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Relationship between histological stage and neutrophil to lymphocyte ratio in chronic hepatitis C

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Abstract

Aim: The histological stage is crucial for the management of the patients with chronic hepatitis C. Because of the invasiveness and some limitations of liver biopsy a lot of noninvasive tests are in search intensively to use instead of liver biopsy. In this study, we searched the relationship of neutrophil to lymphocyte ratio with the stage of inflammation and fibrosis in histology in patients with chronic hepatitis C.

Materials and Methods: This study retrospectively investigated data of 62 patients with chronic hepatitis C and 40 healthy controls.

Results: Mean neutrophil to lymphocyte ratio values in chronic hepatitis C and control groups were 1.86 (0.89-3.94) and 1.38 (0.73-2.93) respectively (p=0.001). In the chronic hepatitis C group there were 23 (%37) patients with advanced fibrosis (Ishak score>2) and 39 (%63) patients with mild fibrosis (Ishak score≤ 2). In patients with advanced fibrosis, mean neutrophil to lymphocyte ratio was high according to patients with mild fibrosis (2.10 (1.21-3.54) and 1.71(0.89-3.94) respectively, p=0.006). In receiver operating characteristic (ROC) curve analysis, cut off value for neutrophil to lymphocyte ratio in advanced fibrosis was 1.76 (sensitivity 86.9%, specificity 61.5%, NPV 88.9%, PPV 57.1%, AUC: 0.711).

Conclusion: Neutrophil to lymphocyte ratio can predict fibrosis stage in chronic hepatitis C. But more studies are necessary to use neutrophil to lymphocyte ratio in clinical practice or how this parameter change with treatment.

Introduction

Hepatitis C virus (HCV) is one of the frequent etiologic factor of chronic liver disease, and it is estimated that the number of patients with chronic hepatitis C worldwide is 130-210 million [1]. Measuring the histological stage of the disease is crucial for the management of chronic hepatitis C (CHC). Histological examination is still the gold standard for the staging of inflammation and fibrosis [2]. Limiting factors of biopsy include its invasiveness, various complications, variability in evaluation among pathologists, and sampling error [3]. Many alternative non-invasive techniques such as various biochemical, serological, and imaging methods have been studied to estimate the stage of the disease in CHC (fibro test, APRI score, transient elastography, MR elastography, etc.) [4-6].

Some hemogram-derived inflammatory markers are associated with hepatitis [7,8]. The blood neutrophil to lymphocyte ratio (NLR) is a basic subclinical indicator of inflammation that can be calculated from the leukocyte formula. This value integrates information about two different immune pathways owing to neutrophils revealing continuing inflammation and lymphocytes as the regulatory mechanism [9]. The NLR is affected by a variety of inflammatory conditions, including irritable bowel disease, Covid-19 infection, fatty liver, inflammatory bowel disease, diabetes mellitus, cardiac problems, and thyroiditis [10-15]. In recent studies, it was shown that in non-alcoholic fatty liver disease (NAFLD) and chronic hepatitis B, NLR obviously related with the histological stage of the disease, and could be used to identify advanced-stage patients [16,17]. Considering all this information, it is suggested that the NLR is an index of the entire inflammatory system and could provide information about the degree of liver damage in CHC, and could be used to estimate the stage of the disease separately or in combination with other non-invasive

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tests as an alternative to biopsy. Although there are many studies investigating the relationship between NLR and liver fibrosis in hepatitis due to other etiological causes, there is limited number of studies in patients with CHC. In this study, we wanted to investigate whether there is an association between NLR and the histological stage in patients with chronic hepatitis C.

Materials and Methods

We retrospectively analyzed the records of chronic hepatitis C patients who were followed up by gastroenterology clinic of our hospital. Patients with known HCV RNA positivity for at least 6 months and whose CHC diagnosis was confirmed by histology were included in the study. Patient who did not undergo liver biopsy were excluded from the study. Complete blood count, leukocyte formula, biochemistry results performed simultaneously with liver biopsy and demographic data of the participants were collected retrospectively. Patients who did not have data on whole blood count, leukocyte formula, and liver enzymes within 1 week from the date of the liver biopsy were excluded from the study.

Patients with cirrhosis, hepatitis B virus infection, alcohol use >20 g/day, autoimmune hepatitis and metabolic disorders, which may cause chronic liver disease were excluded from the study. Also patients with hepatocellular cancer, other malignancies, hematological, rheumatological or renal diseases were not included in the study.

As the control group, patients who applied to the gastroenterology outpatient clinic of our hospital with dyspeptic complaints and had no known disease were included. Those with a history of liver disease, presence of active infection, malignancy, hematological, rheumatological or renal disease, alcohol use>20g/day, as well as with abnormal liver enzyme levels, complete blood count, albumin and hemostasis test results, and those with HBs Ag, HCV and HIV positivity, fatty liver or space-occupying lesions on USG were not included in the control group.

Patients with an ISHAK staging score of $> 2/6$ in pathology reports were considered to be advanced fibrosis, while those with $\leq 2/6$ were considered to be mild fibrosis. The NLR was found by dividing the absolute neutrophil count by the absolute lymphocyte count from the patients' leukocyte formulas. And also AST to platelet ratio index (APRI) were used as a non-invasive test for the evaluation of histological stage [18]. APRI test was created by the formula of [(serum AST /reference AST) × 100] / platelet. NLR and APRI scores were compared between the advanced fibrosis, the mild fibrosis and the control groups.

In this retrospective study, we used non-probable purposive sampling method. Sample size was calculated that a minimum of 33 patients in the patient and control groups should be included in order to prove that 0,78 area under the receiver operating curve ROC curve is significant against the null hypothesis value of 0,5 (Table 4), when the type-I error level is 0,05 and the Type-II error level is 0,20. At this point, it can be said that the study design has sufficient sample size for each group.

This study was approved by the Ethics Committee of our hospital (Ankara Training and Research Hospital Clinical Research Ethics Committee, No. 2012-344) and conducted in accordance with the World Medical Association Declaration of Helsinki.

Statistical analysis

Statistical analyzes were conducted via the software of PASW Statistics 17 (SPSS, Chicago, IL, USA). The statistical significance of categorical variables was analyzed via the chi-square test. Whether the measurable parameters in the group showed normal distribution was analyzed with the Kolmogorov – Smirnov test. Normally distributed variables were shown as mean, + and – (±) standard deviation (SD). Mann-Whitney U test was used when comparing independent subgroups without normally distributed. Independent samples t-test was used for parametric groups. The difference between the chronic hepatitis C group and the control group was compared with the analysis of variance (ANOVA) test. When determining the cut-off values; ROC analyses , sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) were used. A two-tailed p value of 0.05 or less was considered statistically significant.

Results

Sixty two patients diagnosed with CHC who had undergone liver biopsy and 40 healthy controls were included in

Table 1. Characteristics of the study participants.

	CHC Patients (n=62)	Control patients (n=40)	p
Mean age (years)	48.1± 10	45.4 ± 11	0.257
Sex (M/F)	28 / 34	20/20	0.633
BMI	27.9 ± 5.7	29.5 ± 6.5	0.461
INR*	1.04 ± 0.09	0.93 ± 0.06	0.000
Leukocyte (/mm^3x10^3)	7.13 ±1.7	7.04 ±1.9	0.813
Platelet count(/mm^3x10^3)*	215 (99-365)	249 (132-504)	0.048
NLR*	1.86 (0.89-3.94)	1.38 (0.73-2.93)	0.000
APRI*	0.55 (0.16-3.91)	0.21 (0.10-0.54)	0.000

Data are presented as median (range) or mean±SD. * Statistically significant difference found in CHC compared with controls.

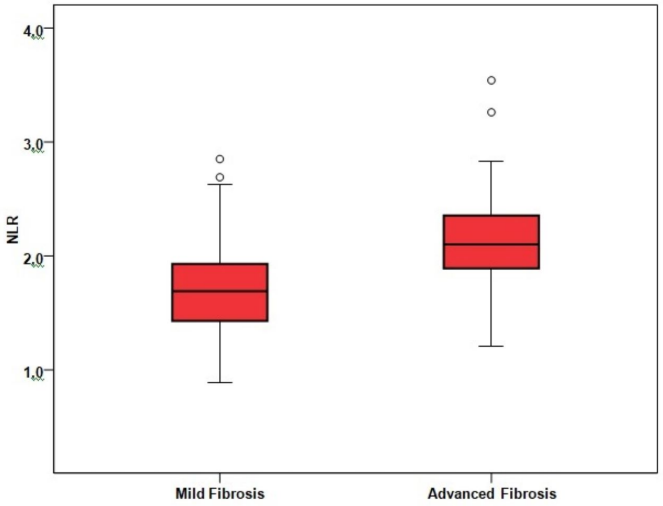

Figure 1. Box plot of mild fibrosis versus severe fibrosis.

the study. 28 of the patients in the CHC group were male and 34 were female. In the control group, 20 of the patients were male and 20 were female. The mean age was 48.1 and 45.4 in the CHC and control groups, respectively. In terms of both gender and age, there was no difference between two groups. NLR, APRI score, and INR values were found to be significantly higher in the CHC group compared to the control group. The NLR values of the CHC group and the control group were determined to be 1.86 (0.89-3.94) and 1.38 (0.73-2.93), respectively ($p<0.001$). Tables 1 and 2 show the demographic and laboratory data of the patients.

In the CHC group, 23 (37%) patients had advanced fibrosis and 39 (63%) had mild fibrosis. In the advanced fibrosis group, the mean NLR value was higher with respect to the mild fibrosis group (2.10 (1.21-3.54) and 1.71 (0.89-3.94), ($p=0.006$) (Figure 1). Table 3 shows the characteristics of the advanced and mild fibrosis groups.

Table 2. Biochemical parameters of study participants.

	CHC Patients (n=62)	Control patients (n=40)	p
ALT (N:0-40 U/l)*	58 (17-870)	20 (9-46)	0.000
AST (N:0-40 U/l)*	44.5 (18-265)	20 (16-31)	0.000
ALP (N:40-130 U/L)*	82 (32-150)	66.5 (26-139)	0.000
GGT (N:8-61 U/L)*	44.5 (12-345)	15.5 (8-67)	0.000
T.Bil (N <1.2 mg/dl)*	0.71 (0.26-1.6)	0.5 (0.23-1.3)	0.001
D.Bil (N <0.3 mg/dl)*	0.2 (0-0.8)	0.11 (0-0.4)	0.000
HCV-RNA (copy/ml)	$61x10^4$ ($58x10^2$-$53x10^6$)		
AFP	5.5 (1.2 -34.4)		
Staging (0-6)	2 (0-5)		
Grading (0-18)	8 (4-14)		
Presence of hepaticsteatosis	21 (33.9%)		

Data are presented as median (range) or mean±SD. * Statistically significant difference found in CHC compared with controls.

Table 3. Biochemical values of the patients according to their fibrosis level in the liver biopsy.

	Advanced Fibrosis§ (n=23)	MildFibrosis§ (n=39)	p
HCV-RNA	$58x10^4$ ($53x10^3$-$12x10^6$)	$63x10^4$ ($58x10^2$-$53x10^6$)	0.374
NLR*	2.10 (1.21-3.54)	1.71(0.89-3.94)	0.006
BMI (kg/m^2)	27.6 ± 5.08	28.1±6.39	0.838
APRI*	0.99 (0.29-3.31)	0.46 (0.16-3.91)	0.000
ALT*	107 (23-870)	58 (31-332)	0.017
AST*	85 (30-233)	44 (28-233)	0.004
INR*	1.13 (1.02-1.29)	0.98 (0.92-1.11)	0.000
Platelet count*	184 (99-287)	238 (143-365)	0.003
Total Bilirubin	0.66 (0.51-0.80)	0.65 (0.46-0.93)	0.051
Mean age (years)	48.3 ± 8.0	48.0 ± 10.0	0.622
Sex (M/F)	15 / 8	26 / 13	0.513

§: Advanced fibrosis is defined with Ishak staging score >2 §: Mild fibrosis is defined with Ishak staging score ≤2 *: Statistically significant difference found in patients with advanced fibrosis compared with mild fibrosis in CHC patients.

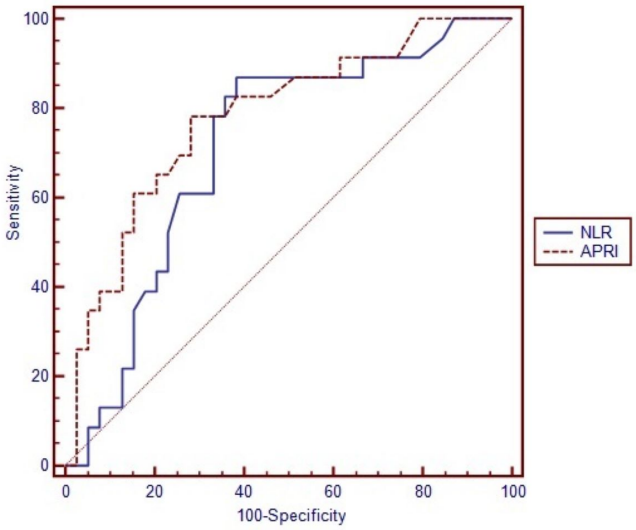

Figure 2. ROC curves of NLR and APRI for differentiating advanced fibrosis from mild fibrosis.

Receiver operating characteristic (ROC) curve analysis determined a cut-off NLR value of 1.76 for advanced fibrosis (with a sensitivity of 86.9%, specificity of 61.5%, NPV of 88.9%, PPV of 57.1%, AUC: 0.711). Besides, the determined cut-off value of APRI for advanced fibrosis was 0.56 (with a sensitivity of 78.2%, specificity of 71.7%, NPV of 84.8%, PPV of 62.1%, AUC: 0.780) (Figure 2, Table 4).

Discussion

In our study, in the CHC group NLR was higher with respect to the control group. Moreover, in the advanced fibrosis group NLR was also higher with respect to the mild fibrosis group in the within-group analysis of the CHC patients.

In systemic inflammation, NLR is a helpful prognostic marker integrating the detrimental impact of neutrophils, which reflect inflammation, and lymphopenia, which reflects physiological stress. Studies so far have revealed that NLR is an indicator of the inflammatory state of the body and could be used to predict prognosis in conditions such as solid tumors, acute coronary syndrome, and acute pancreatitis [19-21].

The virus entering the body due to HCV exposure is presented to CD4+ T lymphocytes by antigen-presenting cells in case of acute infection. Here, subgroups of T helper (Th) cells act and aggravate the cellular immune response by stimulating the release of Th1 cytokines; meanwhile, they also create an immune response against the virus by activating the humoral immune response over Th2 cells. This is always accompanied by a cytotoxic T cell response. Following all this acute viral response, chronic liver damage occurs as a product of inadequate viral clearance, which consists of defective neutralizing antibodies and a virus-infected polyclonal T lymphocyte cell group [22,23].

Liver fibrosis is a complex event that occurs due to various etiologies in chronic liver diseases and is consist of the disproportionate deposition of the extracellular ma-

Table 4. Overall accuracy and ROC analyses of NLR and APRI to differentiate mild fibrosis from severe fibrosis according to liver histology.

	AUC	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
NLR (cut-off: 1.76)	0.711	86.96	61.54	88.9	57.1
APRI (cut-off: 0.56)	0.780	78.26	71.79	84.8	62.1

trix in the liver parenchyma, which occurs during the normal recovery process of the liver. CHC might play a decisive role on NLR both with its direct impacts and with its triggering impacts on metabolic syndrome, diabetes, and fatty liver. In CHC and other chronic liver diseases, hepatic satellite cell activation is results in an inflammatory response and affects leukocytes. Besides, stellate cells can impact lymphocyte proliferation or apoptosis by acting as antigen-presenting cells. Contrary to this, specific lymphocyte populations also affect stellate cells [24]. All these pathogenetic mechanisms indicate the significance of lymphocyte-stellate cell interaction in liver fibrosis.

On the other hand, nearly 50% of patients with HCV infection have fatty liver and it adversely impacts the prognosis of the disease [25]. When the pathogenesis of the metabolic syndrome is considered, it is noticed that inflammation plays a key role here as well. Likewise, this situation is similar to fatty liver disease, which is mostly associated with metabolic syndrome. In a recent study involving 91 patients, it has been demonstrated that NLR is associated with inflammatory activity and advanced fibrosis in 'non-alcoholic fatty liver disease' (NAFLD) and could be benefited to identify patients with advanced-stage [16]. In another study, it has been revealed that NLR is related with systemic inflammation in patients with hypertension and diabetes mellitus [25]. In all of these, insulin resistance is at the center. Studies have suggested that HCV core protein leads to insulin resistance with the activation of cytokine signaling system family and TNF alpha. This activation appears to be a secondary outcome of inflammation [26]. In their study with 234 CHCs and a control group of 50 individuals, Abdel-Razik et al. determined that if they had insulin resistance (HOMA-IR>3) and advanced fibrosis, CHC patients had higher NLR [27]. Similarly, in our study, we found NLR to be higher in CHC group with respect to control group. Furthermore, we also found that patients with CHC and advanced fibrosis had higher NLR value with respect to patients with CHC and mild fibrosis. But, in our study, the insulin resistance of the patients was not evaluated.

In our study, we found NLR to be higher in the CHC group with respect to the controls. Besides, we also found that patients with CHC and advanced fibrosis had higher NLR value with respect to patients with CHC and mild fibrosis. Nonetheless, the relationship between NLR and histological stage is still controversial. In 3 different studies, it was suggested that the platelet to lymphocyte ratio in HCV-related liver disease was related to the histological stage of the CHC; however, no correlation was found between NLR and these parameters [28-30]. In the study of Coskun BD et al., it was found that NLR was not related to histological stage and cirrhosis in CHC patients [31]. In a study conducted with HBV and/or HCV infected individuals, NLR was significantly lower in both HBV and HCV-infected patients, unlike our study [32]. Based on all these findings, it is considered that further studies are needed to introduce NLR into routine clinical practice to determining histologic stage in CHC.

The APRI test is another non-invasive test for predicting histological stage in CHC using AST and platelet count. The APRI score have studied in differentiating advanced fibrosis in chronic liver diseases due to etiologies such as hepatitis B, hepatitis C, NAFLD, and autoimmune hepatitis [33-36], but there are few studies in the literature that compare APRI score with NLR to determine the histological stage of CHC. Lee et al reported that patients with chronic hepatitis B and advanced fibrosis have higher NLR and APRI score [37]. Ding et al. on the other hand, suggested that NLR is inversely related to fibrosis in patients with chronic hepatitis B, and that the APRI score is better at predicting fibrosis [38]. A study in patients with autoimmune hepatitis reported relation between fibrosis stage and APRI, but not NLR [39]. In a study, the APRI test identified advanced fibrosis in CHC with an accuracy of 51% and cirrhosis with an accuracy of 81% [40]. In the study of Snyder et al., when the APRI score was 0.6, in the analysis of 350 CHC patients in the retrospective group, the score was 63.4% sensitive and 71.3% specific in distinguishing mild and advanced fibrosis, and when 150 CHC patients in the prospective group were analyzed, it was 80.6% sensitive and 83.5% specific [41]. In our study, in addition to invasive liver biopsy, we compared NLR with the noninvasive test, APRI, and found that NLR was as accurate as the APRI test in determining histological stage. When the threshold value for the APRI score was 0.56, the sensitivity was 78.2% and the specificity was 71.7%, and it was akin to the findings of the studies conducted with CHC patients. But in another study, it was reported that APRI score was associated with fibrosis in uremic and non-uremic patients; however, they did not find a relationship between NLR and fibrosis [42].

The main limitations of this study were it was a retrospective study and the number of study population is relatively small.

Conclusion

In conclusion, recently, non-invasive tests that can be used in the follow-up of the patients with liver disease have come to the fore, since biopsy is invasive, has various complications, and is not preferred by patients. Yet, the relationship between NLR and liver fibrosis is still controversial today. Hence, further studies are needed to introduce it into routine clinical practice and to find out how this parameter changes with treatment.

Ethics approval

This study was approved by the Ethics Committee of our hospital (Ankara Training and Research Hospital Clinical Research Ethics Committee, No. 2012-344) and conducted in accordance with the World Medical Association Declaration of Helsinki.

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