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**Columns:** **PROSPECTİVE STUDY**

**Is neutrophil to lymphocyte ratio associated with liver fibrosis in patients with chronic hepatitis B?**

Kekilli M *et al*. Neutrophil to lymphocyte ratio in chronic hepatitis B

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**Abstract**

**AIM :** To explore the association between neutrophil to lymphocyte (N/L) ratio and the fibrosis degree of liver ﬁbrosis in cases with chronic hepatitis B infection.

**METHODS:** Between December 2011 and February 2013, 129 consecutive chronic hepatitis B patients who were admitted to the study hospitals for histological evaluation of chronic hepatitis B related liver ﬁbrosis were included in this retrospective study. The participants were separated into two groups based upon the fibrosis score: individuals with a fibrosis score of F0 or F1 were included in the “no/minimal liver fibrosis” group, whereas patients with a fibrosis score of F2, F3, or F4 were included in the “advanced liver fibrosis” group. The statistical package for social sciences 18.0 for Windows was used to analyze the data. A *P* value of < 0.05 was accepted as statistical significant.

**RESULTS:** Three experienced pathologists were blindly evaluated the ﬁbrotic status and inﬂammatory activity of 129 liver biopsy samples of chronic hepatitis B patients. After the histopathological examination “no/minimal fibrosis” group included 79 individuals, while the “advanced fibrosis” group included 50 individuals. Mean (N/L) ratio levels were notably lower in cases with advanced fibrosis when compared with patients with no/minimal fibrosis. The mean value of the aspartate aminotransferase-platelet ratio index was extremely higher in cases with advanced fibrosis in comparison with individuls with no/minimal fibrosis.

**CONCLUSION:** Depressed levels of peripheral blood N/L ratio were found to give high sensitivity, speciﬁcity and predictive values in chronic hepatitis B virus (CHB) patients with significant fibrosis. The prominent finding of our research suggests that N/L ratio can be used as a novel noninvasive marker of fibrosis in patients with CHB.

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**Key words:** Chronic hepatitis B; Liver fibrosis; Neutrophil to lymphocyte ratio; Fibrotic stage; İnﬂammatory activity; Non-invasive marker

**Core tip:** Depressed levels of peripheral blood neutrophil to lymphocyte ratio found to give high sensitivity, specificity and predictive values in chronic hepatitis B virus (CHB) patients with significant fibrosis. The main finding of our study relates to the identification of neutrophil to lymphocyte ratio as a novel noninvasive marker of fibrosis in patients with CHB.

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**INTRODUCTION**

More than 350 million human beings globally suffer from chronic hepatitis B virus (CHB) infection[1-2]. Assessment of the degree of liver ﬁbrosis is crucial for prognostic and therapeutic decisions in cases with chronic hepatitis B[3]. Presently, liver biopsy is the gold standard for estimating the seriousness of liver fibrosis. Anyway, the exactness of this invasive procedure is influenced by technical and methodological interventions, for example nearly 20% of the patients experience misclassiﬁcation of ﬁbrosis stage[4]. Nowadays, non-invasive methods have become favorable as an alternative for liver biopsy for predicting liver ﬁbrosis like Fibro Test, mean platelet volume, FibroIndex and Hepascore[5–12]. However, larger part of these methods is not readily available and not cost-effective.

Liver ﬁbrosis is an inevitable process in CHB. Many inﬂammatory cytokines, such as transforming growth factor-beta (TGF-beta) and platelet-derived growth factor, have been displayed to activate hepatic stellate cells and advanced extracellular matrix deposition, which will eventually conduct to liver ﬁbrosis[13-16]. The neutrophil to lymphocyte (N/L) ratio is a noninvasive and inexpensive marker of inﬂammation which can be simply acquired from the complete blood count. This marker combines data from two distinctive pathways, the lymphocytes that portray the regulatory pathway and the neutrophils that are liable for ongoing inﬂammation[17,18]. Alkhouri *et al*[21] exhibited that among individuals with nonalcoholic fatty liver disease, the N/L ratio is intensely related with histological changes and can be used to recognize cases with progressive disease. In the literature, it has been shown that besides chronic inflammatory diseases, malignancy, many infections, cardiac problems, diabetes, renal and/or hepatic failure, metabolic syndrome, thyroid disease, and many drugs may easily influenced the N/L ratio[17,19-21].

In this research, we aimed to explore the association between the N/L ratio and the severity of liver ﬁbrosis in cases with chronic hepatitis B infection.

**MATERIALS AND METHODS**

Between December 2011 and February 2013, 129 consecutive patients infected with chronic hepatitis B, who admitted to the study hospitals for histological assessment of liver ﬁbrosis, were included in this retrospective study. The participants were chosen from three hospitals in Turkey: Hitit University Hospital, Gulhane Military Medical School Ankara Hospital and Gulhane Military Medical School Haydarpasa Training Hospital.

All cases were treatment naïve CHB patients. Patients who regularly drink > 20 g alcohol/wk, those with antibiotic and/or antiinflammatory drug use, decompensated liver disease, renal failure, thyroid disease, co-infections, chronic inflammatory disease, diabetes, hepatocellular carcinoma and other malignancies, previous liver surgery or liver transplantation were excluded from the study.

Demographic, clinical and laboratory data were collected. Hematological and standard biochemical parameters were tested at the same time as the liver biopsy, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, gamma glutamyl transpeptidase (GGT), albumin, alpha-1 globulin, alpha- 2 globulin, beta globulin, gamma globulin, albumin/ globulin ratio, prothrombin time (PT), and alpha fetoprotein (AFP). The NLR was calculated by dividing the neutrophil count by the lymphocyte count. APRI, AAR, API and CDS were determined according to the following accepted formulas:

AAR: AST/ALT

API: Age (year): < 30= 0; 30 – 39=1; 40 – 49 = 2; 50 – 59=3; 60 – 69=4; > 70=5, PLT count (10 9 /L): ≥ 225 = 0;200 - 224 = 1; 175 – 199 = 2; 150 – 174 = 3; 125 – 149 = 4; ≤ 125 = 5 API is the sum of the above

CDS: PLT count (10 9 /L): > 340 = 0; 280 – 339 = 1; 220 – 279 = 2; 160 – 219 = 3; 100 – 159 = 4; 40 – 99 = 5; < 40 = 6, ALT/AST ratio: > 1.7 = 0; 1.2 – 1.7 = 1; 0.6 – 1.19 = 2; < 0.6 = 3 INR: < 1.1 = 0; 1.1 – 1.4 = 1; > 1.4 = 2

CDS is the sum of the above

APRI: [(AST/ULN)/PLT (10 9/L)] × 100

Liver biopsy samples were acquired with a 17 G needle applying an ultrasonography-guided technique. The obtained biopsy samples were ﬁxed in 4%-buffered formalin and then inserted in parafﬁn. Biopsy samples were prepared with hematoxylin and eosin and Masson trichrome stain for microscopic evaluation. In case of inadequate number of portal tracts (< 6) and/or length (< 1.5 cm), liver biopsy samples were excluded from ultimate analysis. All biopsy samples were evaluated by same three experienced pathologists and these pathologists were blinded to the clinical data of the cases.

The histological activity was assessed according to the Histological Activity Index score and fibrosis score was estimated according to Metavir Scoring System. The cases were separated into two groups based up on the fibrosis score: patients with a score of F0 or F1 were chosen as “no/minimal fibrosis” group, while patients with a score of F2, F3, or F4 were chosen as “advanced fibrosis” group[22].

***Statistical methods***

Data was analysed using the Statistical Package for Social Sciences (SPSS) 18.0 for Windows and expressed as mean ± SD for normally distributed variables, as median and range for non-normally distributed variables, and count and percent for categorical variables. Categorical variables were compared by chi-squared test or Fisher exact test and continuous variables were compared by Student’s *t*-test or Mann–Whitney test as appropriate. Receiver operating characteristics analysis was practiced to appraise the likely usefulness of N/L ratio in recognizing patients with liver ﬁbrosis. The cut-off values which raised both sensitivity and speciﬁcity were preferred. A p value of < 0.05 was accepted as statistical significant.

**RESULTS**

The mean age of the patients was 43.9±17.6 years (92 male and 37 female). In our research, 92 patients (71.4%) had CHB with negative HBe antigen, and 37 patients (28.6%) had CHB with positive HBe antigen. After evaluating the biopsy samples in accordance with METAVIR scoring system, 37 cases (28.7%) had a ﬁbrosis stage of F0, 42 (32.6%) had a liver ﬁbrosis stage of F1, 19 (14.7%) had a stage of F2, 26 (20.2%) had a stage of F3, and 5 (3.9%) had a stage of F4. In general, the “no/minimal fibrosis” group included 79 patients, while the resting 50 individulas were in the “advanced fibrosis” group. The demographic, biochemical, and histological features of the cases are displayed in Table 1.

The two groups were assessed regarding N/L ratio values. Mean N/L ratio values were notably lower in cases with advanced fibrosis when comparing to individuals with no/minimal fibrosis (*P* = 0.001). ROC curve analysis revealed that the optimum cut-off point of ≤ 1.9 had the highest sensitivity (80.0%) and speciﬁcity (53.2%) for the discerning of fibrosis ≥ 2 in CHB patients (Figure 1) with an area under the curve (AUC) of 0.67 (95%CI: 0.58-0.76).

No significant difference was present between the two groups regarding sex. However, a meaningful difference was found between two groups in terms of age. The study groups were divided into subgroups according to sex, age, HAI and Metavir score. Mean age was 52.28 ± 4.7 for males and 46.63±3.26 for females (*P* = 0.243). Median HAI score was 7 (3-12) for females and 7 (2-11) for males (*P* = 0.177). Median Metavir score was 3 (0-6) for females, and 2 (0-6) for males (*P* = 0.277). The mean platelet and neutrophil counts were meaningfully lower in advanced fibrosis group when comparing with no/minimal fibrosis group. Mean corpuscular volume was significantly higher in cases with advanced fibrosis in comparison with patients with no/minimal fibrosis. The mean serum AST, ALT, and total bilirubin levels were significantly higher in cases with advanced fibrosis. The mean values of APRI and AAR index were significantly higher in individulas with significant fibrosis. HAI index was significantly higher in patients with advanced fibrosis (Table 2).

**DISCUSSION**

In this research, we evaluated N/L ratio as a surrogate marker for severity of liver fibrosis in patients with CHB. Our results revealed that CHB patients with advanced fibrosis have significantly lower N/L ratio rather than CHB patients with no/minimal fibrosis. In other words, decreased levels of peripheral blood N/L ratio were found to give high sensitivity, speciﬁcity and predictive values in CHB patients with advanced fibrosis. In the light of our findings, it can be suggested that N/L ratio can be accepted as a novel noninvasive marker of fibrosis in patients with CHB.

In patients with CHB, the detection of liver ﬁbrosis degree is an inevitable step for antiviral treatment. Still, as an invasive procedure, liver biopsy is the gold standard in the evidenced based therapy of CHB patients. Nowadays, non-invasive methods for evaluation of liver ﬁbrosis degree is favorable in patients with CHB[23-25].

In general, lymphomononuclear cells play a pivotal role in inflammatory pathways on the road to cirrhosis[26]. At the end of our study we noticed that neutrophil count was notably lower in cases with advanced fibrosis compared with patients with no/minimal fibrosis. A subject open to debate that N/L ratio may not exactly express the mononuclear inflammation occurring at the tissue level. However, a recent paper by Alkhouri *et al*[27] exhibited that the N/L ratio was elevated in patients with NASH and significant fibrosis compared with patients who did not have NASH.

N/L ratio is a non-complex and easily available index of systemic inﬂammatory response that correlates with prognosis in advanced disease states. In the literature N/L ratio has been researched in various inﬂammatory status and neoplastic diseases such as ulcerative colitis, crohn disease, acute pancreatitis, colorectal cancer, breast neoplasms, lung cancer and hepatocellular carcinoma[28-34]. Furthermore, in the light of current suggestions, N/L ratio is practical for estimating survival after coronary interventions[34] and non-ST-segment elevation myocardial infarction[35]. Moreover, it has been exhibited that this ratio may be efficacious in forecasting outcomes among individuals who underwent liver resection operations or liver transplantation surgery in case of hepatocellular carcinoma[31,36]. Our current findings showed that NLR values are considerably lower in cases with advanced liver fibrosis.

Even though prothrombin time (PT) is suggested to be prolonged with the progression to liver cirrhosis, some researchers have displayed that lengthening of PT is not an exact marker of fibrosis[10,40,42,46]. In our study we noticed that PT was not significantly prolonged in cases with advanced liver fibrosis.

Although there are papers suggesting low platelet counts to be related with advanced hepatic fibrosis, there are other studies addressing the contrary idea[5,37,38–42,44–46]. In this current research we found that the mean platelet count was considerably lower in cases with advanced fibrosis.

Previously, it has been exhibited that serum AST level is not closely related with fibrosis degree in cases with CHB. In the literature, there have been a few studies suggesting AST is an exact predictor of hepatic fibrosis[10,39-41,44-46]. However in this researc, we have found a relationship between serum AST levels and hepatic fibrosis. On the other hand, despite the suggestions of papers regarding serum ALT level is not associated with the fibrosis scores of cases with CHB[10,37,39-41,44,46], we found an association between serum ALT level and fibrosis in our study.

In the literature, previously, it has been shown that individuals with higher serum HBV DNA levels have higher fibrosis scores[37,38,40,43-46]. However, no association was found between serum HBV DNA levels and hepatic fibrosis scores in our research.

In conclusion, the present study has showed for the ﬁrst time that in patients with CHB, N/L ratio is powerfully associated with histological severity and can be used to identify patients with advanced disease. If our data is approved in future studies, we believe that a standardized cut-off value for N/L ratio would simplify the determination of advanced fibrosis in patients with CHB. We hence suggest that N/L ratio, a low-cost and easily useful test, provides a beneficial and speedy evaluation of fibrosis for patients with CHB. In the light of our findings it can be expressed that the N/L ratio, in combination with other noninvasive parameters, may assist determining individuals at high risk of having advanced and progressive disease.

**COMMENTS**

***Background***

Assessment of the degree of liver ﬁbrosis is crucial for prognostic and therapeutic decisions in cases with chronic hepatitis B. Presently, liver biopsy is the gold standard for estimating the seriousness of liver fibrosis. Anyway, the exactness of this invasive procedure is influenced by technical and methodological interventions, for example nearly 20% of the patients experience misclassiﬁcation of ﬁbrosis stage. The neutrophil to lymphocyte (N/L) ratio is a noninvasive and inexpensive marker of inﬂammation which can be simply acquired from the complete blood count.

***Research frontiers***

N/L ratio combines data from two distinctive pathways, the lymphocytes that portray the regulatory pathway and the neutrophils that are liable for ongoing inﬂammation. It has been exhibited that among individuals with nonalcoholic fatty liver disease, the N/L ratio is intensely related with histological changes and can be used to recognize cases with progressive disease. Besides chronic inflammatory diseases, malignancy, many infections, cardiac problems, diabetes, renal and/or hepatic failure, metabolic syndrome, thyroid disease, and many drugs may easily influenced the N/L ratio.

***Innovations and breakthroughs***

In this research, we evaluated N/L ratio as a surrogate marker for severity of liver fibrosis in patients with chronic hepatitis B virus (CHB). Our results revealed that CHB patients with advanced fibrosis have significantly lower N/L ratio rather than CHB patients with no/minimal fibrosis. In other words, decreased levels of peripheral blood N/L ratio were found to give high sensitivity, speciﬁcity and predictive values in CHB patients with advanced fibrosis. In the light of our findings, it can be suggested that N/L ratio can be accepted as a novel noninvasive marker of fibrosis in patients with CHB.

***Applications***

The present study has showed for the ﬁrst time that in patients with CHB, N/L ratio is powerfully associated with histological severity and can be used to identify patients with advanced disease. If our data is approved in future studies, we believe that a standardized cut-off value for N/L ratio would simplify the determination of advanced fibrosis in patients with CHB. We hence suggest that N/L ratio, a low-cost and easily useful test, provides a beneficial and speedy evaluation of fibrosis for patients with CHB.

***Terminology***

In patients with CHB, the detection of liver ﬁbrosis degree is an inevitable step for antiviral treatment. Still, as an invasive procedure, liver biopsy is the gold standard in the evidenced based therapy of CHB patients. Nowadays, non-invasive methods for evaluation of liver ﬁbrosis degree is favorable in patients with CHB. N/L ratio is a non-complex and easily available index of systemic inﬂammatory response that correlates with prognosis in advanced disease states. In the literature N/L ratio has been researched in various inﬂammatory status and neoplastic diseases such as ulcerative colitis, crohn disease, acute pancreatitis, colorectal cancer, breast neoplasms, lung cancer and hepatocellular carcinoma.

***Peer review***

The manuscript investigated the association between N/L ratio and the severity of the liver fibrosis in patients with chronic hepatitis B infection. Their results showed that N/L ratio was decreased in CHB patients with significant fibrosis. The study was innovation and might provide a noel non-invasive marker of fibrosis in CHB patients. It is a well-designed study that offers more to our knowledge in this very interesting field.

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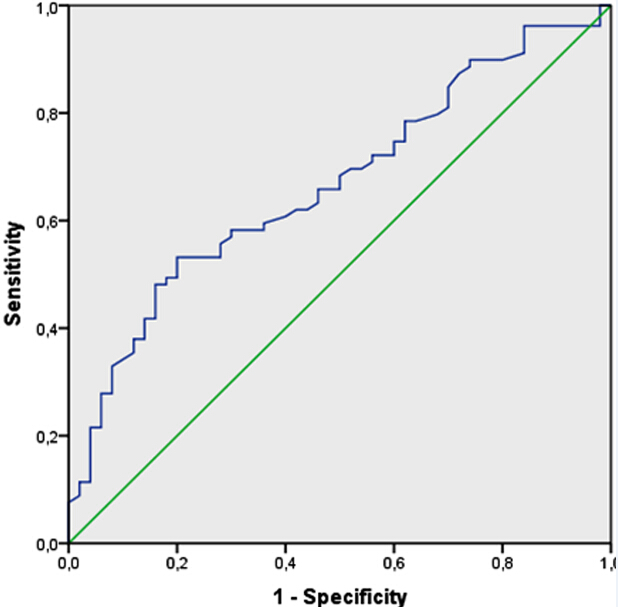
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**Figure 1 Receiver operating characteristics curve analysis of N/L ratio for the severity of liver ﬁbrosis in patients with chronic hepatitis B infection.**



**Table 1 Demographic, biochemical, and histological characteristics of patients**

|  |  |
| --- | --- |
| **Characteristic** | |
| *n* | 129 |
| Sex (Male/Female) | 92/37 |
| Age (yr) | 43.9 ± 17.6 (range,18-81) |
| Hemoglobin (g/dL) | 14.7 (13.4-15.6) |
| White blood cell (× 103 µL) | 6300 (5400-7400) |
| Platelet (× 103 µL) | 217000 (180000-266000) |
| Red blood cell distribution width | 13.2 (12.5-13.5) |
| Mean corpuscular volume | 89.2 (85-91.3) |
| Platelet distribution width | 15.8 (12.9-16.3) |
| Aspartate aminotransferase (U/L) | 41 (28-67) |
| Alanine aminotransferase (U/L) | 54 (33-99) |
| HBeAg (+) | 37 |
| HBVDNA (IU/mL) | 676500 (89000-13113084) |
| Histology Activity Index | 6 (4-8) |
| Fibrosis |  |
| 0 | 37 (28.7) |
| 1 | 42 (32.6) |
| 2 | 19 (14.7) |
| 3 | 26 (20.2) |
| 4 | 5 (3.9) |

**Table 2 Demographic and biochemical characteristics of patients with significant fibrosis and patients with no/minimal fibrosis**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Fibrosis < 2** | **Fibrosis ≥ 2** |  | |
| *n* | 79 | 50 |  |
| Age | 37 (23-53) | 55 (37.8-65) | < 0.001 |
| Sex (Male/Female) | 57/22 | 35/15 | 0.8 |
| HbeAg (+) | 23 | 14 | 0.94 |
| HBV DNA (IU/mL) | 460000 (47219-9643500) | 1215000 (165250-18492000) | 0.13 |
| HAI | 4 (3-6) | 8 (7-10) | < 0.001 |
| Hemoglobin (g/dL) | 14.7 (13.5-15.7) | 14.8 (13.2-15.6) | 0.76 |
| White blood cell (× 103 µL) | 6300 (5600-7450) | 5650 (4950-7350) | 0.32 |
| Platelet (× 103 µL) | 235000 (185500-270000) | 198500 (167750-242500) | 0.047 |
| Red blood cell distribution width | 13.4 (12.5-13.7) | 13.0 (12.5-13.4) | 0.51 |
| Mean corpuscular volume | 88 (83.8-92) | 90.7 (87.2-92.8) | 0.006 |
| Platelet distribution width | 15 (12.7-16.5) | 16.1 (13.6-16.2) | 0.46 |
| Neutrophil | 50.7% (5.3-62.4) | 41.7% (3.0-54.5) | 0.005 |
| Lymphocyte | 25.2% (2.4-33.0) | 23.6% (2.1-35.2) | 0.92 |
| Neutrophil lymphocyte ratio | 1.9 (1.3-2.6) | 1.5 (1.1-1.8) | 0.001 |
| Prothrombin time (INR) | 1.05 (0.95-1.10) | 1.05 (0.99-1.13) | 0.43 |
| Aspartate aminotransferase (U/L) | 33 (24-52) | 49 (41-109) | < 0.001 |
| Alanine aminotransferase (U/L) | 52 (28-85) | 54.5 (42-137) | 0.03 |
| Albumin (g/dL) | 4.3 (4.1-4.5) | 4.3 (4.2-4.7) | 0.16 |
| AAR | 0.73 (0.56-0.93) | 0.79 (0.67-1.07) | 0.03 |
| API | 3 (1-4) | 3 (2-5.25) | 0.21 |
| CDS | 3 (3-4.75) | 4 (3-5) | 0.12 |
| APRI | 0.35 (0.21-0.55) | 0.73 (0.45-1.0) | < 0.001 |

AAR: AST/ALT, API: Age (yr): < 30 = 0; 30 – 39=1; 40-49 = 2; 50-59 = 3; 60-69 = 4; > 70 = 5, PLT count (10 9 /L): ≥ 225 = 0; 200-224 = 1; 175-199 = 2; 150-174 = 3; 125 – 149=4; ≤ 125 = 5 API is the sum of the above; CDS: PLT count (10 9 /L): > 340 = 0; 280-339 = 1; 220-279 = 2; 160 – 219 = 3; 100-159=4; 40-99 = 5; < 40 = 6, ALT/AST ratio: > 1.7 = 0; 1.2 – 1.7 = 1; 0.6-1.19 = 2; < 0.6 = 3 INR: < 1.1 = 0; 1.1 – 1.4=1; > 1.4 = 2 CDS is the sum of the above; APRI: [(AST/ULN)/PLT (10 9/L)]x100 INR:  International Normalized Ratio.