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Clinical utility of Neutrophil Lymphocyte Ratio (NLR) as a marker of Spontaneous Bacterial Peritonitis (SBP) in patients with cirrhosis-An exploratory study

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Abstract

Background and objective: The diagnosis of spontaneous bacterial peritonitis (SBP) is made by presence of ≥250 polymorphonuclear neutrophil (PMN)/mm^3 in the ascitic fluid. Paracentesis despite being the gold standard has its inherent risks and complications. Blood neutrophil-lymphocyte ratio is a simple test for inflammation. Highly sensitive C reactive protein (hsCRP) is a marker of inflammation which is mainly synthesized by the liver. We aimed to evaluate clinical utility of NLR and hsCRP as less invasive tests for diagnosis of SBP.

Methods: Fifty cases of cirrhosis with ascites with SBP and 50 age and sex matched controls of cirrhosis with ascites without SBP were enrolled for the study. NLR was calculated and hsCRP value was determined in both the groups and compared using independent t test. The sensitivity and specificity of NLR was estimated as a test for SBP diagnosis by using receiver operator characteristics (ROC) curve.

Results: NLR was found to be significantly higher in SBP patients (6.75 +/- 2.7) than those without it (2.81+/-1.06) with p value < 0.01. hsCRP was raised in both groups, 18.93+/-5.00 and 17.46+/-6.19 in cases and controls respectively, but there was no statistical difference between the two groups. For SBP diagnosis, a blood NLR > 3.38 had a sensitivity of 94% and a specificity of 80%.

Interpretation and conclusions: NLR could be used as a novel and less invasive test for diagnosis of SBP. hsCRP has a blunted rise in patients with cirrhosis with SBP and cannot be used as diagnostic marker.

Keywords: Highly sensitive C reactive protein; Neutrophil lymphocyte ratio; Spontaneous bacterial peritonitis.

1. Introduction

Spontaneous Bacterial Peritonitis (SBP) is a common and severe complication of cirrhosis with ascites with a prevalence of approximately 10-30% [1]. Mortality in untreated cases of SBP is found to be as high as 80% in some studies [2]. The presence of SBP is suspected when a patient presents with suggestive symptoms and signs such as fever, abdominal pain and alteration in mental status. Although many patients are asymptomatic and are detected when they undergo routine paracentesis after being admitted for other medical conditions.

The diagnosis of SBP requires an invasive approach that is recommended for all patients of cirrhosis with above symptoms and signs ; or being admitted for other reasons such as gastrointestinal bleed, hepatic encephalopathy or

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rapid impairment in renal function without any precipitating factor [1]. Ascitic fluid analysis for diagnosis of SBP requires PMN Ascitic fluid count and culture. Culture is negative in approximately 30-50% cases despite sensitive methods [3,4]. Secondly, PMN count is cumbersome, requiring automated cell counter; sometimes cannot be done on emergency basis and is prone to human error. Hence, there is a need for some less invasive biomarker which can predict SBP without the need for repeated paracentesis. Various quick, simple and less invasive rapid bedside diagnostic tests for SBP are being studied like Leucocyte Esterase levels in urine [2,5]. SBP is an inflammatory state and inflammatory markers are notably stimulated in SBP despite the low ascitic fluid bacterial concentration. In patients with SBP, inflammatory markers such as interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α) and α -1-antitrypsin (AAT) have been observed to be elevated in various studies [6,7]. Procalcitonin, a pro-inflammatory marker which increases in response to bacterial infections was also found to be raised among patients with SBP in a meta-analysis of 7 studies conducted in China in 2015 [8].NLR is a simple parameter to easily assess the inflammatory status of a subject. It has been suggested as a marker of systemic inflammation and shows the relationship between two different immune pathways. The neutrophil count reflects ongoing inflammation, whereas the lymphocyte count represents the immune regulatory pathway. NLR has also been found to be raised in cirrhosis, as cirrhosis is an inflammatory state due to various aetiologies like, impaired bacterial clearance by liver due to sinusoidal fibrosis, dysbiosis, leaky gut and release of ligands from necrotic hepatocytes, termed as damage-associated molecular patterns (DAMPs) [9-11]. There is also derangement of innate and adaptive immunity due to effects of cirrhosis on each cell line individually and reduced expression of MHC class II proteins [9,12,13]. This leads to a variation in NLR ratio in cirrhosis. Association of NLR with the severity of fibrosis of liver due to various etiologies and in predicting the outcome has been well documented in various studies [14-16].

So, SBP being an inflammatory complication of cirrhosis with ascites and NLR a marker of inflammation if found associated with SBP can become a less invasive marker to diagnose SBP in cirrhosis.

2. Material and methods

2.1. Study design

Case Control Study

2.2. Setting

The study was undertaken in the Department of Medicine at University College of Medical Sciences (UCMS) and Guru Teg Bahadur Hospital (GTBH). Subjects were recruited from OPD, emergency and wards of the hospital between the periods of November 2017 to April 2019.

2.3. Consent and ethics

Written informed consent was taken from each subject and institutional ethical clearance was taken.

2.4. Participants

Patients presenting to the medicine OPD, emergency and admitted in wards, diagnosed with cirrhosis on clinical, biochemical and radiological examination in the age group of 18-60 years of both sex and fulfilling the inclusion and exclusion criteria were enrolled for the study.

2.5. Study size

According to a study published in April 2018, aimed at evaluating the diagnostic utility of NLR in SBP, the sensitivity of NLR at >2.89 was found to be 80.3% for diagnosis of SBP [17]. Taking the prevalence of SBP in cirrhosis as 20%, to estimate an absolute difference of 10% in sensitivity, with alpha value 5%, a sample size of 305 cases was required [1].But due to constrain of time and resources, a minimum of 50 cases of cirrhosis with ascites with SBP/CNNA and 50 age and sex matched controls of cirrhosis with ascites without SBP/CNNA were enrolled.

2.6. Inclusion criteria

- Age 18-60 years.

- Patients with cirrhosis due to any cause, as proven by, ultrasound abdomen suggestive of shrunken and coarse echotexture and Doppler USG of splenoportal venous axis suggestive of portal hypertension were included in the study.

2.7. Exclusion criteria

- Patients who had received antibiotics within the last 7 days or were on antibiotic prophylaxis for SBP.

- Patients with any infection other than SBP (like Urinary Tract Infection (UTI), Tuberculosis, etc.), neoplastic disorders, active autoimmune disorders, obesity (Body Mass Index (BMI)>30), or any other chronic systemic illness like Diabetes Mellitus (DM), Chronic Obstructive Pulmonary Disease (COPD), Chronic Kidney Disease (CKD), Coronary Artery Disease (CAD), Human Immunodeficiency Virus (HIV), etc.

2.8. Method

The patients between the age group of 18 to 60 years with cirrhosis of any cause as proven on ultrasound abdomen and doppler of splenoportal venous axis, were evaluated with a detailed history and examination to rule out any infection other than SBP (like UTI, tuberculosis, etc.), malignancy, autoimmune diseases, obesity or any other chronic systemic disease like DM, COPD, CKD, CAD, HIV, etc. The patients who had taken antibiotics within last 7 days or were on antibiotic prophylaxis for SBP were excluded from the study. Diagnostic paracentesis was performed in all the patients for cytology (TLC/DLC), sugar, protein, albumin, culture/sensitivity and serum ascites albumin gradient (SAAG).The diagnosis of SBP was made when at least 250 PMN/mm^3were present in ascitic fluid with positive ascitic fluid culture in the absence of secondary peritonitis and haemorrhagic ascites. The diagnosis of CNNA was made when >250 PMN/mm^3were present in ascitic fluid with negative ascitic fluid culture. Patients having SBP/CNNA on ascitic fluid analysis were taken as cases and patients without evidence of SBP/CNNA were taken as controls. Both cases and controls underwent routine physical examination including BMI, laboratory testing and X-ray chest. Lab tests included Complete Blood Count (CBC), Urine Routine microscopy (U-R/M), Blood Urea (BU), Serum Electrolytes (S. Na^+/S. K^+), Random Blood Sugar (RBS), Liver Function Tests (LFT), Kidney Function Tests (KFT) and special investigations like hsCRP and NLR.

2.9. Statistical analysis

Data collected was entered into MS Excel spreadsheet and was analysed with SPSS 20.0 software. Data was cleaned and errors were corrected. For comparing qualitative parameters, we applied chi-square test and for quantitative parameters we applied unpaired t tests for comparing the 2 groups. Logistic regression was done to obtain the best predictors of SBP. p value of <0.05 was considered as significant.

3. Results

The study recruited 100 patients of cirrhosis with ascites. The cases comprised of 50 patients with Spontaneous Bacterial Peritonitis (SBP)/Culture Negative Neutrophilic Ascites (CNNA) and were compared with 50 age and sex matched controls with non-infective ascites. Patients were assessed for their demographic variables, clinical features, complications and laboratory measurements including Neutrophil to Lymphocyte ratio (NLR) and hsCRP.

3.1. Demographic variables

The mean age for the control group and case group were 43.94 +/- 12.78 and 41.66 +/- 1.60 respectively. Independent t-test revealed a p value of 0.334 i.e. there was no significant difference between the two groups. The study group comprised of 42 males and 8 females and the control group comprised of 35 males and 15 females. Chi-square test revealed a p value of 0.096 i.e. there was no statistically significant difference between the frequencies of sex distribution across the two groups. Thus, the two groups were matched for age and sex (Table 1,2; Figure 1,2).

Table 1 Age distribution

	Controls	Cases	P value

	Mean	Std. Dev	Mean	Std. Dev	
Age	43.94	12.772	41.66	10.60	0.334

Significant at p value< 0.05

Table 2 Sex Distribution

	Controls		Cases		P value
	N	Percentage	N	Percentage	
Males	35	70	42	84	0.096
Females	15	30	8	16	

Significant at p value< 0.05

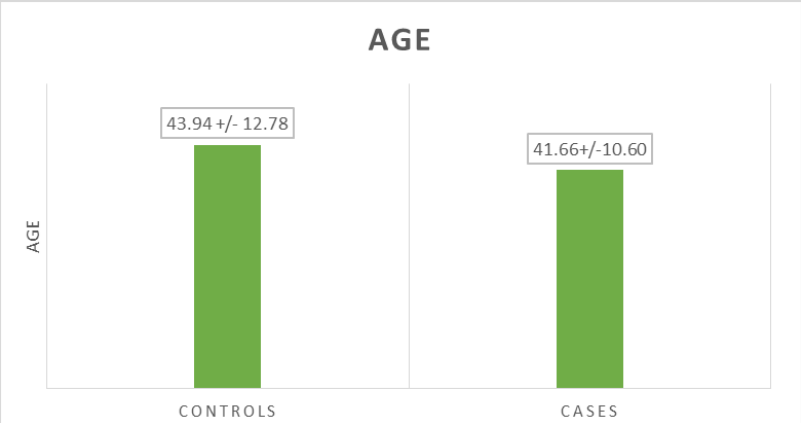

Figure 1 Age of Distribution

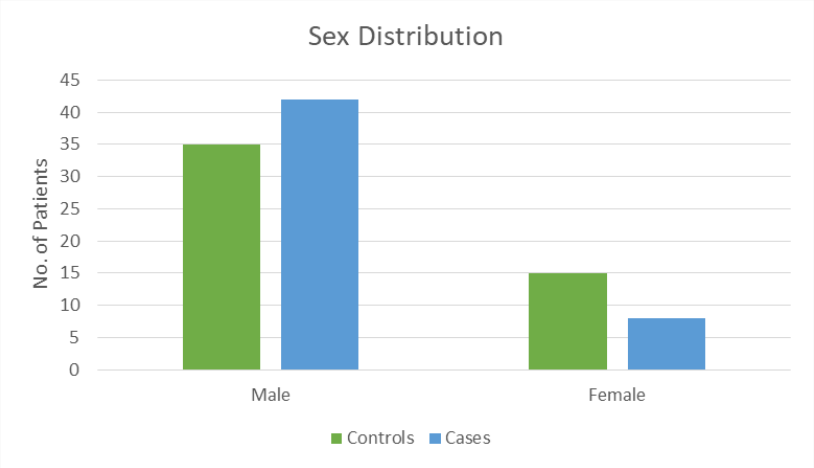

Figure 2 Sex Distribution

3.2. Comparison of NLR between cases and controls

The mean NLR in patients with and without SBP/CNNA was found to be 6.73+/-2.7 and 2.81+/-1.06 respectively (Table 3; Figure 3). The difference was statistically significant with p value 0.00. The Receiver Operating Characteristic (ROC)

curve analysis demonstrated that a cut-off of blood NLR >3.38 has a sensitivity of 94% and specificity of 80% in diagnosing SBP among patients with ascites (Figure 4).

Table 3 Comparison of NLR and hsCRP between cases and controls

	Controls		Cases		P value
	Mean	Std. Dev	Mean	Std. Dev	
NLR	2.81	1.06	6.73	2.70	0.00
hsCRP(mg/L)	17.46	6.19	18.93	5.00	0.194

Significant at p value< 0.05

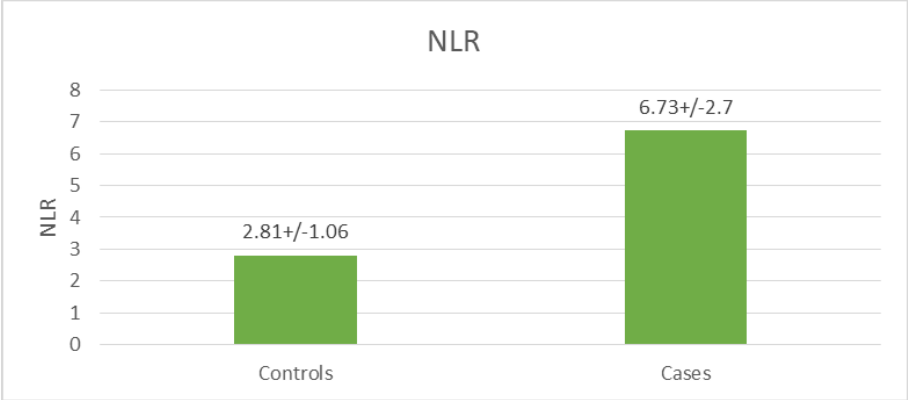

Figure 3 Comparison of NLR between cases and controls

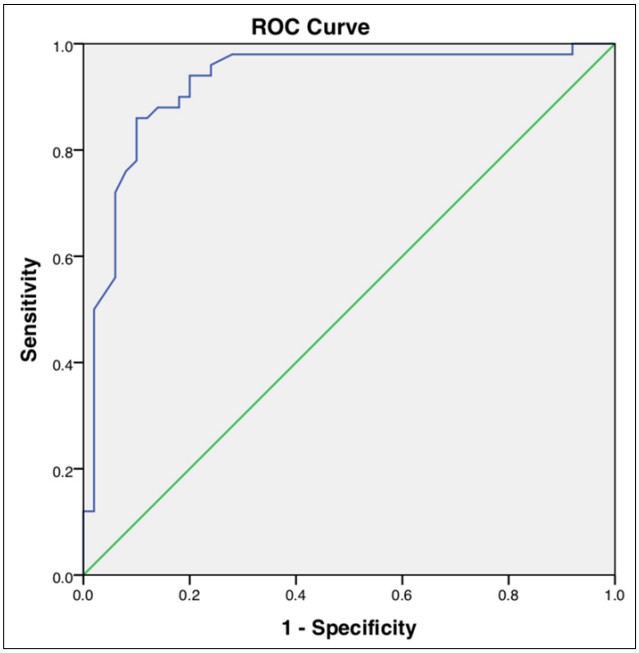

Figure 4 ROC analysis to obtain cut-off value of NLR

3.3. Comparison of hsCRP between cases and controls

The hsCRP was raised in both groups, 17.46+/-6.19 and 18.93+/-5.00 in controls and cases respectively, as compared to normal value but there was no statistical difference in values of hsCRP in patients of cirrhosis with ascites with or without SBP/CNNA (p value=0.194) (Table 3; Figure 5).

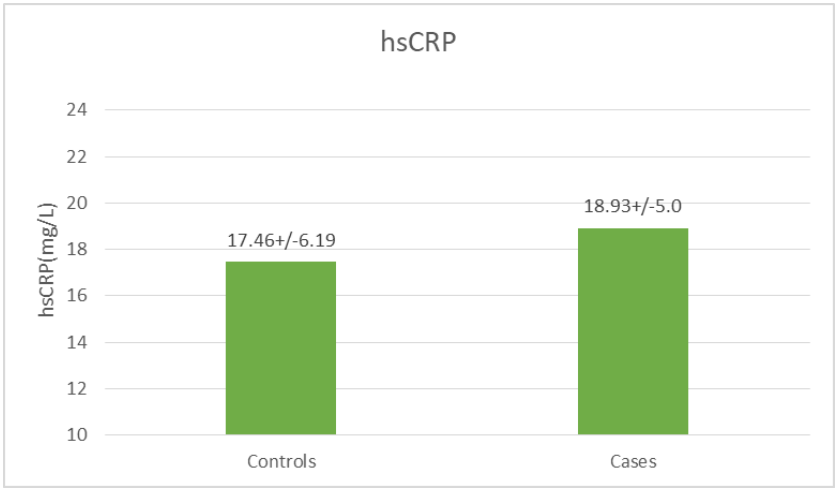

Figure 5 Comparison of hsCRP between cases and controls

3.4. Correlation of NLR and hsCRP

On correlation analysis between NLR and hsCRP, a negative correlation was found among controls but was statistically insignificant (r=-0.18, p value=0.194). The correlation among cases was positive but the coefficient of correlation was low (r=0.30, p value=0.04) (Figure 6).

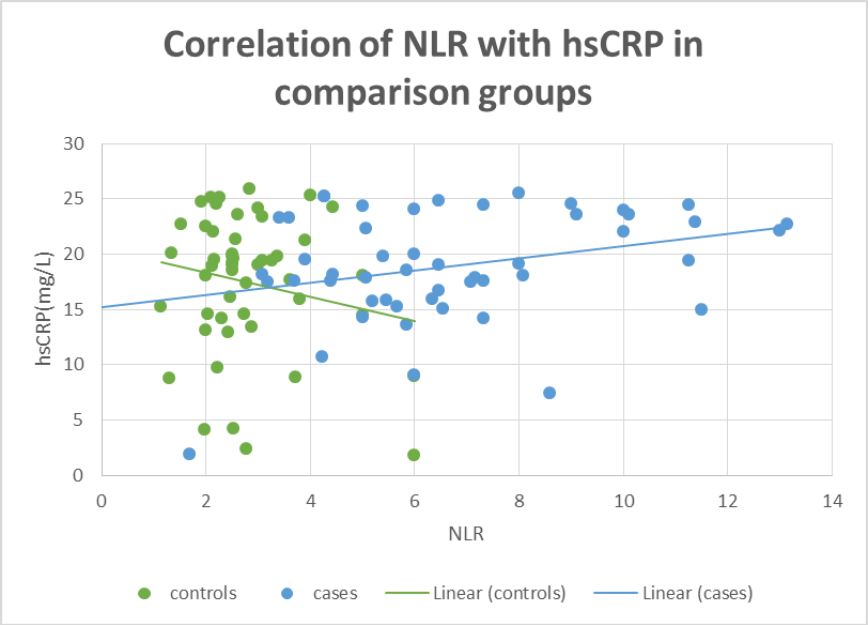

Figure 6 Correlation of NLR and hsCRP

3.5. Comparison of NLR and hsCRP between complications of cirrhosis

On comparison of NLR and CRP in patients having complications with those without complications (viz-hepatic encephalopathy, upper GI bleed and hepatorenal syndrome) there was no significant difference with p value being 0.414, 0.459, 0.08; 0.055, 0.438, 0.702 in cases and controls respectively (Table 4 & 5).

Table 4 Univariate analysis of NLR in Complications

	Present		Absent		P value
	Mean	S.D.	Mean	S.D.	
Hepatic encephalopathy	5.62	3.25	4.27	2.47	0.414
Upper GI bleed	4.88	2.85	4.74	2.86	0.459
Hepatorenal syndrome	5.50	2.76	4.34	2.82	0.08

Significant at p value< 0.05

Table 5 Univariate analysis of hsCRP in Complications

	Present		Absent		P value
	Mean	S.D.	Mean	S.D.	
Hepatic encephalopathy	19.73	4.52	17.30	6.07	0.055
Upper GI bleed	17.42	5.16	18.46	5.82	0.438
Hepatorenal syndrome	18.63	5.76	17.94	5.62	0.702

Significant at p value< 0.05

3.6. Distribution of Clinical variables between the two groups (Table 6; Figure 7)

- On analysing frequencies of occurrence of *fever across* two groups, fever was present in 28 patients in cases and 5 patients among the controls. The p value was 0.00 which was statistically significant.
- The frequency of presence of *jaundice* in the study group was 44 as compared to 27 in the control group with the comparison being statistically significant with p value of 0.00.
- *Abdominal pain* was present in 31 cases as compared to 5 controls and the comparison was statistically significant with p value of 0.00.
- On analysis of presence or absence of *increased abdominal distension* between the 2 groups, 38 patients of the study group had increased abdominal distension as compared to 23 patients in the control group. The p value was 0.002 which was statistically significant.
- *Decreased urine output* was seen more among cases than controls but the analysis was statistically insignificant with p value of 0.248.
- The frequency of presence of *altered sensorium* in the study group was 24 as compared to 13 in the control group with the comparison being statistically significant with p value of 0.023.

Table 6 Distribution of clinical features between case and control

Clinical variables	Controls		Cases		P value
	N	Percentage	N	Percentage	
Fever	5	10	28	56	0.00
Jaundice	27	54	44	88	0.00
Abdominal pain	5	10	31	62	0.00
Increased abdominal distention	23	46	38	76	0.002
Decreased urine output	10	20	15	30	0.248
Altered sensorium	13	26	24	48	0.023

Significant at p value< 0.05

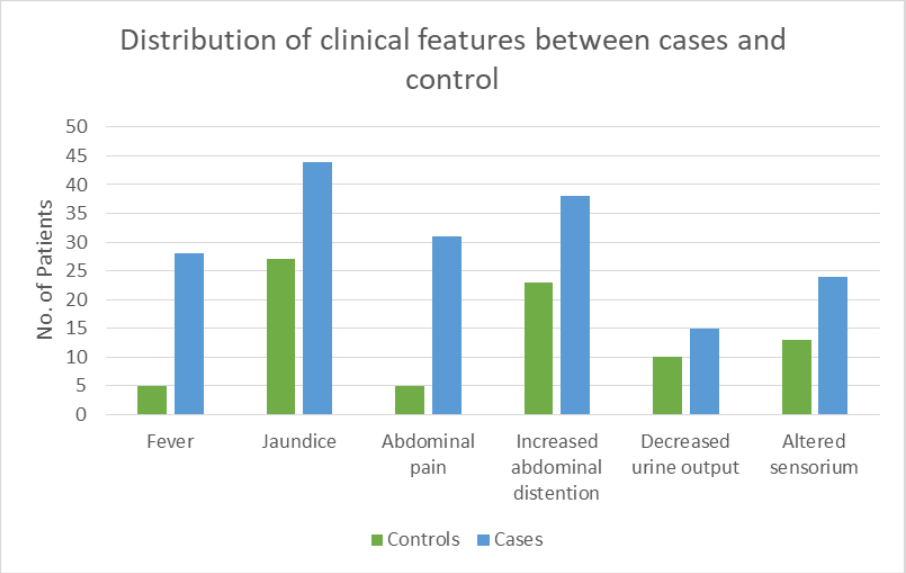

Figure 7 Distribution of Clinical features between case and control

3.7. Logistic regression of NLR and clinical features giving chance of (odds ratio) having SBP

Logistic regression analysis was used to determine chance of having SBP with various clinical features and NLR. The results are depicted in table 7.

- Increase of 1 unit in NLR amounts to 2.75 times chance of having SBP.
- In the presence of *fever* chances of having SBP are 11.46 times.
- In the presence of *Jaundice* chances of having SBP are 6.25 times.
- In the presence of *abdominal pain* chances of having SBP are 14.68 times.
- In the presence of *increased abdominal distension* chances of having SBP are 3.72 times.
- In the presence of *altered sensorium* chances of having SBP are 2.63 times.

Table 7 Logistic regression Of NLR and clinical features giving chance of (Odds Ration) having SBP

	B coefficient	Odds Ration	P value
NLR	1.01	2.75	0.00
Fever	19.60	11.46	0.00
Jaundice	12.44	6.25	0.00
Abdominal Pain	23.50	14.68	0.00
Increased Abdominal Distension	9.06	3.72	0.00
Altered Sensorium	5.07	2.63	0.02

Significant at p value< 0.05

3.8. Step-wise logistic regression predicting the best risk factors (Table: 8)

The 6 significant risk factors (NLR, fever, jaundice, abdominal pain, increased abdominal distention and altered sensorium) were entered into step-wise logistic regression which concluded that NLR, fever, jaundice and Abdominal pain are the 4 best predictors of SBP.

In presence of fever, jaundice and abdominal pain among patients with cirrhosis and ascites an increase of 1 unit in NLR amounts to 2.59 times chance of having SBP.

Table 8 Best predictors for SBP

	B coefficient	Odds Ratio	P value
NLR	0.95	2.59	0.00
Fever	3.48	32.36	0.008
Jaundice	3.51	33.36	0.008
Abdominal Pain	2.77	15.92	0.002

Significant at p value< 0.05

3.9. Logistic regression to assess the risk of SBP due to NLR adjusted for different clinical symptoms and signs (Table 9-11)

On logistic regression to assess the risk of SBP due to NLR adjusted for different clinical symptoms and signs, we found that in the presence of fever, abdominal pain and jaundice the chances of having SBP/CNNA among patients of cirrhosis with ascites was 2.64 times, 2.66 times and 2.77 times respectively with every 1 unit increase in NLR.

Table 9 Logistic regression Of NLR with fever giving chance of (Odds Ration) having SBP

	B coefficient	Odds Ratio	P value
NLR	0.97	2.64	0.00
Fever	2.17	8.77	0.002

Significant at p value< 0.05

Table 10 Logistic regression Of NLR with jaundice giving chance of (Odds Ration) having SBP

	B coefficient	Odds Ratio	Significance
NLR	1.02	2.77	0.00
Jaundice	2.11	8.27	0.009

Significant at p value< 0.05

Table 11 Logistic regression Of NLR with abdominal pain giving chance of (Odds Ration) having SBP

	B coefficient	Odds Ratio	P value
NLR	0.98	2.66	0.00
Abdominal pain	2.83	17	0.00

Significant at p value< 0.05

4. Discussion

In our study we estimated and compared NLR between patients of cirrhosis with ascites with and without SBP/CNNA. Normal value of NLR reported for a healthy individual is 1.6 [14]. NLR is higher in cirrhosis as it is an inflammatory state [14-16]. In compensated cirrhosis, there occurs sterile systemic inflammation due to release of ligands from necrotic hepatocytes, termed as damage-associated molecular patterns (DAMPs). With onset of decomposition, release of other inflammation associated ligands and translocation of bacteria and bacterial products (*e.g.*, lipopolysaccharide, methylated DNA) from the gut triggers systemic inflammation predisposing the patient to development of SBP. In cirrhosis these are termed as pathogen associated molecular patterns (PAMPs) [9,11]. There occurs an increase of pro-inflammatory cytokines and leukocyte activation antigens like TNF-α, IL-1β, IL-6, interferon-γ, IL-17, IL-18, ICAM-1, and VCAM-1 with continuous influx of PAMP and a decrease in levels of anti-inflammatory cytokines like IL-10 and TGF-β

[9,12,13]. Multiple studies have shown the association of NLR with cirrhosis and documented it as a marker to predict prognosis in patients of hepatitis, fibrosis and cirrhosis [14-16].In our study the mean NLR in patients with and without SBP/CNNA was found to be 6.73+/-2.7 and 2.81+/-1.06 respectively, which is consistent with the published literature showing NLR in the range of 1.8 in early fibrosis to 2.9 in cirrhosis [14]. The difference was statistically significant with p value of 0.00.

The role of neutrophil to lymphocyte ratio in diagnosis of bacterial infections in patients with fever was evaluated in Norway in 2017 where the patients with bacterial infections had a significantly higher NLR (mean: 12.23), than those without infection (mean: 5.02), or those with a viral infection (mean: 2.41) [18].NLR has also been documented to rise in sepsis and septic shock and correlates with severity of clinical course [19].

Only one study (published in April 2018) is available in literature which has evaluated role of NLR in SBP. The study aimed at evaluating the diagnostic utility of NLR and CRP in SBP. NLR was compared between 180 cirrhotic patients with and without SBP. The mean NLR in patients with and without SBP was found to be 4.5(3.2-8.7) and 2.1(1.6-2.6) respectively with p value< 0.0012 which are in agreement with those found in our study [17].In our study, it was found that every increase of NLR by 1 unit amounts to 2.75 times more chances of having SBP/CNNA in logistic regression (Table 7). When a cut-off of blood NLR value >3.38 is taken, then the likelihood of having SBP/CNNA can be predicted with 94% sensitivity and 80% specificity (Figure 4), which is similar to the study published in this regard [17]. In this study with a cut-off of NLR >2.89, sensitivity of 80.3% and specificity of 88.9% has been reported for SBP diagnosis in patients of cirrhosis with ascites.

CRP is the prototype human acute phase reactant and a well-known marker of systemic inflammation [20]. Hepatocytes are the primary site for synthesis of CRP. It is mainly synthesised in response to IL-6, and also to lesser extent to IL-1 and IL-17, during the acute phase of inflammation [21]. hsCRP was measured in cases and controls using a solid phase ELISA with a normal value of 0.068 to 8.2 mg/L. hsCRP was raised in both cases and controls (18.93+/-5.00 and 17.46+/-6.19 respectively) as compared to normal value but there was no statistically significant difference in patients with and without SBP/CNNA(p value=0.194). Cirrhosis is an inflammatory condition and it is well expected that CRP should rise in cirrhosis [22,23]. The lack of increase in SBP has been well elucidated and explained in number of studies. Experimental and clinical observations have suggested a dose response relationship between CRP and inflammatory stimulus and with clinical indices of illness severity [24,25]. In patients of cirrhosis with SBP, Spahr et al. observed limited diagnostic value of CRP measurement [26]. A study done by Hongli et al. in 2016 regarding the role of serum procalcitonin and CRP in predicting SBP in patients of advanced liver cirrhosis concluded that CRP in ascitic fluid infection patients does not provide diagnostic accuracy [27]. The basic levels of CRP in patients with cirrhosis is higher than in patients without cirrhosis, but when infection occurs, the more serious the liver disease, the lower the increase in CRP [28]. Therefore, the predictive power of CRP for infections is weak in patients with advanced cirrhosis as was shown byJanum et al., in the year 2011. The study concluded that the prognostic capacity of initial CRP levels in patients with bacteraemia with CLD is weak [29].But a recent study published discordant results and showed higher CRP levels in SBP with cirrhosis in comparison to controls without SBP [17]. However, they also concluded that CRP elevation in patients of cirrhosis with superimposed SBP shows a blunted rise, which is consistent with the existing literature on rise of levels of CRP among cirrhotic patients with bacterial infections [17,26-30].

A negative correlation was found between NLR and hsCRP in controls (r=-0.18) but was statistically insignificant (p value=0.19). In cases, the correlation between NLR and hsCRP was positive but the coefficient of correlation was low (r=0.30, p value=0.04). The above weak correlation can be explained by the fact that CRP is produced in hepatocytes on cytokine stimulation and NLR also rises in inflammatory conditions with increase in proinflammatory cytokines in cirrhosis but CRP production is unpredictable in cases of hepatic failure. It is unclear how much CLD will influence the hepatic synthetic property to respond normally [26,29]. The weak correlation between CRP rise and infection/inflammation in cirrhotic patients has been shown in numerous studies [26-30].

In our study, 24 patients among the cases had hepatic encephalopathy and 13 in controls, with comparison being statistically significant (p value =0.023). Frequency of presence of upper gastrointestinal bleed and hepatorenal syndrome was more in cases than in controls, but the comparison was statistically insignificant (Figure 7).On comparison of NLR and CRP in patients having complications with those without complications (viz-hepatic encephalopathy, upper GI bleed and hepatorenal syndrome) there was no significant difference in p value being 0.414, 0.459, 0.08; 0.055, 0.438, 0.702 in cases and controls respectively (Table 11).On review of existing literature, no studies have been published on the diagnostic value of NLR or hsCRP in predicting hepatic encephalopathy, upper GI bleed or hepatorenal syndrome among patients with cirrhosis.

5. Conclusion

SBP is a common and frequently fatal complication of cirrhosis with ascites which is diagnosed by paracentesis.

There is a need for some less invasive method for diagnosis of SBP as paracentesis has its inherent side effects.

We propose NLR > 3.38 for predicting occurrence of SBP in cirrhosis with ascites with sensitivity of 94% and a specificity of 80% and with each unit rise in NLR the probability of having SBP in the above patient's increases 2.75 times.

Also, we conclude that hsCRP has a blunted rise in patients of cirrhosis superimposed by a bacterial infection and cannot be used as a diagnostic marker for SBP and it does not correlate with rise of NLR in SBP.

Also, NLR is not affected by any other superimposed complication of cirrhosis studied viz. hepatic encephalopathy/hepatorenal syndrome/upper GI bleed.

Compliance with ethical standards

Disclosure of conflict of interest

None.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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