infection (n = 53)	p[a]
Age (years)	60 ± 10	60 ± 11	59 ± 10	0.79
Gender (male)	85 (74.5%)	44 (72.1%)	41 (77.4%)	0.66
Infection type			SBP = 19 (28.3%) Bacteremia = 13 (19.4%) Urinary = 10 (14.9%) Respiratory = 11 (16.4%) Other = 14 (20.8%)	
Etiology				
Alcohol	72 (63%)	40 (65.5%)	32 (60.3%)	0.56
HBV/HCV	35 (30.7%)	18 (29.5%)	17 (32.07%)	0.76
Other	7 (6.14%)	3 (4.91%)	4 (7.54%)	0.56
Decompensation				
Ascites	72 (63%)	32 (52.4%)	40 (75.47%)	0.01
PHT bleeding	22 (19%)	18 (29.5%)	4 (7.54%)	0.04
Encephalopathy	5 (4%)	1 (1.63%)	4 (7.54%)	0.12
Jaundice	15 (13%)	10 (16.39%)	5 (9.43%)	0.27
Child Pugh score	10 ± 2	10 ± 1.9	11 ± 1.9	<0.0001
CLIF-SOFA score	9 ± 3	7 ± 1.60	10 ± 2.85	<0.0001
ACLF grade	n = 45 (39.4%)	n = 13 (21.3%)	n = 32 (60.3%)	<0.0001
	Grade 1 = 21 (46.6%)	Grade 1 = 10(76.92%)	Grade 1 = 11 (34.37%)	
	Grade 2 = 11 (24.4%)	Grade 2 = 2(15.38%)	Grade 2 = 9 (28.12%)	
	Grade 3 = 13 (28.8%)	Grade 3 = 1(7.69%)	Grade 3 = 12 (37.5%)	
MELD-Na score	23 ± 8	21 ± 7.06	26 ± 7.6	<0.0001
ALT (UI/l)	75.13 ± 137.52	55.23 ± 76.47	98.48 ± 183.37	0.11
AST (UI/l)	163.46 ± 751.26	84.1 ± 79.47	255.04 ± 1097.78	0.62
Creatinine (mg/dl)	1.36 ± 1.14	1 ± 0.7	1.77 ± 1.39	<0.0001
Albumin (g/dl)	2.86 ± 0.5	2.76 ± 0.5	2.59 ± 0.49	0.02
Bilirubin (mg/dl)	5.47 ± 5.96	5.27 ± 5.86	5.71 ± 6.10	0.30
Sodium (mEq/l)	135 ± 6.9	135.59 ± 7.36	134.42 ± 6.4	0.12
Platelet count $\times 10^3/mm^3$	120 ± 90	117.42 ± 63.92	124.79 ± 113.79	0.52

ACLF, acute on chronic liver failure; ALT, alanine-amino-transferase; AST, aspartate-aminotransferase; CLIF-SOFA, chronic liver failure-sequential organ failure assessment; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD-Na score, modified end stage liver disease-Na score; PHT, portal hypertension; SBP, spontaneous bacterial peritonitis; SD, standard deviation.

[a] Comparison between patients with and without bacterial infection.

2.2. Statistical analysis

Statistical analysis was performed using SPSS software version 20 (SPSS Inc, USA). Continuous variables were expressed as mean or median and categorical variables as counts and percentages. Categorical variables were analyzed using the Chi-squared test. Continuous variables were analyzed using the unpaired *t* test or Mann–Whitney *U* test, according to normality distribution in the population. Receiver-operating characteristic (ROC) curves were generated to assess the diagnostic performances. Sensibility (Se), specificity (Sp), positive and negative likelihood ratio (+LR; −LR) and accuracy were calculated. Optimal cut-off values were calculated using the Youden index and DeLong test was used for comparing the ROC curves. McNemar tests were used in a 2 × 2 contingency table for assessing differences in the proportion of misclassified patients for comparing the accuracies of different markers.

Univariate and multivariate Cox regression analyses of predictors of mortality were performed and the results were expressed as HR (hazard ratio) with their 95% CIs. Variables found to be associated with a 28-day mortality with a p value <0.1 in the univariate analysis were included in a multivariate analysis, with stepwise backward elimination procedure (entry $p < 0.05$; drop $p > 0.1$).

We used the log transformation of presepsin in order to exclude outlying data and to have the variable normally distributed, thus to facilitate the interpretability of the data.

3. Results

3.1. Patient's characteristics

One hundred fourteen consecutive patients (75% males) with decompensated cirrhosis were hospitalized between January 2017 and January 2018 and enrolled in our study. The main characteristics of the study group are shown in Table 1.

Alcoholism (63%) was the predominant etiology. Twenty-six patients (23%) with severe alcoholic hepatitis confirmed by transjugular liver biopsy were identified. The most frequent decompensating event was ascites (63% of the cases) followed by variceal bleeding (19%), jaundice (13%) and hepatic encephalopathy (4%).

Fifty-three (46%) patients had bacterial infections at admission and 14 (27.6%) of them had infections at multiple sites. Spontaneous bacterial peritonitis (SBP) was the most frequent infection (28.3% of the infected cases) followed by spontaneous bacteremia (19.4%), respiratory tract infections (16.4%) and urinary tract infections (14.9%) (Table 1).

Variables associated with liver function (MELD-Na, CLIF-SOFA scores, ACLF grade) as well as creatinine were significantly different between infected and non-infected patients.

ACLF was present in 45 (39%) patients, 32 (71%) of whom were patients with infection. In the remaining patients, ACLF was precipitated by alcoholic hepatitis. There was also a significant difference regarding the severity of ACLF between infected and non-infected patients, as 77% in the non-infected group had only ACLF grade 1, while 65.6% of the patients in the infected group had grades 2 and 3 ACLF.

Among the patients with bacterial infections, 30 (56%) had fulfilled criteria for sepsis. SBP was the most common infection associated with sepsis: 16 out of 30 patients (51.6%).

Nine patients, of whom 5 presented infections, were lost to follow up after discharge.

3.2. Infection markers in study group

CRP, PCT, presepsin, and resistin had significantly higher values in patients with infection and sepsis as compared with non-infected patients. (Supplementary Table 1).

Table 2
Diagnostic performances of the tested infection markers.

	AUROC (95%CI)	Se	Sp	Best cut-off level*	Accuracy	+LR	−LR	
Infection								
CRP (mg/dl)	0.74 (0.64–0.83)#		0.49	0.96	6.29	74.5%	9.97	0.53
PCT (ng/ml)	0.71 (0.61–0.81)#		0.59	0.76	0.47	67%	2.44	0.54
Presepsin (pg/ml)	0.75 (0.67–0.84)#		0.50	0.86	1444.5	70%	3.88	0.56
Resistin (ng/ml)	0.73 (0.62–0.83)#		0.61	0.78	20.3	71%	2.77	0.49
Sepsis								
CRP (mg/dl)	0.78 (0.68–0.87)#		0.78	0.69	3.39	72%	2.56	0.31
PCT (ng/ml)	0.73 (0.61–0.84)#		0.64	0.77	0.49	67%	2.07	0.51
Presepsin (pg/ml)	0.82 (0.73–0.90)#		0.67	0.85	1444.5	80%	4.33	0.37
Resistin (ng/ml)	0.71 (0.59–0.84)^		0.68	0.70	20.3	70%	2.29	0.45

CRP, C-reactive protein; PCT, procalcitonin; +LR, positive likehood ratio; −LR, negative likehood ratio; Se, sensibility; Sp, specificity.
* According to the Youden index.
# $p < 0.001$.
^ $p = 0.004$.

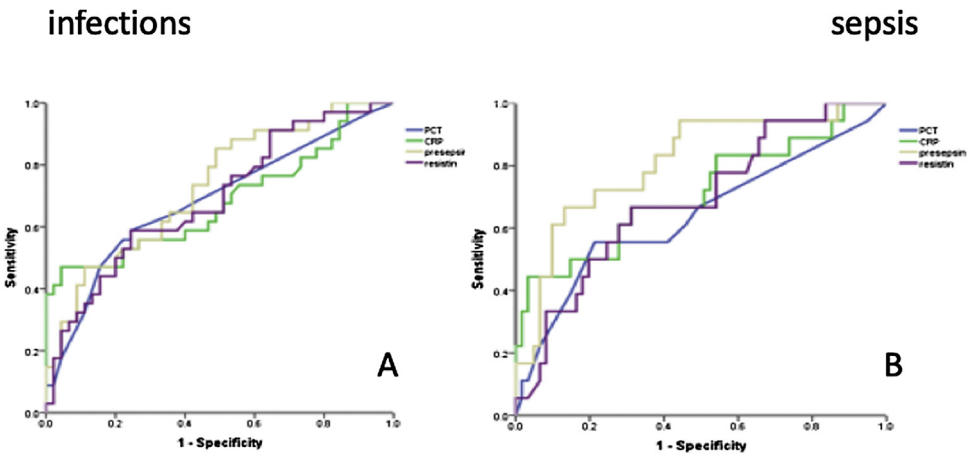

Fig. 1. (A) ROC curves of presepsin, resistin, C-reactive protein and procalcitonin for diagnosis of bacterial infections; (B) ROC curves presepsin, resistin, C-reactive protein and procalcitonin for diagnosis of sepsis.

The performances of CRP, PCT, presepsin, and resistin for diagnosis of infection and sepsis are listed in Table 2 and Fig. 1A and B, respectively.

Presepsin performance (AUROC = 0.75; 95%CI: 0.67–0.84, $p < 0.001$) for diagnosis of infection was not significantly different from CRP, PCT and resistin (DeLong test $p = 0.87$, $p = 0.54$ and $p = 0.76$, respectively).

According to the Youden index the best cut-off for presepsin serum levels in diagnosis of infection and sepsis were similar, 1444 pg/ml. Using this cut-off, 70% of the patients were correctly classified as infected and 80% as having sepsis. However, when we compared the cut-off serum levels of 600 pg/ml, as recommended for the diagnosis of infection and sepsis in non-cirrhotic patients with our cut-off level, the accuracy was lower: only 60% versus 70% (McNemar test, $p = 0.2$) for infection and significantly lower: 53% versus 80% (McNemar test p-value <0.0001) for sepsis diagnosis [20].

As can be seen in Table 2, resistin had similar performance for bacterial infection and sepsis diagnosis in cirrhotic patients as CRP, PCT and presepsin. Resistin cut-off level was 20 ng/ml for diagnosis of both bacterial infection and sepsis with an accuracy of 71% and 70%, respectively. Using a cutoff of 36.5 ng/ml, validated in non-cirrhotic patients, the accuracy was 67% for infection and 73% for sepsis diagnosis in our population [14].

3.3. Prognosis analysis

Thirty-nine patients died within 28 days. The most frequent cause of death was sepsis and multiple organ failure in 23 (59%) patients, followed by liver failure (including hepato-renal syndrome) in 12 (31%) patients and other causes in 4 (10%) patients.

All markers of infections were significantly different between patients who survived and those who died within 28 days (Supplementary Table 2).

Variables associated with a 28-day mortality in univariate analysis were included in the multivariate analysis using the Cox regression model. In order to avoid collinearity and overfeeding the models, six models comprising 3 or 4 variables of the above mentioned were tested (Table 3). Variables associated with liver function (Child–Pugh or MELD score), kidney dysfunction (serum creatinine) and presence of infection were independently associated with 28-day mortality. Among the infection markers, only presepsin and CRP proved to be independently associated with the end-point.

The performances of presepsin, resistin, CRP and PCT for predicting 28-day survival were AUROC = 0.74 (95%CI: 0.64–0.84) ($p < 0.001$), 0.69 (95%CI: 0.57–0.82) ($p = 0.006$), 0.74 (95%CI: 0.64–0.84) ($p < 0.001$) and 0.70 (95%CI: 0.59–0.81) ($p = 0.001$), respectively.

Interestingly, using the 1444.5 pg/ml cut-off for presepsin, the patients at risk of dying within 28 days were correctly identified with an accuracy of 72%. Survival in patients with presepsin <1444.5 pg/ml at admission was significantly higher than in those with presepsin levels ≥1444.5 pg/ml (Fig. 2).

Presepsin at 48 h after admission was available in 67 patients of whom 17 died during hospitalization and 26 died within 28 days. Δ presepsin (presepsin at 48 h minus presepsin at admission) was significantly associated with 28-day mortality (HR = 9.24; 95%CI:

Table 3
Univariate and multivariate analysis of variables associated with 28-day mortality.

Univariate	HR (95%CI)	p	Multivariate	HR (95%CI)	p
Infection	3.77 (1.90–7.46)	<0.001	**Model 1**		
Child–Pugh score	1.3 (1.1–1.5)	0.002	Child–Pugh score	1.2 (1–1.44)	0.05
MELD-Na	1.1 (1.6–1.15)	<0.001	Creatinine	1.1 (0.92–1.5)	0.19
INR	1.76 (1.34–2.32)	<0.001	Na	1 (0.95–1.05)	0.89
Creatinine	1.47 (1.21–1.79)	<0.001	Presepsin[a]	5.5 (2.36–13.21)	<0.001
Na	0.94 (0.91–0.96)	0.009			
Albumin	0.46 (0.24–0.88)	0.01	**Model 2**		
Presepsin[a]	7.1 (3.16–15.95)	0.0001	MELD-Na	1.06 (1.01–1.11)	0.001
Δ presepsin[a]	1.60 (1.12–2.29)	0.01	Albumin	0.74 (0.37–1.47)	0.4
Δ presepsin ≥500 pg/ml	7.98 (3.52–18.07)	<0.001	Presepsin[a]	3.6 (1.4–9.2)	0.008
Resistin	1.03 (1.01–1.05)	0.002			
CRP	1.15 (1.09–1.21)	<0.001	**Model 3**		
PCT	1.16 (1.06–1.26)	0.001	Child–Pugh score	1.28 (1.00–1.64)	0.04
			Creatinine	1.1 (0.81–1.49)	0.52
			Na	0.93 (0.88–0.98)	0.01
			Δ presepsin ≥500 pg/ml	9.24 (3.66–23.27)	<0.001
			Model 4		
			Child–Pugh score	1.08 (0.85–1.37)	0.50
			Creatinine	1.51 (1.20–1.90)	<0.001
			Na	0.96 (0.92–1.01)	0.20
			Resistin	1.01 (0.99–1.04)	0.15
			Model 5		
			Child–Pugh score	1.24 (1.03–1.48)	0.01
			Creatinine	1.34 (1.07–1.69)	0.009
			Na	1 (0.95–1.05)	0.79
			CRP	1.1 (1.04–1.17)	0.001
			Model 6		
			PCT	1.09 (0.99–1.19)	0.05
			MELD-Na	1.08(1.03–1.13)	0.001
			Albumin	0.85 (0.42–1.70)	0.64

CRP, C reactive protein; Δ, delta; HR, hazard ratio; Na, sodium; INR, international normalised ratio; MELD-Na, modified end stage liver disease-Na score; PCT, procalcitonin.
[a] Logarithmized.

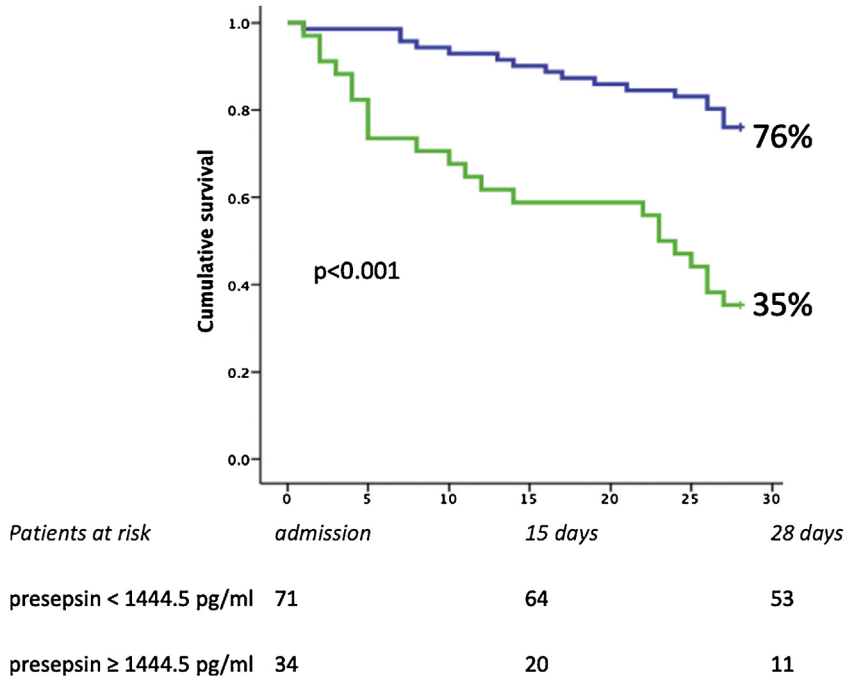

Fig. 2. Probability of survival according to presepsin value at admission (threshold 1444.5 pg/ml).

3.66–23.27, p < 0.008) and had good performances in predicting it: AUROC = 0.85 (95%CI: 0.74–0.95) (p < 0.0001).

An increase in presepsin levels at 48 h of more than 500 pg/ml had 78% (p < 0.0001) accuracy for predicting 28-day mortality. Survival in patients whith Δ presepsin ≥500 pg/ml at 48 h was significantly lower as compared with patients with a Δ presepsin <500 pg/ml (Fig. 3).

4. Discussion

In our study we found that both presepsin and resistin may be reliable markers of bacterial infections in patients with decompensated cirrhosis. However, these had a similar diagnostic performance for bacterial infection and sepsis when compared to CRP and PCT. Similar results were reported in a previous study:

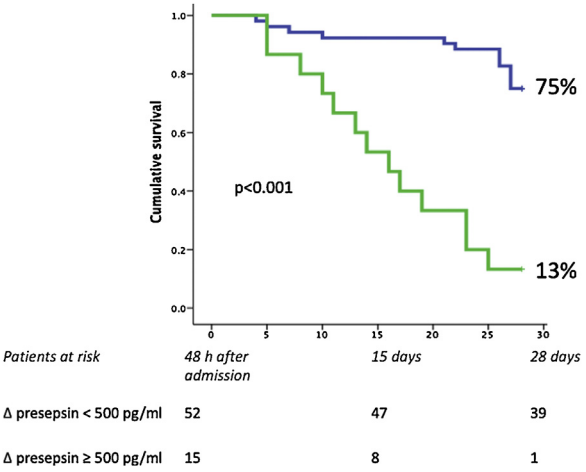

Fig. 3. Probability of survival according to the presepsin increasement during the first 48 h after admission (threshold 500 pg/ml).

as presepsin was not superior to PCT for the diagnosis of severe bacterial infections in patients with liver cirrhosis [11]. Based on these findings, no marker of infection or sepsis may be preferred to others, and the decision to use one or the other should be based on the local availability and expertise. A recent meta-analysis in patients without liver diseases confirmed similar results [21,22].

Theoretically, some of the drawbacks of the classical markers, such are the lack of specificity for CRP, which may have increased values in various inflammatory conditions or malignancies [23–25] or the fact that PCT in sepsis is synthetized mostly in the liver, may be overcome by new markers such as presepsin, which increases very rapidly after polymorphonuclear and monocytes exposure to LPS [25]. However, it should be emphasized that the cut-offs validated in patients without cirrhosis cannot be used in decompensated cirrhosis. In non-cirrhotic patients, the best cut-off level for severe sepsis was 600 pg/ml [20]. However, when we tested these cut-off values for the diagnosis of sepsis in our study group, the accuracy was only 53%. Our study found that the best cut-off level of presepsin for diagnosis of sepsis was 1444 pg/ml, similar to previously published results [11]. The higher presepsin levels in liver cirrhosis may be explained by the bacterial translocation that characterizes advanced cirrhosis. However, this hypothesis must be confirmed by further studies.

Resistin is an adipose tissue derived hormone in mice and humans, firstly described as responsible for insulin resistance in obesity and type 2 diabetes. It has been also demonstrated that in humans resistin is related to inflammatory processes due to its origin from macrophages [26]. Its value seems to be also increased by endotoxins [13].

Thus, the role of resistin as a marker of sepsis has been investigated in the last years. Recently, it has been shown that resistin is a useful marker for diagnosing and assessing the severity of sepsis in non-cirrhotic populations [27,28,29].

Cirrhosis is characterized by insulin resistance, mainly due to portal blood shunting to the systemic circulation [30]. The role of resistin as a marker of insulin resistance in cirrhosis was investigated by some authors and values were positively correlated with disease stage and negatively with survival [15,31].

To the best of our knowledge, the role of resistin as a marker of infection and sepsis in cirrhotic patients has not been investigated until now. In our study resistin showed similar performances to presepsin, CRP and PCT for the diagnosis of bacterial infections and sepsis.

There is increasing evidence for the prognostic role of presepsin dynamics in severe sepsis and septic shock in the general population [32,33]. Our study confirms for the first time these data in patients with decompensated liver cirrhosis. Presepsin dynamics correlated better with mortality than baseline values, thus an increase in presepsin level of at least 500 pg/ml in the first 48 h after admission is independently associated with 28-day mortality and has a 78% accuracy in predicting it.

Despite previous evidences that higher baseline resistin levels are associated with lower long-term survival, we did not confirm independent association between resistin and 28-day mortality [15]. However, the population included in our study is completely different as all patients had decompensated liver cirrhosis, and, under these circumstances, resistin is probably losing its prognostic role.

Interestingly, we found much lower levels of resistin in patients with sepsis and cirrhosis as reported in the non-cirrhotic population [14]. Considering the origin of resistin in the adipose tissue, a possible cause for its lower values could be the lower nutritional status that characterizes the patients with decompensated cirrhosis. The prevalence of malnutrition has been shown to be up to 73% and 94% of Child–Pugh B and C classes, respectively [34].

Apart from presepsin, in our study, only CRP was independently associated with 28-day mortality, a finding that is consistent with data from the literature. Elevated CRP proved to predict 3-month mortality either at admission or in the dynamic changes during hospitalization [35]. Moreover, CRP values at discharge after the resolution of a bacterial infection seem to be associated with early hospital readmission in patients with cirrhosis [36].

The main drawback of our study is that it included a single center experience with a relatively low number of patients that did not allow subgroup analysis. Furthermore, for financial reasons we were not able to correlate presepsin with bacterial translocation markers such as LPS and LBP, and we did not evaluate the dynamic of the other markers, especially resistin.

However, as far as we know, this is the first study that compares resistin and presepsin with the" classic" infection markers, like CRP and PCT for the diagnosis of bacterial infections and sepsis in patients with decompensated liver cirrhosis.

5. Conclusions

In our study PCT, CRP, presepsin and resistin had similar accuracy in diagnosis of infection and sepsis in decompensated cirrhotic patients. Only presepsin and CRP had a prognostic relevance in decompensated cirrhosis. Moreover, the 48 h dynamic of presepsin may be a better prognostic indicator in patients with decompensated cirrhosis. Further studies on larger groups of patients are needed.

Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dld.2019.05.025.

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