

Utility of Neutrophil to Lymphocyte Ratio as a Predictor of Complications in Patients with Liver Cirrhosis

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Abstract: ***Background:** Cirrhosis is a serious and irreversible disease which is considered as the final stage of chronic liver disease. The major complications of cirrhosis include ascites, hepatic encephalopathy, upper GI bleed, and spontaneous bacterial peritonitis. [4] The neutrophil to lymphocyte ratio (NLR) is a biomarker of immune dysregulation in patients with cirrhosis and is inexpensive to measure. The present study was conducted to examine the association of neutrophil to lymphocyte ratio with complications, and decompensation in patients with cirrhosis of liver. **Materials & Methods:** This was conducted on 50 patients in the department of Medicine, Government Medical College, Amritsar. The study protocol was approved by the institutional ethics committee. The patients were enrolled in the study after obtaining written informed consent. All the patients were interviewed and clinically examined. Neutrophil to lymphocyte ratio was calculated for every patient. The results were then analyzed. **Results:** The mean age was 52.50 + 8.31 years with a male preponderance (78% male vs 22% female patients). Neutrophil - lymphocyte ratio (NLR) was normal (<3) in 19 (38%) patients, while it was elevated (>3) in 31 (62%) patients. NLR was in the range of 1.47 - 18.33. Majority of the patients (38 patients; 76%) had various complications. Out of these complications, ascites (76%) was the most common complication followed by Hepatic encephalopathy (52%), upper GI bleed (36%), and Spontaneous bacterial peritonitis (26%). The relation of NLR was significant for alcoholism, hepatic encephalopathy, spontaneous bacterial peritonitis, upper GI bleed and ascites; and highly significant for Child - Turcotte - Pugh (CTP) scoring. **Conclusion:** The present study found that NLR, which is widely available and inexpensive biomarker of systemic inflammation, can be used as a screening tool in predicting occurrence of complications (e. g., hepatic encephalopathy, spontaneous bacterial peritonitis, ascites, and upper GI bleed) and indirectly predicting the short - term mortality in patients with liver cirrhosis. It can also be used as prognostic marker to detect decompensation in these patients.*

Keywords: Liver cirrhosis, Neutrophil to lymphocyte ratio, Ascites, Child - Turcotte - Pugh (CTP) scoring, Spontaneous bacterial peritonitis

1. Introduction

Cirrhosis is a serious and irreversible disease which is considered as the final stage of chronic liver disease. [1] It is defined as the development of regenerative nodules with surrounding fibrous bands in response to chronic liver injury, that ultimately leads to end stage liver disease. It is a major cause of mortality and morbidity worldwide. [2] In India, hepatitis B virus (HBV) is the most common cause of cirrhosis, although increasing alcohol abuse is likely to replace HBV as the predominant cause. [3] The major complications of cirrhosis include oesophageal varices, ascites, hepatic encephalopathy, hepatorenal syndrome, and spontaneous bacterial peritonitis. [4] The neutrophil to lymphocyte ratio (NLR) is a biomarker of immune dysregulation in patients with cirrhosis and is inexpensive to measure. [5] The present study was conducted to examine the association of neutrophil to lymphocyte ratio with complications, and decompensation in patients with cirrhosis of liver.

2. Materials and Methods

This study was conducted on 50 patients of liver cirrhosis admitted in the department of Medicine, Guru Nanak Dev Hospital, Government Medical College, Amritsar (Punjab). The study protocol was reviewed and

approved by the institutional ethics committee. The patients were enrolled in the study after obtaining written informed consent.

Inclusion criteria

- Patients diagnosed to have liver cirrhosis based on clinical features/ biochemical investigations and ultrasonography.
- Patients who gave consent to participate in the study.

Exclusion criteria

- Patients with following disease conditions - Covid 19 infections, malaria, dengue, hepatocellular carcinoma, coronary artery disease, and stroke.
- Patients on steroid therapy.
- Patients who were part of any other study during this period.
- Patients who did not give consent to be a part of the study.

All the patients were clinically examined. The enrolled patients underwent the following investigations - complete hemogram, liver function tests, renal function tests, ultrasound whole abdomen, and viral abdomen. Upper gastrointestinal endoscopy and ascitic fluid analysis were performed as and when required.

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Neutrophil to lymphocyte ratio was calculated at admission in patients with cirrhosis. NLR ratio was calculated from the blood samples collected from the study subjects by dividing the absolute Neutrophil count by the absolute Lymphocyte count. The samples collected were analysed in coulter principle machine cell counter and the total cell count, differential cell count of the WBC were obtained. The calibration of the cell counter machines was absolute up - to date and was verified. There was no inter observer variability as the samples were analysed by automated machines. The results of observations of individual patients were tabulated and analyzed using SPSS version 26, IBM, USA.

3. Results

Baseline data of patients: The mean age was 52.50 + 8.31 years (with maximum number of patients in the age group of 41 - 50 years). There was a male preponderance (78% male vs 22% female patients). Neutrophil - lymphocyte ratio (NLR) was normal (<3) in 19 (38%) patients, while it was elevated (>3) in 31 (62%) patients. In patients of elevated NLR, 17 (34%) patients had NLR in the range of 3 - 6, followed by 10 (20%) patients in the range of 6 - 10, and 4 (8%) patients had >10 NLR. NLR was in the range of 1.47 - 18.33. Majority of the patients (38 patients; 76%) had various complications. Out of these complications, ascites (76%) was the most common complication followed by Hepatic encephalopathy (52%), upper GI bleed (36%), and Spontaneous bacterial peritonitis (26%).

Relation of Neutrophil - lymphocyte ratio with various factors: With respect to complications, all patients with no complications fell in normal NLR group. Amongst patients with complications, 31 (81.6%) patients fell in high NLR

group while 7 (18.4%) patients fell in normal NLR group (p - value 0.001; highly significant). The distribution of patients according to Child - Turcotte - Pugh (CTP) scoring indicated 22 (44%) patients were in CTP class C group, followed by 20 (40%) patients in CTP class B group and only 8 (16%) patients in CTP class A group. Amongst CTP class A group, all patients had NLR < 3. In CTP class C group, all patients had NLR > 3. In CTP class B group, 11 (55%) patients had normal NLR, while 9 (45%) patients had elevated NLR. Chi - square test of association between NLR and CTP class was highly significant (p=0.0001).

In alcoholic group of patients, 26 (74.3%) patients fell in the elevated NLR group, whereas among 15 non - alcoholic patients, 5 patients (33.3%) were in elevated NLR group (p - value 0.006; significant). Among 26 patients with hepatic encephalopathy, 24 (92.3%) patients fell in the high NLR group. Whereas amongst 24 patients without hepatic encephalopathy, 7 (29%) patients were in elevated NLR group (p - value 0.002; significant). All the 13 patients with spontaneous bacterial peritonitis (SBP) had elevated NLR. Out of 37 patients without SBP, 18 (48.7%) had elevated NLR. Chi - square test of association between NLR and SBP was significant (p=0.0002).

Among 38 (76%) patients with ascites, 31 (81.6%) patients had elevated NLR. While remaining 7 (18.4%) patients had normal NLR. All the 12 patients without ascites had normal NLR (p - value 0.006; significant). All 18 (36%) patients who suffered upper GI Bleed at presentation or developed in due course of study had elevated NLR. Among patients without upper GI bleed, 19 (59.4%) patients had normal NLR and 13 (40.6%) patients had elevated NLR (p=0.003; significant).

Table 1: Baseline characteristics of patients

Parameters	Variables	Total
Age (years)	31 - 40	3 (6%)
	41 - 50	20 (40%)
	51 - 60	19 (38%)
	61 - 70	8 (16%)
Gender	Male	39 (78%)
	Female	11 (22%)
Neutrophil - lymphocyte ratio levels	Normal (<3)	19 (38%)
	Elevated (>3)	31 (62%)
Neutrophil - lymphocyte ratio values	<3	19 (38%)
	3 - 6	17 (34%)
	6 - 10	10 (20%)
	>10	4 (8%)
Complications	Ascites	38 (76%)
	Upper GI bleeding	18 (36%)
	Hepatic encephalopathy	26 (52%)
	Spontaneous bacterial peritonitis	13 (26%)
	No complications	12 (24%)
Alcoholism	Absent	15 (30%)
	Present	35 (70%)

Table 2: Relation of Neutrophil - lymphocyte ratio with various factors

Factors	Variables	Normal NLR (<3)	Elevated NLR (>3)	p - value
Complications	Present	7 (18.4%)	31 (81.6%)	0.001
	Absent	12 (100%)	0	
Child - Turcotte - Pugh (CTP) class	CTP class A	8 (100%)	0	0.0001
	CTP class B	11 (55%)	9 (45%)	
	CTP class C	0	22 (100%)	
Alcoholism	Absent	10 (66.7%)	5 (33.3%)	0.006
	Present	9 (25.7%)	26 (74.3%)	
Hepatic encephalopathy	Absent	17 (71%)	7 (29%)	0.002
	Present	2 (7.7%)	24 (92.3%)	
Spontaneous bacterial peritonitis	Absent	19 (51.3%)	18 (48.7%)	0.0002
	Present	0	13 (100%)	
Ascites	Absent	12 (100%)	0	0.0006
	Present	7 (18.4%)	31 (81.6%)	
Upper GI bleed	Absent	19 (59.4%)	13 (40.6%)	0.003
	Present	0	18 (100%)	

4. Discussion

Patient's demographics: The mean age group was 52.50 + 8.31 years. Maximum number of patients in the age group of 41 - 50 years. Least number of patients were present in the extreme age groups (6% in 31 - 40 years and 16% in 61 - 70 years). Hence, cirrhosis occurs exclusively in the middle - aged people from 30 to 60 years, which is the most productive phase of an individual's career in all aspects, which makes cirrhosis of liver a huge burden both for the society and for the family of the patient. There was a male preponderance (78% male vs 22% female patients). The predominance of male patients can be directly correlated to the higher prevalence of alcoholism in males as compared to the females.

Vineeth VK et al (2020) reported that the mean age of the study was 53.91±10.9 years with maximum patients between the age group 51 - 60 years (38.3%). There were 108 male and 12 female patients. [6] Sungkar T et al (2019) enrolled 54 liver cirrhosis patients (37 males and 17 females) and found the mean age for the cohort was 52.76±12.57 years. [7]

Baseline characteristics: Neutrophil - lymphocyte ratio (NLR) is the ratio of absolute count of neutrophils to the absolute count of lymphocytes. The normal cut - off value of NLR was taken as 3. NLR was normal (<3) in 19 (38%) patients, while it was elevated (>3) in 31 (62%) patients. The mean NLR value is 5.0056 ± 3.54. Vineeth VK et al (2020) reported a mean NLR of 5.8250. [6] Biyik M et al (2013) demonstrated a mean NLR of 2.72 and concluded that the mortality rate was significantly higher (odds ratio was 8.9) in patients of liver cirrhosis with an NLR higher than 2.72 compared with lower NLR values. [8]

Majority of the patients (38 patients; 76%) had various complications. Out of these complications, ascites (76%) was the most common complication followed by Hepatic encephalopathy (52%), upper GI bleed (36%), and Spontaneous bacterial peritonitis (26%). Maccali C et al (2021) reported the following complications in cirrhotic patients - upper gastrointestinal bleeding (40.0%), ascites (52.2%), hepatic encephalopathy (49.4%), and bacterial infections (44.7%). Nand N et al (2015) reported that common complications encountered were ascites (72%),

hepatorenal syndrome (35%), hepatic encephalopathy (59%) and gastrointestinal bleeding (59%).

Relation of Neutrophil - lymphocyte ratio with various factors: The relation of Neutrophil - lymphocyte ratio was assessed with various factors e. g., alcoholism, hepatic encephalopathy, spontaneous bacterial peritonitis, ascites, and upper GI bleed.

- **Relation with complications** - With respect to complications, all patients with no complications fell in normal NLR group, while 31 (81.6%) patients with complications fell in high NLR group (p - value 0.001; highly significant). Vineeth VK et al (2020) reported that as the NLR increased, the incidence of complications also increased with 66.7% of patients with NLR >12 having more than 2 complications (i. e., hepatic encephalopathy with SBP). [6] He Q et al (2016) found that NLR in decompensated cirrhosis were significantly higher than compensated cirrhosis (3.84 ± 3.27 vs. 1.71 ± 0.65, P < 0.001). [11]
- **Relation with Child - Turcotte - Pugh (CTP) class** - Amongst CTP class A group (8 patients), all patients had NLR < 3. In CTP class C group (22 patients), all patients had NLR > 3. In CTP class B group (20 patients), 11 (55%) patients had normal NLR, while 9 (45%) patients had elevated NLR. Chi - square test of association between NLR and CTP class was highly significant (p=0.0001). Sungkar T et al (2019) found a significant correlation between NLR and CTP score (p=0.008) and it was positively correlated (r=0.326). [7] L Chen et al (2014) demonstrated that patients with Child - Pugh C presented higher values of NLR, indicating that NLR is related to the severity of liver disease. [12] Probawati W et al (2016) also found that NLR positively correlated with CTP score.
- **Relation with alcoholism** - In alcoholic group of patients, 26 (74.3%) patients fell in the elevated NLR group, whereas, 5 (33.3%) non - alcoholic patients were in elevated NLR group (p - value 0.006; significant). Nand N et al (2015) reported that NLR correlated with alcohol consumption, with significant rise in heavy drinkers. [10] Maccali C et al (2021) reported higher NLR values in patients of alcoholic etiology of cirrhosis than those non - alcoholic cirrhotic patients (4.86 vs 3.64, P=0.003). [9]

- **Relation with hepatic encephalopathy** - Among 26 patients with hepatic encephalopathy, 24 (92.3%) patients fell in the elevated NLR group. Whereas amongst 24 patients without hepatic encephalopathy, 7 (29%) patients were in elevated NLR group (p - value 0.002; significant). Nand N et al (2015) found that a higher NLR (>4.5) was associated with higher risk of developing complications like hepatic encephalopathy, and as cites. It also showed positive correlation with hepatic encephalopathy and mortality rate. ^[10]
- **Relation with SBP and ascites** - All the 13 patients with SBP had elevated NLR. Out of 37 patients without SBP, 18 (48.7%) had elevated NLR. Chi - square test of association between NLR and SBP was significant (p=0.0002). Among 38 (76%) patients with ascites, 31 (81.6%) patients had elevated NLR. Iliaz et al (2018) found higher NLR values in patients with cirrhosis diagnosed with spontaneous bacterial peritonitis. ^[14]Baweja A et al (2021) also reported NLR to be significantly higher in SBP patients (6.75 +/- 2.7) than those without it (2.81 +/- 1.06) with p value < 0.01. ^[15]
- **Relation with upper GI bleed** - All 18 (36%) patients who suffered upper GI Bleed at presentation or developed in due course of study had elevated NLR. Among patients without upper GI bleed, 19 (59.4%) patients had normal NLR and 13 (40.6%) patients had elevated NLR (p=0.003; significant). Cihan Bedel et al found that the mean NLR levels were found significantly higher in the patients of cirrhosis (5.51) compared to the control group (3.84) (P<0.001). ^[16]

5. Conclusion

The present study found that NLR, which is widely available and inexpensive biomarker of systemic inflammation, can be used as a screening tool in predicting occurrence of complications (e. g., hepatic encephalopathy, spontaneous bacterial peritonitis, ascites, and upper GI bleed) and indirectly predicting the short - term mortality in patients with liver cirrhosis. It can also be used as prognostic marker to detect decompensation in these patients.

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