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The Utility of Serum Procalcitonin Measurement in the Diagnosis of Spontaneous Bacterial Peritonitis in Liver Cirrhosis patients

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Abstract
Background: Ascites in cirrhosis has a poor prognosis, with mortality rates of around 40% at one year and 50% at two years. It is also associated with other complications, such as spontaneous bacterial peritonitis (SBP), which can lead to hepatorenal syndrome (HRS) in 30% of patients. Diagnostic paracentesis is the gold standard for diagnosing SBP. Serum biomarkers such as procalcitonin (PCT) have recently received a lot of attention for the early detection of SBP.
Objective: To determine the usefulness of measuring serum procalcitonin levels in patients with liver cirrhosis and ascites for the diagnosis of spontaneous bacterial peritonitis.
Patients and methods: A cross-sectional case-control study that was conducted on ninety (90) patients diagnosed with liver cirrhosis. They were divided into three groups: Group (A) included 30 cirrhotic patients with ascites diagnosed as spontaneous bacterial peritonitis, Group (B) included 30 cirrhotic patients with ascites but without spontaneous bacterial peritonitis, and Group (C) included 30 cirrhotic patients without ascites as a control group.
Results: Serum procalcitonin levels in SBP patients were significantly higher than in sterile ascites and cirrhotic patients without ascites with a P value of 0.001. It had a better cutoff value of 0.315 ng/ml, sensitivity of 87% and specificity of 97% than serum CRP that had a cutoff value of 16 mg/L, sensitivity of 76% and specificity of 90% in cirrhotic patients for predicting ascitic fluid infection.
Conclusion: In cirrhotic patients, serum procalcitonin levels appear to provide a satisfactory diagnostic accuracy in the diagnosis of spontaneous bacterial peritonitis, with a suggested cut-off value of 0.315 ng/ml. Further studies are needed to determine the widespread use of serum PCT as a predictor of SBP clinically.
Keywords: liver cirrhosis, Ascites, Procalcitonin, Spontaneous bacterial peritonitis (SBP).

INTRODUCTION

Cirrhosis of the liver is a leading cause of morbidity and mortality. Cirrhosis results from distortion of hepatic architecture characterized by diffuse nodular regeneration, fibrosis, and collapse of liver structures. This distortion leads to portal hypertension because of increased resistance to portal blood flow [(1)]. In cirrhosis, portal hypertension and splanchnic vasodilation result mainly from increased production of nitric oxide, which is the main pathophysiological mechanism of ascites [(2)]. One of the complications that can occur in ascitic patients is SBP, which can result in HRS in 30% of cases [(3)].

In hospitalised patients with liver disease, early diagnosis of SBP is essential. Due to the lack of symptoms in the early stages of SBP, that represents a problem for clinicians [(4)]. Currently, most guidelines indicate that all patients with ascites admitted to the hospital undergo a diagnostic paracentesis, regardless of clinical suspicion. A count of ascites polymorphonuclear cells (PMN) greater than 250 cells/mm^3 confirms the diagnosis [(5)]. During the paracentesis procedure, problems may occur, such as the introduction of pathogenic microorganisms into the ascites along with the needle. As a result, the availability of blood samples for routine examination is easier and more secure than using ascitic fluid. As a result, serum biomarker assessment has recently attracted a lot of attention for early identification of SBP [(6)].

In healthy individuals, procalcitonin (PCT) is a calcitonin precursor naturally produced by thyroid C-cells. If infection is not present, the extra-thyroidal expression of the PCT gene, which is present in the liver, lung, kidney, adrenal tissue, monocytes, granulocytes, testis, prostate gland, and small intestine, is suppressed and falls below the detection limit for clinical assays. Whereas, microbial illness, particularly bacterial infection, stimulates PCT gene expression with blood PCT levels rising 4 hours after the onset of systemic infection and peaking between 8 and 24 hours [(7)].

The aim of this study was to determine the usefulness of measuring serum procalcitonin levels in patients with liver cirrhosis and ascites for the diagnosis of spontaneous bacterial peritonitis.

PATIENTS AND METHODS

This cross-sectional case-control study that was conducted at Ain Shams University Hospitals from 2016 to 2018. The study included ninety cirrhotic patients. They were divided into three groups: Group (A) included 30 cirrhotic patients with ascites who had spontaneous bacterial peritonitis proved by ascitic fluid examination, group (B) included 30 cirrhotic patients with ascites but no spontaneous bacterial peritonitis proved by ascitic fluid examination and group (C) included 30 cirrhotic patients without ascites as a control group.

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Inclusion criteria: Group A included patients with cirrhotic ascites who were proved to have SBP on the basis of clinical and laboratory diagnostic criteria. Whereas, the selection of controls included adult cirrhotic patients who presented with ascites (group B) and without ascites (group C) and did not have existing evidence of SBP based on clinical and laboratory diagnostic criteria.

Exclusion criteria: Patients that had other sites of bacterial infection, positive bacterial cultures including blood, urine, and sputum, and non-hepatic causes of ascites, e.g. cardiac, renal, and malignant ascites.

All participants in this study underwent:

- **Complete medical history as well as a thorough clinical examination with a focus on** the presence of jaundice, size of the liver and spleen, hepatic encephalopathy, abdominal tenderness, and the presence of ascites or lower limb edema.
- **Routine laboratory tests, which included** liver profile (serum albumin, total protein, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), serum total and direct bilirubin, PT and INR). Besides, complete blood count, kidney function tests (serum creatinine, urea, blood Na and K), urine analysis, serum alpha-fetoprotein, ESR, C-reactive protein and blood, urine, and sputum cultures to exclude other sites of bacterial infection.
- **Imaging techniques included** abdominal ultrasound, chest x-ray, electrocardiography and echocardiography to evaluate cardiac function and exclude cardiac causes of ascites.
- **Ascitic fluid examination.**
- **Serum procalcitonin level by chemiluminescence assay** with a detection limit of 0.5 ng/mL.

Ethical approval:

The Ethics Committee of Ain Shams University's Faculty of Medicine accepted the study protocol, which followed the ethical requirements of the 1975 Declaration of Helsinki and its appendices (FWA 000017585). An informed written consent was obtained from each participant included in this study.

Data Management and Analysis:

Using the statistical package for social science, the obtained data were edited, coded, tabulated, and uploaded to a PC (IBM Corp. Released 2011). The data were supplied, and suitable analysis was performed for each parameter based on the type of data gathered. (Armonk, NY: IBM Corp., IBM SPSS Statistics for Windows, Version 20.0). For parametric numerical data, descriptive statistics included mean, standard deviation (SD), and range. For non-parametric numerical data, descriptive statistics included median and interquartile range (IQR), as well as frequency and percentage. Analytical statistics included ANOVA test, Student t test and Kruskal-Wallis test (bon ferroni test). Correlation analysis (using spearman's method), Chi-Square test, and ROC Curve (receiver operating characteristic). P-value > 0.05 indicating non-significant (NS), $P \leq 0.05$ indicating significant (S), and $P < 0.01$ indicating highly significant (HS).

RESULTS

There was no statistically significant difference between the three studied groups. As regards personal data (age and sex) (P 0.42 and 0.873 respectively) and CBC parameters including hemoglobin and WBCs (P 0.284 and 0.475 respectively). However, there was a significant difference in platelet count between groups A and C (Table 1).

Table (1): Comparison between three study groups as regards demographic data

		Group						F/x^2	P
		SBP		Cirrhosis with sterile ascites		Cirrhosis without ascites			
		Mean	± SD	Mean	±SD	Mean	±SD		
Age		53.93	7.82	53.23	10.28	50.93	9.3	0.87*	0.42
Gender	Male	16	53.3%	18	60%	17	56.7%	0.27**	0.873
	Female	14	46.7%	12	40%	13	43.3%		

*ANOVA **Chi-Square Tests

The PCT was highest in group (A) with a level of 1.23 ng/l with a highly significant difference between group A (SBP) and both groups B (sterile ascites) and group C (liver cirrhosis without ascites) (p value 0.001). Besides, there was a statistically highly significant difference between the three groups as regards ESR, CRP, PCT and polymorph nuclear cells (PMN) in ascitic fluid (p 0.01), as described in table (2).

Table (2): Comparison between three study groups as regards ESR, CRP, PCT and polymorph nuclear cells (PMN) in ascitic fluid

	SBP (Gr A)	Cirrhosis with	Cirrhosis without	test	P
	Median Mean	Median Mean ±	Median Mean		
ESR (mm)	91	42.5	43	9.3*	**0.0**
CRP (mg/l)	32	6.16	4.05	33	**0.0**
PCT (ng/ml)	0.93	0.13	0.1	47	**0.0**
Ascitic polymorph	372 ± 18.8	175 ± 4.2		9.3**	**0.001**

*Kruskal-wallis test(bon ferroni test) **student t test
a Group A Vs Group B (S), Group A Vs Group C (HS), Group B Vs. Group C (NS) b Group A Vs Group B (HS), Group A Vs Group C (HS), Group B Vs Group C (S) c Group A Vs Group B (HS), Group A Vs Group C (HS), Group B Vs Group C (NS)

In group A, there was a high positive significant correlation between renal function tests (creatinine and urea) and serum PCT (rs values of 0.777 and 0.761 respectively and p value 0.000), as well as a positive significant correlation between the INR and PCT (rs value of 0.360 and p value of 0.05). Whereas, there was non-significant correlation between CBC, albumin, bilirubin, serum alpha fetoprotein (s. AFP) and serum PCT as shown in table (3).

Table (3): Correlations between CBC, liver function test, s. AFP, renal function tests and serum PCT among group A (cases)

	S.PCT	
	r_s	P
HB (gm/dl)	0.321	0.07
PLT (x 10^3/mm^3)	0.334	0.14
WBC (x 10^3/mm^3)	0.276	0.72
Serum albumin (gm/dl)	0.219	0.244
Serum bilirubin (mg/dl)	0.187	0.322
INR	0.360	**0.05**
S.AFP (ng/ml)	0.049	0.798
Serum creatinine (mg/dl)	0.777	**0.000**
Serum urea (mg/dl)	0.761	**0.000**

**Spearman Correlation

Serum PCT and ESR & CRP had a significant positive correlation among group A cases. In addition, a significant positive correlation was found between polymorph nuclear cells (PMN) in ascitic fluid and serum PCT in the same group (SBP) as shown in table (4) and figures (1, 2 & 3).

Table (4): Correlations between ESR, CRP, polymorph nuclear cells in ascitic fluid and serum PCT among group A cases

	S.PTC	
	r_s	P
ESR (mm)	0.437	**0.016**
CRP (mg/l)	0.421	**0.021**
Ascitic polymorph nuclear cells (cell/ mm^3)	0.401	**0.028**

**Spearman Correlation

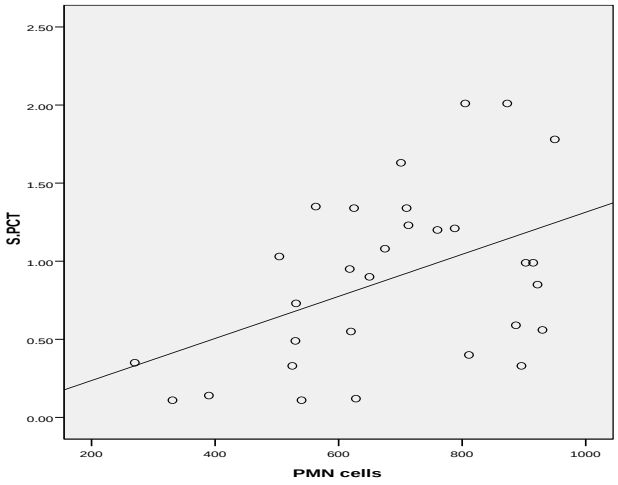

Figure (1): Correlations between polymorph nuclear cells (PMN) in ascitic fluid and serum PCT among group A cases (SBP)

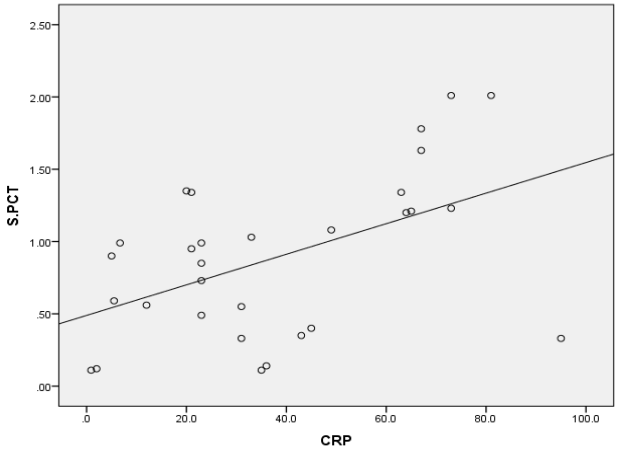

Figure (2): Correlations between serum CRP and serum PCT among group A cases

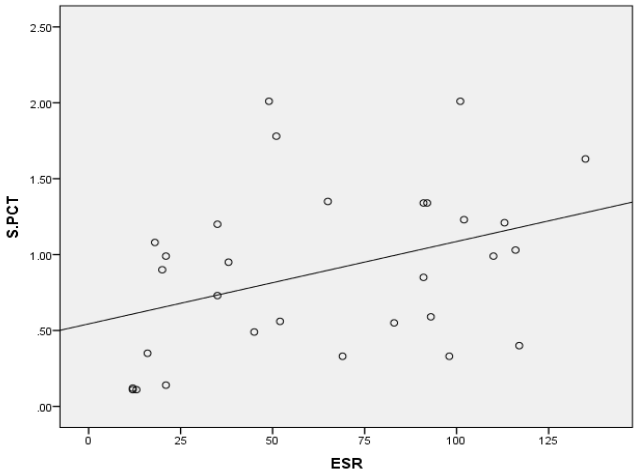

Figure (3): Correlations between serum ESR and serum PCT among group A cases.

Table (5): The sensitivity, specificity, cut of value and accuracy of the serum PCT and CRP for the diagnose of patients with clinical manifestations of suspected spontaneous bacterial peritonitis.

Cutoff level	AUC(CI)‡	Sensitivity	Specificity	PPV*	NPV**	P	Sig
PCT ≥0.315	0.919(0.844 to 0.995	86.67	96.67	96.3	87.9	0.001	HS
CRP ≥16	0.825(0.704 to 0.96)	75.86	90.00	88.0	79.4	0.001	HS

‡Area under curve (confidence interval) *positive predictive value **negative predictive value

Using roc curve, it showed that PCT could be used to discriminate SBP from cirrhotic ascitic cases at a cut off level of ≥ 0.315 with 87% and 97% sensitivity and specificity respectively and AUC value of 0.919.

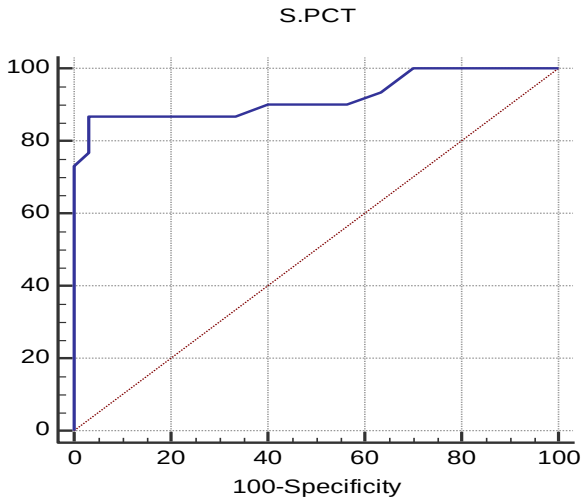

Figure (4): ROC curve using PCT to discriminate SBP from cirrhotic ascitic cases

DISCUSSION

Ascites in cirrhosis has a poor prognosis, with mortality rates of around 40% at one year and 50% at two years. It is also associated with other complications, such as SBP, which was diagnosed by ascetic fluid PMN leukocyte counts > 250/mm^3 **(8).** During the paracentesis procedure, problems may occur, such as the introduction of pathogenic microorganisms into the ascites along with the needle. As a result, a simple-to-use, quick, and reliable diagnostic biomarker as procalcitonin is required **(9).** This study aimed to evaluate the usefulness of measuring serum PCT in patients with liver cirrhosis and ascites for the diagnosis of SBP.

Our study showed that there was no statistically significant difference between the three study groups as regards age and sex (P 0.42 and 0.873 respectively).

As regards, inflammatory markers, our study found that serum procalcitonin levels in SBP patients were significantly higher than in sterile ascites and in cirrhotic patients without ascites, with a P value of 0.001. PCT was better than serum CRP in predicting ascitic fluid infection in cirrhotic patients, with a cut off value of 0.315 ng/ml, sensitivity of 87% and specificity of 97% compared to serum CRP, with a cutoff value of 16 mg/L, sensitivity of 76% and specificity of 90%. This corresponds to the findings of **Viallon *et al.*** **(10)** who observed that procalcitonin levels in serum to be one of the best biomarkers for the diagnosis of SBP, with a cut-off value of 0.75 ng/ml, sensitivity of 95%, and specificity of 98%. In addition, our result comes in accordance with the study of **Yuan *et al.*** **(11)** who found that the concentration of PCT at a cut-off value of 0.48 ng/mL with sensitivity of 95% and specificity of 79% was better than CRP at a cut-off value of 16.15 mg/L with sensitivity of 64% in predicting ascitic fluid infection in cirrhotic patients. Moreover, the study done by **Cekin *et al.*** **(12)** is matching with our results where they reported that at a cut off value of 0.42 ng/mL serum procalcitonin level in patients with cirrhosis-related infected ascites was significantly elevated, with a sensitivity of 78% and specificity of 75%. Additionally, procalcitonin was better than CRP at a cut off value of 17 mg/L in predicting ascitic fluid infection in cirrhotic patients. Moreover, the study done by **Connert *et al.*** **(13)** comes in accordance with our results and demonstrated that serum PCT levels greater than 0.58 ng/mL are a reliable marker of ascitic fluid infection in decompensated cirrhotic patients, with a sensitivity of 92% and specificity of 78%. Whereas, C-reactive protein levels in the blood were unable to distinguish between the presence and absence of a bacterial infection. In addition, our results match with **Wu *et al.*** **(14)** who found that serum PCT level at a cut off value of 0.7 ng/mL with sensitivity of 77% and specificity of 61% was more accurate marker than CRP at a cut off value of 15.53 mg/L with sensitivity of 75% and specificity of 61% in diagnosis of SBP. In contrast to our study, **Lesiska *et al.*** **(15)** reported that serum PCT level with sensitivity of 30% is not a good marker for predicting SBP. This may be because of the small number of patients in this study, which included 22 patients with sterile ascites and 10 patients with SBP. Also, **Spahr *et al.*** **(16)** **(**who carried their study on a total number of 20 cirrhotics with or without spontaneous bacterial peritonitis) found that PCT measurement is not an accurate diagnostic test in SBP, presumably due to the lack of systemic inflammatory response syndrome in this condition and the small number of patients included in this study.

Regarding PMN in ascitic fluid, our study showed a highly significant difference between group A (SBP) and group B (sterile ascites) (p value 0.001). This comes in accordance with the study of **Wu *et al.*** **(14)** who found a significant difference in PMN count in ascitic fluid between patients with SBP and those with sterile ascites (P 0.05).

As regards liver function tests, our results showed that INR levels were significantly increased in the serum of patients with cirrhosis-related infected ascites than in those of non-infected or cirrhotic patients with no ascites (p value 0.001). Furthermore, a highly significant positive correlation between serum procalcitonin and INR was observed. This comes in accordance with the study done by **Paul *et al.*** [17] who reported that INR was significantly higher in patients with SBP compared to those without SBP.

Regarding serum AFP, there was no significant correlation between s. AFP and serum PCT among group A cases (p value 0.798). These findings are consistent with the findings of **Wei *et al.*** [18]**,** who found no significant association between s. AFP and serum PCT in patients with SBP.

CONCLUSION

In cirrhotic patients, serum procalcitonin levels appear to provide a satisfactory diagnostic accuracy in the diagnosis of spontaneous bacterial peritonitis, with a suggested cut-off value of 0.315 ng/ml. Further studies are needed to determine the widespread use of serum PCT as a predictor of SBP clinically.

List of abbreviations:

HCV Hepatitis C virus, ALT Alanine Aminotransferase, AST Aspartate Aminotransferase, INR International Normalized Ratio, AFP alpha-fetoprotein, PMN polymorph nuclear cells, SBP spontaneous bacterial peritonitis, PCT procalcitonin, CRP C-reactive protein.

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