Value of Macrophage Inflammatory Protein 1 Beta and Platelet Indices in Diagnosis of Spontaneous Bacterial Peritonitis

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Background and study aim: Spontaneous bacterial peritonitis (SBP) is a serious complication of decompensated liver cirrhosis. It may be presented with atypical symptoms or asymptomatic, so ascitic fluid examination is recommended beside the clinical evaluation for the diagnosis of SBP. This study aimed to evaluate the value of macrophage inflammatory protein Iβ (MIP Iβ) and platelet indices as diagnostic markers for spontaneous bacterial peritonitis.

Patients and Method: This is a cross-sectional study comprised 75 cirrhotic patients. Patients were divided into two groups according to the presence of ascites: group I: Comprising 50 cirrhotic patients with ascites who were classified into: group Ia comprising 25 patients with SBP, group Ib comprising 25 without SBP, and group II: Comprising 25 cirrhotic patients without ascites with other bacterial infections. All patients were subjected to history taking, full clinical examination, ultrasonographic examination; laboratory investigation (complete blood count (CBC), liver, and kidney function tests and serum C reactive protein (CRP)), Diagnostic paracentesis and ascetic fluid examination were done for all ascitic patients. Measurement of MIP Iβ in serum and ascitic fluid was done.

Results: significant increases in CRP, white blood cell count, mean platelet volume (MPV) and platelet distribution width (PDW), were found in SBP group compared to other groups (P<0.001). Serum MIP-1β level at a cut-off value >85 pg/ml could predict presence of SBP, with a sensitivity 100% and a specificity 44%. Ascitic MIP-Iβ at a cut-off value of > 120 pg/ml could predict the presence of SBP with sensitivity 68% and specificity 100%. Cut-off value for MPV was (> 8.5 fl) could predict SBP presence, with sensitivity 76% and specificity 52%. Cut-off value for PDW was (> 15 fl) could predict SBP presence, with sensitivity 84% and specificity 84%.

Conclusion: Serum and ascitic MIP-1β and platelets indices are useful diagnostic biomarkers for spontaneous bacterial peritonitis .

INTRODUCTION

Ascites is the most common complication of liver cirrhosis. Spontaneous bacterial peritonitis (SBP) is considered the most serious bacterial infection in decompensated liver cirrhosis. It represents ascitic fluid infection in the absence of the infection source. Asymptomatic SBP is common as 30% of patients are totally asymptomatic so, diagnostic paracentesis should be done for all patients with ascites on hospitalization **[1, 2]**. The high mortality rate of untreated SBP cases has declined because of early diagnosis and successful therapy of SBP **[3]**. Diagnosis of SBP is done by the presence of PMN leukocyte count of at least 250/mm^2 in ascitic fluid. Manual methods for the count of polymorphonuclear neutrophils (PMNs) consume a long time and have an elevated error rate **[4, 5]**. Positive ascitic fluid culture confirms the diagnosis of SBP, but it is negative in 40% of SBP patients. Due to low concentration of bacteria and there is a mistake to wait 48 hours for culture result before starting SBP

therapy. Therefore, alternative tests for accurate and early diagnosis of SBP are needed **[6]**. The prothrombotic factors linked to inflammatory mediators are produced by platelets and play a role in the starting and spread of inflammation. Multiple granules are present inside large sized platelets and affect their role in hemostasis and inflammation with maximum efficiency **[7]**. So, the mean platelet volume (MPV) and platelet distribution width (PDW) are considered markers of platelet function and activity **[8]**. MIP-Iβ is one of the chemokines family that is produced by macrophages, dendritic cells and activated lymphocytes induced by bacterial toxins. MIP Iβ activates PMN and is involved in acute inflammation. Short half-lives of chemokines make them more suitable for diagnostic purposes than other inflammatory markers. The diagnostic value of MIP Iβ in bacterial infection is inadequately recognized **[9]**. For this respect, the aim of this study was to evaluate the value of serum and ascitic MIP Iβ and platelet indices (MPV and PDW) as diagnostic markers for SBP.

SUBJECTS AND METHODS

Study design:

A cross-sectional study was carried out in Tropical Medicine Department, Zagazig University Hospital during the period from October 2018 to June 2019. The study comprised 75 cirrhotic patients. They were 67 males and 8 females and their age ranged from 45 to 65 years.

Patients were divided into two groups according to presence of ascites:

- **Group I:** Comprised 50 cirrhotic patients with ascites who were classified into:

  Group **I**a: comprised 25 patients with SBP.

  Group **I**b: comprised 25 patients without SBP.

- **Group II:** Comprised 25 cirrhotic patients without ascites with other bacterial infections (chest infection diagnosed by chest x-ray, urinary tract infection diagnosed by urine analysis ... etc).

Inclusion criteria: Cirrhotic patients with or without ascites who were diagnosed by clinical findings, laboratory parameters and radiological investigations.

Exclusion criteria: Patients who had malignancies, connective tissue disorders, end-stage chronic kidney failure, advanced heart failure, chronic obstructive pulmonary disease, HIV and impaired level of consciousness.

Method:

All study patients were subjected to:

1) **Thorough history taking**.
2) **Clinical examination**.
3) **Ultrasonographic examination** was done for all patients using esoate MY Lab 20 plus machine.
4) **Laboratory investigation** (CBC, liver and kidney function tests, ESR 1st hour and serum CRP). Platelet indices; mean platelet volume (MPV) and platelet distribution width (PDW) were measured.
5) **Diagnostic paracentesis** was done for all patients with ascites under complete aseptic conditions. Ascitic fluid was examined: Color and aspect, 20 ml was inoculated into two blood culture bottles (10 ml for aerobic and 10 ml for anaerobic) immediately at bedside using a new sterile needle, 1 ml was injected into a purple top EDTA blood-drawing tube for traditional manual cell counting of PMN, 10 ml was injected into red top blood-drawing tube for chemistry of ascitic fluid (Albumin, protein content, Glucose And LDH), 10 ml for determination of MIP-1β.
6) **Macrophage Inflammatory Protein-1-Beta "MIP-1β" (both in serum and ascitic fluid)** was measured by enzyme-linked immunosorbent assay "ELISA" kits supplied by TECAN Infinite F50 ELIZA Reader (Singapore). (5 ml of blood and 10 ml of the ascitic fluid were allowed to clot in room air for 10 – 20 min then centrifuged at the speed of 2000 – 3000 rpm for 20 min and the supernatant was removed, Serum samples were kept at - 80°C till the time of the assay). These samples were used for the assessment of ascitic MIP-1β.

Statistical Analysis

The data were tabulated and statistically analyzed using and SPSS version-24 software package. The comparison was done using One-way Anova test or (F) test, Kruskal-Wallis "KW" test is a non-parametric alternative to the one-way ANOVA test for independent measures,

Chi-square χ^2 test for significance for the difference between more than two proportions. Fisher's exact test used to determine whether there are nonrandom associations between two categorical variables. Sensitivity, Specificity, Positive predictive value "PPV" and Negative predictive value "NPV" were detected. Calculations of the optimized cutoff points for inflammatory markers of SBP were done using the Receiver Operating Characteristic (ROC) curve. Also, area under the curve (AUC) was calculated. The statistical significance level was set at 5% (P<0.05).

RESULTS

41 The demographic data of the study population are presented in (Table 1). There was no statistically significant difference between the study groups regarding age and sex (P-value > 0.05).

Clinical data of the study groups are presented in (Table 2). Fever was the most common symptom in groups (Ia and II) with a statistically significant difference compared with groups Ib (p-value = 0.003). GI bleeding was the common symptom in groups (Ia and Ib) with a statistically significant difference compared with group II patients (p-value = 0.001). There was no significant difference between the study groups regarding abdominal pain and abdominal tenderness (p-value = 0.14 and 0.65, respectively). Jaundice was more frequent in group Ia with a statistically significance difference compared with group II (p-value = 0.03).

The culture of ascitic fluid in patients with SBP was positive in 13 (52%) patients. The causative organisms were *E. coli* in 7 patients, *Klebsiella* in 4 patients and *S. aureus* in 2 patients (Table 3).

There was a significant increase in WBCs count, platelet count, platelet indices (MPV and PDW) and serum level of MIP Iβ in groups Ia and II compared with the group Ib (p-value <0.001, p-value = 0.001 and p-value <0.001 respectively). Serum level of CRP was significantly increased in group Ia patients compared with the other groups under study. ESR at 1st hour was increased in group Ia without a significant difference compared with groups Ib and II (p-value = 0.429 and 0.272, respectively) (Table 4).

Patients with SBP in group (Ia) had significantly higher ascitic MIP-1β, TLC, PMN, Albumin and significant lower glucose level and protein content in comparison with those in group (Ib) (Table 5).

Serum MIP-1β had a significant positive correlation with other laboratory parameters in SBP patients (WBCs, MPV, PDW, CRP, Ascitic MIP-1β and PMN count) and a significant negative correlation with platelet count. Platelet indices (PDW and MPV) had a significant positive correlation with other laboratory parameters (WBCs, MPV, serum and ascitic MIP-1β, CRP, ascitic TLC count, ascitic PMN cells count and ascitic proteins) (Table 6).

Serum MIP-1β level at cut off value > 85 pg/ml could predict presence of SBP, with sensitivity 100%, specificity 44%. MPV at cut off value > 8.5 fl could predict presence of SBP with sensitivity 76%, specificity 52%. While, PDW at cut off value > 15 fl could predict the presence of SBP with sensitivity 84%, specificity 84% (Table 6 and figure 1).

Ascitic MIP-1β level at cut off value > 120 pg/ml could predict presence of SBP, with sensitivity 68%, specificity 100%, PPV 100% and NPV 75% with overall accuracy 84% (Table 7 and figure 2).

Table (1): Demographic data of the studied groups.

Variable	Group (Ia) N = 25	Group (Ib) N = 25	Group (II) N = 25	F test	p- value
Age (Years):					0.4
- Mean ± SD	52.4 ± 4.5	50.8 ± 6.2	52.6 ± 4.2	0.9	NS
	N (%)	**N (%)**	**N (%)**		
Sex:					
- Male	23 (92.0%)	22 (88.0%)	23 (92.0%)	0.32	0.3
- Female	2 (8.0%)	3 (12.0%)	2 (8.0%)		NS

Table (2): Clinical findings of studied groups.

Variable	Group (Ia) N = 25	Group (Ib) N = 25	Group (II) N = 25	X^2	p- value
	N (%)	N (%)	N (%)		
Presenting Symptoms					
Fever:					
- Yes	18 (72.0%)	6 (24.0%)	14 (56.0%)	11.9	0.003 [a, c]
- No	7 (28.0%)	19 (76.0%)	11 (44.0%)		
GI Bleeding:				7.78	
- Yes	9 (36.0%)	6 (16.0%)	0 (0.0%)		0.005 [b, c]
- No	16 (64.0%)	19 (84.0%)	25 (100.0%)		
Abdominal pain:					
- Yes	7 (28.0%)	3 (12.0%)	9 (36.0%)	3.95	0.14
- No	18 (72.0%)	22 (88.0%)	16 (64.0%)		NS
Presenting Signs					
Jaundice:					
- Yes	10 (40.0%)	6 (16.0%)	2 (8.0%)	7.01	0.03 [b]
- No	15 (60.0%)	19 (84.0%)	23 (92.0%)		
Abdominal Tenderness:					
- Yes	6 (24.0%)	1 (4.0%)	7 (28.0%)	5.44	0.65
- No	19 (76.0%)	24 (96.0%)	18 (72.0%)		NS

a: group (Ia) vs group (Ib); **b:** group (Ia) vs group (II); **c:** group (Ib) vs group (II)

Table (3): Culture of ascitic fluid in patients with Spontaneous bacterial peritonitis (SBP).

Variable	Group (Ia) N = 25
Culture:	
- Positive	13 (52.0%)
- Negative	12 (48.0%)
Causative Bacteria:	
- *E. coli*: N (%)	7 (53.8%)
- *Klebsiella*: N (%)	4 (30.7%)
- *Staph. Aureus*: N (%)	2 (15.5%)

Table (4): Laboratory data of the studied groups.

Variable	Group (Ia) N = 25	Group (Ib) N = 25	Group (II) N = 25	F test	p- value
Hemoglobin: (g/dl) - Mean ± SD	9.7 ± 0.8	9.9 ± 0.7	10.1 ± 1.3	0.9	0.42 NS
WBCs: (10^3cell/cm^3) - Mean ± SD	15.0 ± 2.7	6.08 ± 1.2	14.2 ± 2.0	145.5	<0.001 a, c
Platelets: (10^3cell/cm^3) - Mean ± SD	100 ± 19	130 ± 21.7	145 ± 22	29.93	<0.001 a, b, c
MPV: (fl) - Mean ± SD	10.96 ± 2.9	5.5 ± 1.3	8.4 ± 1.26	49.5	<0.001 a, b, c
PDW: (fl) - Mean ± SD	25.28 ± 8.8	8.08 ± 1.7	13.3 ± 2.2	59.6	<0.001 a, b, c
Total Bilirubin: (mg/dl) - Mean ± SD	2.5 ± 0.4	1.7 ± 0.6	1.8 ± 0.7	14.1	<0.001 **a, b**
S. ALT: (IU/L) - Mean ± SD	81.24 ± 6.7	62.6 ± 7.1	55.6 ± 8.3	66.7	<0.001 **a, b, c**
S. AST: (IU/L) - Mean ± SD	83.6 ± 4.8	71.4 ± 6.8	65.9 ± 7.4	49.6	<0.001 **a, b, c**
Total Protein:(g/dl) - Mean ± SD	5.6 ± 0.3	5.6 ± 0.7	6.1 ± 0.3	7.8	0.001 **b, c**
S. Albumin:(g/dl) - Mean ± SD	2.7 ± 0.42	3.1 ± 0.39	3.5 ± 0.67	15.4	<0.001 **a, b, c**
S. Creatinine: (mg/dl) - Mean ± SD	2.04 ± 0.28	1.6 ± 0.25	1.45 ± 0.24	35.5	<0.001 a, b, c
INR: - Mean ± SD	2.1 ± 0.67	1.7 ± 0.49	1.61 ± 0.67	4.484	0.015 **a, b**
Serum MIP-1β: (pg/ml) - Mean ± SD	157.04 ± 53.9	119.9 ± 52.5	144.8 ± 51.3	3.247	0.045 a, c
CRP: (cell/cm^3) - Mean ± SD	68.08 ± 17.8	22 ± 7.4	36.2 ± 7.05	99.14	<0.001 a, b, c
ESR 1st hour: (cell/cm^3) - Mean ± SD	33.0 ± 12.1	29.4 ± 7.1	32.8 ± 12.7	0.857	0.429 NS

a: group (Ia) vs group (Ib); **b:** group (Ia) vs group (II); **c:** group (Ib) vs group (II)
MIP Iβ: macrophage inflammatory protein I beta

Table (5): Ascitic fluid analysis and MIP-1β among ascetic patients.

Variable	Group (Ia) N = 25	Group (Ib) N = 25	KW test	p- value
Ascitic MIP-1β: (pg/ml) - Mean ± SD	289.2 ± 155.3	52.36 ± 35.04	14.3	<0.001 HS
TLC: (cell/cm^3) - Mean ± SD	519.2 ± 192.5	245.6 ± 148.6	21.0	<0.001 HS
PMN: (cell/cm^3) - Mean ± SD	900 ± 434.01	139.2 ± 125.5	33.4	<0.001 HS
Protein: (mg/dl) - Mean ± SD	1140.8 ± 712.5	1828.4 ± 860.4	9.471	0.003 S
Albumin: (mg/dl) - Mean ± SD	1097.0 ± 534.2	704.9 ± 416.04	6.861	0.009 S
Glucose: (mg/dl) Mean ± SD	79.45 ± 24.73	110.4 ± 48.95	7.962	0.007 S

KW Kruskal-Wallis test

Table (6): Correlation of serum MIP-1B and platelet indices with other laboratory parameters in patient with SBP.

	Serum MIP-1β(pg/ml)		**PDW**(fl)		**MPV**(fl)	
	r	**P**	**r**	**P**	**r**	**P**
Hemoglobin (g/dl)	- 0.297	0. 112	- 0.28	0.176	- 0.03	0.885
RBCs (10^3cell/cm^3)	- 0.305	0.07٩	- 0.358	0.079	- 0.068	0.745
WBCs (10^3cell/cm^3)	0. 592	0.008	0.454	0.021	0.492	0.012
Platelets (10^3cell/cm^3)	- 0.613	0.001	- 0.101	0.416	- 0.218	0.076
PDW (fl)	0.436	0.005			0.551	0.0٠6
MPV(fl)	0.545	0.003	0.551	0.006		
Creatinine (mg/dl)	0.277	0.114	0.16	0.446	0.27	0.192
Bilirubin (mg/dl)	0.348	0.18	0.316	0.124	0.821	<0.001
ALT (IU/L)	0.289	0.276	0.247	0.095	0.063	0.769
AST (IU/L)	0.253	0.167	0.268	0.101	0.091	0.814
Albumin: (g/dl)	0.171	0.415	0.06	0.777	0.271	0.19
Total Protein: (g/dl)	- 0.274	0.184	-0.113	0.592	- 0.328	0.109
Serum MIP-1β : (pg/ml)			0.436	0.005	0.545	0.003
CRP (cell/cm^3)	0.579	0.003	0.604	0.001	0.527	0.006
ESR (cell/cm^3)	0.133	0.525	0.245	0.238	0.184	0.379
Ascetic MIP-1β : (pg/ml)	0.741	<0.001	0.635	0.001	0.622	0.001
Ascetic TLC: (10^3cell/cm^3)	0.064	0.76	0.469	0.018	0.427	0.013
Ascetic PMN: (10^3cell/cm^3)	0.644	0.001	0.497	0.020	0.432	0.026
Ascetic Protein : (g/dl)	0.085	0.685	0.513	0.009	0.527	0.009

WBCs: *White blood cells* MPV: mean platelet volume MIP Iβ: macrophage inflammatory protein I beta
PDW: platelet distribution width CRP: C-reactive protein PMN**:** poly morph nuclear

Table (7): Reliability data for clinical performance of serum and ascitic fluid inflammatory markers as predictors of SBP.

Variable	**Cut off**	**AUC**	**p-value**	**PPV**	**NPV**	**Sensitivity**	**Specificity**	**Accuracy**
Serum inflammatory markers								
Serum MIP-1β	>85 pg/ml	0.864	<0.045	64.1%	100.0%	100.0%	44.0%	72.0%
MPV	> 8.5 fl	0.885	<0.001	61.3%	68.4%	76.0%	52.0%	64.0%
PDW	> 15 fl	0.972	<0.001	84.0%	84.0%	84.0%	84.0%	84.0%
Ascitic inflammatory markers								
Ascitic MIP-1β	>120pg/ml	0.811	<0.001	100%	75%	68%	100.0%	84.0%

AUC: area under curve **PVP:** positive predictive value
NPV: negative predictive value MIP Iβ: macrophage inflammatory protein I beta

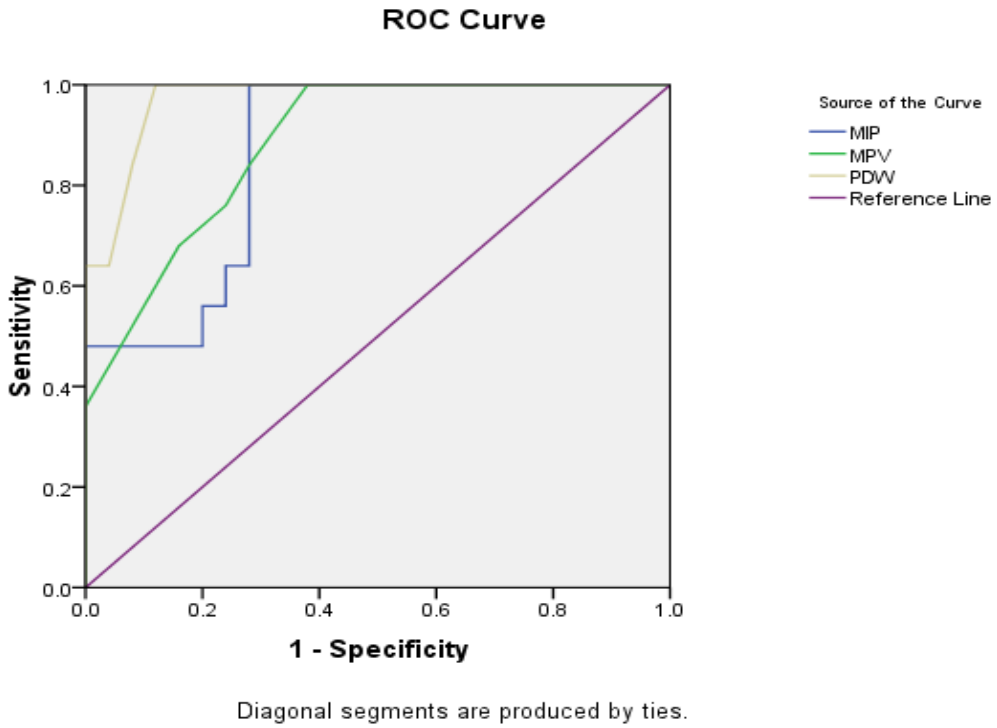

Figure (1): Receiver operating curve (ROC) for serum inflammatory markers as predictors of SBP.

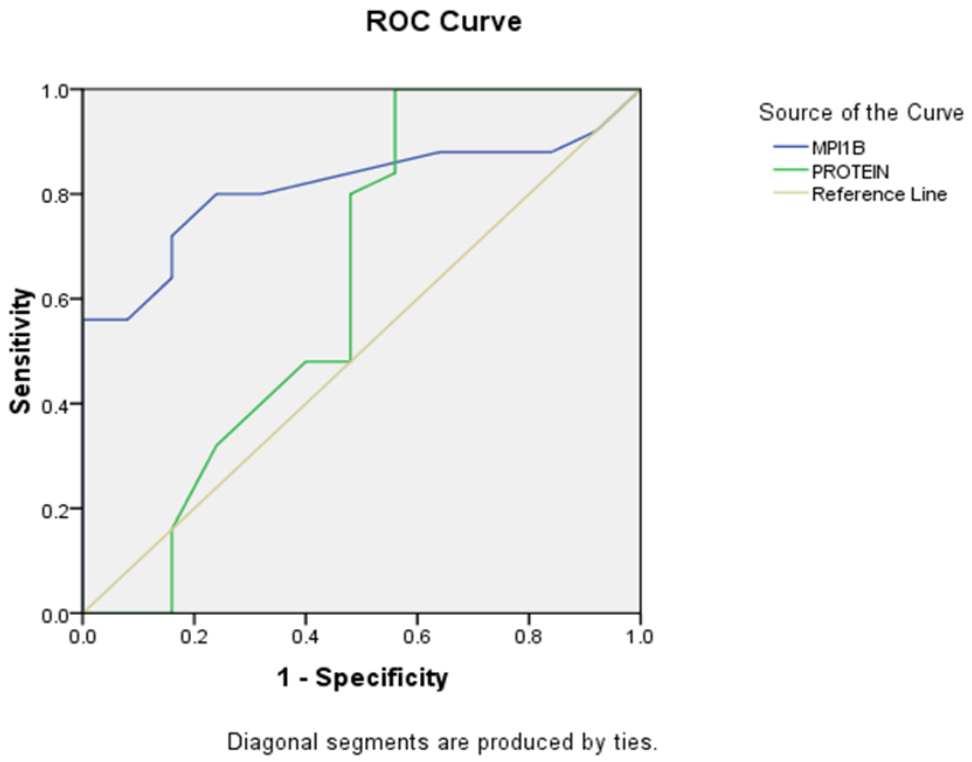

Figure (2): Receiver operating curve (ROC) for ascetic fluid markers as predictors of SBP.

DISCUSSION

Spontaneous bacterial peritonitis is the most serious complication of bacterial infections in patients with decompensated liver cirrhosis, so rapid diagnosis and prompt treatment of this condition is essential to prevent serious morbidity and mortality. This study assessed the role of serum and ascitic MIP-Iβ and platelet indicators (MPV and PDW) in the diagnosis of SBP.

This study revealed that fever was the commonest clinical presentation recorded in 72% of SBP patients and followed by jaundice in 40% of patients. GI bleeding was reported in 63% of patients. These results agreed with the results of Căruntu and Benea **[10]** and Mohammad et al. **[11]**. Our study revealed that 20% of patients were asymptomatic. These results were in agreement with those of Wallerstedt et al. who reported that asymptomatic patients of SBP constitute a relatively high percentage **[12]**.

The present study revealed that among SBP group culture was positive in 52% of patients. The isolated organisms were *E. coli, Klebsiella* and *Staphylococcus aureus* (53.8%, 30.7%, 15.5%) respectively. This result was in agreement with Khorshed et al., who reported that only 30% of SBP patients were culture positive and the isolated organisms were *E. coli, Klebsiella, Staphylococcus aureus* and *Pseudomonas* (60%, 26%, 7% and 7%) respectively **[13]**. On the other hand, Lesiriska et al. reported that culture was negative in 100% of 10 studied patients with SBP **[9]**. This difference can be attributed to the difference in population samples. In the study of Lesiriska et al., most of the patients were alcoholic cirrhosis, while in this study all patients were cirrhotic due to HCV. Furthermore, this difference may be due to the difference in the volume of cultured fluid, which has dramatically impact on the concentration of bacteria and sensitivity of ascitic fluid culture **[4].** In this study the sample of cultured ascitic fluid was 20 ml. but in the other study ascitic fluid sample was 5 ml.

This study revealed that there was a significant increase in the platelet indices (MPV and PDW) in SBP group compared to the other study groups (p- value <0.001). This result was in accordance with that of Abdel-Razik et al. **[14].** On the other hand, these results disagreed with those reported by ***Suvak et al.*** who concluded that there was a significant increase in MPV in patients with SBP. Meanwhile, PDW was not significantly increased in patients with SBP **[8]**. Also, the study conducted by El kafoury et al., revealed no significant differences in MPV and PDW between the studied groups with and without SBP. MPV showed significant increase in SBP patients when compared with other groups, while PDW was higher in SBP patients but no significant difference **[15]**.

The MPV and PDW are indicators of platelet activation and inflammatory sequelae during the occurrence of SBP. The increase in MPV and PDW in patients with SBP can be explained by that there are variable sized platelets, the platelet destruction in the spleen and the increased interleukin 6 (IL6) levels in cirrhotic patients that lead to more variable sized platelet formation by the bone marrow and this leads to increase MPV and PDW **[8, 16].**

In this work, C-reactive protein (CRP) was high in all groups under study, but it was significantly elevated in the group of SBP compared to other groups. Elevated CRP in our patients can be explained by that CRP is an acute phase protein produced by the liver in response to infection and it has been considered an indicator of SBP **[2].** Also, Preto-Zamperli et al., and Kadam et al. reported that the serum and ascitic fluid level of CRP was increased in SBP **[17, 18]**. On the other hand, Lesińska et al. reported that there was no significant difference between groups under study regarding CRP **[19]**. This difference can be explained by different population sample size.

The level of ESR at 1st hour was elevated in all groups under study, but with no significant difference between them. These findings run parallel to those reported by El kafoury et al. **[15]** and Metwally et al. **[20].**

Our study revealed that there was a highly significant increase in ascetic MIP-1β level in SBP cases (p-value < 0.001). This result was nearly similar to those of Lesiriska et al. **[9]** who reported that there was a significant increase in ascetic MIP-1β in SBP patients (p-value < 0.01). These results were explained by that the ascitic MIP 1β was secreted from the peritoneal macrophage in case of SBP **[9]**.

Regarding the serum level of MIP-1β, our study revealed that it was significantly high in patients with SBP and cirrhotic patients with infections

other than SBP. These results were in a partial agreement with the results of Khorshed et al. who reported that the serum level of MIP1β was increased in patients with SBP **[13]**. Also, this result is in concord with that of Holub et al. **[21]** who showed that the serum MIP1β was significantly high in community- acquired bacterial infections. This can be explained by the fact that serum MIP-1β is generated by circulating monocytes or extrahepatic macrophages not only get from infected ascitic absorbed from peritoneal cavity to systemic circulation (700- 900ml)/ day **[9]**.

Receiver operating characteristic curve (ROC) analysis in this study revealed that, ascitic and serum MIP-1β at cutoff values of (120, 85 pg/ml) respectively, could diagnose SBP and serum levels of MIP-1β showed lower diagnostic yield. This agreed with Khorshed et al. who reported that, ascitic and serum MIP-1β at cutoff values of (121.9, 85.2 pg/ml) respectively, could detect SBP **[13]**.

Our study revealed that the optimal cutoff values of serum MPV and PDW were (> 8.5 fl and > 15 fl) respectively, for the diagnosis of SBP. This result was consistent with the findings of Abdel-Razik et al. **[14]** who reported that cutoff value of MPV and PDW for the diagnosis of SBP were (8.77 fl and 17.8 fl) respectively.

CONCLUSION

Ascitic and serum MIP-1β and platelet indices (MPV and PDW) are valuable and could help the early diagnosis of asymptomatic cases and ascitic fluid culture-negative cases of SBP.

Ethical approval: An informed written consent was obtained from the studied patients. All procedures were approved by Zagazig University Institutional Review Board (IRB), the ethical committee of Zagazig University Hospitals.

Conflict of Interest: None declared.

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