IJMA

International Journal of Medical Arts

Volume 7, Issue 9 (September 2025)

http://ijma.journals.ekb.eg/

P-ISSN: 2636-4174

E-ISSN: 2682-3780

Available online at Journal Website
https://ijma.journals.ekb.eg
Main Subject [Internal Medicine]

Original Article

Role of Serum Homocysteine in Spontaneous Bacterial Peritonitis

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Article information

Received: 27-05-2025

Accepted: 23-06-2025

DOI: 10.21608/ijma.2025.206221.1671

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Citation: Younes MEA, Hashem YA, Ghazy AM, Shaheen MAA, Abdelrazik OM. Role of Serum Homocysteine in Spontaneous Bacterial Peritonitis. IJMA 2025 Sept; 7 [9]: 6045 - 6050. doi: 10.21608/ijma.2025.206221.1671

Abstract

Background: Spontaneous bacterial peritonitis [SBP] is a severe and potentially life-threatening infection that commonly occurs in patients with liver cirrhosis and ascites. The pathogenesis of SBP is not fully understood, but several risk factors have been identified. Recent studies suggest that serum homocysteine levels may play a role in the development and progression of SBP.

Aim of the work: The aim of this study was to investigate the association between serum homocysteine levels and SBP, and to determine if homocysteine can serve as a potential biomarker for the early detection and follow-up of SBP.

Patients and methods: A prospective observational study included 60 patients diagnosed with post-HCV cirrhosis and ascites between May 2022 and May 2023. Participants were divided into two groups: Group I [n=30] consisted of patients without SBP, while Group II [n=30] included those with SBP. Clinical data, severity of hepatic decompensation via MELD and Child–Pugh scores, and laboratory and ascitic fluid analyses were collected. Serum homocysteine levels were measured using ELISA both at baseline and after five days of antibiotic treatment in the SBP cohort.

Results: Serum homocysteine levels were significantly higher in the SBP group before treatment [17.95 ± 5.89 vs. 12.55 ± 4.48, p=0.0002] and decreased after treatment [p=0.005]. ROC analysis indicated that serum homocysteine is a strong diagnostic biomarker [AUC=0.901] with high sensitivity [90.4%] and specificity [93.5%].

Conclusion: Serum homocysteine levels are significantly elevated in patients with spontaneous bacterial peritonitis, indicating its potential as a reliable biomarker for early diagnosis and assessment of liver status in cirrhotic patients.

Keywords: Ascites; Homocysteine; Liver Cirrhosis; Peritonitis.

INTRODUCTION

Spontaneous bacterial peritonitis [SBP] is a severe complication of cirrhosis associated with significant morbidity and mortality [1]. It results from bacterial infection of ascitic fluid in the absence of a surgically treatable source of infection [2].

The overall prevalence of SBP in cirrhotic patients with ascites ranges from 10-30%, making it one of the most common infections in this population [3]. Untreated SBP has an extremely poor prognosis, with reported in-hospital mortality rates approaching 80%. Even with appropriate antibiotic treatment, short-term mortality remains high at 20-40% [4]. SBP exponentially increases the risk of other complications including renal impairment, hepatic encephalopathy, and variceal bleeding. Given its high prevalence and association with deteriorating liver function and mortality, SBP poses a major challenge in the management of patients with advanced cirrhosis [5]. The exact pathogenesis of SBP remains incompletely understood. It is thought to involve translocation of gut bacteria across the intestinal wall, which is facilitated by increased intestinal permeability in advanced cirrhosis. However, the mechanism underlying the increased permeability is still unclear [6].

Homocysteine is a sulfur-containing amino acid derived from methionine through demethylation. Elevated levels of homocysteine, referred to as hyperhomocysteinemia, are associated with oxidative stress and vascular endothelial dysfunction [7]. In addition to its vascular effects, emerging evidence suggests homocysteine may play a role in modulating immune function and the host's susceptibility to infection [8]. Homocysteine has been shown to impair neutrophil chemotaxis, phagocytosis, and intracellular killing ability. It induces neutrophil extracellular trap formation and depletion, altering innate antibacterial defenses [9].

Elevated levels of the amino acid homocysteine have been associated with several complications of liver cirrhosis, including portal hypertension, hepatorenal syndrome, and hepatic encephalopathy [10]. Recent studies suggest homocysteine may also play a role in the pathogenesis of spontaneous bacterial peritonitis [SBP]. Homocysteine is known to impair intestinal barrier function by disrupting tight junctions between intestinal epithelial cells. This could potentially facilitate translocation of gut bacteria into the ascitic fluid, an important first step in SBP development [11-14].

Spontaneous bacterial peritonitis is a severe infection leading to significant morbidity and mortality [15]. Previous studies have suggested a potential association between elevated serum homocysteine levels and increased risk of infectious complications in various diseases [16-18]. However, to date, few studies have specifically investigated the role of serum homocysteine in SBP. Therefore, there is a notable gap in our knowledge regarding the potential involvement of serum homocysteine in the development and clinical outcomes of SBP. This study aims to evaluate the association between serum homocysteine levels and the occurrence, severity, and follow-up of SBP.

PATIENTS AND METHODS

A prospective observational study where 60 patients diagnosed with cirrhosis and ascites were included in this study. Between May 2022 to May 2023, patients were selected from the Department of Hepatology, Gastroenterology and Infectious Disease at Ahmed Maher Teaching Hospital.

The inclusion criteria included patients aged 18 years or older with a diagnosis of post-HCV cirrhosis and ascites. Patients with a history of previous SBP, antibiotic treatment within the past two weeks, or other concurrent infections were excluded. The enrolled participants were assigned to two groups: Group I [n=30] comprised thirty patients without SBP, and Group II [n=30] comprised thirty cases with SBP. The diagnosis of ascites was established through a combination of clinical evaluation, physical examination, and diagnostic investigations [ultrasound]. Diagnosis of HCV was confirmed by positive HCV RNA test. The diagnosis of cirrhosis is determined by considering morphological, clinical, and biochemical factors, as well as endoscopic findings that suggest portal hypertension or indications of advanced liver disease. SBP diagnosis was established by identifying an ascitic fluid polymorphonuclear [PMN] cell count of 250/mm^3 or higher, with a positive bacterial culture [19].

Ethics Considerations: This study was conducted in accordance with ethical guidelines and obtained approval from the Institutional Research Board [IRB] at Faculty of Medicine, Al-Azhar University. Informed consent was obtained from all participants before enrollment in the study.

Data Collection: A thorough patient history was obtained, documenting factors such as age, gender, and presenting symptoms indicative of spontaneous bacterial peritonitis, including abdominal pain and fever. The severity of hepatic decompensation was measured using the MELD scoring system and the Child–Pugh classification [20].

Investigations: The complete blood count [CBC] included measurements of hemoglobin concentration [Hb%], red blood cell [RBC] count, white blood cell [WBC] count, and platelet count. The liver profile assessed levels of alanine aminotransferase [AST and ALT in IU/L], serum albumin [mg/dl], total and direct serum bilirubin [mg/dl], prothrombin time [sec], international normalized ratio [INR], alkaline phosphatase [ALP], and fasting blood glucose [mg/dl].

Analysis of Ascitic Fluid Samples: Following the Infectious Diseases Society of America's guidelines, 10 milliliters of ascitic fluid were centrifuged, and the supernatant was aliquoted and stored at -20 °C. Biochemical analyses included glucose, albumin, and total protein levels. Cytological assessment involved leukocyte count with differential analysis. For bacteriological evaluation, cultures and sensitivity tests were conducted, and follow-up cytological samples were collected from patients with spontaneous bacterial peritonitis after five days of treatment.

Serum homocysteine levels were measured using ELISA both at baseline and after five days[21] of antibiotic treatment [in the SBP cohort].

Pelvi-Abdominal Ultrasonography: Ultrasonography was performed to evaluate the size and echogenicity of the kidneys, liver, and spleen, as well as to assess the presence of ascitic fluid and corticomedullary differentiation in the kidneys.

Statistical analysis: The Social Science Statistical Software [SPSS] version 22 was applied. Continuous variables were expressed as mean ± standard deviation [SD] and analyzed using the t-test, while categorical variables were presented as frequencies and percentages and analyzed using the Chi-square test. Correlation

analyses were conducted to assess relationships between serum homocysteine levels and various clinical parameters before and after treatment. A Receiver Operating Characteristic [ROC] curve was constructed to determine the diagnostic performance of serum homocysteine as a biomarker for SBP, calculating the Area Under the Curve [AUC], sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV] for various cutoff values. P-values < 0.05 were regarded as statistically significant.

RESULTS

The comparative analysis reveals no significant differences in age [p=0.644] or gender distribution [p=0.302] between patients with spontaneous bacterial peritonitis [SBP] and those without. However, fever [66.7%] and abdominal pain [83.3%] are significantly more common in the SBP group [p<0.001], along with a higher occurrence of encephalopathy [p=0.023]. Other clinical manifestations and liver function scores are comparable [Table 1]. Table [2] presents laboratory findings comparing the two studied groups. While hemoglobin levels, platelet counts, and liver enzymes [ALT and AST] show no significant differences between the groups, total leukocyte count [TLC] is significantly higher in the SBP group [p<0.001]. Additionally, albumin levels are lower in SBP patients [p=0.043]. Alkaline phosphatase levels are also significantly elevated in the SBP group [p=0.02]. Table [3] reveals significant differences in ascitic fluid findings between studied patients. The SBP group shows a markedly elevated polymorphonuclear [PMN] cell count [336.51 ± 54.32] compared to the No SBP group [165.2 ± 46.47, p<0.001]. Additionally, albumin levels are higher in the SBP group [0.655 ± 0.351 vs. 0.438 ± 0.147, p=0.003], and neutrophil counts are significantly raised [69.24 ± 12.67 vs. 51.37 ± 18.43, p<0.001]. Other parameters do not show significant differences. Table [4] presents serum homocysteine levels in patients with SBP before and after treatment. Initially, the SBP group exhibits significantly elevated homocysteine levels [17.95 ± 5.89] compared to the No SBP group [12.55 ± 4.48, p=0.0002]. After treatment, homocysteine levels in the SBP group decrease to 14.34 ± 4.63, with a significant reduction confirmed by a paired t-test [p=0.005]. Table [5] summarizes the correlation between serum homocysteine levels and various clinical parameters before and after treatment. Several parameters show significant correlations with homocysteine levels before treatment. Child-Pugh score [r=0.513, p<0.001] and MELD score [r=0.489, p<0.001] are strongly correlated, indicating that higher homocysteine levels are associated with worse liver function. Albumin shows a significant negative correlation [r=-0.382, p=0.003], suggesting that lower albumin levels are associated with higher homocysteine [Table 5]. After treatment, correlations shift slightly but maintain significance for several parameters. ALT [r=0.371, p=0.018] and AST [r=0.332, p=0.009] levels show strong positive correlations with homocysteine. The Child-Pugh [r=0.521, p<0.001] and MELD [r=0.470, p=0.001] scores also continue to show significant positive correlations, reflecting persistent associations between liver function severity and homocysteine levels [Table 5]. The ROC analysis reveals that serum homocysteine is a strong diagnostic biomarker for spontaneous bacterial peritonitis, with an AUC of 0.901, sensitivity of 90.4%, specificity of 93.5%, and impressive negative predictive value of 98.1% [Figure 1].

Table [1]: Demographic and clinical data among studied cases

		SBP [n=30]	No SBP [n=30]	t / χ^2	P
Age [years], mean ± SD		59.32 ± 9.46	58.24 ± 8.54	0.464	0.644
Sex	Male	18 [60%]	14 [46.7%]	1.1	0.302
	Female	12 [40%]	16 [53.3%]		
BMI [kg/m^2], mean ± SD		26.37 ± 3.69	25.58 ± 3.74	0.214	0.831
Clinical manifestations	Fever	20 [66.7%]	5 [16.7%]	15	**<0.001**
	Vomiting	5 [16.7%]	1 [3.3%]	2.96	0.085
	Abdominal pain	25 [83.3%]	6 [20%]	24	**<0.001**
	Diarrhea	3 [10%]	1 [3.3%]	1.1	0.302
	Constipation	15 [50%]	8 [26.7%]	3.46	0.063
	Jaundice	24 [80%]	19 [63.3%]	2.1	0.152
	Splenomegaly	23 [76.7%]	21 [70%]	0.341	0.559
	Bleeding	2 [6.7%]	4 [13.3%]	0.741	0.389
	Encephalopathy	7 [23.3%]	1 [3.3%]	5.19	**0.023**
	Moderate	17 [56.7%]	13 [43.3%]		
	Severe	4 [13.3%]	2 [6.7%]		
Child-Pugh class	B	19 [63.3%]	17 [56.7%]	0.278	0.598
	C	11 [36.7%]	13 [43.3%]		
Child-Pugh score, mean ± SD		12.35 ± 1.3	12.09 ± 1.21	0.802	0.426
MELD, mean ± SD		20.64 ± 4.98	20.14 ± 4.55	0.406	0.686

Table [2]: Laboratory findings of studied cases

	SBP [n=30]	No SBP [n=30]	t	P
Hemoglobin [g/dL], mean ± SD	11.22 ± 1.67	11.81 ± 1.22	1.36	0.18
TLC [× 10^3/L], mean ± SD	12.23 ± 3.41	7.98 ± 2.39	5.6	**<0.001**
Platelets [× 10^3/L], mean ± SD	120.41 ± 40	115 ± 45	0.49	0.62
ALT [U/L], mean ± SD	82.34 ± 27.95	75.27 ± 29.89	0.94	0.35
AST [U/L], mean ± SD	93.52 ± 37.95	89.9 ± 34.66	0.39	0.70
Albumin [g/dL], mean ± SD	2.23 ± 0.826	2.65 ± 0.71	2.1	**0.043**
Total bilirubin [mg/dl], mean ± SD	2.17 ± 0.941	1.85 ± 0.63	1.55	0.13
Alkaline phosphatase [U/L], mean ± SD	228.43 ± 93.22	175.11 ± 79.31	2.39	**0.02**
Creatinine [mg/dl]	1.18 ± 0.525	1.02 ± 0.518	1.19	0. 240

Table [3]: Ascitic fluid findings of studied cases

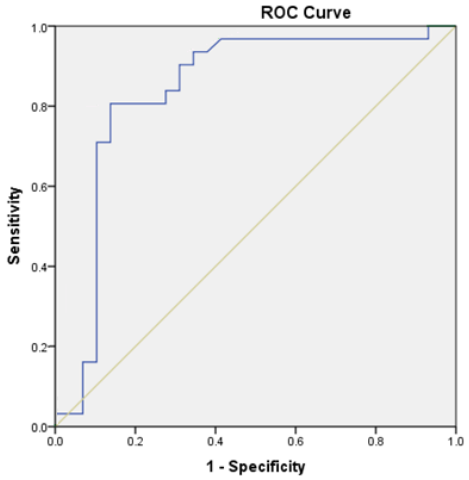
	SBP [n=30]	No SBP [n=30]	t	P
PMN count [cells/µL], mean ± SD	336.51 ± 54.32	165.2 ± 46.47	**13**	**<0.001**
Glucose [g/dL], mean ± SD	148.34 ± 56.71	141.81 ± 35.22	.536	.594
Total proteins [g/dL], mean ± SD	1.32 ± 0.645	1.2 ± 0.481	.817	.417
Albumin [g/dL], mean ± SD	0.655 ± 0.351	0.438 ± 0.147	**3.12**	**0.003**
PH, mean ± SD	7.4 ± 0.352	7.47 ± 0.308	.819	.416
Neutrophil, mean ± SD	69.24 ± 12.67	51.37 ± 18.43	**4.38**	**<0.001**

Table [4]: Serum homocysteine level of the two study groups before and after management

	SBP [n=30]	No SBP [n=30]	t	P
Before treatment				
Serum homocysteine, mean± SD	17.95 ± 5.89	12.55 ± 4.48	4	**0.0002**
After treatment				
Serum homocysteine, Mean± SD	14.34 ± 4.63	--		
Paired t-test	2.66			
P value	**0.005**			

Table [5]: Relationship of homocysteine and other group SBP parameters

Homocysteine	Before treatment		After treatment	
	r	P	r	P
Hb	0.213	0.118	0.159	0.211
TLC	0.367	0.014	***0.211***	***0.047****
PLT	0.156	0.206	0.108	0.322
FBS	***0.332***	***0.021****	0.240	0.052
ALT	***0.264***	***0.029****	***0.371***	***0.018****
AST	***0.210***	***0.033****	***0.332***	***0.009****
Albumin	***-0.382***	***0.003****	***-0.315***	***0.012****
Total bilirubin	***0.271***	***0.025****	0.230	0.063
ALP	***0.326***	***0.017****	***0.392***	***0.026****
INR	0.124	0.221	0.137	0.462
TC	0.193	0.387	0.153	0.144
TG	0.142	0.364	0.224	0.126
LDL	0.176	0.343	0.299	0.103
Creatinine	***-0.253***	***0.039****	***-0.284***	***0.031****
Child-Pugh score	***0.513***	***<0.001****	***0.521***	***<0.001****
MELD	***0.489***	***<0.001****	***0.470***	***0.001****



Cut off	AUC	S.E.	Sig.	95% CI	Sensitivity	Specificity	PPV	NPV
≥14.3 µmol/l	0.901	.058	**<0.001**	0.78 - 1.0	90.4%	93.5%	68.4%	98.1%

CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value.

Figure [1]: ROC curve for serum homocysteine as an early diagnostic biomarker for SBP

DISCUSSION

This study provides compelling evidence that serum Hcy is significantly elevated in patients with SBP and decreases following appropriate antibiotic therapy. This finding supports the hypothesis that Hcy plays a pivotal role not only as a biomarker but potentially in the pathophysiology of SBP.

Our results showed a significant difference in clinical presentation between the SBP and non-SBP groups, especially in symptoms such as abdominal pain, fever, and hepatic encephalopathy.

These findings mirror those of **Makhlouf *et al.*** [22], who also reported abdominal pain as a leading symptom in SBP patients.

In contrast, **Hamed *et al.*** [23] noted no significant clinical differentiation, suggesting variable sensitivity of clinical signs in different patient populations.

Laboratory findings in our cohort revealed elevated TLC, reduced serum albumin, and higher ALP in SBP patients. These markers align with an active inflammatory state and compromised hepatic synthetic function.

These results are comparable to findings by **Abd Ellatif *et al.*** [13], who also demonstrated significant variations in CRP and ESR levels in SBP, although other labs such as liver enzymes were inconsistent across studies.

A major focus of our investigation was on the role of homocysteine in SBP. Elevated Hcy levels in SBP patients [17.95 ± 5.89 µmol/L] compared to non-SBP [12.55 ± 4.48 µmol/L] are consistent with findings by **Abdel-Razik *et al.*** [12] and **Abd Ellatif *et al.*** [13]

Elevated Hcy may contribute to SBP via multiple mechanisms: impairment of gut barrier integrity, enhancement of bacterial translocation, and promotion of systemic inflammatory responses. Additionally, Hcy is implicated in neutrophil dysfunction and oxidative stress, both of which are known contributors to infectious complications in cirrhosis [24, 25].

ROC analysis in our study revealed an AUC of 0.901 for Hcy, with excellent sensitivity [90.4%] and specificity [93.5%] at a cutoff of 14.3 µmol/L. This diagnostic performance surpasses earlier reports by **Hamed *et al.*** [23], whose AUC for Hcy was 0.754, likely due to population differences and assay sensitivity.

Kabeel *et al.* [14] also reported lower cutoff values, highlighting potential variability based on study design and patient selection.

Correlations between Hcy and liver severity indices [Child-Pugh, MELD], inflammatory markers [ALT, AST, TLC], and albumin were strong, confirming its link to hepatic decompensation. The inverse correlation with albumin is particularly notable, as hypoalbuminemia may exacerbate the systemic bioavailability and toxic effects of circulating homocysteine.

From a pathophysiological standpoint, homocysteine may contribute to the hyperdynamic circulation seen in cirrhosis by promoting endothelial dysfunction and nitric oxide overproduction [26, 27]. It also increases the activity of guanylate cyclase and contributes to vasodilation and systemic hypotension. These mechanisms may create a favorable environment for bacterial translocation and infection, reinforcing the clinical association observed in this study [28].

Moreover, studies have shown that endotoxemia and persistent low-grade inflammation in cirrhosis contribute to increased Hcy through inhibition of methionine synthase and other methylation pathways. Elevated circulating endotoxins may upregulate Hcy production and suppress its metabolism, explaining why Hcy levels remain high in the acute setting of SBP [12, 29].

While these findings are promising, limitations must be acknowledged. This is a single-center study with a relatively small sample size, which may limit generalizability. Longitudinal studies assessing Hcy levels post-treatment and recurrence risk could provide further insights into its prognostic value.

In conclusion, this study identifies serum homocysteine as a potential diagnostic and prognostic marker in SBP. Its strong correlation with clinical, biochemical, and inflammatory parameters highlights its relevance in cirrhotic patients. Further research should explore its utility as a target for intervention and its role in the broader immunopathology of liver cirrhosis.

Financial and Non-Financial Relationships and Activities of interest: None.

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IJMA

International Journal of Medical Arts

Volume 7, Issue 9 (September 2025)

http://ijma.journals.ekb.eg/

P-ISSN: 2636-4174

E-ISSN: 2682-3780