Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://dx.doi.org/10.21608/zumj.2022.143729.2582 Volume 28, Issue 6, November 2022(365-373) Supplement Issue
Manuscript ID ZUMJ-2206-2582 (R4)
DOI **10.21608/zumj.2022.143729.2582**

ORIGINAL ARTICLE

Neutrophil to Lymphocyte Ratio as a Predictor for Spontaneous Bacterial Peritonitis in Patients with Cirrhotic Ascites

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Submit Date 2022-06-13
Revise Date 2022-06-26
Accept Date 2022-06-24

ABSTRACT

Background: The most prevalent infection in cirrhotic individuals is spontaneous bacterial peritonitis (SBP). Acute GI bleeding, a history of SBP, or low ascetic fluid protein contents are all risk factors for the development of SBP in cirrhotic individuals. The purpose of this study was to see if the neutrophil-to-lymphocyte ratio (NLR) could predict spontaneous bacterial peritonitis in individuals with liver cirrhosis. **Patients and methods**: This prospective, case-control and observational study was conducted at Internal Medicine Department, Zagazig University Hospitals during the period from June 2021 to March 2022. The study included 100 cirrhotic patients. The patients were divided into two groups: Group I included 50 cirrhotic patients with SBP (case group) and group II included 50 cirrhotic patients without SBP (control group). Neutrophil to lymphocyte ratio was calculated for all patients. **Results**: In this study, there was statistically significant difference between the two studied groups in neutrophil count, lymphocyte count and increased neutrophil to lymphocyte ratio (group 1 had increased neutrophils and decreased lymphocytes than group 2). **Conclusion**: We can conclude the clinical utility of NLR as a biomarker predictive factor in the occurrence of spontaneous bacterial peritonitis (SBP) .

Key words: Spontaneous bacterial peritonitis, neutrophil-to-lymphocyte ratio, Chronic liver, Neutrophil

INTRODUCTION

Cirrhosis of the liver is the terminal stage of all chronic liver disorders. And it is the 11th most common cause of death, accounting for 1.16 million fatalities per year. The consequences of liver cirrhosis are the leading cause of death in these people**[1].**

Viral infections, chemical damage, autoimmune and metabolic illnesses are all possible causes of liver injury **[2].**

According to the studies, people with liver cirrhosis are more susceptible to bacterial infection. The chance after admission is 25-35 percent [3]. This risk is 4-5 times higher than the overall population's risk[4]. The most prevalent infections in cirrhosis include urinary tract infection, pneumonia, spontaneous bacterial peritonitis (SBP), and sepsis. However, different studies around the world show varied proportions of these illnesses**[5].**

In patients with cirrhosis and ascites, spontaneous bacterial peritonitis (SBP) is one of the most common bacterial infections, occurring in 10% to 30% of these people [6].

The incidence of SBP in cirrhosis has been estimated to be 20% on average, with a mortality rate of more than 50% **[7,8] .**

Bacterial infections are a common cirrhosis complication [9]. They account for 25% to 46% of cirrhotic patients' hospitalizations due to acute decompensation episodes and associated with significant morbidity and mortality [10]. The risk of death post bacterial infections more than quadruple the risk of death in patients with

decompensated cirrhosis, with a 30% mortality rate after the first month and a 63% mortality rate after the first year[11].

The neutrophil-to-lymphocyte ratio (NLR) is a simple and affordable diagnostic method of systemic inflammation in individuals with liver disease [12]. The lymphocyte count indicates the immune regulatory mechanism and the neutrophil count helps to identify ongoing inflammation [13,14].

The diagnostic issues arise from the fact, which the symptomatology of individuals with SBP ranges from the presence of usual signs to their absence. As a result, quick identification and appropriate treatment can help to lower the rate of adverse outcomes [8]. The purpose of this study is to determine the role of neutrophil-to-lymphocyte ratio (NLR) as a predictor of spontaneous bacterial peritonitis (SBP) in patients with cirrhosis of the liver at Zagazig University Hospitals.

PATIENTS AND METHODS

Following permission from the ethical clearance committee and verbal agreement from all patients. A prospective, case-control, and observational study was carried out at the Internal Medicine Department of Zagazig University Hospitals from June 2021 to March 2022. The study included 100 cirrhotic patients. Approval to conduct the study was obtained from the research committee of faculty of medicine, Zagazig University (IRB# 8066-4-10-2021). The work was done in conformity with the World Medical Association's Code of Ethics (Declaration of Helsiniki 1979) for human studies.

Inclusion criteria: Males and females between the ages of 18 and 65. Patients who are cirrhotic and ascetic, with or without spontaneous bacterial peritonitis. **Exclusion criteria:** Patients who are pregnant. Patients suffering from ascites caused by causes other than cirrhosis, such as congestive heart failure and abdominal TB. Patients with peritonitis caused by intra-abdominal surgery or other infectious causes (respiratory or urinary). Patients refuse to give consent.

The patients were separated into two groups: 50 cirrhotic patients with spontaneous bacterial peritonitis (SBP) and 50 cirrhotic patients without SBP.

All patients were subjected to Demographic data taking, complete clinical examination for detection of stigmata of liver cell failure, jaundice, ascites, splenomegaly, hepatic encephalopathy…. etc. Ultrasonography for diagnosis of cirrhosis as a shrunken liver (small and nodular), enlarged spleen and portal hypertension (dilated portal vein, hilar varices), ascites and HCC. Laboratory investigations included Complete Blood Count (CBC) by Sysmex XS (Sysmex Corporation, Japan). PT and international normalized ratio (INR) by Sysmex CS 2100 coagulometer (Sysmex Corporation, Japan). Liver function tests including serum albumin and total bilirubin, AST, ALT by Roche Cobas 8000-c702 (Roche Diagnostics, Germany). Kidney function tests including serum creatinine and blood urea nitrogen (BUN) by Roche Cobas 8000-c702 (Roche Diagnostic, Germany).

On admission, a complete blood count (CBC) with automated differential counts of neutrophils and lymphocytes was performed to determine the Neutrophil-to-Lymphocyte Ratio (NLR). The neutrophil-to-lymphocyte ratio was computed by dividing the neutrophil count by the lymphocyte count from the same automated blood samples.

The diagnosis of SBP was made in accordance with European criteria, namely polymorph nuclear leukocytes (PMNs) ≥ 250 cells/mm^3 (0.25 x 10^9/L) ± WBC ≥ 500/ml in ascetic fluid sample**[4].**

Statistical analysis :

All data were collected, tabulated and statistically analyzed using SPSS 20.0 for windows (SPSS Inc., Armonk, NY, USA).

RESULTS

Table 1; showed that no statistical significance between the two groups as regard sex,and age. 67 (67%) males and 33 (33%) (M: F, 1:7.5) females their age was range from (18 to 65 years) with mean age 50.5±11.41 years, who had Fine Needle Aspiration Cytology (FNAC). There is no statistically significant difference between patients as regard past history of chronic disease (P > 0.05).

Table 2; showed that there is no statistically significant difference between patients as regard past Clinical presentation (P

> 0.05), As regard liver and spleen but high significance as regard ascites, and hepatic encephalopathy.

Table 3; that there was showed statistical significance as regard White Blood Cell Scintigraphy (WBCs), high significance as regard, Hemoglobin (HB), and platelate (PLT) count.

Table 4; that there was statistically significant difference between the two studied groups in neutrophils count, lymphocytes count and increased neutrophils to lymphocytes ratio (group**1** had increased neutrophils and decreased lymphocytes than group **2**).

Table 5; shows no significance as regard alanine transaminase (ALT), **aspartate aminotransferase** (AST), Total Serem Billrubin (TSB) and albumin, high statistical significance as regard international normalized ratio (INR) and prothrombin time test (PT).

Table 6; shows high statistical significance as regard kidney function test.

There was statistically significant positive correlation between ascetic fluid polymorgh and Neutrophil-lymphocyte ratio (NLR) **Figure 1**.

The results derived from the ROC curve showed that cut off value of neutrophil-to-lymphocyte ratio (NLR) ≥4.8 at this point sensitivity and specificity (91.3 and 90.4; respectively) **Figure 2**.

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

Demographic data	Group 1 (N=50)		Group 2 (N=50)		p-value (Sig.)
	No.	%	No.	%	
Sex					
Male	35	70%	32	64%	0.451 (NS)
Female	15	30%	18	36%	
Age (years)					
Mean ± SD	52.96 ± 7.64		49.09 ± 11.07		0.052 (NS)
Smoking					
NO	21	42%	30	60%	0.096 (NS)
YES	29	38%	20	40%	
Co-morbidities					
Diabetes					
YES	32	64%	25	50%	0.4397 (NS)
No	18	36%	25	50%	
Hypertension					
No	49	98%	50	100%	1.000 (NS)
Yes	1	2%	0	0%	
Others					
IHD Renal Thyroid	4 3 5	8% 6% 10%	8 6 6	16% 12% 12|%	0.4397 (NS)
No	38	76%	30	60%	

IHD; Ischemic Heart Disease.

Table (2): Clinical presentation of the studied groups.

Clinical presentation	Group 1 (N=50)		Group 2 (N=50)		p-value (Sig.)
	No.	%	No.	%	
Hematemesis					
No	32	64%	36	72%	
Yes	18	36%	14	28%	
Abdominal pain					
No	15	30%	35	70%	0.389

Yes	35	70%	15	30%	(NS)
Hepatic encephalopathy					
Absent	38	76%	50	100%	<0.001 (HS)
Present	12	24%	0	0%	
Fever					
Absent	28	56%	50	100%	
Present	22	44%	0	0%	
Jaundice					
No	32	64%	36	72%	
Yes	18	36%	14	28%	
HCC					0.369 (NS)
NO	48	96%	49	98%	
YES	2	4%	1	2%	

HCC; Hepatic Cell Carsenoma.

Table (3): Complete blood picture of the studied groups.

Complete blood picture	Group 1 (N=50)	Group 2 (N=50)	p-value (Sig.)
WBCs (x10^3/mm^3)			
Mean ± SD	9.67 ± 4.64	7.86 ± 3.31	0.041 (S)
Hb (gm/dl)			
Mean ± SD	9.39 ± 1.11	12.29 ± 1.84	<0.001 (HS)
Plt count (x10^3/mm^3)			
Mean ± SD	82.73 ± 32.20	139.11 ± 44.20	<0.001 (HS)

WBC; With Blood Cell. Hb; Hemoglobin. PLt; Platelet.

Table (4): Comparing neutrophils to lymphocytes ratio (*NLR*) between the studied groups:

	Group 1 (N=50)	Group 2 (N=50)	F-test	p-value (Sig.)
Neutrophils count **mean ± SD** **Range**	7.9±1.11* (5.2-9.3)	6.6±0.5 (2.8-9.2)	20.7	0.003*
Lymphocytes count **mean ± SD** **Range**	1.28±0.2* (1.1-2.0)	1.55±0.3 (1.1-2.2)	Kruskal wallis test=12.1	0.001**
NLR	6.3±1.5* (3.3-8.4)	4.3±1.2 (2.3-7.9)	20.7	0.001**

****Statistically highly significant difference (P ≤ 0.001)**
***Statistically significant difference (P ≤ 0.05)**
****Statistically highly significant difference (P ≤ 0.001)**
NLR; Neutrophils Lymphocytes Ratio.

Table (5): Liver function test of the studied groups, INR, and PT.

Liver function test	Group 1 (N=50)	Group 2 (N=50)	p-value (Sig.)
ALT (IU/L)			
Mean ± SD	39.40 ± 12	31.55 ± 9.1	0.389 (NS)
AST (IU/L)			
Mean ± SD	37.7 ± 11.6	29 ± 10.1	0.234 (NS)
TSB (mg/dl)			
Mean ± SD	4.59 ± 1.58	2.13 ± 0.42	0.456 (NS)
Albumin (gm/dl)			
Mean ± SD	2.77 ± 0.51	2.85 ± 0.54	0.0543 (NS)
INR			
Mean ± SD	2.00 ± 0.46	1.13 ± 0.15	<0.001 (HS)
PT			
Mean ± SD	16.75 ± 1.982.	13.75 ± 1.982.	<0.001 (HS)

ALT; Alanine Aminotransferase.
AST; Aspartate Aminotransferase.
TSB; Total Serum Bilirubin.
INR; International Normalized Ratio.
PT; Prothrombin Time.

Table (6): Kidney function test of the studied groups.

Kidney function test	Group 1 (N=50)	Group 2 (N=50)	p-value (Sig.)
Creatinine (mg/dl)			
Mean ± SD	1.73 ± 0.99	0.84 ± 0.20	<0.001 (HS)
Urea (mg/dl)			
Mean ± SD	80.21 ± 36.90	30.70 ± 3.57	<0.001 (HS)

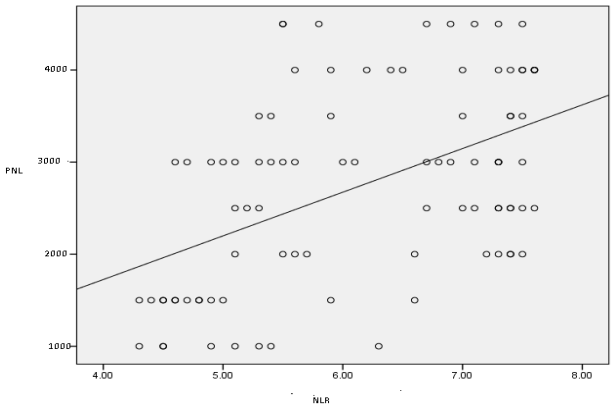
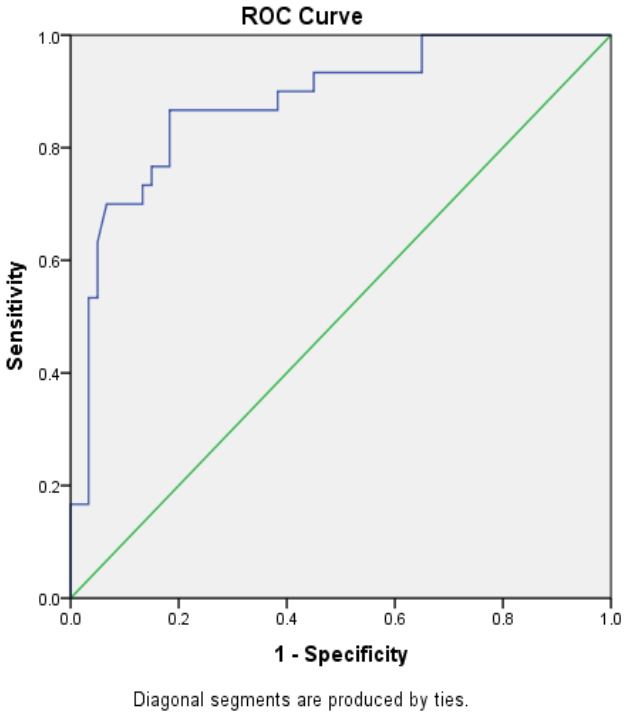


Figure 1. Scatter plot between Neutrophil-lymphocyte ratio (NLR) and ascetic fluid polymorgh (PNL) among the studied group there was statistically significant positive correlation between ascetic fluid polymorgh and NLR**.**



Variable	Cut off	AUC	P	95% CI
NLR	>4.8	0.88	<0.001**	0.83-0.95

Figure (2): Area under ROC curve of neutrophils to lymphocytes ratio between patients with SBP and patients without SBP

DISCUSSION

As a regard of demographic data, the highest percentage of studied patients in group 1 was males (70%) with mean age of 52.96 years old and in group 2 was 64% with mean age of 49.09 years old, with no statistical significance between the studied groups as regard of sex and age. Also, our data were similar to the results of **Metwally et al. [15]** who investigated the potential of various clinical and laboratory factors to predict the development of SBP in Egyptian cirrhotic ascites patients.

Popoiag et al. [16] discovered the clinical and molecular variables linked to SBP this study comprised 216 individuals with hepatic cirrhosis; 72 (33.3 percent) had SBP and 144 did not (66.67 percent). SBP patients were 33.3 percent female and 66.7 percent male, with a mean age of 59.29 years. Patients without SBP were 34.7 percent female and 65.3 percent male, with a mean age of 62.23 years. There were no significant variations in age or gender between the studied groups.

In terms of age, there is a link between being older and being more susceptible to illnesses as one's immune system deteriorates. Furthermore, age is a risk factor for most liver diseases, increasing morbidity and death as compared to younger patients **[17]**.

As a regard of patient comorbidities, patients suffered from liver cirrhosis with different comorbidities, 32 patients (64%) in group 1 and 25 patients (50%) in group 2 were diabetic. One patient (2%) was hypertensive in group 1 only. Other comorbidities were found including ischemic heart disease and renal and thyroid disorders. Statistically, there is no significant difference between patients as regard past history of chronic diseases. **Popoiag et al. [16]** Patients without SBP exhibited a higher proportion of cardiac comorbidities than SBP patients (42.4 vs. 25 percent). There were no significant differences in pulmonary, renal, digestive, or metabolic comorbidities between the two groups. Metwally et al. [15] discovered no statistically

significant difference between the presence and absence of diabetes mellitus.

Diabetics comprised 58% of our patients (58/100). According to Mehta et al. [18], the adjusted risk of decompensated cirrhosis was greater in diabetic patients compared to nondiabetic patients. As regard patient presentation, patients with SBP presented with hematemesis (36%), abdominal pain (70%), hepatic encephalopathy (24%), fever (44%) and jaundice (36%). While patients without SBP (group 2) presented with hematemesis (28%), abdominal pain (30%) and jaundice (28%). Statistically, there is no significant difference between patients as regard past clinical presentation, except for hepatic encephalopathy who showed high significance. **Mellinger et al. [19]** found that in patients with decompensated cirrhosis, a higher MELD score and the onset of hepatic encephalopathy are independent predictors of in-hospital death. However, Popoiag et al. [16] reported no significant changes in hepatic encephalopathy between the SBP and non-SBP groups (HE).

Antibiotics are now considered standard of care in all patients with cirrhosis and gastrointestinal bleeding, whether or not ascites is present[5].

In terms of laboratory findings, there were statistically significant differences in haemoglobin, platelet count, and a significant difference in WBC count across the tested groups. This was in agreement with Metwally et al. [15], who found that in a sample of 59 patients with SBP, the mean value of serum WBC was substantially greater and the mean PLT was significantly lower. Patients in the SBP group had considerably greater serum WBC than patients in the nonSBP group, according to Popoiag et al. [16]. Furthermore, the mean PLT value in patients with SBP was considerably lower than in those without SBP. The mean value of haemoglobin did not differ significantly (Hb).

Due to splenic platelet sequestration, increased platelet breakdown, or decreased platelet synthesis, low platelet counts are prevalent in chronic liver illness. It's been utilised as a proxy for portal hypertension and the severity of liver disease. Infections, particularly sepsis, cause thrombocytopenia, which has been utilised as a predictor of SBP in patients with low ascetic fluid protein[20].

In patients with decompensated liver cirrhosis, NLR is a noninvasive marker that can be used to predict the likelihood of in-hospital infections[10]. An relationship between NLR and the presence of infection in patients with liver cirrhosis was discovered by Piotrowski et al.[11], although with low diagnostic accuracy (AUC=0.606).

In our study, there was a statistically significant difference between the studied groups in neutrophil count, lymphocyte count, and increased neutrophil to lymphocyte ratio (group 1 had increased neutrophils and decreased lymphocytes than group 2). Our findings were consistent with those of Popoiag et al. [16], who discovered that patients in the SBP group had a considerably greater neutrophiltolymphocyte ratio (NLR) than those in the nonSBP group.

In terms of liver function tests, there was no statistical significance between the two groups for ALT, AST, total bilirubin, and albumin, while there was substantial statistical significance for INR and PT. Our findings agreed with those of Metwally et al. [15], who found that the mean value of INR was substantially higher. However, there was no statistically significant difference in serum albumin or alanine aminotransferase readings across the groups, although there was a statistically significant difference in aspartate aminotransferase (AST). Furthermore, our findings are consistent with those of Abdel Rahman et al. [21], who found that when 80 patients with liver cirrhosis were separated into two equal groups, with and without SBP, the mean values of AST and ALT did not differ substantially between the two groups.

However, our findings did not agree with those of Popoiag et al. [16], who discovered that the mean value of serum albumin was considerably lower in individuals with SBP than in those without SBP. The mean values of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) did not differ significantly (ALT).

There was statistically significant difference between the studied groups in neutrophil count, lymphocyte count and increased neutrophil to lymphocyte ratio

(group 1 had increased neutrophils and decreased lymphocytes than group 2). This results were equal to results of **Popoiag et al. [16]** who found that patients in the SBP group had significantly higher neutrophiltolymphocyte ratio (NLR) than patients in the non SBP group.

Patients in the SBP group had significantly greater blood creatinine and urea than patients in the non-SBP group in terms of kidney function tests. Our findings are consistent with those of Metwally et al. [15] and Popoiag et al. [16], who found that patients in the SBP group had significantly higher serum creatinine than those in the nonSBP group, but not with those of Abdel Rahman et al. [21], who found creatinine values to be similar in both groups.

The results of the receiver operating characteristic (ROC) curve showed that sensitivity was 91.3 and specificity was 90.4 at a cutoff value of NLR 4.8. Also, Popoiag et al. [16] employed ROC statistics to find that the sensitivity and specificity of NLR for the diagnosis of SBP were 98.61 and 81.94 percent, respectively, at a threshold value of > 2.4.

This study had a strength point; the nature of the study as prospective one excluding any possible recording or recalling bias. Yet, it had some limitations; it is performed in a single center and relatively small sample size.

CONCLUSION

We can conclude the clinical utility of NLR as a biomarker predictive factor in the occurrence of spontaneous bacterial peritonitis (SBP), a major cause of mortality in patients with liver cirrhosis.

We recommend further large scale multicentric prospective studies to validate our findings.

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To Cite:

Al Shwighy, M., Gomaa, A., Alnaggar, Y., Shaker, S. Neutrophil to Lymphocyte Ratio as a Predictor for Spontaneous Bacterial Peritonitis in Patients with Cirrhotic Ascites. *Zagazig University Medical Journal*, 2022; (365-373): -. doi: 10.21608/zumj.2022.143729.2582