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ARAŞTIRMA YAZISI / RESEARCH ARTICLE

ALKOLİK OLMAYAN YAĞLI KARACİĞER HASTALIĞI TANISI ALAN AŞIRI KİLOLU ÇOCUKLARDA NÖTROFİL LENFOSİT ORANI VE TROMBOSİT LENFOSİT ORANININ HEPATOSTEATOZ DERECESİYLE KARŞILAŞTIRILMASI

COMPARISON OF NEUTROPHIL LYMPHOCYTE RATIO AND PLATELET LYMPHOCYTE RATIO WITH THE DEGREE OF HEPATOSTEATOSIS IN OVERWEIGHT CHILDREN DIAGNOSED WITH NON-ALCOHOLIC FATTY LIVER DISEASE

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ÖZET

AMAÇ: Nötrofil-lenfosit oranı (NLR) ve trombosit-lenfosit oranı (PLR) değerlerinin grade 1 ve 2 hepatosteatozda farklı olup olmadığını değerlendirmeyi amaçladık.

GEREÇ VE YÖNTEM: Çalışma için 2021 - 2023 yılları arasında pediatrik gastroenteroloji bölümünde hepatosteatoz tanısı alan hastaların kayıtları retrospektif olarak incelendi. Çalışmaya 18 yaşından küçük ve ultrasonografide hepatosteatoz tanısı alan hastalar dahil edildi.

BULGULAR: 18 yaş altı hepatosteatozlu 76 hasta değerlendirildi. Elli üç (%69,7) hasta grade 1 ve 23 (%30,3) hasta grade 2 idi. Grade 2 hastaların yaş ortalaması (12,0 ± 3,9), grade 1 hastaların yaş ortalamasından (9,5 ± 2,6) daha yüksekti. Vücut kitle indeksinin grade 2 hepatosteatozda daha yüksek olduğu bildirildi (21,4 ± 2,5'e karşı 25,8 ± 4,7; P < 0,001). Aspartat aminotransferaz (AST) (28,1 ± 12,9'a karşı 35,2 ± 22,2; P = 0,088) ve Alanin aminotransferaz (ALT) (32,0 ± 15,3'e karşı 39,5 ± 21,4; P = 0,089) değerleri grade 2 grubunda daha yüksekti ancak anlamlı olarak farklı değildi. NLR (2,5 ± 1,2 vs 3,2 ± 1,7; P= 0,041) ve PLR (140 ± 58 vs 175 ± 75; P= 0,031) grade 2'de anlamlı derecede daha yüksekti.

SONUÇ: NLR ve PLR değerlerinin hepatosteatozun ilerlemesinde yüksek öngörücü değere sahip parametreler olarak kullanılması muhtemeldir. Hepatosteatozun ilerlemesinde inflamatuvar sürecin rolü önemlidir.

ANAHTAR KELİMELER: Hepatosteatoz, Nötrofil-lenfosit oranı, Trombosit-lenfosit oranı, Aspartat aminotransferaz, Alanin aminotransferaz.

ABSTRACT

OBJECTIVE: We aimed to evaluate whether neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) values differ in grade 1 and 2 hepatosteatosis.

MATERIAL AND METHODS: For the study, the records of patients diagnosed with hepatosteatosis in the pediatric gastroenterology department between 2021 and 2023 were examined retrospectively. Patients younger than eighteen years of age and diagnosed with hepatosteatosis on sonographic examination were included in the study.

RESULTS: Seventy-six patients under 18 years of age with hepatosteatosis were evaluated. Fifty-three (69.7%) patients were grade 1 and 23 (30.3%) were grade 2. The mean age of grade 2 patients (12.0 ± 3.9) was higher than that of grade 1 patients (9.5 ± 2.6). Body mass index was reported to be higher in the grade 2 hepatosteatosis (21.4 ± 2.5 vs 25.8 ± 4.7; P < 0.001). AST (28.1 ± 12.9 vs 35.2 ± 22.2; P= 0.088) and ALT (32.0 ± 15.3 vs 39.5 ± 21.4; P= 0.089) values were higher in the grade 2 group but were not significantly different. NLR (2.5 ± 1.2 vs 3.2 ± 1.7; P= 0.041) and PLR (140 ± 58 vs 175 ± 75; P= 0.031) were significantly higher in the grade 2.

CONCLUSIONS: NLR and PLR values are likely to be used as parameters with high predictive value in the progression of hepatosteatosis. The role of the inflammatory process in the progression of hepatosteatosis is important.

KEYWORDS: Hepatosteatosis, Neutrophil-lymphocyte ratio, Platelet-lymphocyte ratio, Aspartate aminotransferase, Alanine aminotransferase.

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INTRODUCTION

Fat infiltration of the liver (more than 5% of hepatocytes), proven by imaging, direct measurement, or histological examination, leads to hepatosteatosis (1). Although clinical liver biopsy provides a definitive diagnosis of hepatosteatosis, the most commonly used methods for diagnosis are liver function tests and ultrasonography, which are non-invasive procedures. Obesity is defined as abnormal or excessive fat accumulation and a serious risk factor for hepatosteatosis. The World Health Organization defines obesity as having a body mass index >95. percentile (>2 SD) (2). As the severity of hepatosteatosis increases, the age, liver diameter and body mass index of the patients increase (3, 4).

In hepatosteatosis, fat-infiltrated liver cells are exposed to inflammation and fibrosis as the disease progresses. It has been shown in the literature that this inflammation, systemic inflammatory index and pan immune inflammation value [(neutrophil count × platelet count × monocyte count)/ lymphocyte count] increases with the degree of hepatosteatosis (5). Since neutrophils, lymphocytes and platelets play a role in inflammation, we thought that these values and the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) values. During systemic inflammation, it is well known that the classification of circulating white blood cells (WBC) is altered. These changes are usually seen as lymphocytopenia and neutrophilia. Recently, WBC and its subgroup counts have begun to be used as biomarkers for inflammation in various diseases. The neutrophil-to-lymphocyte ratio (NLR) serves as a marker of subclinical inflammation and is used to assess inflammation in both autoimmune and non-autoimmune conditions. PLR, like NLR, is an inflammatory index measured in routine blood tests, and its variation may indicate inflammation and cytokine activity (6). We thought that, these markers may play a crucial role in the progression of hepatosteatosis and may be useful for prediction as well as follow up beside the classical methods. In this study, we aimed to evaluate whether NLR and PLR values differ in grade 1 and 2 hepatosteatosis.

MATERIAL AND METHODS

For the study, the records of patients diagnosed with hepatosteatosis in the pediatric gastroenterology department between 2021 and 2023 were examined retrospectively. Patients younger than eighteen years of age and diagnosed with hepatosteatosis on sonographic examination were included in the study. Patients with congenital metabolic disease, infection or chronic disease that could affect neutrophil and lymphocyte values, and patients with hematological disease that could affect platelet values were not included in the study.

Patients' ages, gender, height, weight and body mass index values were noted on the system. Children's heights were measured in centimeters with meters mounted on the wall while barefoot. Weight was measured in kilograms with the children wearing light clothing. Body mass index value was obtained by dividing the weight in kilograms by the square of the height in meters. Measurements enabled the identification of obese children using the World Health Organization's percentile calculation program (7). Fasting serum glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), parathormone, calcium, neutrophil, platelet and lymphocyte values were noted. NLR was calculated by dividing the neutrophil value by the lymphocyte value. PLR was obtained by dividing the platelet value by the lymphocyte value.

Abdominal ultrasonography data were evaluated retrospectively. Hepatosteatosis grading were as follows; for grade 1, there is mild echogenicity in the liver parenchyma, for grade 2, there is a further increase in the parenchymal echo or slight deterioration in the visualization of the diaphragm and intrahepatic vessels, and for grade 3, there is a serious increase in parenchymal echogenicity and the echo of the diaphragm and intrahepatic vessels cannot be distinguished (5). The patients were divided into two groups as grade 1 and grade 2 according to their sonographic evaluation. There was no patient with grade 3 hepatosteatosis.

Ethical Committee

All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Local Central Ethics Committee Approval received (Kayseri City Education and Research Hospital Ethics Committee, Decision date: 30.07.2024, Decision number: 152). Informed consent was obtained from the cases or their legal guardians.

Statistical Analysis

In the study, categorical data were expressed as numbers and percentages. The chi-square test was used to analyze categorical data. When evaluating numerical data, mean ± standard deviation was used. Student-T test was used to compare the data. Receiver operating characteristic (ROC) test was used to determine the ideal cut-off value of NLR and PLR values so that it can be used to predict Grade 2 patients. Area under curve (AUC) was calculated in the table. Sensitivity and specificity values were analyzed according to the cut-off value obtained in the ROC analysis. Data recording and statistical analyzes were performed using SPSS (statistical package for the social sciences) software (version 17, SPSS, Inc, Chicago, IL). A p-value of <0.05 was considered to indicate statistical significance.

RESULTS

Seventy-six patients under 18 years of age with hepatosteatosis were evaluated. Fifty-three (69.7%) patients were grade 1 and 23 (30.3%) were grade 2. The mean age of grade 2 patients (12.0 ± 3.9) was higher than that of grade 1 patients (9.5 ± 2.6). Girls were more common in both groups (58.5% in group 1 and 52.2% in group 2). Body mass index was reported to be higher in the grade 2 hepatosteatosis (21.4 ± 2.5 vs 25.8 ± 4.7; P < 0.001). AST (28.1 ± 12.9 vs 35.2 ± 22.2; P= 0.088) and ALT (32.0 ± 15.3 vs 39.5 ± 21.4; P= 0.089) values were higher in the grade 2 group but were not significantly different. ALP was higher in the grade 2 group (221 ± 42 vs 238 ± 52; P= 0.153). Parathormone and calcium levels did not differ between the groups. The mean neutrophil level (5135 ± 2027 vs 5760 ± 1082; P= 0.168) was higher in the grade 2 group, but the result was not statistically significant. Platelet level was higher in the grade 2 patients and significantly different (P= 0.047). NLR (2.5 ± 1.2 vs 3.2 ± 1.7; P= 0.041) and PLR (140 ± 58 vs 175 ± 75; P= 0.031) were significantly higher in the grade 2 patients. Clinical and laboratory data of the patients in the study group are summarized in **Table 1**.

Table 1: Clinical and laboratory characteristics of hepatosteatosis patients

	Grade 1 (53)	Grade 2 (23)	P
Age, (years)	9.5 ± 2.6	12.0 ± 3.9	0.002
Gender, n (%)			0.397
- Female	31 (58.5)	12 (52.2)	
- Male	22 (41.5)	11 (47.8)	
Height, (cm)	135 ± 14	146 ± 21	0.007
Weight, (kg)	40 ± 12	59 ± 24	<0.001
Body mass index, (kg/m²)	21.4 ± 2.5	25.8 ± 4.7	<0.001
Aspartate Aminotransferase, (IU/L)	28.1 ± 12.9	35.2 ± 22.2	0.088
Alanine Aminotransferase, (U/L)	32.0 ± 15.3	39.5 ± 21.4	0.089
Alkaline phosphatase, (IU/L)	221 ± 42	238 ± 52	0.153
Parathormone, (pg/mL)	53.2 ± 15.2	54.2 ± 16.6	0.797
Calcium, (mg/dL)	9.6 ± 0.6	9.5 ± 0.6	0.482
Fasting blood glucose, (mg/dL)	85.4 ± 4.0	88.0 ± 5.6	0.025
Neutrophil	5135 ± 2027	5760 ± 1082	0.168
Platelet (*10³)	282 ± 66	318 ± 79	0.047
Lymphocyte	2218 ± 656	2041 ± 670	0.285
Neutrophil lymphocyte ratio	2.5 ± 1.2	3.2 ± 1.7	0.041
Platelet lymphocyte ratio	140 ± 58	175 ± 75	0.031

ROC analysis was performed to determine the cut-off of NLR and PLR values that can be used to predict grade 2 hepatosteatosis **(Figure 1)**. The area under curve for NLR was 0.615 (P= 0.016) and the cut-off value was calculated as >2.5. Sensitivity and specificity values were analyzed as 73.9% and 64.2%, respectively. The AUC value for PLR was 0.641 (P= 0.052) and the cut-off value was reported as >140. Sensitivity and specificity were analyzed as 60.9% and 64.2%, respectively.

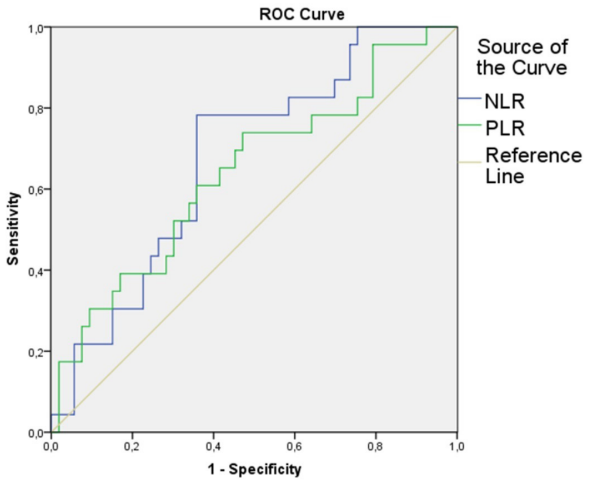

Figure 1: ROC curve of NLR and PLR to identify patients likely to grade 2 hepatosteatosis.

DISCUSSION

The prevalence of obesity and related health concerns are increasing among all pediatric age groups in both developed and developing countries. As a result, new noninvasive tech-

niques are needed to evaluate the severity of the disease and the outcome (2). Thus, we evaluated the differences between grade 1 and 2. The most important finding in our study was grade 1 and 2. NLR and PLR values, which are important indicators of fibrosis and inflammation, were significantly higher in grade 2 hepatosteatosis than those in grade 1 hepatosteatosis.

The pathogenesis of hepatosteatosis is not fully known. According to the "2 hit" theory, insulin resistance in hepatocytes is the main cause of triglyceride accumulation and increases the sensitivity of liver cells to the "second hit". Factors are thought to be effective in the second hit are oxidative stress damage, cytokines, endotoxins and environmental toxins, and the resulting inflammatory process begins (8). Additionally, fibrosis that occurs in advanced grades begins on the basis of inflammation (5, 9). Oxidative stress and increased proinflammatory cytokines are the main mechanisms of fatty acid-induced damage. Lipotoxic damage to hepatocytes releases cytokines and chemokines, which then activate innate and adaptive immune cells, including macrophages, dendritic cells, lymphocytes, and neutrophils, creating an inflammatory cascade (10, 11). Average systemic inflammatory index and pan-immune inflammation values, which are thought to reflect the systemic inflammatory process, were found to be higher in hepatosteatosis with advanced grade. In regression analysis, pan-immune inflammation was shown to be an independent risk factor for the occurrence of hepatosteatosis (5). Studies in the literature have shown that inflammatory parameters such as NLR, PLR, and systemic inflammatory index are higher in patients with non-alcoholic fatty liver disease (12-16). In our cohort, consistent with the literature, the inflammatory process is thought to increase the progression of hepatosteatosis. We found that NLR and PLR were significantly higher in the patients with grade 2 than patients with grade 1.

Rapidly increasing obesity in the pediatric population is thought to increase the frequency of hepatosteatosis (3, 4). Mean BMI values were found to be higher in hepatosteatosis patients than in the control group (17). It also shows that improvement in steatosis is achieved by up-regulation of both β- and whole fatty acid oxidation without directly affecting lipogenesis (18). Similar to the literature, in our study, patients with grade 2 hepatosteatosis were found to have higher BMI values than patients with grade 1 hepatosteatosis had. Additionally, a positive correlation was observed between AST and ALT values of liver function tests and hepatosteatosis grade (11,19). In our study, liver function tests were observed to be higher in grade 2 patients. Furthermore, in a study conducted to understand the pathophysiology, mean shear wave elastography values were significantly higher in overweight/obese patients with hepatosteatosis than in healthy controls, suggesting liver stiffness in overweight/obese children (20). Statistically significant correlations were found between shear wave elastography values and weight and BMI values. The results showed that the SWE value increased with increasing weight and BMI (20).

There are some shortcomings of our study. First of all, it can be said that it is organized in a retrospective nature. Secondly, the number of patients is small. However, homogeneous patients in the pediatric age group add value to the study.

In conclusion, NLR and PLR values are likely to be used as parameters with high predictive value in the progression of hepatosteatosis. The role of the inflammatory process in the progression of hepatosteatosis is important. The inflammatory parameters, which play an important role in the pathogenesis of non-alcoholic fatty liver disease, can be used to follow-up the disease. Prospective studies on the subject are needed.

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