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Original Article

The Neutrophil-to-Lymphocyte Ratio as A Noninvasive Marker in Patients with Biopsy-Proven Non-Alcoholic Steatohepatitis

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Abstract

Objective: Non-alcoholic fatty liver disease is a global health problem with an increasing prevalence. The neutrophil-to-lymphocyte ratio is a cheap inflammatory parameter that can be easily calculated from routine complete blood count tests. This study was designed to investigate the neutrophil-to-lymphocyte ratio in patients with non-alcoholic steatohepatitis and simple hepatosteatosis.

Methods: Fifteen patients with biopsy-proven non-alcoholic steatohepatitis, 65 patients with simple steatosis diagnosed with abdominal ultrasound, and 65 healthy controls were included. Anthropometric measurements were obtained during a routine physical examination. The neutrophil-to-lymphocyte ratio was calculated from routine complete blood count tests, and its relationship with various clinical and laboratory parameters was analyzed.

Results: The mean neutrophil-to-lymphocyte ratio was 2.16±0.49 in the patients with non-alcoholic steatohepatitis, 1.62±0.43 in the patients with simple steatosis, and 1.51±0.31 for healthy controls; the difference among the groups of patients were statistically significant ($p<0.001$). A paired analysis revealed that patients with non-alcoholic steatohepatitis had a significantly higher neutrophil-to-lymphocyte ratio than patients with simple steatosis and healthy controls, whereas the difference between the latter two groups of patients was not statistically significant. The neutrophil-to-lymphocyte ratio was not associated with the degree of steatosis on performing abdominal ultrasound and with histological findings of liver biopsies ($p>0.05$). ROC analyses for the neutrophil-to-lymphocyte ratio to differentiate patients with steatohepatitis revealed an AUC of 0.868 (95% CI: 0.781–0.956) and 86.5% sensitivity and 81% specificity for the selected cut-off value of 1.793.

Conclusion: The results of this study showed that the neutrophil-to-lymphocyte ratio was higher in patients with steatohepatitis than in patients with simple steatosis and healthy controls. Taking into account that the difference between patients with simple steatosis and healthy controls was not statistically significant, the increased neutrophil-to-lymphocyte ratio in the patients with steatohepatitis can be attributed to a low level of systemic inflammation accompanying the hepatic inflammation.

Keywords: Neutrophil-to-lymphocyte ratio, non-alcoholic fatty liver disease, steatohepatitis

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a major health problem worldwide. While varying among countries, the prevalence of NAFLD is steadily increasing globally and particularly in developed countries (1). Its prevalence is estimated to be around 20–30% in Western countries and 5–18% in Asia, and its worldwide prevalence is estimated to be 24.4% (2, 3). The NAFLD spectrum ranges from a benign clinical picture, such as simple liver steatosis, to inflammation, hepatocyte damage, and non-alcoholic steatohepatitis (NASH) that is characterized by fibrosis, cirrhosis, and hepatocellular carcinoma development. Currently, NAFLD is one of the most common causes of liver cirrhosis and related liver transplants in developed countries (4). Although the pathogenesis of NAFLD is not well known, there are reports suggesting that intestinal metabolic products, microbiota, various immunological mechanisms, pro-inflammatory mediators released from the adipose tissue, and various cytokines play a role in the pathogenesis (5, 6). Although the pathogenesis is not fully known, risk factors associated with NAFLD have been well defined. In particular, the association of metabolic syndrome and its components [obesity, hypertension, dyslipidemia, and type 2 diabetes mellitus (DM)] with NAFLD has been shown in the literature (7). In the NAFLD spectrum, NASH patients have a discriminatory significance for the prognosis because unlike simple liver steatosis, NASH is characterized by progressive inflammation and fibrosis and has the potential to progress to cirrhosis. However, unfortunately, there are currently no optimal noninvasive diagnostic methods with high specificity and sensitivity that can be used to diagnose NASH patients. Imaging methods demonstrate liver steatosis, but these methods are unable to demonstrate inflammation and early-stage fibrosis. There are no validated biochemical markers that can distinguish NASH patients from simple steatosis patients. For these reasons, liver biopsy in diagnosing NASH is still considered as the gold standard. Although liver biopsy is a low-risk procedure, it can cause many complications, particularly hemorrhage and even death (albeit rarely), due to the fact that liver biopsy is an invasive procedure.

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The neutrophil-lymphocyte ratio (NLR) is an inexpensive inflammatory indicator that can be calculated with a simple blood count. There are publications in the literature showing that the NLR is associated with various inflammatory diseases, many cancers, and various liver diseases (8-10). In this study, we aimed to investigate the relationship of NLRs in NAFLD with various clinical and laboratory parameters.

Methods

A total of 145 subjects, including 15 NASH patients diagnosed by liver biopsy (group 1), 65 simple liver steatosis patients diagnosed by abdominal ultrasonography (group 2), and 65 healthy controls (group 3) were included. The study was approved by the Necmettin Erbakan University Meram School of Medicine Ethics Committee. Written informed consent was obtained from the included subjects, and volunteer consent forms were signed. The NASH group consisted of patients with an elevated hepatic function test lasting longer than 6 months, with no other liver or biliary tract disease, with hyperechogenic liver on ultrasonography, and whose NASH diagnosis was confirmed by liver biopsy. Patients with normal serum transaminase levels and patients in whom hyperechogenic and fatty livers were detected by abdominal ultrasonography were included in the simple liver steatosis group. According to the findings of abdominal ultrasonography, the grading of liver steatosis has been defined as grade 0=no steatosis; grade 1=slight diffuse echogenicity increase and normal diaphragm and intrahepatic vessel echogenicity; grade 2=moderate echogenicity increase, slight graying in intrahepatic vessel echogenicity, and diaphragmatic echogenicity; and grade 3=marked increase in liver echogenicity with imperceptible periportal and hepatic venous echogenicity and obscuration of diaphragm. Healthy individuals who had normal serum transaminase levels, no liver fattening on abdominal ultrasonography, and had no known systemic disease were included in the control group. Other possible chronic liver diseases were eliminated in patients in the NASH and simple steatosis groups by examining the hepatitis B surface antigen, hepatitis B core antigen, anti Hepatitis C virus antibody, antinuclear antibody, anti-smooth muscle antibody, anti-liver-kidney microsomal antibody, serum copper and ceruloplasmin levels, and transferrin saturation. Patients with known liver disease, who consumed alcohol (>20 g/day for men, >10 g/day for women), with known cancer, and with autoimmune disease or an active infection were excluded. Anthropometric measurements were taken while a routine physical examination was performed in the patient and control groups. Patients' body weights were measured in light clothing using calibrated scales. The body mass index (BMI) was calculated using the formula "body weight (kg)/height $(m)^2$."

Blood samples were taken from the subjects on an empty stomach in the morning. Fasting blood glucose, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and gamma-glutamyltransferase (GGT) levels were measured using an autoanalyzer (Abbott Architect 16000, Abbott Laboratories, Abbott Park, IL, USA) and the hemograms were studied using automatic Coulter devices.

The AST-to-platelet ratio index (APRI) and fibrosis-4 (FIB-4) scores, as noninvasive fibrosis scores, for all three groups were calculated using the following formulae: APRI=(AST/AST upper limit of normal)/Plt (10^9/L)]×100 and FIB-4=[age (years)×AST (U/L)]/([Plt (10^9/L)]×(ALT (U/L)]$^{1/2}$).

Statistical analysis

The Statistical Package for the Social Sciences 19.0 (SPSS Armonk, NY: IBM Corp.) package program was used for statistical analysis. Continuous variables were expressed as mean±standard deviation and categorical data as frequency and percentage (n, %). In order to test for the significance of differences between three or more groups, one-way ANOVA test was used when tested parameter was normally distributed, and Kruskal Wallis test was used when the distribution was not normal. When the difference was statistically significant, the two groups were compared using the independent sample t-test for variables with normal distribution and the Mann–Whitney U test for variables without normal distribution. ROC curves were used to determine cut-off values associated with the tested variables and to calculate the sensitivity and specificity. Negative and positive predictive values were calculated for the determined cut-off values. $p<0.05$ was considered statistically significant.

Results

The mean age of the study group was 49.0±13.0 years. There was no statistically significant difference between the groups in terms of age and sex distribution. Fasting blood glucose, AST, ALT, and GGT levels were significantly higher in the NASH group when compared to the simple steatosis group and healthy control group. While 76.4% of the patients had DM and 52.9% of them had hypertension in the NASH group, there was DM in 7.7%, impaired fasting glucose in 27.7%, and hypertension in 13.8% of the simple steatosis group. Clinical, laboratory, and demographic characteristics of the study groups are summarized in Table 1.

When analyzed in terms of the anthropometric measurements, the BMI and waist-hip ratios of the patients in the NASH and simple steatosis groups were significantly higher than the healthy controls ($p=0.005$ and $p<0.001$, respectively). When the NASH and simple steatoses groups were compared, while there was no difference between the two groups in terms of BMI ($p=0.22$), the waist-hip ratio was observed significantly higher in the NASH group ($p=0.04$).

The mean NLR was 2.16±0.49 in the NASH group, 1.62±0.43 in the simple steatosis group, and 1.51±0.31 in the healthy controls; and the difference among the three groups was statistically significant ($p<0.001$). It was found in paired comparisons that the NLR was significantly higher in NASH patients than both the simple steatosis and healthy control groups ($p<0.001$ for both), but there was no difference between the simple steatosis and healthy control groups ($p=0.086$). The NLR in all three groups is given in Figure 1.

The liver biopsy findings of patients in the NASH group are summarized in Table 2. There was no significant relationship between the NLR and histological findings in the liver biopsy (ballooning, steatosis grade, inflammation and fibrosis grade, etc...) ($p>0.05$).

When analyzed in terms of abdominal USG findings, while steatosis grade 1 was found in 8 patients (53.3%), steatosis grade 2 in 3 patients (20%), and steatosis grade 3 in 4 patients (26.7%) in the NASH group; steatosis grade 1 was found in 33 patients (50.8%), steatosis grade 2 in 26 patients (40%), and steatosis grade 3 in 6 patients (9.2%) in the simple steatosis group. No significant relationship between the NLR and the steatosis grade in the USG was found for the NASH or the simple steatosis groups ($p=0.60$ and $p=0.332$, respectively).

Table 1. Demographic and clinical features in the patient and control groups

	NASH	Simple Steatosis	Control	p
Age (years)	51.0±9.6[a]	51.3±10.5[a]	46.3±15.5[a]	0.077
Female (n, %)	10. %66.7	39. %60	40. %61.5	0.891
NLR	2.16±0.49[a]	1.62±0.43[b]	1.51±0.31[b]	<0.001
BMI (kg/m^2)	30.66±7.70[a]	27.87±3.34[a]	23.64±2.23[b]	<0.001
Waist-hip ratio	0.95±0.11[a]	0.89±0.54[b]	0.83±0.91[c]	<0.001
Leucocyte (103/µL)	7.72±1.97[a]	7.34±1.90[a]	6.76±1.41[a]	0.055
Neutrophil (103/µL)	4.75±1.40[a]	4.05±1.29[a]	3.60±0.89[b]	0.001
Lymphocyte (103/µL)	2.24±0.59[a]	2.57±0.70[a]	2.42±0.56[a]	0.149
Hb (g/dL)	13.5±1.8[a]	14.5±1.4[a]	14.1±1.6[a]	0.082
Htc (%)	40.6±4.5[a]	42.3±5.5[a]	41.5±4.1[a]	0.357
RDW (%cv)	14.3±1.5[a]	13.3±1.2[b]	13.1±0.8[b]	<0.001
Plt (10^6/µL)	246.5±88.4[a]	272.6±57.3[a]	252.8±63.3[a]	0.138
MPV (fL)	10.3±0.9[a]	10.0±0.9[a]	10.3±0.9[a]	0.293
FBG (mg/dL)	151.9±69.1[a]	101.7±12.1[b]	92.2±29.4[b]	<0.001
AST (U/L)	61.9±34.5[a]	20.9±5.7[b]	21.1±5.1[b]	<0.001
ALT (U/L)	95.5±74.6[a]	26.1±12.7[b]	21.8±13.3[b]	<0.001
GGT (U/L)	149.9±313.8[a]	33.8±35.1[b]	22.2±12.2[b]	0.041
ALP (U/L)	115.3±110.4[a]	86.0±35.9[a]	64.2±18.4[a]	0.060
Albumin (g/dL)	4.0±0.7[a]	4.3±0.3[a]	4.4±0.3[b]	0.033
T. cholesterol (mg/dL)	213.3±68.6[a]	217.7±63.2[a]	188.8±31.4[a]	0.33
Triglyceride (mg/dL)	169.3±66.0[a, b]	177.1±96.4[b]	111.3±57.2[a]	0.047
APRI	0.77±0.56[a]	0.23±0.10[b]	0.25±0.09[b]	<0.001
FIB-4	1.5±1.12[a]	0.87±0.44[b]	0.94±47[b]	0.005

NLR: neutrophil-lymphocyte ratio; BMI: body mass index; Hb: hemoglobin; Htc: hematocrit; RDW: red cell distribution width; Plt: platelet; MPV: mean platelet volum; FBG: fasting blood glucose; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyltransferase; ALP: alkaline phosphatase; T. cholesterol: total cholesterol; APRI: AST-to-platelet ratio index; FIB-4: fibrosis-4 score

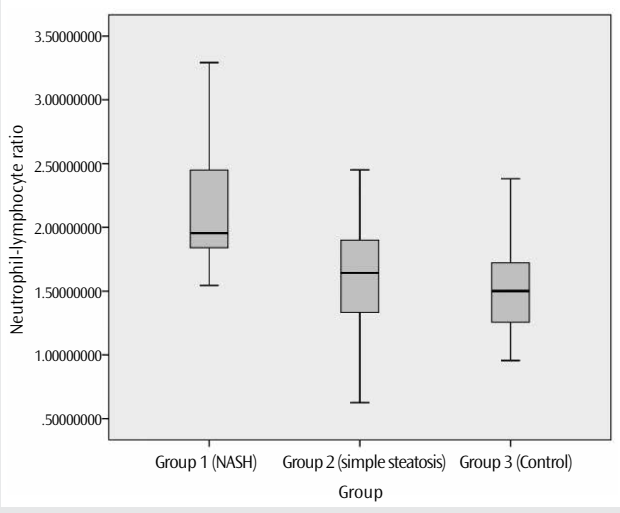

Figure 1. Neutrophil-lymphocyte ratios in the patient and control groups
NASH: Non-alcoholic steatohepatitis

Table 2. Liver biopsy findings in non-alcoholic steatohepatitis patients

Histological finding	n (%)
Degree of steatosis	
5%-33%	8 (53.3)
33%-66%	5 (33.3)
>66%	2 (13.4)
Inflammation	
Grade 1	8 (53.3)
Grade 2	4 (26.7)
Grade 3	3 (20)
Aneurism	
None	5 (33.3)
Mild	4 (26.7)
Severe	6 (40.0)
Fibrosis	
None	4 (26.7)
Mild	6 (40.0)
Moderate	1 (6.6)
Severe	4 (26.7)

When assessed in terms of the noninvasive fibrosis scores, APRI and FIB-4 scores in the NASH group were significantly higher than those of the simple steatosis and healthy control groups (p<0.001 and p=0.005, respectively).

In the ROC analyses conducted to distinguish the NASH patients, for APRI, the AUC was found to be 0.878 (95% confidence interval: 0.765–0.992); for the selected 0.324 cut-off value, the sensitivity was found as 80% and the specificity as 82.5%; for the NLR, the AUC was found to be 0.868 (95% confidence interval: 0.781–0.956), the sensitivity to be 86.5%, and the specificity to be 81% for the selected 1.793 NLR cut-off value (Figure 2). In the case of combined use of APRI and NLR, in the ROC curve for NLR whose cut-off value was determined as 0.324 for APRI; the AUC was found to be 0.856 (95% confidence interval: 0.689–1.0); for the 1.793 NLR cut-off value, the sensitivity was found to be 83.3%, and the specificity was found to be 90.9%. The calculated predictive value was found to be 90.9% and the negative predictive value was found to be 83.3%.

Discussion

The pathogenesis of NAFLD has not yet been fully elucidated, and it is thought to be multifactorial. Genetic factors, intestinal metabolic products, microbiota, various immunological mechanisms, and cytokines may play a role in pathogenesis. Obesity, DM, and metabolic syndrome are risk factors whose association with NASH has been proven in a number of studies. In our study, 76.4% of the patients in the NASH group had DM and 52.9% of them had hypertension. In addition, the BMI and waist-hip ratios of the patients in the NASH and simple steatosis groups were found to be significantly higher than those in the healthy control group. Waist-hip ratios were also higher in NASH patients than in simple steatosis patients

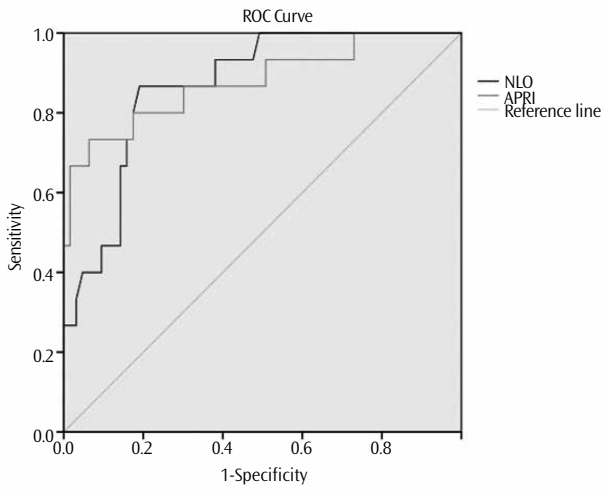

Figure 2. ROC curve
NLO: neutrophil-lymphocyte ratio; APRI: AST to platelet ratio index

and healthy controls. This indicates the presence of central obesity in these patients. Central obesity has been shown in the literature to be a risk factor for NASH (11).

The NLR is a simple and inexpensive indication of systemic inflammation; its association with various autoimmune inflammatory diseases and cancers has been demonstrated in a number of studies (12, 13). In the literature, the NLR has also been found to be associated with various liver diseases (14, 15). In the results of this study, it was observed that the NLR was higher in NASH patients than in the healthy controls and simple liver steatosis patients. There was no statistical difference between the simple steatosis group and healthy control group in terms of NLR. This suggests that the increase in NLR was due to low-level inflammation accompanying NASH. Several studies in the literature have reported that various pro-inflammatory cytokines, such as TNF-α, IL-6, IL-1α, IL-1β, and IL-18, play a role in the pathogenesis of NASH and that the clinical picture is also accompanied by a low level of systemic inflammation (16-19). In addition, NASH and metabolic syndrome accompanying NASH have been to be associated with increased cardiovascular risk; it has been suggested that accompanying low-level inflammation is responsible for this increased risk (20). The fact that there are no relationships between the degree of steatosis on USG and NLR and between simple steatosis and healthy control groups in terms of NLR also supports the hypothesis that the increase in NLR is secondary to the increase in inflammation in the liver and the concomitant low level of systemic inflammation in NASH patients.

AST-to-platelet ratio index and FIB4 scores are non-invasive scores used as indicators of fibrosis in various chronic liver diseases (21, 22). In our study, it was found that APRI and FIB-4 scores were significantly higher in the NASH group than in the simple steatosis and healthy control groups, which was an expected finding. Statistical analysis showed that the combined use of the APRI score and NLR could be a non-invasive marker for distinguishing NASH patients from among those in whom steatosis was detected through USG.

In this study, the fact that all NASH patients were diagnosed with liver biopsy in addition to clinical, laboratory, and imaging methods is one of the strongest aspects of the study. On the other hand, the fact that the number of patients was limited and that this was a cross-sectional study constitutes the weakness of the study. One last thing to mention is that, in our study, simple liver steatosis group consisted of patients with normal serum transaminase levels whom hepatosteatosis was detected with abdominal ultrasound. However, although the transaminase levels were normal, it should be kept in mind that some of these patients may have histological findings of steatohepatitis. From a scientific point of view, it may be appropriate to precisely exclude steatohepatitis by also performing liver biopsy in these patients for a more ideal study design. However, it should not be forgotten that performing liver biopsy in patients with normal liver transaminase levels and steatosis findings only through imaging methods may cause ethical problems. Therefore, liver biopsy was not performed in patients in the simple steatosis group in our study design. We believe that prospective studies involving a greater number of patients will be appropriate for a better clarification of the relationship of NLR and NASH with simple liver steatosis.

Conclusion

In conclusion, the NLR is increased in NASH patients. This increase is probably due to inflammation in the liver and concomitant low-level systemic inflammation. Although it seems not appropriate to use the NLR solely as a marker alone in the diagnosis of NASH patients, we believe that its use, together with other diagnostic methods and scoring systems, would be useful in the management of patients with NAFLD and the selection of patients to be biopsied.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Necmettin Erbakan University Meram School of Medicine.

Informed Consent: Verbal informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.A.; Design - M.A., R.D.; Supervision - M.A.; Data Collection and/or Processing - M.A., R.D.; Analysis and/or Interpretation - M.A., R.D.; Literature Review - M.A., R.D.; Writing - M.A., R.D.; Critical Review - M.A.

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