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Evaluation of Serum Presepsin in the Diagnosis and the Prognosis of Cirrhotic Patients with Ascites

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Background: Liver cirrhosis is a serious problem associated with spontaneous bacterial peritonitis and renal dysfunction. Presepsin is a soluble Cluster of Differentiation 14 (CD14) Protein subtype that has been implicated as an important biomarker in many diseases.
Objective: To assess the clinical value of presepsin as a diagnostic and prognostic marker for spontaneous bacterial peritonitis in cirrhotic patients.
Patients and Methods: This cross-sectional study was carried out on 60 cirrhotic patients with ascites. The data were collected from Internal Medicine Hospital Inward and ICUs of Internal Medicine.
Results: Serum presepesin had a significant negative correlation with serum albumin (r_s = -0.350, p = 0.006) and a significant positive correlation with platelet count (r_s =0.547, p < 0.001). In the Spontaneous bacterial peritonitis (SBP) group, presepesin correlated significantly positively with total leukocytic count (r_s =0.547, p < 0.001). The level of serum presepsin significantly increased with the group suffering from Hepatorenal syndrome (HRS) than the ascites group after adjusting for age, C-reactive Protein (CRP) level, and total leukocytic count. Similarly, the level of serum

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presepsin significantly increased with the SBP group than the ascites group after adjusting for age, CRP level, and total leukocytic count.
Conclusion: presepsin is a promising biomarker in the diagnosis of bacterial infections and hepatorenal syndrome in cirrhosis. However, the diagnostic and prognostic value of presepsin needs further studies.

Keywords: Prothrombin time; acute-on-chronic liver failure; chronic liver disease.

1. INTRODUCTION

Chronic liver injury induces hepatic stellate activation, with progressive fibrosis leading to portal hypertension [1]. Patients with cirrhosis who are in a decompensated state are at the highest risk of developing spontaneous bacterial peritonitis (SBP) [2]. Spontaneous bacterial peritonitis is the most frequent and life-threatening bacterial infection in cirrhotic patients with ascites leading to hepatorenal syndrome (HRS) [3]. Hepatorenal syndrome is the end-stage due to the reduction of renal perfusion. [4] Therefore, specific biomarkers are needed for early diagnosis and proper treatment.

The Cluster of Differentiation 14 (CD14) Protein subtype has two forms: membrane-bound CD14 (mCD14) and soluble CD14 (sCD14) [5].

Presepsin (soluble CD14 subtype, sCD14-ST) is a 13-KD cleavage product of the CD14 receptor that recognizes the different cell structures of both Gram-negative and positive bacteria. [6] Presepsin in the circulation can be perceived as a witness of activated monocyte macrophage in response to pathogens [6].

1.1 Aim of the Work

The study is to assess the clinical value of presepsin as a diagnostic and prognostic marker for SBP in cirrhotic patients.

2. PATIENTS AND METHODS

It is a cross-sectional study carried out on 60 cirrhotic patients with ascites. The data was collected at the Internal Medicine Hospital Inward and the ICUs of Internal Medicine at Tanta University Hospitals. The study was done within six months starting from 1 September 2018 to 28 February 2019.

2.1 Patients

The patients were divided into three groups:

- **Group 1**: 20 patients with cirrhosis and ascites (as a control group).
- **Group 2**: 20 patients with cirrhosis and ascites complicated by spontaneous bacterial peritonitis.
- **Group 3:** 20 patients with cirrhosis and ascites complicated by spontaneous bacterial peritonitis and hepatorenal syndrome.

2.2 Study Design

cross-sectional study.

2.3 Methods

2.3.1 All patients were subjected to the following

History taking. Clinical examination: Including general examination and abdominal examination. Investigational studies: Laboratory: Complete blood count. Liver biochemistry (serum bilirubin, total, direct and indirect, SGOT, SGPT, serum albumin, prothrombin time, and activity). Renal function tests: (serum creatinine and blood urea). Serum sodium and potassium. C-reactive protein. Fasting plasma glucose and postprandial plasma glucose. Serum ascites albumin gradient (SAAG). Serum presepsin level. Radiology: pelviabdominal ultrasound.

2.3.2 The inclusion criteria

Decompensated liver disease with ascites.

2.3.3 The exclusion criteria

- Heart failure.
- Chronic kidney disease.
- Hepatorenal syndrome is not due to spontaneous bacterial peritonitis.
- Diabetes mellitus.
- Infections other than spontaneous bacterial peritonitis.

2.4 Calculation of Study

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS)

version 26. (Hinkle et al., 2003). This was also aided with using the Chi-square and Post-hoc tests, as well as the multinomial logistic regression analysis, ROC Curve, and Welch ANOVA.

3. RESULTS

This is a statistical study carried on 60 patients classified into three groups, group 1 (ascites), group 2 (ascites with Spontaneous bacterial peritonitis (SBP)), group 3 (ascites with Hepatorenal syndrome (HRS)). Their ages ranged from 34 to 76 years, with a mean age (SD) of 58.0 (8.2) years old. Men constituted 48.3% of the studied patients, while women constituted 51.7% as shown in table (1). When we compared the age among three groups, found a statistically significant difference in the mean age ($p = 0.006$), the SBP group had a significantly higher mean age than the ascites group (62.2 ± 6.8 vs. 53.1 ± 9.5, $p = 0.004$) and no significant differences in the mean age between the ascites and HRS groups ($p = 0.069$) nor between the HRS and SBP groups ($p = 0.168$) as shown in table (2). We made a correlation between serum presepesin level and relevant biomarkers (in all patients and then within each group), found that presepsin had a significant, negative, moderate correlation with serum albumin (r_s=-0.350, $p = 0.006$), and a significant positive, moderate correlation with platelet count (r_s= 0.547, $p < 0.001$). Correlations within the ascites and HRS groups were not statistically significant. In the SBP group, presepesin correlated significantly, positively, and moderately with total leukocytic count (r_s= 0.574, $p = 0.010$) as shown in Table (3). Also, when we made a multinomial logistic regression analysis to assess the effect of age, C-reactive Protein (CRP), presepsin, and total leukocytic count on the medical condition of the patient found that (firstly between HRS, Ascitic groups) the presepsin level was significantly increased in HRS than ascites (OR = 1.074, 95% CI= 1.015 - 1.137, $p = 0.014$), after adjusting for age, CRP level and total leukocytic count. Similarly, the level of presepsin was significantly increased in SBP than ascites (OR = 1.092, 95% CI= 1.022 - 1.167, $p = 0.009$), after adjusting for age, CRP level, and total leukocytic count as shown in Table (4). When we compared presepsin, CRP, creatinine, and urea as the best diagnostic marker for differentiating between three groups found that the creatinine is the best marker for differentiating HRS than ascites then presepsin, urea, and CRP (AUCs = 1.000, 0.961, 0.835, and 0.540, respectively) as shown in Table (5). Similarly, presepsin is the best marker in differentiating SBP from ascites followed by CRP, urea, and creatinine (AUCs = 1.000, 0.910, 0.758, and 0.628, respectively) as shown in Table (6). Also, creatinine is the best marker in differentiating HRS from SBP then CRP, presepsin, and urea (AUCs = 1.000, 0.903, 0.888, and 0.753, respectively) as shown in Table (7).

Table 1. Demographic data of the studied patients (total n = 60)

Range		34.0 - 76.0
Mean ± SD		58.0 ± 8.2
Male	n (%)	29 (48.3%)
Female	n (%)	31 (51.7%)
Ascites	n (%)	20 (33.3%)
HRS	n (%)	20 (33.3%)
SBP	n (%)	20 (33.3%)

n: number; SD: standard deviation

Table 2. Comparison of age among the studied groups (total n = 60)

	Ascites (n = 20)	**HRS (n = 20)**	**SBP (n = 20)**	**Total (n = 60)**	**Test statistic**	**P**
Range	34.0 - 70.0	49.0 - 67.0	48.0 - 76.0	34.0 - 76.0	F_w=5.973	0.006* p1=0.069
Mean ± SD	53.1 ± 9.5	58.7 ± 5.1	62.2 ± 6.8	58.0 ± 8.2		p2=0.004* p3=0.168

*n: number; SD: standard deviation; F_w: Welch ANOVA; X^2_{ChS}: Pearson's Chi-square test; p1: p-value from post-hoc test between Ascites & HRS; p2: p-value from post-hoc test between Ascites & SBP; p3: p value from post-hoc test between HRS & SBP; * significant at p <0.05*

Table 3. Spearman's rank-order correlation for presepesin

		Presepsin			
		Total	**Ascites**	**HRS**	**SBP**
Total bilirubin (mg/dl)	r_s	0.057	-0.284	0.278	-0.059
	P	0.668	0.224	0.235	0.804
Direct bilirubin (mg/dl)	r_s	0.200	-0.130	0.314	0.108
	P	0.125	0.585	0.177	0.649
Serum albumin (g/dl)	r_s	-0.350	-0.095	0.331	0.071
	P	0.006*	0.691	0.154	0.765
Serum creatinine (mg/dl)	r_s	-0.079	0.163	0.067	-0.383
	P	0.549	0.493	0.779	0.096
Platelet count (x103/cmm)	r_s	0.547	0.115	0.390	-0.157
	P	<0.001*	0.629	0.089	0.510
Total leukocytic count (x103/cmm)	r_s	-0.004	0.200	-0.196	0.574
	P	0.978	0.398	0.407	0.010*

*r_s: correlation coefficient; * significant at p <0.05*.

Table 4. Multinomial logistic regression analysis (total n = 60)

Diagnosis		**B**	**SE**	**Wald**	**p**	**OR**	**95% CI for OR**
HRS [a]	Age	0.027	0.109	0.063	0.802	1.028	0.831 - 1.271
	CRP	-0.537	0.477	1.271	0.260	0.584	0.229 - 1.487
	Presepsin	0.072	0.029	6.061	0.014*	1.074	1.015 - 1.137
	Total leukocytic count	0.089	0.186	0.228	0.633	1.093	0.759 - 1.574
SBP [a]	Age	0.225	0.190	1.406	0.236	1.252	0.863 - 1.816
	CRP	-0.035	0.452	0.006	0.938	0.965	0.398 - 2.340
	Presepsin	0.088	0.034	6.771	0.009*	1.092	1.022 - 1.167
	Total leukocytic count	-0.470	0.391	1.444	0.229	0.625	0.290 - 1.345

*a: reference category is Ascites; B: regression coefficient; CI: confidence interval; OR: odds ratio; SE: standard error; * significant at p<0.05.*

Table 5. Comparison between presepsin, CRP, urea, and serum creatinine as diagnostic (predictive) markers for differentiating Ascites vs HRS as regards area under ROC curve, sensitivity, and Specificity (total n = 40)

Parameters	**Presepsin**	**CRP**	**Urea**	**Creatinine**
AUC	0.961	0.540	0.835	1.000
(95% CI)	(0.847 – 0.997)	(0.375 – 0.698)	(0.684 – 0.933)	(0.912 – 1.000)
p – value	<0.001*	0.537	<0.001*	<0.001*
Cut off value	>60	≤ 6	>58	>3
Sensitivity (%)	95.0	90.0	85.0	100.0
Specificity (%)	100.0	30.0	85.0	100.0
p-value from Pairwise comparisons of AUCs				
	Presepsin	**CRP**	**Urea**	**Creatinine**
Presepsin		<0.001*	0.149	0.321
CRP	<0.001*		0.003*	<0.001*
Urea	0.149	0.003*		0.028*
Creatinine	0.321	<0.001*	0.028*	

*AUC: area under the curve; CI: confidence interval; * significant at p<0.05.*

Table 6. Comparison between presepsin, CRP, urea, and serum creatinine as diagnostic (predictive) markers for differentiating Ascites vs SBP as regards area under ROC curve, sensitivity, and Specificity (total n = 40)

Parameters	Presepsin	CRP	Urea	Creatinine
AUC	1.000	0.910	0.758	0.628
(95% CI)	(0.912–1.000)	(0.776-0.977)	(0.596-0.879)	(0.461-0.775)
p – value	<0.001*	<0.001*	0.002*	0.156
Cut off value	>60	>9	>45	≤1.2
Sensitivity (%)	100.0	85.0	95.0	95.0
Specificity (%)	100.0	100.0	60.0	30.0
p-value from Pairwise comparisons of AUCs				
	Presepsin	**CRP**	**Urea**	**Creatinine**
Presepsin		0.073	0.004*	<0.001*
CRP	0.073		0.122	0.004*
Urea	0.004*	0.122		0.398
Creatinine	<0.001*	0.004*	0.398	

AUC: area under the curve; CI: confidence interval

Table 7. Comparison between presepsin, CRP, urea, and serum creatinine as diagnostic (predictive) markers for differentiating HRS vs SBP as regards area under ROC curve, sensitivity, and Specificity (total n = 40)

Parameters	Presepsin	CRP	Urea	Creatinine
AUC	0.888	0.903	0.753	1.000
(95% CI)	(0.748 - 0.965)	(0.767- 0.973)	(0.591 - 0.875)	(0.912-1.000)
p – value	<0.001*	<0.001*	0.001*	<0.001*
Cut off value	>190	>6	≤80	≤1.3
Sensitivity (%)	70.0	85.0	80.0	100.0
Specificity (%)	95.0	90.0	60.0	100.0
p-value from Pairwise comparisons of AUCs				
	Presepsin	**CRP**	**Urea**	**Creatinine**
Presepsin		0.713	0.145	0.034*
CRP	0.713		0.095	0.036*
Urea	0.145	0.095		0.001*
Creatinine	0.034*	0.036*	0.001*	

4. DISCUSSION

Infectious episodes are the important cause of the progression of liver failure and its related complications [7]. Early recognition of bacterial infections is essential, however, their accurate identification is challenging from both the clinical [8] and the laboratory point of view [9].

Regarding the hemoglobin level, our findings agreed with Michael et al., who found that anemia was a risk factor for AKI (P=0.018) [10]. But Lasheen et al., found that the Hb level was significantly lower in AKI patients than non-AKI [11].

Concerning the leukocytic count, our results were in line with Thabut et al., who found TLC was high in AKI than SBP [10,12] and in contrast with, Wang and Zhang, who found no difference in peripheral blood RBC, peripheral blood PLT, peripheral blood Hb patients between study group and control group [13].

As regards the median CRP titer, our results were in harmony with the study by Wang and Zhang, who found there was a significant difference in serum CRP between the study group and control group [12] and against with Lasheen et al., and Thabut et al. found that CRP was significantly higher in cirrhotic patients who developed AKI than those without AKI [12,11].

The median presepsin level in our results was in harmony with, Papp et al., and Fischer et al. found that the level of serum presepsin was significantly higher in patients with infection as compared to those without [14]. Similarly, Elefsiniotis et al., and Okasha et al., found that patients with decompensated cirrhosis exhibited

significantly higher baseline levels of presepsin than patients with compensated cirrhosis, especially in those who developed acute kidney injury compared to those who did not [15,16].

Concerning the serum presepesin's correlation with serum albumin, as well as the leukocytic and platelet counts, their results in our study were in an agreement with Papp et al., and Masson et al., who found that serum presepsin level was positively correlated with classic markers of bacterial infections, such as different WBC parameters, but also with liver function tests [14,17]. In contrast, Fujii et al. found platelet counts were significantly lower in the increased presepsin group [18].

Similar to our findings in regards to the presepsin level, it significantly increased with the SBP group than the ascites group after adjusting for age, CRP level, and total leukocytic count. So, presepsin could be considered a highly specific marker for the diagnosis of bacterial infections in comparison to other sepsis markers [19]. Due to sensitivity and specificity.

On the other hand, CRP is not accurate in advanced liver disease because it is synthesized by the liver along with other acute phase proteins so, its value may remain low even in the presence of bacterial infection in advanced liver disease and may have false elevations in the uninfected patients with decompensated cirrhosis due to the systemic inflammation that characterizes the advanced liver disease, leading to a decrease in the ability of CRP to detect bacterial infections in these circumstances [9, 20].

Our results were supported by Endo et al., Sharafeddin et al., and Novelli et al. showed that serum presepsin was a good predictor of bacterial infection and the measurement of serum presepsin concentrations is useful for evaluating the severity of the infection and also for monitoring the clinical responses to therapeutic interventions [21,22,23].

In accordance, Bota et al. reported that the predictive power of CRP was weak for the infections in critically ill patients with cirrhosis in the intensive care unit (ICU) which is also in agreement with our results. But, Tsiakalos et al., consider CRP to be the best early biomarker of infection in patients with cirrhosis. Therefore, the Combination of CRP with serum presepsin is the best, as in the study of Papp et al., reported that this combination amends the identification efficacy of the infectious episode and the serum presepsin was able to distinguish severe infectious episodes from non-severe ones more properly compared to CRP only [14,24,25].

5. CONCLUSION

There are many risk factors for liver cirrhosis complicated with SBP and HRS. we concluded that many obstacles in the diagnostic criteria exist, but as yet, no reliable diagnostic marker exists for HRS and SBP. Future directions should include the development of an accurate diagnostic test. This is important as an earlier diagnosis and thus treatment is likely to improve survival.

We concluded a correlation between serum presepesin level and relevant biomarkers. Specifically, the creatinine appeared to be the best diagnostic marker for differentiating HRS, while presepsin was the best marker in differentiating SBP.

6. LIMITATIONS

The sample size of 60 participants needed to be larger. Although over the last century, much has been learned about the pathophysiology, clinical behavior, and natural history of these complications, and a standardized diagnostic criterion have been developed and implemented worldwide, allowing for more uniform diagnosis and consistent reporting of the disease. But more researches need to be conducted.

CONSENT

Written informed consent was obtained from all patients after a full explanation of the benefits and risks.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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