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Original article

The role of absolute neutrophil count, mean platelet volume and lymphocyte monocyte ratio as a simple blood markers in the diagnosis and prediction of treatment response in spontaneous bacterial peritonitis in Egyptian cirrhotic patients

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ABSTRACT

Background and aim: A potentially fatal side effect of decompensated liver cirrhosis is ascites. One potentially dangerous consequence in cirrhotic individuals with ascites is spontaneous bacterial peritonitis (SBP). Diagnostic paracentesis is a method used to diagnose SBP, although it is an invasive procedure. Numerous noninvasive markers were investigated in SBP diagnosis. Thus, this study aimed to assess the clinical utility of the noninvasive markers for the diagnosis and treatment response in patients with SBP, namely the lymphocyte monocyte ratio (LMR), mean platelet volume (MPV), and absolute neutrophil count (ANC). **Patients and methods:** This study included 162 cirrhotic patients was conducted. They were divided into 2 groups, group I included 101 cirrhotic patients with SBP and group II included 61 cirrhotic patients without SBP. ascitic fluid sampling and complete blood count (CBC) including ANC, LMR and MPV were done. **Results:** There was a significant difference between the 2 groups as regard ANC and LMR (p<0.05). In SBP group there was a significant difference in ANC, LMR, MPV before and after the standard\antibiotic treatment. Absolute neutrophil count had sensitivity 79.21%, specificity 63.93% However, the LMR had sensitivity 91.09 %, specificity 68.85 % and MPV had sensitivity 83.17%, specificity 62.30%. When ANC, LMR and MPV were combined, the sensitivity was 91.10% and specificity was 91.80%. **Conclusion:** This study suggests that the ANC, MPV, and LMR may be utilized as noninvasive markers for the diagnosis of SBP and prediction of treatment response, enabling prompt detection of SBP to minimize its consequences.

Introduction

A dangerous side effect of decompensated liver cirrhosis is ascites, although numerous pathogenic mechanisms have been linked to the development of ascites, it is most likely that 75% of cases arise from portal hypertension in the context of liver cirrhosis, with the remaining cases coming from inflammatory, infiltrative, and infectious processes [1]. One potentially dangerous consequence that might arise in cirrhotic patients with ascites is spontaneous bacterial peritonitis (SBP). About 10 to 30 percent of patients with cirrhosis develop SBP [2].

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About 40 to 70 percent of patients with SBP often die, with a hospital mortality rate of roughly 20 percent. Bacterial translocation, increased intestinal permeability, changes in the gut microbiota are the causes of SBP [3]. Furthermore, the immune system dysfunction seen in advanced cirrhotic patients may play an important role [4].

The late onset of symptoms, high recurrence rate, and various pathogenic organisms are the key reasons for the relevance of SBP [5]. When assessing the severity and necessity for admission to an intensive care unit for various infections, including SBP, the blood neutrophil count has diagnostic validity [6].

Moreover lymphocyte monocyte ratio (LMR) is a crucial indicator of systemic inflammatory reactions. They serve as a crucial indicator of how well the immunological and inflammatory systems are balanced. Prothrombotic substances, which are inflammatory indicators and play an essential role in the inflammatory cascade, are prevalent in circulating platelets [7].

Mean platelet volume (MPV) is regarded as a measure of platelet function and activation because the platelet content of granules increases as platelet size increases, enabling them to carry out their hemostatic and pro-inflammatory actions more effectively. According to certain research, MPV is associated with higher risk of myocardial infarction, cerebrovascular illness, Alzheimer's disease, hypertension, and celiac disease [8]. The diagnosis of SBP is still based on diagnostic paracentesis, despite the fact that numerous invasive and non-invasive indicators have been investigated as diagnostic techniques. [9].

Diagnostic paracentesis, however, is an intrusive procedure that requires additional non-invasive diagnostic equipment due to its numerous risks, including wound infection, abdominal wall hematoma, and spontaneous hemoperitoneum [9]. Therefore, the purpose of this study is to assess the clinical importance of MPV, LMR, and ANC as new, easy- to use, affordable, non- invasive biochemical indicators for diagnosis and therapy response prediction in SBP patients.

Patients and methods

This case control study included 162 cirrhotic patients with or without SBP who attended to Tanta tropical medicine department, faculty of medicine, after obtaining institutional ethical approval (approval code: 36154/12/22) and following the provisions of ethical guidelines of the 1975 declaration of Helsinki. The diagnosis of cirrhosis was made on the basis of clinical, laboratory, ultrasound (US) findings , while we excluded patients who had any cause of sepsis other than SBP (e.g., chest infection and urinary tract infection) , non-cirrhotic ascites (e.g., malignant ascites, tuberculous ascites) , acute hepatic failure , hepatic encephalopathy, taken antibiotics prior to hospital admission or on anticoagulant drugs , renal or heart failure, malignant disorders , autoimmune diseases and secondary bacterial peritonitis due to any surgical causes.

After obtaining informed consent all enrolled patients were divided into 2 groups, group I included 101 cirrhotic patients were diagnosed with SBP and group II included 61 cirrhotic patients without SBP as a control group .

All patients were subjected to full history taking, thorough clinical examination, ultrasound on abdomen and pelvis.

Patients were defined clinically according to the modified Child -Turcotte-Pugh classification

Laboratory investigations were done for all patients included the following: ascitic fluid sampling (10 ml) under complete aseptic technique using the standard paracentesis technique, before beginning the procedure, ensure the patient's urinary bladder is empty, it is recommended to use the left lower quadrant of the abdominal wall as the entry point for the needle. This location is considered the safest and most favorable due to the thinner abdominal wall and deeper pocket of fluid, cleanse the skin with an antiseptic solution, administer local anesthesia to the skin then insert the needle attached to a syringe directly perpendicular to the skin or use the z-track method, which is thought to decrease the chance of fluid leakage after the procedure.

Apply negative pressure to the syringe during needle insertion until a loss of resistance is felt and a steady flow of ascitic fluid is obtained. After collecting sufficient fluid in the syringe for fluid analysis, either remove the needle and hold pressure to stop bleeding from the insertion site [11].

The sample of ascitic fluid was sent for biochemical analysis. In accordance with global criteria, SBP was identified when the ascitic fluid's polymorph nuclear neutrophil (PMN) cell count was ≥250/mm3, regardless of whether an ascitic fluid culture was positive., in the absence of secondary

peritonitis and hemorrhagic ascites, was used to establish the diagnosis of SBP [12].

Ten milliliters of blood were taken from patients in EDTA tubes (purple top) at admission and then examined for the following: complete blood count (CBC) analysis which was performed in hematology laboratory of Tanta university hospital. ANC, LMR and MPV were calculated using routine laboratory tests.

MPV measurement should be done within 2 h of blood sampling because MPV increases when platelet swell in EDTA [13]. So CBC analysis was performed within 2 h after blood samples were taken with automated hematology analyzer, also, liver function tests, renal function tests and INR were done for all patients. Another paracentesis were done after 48 h of initial treatment to check the response to treatment, Response to antibiotic treatment is defined as a 25% reduction in PMN count.

In SBP group, ascitic fluid sampling, CBC including ANC, MPV and LMR were re-evaluated at the 5th day of antibiotic treatment . After a primary episode of SBP, the recurrence rate at one year is approximately 70%, with a 1-year overall survival rate of 30 to 50% among persons who do not receive antibiotic prophylaxis. Secondary antibiotic prophylaxis in a person with cirrhosis who has a prior history of SBP reduces the risk of SBP recurrence from 68% to 20%. Accordingly, most experts recommend daily long-term antimicrobial prophylaxis for persons with a history of one or more episodes of SBP[14].Several studies have shown that oral norfloxacin 400 mg daily prevents SBP in persons with low-protein ascites and those with previous history of SBP [15].

Statistical analysis of the data

Data were fed to the computer and IBM SPSS software package version 20.0 was used to analyze the data (Armonk, NY: IBM Corp). Categorical data were represented as numbers and percentages. Chi-square test was used for investigating the relationship between the categorical variables. Conversely, they were tested for normality by the Kolmogorov- Smirnov test. Quantitative data were expressed as range (minimum and maximum), mean, standard deviation and median Student t-test was used to compare two groups for normally distributed quantitative variables. On the other hand Mann Whitney test was employed to compare two groups for not normally distributed quantitative variables. Wilcoxon signed ranks test for abnormally distributed quantitative variables, to compare between two periods while paired t-test for normally distributed quantitative variables, to compare between two periods. Significance of the obtained results was judged at the 5% level.

Results

This Study included 162 cirrhotic ascetic patients. They were categorized into 2 groups : group 1 included 101 patients diagnosed with SBP and group 2 included 61 patients were cirrhotic without SBP as a control group who were no significant difference in age and sex among the two groups and according to the Child-Pugh classification, 17 (16.8%) of the patients were Child B, and 84 (83.2%) patients were child C in the SBP group while 12 (19.7%)of the patients were Child B and 49 (80.3%) patients were Child C in the control group as shown in **table (1).** As regard blood biochemical parameters, there were a statistically significant increase in ascetic total leucocytic count (TLC) , ascetic fluid neutrophil , blood TLC, monocyte, lymphocyte, ANC and INR in group1 ($p<0.05$) ,while there was a significant decrease in LMR ,platelet count and serum albumin in group 1($0<0.05$) but there wasn't a statistically significant difference in MPV, ALT, AST and total bilirubin as demonstrated in **table (2).**

The patients in SBP group were evaluated before and after the standard antibiotic showed a statistically significant increase in ascetic total leucocytic count (TLC) , ascetic fluid neutrophil , blood TLC, monocyte, lymphocyte, ANC and INR before treatment ($p<0.05$) ,while there was a significant decrease in LMR ,platelet count and serum albumin pretreatment ($p<0.05$) but there wasn't a statistically significant difference in MPV, ALT, AST and total bilirubin **(Table 3).** ROC curve analysis was applied to determine the best non-invasive marker that could evaluate the treatment response and to determine the cut-off value for them. After ROC curve analysis, the best cut-off value for ANC was found to be >4.2 (103/cmm) with sensitivity 79.21%, specificity 63.93%, positive predictive value 78.4%, and negative predictive value 65.0 % .However, the best cut-off value for LMR was found to be ≤2.1 with sensitivity 91.09 %,specificity 68.85 %,positive predictive value 82.9%, and negative predictive value 82.4% . But cut-off value for MPV was >8.5 fl with sensitivity 83.17%, specificity 62.30%, positive predictive value 78.5 %, and negative predictive value 69.1% as shown in **table (4)** and **figure (1).**

Additionally, multivariate binary logistic regression analysis was employed in assessing the prognostic performance for ANC, LMR and MPV. When ANC, LMR and MPV were combined together, the sensitivity (91.10%), specificity (91.80%), PPV (94.85%) and NPV (86.15%) as shown in **table (5)** and **figure (2).**

Table 1. Demographic and clinical characteristics of the studied groups.

	Group 1 (SBP) (n = 101)	**Group 2 (control group) (n=61)**	***P* value**
Age Mean ± SD	56.7 ± 8.6	58.6 ± 7.3	0.140
Sex Male	62 (61.4%)	35 (57.4%)	0.614
Female	39 (38.6%)	26 (42.6%)	
Child score			
Child B	17 (16.8%)	12 (19.7%)	0.648
Child C	84 (83.2%)	49 (80.3%)	
Median (Min. – Max.)	10 (9 – 14)	10 (9 – 12)	
Splenomegaly			
Yes	50 (49.5%)	32 (52.5%)	0.716
No	51 (50.5%)	29 (47.5%)	

SD: Standard deviation,, *p: p* value for comparing between the two studied groups , *: Statistically significant at $p \leq 0.05$

Table 2. Laboratory parameters of the studied groups.

	Group 1 (SBP) (n = 101)	**Group 2 (control group) (n=61)**	***P* value**
TLC In ascitic fluid(cell/mm3) Median (Min. – Max.)	700 (450 – 3750)	241 (90 – 350)	<0.001*
Ascitic fluid neutrophil (cell/mm3) Median (Min. – Max.)	580 (315 – 3000)	180 (50 – 240)	<0.001*
Hemoglobin (g/dl) Mean ± SD.	10 ± 0.7	10.1 ± 0.7	0.409
TLC (10^3/cmm) Median (Min. – Max.)	10 (4.7 – 19)	6.3 (4.6 – 9.8)	<0.001*
ANC (10^3/cmm) Median (Min. – Max.)	7.40 (2.20 ± 16)	3.9 (2.3 – 7.5)	<0.001*
Lymphocyte (10^3/cmm) Mean ± SD.	1.6 ± 0.2	1.5 ± 0.1	0.031*
Monocyte (10^3/cmm) Mean ± SD.	0.8 ± 0.1	0.7 ± 0.1	<0.001*
LMR Mean ± SD.	1.84 ± 0.26	2.2 ± 0.1	<0.001*
MPV(7-9)fl Mean ± SD.	10.15 ± 1.28	9.66 ± 9.82	0.626
Platelets (10^3) Median (Min. – Max.)	98 (24 – 252)	120 (51 – 240)	<0.001*
ALT (U/L) Median (Min. – Max.)	34 (13 – 767)	36 (20 – 90)	0.218
AST (U/L) Median (Min. – Max.)	59 (12 – 848)	45 (18 – 101)	0.064
Total bilirubin(mg/dl) Median (Min. – Max.)	2.3 (0.7 – 26.9)	2 (0.9 – 12)	0.052
INR Median (Min. – Max.)	1.8 (1 – 3.3)	1.5 (1 – 3)	0.002*
Serum albumin (g/dl) Median (Min. – Max.)	2.5 (1.9 – 3.1)	3 (2.3 – 3.8)	<0.001*
Serum Creatinine (mg/dl) Median (Min. – Max.)	1.5(0.9 – 2.8)	1.1(0.8 – 1.3)	<0.001*

ALT: alanine aminotransferase, AST: aspartate aminotransferase, ANC: Absolute neutrophil count, TLC :total leucocytic count ,INR: international normalized ratio, LMR :Lymphocyte to monocyte ratio, MPV: Mean platelet volume. , FL: femtoliters..

Table 3. Laboratory parameters in group 1(SBP) pre-treatment and post treatment (n= 101).

	Pre treatment	**Post treatment**	***P* value**
TLC In ascitic fluid (cell/mm3) Median (Min. – Max)	700(450 – 3750)	189(35 – 500)	<0.001*
Ascitic fluid neutrophil(cell/mm3) Median (Min. – Max.)	580 (315 – 3000)	126 (15 – 250)	<0.001*
Hemoglobin (g/dl) Mean ± SD.	10 ± 0.7	9.8 ± 0.9	0.124
TLC (10^3/cmm) Median (Min. – Max.)	10 (4.7 – 19)	6.3 (4.6 – 9.8)	<0.001*
ANC (10^3/cmm) Median (Min. – Max.)	7.40 (2.20 ± 16)	4 (2 – 7.9)	<0.001*
Lymphocyte (10^3/cmm) Mean ± SD.	1.6 ± 0.2	1.5 ± 0.1	0.206
Monocyte (10^3/cmm) Mean ± SD.	0.8 ± 0.1	0.7 ± 0.1	<0.001*
LMR Mean ± SD.	1.84 ± 0.26	2.3 ± 0.1	<0.001*
MPV fl Mean ± SD.	10.15 ± 1.28	8.3 ± 0.7	<0.001*
Platelets (10^3) Median (Min. – Max.)	98 (24 – 252)	100(50-366)	0.080
ALT (u/l) Median (Min. – Max.)	34 (13 – 767	31 (10 – 100)	0.997
AST (u/l) Median (Min. – Max.)	59 (12 – 848)	45(18 – 102)	0.067
Total bilirubin(mg/dl) Median (Min. – Max.)	2.3 (0.7 – 26.9)	2 (0.6 – 12)	0.360
INR Median (Min. – Max.)	1.8 (1 – 3.3)	1.6 (1 – 3)	0.034*
Serum albumin (g/dl) Median (Min. – Max.	2.5 (1.9 – 3.1)	2.6 (1.8 – 23)	0.203

ALT: alanine aminotransferase, AST: aspartate aminotransferase, ANC: Absolute neutrophil count, TLC :total leucocytic count ,INR: international normalized ratio, LMR :Lymphocyte to monocyte ratio, MPV: Mean platelet volume, FL: femtoliters

Table 4. Prognostic performance for ANC, LMR and MPV in diagnosis and prediction of treatment response in SBP.

	AUC	**P**	**95% C.I**	**Cut off**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
ANC	0.795	<0.001*	0.729 – 0.862	>4.2	79.21	63.93	78.4	65.0
LMR	0.915	<0.001*	0.865 – 0.964	≤2.1	91.09	68.85	82.9	82.4
MPV	0.859	<0.001*	0.800 – 0.917	>8.5	83.17	62.30	78.5	69.1

AUC: Area Under a Curve , *p* value: Probability value , CI: Confidence Intervals NPV: Negative predictive value , PPV: Positive predictive value, * Statistically significant at $p \leq 0.05$

Table 5. Prognostic performance for combination ANC & LMR and MPV in diagnosis and prediction of treatment response in SBP:

	AUC	P	95% C.I	Sensitivity	Specificity	PPV	NPV
ANC , LMR and MPV	0.965	<0.001 *	0.936 – 0.994	91.10	91.80	94.85	86.15

Figure 1. ROC curve for ANC, LMR and MPV in diagnosis and prediction of treatment response in SBP.

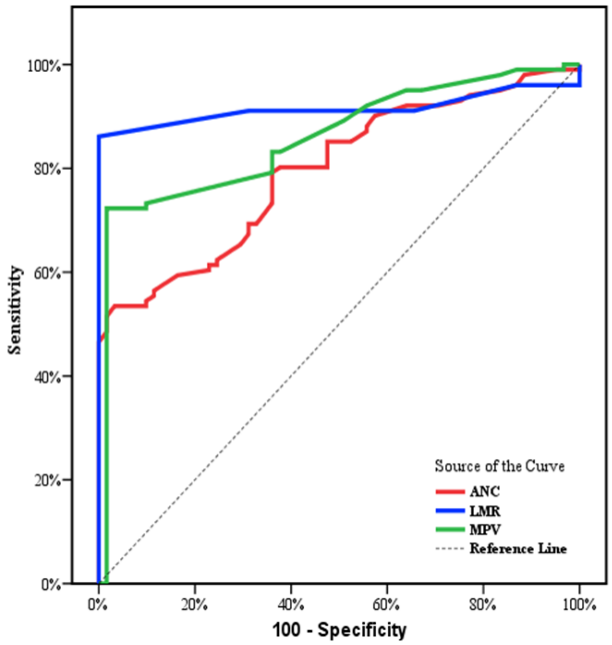
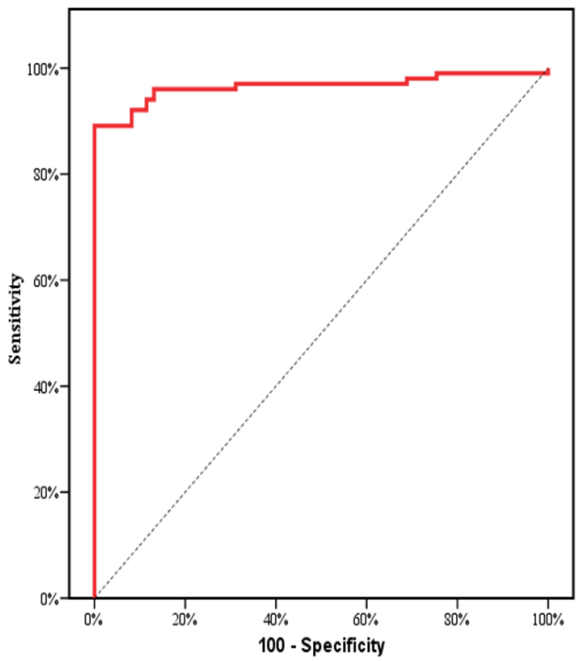


Figure 2. ROC curve for ANC, LMR and MPV in diagnosis and prediction of treatment response in SBP.



Discussion

Spontaneous bacterial peritonitis (SBP) is a bacterial infection affects ascitic fluid without any suspected source of intra-abdominal infection. In spite of improvement in treatments, SBP remains associated with a mortality as high as 20%, as well as high recurrence rates after initial infection [16].

So early detection and treatment of SBP are very crucial, as it is associated with better results and reduce mortality rate. On the other hand, diagnosis of SBP is established when the fluid absolute neutrophil count is greater than 250 cells/ mm3 and is further confirmed with positive cultures [17]. This method of diagnosis is an invasive, time-consuming, and operator-dependent approach [18].

Delaying paracentesis by 12 hours resulted in a 2.7-fold increase in odds of death. Therefore clinicians should perform paracentesis as soon as possible [19,20]. Therefore, in order to improve results, it is imperative to create a quick, easy, affordable, objective, and reliable approach for diagnosing SBP [21].

This was the goal of our study to evaluate the role of ANC ,MPV and LMR as simple blood markers in the diagnosis and prediction of treatment response in spontaneous bacterial peritonitis.

Regarding ANC on comparing the group of SBP patients and the control group our study showed a highly statistically significant increase (p<0.001), also on comparing the ANC of the patients before treatment and after treatment of SBP ,there was a highly statistically significant increase (p<0.001) .ROC curve analysis was applied to determine the best cut off value for ANC that could evaluate the treatment response and to determine its sensitivity and specificity. After ROC curve analysis, the best cut-off value for ANC was found to be >4.2 (103/cmm) with sensitivity 79.21%, specificity 63.93%, positive predictive value 78.4%, and negative predictive value 65.0 %.

These results can be attributed to the fact that, white blood cells (leukocytes) are a defence line against bacterial infection. The most abundant leukocytes are neutrophil, which are the first line of defence against microbial invasion [22].Moreover, absolute neutrophil count can be used as a predictive factor for infections ,in general, bacterial infection is suspected if neutrophil in the blood are increased [23]. These were consistent with **Sheta et al.**'s findings [24], which indicated that patients with SBP had ANC at a considerably higher rate than those without SBP. Additionally, they discovered that ANC can distinguish SBP from nonSBP with 84% sensitivity and 78% specificity at a cutoff point of >2.804, with AUC equal to 0.88 and positive and negative predictive values of 79.4% and 83.6, respectively.

Similar ideas have been presented in other studies [25-27] which corroborate our findings regarding the blood neutrophil count's diagnostic value as a non-invasive test for the detection of various illnesses. Another parameter in our study was the LMR. We found a highly statistical significant decrease (p<0.001) between the SBP group and the non SBP group and also a highly statistical significant decrease (p<0.001) among the patients before treatment and after treatment ,a ROC curve analysis showed the best cut-off value for LMR to detect the presence of SBP was found to be ≤2.1 with sensitivity 91.09 %,specificity 68.85 %,positive predictive value 82.9%, and negative predictive value 82.4% .

These results can be justified as LMR are an important index of systemic inflammatory responses. They are an important marker for the balance of inflammatory and immune systems. **Piotrowski et al.** showed that LMR was the greatest obvious indicator of bacterial infection in people with cirrhosis. They reported that LMR was significantly lower in patients with infection than in those without infection [28].

Our results agreed with those of **Barutcu et al. who** also found LMR was significantly lower in patients with culture negative neutrocytic ascites (CNNA) than in patients without ascitic fluid infection and was significantly higher after treatment [29].

Our study also assessed MPV's contribution to the diagnosis and efficacy of treatment for SBP. An indication of platelet activation is MPV.Compared to small platelets, large platelets exhibit

higher levels of metabolic and enzymatic activity. In addition to their hemostatic role, they contribute to inflammation through the release of chemokines and the activation and recruitment of neutrophils to infection and injury sites. **Galvez-Martinez et al.** found that MPV may be used as a predictor of systemic inflammatory response in cirrhotic patients with CNNA [30]. However in our study there was no statistically significant difference between the SBP group and the non SBP group p (>0.6). this disagree with the results of Abudeif et al

who found that patients with SBP had significantly higher MPV levels than those without SBP (p < 0.001) [31].

But regarding the comparison of MPV levels among the patients before and after treatment of SBP our study showed a highly statistically significant variation (p<0.001). When ROC curve analysis was done a cut-off value for MPV was determined >8.5 FL(femtoliters) with sensitivity 83.17%, specificity 62.30%, positive predictive value 78.5 %, and negative predictive value 69.1%. This cut off value came close to that reported by Abudeif et al which was 8.8 FL as well as other studies [31-35].

Our findings also agreed with those of **Barutcu et al.** who found that MPV level was statistically significantly lower after antibiotic treatment in CNNA patients [29].

Furthermore, multivariate binary logistic regression analysis was used to evaluate prognostic performance for ANC , LMR and MPV. When ANC , LMR and MPV were combined together, the sensitivity (91.10%), specificity (91.80%), PPV (94.85%) and NPV (86.15%) .Our study was the first to combine those markers together which improved the sensitivity, specificity and predictive values of each individual marker.

Conclusion

According to our current study , the ANC, MPV and LMR may be used as a novel, easy, cheap, non-invasive markers in the diagnosis of SBP and also in prediction of treatment response which require only routine laboratory test and this will allow rapid diagnosis and treatment of SBP and this may help to reduce its fatal complications.

Abbreviations:

ANC: absolute neutrophil count.

MPV : mean platelet volume .

LMR: lymphocyte monocyte ratio.

SBP :spontaneous bacterial peritonitis.

CNNA :culture negative neutrocytic ascites.

TLC :total leucocytic count.

Hb: Haemoglobin concentration.

WBCs: White blood cells.

ALT: Alanine aminotransferase.

AST: Aspartate aminotransferase .

INR : International Normalized Ratio)

FL: femtoliters

US: ultrasound

SD: Standard deviation.

ROC: Receiver operating characteristic curve.

Ethical approval

Ethics committee approval was received for this study from the Institutional Review Board of Tanta Faculty of Medicine (approval code: 36154/12/22 and following the provisions of ethical guidelines of the 1975 declaration of Helsinki.

Consent for publication: each participant provided a written informed consent.

Availability of data and material: All data and material of the article are readily available on reasonable request.

Authors contributions

All authors had direct exposure to the study data and read and agreed with the final text.

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Declaration of competing interest

There are no conflicts of interest related to this study.

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