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Original Research Article

Neutrophil to lymphocyte ratio and correlation with hepatic fibrosis in patients with chronic hepatitis B

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ABSTRACT

Background: Chronic hepatitis B (CHB) is a dynamic condition involving interaction between the hepatitis B virus, hepatocyte and host immune system. Neutrophil-lymphocyte ratio (NLR) is a cheap, easily available bedside inflammatory marker. The aim of the study was to assess the role of NLR to assess the fibrosis in CHB patients
Methods: It was a prospective cross-sectional study done between January 2021-December 2021, 61 patients with CHB of age 16-50 years were included. Basic demographic and laboratory parameter were assessed. Fibrosis was assessed using fibroscan (ECHOSENS) 502 model. Using NLR cut-off of 1.9 fibrosis was assessed in different groups.
Results: The mean age was 34±13.1 years, 66% were male patients. The mean haemoglobin, total count, platelet counts were 11.3±2.1 g/dl, 7250±2100 cells/ml, 146000±26000/ml respectively. The 38 (62.3%) patients were HBeAg positive and 23 (37.7%) patients HBeAg negative. The 28 (45.1%) patients had no significant fibrosis (<8 kpa) and 33 (54.09%) patients had significant fibrosis (>8 kpa). The 33 patients with significant fibrosis 30 patients had NLR of less than 1.9 and 3 had NLR>1.9. The 28 patients who had fibrosis of less than 6.5 kpa, 26 had NLR more than 1.9 and 2 patients with less than 1.9. Mean N/L ratio values were notably lower in cases with advanced fibrosis when compared to individuals with no/minimal fibrosis ($p<0.0001$). APRI was among 0.32±0.18 and 0.86±0.21 among patients with NLR<1.9 and >1.9 respectively ($p=0.0001$)
Conclusions: Decreased N/L ratio is significantly associated with fibrosis severity and can be utilised to identify patients with advanced disease.

Keywords: CHB, Fibrosis, Neutrophil to lymphocyte ratio, Fibroscan

INTRODUCTION

Hepatitis B virus (HBV) infection is a global public health problem in spite of large-scale efforts to control this disease through education, screening, and vaccination programs.[1] Chronic HBV infection is, defined as hepatitis B surface antigen (HBsAg) positivity for≥6 months. Maternal-foetal transmission of hepatitis B virus is an important problem, particularly in endemic areas such as Southeast Asia and Africa about 400 million human beings are chronically infected with hepatitis B which causes about 1 million deaths every year from decompensated cirrhosis or HCC.[2-4] CHB may lead to liver failure during the long disease process when patients are exposed to various factors such as HBV mutations, coinfection with other hepatotropic viruses, alcohol overdose and bacterial infections.[5] To date, liver transplantation is still the only effective treatment option that could alter the grave prognosis of HBV-related acute liver failure.[4]

In CHB patients, the identification of liver fibrosis degree is an important step for antiviral treatment.[5] Liver biopsy is the gold standard in detecting fibrosis in CHB patients is invasive and has various complications and there is practical difficulty in getting consent for liver biopsy.[6]

Nowadays, physicians and patients prefer non-invasive methods for evaluation of liver fibrosis degree in patients with CHB. In particular, lymphomononuclear cells have an important role in inflammatory pathways on the road to cirrhosis. In this study we attempted to study the relation between neutrophil to lymphocyte ratio in assessing the fibrosis in CHB. NLR is a simple and easily available tool of systemic inflammatory response that relates with prognosis in advanced disease states[7]. Even though many models which predicts prognosis of this disease have been suggested, a simpler, cheaper and more accurate biomarker is needed urgently. NLR is calculated from complete blood count and differential leukocyte count. NLR recently has emerged as a new biomarker of inflammation, which predicts the prognosis.[8]

The increased NLR values are associated with poor outcomes for COVID-19 infection and various types of cancers, including colorectal cancer, oesophageal cancer, gastric cancer, non-small-cell lung cancer, ovarian cancer and pancreatic cancer. Importantly, it has been reported that the NLR value was an independent prognostic parameter in cardiovascular disease. NLR if found useful, could be a useful tool in analysing the severity of liver fibrosis, especially in resource constraint setup.[9-12] Studies done using NLR as a marker of fibrosis in CHB is sparse in Indian literature and still scanty information available regarding the correlation with fibroscan. Hence, we thought the study could be useful if found significant.

METHODS

This was a prospective cross-sectional study, which was conducted in the department of digestive health and diseases, Government peripheral hospital, Annanagar which is attached to government Kilpauk medical college, Chennai. This study included 61 patients with CHB who were willing to give consent and of 18- 50 years of age. Study was done between Jan 2021-Dec 2021.

An informed consent was obtained and detailed history regarding presentation, past history of jaundice, diabetes, systemic hypertension, dyslipidaemia was collected. Personal history of smoking, alcohol consumption, tattooing and sexual history were obtained. Patients with CHB patients who regularly drank more than 20 gm alcohol per week, decompensated liver disease, diabetes, obese, patients with metabolic syndrome, Co infection with Hepatitis C and HIV, renal failure, hepatocellular carcinoma and other malignancies, patients who did not give consent for the study, ALT more than 5-fold or above were excluded.

Blood was collected for complete blood count with differential count of leukocytes, liver function test, HbsAg and anti HCV, HBV DNA load, prothrombin time, random blood sugar, urea and creatine. Fibrosis was assessed by fibroscan in all the patients using fibroscan (ECHOSENS) 502 touch model, version 5. The probes used were M probe or the standard probe which induces a central frequency of 3.5 MHZ which measures to a depth of 25 to 65 mm. For obese individuals XL probe is used which generates a frequency of 2 MHZ and can measure up to a depth of 75 mm. Fibroscan measure a stiffness from 1.5 kPa to a maximum of 75 kPa. A value of up to 6.5 kpa is normal. A value between 6.6 to 7.9 kpa correlates with Metavir F1 and a value between 8-12.5 suggests F2/F3 and a value above 12.5 suggests F4. The data was entered in MS EXCEL spreadsheet and analysis was done using statistical package for social sciences (SPSS) version 24.0.

RESULTS

Total of 85 patients with CHB was assessed, 24 were excluded as not fitting our criteria and 61 patients was included in the study. The mean age was 34±13.1 years, 66% were male patients. The mean Hb was 11.3±2.1 g/dl, mean total white blood count was 7250±2100/ml, mean platelet count was 146000±26000/ml. mean neutrophil count was 46±12%, mean lymphocyte count was 42±16%, 38 (62.3%) patients were HBeAg positive and 23 (37.7%) patients HBeAg negative. Mean albumin was 3.5±1.2 g/dl.

Fibrosis

The fibroscan scores were evaluated and sub grouped into F0/F1 (fibrosis score less than 8 kpa) and significant fibrosis (F2 and above) more than 8 kpa. Around 28 (45.1%) patients had no significant fibrosis and 33 (54.09%) patients had significant fibrosis. Five (8.2%) patients had stage four fibrosis (cirrhosis).

Table 1: The demographic and laboratory parameters of the patients included in the study.

Characteristics	Variables
N	61
Sex (male/female)	40/21
Age (years)	34±13.1
Hemoglobin (g/dl)	11.3±2.1
White blood count (per ml)	7250±2100
Platelet (per ml)	146000±26000
Aspartate aminotransferase (U/l)	43±16
Alanine aminotransferase (U/l)	60±23
Albumin (g/dl)	3.5±1.2
HBeAg (+)	38
Fibrosis	
F0/F1	28
≥F2	33

Fibrosis and NLR

The two groups were analysed for NLR values. Using a cut off value of NLR 1.9, the severity of fibrosis was analysed (significant/advanced fibrosis group and no fibrosis group). Of these 33 patients with significant

fibrosis 30 patients had NLR of less than 1.9 and 3 had NLR>1.9. Among 28 patients who had fibrosis of less than 6.5 kpa, 26 had NLR more than 1.9 and 2 patients with less than 1.9. Mean N/L ratio values were notably lower in cases with advanced fibrosis when compared to individuals with no/minimal fibrosis (p<0.0001). The sensitivity and specificity of NLR value below 1.9 for detecting significant fibrosis is 90.91% and 92.86% respectively. Male patients had a significantly low NLR values compared to females. Mean AST/ALT values were higher among patients with NLR<1.9 (Table 2). Mean APRI was among 0.32±0.18 and 0.86±0.21 among patients with NLR≤1.9 and >1.9 respectively (p=0.0001).

Table 2: Demographic and biochemical details of patients with significant fibrosis and without fibrosis.

Characteristics	NLR ≤1.9	NLR>1.9	P value
N	33	28	
Sex (male/female)	27/6	13/15	0.003
Age (years)	38±8.1	32±6.5	0.2
Haemoglobin (g/dl)	10.2±2.8	11.3±1.9	0.45
White blood count (per ml)	9360±1900	5600±1100	0.06
Platelet (per ml)	132000±13000	156000±56000	0.0002
Aspartate aminotransferase (U/l)	56±21	38±16	0.006
Alanine aminotransferase (U/l)	74±32	42±18	0.002
Albumin (g/dl)	3.3±1.3	3.6±1.5	0.4
APRI (AST-Platelet ratio index)	0.32±0.18	0.86±0.21	0.0001
HBVDNA load (IU/ml)	215300±23000	252000±18000	0.6
HBeAg+	20	18	0.08
HBeAg-	13	10	0.07
Fibrosis			
F0/F1	2	26	<0.0001
≥F2	30	3	<0.0001

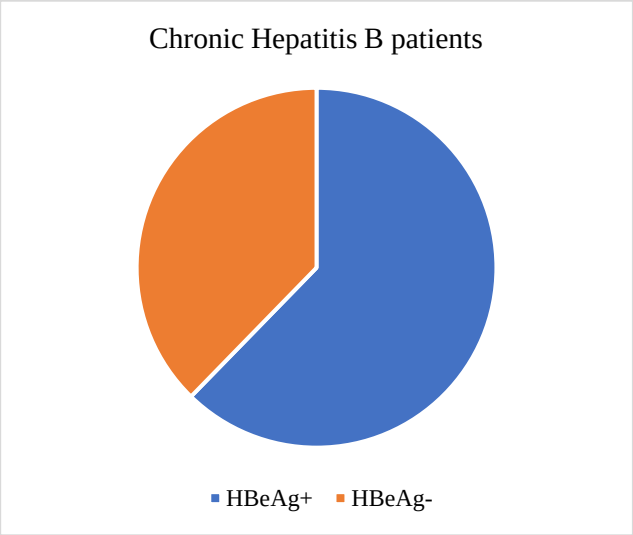

Figure 1: Patients HBeAg status.

DISCUSSION

In this present study, we assessed NLR as a novel surrogate marker for assessing the severity of liver fibrosis in CHB patients. The results of our study shows that patients with CHB and advanced fibrosis have a significantly lower NLR compared to CHB patients with no/minimal fibrosis.

Thus, decreased levels of the peripheral blood NLR were found to give high sensitivity, specificity and predictive values in CHB patients with advanced fibrosis. With these findings, it is suggested that the NLR is a novel non-invasive marker of fibrosis in CHB patients. In CHB patients, identification of the degree of liver fibrosis is necessary and corner stone for starting antiviral treatment. Biopsy of liver though it's a gold standard, is an invasive procedure. Hence, non-invasive methods are preferred for evaluating degree of liver fibrosis. Hepatic lobular inflammation plays a key role in fibrosis and cirrhosis in CHB patients.[13-15] Peripheral lymphocyte and mononucleated cells have an essential role in these inflammatory pathways during development of fibrosis and cirrhosis.[16]

It is controversial whether the NLR exactly reflects the mononuclear inflammation occurring at the tissue level. A recent study by Alkhouri et al revealed that the NLR was higher in patients with non-alcoholic steatohepatitis and significant fibrosis when compared with patients without significant fibrosis.[17] But study by Kekilli et al shows that NLR is significantly lower and values of less than 1.9 is useful for predicting fibrosis. NLR is an easily available index of systemic inflammatory response that correlates with prognosis in advanced disease states.[9]

In the literature, the NLR has been studied in various neoplastic and inflammatory states like ulcerative colitis,

acute pancreatitis, Crohn's disease, breast cancer, colorectal cancer, lung cancer and hepatocellular malignancy.[10-12] NLR demonstrated that it is efficacious in patients with hepatocellular carcinoma for predicting outcomes following liver resection/liver transplantation.[18] Our study depicts that NLR values significantly lower in patients having progressive fibrosis of liver.

As evidence in literature shows that low platelet counts are associated with advanced hepatic fibrosis, we found that the mean platelet count was significantly lower in patients with advanced fibrosis in our study.[19] In the literature, some studies have revealed that AST is correlated well with severity of fibrosis and predicts hepatic fibrosis.[20]

In this present study, we found a relationship between serum AST levels and hepatic fibrosis was significant. Despite the suggestion of many studies which suggests that serum ALT level is not correlated with the fibrosis severity in CHB patients. This study shows there exists a significant association between the NLR and serum ALT levels, thus suggesting the association between ALT and fibrosis. Literature shows an association with HBV DNA load and fibrosis suggesting higher serum HBV DNA levels had higher fibrosis scores.[21] Contrast to this was found in our study as there no significant difference between serum HBV DNA levels among two groups.

Limitations of the study were sample size is less, liver biopsy was not done.

CONCLUSION

Decreased N/L ratio is significantly associated with fibrosis severity and can be utilised to identify patients with advanced disease. A standardized cut-off value for NLR would simplify the determination of advanced fibrosis in patients with CHB. NLR, a low-cost and easily useful test, provides a beneficial and speedy evaluation of fibrosis for patients with CHB.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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