Clinical Research

Are Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio Correlated with Hepatosteatosis in Obese Children?

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ABSTRACT

Objective: To investigate the utility of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in predicting steatosis, a severe complication of obesity, in obese pediatric patients.

Material and Method: Patients diagnosed with obesity followed at the pediatric gastroenterology outpatient clinic between June 2020 and November 2021 were included in this study. The patients were divided into two groups based on the presence of hepatosteatosis. Neutrophil-to lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were compared between the two groups.

Results: There were 34 patients in the group without steatosis and 35 patients in the group with steatosis. Obese patients in the non-steatosis group had a mean body weight of 67.5 kg, mean height of 151.5 cm, mean BMI of 27.8 and a mean BMI SDS of 2.4. Obese patients in the non-steatosis group had a mean body weight of 62 kg, mean height of 150 cm, mean BMI of 27.1 and a mean BMI SDS of 2.3. There was no significant difference between the groups in terms of body weight, height, BMI and BMI SDS values ($p>0.05$). When the groups were compared, the steatosis group showed higher NLR and PLR compared to non-steatosis group. The NLR values were 0.94 (0.78-1.54) in the non-steatosis group and 1.57 (1.05-2.21) in the steatosis group ($p =0.005$). The PLR values were 83.9 (67.3-111.7) in the non-steatosis group and 106.6 (93.4-138.2) in the steatosis group ($p =0.003$).

Conclusion: NLR and PLR can be used as simple, easy and independent markers for the prediction of steatosis in obese patients.

Keywords: *Obesity, Children, Steatosis, Neutrophil-To-Lymphocyte Ratio, Platelet-To- Lymphocyte Ratio.*

ÖZ

Obez Çocuklarda Nötrofil Lenfosit Ve Trombosit Lenfosit Oranı Hepatosteatoz İle İlişkili Midir?

Amaç: Obez çocuk hastalarda, obezitenin ciddi bir komplikasyonu olan steatoz öngörmede nötrofil-lenfosit oranı ve trombosit-lenfosit oranının kullanılabilirliğini araştırmaktır.

Gereç ve Yöntem: Haziran 2020-Kasım 2021 tarihleri arasında çocuk gastroenteroloji polikliniğinde takipli obezite tanılı olgular çalışmaya dahil edildi. Hepatosteatoz varlığına göre iki gruba ayrıldı. Olguların nötrofil-lenfosit oranı ve trombosit-lenfosit oranı gruplar arasında karşılaştırıldı.

Bulgular: Steatoz olmayan hasta grubunda 34 hasta, steatoz olan grupta 35 hasta var idi. Steatoz olmayan obez hasta grubundaki hastaların vücut ağırlığı 67.5 kg, ortalama boy 151.5 cm, ortalama VKİ 27.8 ve VKİ SDS 2.4 olarak ölçüldü. Steatoz olan obez hasta grubundaki hastaların vücut ağırlığı 62 kg, ortalama boy 150 cm, ortalama VKİ 27.1 ve VKİ SDS 2.3 olarak ölçüldü. Her iki grupta kilo, boy, VKİ ve VKİ SDS değerleri açısından istatistiksel olarak anlamlı fark saptanmadı ($p>0.05$). Gruplar arasında karşılaştırma yapıldığında nötrofil-lenfosit oranı ve trombosit-lenfosit oranı steatoz olan grupta yüksek idi. Nötrofil-lenfosit oranı steatoz olmayan grupta 0.94(0.78-1.54), steatoz olan grupta 1.57(1.05-2.21), ($p =0.005$) idi. Trombosit-lenfosit oranı steatoz olmayan grupta 83.9(67.3-111.7), steatoz olan grupta 106.6(93.4-138.2), ($p =0.003$) idi.

Sonuç: Nötrofil-lenfosit oranı ve trombosit-lenfosit oranı, obez hastalarda steatoz tahmini için basit, kolay ve bağımsız belirteç olarak kullanılabilir.

Anahtar Sözcükler: *Obezite Çocuk, Steatoz, Nötrofil-Lenfosit Oranı, Trombosit-Lenfosit Oranı.*

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Obesity is a chronic metabolic condition characterized by abnormal and excessive accumulation of fat in the body that impairs health. Childhood obesity has rapidly become a global health concern with a dramatic increase in its prevalence and incidence, especially in the developed countries but also in developing countries (1). The prevalence of obesity was 39.8% in 2015-2016 in the USA, and it is predicted that nearly one in two adults will become obese by 2030 (2). As the prevalence of obesity increases, the prevalence of obesity-

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related comorbidities also increases (3).

It is known that obesity complications that affect the morbidity and mortality in adults also occur in children and adolescents. Non-alcoholic fatty liver disease (hepatosteatosis), one of the well-recognized complications of obesity, is also the most common liver disease all over the world. Hepatosteatosis is defined as the presence of steatosis in more than 5% of hepatocytes in the absence of significant alcohol intake, medication use or a genetic disease (4). Non-alcoholic steatohepatitis (NASH) develops in one-quarter of individuals with hepatosteatosis and subsequent progression to liver cirrhosis occurs in one-fourth of them.

The complete blood count (CBC) is an easy and inexpensive test that includes leukocyte, neutrophil, lymphocyte and platelet counts, all of which are used as inflammatory markers. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are inexpensive and widely available hemogram parameters. While the neutrophil-to-lymphocyte ratio is used as a predictor of systemic and local inflammation, the platelet-to-lymphocyte ratio serves to predict inflammation and platelet aggregation. Elevations of these two ratios are considered as a predictor of poor prognosis. Both parameters are also used to predict prognosis in rheumatic diseases, COPD, pulmonary thromboembolism and concomitant community-acquired pneumonia as well as for the prediction of cardiovascular and renal complications in diabetic patients (5-9). Hepatosteatosis affects one-half of obese children. Therefore, it would be useful to diagnose hepatosteatosis in obese children as early as possible. While ultrasonography is widely used for the diagnosis of hepatosteatosis, it could be more readily detected by a routine complete blood count. The aim of this study was to investigate the utility of NLR and PLR in predicting steatosis, a severe complication of obesity, in obese pediatric patients.

MATERIAL AND METHOD

Patients diagnosed with obesity followed at the pediatric gastroenterology outpatient clinic between June 2020 and November 2021 were included in this single-center retrospective study. Since the body mass index (BMI) is a simple, practical, inexpensive and reliable tool, it is often used for the diagnosis of obesity in children. BMI is calculated by dividing the body weight in kilograms by the height in meters squared using the formula: body weight (kg) / height² (m²). BMI varies according to age and sex in children and adults and accordingly, age- and sex-specific BMI percentiles and charts have been developed. A child or adolescent is diagnosed as overweight if the BMI is between the 85th and the 95th percentiles for age and sex and as obese if the BMI is above 95th percentile (10). At our center, abdominal ultrasound (US) imaging, routine biochemistry panel (AST, ALT, albumin, glucose, lipid profile, CRP) and hemogram analysis are performed for all patients diagnosed with obesity.

Hemoglobin, neutrophil, lymphocyte and leukocyte counts were obtained from the CBC reports. For hemogram analysis, an adequate amount of venous whole blood samples was drawn into vacuum K2-EDTA blood collection tubes with a purple cap after 8-12 hours of fasting. The blood tubes were then inverted 8-10 times and tested on an automated analyzer (Cell-Dyn Ruby Analyzer; Abbott, Abbott Park, IL) within 6 hours of collection. Neutrophil-to-lymphocyte ratio and platelet-to- lymphocyte ratio were calculated. NLR was calculated by dividing neutrophil count by lymphocyte count, and PLR by dividing neutrophil count by platelet count. Age, sex and anthropometric measurements of the patients were noted.

Patients with an active infectious disease, diabetes mellitus, systemic hypertension, hyperlipidemia, chronic disease, syndromic obesity or hypothyroidism and smokers were excluded from the study.

Steatosis was classified into three grades according to abdominal ultrasound findings: Grade 1, only mild diffuse increase in the echogenicity of the liver; Grade 2, moderate increase in the echogenicity of the liver with slightly impaired visualization of intrahepatic vessels; Grade 3, marked increase in the echogenicity of the liver with poor or no visualization of intrahepatic vascular structures and posterior segment of the right lobe of the liver. Patients were divided into two groups based on the presence of hepatosteatosis. Approval was obtained from the local ethics committee prior to initiation of the study.

Statistical Analysis

Statistical analysis was conducted to evaluate two groups according the presence of hepatosteatosis in obese patients. Kolmogorov-Smirnov test was used to check whether numerical laboratory and demographic data followed a normal distribution. Independent samples t-test or Mann–Whitney U test was used for comparison of two groups as appropriate. All statistical analyses were performed using IBM SPSS for Windows, version 23.0 (IBM Corp.; Armonk, NY) software package, and the level of significance was set at 0.05.

RESULTS

Sixty-nine patients presenting to the pediatric gastroenterology outpatient clinic due to obesity between the study dates were included in the study and divided into two main groups based on the presence of hepatosteatosis. On abdominal ultrasound imaging, hepatosteatosis was absent in 34 patients and present in 35 patients. Grade 1 hepatosteatosis was detected in 22 patients and grade 2 hepatosteatosis in 13 patients. The mean age of the patients without steatosis was 136 ± 34.3 months and that of patients with steatosis was 131.9 ± 35.3 months. The group of obese patients without steatosis had a mean body weight of 67.5 kg,

mean height of 151.5 cm, mean BMI of 27.8 kg/m^2 and BMI SDS of 2.4. The corresponding figures for the group of obese patients with steatosis were 62 kg, 150 cm, 27.1 kg/m^2 and 2.3, respectively. There was no significant difference between the groups in terms of body weight, height, BMI and BMI SDS (p >0.05). Demographic characteristics of both groups are summarized in table 1.

Table 1. *Demographic characteristics of obese patients with or without hepatosteatosis.*

Parameters	Hepatosteatosis Absent (n =34)	Hepatosteatosis Present (n =35)	p-value
Age (months)	136.03 ± 34.34	131.94 ± 35.38	0.628
Body weight (kg)	67.50 (46.75-74)	62 (49-74)	0.705
Height (cm)	151.50 (134.50-159.25)	150 (134-156)	0.635
BMI (kg/m^2)	27.80 (25.6-30)	27.1 (25.4-30.4)	0.760
BMI SDS	2.4 (2.1-2.7)	2.3 (2-2.7)	0.741

BMI SDS: body mass index standard deviation score.

Laboratory workup of the patients showed significantly higher neutrophil and leukocyte counts and lower lymphocyte count in the group with hepatosteatosis (Table 2).

Table 2. *Laboratory results of obese patients with or without hepatosteatosis.*

Parameters	Hepatosteatosis Absent (n =34)	Hepatosteatosis Present (n =35)	p-value
Neutrophils	3500 (2891.75-4325)	4310 (3223-5883)	**0.021**
Lymphocytes	3455 (2604-4348)	3000 (2400-3300)	**0.046**
Platelets	310457.14 ± 84670.41	317264.72 ± 59850.47	0.702
C-reactive protein	0.3 (0.27-0.8)	0.5 (0.2-1.2)	0.184
AST	25.50 (21-33,25)	27 (22-59)	0,296
ALT	18 (16-25,50)	22 (17-53)	0,062

AST: aspartate aminotransferase, ALT: alanine aminotransferase.

Consistently, NLR and PLR were significantly higher in the group with hepatosteatosis. Median (interquartile ranges) NLR values were 0.94 (0.78-1.54) in patients without steatosis and 1.57 (1.05-2.21) in patients with steatosis (p =0.005). Median (interquartile ranges) PLR values were 83.9 (67.3-111.7) in patients without steatosis and 106.6 (93.4-138.2) in in patients with steatosis (p =0.003) (Figure 1).

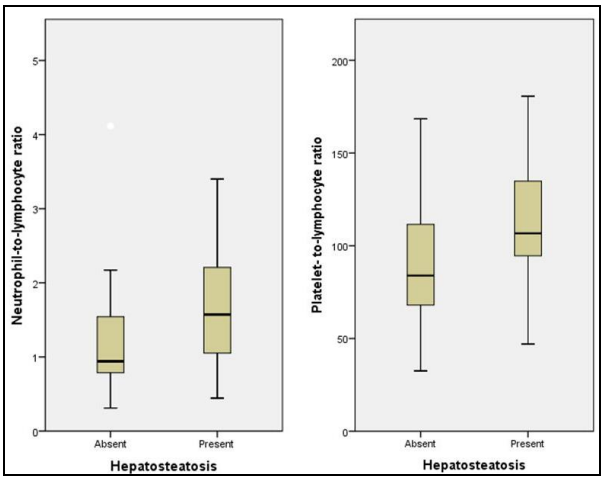

Figure 1. *Box plots of neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in obese patients with or without hepatosteatosis.*

DISCUSSION

Obesity is the result of an interplay between genetic and environmental factors which interact with energy metabolism and fat tissue. Obesity is defined as excessive accumulation of body fat due to high energy intake that may impair health. It is a complex and multifactorial metabolic disorder that affects not only adults but children as well. The prevalence of childhood obesity is rising in all pediatric age groups especially in developed countries but also in developing countries, and is an increasing health concern across the world (11-13). Childhood obesity should be taken seriously by parents to prevent the development of serious health problems now and in the future.

Increased prevalence of obesity is associated with increased prevalence of obesity-related disorders. Many health issues are associated with obesity, including cardiovascular disease, hypertension, type 2 diabetes and hepatosteatosis (14). The liver is an important site for the synthesis of acute phase proteins. Monokines IL-1, IL-6 and TNF-α, which are synthesized and released by stimulated monocytes are considered as mediators of acute phase proteins in the liver (15). Inflammatory cytokines are secreted by the adipose tissue and cause liver disease. After being synthesized in a local lesion at the initial stage of inflammation, IL-6 moves to the liver via bloodstream, leading to a rapid induction of several acute phase proteins (16). Hepatosteatosis is a well-known complication of obesity and the most common liver disease across the globe. Hepatosteatosis is defined as steatosis affecting more than 5% of the liver weight in the absence of excessive alcohol intake, medication use or a genetic disorder (4). Hepatosteatosis is of significance because 25% of affected patients develop steatohepatitis and 25% of them develop liver cirrhosis. While the incidence of fatty liver disease ranges from 10 to 77% in obese children, 38% of children with fatty liver disease are obese. In line with previous reports, hepatosteatosis was identi-

fied in 50.7% of the obese patients in the current study. Hepatosteatosis is infrequent in children under 8 years of age, and the mean age at presentation is 12 years (17). Consistently, the mean age of the patients with hepatosteatosis was 136 months in our study. Children with hepatosteatosis are mostly obese and asymptomatic. Hepatosteatosis has gained significance worldwide due to its common occurrence in the general population and its progression to liver cirrhosis and liver failure. With an alarmingly increasing prevalence across the globe, obesity is a major nutritional problem that affects 25-30% of children (18, 19).

In obesity, leptin and other chemokines are involved in the transmigration of bone marrow-derived monocytes into fat tissue, resulting in increases in IL-6, TNF-α and many other cytokines. In turn, this leads to an elevation of acute phase proteins such as CRP. All of these events explain the chronic low-grade inflammation that actively contributes to changes in hematologic parameters (2). In obese individuals, inflammatory cells infiltrate into adipose tissue and inflammatory cells and adipocytes induce chronic systemic inflammation by producing cytokines (20, 21). Neutrophils, lymphocytes and platelets are major components of blood that are involved in inflammatory process (22). In recent years, it has been shown that NLR and PLR are markers of systemic inflammation and may be correlated with prognosis in a number of cardiovascular diseases, malignancies and chronic inflammatory conditions. Both NLR and PLR can be easily measured and have emerged as practical markers that can provide valuable information for the diagnosis and prognosis of various diseases. Increased neutrophil count and elevated NLR have been demonstrated in obese patients in a study by Atmaca et al. (23). In a study by Aydın et al. involving obese adolescents, greater NLR was found in obese patients with hepatosteatosis than in healthy controls (24). In a study by Furuncuoğlu et al. (25) in 223 obese patients aged 18 to 65 years, higher white blood cell and neutrophil counts were detected in obese individuals versus control group. Similarly, neutrophil count and NLR were found to be higher in obese patients with hepatosteatosis compared to patients without hepatosteatosis and the difference between the two groups was significant. Platelets interact with endothelial cells, leukocytes and progenitor cells, thereby triggering migration of inflammatory cells into the site of injury and release of inflammatory cytokines in abundance and eventually, creating an inflammatory environment in the lesion area. İn inflammatory events, the platelet count increases and lymphocyte count decreases, resulting in an increase in the platelet/lymphocyte ratio (26). NLR and PLR can be easily obtained through peripheral blood count to identify inflammation. Both NLR and PLR measurements cost less and are more valuable compared to some other markers including IL-6, IL-8 and TNF-alpha. In this study, obese patients with steatosis showed higher neutrophil and platelet counts and lower lymphocyte count compared to obese patients without steatosis.

A number of limitations should be noted for this study. First, this was a single-center study with a limited sample size. Secondly, due to the retrospective design of the study, we cannot exclude the possibility that potential preanalytical errors in routine evaluation of hemogram analysis may have been overlooked. Nevertheless, preanalytical process for hemogram analysis is thoroughly followed at our center.

Conclusion

Recently, combinations of different test parameters have been used for the follow-up of many diseases (27). Neutrophils, lymphocytes and platelets are major blood cells that are involved in inflammatory disorders. As a rapid, inexpensive and convenient tool, routine complete blood count will facilitate the detection of hepatosteatosis. In this study, we found that NLR and PLR values were significantly higher in obese pediatric patients with hepatosteatosis compared to control group. NLR and PLR can be used as simple, easy and independent markers for the prediction of steatosis in obese patients.

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