Evaluation of Neutrophil-to-Lymphocyte Ratio (NLR) and Its Correlation with Severity of Liver Cirrhosis Based on Child-Turcotte-Pugh Score in a Tertiary Care Hospital, Barpeta, Assam

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ABSTRACT

BACKGROUND

Liver cirrhosis (LC) is the final common pathway for all chronic liver diseases. It is a major cause of morbidity and mortality in adults globally. Systemic inflammation has now been proposed to play a crucial role in the natural history of progressive liver damage and is one of the main causes of precipitating compensated liver cirrhosis to decompensated state. Neutrophil to lymphocyte ratio (NLR) has been considered as an important inexpensive biomarker to indicate ongoing inflammation in patients with cirrhosis. The purpose of this study was to find out if there is any significant correlation between neutrophil to lymphocyte ratio and Child Turcotte Pugh score (CTP) among liver cirrhosis patients.

METHODS

We conducted a cross sectional study involving patients diagnosed with liver cirrhosis in Fakhruddin Ali Ahmed Medical College & Hospital, Barpeta, from November 2019 to January 2021. All patients were diagnosed based on clinical history, examination and ultrasound. The study enrolled 101 cirrhotic patients irrespective of aetiology. Total white blood cell (WBC) count, neutrophil count and lymphocyte count were recorded and neutrophil to lymphocyte count was calculated. Child Turcotte Pugh score was calculated by taking data from medical records of the patients.

RESULTS

Out of the 101 patients enrolled in our study, majority were males (78). A significant correlation was found between NLR and CTP score in liver cirrhosis patients. The patients with NLR < 3 showed mean CTP score of 6.1 ± 0.55, with NLR in between 3 to 6 showed CTP score of 8.2 ± 1.2 and with NLR > 6 showed mean CTP score of 11 ± 0.76

CONCLUSIONS

NLR can be used as a single independent biomarker and a simpler scoring system for assessment of severity of liver cirrhosis but needs further studies and evaluation.

KEYWORDS

Neutrophil-to-Lymphocyte Ratio, Child-Turcotte-Pugh Score, Cirrhosis

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DOI: 10.18410/jebmh/2021/616

How to Cite This Article:
Sarma PK, Roy P, Ahmed NU, et al. Evaluation of neutrophil-to-lymphocyte ratio (NLR) and its correlation with severity of liver cirrhosis based on child-Turcotte-Pugh score in a tertiary care hospital, Barpeta, Assam. J Evid Based Med Healthc 2021;8(38):3395-3400. DOI: 10.18410/jebmh/2021/616

Submission 09-08-2021,
Peer Review 15-08-2021,
Acceptance 08-09-2021,
Published 20-09-2021.

BACKGROUND

Liver cirrhosis is defined as diffuse hepatic process characterized by fibrosis and conversion of normal liver architecture into structurally abnormal nodule.[1] It is the final common pathway for all chronic liver diseases. Cirrhosis currently causes 1.16 million deaths making it the 11th most common cause of death.[2,3] It is a major cause of morbidity and mortality in adults globally. Systemic inflammation has now been proposed to play a crucial role in the natural history of progressive liver damage. Cirrhosis associated immune dysfunction syndrome (CAID) is an entity characterised by combination of systemic inflammation and immune deficiency state. It has been described as a multifactorial process which may be secondary to an infectious or non-infectious stimulus.[4,5] The systemic inflammation has been attributed with worsening of liver failure and poor outcome. Dysfunction of innate and adaptive immune system leading to increase in pro inflammatory cytokines is responsible for local as well as systemic injury in patients with cirrhosis.[6,7]

There is an overwhelming evidence of role of inflammatory markers in pathogenesis of liver disease. So, a number of surrogate serum markers have been studied as a prognostic guide for predicting outcome and improving management of decompensated liver disease. Neutrophil to lymphocyte ratio is one such cost effective, readily available and easily calculated marker of systemic inflammation. Neutrophil count helps in identifying ongoing inflammation and lymphocyte count represents immune regulatory pathway.[8] Studies have shown NLR to be useful in predicting outcome and mortality in patients with viral hepatitis, hepatocellular carcinoma, liver transplantation and non-alcoholic fatty liver disease.[9,10,11,12] It has been shown that high levels of NLR could predict a risk of recurrence in patients with various malignancies.

Application of scoring system is useful to predict the outcome and severity of cirrhotic patients. Child-Turcotte-Pugh score that consists of five variables (serum bilirubin level, serum albumin, international normalized ratio (INR), ascites and hepatic encephalopathy) and model for end-stage liver disease (MELD) score which includes the patient's serum bilirubin and creatinine levels and the international normalized ratio for prothrombin time are common scoring systems used in assessing the severity of liver cirrhosis. However, Child-Pugh has some limitations including subjective indexes, such as hepatic encephalopathy and ascites, which may be affected by the use of lactulose and diuretics. The calculation of MELD score is very complex, thus limiting its clinical application. Various studies have shown NLR as an important biomarker of ongoing inflammation and can reflect a person's immunity to liver cirrhosis.[13]

In developing countries where resources are deficient, NLR is an ideal test for early detection of infection and inflammation. Recently, NLR has also emerged as a predictor of mortality independent of MELD scores in patients with cirrhosis and with hepatocellular carcinoma, as well as in candidates on the liver transplantation list.[13,14] Hence, we conducted this study to correlate the association of neutrophil to lymphocyte ratio with severity of liver cirrhosis and comparing it with CTP may be a simple and inexpensive method for assessing the prognosis of cirrhotic patients and as a predictor of complication. Thereby, it can help in slowing the progression of the disease by early detection and timely intervention.

METHODS

This cross-sectional study was conducted in the Department of General Medicine, Fakhruddin Ali Ahmed Medical College & Hospital (FAAMCH), Barpeta from November 2019 to January 2021. Ethical clearance was obtained from the Institutional Ethical Committee and written informed consent was taken from each patient. A total of 101 patients who fulfilled the criteria and admitted during the period were enrolled for the study. Those patients of age 18 years and above, diagnosed with liver cirrhosis (by clinical history, examination and ultrasound) were included in the study. Patients with presence of immune-deficiency diseases, diabetes mellitus, on oral and/or parenteral corticosteroid therapy or other treatments that may affect serum cytokine levels, similar to interferon or antiviral agents for a period of 6 months or less prior to blood sampling, hepatocellular carcinoma or history of any malignancy, dyslipidaemia, acute liver failure, autoimmune disease and pregnancy were excluded from the study because it could affect the laboratory result particularly leukocyte count. An elaborate history, clinical examination, routine laboratory investigations and ultrasonography was done. Inclusion criteria for cirrhosis on sonography were coarse echotexture, nodular liver with or without free fluid, splenomegaly and portal hypertension. Patients with cirrhosis and without ascites or varices were considered as compensated cirrhosis and patients with cirrhosis and ascites, variceal bleed or encephalopathy were considered as decompensated cirrhosis. Laboratory tests were done for all patients which included complete blood count (CBC), renal function and liver function test (LFT). Absolute neutrophil count and absolute lymphocyte count were obtained and accordingly NLR was calculated.

The severity of the liver cirrhosis was evaluated using Child-Turcotte-Pugh score. The scoring ranges from 5 - 15 points and the patients were categorised into three groups -class: A (5 - 6), B (7 - 9), and C (10 - 15) as below (Table. 1)

Clinical and Lab Criteria	Points 1	2	3
Encephalopathy	None	Mild to moderate	Severe
Ascites	None	Mild to moderate	Severe
S. bilirubin (mg/dL)	< 2	2 - 3	➢ 3
S. albumin (gm/dL)	> 3.5	2.8 - 3.5	< 2.8
Prothrombin time	< 4	4 - 6	> 6
Seconds prolonged INR	< 1.7	1.7 - 2.3	> 2.3

Table 1. Child-Turcotte-Pugh score

Child-Turcotte-Pugh class obtained by adding score for each parameter (total points)
Class A = 5 to 6 points (least severe liver disease)
Class B = 7 to 9 points (moderately severe liver disease)
Class C = 10 to 15 points (most severe liver disease)

Statistical Analysis

The data was collected and tabulated as percentage of the values using Statistical Package for the Social Science (SPSS version 21). Mean and standard deviation of different variables including Child-Turcotte-Pugh score were calculated. Significant result was noted as P value < 0.05 was obtained from the analysis. The correlation between NLR and different variables was evaluated using Spearman correlation test.

RESULTS

The cross-sectional study enrolled 101 radiologically diagnosed liver cirrhosis patients, of which 78 were males and 23 were females.

Gender	N	%
Male	78	77.23
Female	23	22.77
Total	**101**	**100**

Table 2. Gender Distribution

Out of the 101 patients, 13 patients were in the age group of 20 - 29 years, 49 patients were in the age group of 30 - 39 years, 34 patients were in the age group of 40 - 49 years and 5 patients were in the age group of 50 - 59 years. Mean age was 37.78 ± 6.7 (range 25 – 56) years in the entire group, while it was 38.03 ± 6.38 years (range: 27 – 56) for men and 36.86 ± 7.54 years (range 25– 51) for women.

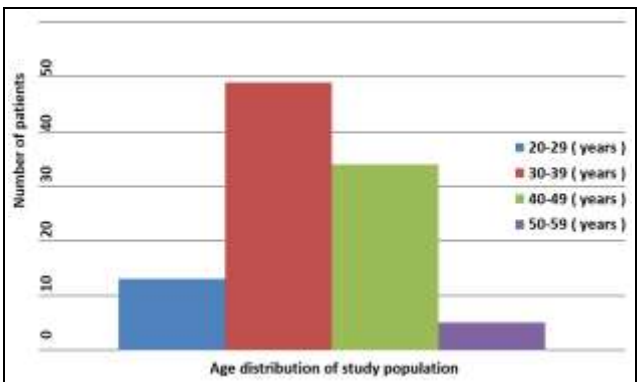

Figure 1. Age Distribution of Study Population

The laboratory values including haemoglobin (Hb), platelet count, serum iron, total iron binding capacity (TIBC), prothrombin time, INR, total bilirubin, blood urea, serum creatinine and serum albumin (mean ± SD) of the patients are tabulated as follows (Table 3):

Characteristics	Cirrhotic Patients
Haemoglobin (g/dL)	8.82 ± 3.2
Platelet count (x109/dL)	112.23 ± 10.5
Serum iron (µg/dL)	28.4 ± 8.7
Total iron binding capacity (µg/dL)	163.72 ± 9.23
Prothrombin time (Secs)	16.3 ± 6.12
INR	1.78 ± 0.59
Total bilirubin (mg/dL)	2.19 ± 1.43
Urea (mg/dL)	30.1 ± 9.21
Creatinine (mg/dL)	1.1 ± 1.68
Albumin (g/dL)	3.2 ± 0.93

Table 3. Laboratory Characteristics of Study Population

The patients were divided into three groups based on NLR: patients having NLR < 3, 3 ≥ NLR ≤ 6, and NLR > 6. The mean age of the patients in group NLR < 3 was 40.6 ± 7.6 years (n = 13), in group 3 ≥ NLR ≤6 was 36 ± 6 years (n = 67) and in group NLR > 6 was 37 ± 8.3 years (n = 21).

The laboratory parameters (mean ± SD) were tabulated into three groups according to the NLR score and correlation analysis was done. Significant correlations were found between NLR score and serum albumin, serum bilirubin and INR. Mean serum albumin of the patients in the NLR < 3 group was 3.63 ± 0.23, in the 3≥ NLR ≤6 group was 3.36 ± 0.23 and in the NLR > 6 group was 2.7 ± 0.54. Mean serum bilirubin of the patients in the NLR < 3 group was 1.40 ± 0.28, in the 3 ≥ NLR ≤ 6 group was 2.10 ± 0.66 and in the NLR > 6 group was 3.01 ± 0.52. Mean INR were 1.31 ±0.16, 1.70 ± 0.46 and 2.4 ± 0.39 for NLR < 3, 3 ≥ NLR ≤ 6 and NLR > 6 respectively.

Variables	NLR < 3	3 ≥ NLR ≤ 6	NLR > 6.	P
Albumin	3.63 ± 0.23	3.36 ± 0.23	2.7 ± 0.54	0.001
Total bilirubin	1.40 ± 0.28	2.10 ± 0.66	3.01 ± 0.52	0.001
INR	1.31 ±0.16	1.70 ± 0.46	2.4 ± 0.39	0.001

Table 4. Laboratory Parameters of CTP Score

Correlation between NLR and CTP

The CTP score of each NLR group was calculated using clinical parameters (ascites, encephalopathy) and laboratory parameters (serum albumin, total bilirubin, INR) (Table 5). 26.31 % of the patients with NLR < 3 showed CTP score of 6 - 7, 42.1 % with NLR in between 3 to 6 showed CTP score of 8 - 9 and 31.57 % with NLR > 6 showed CTP score 10 - 15. There was a strong, positive correlation between NLR and CTP, which was statistically significant (P < 0.001).

Variable	NLR < 3	3 ≥ NLR ≤ 6	NLR > 6.	P
CTP score	6.10 ± 0.55	8.2 ± 1.2	11 ± 0.76	0.001

Table 5. Correlation between NLR and CTP score

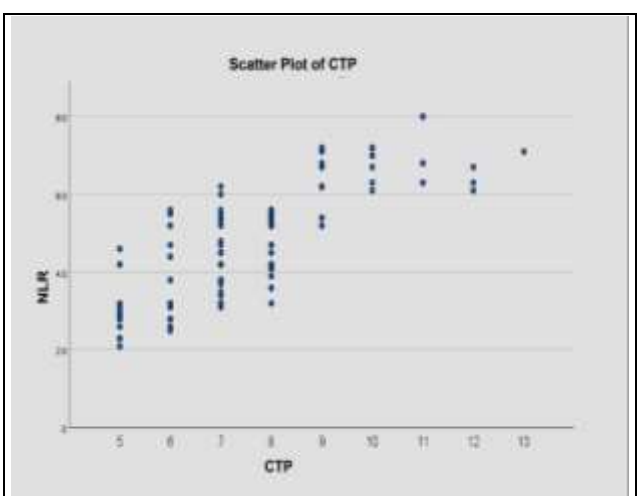

Figure 2. Scatter Plot of NLR by CTP

DISCUSSION

In the present cross-sectional study, we tried to find the correlation between NLR and Child-Turcotte- Pugh Score

without emphasizing on the outcome of the disease. Based on the study, it was observed that NLR had a significant correlation with Child-Turcotte- Pugh score. Thus, the scoring system could be used as severity predictor among decompensated liver cirrhotic patients. It provides evidence that a patient with high NLR value tends to have higher CTP score. CTP score consists of five indicators which also relates to prognosis of liver cirrhotic patients.[15,16] In the study, it was found that NLR was higher in patients grouped under the class B and C of Child-Turcotte- Pugh Score, correlating with the severity of the disease at presentation. Thus, indicating it as a useful tool to assess the severity in patients with liver cirrhosis.

Blood leucocyte count has previously been used as a surrogate marker for sepsis. Many studies demonstrated leukocyte count as an independent predictor of short-term mortality in patients with acute chronic liver failure. [17] However, in patients with cirrhosis it is difficult to make a diagnosis of infection solely based on leucocyte count as it has its own drawbacks. Cirrhotic patients demonstrate abnormal haematological parameters which include anaemia, thrombocytopenia and leukopenia. The pathogenesis described for pancytopenia is multifactorial, with portal hypertension induced sequestration and bone marrow suppression accounting for majority of the cases.[18] Once a patient develops infection, the total count is bound to rise. However, there are evidence which say in 50 % bacteraemia, total count can be normal.[19] Hence, there is no consensus for a leucocyte cut-off point for diagnosing infection.

Neutrophils are the most abundant immune cell population in the body, functioning as "first responders" for detection of invading pathogens.[20] Classical neutrophil effector functions include release of granular contents, cytokines, reactive oxygen species production and release of extracellular traps (NETs) that capture bacteria.[21] During sepsis, neutrophils migrate to liver sinusoids and release NETs,[22] adhere to platelets and contribute significantly to hepatic pathology.

NLR reflects systemic inflammation as well as immune dysregulation and has previously been shown to predict prognosis in stable patients (i.e., without acute decompensation) with end-stage cirrhosis listed for liver transplantation (LT).[23] It has been postulated that this prognostic ability of NLR reflects multiple pathways of the pathophysiology underlying chronic liver disease including induction of low-dose endotoxinemia, which in turn results in a deleterious systemic inflammatory response in cirrhotic patients.[23] As a consequence of such systemic inflammation, the intestinal barrier in cirrhotic patients is compromised. In addition, there may be a qualitative functional defect of neutrophils in cirrhotic patients – beyond their mere ratio to lymphocytes contributing to poor outcomes such as infection, organ failure and mortality.[24]

Practically, NLR represents an easily accessible objective parameter, much like the three laboratory variables that are used to calculate the MELD score itself. As such, NLR is an important emerging variable that can be readily calculated and used by clinicians to inform their understanding of patients with MELD ≤ 20 – a population that we know has a mortality underestimated by MELD alone. A high calculated NLR (≥ 4) may therefore aid in determining risk for cirrhotic decompensation, need for increased monitoring or prophylactic antimicrobial coverage, and urgency for expedited LT in candidates with low MELD.

Indeed, realizing that these conventional methods underestimate mortalities, several objectives, prognostic biomarkers have been explored. These include C reactive protein, serum free cortisol, and vitamin D, all of which may like NLR – reflect systemic inflammatory stress.[25] However, all three of these are potentially confounded by liver disease itself, as the liver is involved physiologically in the production of CRP, in the production of carrying proteins for cortisol, and in hydroxylation of vitamin D. NLR, in contrast, reflects a peripheral inflammatory response.

In the study conducted by He et al. NLR was significantly higher in decompensated than in compensated cirrhosis patients.[26] It was explained that in the state of decompensated cirrhosis there is a complex relationship between the systemic inflammation process and immune system.[27] In cases of compensated cirrhosis, the ligand released from damaged hepatocytes, mentioned as damaged-associated molecular patterns (DAMP) are recognised by the immune system. This results in a sterile systemic inflammation whereas in case of decompensated liver cirrhosis, ligands produced from bacterial components are transported from intestinal tracts into the circulation via static portal circulation and fragility of the gut wall.[28]

Generally, raised neutrophil count suggests on-going systemic inflammation while raised lymphocyte count positively correlates with endotoxin released by the pathogenic organism and cirrhotic severity.[10,29] Nevertheless, its applicability on daily clinical basis is certain since the time-saving and non-invasive interpretation could directly be made by clinician.[30] Other than that, the importance of identifying high NLR patients is to give new severity and mortality predictor. Kalra A et al. has found NLR is associated with cirrhosis stage and liver-related death. Similarly, decompensated liver cirrhotic patients had been used as the inclusion criteria by identifying lowest MELD within 90 days of the samples' death.[10] Leithead JA et al. also suggested NLR as a new prognostic factor for prioritising liver transplant patient.[23]

NLR has been considered as a simple and inexpensive biomarker to reflect clinical conditions like ischaemic heart disease, pneumonia and cancer. Sharma K et al. in his study demonstrated a strong correlation between NLR and CAD (Coronary Artery Disease).[31] H.Shimada et al. in his study showed that in patients of gastric cancer with raised NLR has worst prognosis than those with low NLR.[32] Most studies have shown a higher NLR is associated with poor outcome and prognosis. However, there is no consensus for a definitive cut off value for NLR.

NLR has been demonstrated as an independent marker in predicting mortality in patients with cirrhosis. In a study conducted by Jung Hyun Kwon et al. it was demonstrated that NLR was a useful predictor of mortality of 1-month survival, particularly in Child Pugh class C patients independently.[33] The exact mechanism of NLR to explain its

association with prognosis and correlation with CTP score remains elusive.

In a study conducted by Vineeth V.K et al. he showed that patients with high NLR had a positive correlation with complications, thereby was associated with higher short-term mortality.[34]

In our study, we found a positive correlation between NLR and Child-Turcotte- Pugh Score, P value = 0.001 which was greatly significant. Patients with higher NLR were correlated to Child Turcotte Pugh class B and C, thus showing a positive relationship with the severity of the disease.

CONCLUSIONS

Based on the study, it can be concluded that NLR and CTP score has a positive correlation. NLR could indicate some responses of systemic inflammatory response although the cytokine might have certain role in inflammatory condition (not measured in the study). While CTP score, as severity predictor, is independent of NLR and remains inconsistent in several studies, thus, NLR can be used as an independent biomarker in assessing the severity of the disease and also its prognosis. Thereby, it can help in slowing the progression of the disease by early detection and timely intervention. However, further studies are required to prove its role in using it as a single marker for classifying the severity of cirrhosis.

Limitation of the Study

There were some limitations to the study. It was conducted for a short span of time and therefore adequate sample size could not be collected. Also, as it is a cross-sectional study, follow up of the patients could not be done. In our study, NLR was calculated only one time at admission. Serial monitoring of NLR would be necessary to diagnose complications during hospital stay.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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