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Evaluation of neutrophil HDL-C ratio — a new inflammation marker in non-alcoholic fatty liver disease

Enver Avcı[1], *Mine Ozturk*[2]

[1]*Department of Gastroenterology, Medova Hospital, Konya, Türkiye*
[2]*Department of Endocrinology, Konya City Hospital, Konya, Türkiye*

Abstract

Introduction: Non-alcoholic fatty liver disease (NAFLD) is a global disease estimated to affect one-third of the world's population. NAFLD is the hepatic manifestation of metabolic syndrome. In recent years, formulations have been made using haematological laboratory parameters, and it has been reported to be associated with inflammation and fibrosis in the liver. In this study, we aimed to evaluate the neutrophil to high-density lipoprotein (HDL) cholesterol (HDL-C) ratio (NHR) in patients diagnosed with NAFLD by ultrasonographic imaging for the first time in the literature.

Material and methods: The study was carried out by recruiting men and women between the ages of 18 and 65 years who applied to the check-up outpatient clinic of our hospital. Ultrasonography was used as the diagnostic method for hepatosteatosis in all cases. Venous blood samples were taken from the patients for haematological and biochemical measurements.

Results: The study population consisted of 155 patients, 115 of whom were fatty liver patients and 40 were controls. NHR was determined as 99.6 ± 56.8 in those with grade 1 fatty liver, 114.98 ± 39.2 in those with grade 2, 122.9 ± 51.1 in those with grade 3, and 86.17 ± 35.2 in the control group. In the analysis, NHR was statistically significantly higher in grade 2 and 3 fatty liver patients compared with the control group ($p = 0.03$ and 0.01, respectively). However, there was no statistical difference between grade 1 fatty liver patients and the control group ($p = 0.53$).

Conclusions: We found higher NHR in patients with NAFLD. NHR is a cheap and easy to access parameter. An elevated NHR with FIB-4 in patients with NAFLD may be a marker of liver inflammation or fibrosis. **(Endokrynol Pol 2023; 74 (6): 610–615)**

Key words: *NAFLD; NHR; FIB-4*

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a disease caused by the interaction of many nutritional, genetic, metabolic, and inflammatory factors, and it is estimated to affect one-third of the global population [1]. NAFLD is the hepatic manifestation of metabolic syndrome [2]. NAFLD can be encountered clinically in a wide spectrum ranging from simple steatosis without inflammation and fibrosis to steatohepatitis with inflammation and hepatic damage, cirrhosis, and hepatocellular carcinoma [1]. Liver fibrosis is the most important determinant for long-term outcomes in NAFLD patients, and approximately 10–20% of simple steatoses progress to nonalcoholic steatohepatitis (NASH) [3, 4]. Although liver biopsy is the gold standard in terms of demonstrating liver fat, inflammation, and fibrosis, it is not the first choice due to its invasiveness, risk of complications, and sampling variability [5]. Therefore, laboratory-based formulas such as fibrosis 4 (FIB-4) index, NAFLD fibrosis score (NFS), and APRI score have been developed to predict patients who are more likely to develop serious liver events. The FIB-4 index, one of these formulas, is an alternative to biopsy, which is a non-invasive, simple, inexpensive, and easily reproducible test for fibrosis in NAFLD [6]. However, it has been reported that these scoring systems play a role in the evaluation of fibrosis, but they are not effective in distinguishing patients with simple steatosis from patients with steatohepatitis [7]. In recent years, formulations have been made using haematological laboratory parameters, and it has been reported to be associated with inflammation and fibrosis in the liver [8, 9]. Recently, it has been reported that the neutrophil to high-density lipoprotein (HDL) cholesterol (HDL-C) ratio (NHR) is an inflammation marker and is superior to other formulations in predicting prognosis in some diseases, especially atherosclerotic heart disease [10].

In this study, we aimed to evaluate NHR in patients diagnosed with fatty liver by ultrasonographic imaging, for the first time in the literature, and thus to find a new formulation for the presence of inflammation or fibrosis in the liver.

Enver Avcı, Gastroenterology Department, Medova Hospital, Konya, Türkiye; e-mail: enver.a.dr@gmail.com

Material and methods

This study was conducted prospectively between November 2022 and May 2023. It was performed in accordance with the principles of the Declaration of Helsinki with the ethical approval of the local Clinical Studies Ethics Committee. Informed consent form was obtained from the patients.

Study population

The study was carried out by recruiting men and women between the ages of 18 and 65 years, who applied to the check-up outpatient clinic of our hospital.

Exclusion criteria for both control and fatty liver were as follows:

- 30 g/day alcohol use in men and 20 g/day in women;
- chronic liver disease [hepatitis B surface antigen (HbsAg) or anti-hepatitis C virus (anti-HCV) positivity, autoimmune hepatitis, Wilson's disease, haemochromatosis, alpha-1 antitrypsin deficiency, etc.];
- regular use of drugs that can cause fatty liver (tamoxifen, amiodarone, corticosteroids, etc.);
- chronic inflammatory disease, active malignancy, acute infection, autoimmune disease;
- recent trauma and surgery (in the last 15 days);
- use of drugs that can alter leukocyte and cholesterol levels.

Examination of patients

Anthropometric measurements such as height, weight, and waist circumference were performed on the patients included in the study after routine medical history and physical examination evaluations. Waist circumference (WC) was measured on the skin at the midpoint between the lower rib edge and the anterior superior iliac wing using a tape measure. Body mass index (kg/m^2) was calculated by dividing weight (kg) by height (m) squared.

Diagnosis of hepatosteatosis

Ultrasonography (USG) was used as the diagnostic method for hepatosteatosis in all cases. Hepatosteatosis was evaluated by USG (Siemens, Acuson X700 Ultrasounds, Siemens Medical Solutions USA, Inc.) with a 4.5-MHz wideband curved array transducer. USG was performed by a single gastroenterologist. The grade of hepatosteatosis was assessed as follows: grade 0: no steatosis; grade 1: minimal diffuse increase in hepatic echogenicity; intrahepatic vein borders and diaphragm are clearly seen; grade 2: moderate diffuse increase in hepatic echogenicity; intrahepatic views of vessels and diaphragm slightly impaired; grade 3: severe diffuse increase in hepatic echogenicity. The increase in echogenicity is at a level that prevents the visualization of the intrahepatic vessels and diaphragm.

Measurement of biochemical parameters

Blood samples were taken from the antecubital vein from all patients in the sitting position. Whole blood samples were collected in 2.0 mL dipotassium (K2) ethylene diamine tetraacetic acid (EDTA) vacuum tubes (BD Vacuette® Tube, Greiner Bio-One GmbH, Kremsmünster, Austria). Afterwards, complete blood count was performed using Sysmex XN-550 automatic haematology devices (Sysmex Bornbarch 1, 22848, Norderstedt, Germany).

Venous blood samples for biochemical parameters were collected in an evacuated serum separating clot activator tube (Vacuette®, Greiner Bio-One Kremsmunster, Austria). Fasting blood glucose, fasting insulin, serum total cholesterol, triglyceride, HDL-C, low-density lipoprotein cholesterol (LDL-C), serum albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), and alkaline phosphatase (ALP) concentrations were measured on AU 5800 analyser (Beckman Coulter, Miami, FL, United States).

Calculation of HOMA-IR

Homeostasis assessment model-insulin resistance (HOMA-IR) was calculated according to the following formula:

$$\textit{Fasting glucose (mg/dl)} \times \textit{fasting insulin } (\mu U/ml)/405 \textit{ [11].}$$

Calculation of neutrophil to HDL-C ratio (NHR)

NHR was calculated by dividing the neutrophil count and HDL-C value after determining the neutrophil count and HDL-C values by laboratory measurements.

Calculation of FIB-4

FIB-4 values were calculated automatically using the following formula:

$$\textit{Age (years)} \times \textit{AST [U/L]} / (\textit{platelets } [10^9/L] \times \sqrt{\textit{ALT [U/L]}}) \textit{ [6].}$$

Statistics

The statistical analyses were performed using SPPS v.27.0 (SPSS, Chicago, III, United States) program. Categorical data were expressed in frequency and percentage, and quantitative data were expressed as mean and standard deviation. In the comparison of categorical data, the chi-square test was used, and the independent t-test and Mann-Whitney U test were used for comparison of quantitative data. One-way ANOVA test was used in multi-group comparisons, and Tukey test was used as post-hoc analysis. A p-value < 0.05 was accepted as significant.

Results

The study population consisted of 155 subjects, 115 of whom were fatty liver patients and 40 were controls. Of the patients with fatty liver, 48 were grade 1, 41 were grade 2, and 26 were grade 3. There were 76 (66%) women and 39 (34%) men in the fatty liver group, and 28 (70%) women and 12 (30%) men in the control group (Tab. 1). The mean age of the grade 1 fatty liver group was 46.7 ± 14.4 years, the mean age of the grade 2 fatty liver group was 48.9 ± 15.1 years, the mean age of the grade 3 fatty liver group was 48.8 ± 12.3 years,

Table 1. *Gender distribution of groups*

Gender	Fatty liver (–)	Fatty liver (+)			Total
		Grade 1	Grade 2	Grade 3	
Female	28	33	26	17	104
Male	12	15	15	9	51
Total	40	48	41	26	155

Table 2. *Anthropometric measurements of the groups and laboratory parameters*

Parameters	Fatty liver (–) (n = 40)	Fatty liver(+)			p-values		
		Grade 1 (n = 48)	Grade2 (n = 41)	Grade 3 (n = 26)	Pv-1	Pv-2	Pv-3
Age [year]	42.6 ± 14.6	46.7 ± 14.4	48.9 ± 15.1	48.8 ± 12.3	0.54	0.19	0.32
BMI [kg/m²]	23.5 ± 3.3	26.7 ± 2.62	30.5 ± 3.94	31.8 ± 4.3	0.000	0.000	0.000
WC [cm]	85.88 ± 9.7	94.7 ± 9.6	103.1 ± 8.5	108.6 ± 10.0	0.000	0.000	0.000
Glucose [mg/dL]	95.3 ± 13.2	101.1 ± 16.9	106.4 ± 21.2	125.6 ± 35.6	0.6	0.099	0.000
AST [U/L]	22.5 ± 5.5	25.1 ± 22.4	35.9 ± 13.8	38.3 ± 10.4	0.85	0.0007	0.0004
ALT [U/L]	18.6 ± 8.5	24.4 ± 29.9	33.5 ± 24.8	38.3 ± 19.5	0.63	0.02	0.004
GGT [U/L]	20.4 ± 16.5	25.3 ± 17.7	36.8 ± 28.3	37.4 ± 17.6	0.68	0.003	0.007
Albumin [g/dL]	4.6 ± 0.3	4.4 ± 0.32	4.45 ± 0.35	4.41 ± 0.42	0.35	0.48	0.33
Tot-C [mg/dL]	191.6 ± 47.2	195.5 ± 55.5	204.3 ± 49.9	216.9 ± 50.2	0.98	0.68	0.54
HDL-C [mg/dL]	54.4 ± 12.4	52.7 ± 12.9	46.2 ± 11.8	45.9 ± 10.3	0.91	0.014	0.03
LDL-C [mg/dL]	114.2 ± 41.4	117.6 ± 35.3	123.7 ± 34.1	126.6 ± 36.1	0.97	0.65	0.54
Triglyceride [mg/dL]	122.4 ± 70.98	158.8 ± 161.6	200.9 ± 202.3	208.4 ± 111.2	0.66	0.088	0.106
Insulin [mU/L]	7.29 ± 2.71	9.54 ± 3.86	11.78 ± 5.15	13.96 ± 4.84	0.061	< 0.001	< 0.001
HOMA-IR	1.73 ± 0.73	2.48 ± 1.27	3.15 ± 1.64	4.2 ± 1.59	0.047	< 0.001	< 0.001
Neutrophil [K/Ul]	4494 ± 1578.4	4908 ± 1951.5	5536.1 ± 1356.1	5606.5 ± 1464.2	0.64	0.024	0.038

BMI — body mass index; WC — waist circumference; AST — aspartate aminotransferase; ALT — alanine aminotransferase; GGT — gamma-glutamyl transpeptidase; LDL-C — low-density lipoprotein cholesterol; HOMA-IR — homeostasis assessment model-insulin resistance; Pv-1 — p-value comparing grade 1 with grade 0, Pv-2 — p-value comparing grade 2 with grade 0, Pv-3 — p-value comparing grade 3 with grade 0

and in the control group it was 42.6 ± 14.6 years. There was no statistical difference in age between the group with fatty liver and the control group (p = 0.54, 0.19, and 0.32, respectively). When the groups were compared in terms of body mass index (BMI) and WC, they were statistically significantly higher than the control group in all grades of fatty liver (p = 0.000 and p = 0.000, respectively). AST, ALT, GGT, triglyceride, HDL-C, insulin, HOMA-IR, and neutrophils were statistically significantly higher in the grade 2 and 3 fatty liver group compared to the control group (p < 0.05). However, there was no significant difference between the control group in the parameters other than HOMA-IR in the grade 1 fatty liver group (p > 0.05). Total cholesterol, LDL-C, and serum albumin were compared, and there was no statistically significant difference between the grade 1, 2, and 3 fatty liver groups and the control group (p > 0.05) (Tab. 2).

The groups were compared in terms of FIB-4 index. When the grade 2 group and control group, and the grade 3 group and control group were compared, there was a significant difference between the groups; p values were 0.042 and 0.0086, respectively. However, there was no statistically significant difference between those the grade 1 group and the control group (p = 0.87). When groups with fatty liver were compared with each other in terms of FIB-4, there was a significant difference between grade 1 and grade 2, and grade 1 and grade 3; the p values were 0.028 and 0.044, respectively. However, there was no significant difference between grade 2 and grade 3 (p = 0.997).

NHR was 99.6 ± 56.8 in grade 1, 114.98 ± 39.2 in grade 2, 122.9 ± 51.1 in grade 3, and 86.17 ± 35.2 in the control group. In the analysis, when the grade 2 group and control group, and grade 3 group and control group were compared, there was a significant difference between the groups; p values were 0.03 and 0.01, respectively. However, there was no statistical difference between the grade 1 group and the control group (p = 0.53) (Tab. 3). When the groups with fatty liver were compared with each other in terms of NHR, there was no significant difference between grade 1 and 2, grade 1 and 3, and grade 2 and 3; the p values were 0.41, 0.17, and 0.902, respectively.

Discussion

As far as we are aware, our study is the first in the literature to evaluate NHR in NAFLD. We found that patients with grade 2 and 3 nonalcoholic fatty liver had higher NHR than patients without NAFLD. In addition, the FIB-4 score was higher in these groups.

The progression of disease from steatosis to nonalcoholic steatohepatitis (NASH) and fibrosis in NAFLD is heterogeneous and can take years [12]. NASH is characterized by steatosis, hepatic inflammation, and ballooning, and it may include varying degrees of fibrosis [13]. While in the past the "double hit" hypothesis

Table 3. *Comparison of formulations between groups*

	Fatty liver (–)	Fatty liver (+)			p-values		
		Grade 1	Grade 2	Grade 3	Pv-1	Pv-2	Pv-3
NHR	86.17 ± 35.2	99.6 ± 56.8	114.98 ± 39.2	122.9 ± 51.1	0.53	0.03	0.01
FIB-4	0.87 ± 0.39	0.96 ± 0.59	1.28 ± 0.66	1.3 ± 0.38	0.87	0.042	0.0086

NHR — neutrophil to high-density lipoprotein (HDL) ratio; FIB-4 — fibrosis 4 index; Pv-1 — p-value comparing grade 1 with grade 0, Pv-2 — p-value comparing grade 2 with grade 0, Pv-3 — p-value comparing grade 3 with grade 0

was accepted for the progression of simple steatosis to NASH, today the multiple parallel beat hypothesis is accepted. Accordingly, NASH is an inflammatory process that is caused by the pathological effects of many components such as genetic variations, abnormal lipid metabolism, oxidative stress, impaired immune response, and disorder in the gut microbiota [14, 15]. NAFLD is on its way to becoming the most common cause of liver cirrhosis and hepatocellular cancer [1]. Therefore, it is important to distinguish patients with inflammation or fibrosis in NAFLD and to follow up more closely. Although liver biopsy is the gold standard for demonstrating inflammation and fibrosis in the liver, it is not possible for every patient. Although noninvasive tests such as FIB-4, NFS, and AST to platelet ratio index (APRI), which are created to identify patients to be biopsied, are sensitive for fibrosis, unfortunately they are not sensitive for inflammation [5–7].

Neutrophils, the most abundant white blood cells in humans, are well known as the first-responder defence cells to acute inflammation. However, in recent years, it has been shown that neutrophils also play an important role in chronic inflammation [16]. Diseases such as NAFLD and atherosclerotic heart diseases are chronic inflammatory diseases, in which neutrophil accumulation is one of the important features of inflammation. For example, neutrophils promote macrophage recruitment and exacerbate the inflammatory response initiated by interaction with antigen-presenting cells and increase liver damage. Thus, it makes a vital contribution to the inflammation process [17]. HDL-C protects endothelial cells against the negative effects of LDL-C, removes excess cholesterol from peripheral tissues, and brings it to the liver for excretion. Experimental and clinical studies have shown that HDL-C has a modulating effect on inflammatory cells and inhibits active neutrophil function by impairing cytokine production, migration, and adhesion [18]. Therefore, HDL-C is thought to exert both anti-inflammatory and antioxidant effects. In addition, HDL-C affects neutrophil functions, while activated neutrophils can affect the composition and function of HDL [19]. In light of this information, a new formulation was created by dividing the neutrophil count to HDL-C value, and studies were conducted to investigate the biomarker potential of NHR in cardiovascular diseases. Kou et al. analysed over 400 patients who underwent coronary angiography, and they reported that NHR independently predicted coronary artery disease [18]. Huang et al. compared NHR with monocyte/HDL-C (MHR) and LDL-C/HDL-C parameters in terms of predictive values in elderly patients with acute myocardial infarction (AMI). They found that a higher NHR level was associated with long-term mortality and risk of recurrent AMI, and that NHR had a superior prognostic value for long-term clinical outcomes in elderly patients compared with MHR and LDL-C/HDL-C. In addition, they reported a positive correlation between NHR and the severity of a coronary artery [10]. Başyiğit et al. found that NHR was independently associated with moderate or severe coronary artery stenosis [20]. Ozgeyik et al. found that a higher NHR was associated with increased cardiovascular mortality. They also found that NHR outperformed formulations such as neutrophil/lymphocyte, monocyte/HDL, triglyceride/HDL, HDL/LDL, platelet/lymphocyte, and lymphocyte/HDL in terms of death prediction [21]. In our study, both NHR and FIB-4 scores were higher in the grade 2 and 3 fatty liver groups. However, there was no difference in the grade 1 fatty liver group. We could not find any studies in the literature investigating NHR in NAFLD. However, NAFLD and atherosclerotic cardiovascular diseases are closely related. Various processes such as insulin resistance, dyslipidaemia, hyperglycaemia, oxidative stress, activation of inflammation, endothelial dysfunction, and ectopic lipid accumulation are involved in the pathogenesis of both NAFLD and cardiovascular disease (CVD) [22]. In addition, elevated triglycerides, small dense LDL-C particle increase, and decreased HDL-C levels are known as atherogenic dyslipidaemia and are variably present in patients with NAFLD [23]. Immune findings detected in the liver and systemic circulation in patients with NASH [24] exhibit similar changes to immune findings observed in CVD, suggesting a common immune-inflammatory picture [25]. In recent studies, the increase in cardiovascular

diseases in patients with high FIB-4 scores supports the relationship between the 2 diseases. Vieira-Barbosa et al. found that in a cohort of 81,108 patients at risk for NAFLD, NASH, and NASH, the FIB-4 score was the strongest independent predictor for major adverse cardiovascular events beyond established cardiovascular risk factors and baseline liver diagnosis [26]. In their meta-analysis in patients with CVD, Yan et al. concluded that higher FIB-4 and NFS levels are associated with an increased risk of new cardiovascular events, and cardiovascular and all-cause mortality in patients with cardiovascular disease [27]. In another study, 435 cardiovascular events occurred in a cohort of 5143 patients with stable coronary artery disease proven by angiography in a 7-year follow-up, and it was reported that both NFS and FIB-4 scores were associated with coronary calcification and cardiovascular events [28]. Given this close association of NAFLD with CVD and the pathogenesis of NAFLD, we believe that the high NHR in NAFLD is consistent with the literature.

In our study, NHR was significant only in patients with grade 2 and 3 fatty liver. This seems to be related to worsening of metabolic parameters as the degree of fatty liver increases. For example, parameters such as BMI, WC, insulin, triglyceride, and HDL-C were worse in those with grade 2 and 3 fatty liver disease. Increasing BMI, or obesity, triggers inflammation [29]. This may have resulted in significantly higher levels of neutrophils in grade 2 and 3. As a result, increased neutrophil and decreased HDL-C resulted in significantly higher NHR in these 2 groups. More work is needed on this subject.

Limitations

The most important limitation of our study is that the presence of inflammation and fibrosis could not be documented by liver biopsy. However, nowadays, liver biopsy is risky for medicolegal reasons. Therefore, we consider this limitation to be acceptable. Second, evaluation of fatty liver is based on ultrasound examination, which is somewhat subjective. Third, our study population is relatively small. Fourth, we were unable to determine a cut-off value for NHR.

Conclusion

NHR is a cheap and easy to access parameter. An elevated NHR with FIB-4 in patients with NAFLD may be a marker of liver inflammation or fibrosis. In addition, we believe that it may be beneficial in the risk of cardiovascular disease in patients with NAFLD. There is a need for larger-scale studies on cardiovascular disease in which liver biopsy is also performed.

Ethics statement

The study protocol was approved by Şeyh Edebali University Medical School Ethics Committee.

Author contributions

Concept — E.A., M.O.; design — E.A., M.O.; supervision — E.A., M.O.; resources — E.A.; materials — E.A.; data collection and/or processing — E.A..; analysis and/or interpretation — E.A., M.O.; literature search — E.A.,M.O.; writing manuscript — E.A., M.O.; critical review — E.A., M.O.

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Conflict of interest

The authors declare that they have no competing interest.

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