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Evaluation of Hematological Biomarkers in Childhood Metabolic Dysfunction Associated Steatotic Liver Disease

Çocukluk Çağı Metabolik Disfonksiyon İlişkili Steatotik Karaciğer Hastalığında Hematolojik Biyobelirteçlerin Değerlendirilmesi

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Abstract

Aim: We aimed to investigate the clinical significance and diagnostic value of inflammation-based biomarkers in children with a diagnosis of Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD).

Material and Method: This study was carried out by retrospectively evaluating the files of patients followed up in the Department of Pediatric Hepatology at Selçuk University between July 2022 and January 2023.The study was completed with 120 patients with MASLD diagnosed according to the criteria of the AASLD and EASL, 80 healthy controls.Comparisons were made by calculating laboratory values and formulas through them.

Results:There were 50 (41.7%) girls and 70 (58.3%)boys in the patient group,and 40 girls (50.0%) and 40 boys (50.0%) in the control group.While 80 patients with Grade 0 detected in liver ultrasonography were taken as the control group; 102 (85%) Grade 1 and 18 (15%) Grade 2-3 patients were considered as the patient group.The values of the patients were compared with the values of healthy volunteers.When the WBC, neutrophil, lymphocyte, platelet, MHR, RPR, RLR, MPR, WMR, GPR, SII and FIB-4score values were compared according to liver grading, a correlation was found in the tests performed on the patients.

Conclusion: Our study suggests that the presence of MASLD should be investigated in individuals, and possible complications can be prevented with early diagnosis and treatment approaches.As a result, we think that the use of hematological biomarkers will be useful for the simple and rapid detection of patients with suspected MASLD and who need further examination and treatment.

Keywords: Metabolic dysfunction associated steatotic liver disease, biomarker, chıldren, fatty liver disease

Öz

Amaç: Çalışmamızda Metabolik Disfonksiyon İlişkili Steatotik Karaciğer Hastalığı (MASLD) tanılı çocuklarda inflamasyon temelli biyobelirteçlerin klinik önemi ve tanısal değerini araştırmayı amaçladık.

Gereç ve Yöntem: Bu Çalışma, Temmuz 2022-Ocak 2023 tarihleri arasında Selçuk Üniversitesi Çocuk Gastroenteroloji bölümünde takip edilen hasta dosyalarının retrospektif olarak değerlendirilmesi ile gerçekleştirilmiştir.AASLD ve EASL kriterlerine göre tanı konulan 120 MASL hastası ve 80 sağlıklı kontrol grubu ile çalışma tamamlanmıştır. Laboratuvar değerleri ve bunlar aracılığı ile formüller hesaplanarak karşılaştırmalar yapılmıştır.

Bulgular: Hasta grubunda 50 (%41,7) kız, 70 (%58,3) erkek ve kontrol grubunda ise 40 kız (%50,0), 40 erkek (%50,0) idi.Karaciğer Ultrasonografilerinde Grade 0 tespit edilen 80 hasta kontrol grubu; 102'si (%85) Grade 1 ve 18'i (%15) Grade 2-3 hasta grubu olarak kabul edildi. Hastaların değerleri, sağlıklı gönüllülerin değerleri ile karşılaştırıldı.Yapılan testlerde hastalarda WBC, nötrofil, lenfosit, platelet, MHO, RPO, RLO, MPO, WMO, GPO, Sİİ ve FIB-4 skor değerleri karaciğer Gradelendirilmesine göre karşılaştırıldığında korelasyon tespit edildi.

Sonuç: MASLD'ın erken tespiti için etkili bir izleme göstergesine acilen ihtiyaç duyulmaktadır. Yapmış olduğumuz bu çalışma, kişilerde MASL varlığının araştırılması gerektiğini, erken tanı ve tedavi yaklaşımları ile olası komplikasyonların önüne geçilebileceğini düşündürmektedir.Sonuç olarak MASLD'den şüphelenilen, ileri tetkik ve tedaviye ihtiyaç duyan hastaların basit ve hızlı bir şekilde tespiti için hematolojik biyobelirteçlerin kullanımı faydalı olacağı düşüncesindeyiz.

Anahtar Kelimeler: Metabolik disfonksiyon ilişkili steatotik karaciğer hastalığı, biyobelirteç, çocuklar, yağlı karaciğer hastalığı

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INTRODUCTION

Hepatic steatosis, hepatocyte damage, liver inflammation, and fibrosis, which were associated with overweight or obese people for many years, was published in 1980 by Jurgen Ludwig with the term "Non-Alcoholic Steatohepatitis".[1] It was considered that this definition did not fully elucidate the etiology, was stigmatizing, and contributed to inequality in healthcare. The term "Steatotic Liver Disease Associated with Metabolic Dysfunction" (MASLD) was suggested later in the article published in 2020 by Eslam et al.[2] The nomenclature was changed in 2023 by the Liver Diseases Research Association (AASLD) and the European Liver Diseases Research Association (EASL), predicting that it could improve awareness and patient identification.[3]

MASLD is a healthcare concern with increasing prevalence because of improved living conditions and sedentary lifestyle habits.[4,5] Its global prevalence is 20-50% in obese children and is the most common Chronic Liver Disease (CHD) on a global scale.[6,7] In our country, its prevalence was reported to be 23-62% in obese children.[8-10]

MASLD often has no symptoms but sometimes, liver enlargement may be the only finding on examination. For these reasons, the diagnosis of the disease is made with laboratory findings. Ultrasonography (USI) is among the basic methods employed to detect fatty liver.[3,11] Early detection and evaluation of MASLD and liver fibrosis, monitoring disease development, and choosing appropriate therapeutic modalities for patients are very important.[12,13] Liver biopsy is the gold standard for grading of liver fibrosis and clinical diagnosis. However, it is not always preferred in children because it is an invasive method. Increasing evidence shows that chronic inflammation is considered an important part of its pathophysiology.[14] It is possible to predict the presence and development of MASLD with inflammatory markers.[10,15-17]

In the present study, the researchers planned to investigate the clinical value of novel, non-invasive, and practical inflammatory biomarkers to assess the relationship between hematological biomarkers and MASLD in obese children and to predict the development of MASLD.

MATERIAL AND METHOD

The study was carried out with the permission of Selçuk University Local Ethics Committee (Date: 18.07.2023, Decision No: 2023/352). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study included 120 patients who were diagnosed with MASLD, detected to have adiposity on USI, with excluded autoimmune, metabolic, and infectious causes, and who were not known to have drug and toxin exposure, in the Pediatric Hepatology clinic of the Selçuk University between July 2022 and January 2023.[18] The control group consisted of 80 healthy children who met the inclusion criteria after semi-structured diagnostic interviews. All children were assessed and their gender and age characteristics were recorded. Body Weight (BW-kg), Height (cm), Body Mass Index (BMI), and Body Weight for Height (BWH) measurements were recorded for all patients.

Simultaneous complete blood counts and biochemistry samples with USI were taken from the system of the biochemistry laboratory of the Faculty Hospital were taken from the hospital system by using the Beckman Coulter AU5800, LH780 brand device. Hemoglobin (Hb), platelet distribution width (PDW), the mean platelet volume (MPV), mean corpuscular volume (MCV) and erythrocyte distribution width (RDW) values were recorded from the files. Alanine amino transferase (ALT), aspartate amino transferase (AST), GGT, total protein, albumin, cholesterol, HDLcholesterol, and LDLcholesterol values were assessed. Then, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), lymphocyte/monocyte ratio (LMR), hemoglobin/RDW (HRR), RDW/platelet (RPR), RDW/lymphocyte (RLR), MPV/platelet (MPR), WBC/MPV (WMR), GGT/platelet ratio (GPR), and monocyte/HDL cholesterol (MHR) value and monocyte ratios were calculated. NPAR was calculated by using the formula of "Neutrophil percentage (%)x100/Albumin (g/dL), APRI score was obtained by AST/Platelet count.[18] The formula of [Age×AST(U/L)] / [Platelet count ×√ALT(U/l)][19] and Prognostic Nutritional Index (PNI) (10×Albumin [g/dL])+(0.005 xLymphocyte) were used for FIB-4 score.The SII values were calculated with the formula [SII=Neutrophil×Platelet/Lymphocyte]. The assessments were made according to Selçuk University Medical Faculty. Hematology Laboratory reference values for the present study population.

Liver USI examination was made by using a convex probe (Frequency 3.5-5.0MHz) and the Aplio500 US device (Toshiba Medical Systems, Japan) by the only pediatric radiologist of the hospital, who had 15 years of experience, blinded to the purpose of the study and the laboratory values of the patients. The degree of hepatosteatosis was classified as follows.No steatosis (Grade 0), Mild steatosis (Grade 1), Moderate-severe steatosis(Grade 2-3).[19]

Statistical Analysis

The data were entered into the SPSS 23.0 program. In the comparison of the numerical parameters in the two groups, the Student t-test was employed in those with normal distribution, and the Mann-Whitney U test was used in those who did not. The Kruskal-Wallis test was employed to compare median values in groups of more than two. The ANOVA Test was employed to compare the numerical parameters with normal distribution in more than two independent groups. Confidence intervals and odds ratios were calculated for hematological ratios with Binary Logistic Regression Analysis for MASLD development. The predictive power of indices in predicting disease was specificity, sensitivity, positive and negative predictive value, and Area Under the Curve (AUC). The highest Youden Index([Specificity+Sensitivity]-1) was set as the best possible cut-off point and $p<0.05$ was accepted as the significance level in all analyses.

RESULTS

A total of 200 patient were included in the present study (120 MASL patients of whom 80 were included in the healthy control group with Grade 0 in liver USI). 70 (58.3%) of the patients were male, 50 (41.7%) female. In the healthy control group, 40 (50.0%) were male and 40 (50.0%) were female.When the distribution according to gender was assessed in the patient and control groups, no statistically significant differences were detected (p:0.174). The demographic characteristics are given in **Table 1**.

When the hematological values were assessed, WBC, neutrophil, lymphocyte, platelet count, MPV, PCT, MHR, RPR, RLR, MPR, WMR, GPR, SII, and FIB-4 scores of the patients were compared, statistically significant differences were detected in the control and patient groups. No significant differences were detected between the control and patient groups in terms of MCV, RDW, NLR, PLR, LMR, HRR, PNI, NPAR, and APRI scores (**Table 2**).

When liver USIs were assessed, 80 (40.0%) of the patients were Grade 0 (Control Group), 102 (51%) were Grade 1, and 18 (9.0%) were Grade 2-3. When the patients' WBC, neutrophil, lymphocyte, platelet, MHR, RPR, RLR, MPR, WMR, GPR, SII, and FIB-4 scores were compared according to liver grading, statistically significant differences were detected. However, a statistically significant difference was detected in Hb, monocyte count, RDW, PCT, and MPV. No significant differences were detected between liver grading in terms of NLR, PLR, LMR, HRR, PNI, NPAR, and APRI scores (**Table 3**).

Table 1: The distribution of the demographic characteristics of the patients who participated in the study according to the patient and control groups

	Patient Group		Control Group		p
	n	%	N	%	
Gender					
Boy	70	58.3	40	50.0	0.174
Girl	50	41.7	40	50.0	
Age Group					
<10	21	60.0	14	40.0	
10.1-15.0	56	58.3	40	41.7	0.876
>15.1	43	62.3	26	37.7	
BMI					
<24.9	10	16.9	49	83.1	
25.0-29.9	37	78.7	10	21.3	<0.001
>30.0	35	76.9	4	23.1	

BMI: Body Mass Index.

Table 2: The distribution of the hematological values and indices of patients according to patient and control groups

	Patient Group		Control Group		p
	Mean±SD	Median (Min-max)	Mean±SD	Median (Min-max)	
WBC	8.29±1.98	8.16 (4.45 - 14.56)	7.15±1.88	6.85 (3.84 - 14.27)	<0.001
Neutrophil	4.5±1.57	4.25 (1.52 - 10.5)	3.7±1.12	3.59 (1.69 - 6.71)	<0.001
Lymphocyte	2.84±0.96	2.73 (0.36 - 7.57)	2.49±0.62	2.53 (1.19 - 4.07)	0.005
Hgb	13.99±1.38	13.8 (10.1 - 17.1)	13.69±1.27	13.6 (9.7 - 16.9)	0.131
Platelet	337.22±67.49	339.5 (171 - 502)	305.66±72.57	301 (152 - 531)	<0.001
Monocyte	0.61±0.17	0.6 (0.33 - 1.07)	0.57±0.16	0.53 (0.3 - 1.07)	0.062
MCV	81.76±5.67	81.95 (59 - 92.4)	82.18±4.77	82.6 (64.2 - 93.1)	0.920
RDW	13.48±1.34	13.2 (11.6 - 19.5)	13.2±1.12	13 (11.6 - 17.8)	0.117
PCT	0.33±0.07	0.33 (0.17 - 0.5)	0.31±0.07	0.3 (0.15 - 0.49)	0.024
MPV	9.82±1.02	9.7 (6.15 - 12)	10.13±0.94	9.9 (8.6 - 13.6)	0.025
NLR	1.856±1.465	1.519 (0.527 - 10.167)	1.584±0.641	1.48 (0.577 - 3.783)	0.396
MHR	0.015±0.005	0.013 (0.006 - 0.028)	0.012±0.005	0.011 (0.006 - 0.025)	<0.001
PLR	134.761±72.658	122.869 (26.42 - 744.444)	128.07±36.698	125 (63.415 - 283.673)	0.978
LMR	4.864±1.881	4.676 (0.632 - 15.771)	4.59±1.289	4.695 (2 - 7.682)	0.537
HRR	1.051±0.166	1.062 (0.564 - 1.379)	1.047±0.145	1.04 (0.567 - 1.395)	0.655
RPR	0.042±0.01	0.04 (0.027 - 0.078)	0.046±0.012	0.044 (0.027 - 0.082)	0.008
RLR	5.541±3.755	4.846 (1.77 - 37.778)	5.656±1.59	5.415 (2.948 - 10.672)	0.019
APRI Score	0.075±0.062	0.064 (0.026 - 0.503)	0.066±0.026	0.061 (0.024 - 0.16)	0.303
MPR	0.031±0.008	0.029 (0.015 - 0.057)	0.035±0.011	0.032 (0.018 - 0.078)	0.002
WMR	0.851±0.216	0.817 (0.464 - 1.512)	0.712±0.202	0.681 (0.385 - 1.586)	<0.001
GPR	0.078±0.083	0.056 (0.016 - 0.587)	0.041±0.017	0.038 (0.015 - 0.088)	<0.001
SII	609.425±402.946	524.669 (118.098 - 2660.62)	475.712±201.572	422.522 (172.921 - 1011.941)	0.010
PNI	46.629±3.495	47.012 (30.026 - 54.009)	46.781±2.566	47.007 (39.012 - 52.01)	0.671
FIB-4 Score	0.186±0.094	0.171 (0.041 - 0.659)	0.233±0.079	0.228 (0.083 - 0.446)	<0.001
NPAR	11.66±2.89	11.32 (5.64 - 26.03)	11.21±2.57	11.16 (5.07 - 19.03)	0.486

WBC:White Blood Cell, Hgb: Hemoglobine, MCV:Mean Corpuscular Volume, RDW: Red Cell Distrubition, PCT: Platelecrit; MPV: Mean Platelet Volume, NLR: neutrophil / Lymphocyte Ratio; MHO: Monocyte/HDL Ratio; PLO: Platelet/ Lymphocyte Ratio; LMO: Lymphocyte Monocyte Ratio; HRO: Hemoglobin/RDW Ratio ; RPO: RDW/Platelet Ratio; RLO: RDW/ Lymphocyte Ratio; APRI: AST/PLT; MPR: MPV/Platelet Ratio; WMO: WBC/MPV Ratio; SII: Systemic Immune Inflammation Index

When the ROC Analysis results of the hematological index values for the diagnostic value of MASLD were assessed, the cut-off value of the MHR Value was found to be 0.011, the diagnostic value was AUC 0.66 (0.583-0.746), the specificity was 60.80%, sensitivity was 73.50%. The positive likelihood ratio was calculated as 1.87.When the cut-off value of WMR value was taken as 0.812, the diagnostic value was AUC 0.699 (0624-0.744), and specificity was 77.20% with a sensitivity of 51.30%. The positive likelihood ratio was calculated as 2.25. ROC analysis results of hematological index values for the diagnostic value of patients with MASLD are given in **Table 4**.

Table 3: The comparison of patients' hematological index levels according to Liver Grading

	Grade 0 n:80 (%40.0)		Grade 1 n:102 (%51.0)		Grade 2-3 n:18 (%9.0)		p
	Mean±SD	Median (Min-max)	Mean±SD	Median (Min-max)	Mean±SD	Median (Min-max)	
Age	12.89±2.85	13.06 (7.1 - 17.02)	13.11±3.15	13.9 (6.4 - 17.8)	13.58±2.51	14.5 (8.9 - 17.45)	0.381
BW	55.21±16.85[a]	53.2 (22.8 - 88.6)	79.16±21.61[b]	82.1 (36 - 121)	97.15±38.55[c]	89.75 (52.5 - 152)	<0.001
BW Persentile	56.69±34.83[a]	62 (0.87 - 100)	97.07±6.83[b]	99.46 (55.57 - 100)	99.29±0.87[c]	99.75 (97.88 - 100)	<0.001
BW SDS	0.19±1.61[a]	0.26 (-3.37 - 3.8)	2.61±1.26[b]	2.35 (-0.11 - 6.75)	3.4±1.68[c]	2.81 (1.57 - 7.06)	<0.001
BMI	21.78±4.49[a]	21.12 (14.2 - 35.49)	30.22±5.32[b]	29.33 (21.9 - 46.49)	34.14±9.55[b]	31.2 (23.8 - 50.3)	<0.001
BMI Persentile	59.32±34.78[a]	73 (1 - 100)	96.65±5.75[b]	99 (71 - 100)	98.63±1.36[b]	98.5 (96 - 100)	<0.001
WBC	7.15±1.87[a]	6.85 (3.84 - 14.27)	8.37±2.04[b]	8.22 (4.45 - 14.56)	7.79±1.45[a]	7.56 (5.4 - 10.81)	<0.001
Neutrophil	3.69±1.11[a]	3.59 (1.69 - 6.71)	4.58±1.59[b]	4.30 (1.52 - 10.5)	3.98±1.33[a]	3.97 (1.91 - 7.45)	<0.001
Lymphocyte	2.48±0.62[a]	2.52 (1.19 - 4.07)	2.78±0.90[a]	2.66 (0.36 - 5.74)	3.17±1.2[b]	3.06 (1.58 - 7.57)	0.005
Monocyte	0.57±0.16	0.53 (0.3 - 1.07)	0.62±0.16	0.6 (0.33 - 1.02)	0.6±0.18	0.57 (0.38 - 1.07)	0.062
Hgb	13.69±1.27	13.6 (9.7 - 16.9)	14.04±1.4	13.9 (10.1 - 17.1)	13.63±1.21	13.55 (11.8 - 16.1)	0.070
RDW	13.19±1.12	13.0 (11.6 - 17.8)	13.52±1.42	13.2 (11.6 - 19.5)	13.26±0.77	13.1 (12.1 – 15.0)	0.083
Platelet	305.66±72.57[a]	301 (152 - 531)	340.18±69.8[b]	341 (171 - 502)	321.06±48.31[a]	321.5 (200 - 417)	<0.001
Platelecrite	0.31±0.07	0.30 (0.15 - 0.49)	0.33±0.08	0.33 (0.17 - 0.50)	0.32±0.05	0.32 (0.22 - 0.42)	0.104
MPV	10.13±0.93	9.9 (8.6 - 13.6)	9.78±1.02	9.7 (6.15 – 12.0)	9.98±0.96	9.8 (8.6 - 11.6)	0.099
NLR	1.58±0.64	1.47 (0.58 - 3.78)	1.94±1.55	1.55 (0.53 - 10.17)	1.37±0.64	1.26 (0.59 - 3.42)	0.396
MHR	0.012±0.004[a]	0.010 (0.006 - 0.025)	0.014±0.005[b]	0.013 (0.005 - 0.027)	0.014±0.003[b]	0.015 (0.008 - 0.019)	<0.001
PLR	128.07±36.7	125.0 (63.41 - 283.67)	138.63±76.49	128.08 (47.13-744.44)	112.82±39.84	105.30 (26.42-210.13)	0.978
LMR	4.59±1.29	4.69 (2.0 - 7.68)	4.69±1.57	4.60 (0.63 - 9.19)	5.77±2.99	5.08 (2.04 - 15.77)	0.537
HRR	1.047±0.144	1.039 (0.567 - 1.394)	1.054±0.171	1.066 (0.564 - 1.379)	1.033±0.133	1.022 (0.831 - 1.319)	0.655
RPR	0.045±0.011[a]	0.043 (0.026 - 0.081)	0.041±0.010[b]	0.039 (0.026 - 0.078)	0.042±0.007[b]	0.041 (0.029 - 0.067)	0.008
RLR	5.65±1.59[a]	5.42 (2.95 - 10.67)	5.71±4.01[a]	5.02 (2.25 - 37.78)	4.59±1.49[b]	4.39 (1.77 - 9.49)	0.019
WMR	0.711±0.202[a]	0.680 (0.385 - 1.585)	0.862±0.223[b]	0.826 (0.463 - 1.511)	0.784±0.151[b]	0.749 (0.533 - 1.129)	<0.001
MPR	0.035±0.011[a]	0.032 (0.017 - 0.078)	0.030±0.008[b]	0.029 (0.014 - 0.056)	0.032±0.007[b]	0.030 (0.022 - 0.055)	0.002
GPR	0.040±0.017[a]	0.037 (0.015 - 0.088)	0.070±0.069[b]	0.051 (0.016 - 0.450)	0.116±0.133[c]	0.081 (0.040 - 0.586)	<0.001
SII	475.71 ±201.57[a]	422.52 (172.92-1011.94)	635.12±417.33[b]	538.21 (146.29-2660.62)	451.87±251.8[a]	395.19 (118.1 - 1247.36)	0.010
PNI	46.78±2.56	47.01 (39.01 - 52.01)	46.73±3.62	47.01 (30.02 - 54.01)	46.03±2.66	45.16 (43.01 - 52.04)	0.671
APRI Score	0.07±0.03	0.06 (0.02 - 0.16)	0.07±0.07	0.06 (0.03 - 0.5)	0.07±0.03	0.06 (0.03 - 0.15)	0.303
FIB-4 Score	0.232±0.079[a]	0.227 (0.082-0.445)	0.189±0.099[b]	0.173 (0.041-0.659)	0.168±0.050[b]	0.159 (0.103-0.274)	<0.001
NPAR Score	11.21±2.57	11.16 (5.07-19.81)	11.80±2.98	11.50 (5.63-26.04)	10.88±2.22	11.11 (5.68-15.31)	0.426

BW: Body Weight ; BMI; Body Mass Index; SDS: Standart Deviation Score;WBC: White Blood Cell,;Hgb: Hemoglobine; RDW: Red Cell Distrubition; MPV: Mean Platelet Volume; NLR: Neutrophil / Lymphocyte Ratio; MHR: Monocyte/HDL Ratio; PLR: Platelet/ Lymphocyte Ratio; LMO: Lymphocyte /Monosit Ratio; HRR: Hemoglobin/RDW Ratio; RPR: RDW/Platelet Ratio; RLR: RDW/ Lymphocyte Ratio; APRI: AST/PLT; MPR: MPV/ Platelet Ratio; WMR: WBC/MPV Ratio; GPR: Granulocyte/Platelet Ratio, SII: Systemic Immune Inflammation Index.

Table 4: The ROC analysis results of the hematological values for the diagnostic value of MASLD patients

	AUC (%95 CI)	Cut Off	P	Sensitivity (%)	Spesifisity (%)	+LR	-LR	PPV (%)	NPV (%)	Accuracy (%)
WBC	0.675 (0.599-0.751)	8.09	<0.001	51.67	77.50	2.30	0.62	77.50	51.67	62.00
Neutrophil	0.659 (0.583-0.735)	3.87	<0.001	61.70	67.50	1.89	0.57	74.00	54.00	64.00
Lymphocyte	0.618 (0.540-0.696)	2.60	<0.001	59.20	60.00	1.47	0.68	68.93	49.48	52.35
Platelet	0.635 (0.556-0.715)	331.50	<0.001	54.20	68.80	1.73	0.67	72.22	50.00	52.85
MHR	0.665 (0.583-0.746)	0.011	<0.001	73.50	60.80	1.87	0.43	73.95	59.72	61.49
WMR	0.699 (0624-0.744)	0.812	<0.001	51.30	77.20	2.25	0.63	77.22	51.26	61.62
RPR	0.389 (0.310-0.468)	0.056	0.008	10.83	86.30	0.79	1.03	54.17	39.20	41.00
GPR	0.755 (0.681-0.829)	0.047	<0.001	66.67	73.85	2.84	0.45	79.52	59.26	69.51
MPR	0.370 (0.292-0.449)	0.025	0.002	88.60	11.40	0.84	2.41	55.90	21.62	49.49
SII	0.608 (0.529-0.687)	415.23	<0.001	70.85	50.00	1.42	0.58	68.00	53.33	62.50
FIB-4 Score	0.306 (0.232-0.381)	0.219	<0.001	22.80	66.20	0.41	1.75	38.03	27.56	31.31

AUC: Area under the curve; 95%CI: %95 confidence interval; Cut off: cut-off value; WBC: White Blood Cell; MHR: Monocyte/HDL Ratio; WMR: WBC/MPV Ratio; RPR: RDW/Platelet Ratio; GPR: Granulocyte/Platelet Ratio; MPR: MPV/Platelet Ratio; SII: Systemic Immune Inflammation Index.

Multivariate regression analysis of the hematological indices was made to predict MASLD. Parameters that constituted risk factors in the univariate analysis were put into the models and 3 different models were created in predicting the patients. Nagelkerke R Square was 70.30% in Model 1 obtained by using BMI, WMR, GPR, SII, and MPR parameters. The specificity was 83.3, the sensitivity was 88.0, and the accuracy was 85.9. The Multivariate Regression Analysis results of the Hematological Index values for the diagnostic value of patients with MASLD are given in **Table 5**.

DISCUSSION

MASLD is often associated with obesity, Type 2 Diabetes Mellitus (DM) and Metabolic Syndrome.[19-22] It is unclear which patients will remain with simple steatosis and which will progress to liver cirrhosis or have cardiovascular risk. For this reason, novel biomarkers are needed to show the association with poor prognosis in MASLD.

Studies conducted on hematological parameters are very few in the pediatric population. The potential role of hematological indices in hepatic steatosis has not been investigated adequately. It was argued that Platelet Index Values are associated with the presence, severity, and complications of insulin resistance closely.[23-29] Çiftçi et al study, MPV value was reported to be significantly lower in MASLD patients.[30-32] In the present study, the researchers detected a significantly lower MPV value in the MASLD group when compared to healthy controls.We attributed this to the small number of patients with severe fibrosis.

RDW is an indicator of deterioration during the maturation and differentiation of erythrocytes as a result of oxidative stress and chronic inflammation, and an increased RDW was reported in the literature in the presence of these conditions.[33-35] The RDW value associated with advanced fibrosis in patients with MASLD is elevated than in other liver diseases and this can be employed as indicators.[36-38] In the present study, no statistical significance was detected between the patient and control group in terms of RDW.

It is already known that increased WBC is a risk factor independent of metabolic factors. Lee et al. reported a positive correlation between the WBC count and the prevalence of MASLD and also showed that the elevated WBC count increased the risk of MASLD.[39-42] In the present study, WBC levels were found to be significantly elevated in the patient group when compared to the control group. The WBC level was significantly elevated in Grade 1 patients when compared to Grade 0 patients. When ROC Analysis was made for WBC values and when the cut-off value was taken as 8.09, AUC was calculated as 0.675 (0.599-0.751), specificity 77.50%, and sensitivity 51.67%. When multivariate regression analysis was assessed to predict patients with MASLD, WBC value was found to be an independent risk factor, but it was not statistically significant in model 2. We think that WBC levels may be good diagnostic biomarkers for MASLD patients.

Table 5: The Multivariate Regression Analysis results of the Hematological Index Values for the diagnostic value of MASLD patients

	MULTIVARIATE ANALYSIS							UNIVARIATE ANALYSIS	
	p	OR (%95 CI)	-2 Log likelihood	Nagelkerke R Square	Accuracy	Sensitivity	Spesifity	p	
MODEL 1									
BMI	<0.001	0.694 (0.590-0.817)	84.928	0.703	85.9	88.0	83.3	<0.001	0.678 (0.598-0.769)
WMR	0.050	42.170 (1.005-1769.8)						<0.001	0.030 (0.006-0.161)
GPR	0.003	1.27 (1.08-4.32)						<0.001	0.758 (0.598-0.987)
SII	0.196	0.998 (0.995-1.001)						<0.001	0.998 (0.997-1.00)
MPR	0.007	2.62 (1.48-4.64)						0.002	10.91 (1.10-108.18)
Constant	0.023								
MODEL 2									
BW SDS	<0.001	0.668 (0.563-0.792)	79.036	0.727	86.7	84.7	85.8	<0.001	0.249 (0.157-0.395)
WBC	0.187	1.280 (0.887-1.847)						<0.001	0.720 (0.607-0.854)
MHR	0.600	0.1 (0.01-7.51)						0.002	0.814 (0.745-0.947)
FIB-4	<0.001	9.19 (20.63-409.99)						<0.001	402.040 (11.867-13621.10
GPR	0.005	0.1 (0.02-0.25)						<0.001	0.758 (0.598-0.987)
Constant	<0.001								
MODEL 3									
BMI P	<0.001	0.900 (0.850-0.954)	82.651	0.707	86.6	93.3	82.5	<0.001	0.872 (0.823-0.925)
WMR	0.407	3.108 (0.213-45.41)						<0.001	0.030 (0.006-0.161)
GPR	<0.001	0.874 (0.812-0.954)						<0.001	0.758 (0.598-0.987)
FIB-4	0.024	21.06 (3.70-119.60)						<0.001	402.040 (11.867-13621.10
SII	0.072	0.997 (0.994-1.00)						<0.001	0.998 (0.997-1.00)
Constant	<0.001								

BMI: Body Mass Index; WMR: WBC/MPV Ratio; GPR: Granulocyte/Platelet Ratio; SII: Systemic Immune Inflammation Index; MPR: MPV/Platelet Ratio; BW: Body Weight;, SDS: Standart Deviation Score; WBC: White Blood Cell; MHR: Monocyte/HDL Ratio ; WMR: WBC/MPV Ratio.

Hepatocytes cause neutrophil accumulation as a result of oxidative stress and necrosis in the hepatic inflammatory process of MASLD.[43] In their study, Zhou concluded that neutrophil levels were elevated in the MASLD group compared to the control group.[44,45] In the present study, neutrophil and lymphocyte levels were detected to be significantly elevated in the MASLD patient group when compared to the healthy control group. Neutrophil levels were detected to be significantly elevated in our patients with Grade 1 steatosis when compared to Grade 0 patients. When the neutrophil and lymphocyte ROC analysis were made for the diagnostic value of patients with MASLD, the cut-off value was taken as 3.87 and 2.60, respectively, and the researchers detected high sensitivity and specificity. Based on the results of the present study, we think that neutrophil and lymphocyte levels can be employed together with other biomarkers in patients with MASLD.

The inflammatory response induces increased neutrophil and platelet counts with decreased lymphocyte count and makes their ratios a valuable tool to assess inflammatory status indirectly. Recently, biomarkers such as NLR, PLR, and LMR are employed as potential markers of inflammatory progression.[46,47] In the present study, we couldn't find a statistically significant relationship between NLR, PLR, LMR, and MASLD.

WMR was employed to predict thrombosis-related events, especially in cardio, cerebral, and peripheral vascular diseases.[48,49] Few studies were conducted in the past to determine the relationship between WMR and MASLD, and no studies were conducted in children. It was shown in a previous study that the group with apnea and MASLD had elevated WBC/MPV ratio values than those with MASLD alone, and the WBC/MPV ratio was an independent risk factor for MASLD.[50] In our study, a statistically significant relationship was detected between WMR and MASLD. According to USI, although no significant differences were detected between patients with Grade 1 and Grade 2-3 in terms of WMR levels, it was detected to be significantly lower in patients with Grade 0. When the ROC analysis was made for the value of the cut-off value for the WMR for the diagnostic value of patients with MASLD, it was detected that AUC was 0.699 (0624-0.744), specificity was 77.20%, and sensitivity was 51.30% when the cut-off value was taken as 0.812. WMR value, which is an independent risk factor in the regression analysis, was not significant in the multivariate analysis.

NPAR score is a biomarker that can be employed as an indicator of systemic inflammation.[51,52] Few studies assessed the predictive value of the NPAR score in MASLD or advanced liver fibrosis.[53] No association was detected between patients with MASLD and healthy controls in our study.

Recently, RPR is used as the preferred biomarker in various diseases with its ease of measurement and affordable cost, and it was employed to predict the severity of fibrosis in MASLD patients.[54] When ROC analysis was used for the RPR value for the diagnostic value of patients with MASLD when the cut-off value was determined as 0.056, it was determined that AUC was 0.389 (0.310-0.468), specificity was 86.30%, sensitivity was 10.83%. We think that it can be a good biomarker in predicting MASLD.

Considering the proinflammatory characteristics of monocytes and the anti-inflammatory characteristics of HDL-C, MHR was considered a novel systemic inflammatory marker.[55,56] It is not known whether MHR is associated with MASLD. Adult studies were conducted and there is no literature investigating the orrelation in children. In the present study, the researchers assessed whether the MHR value would be a good biomarker for predicting MASLD in pediatric patients. In a retrospective study, it was shown that there was a significant positive correlation between MHR and age, ALT, and HOMA-IR values.[57-59] The researchers found that the MHR levels were elevated in patients with MASLD compared to healthy controls. When ROC analysis was made for the MHR value to further investigate the diagnostic value of patients with MASLD when the cut-off value was taken as 0.011, it was detected that AUC was 0.665 (0.583-0.746), specificity was 60.80%, and sensitivity was 73.50%. However, although the MHO value was an independent risk factor in the univariate regression analysis, it was not significant in the multivariate analysis. In particular, we predict that each unit increase in the MHR value will cause an increased risk of MASLD by 1.87 times. We think that it can be used as a good biomarker to predict MASLD and its prognosis.

No study was detected in the literature investigating the relationship between SII and MASLD in children. In our study, it was detected that there were elevated levels of SII in patients with MASLD than in healthy controls. According to liver USI, SII levels were detected to be significantly elevated in patients with Grade 1 when compared to Grade 0 patients. To investigate the diagnostic value of patients with MASLD, the cut-off value for the SII value was 415 in the ROC analysis. To investigate the diagnostic value of patients with MASLD, when the cut-off value for the SII value was taken as 415.23 in the ROC analysis, the AUC was 0.608 (0.529-0.687), the specificity was 60.80%, and the sensitivity was 70.85%. In particular, it was determined that each unit increase in the SII value causes a 1.42-fold increase in the risk of MASLD. However, while the SII value was an independent risk factor in univariate regression analysis, it was not significant in multivariate analysis. We think that the SII value can be used as a good biomarker to predict MASLD and predict its prognosis.

Assessing the extent of liver fibrosis in MASLD patients accurately is crucial for prognosis and clinical decision-making.[60] Although biopsy is the accepted gold standard, its use is limited because of its invasiveness and difficulty in reproducing fibrosis monitoring. Because of these limitations, non-invasive tools were developed for use in the staging and follow-up of MASLD and liver fibrosis.[61] Biomarkers not only identify patients with MASLD noninvasively but also

contribute to assessing the severity of Steatohepatitis and fibrosis. In the present study, the researchers employed the GPR, APRI, and FIB-4 scoring systems employed for fibrosis scoring to predict MASLD.

In his study, Lemoine suggested the ratio of GPR, which has higher diagnostic performance than AST, which can routinely identify patients with fibrosis.[62,63] There is no study in the literature investigating the relationship between MASLD and GPR in predicting and predicting prognosis. In our study, we found the GPR level to be higher in patients with MASLD than in healthy controls. When the GPR levels were examined according to the liver grading, we found that the GPR level increased positively as the grade increased and it was statistically significant. To investigate the diagnostic value of patients with MASLD, ROC analysis was performed for the GPO value. When the cut-off value was taken as 0.047, the researchers found an AUC of 0.755 (0.681-0.829), specificity of 60.80%, and sensitivity of 66.67%. We predict that each unit increase in the GPR value will cause a 2.84-fold increase in the risk of MASLD. GPR value, which is an independent risk factor in univariate regression analysis to predict patients with MASLD, attracted our attention as a good biomarker in multivariate analysis.

After the APRI score was defined by Wai et al. its usability and suitability in various CHD were evaluated.[64] In the study conducted by Kruger et al. more positive results were obtained in the APRI score of patients with biopsy-diagnosed MASLD compared to other parameters. When the cut-off value for APRI was taken above 1.5, the AUROC value was 0.85, with 86% specificity, and 75% sensitivity.[65] In the present study, no significant differences were detected between the patient and healthy control groups in terms of APRI score.

The FIB-4 score, which was defined to assess the degree of fibrosis, was compared with other scoring systems in a study that included 576 patients who were diagnosed with MASLD by biopsy in 2012, and it was shown that FIB-4 detected more advanced fibrosis patients with 91% than other formulas.[66,67] In the present study, the researchers detected that MASLD patients had a lower FIB-4 score level than healthy controls. ROC analysis was made to predict patients. When the FIB-4 cut-off value was taken as 0.219, the researchers detected AUC 0.306 (0.232-0.381) with a specificity of 66.20% and sensitivity of 22.80%. Although the FIB-4 score was an independent risk factor in univariate regression analysis, it also contributed significantly to multivariate analysis. We think that it can be employed as a good biomarker to predict MASLD and predict prognosis.

There were several limitations in the present study. The study included a limited number of patients in one single healthcare center, and the diagnosis of MASLD was made by guided USI, and most of the patients did not have biopsy data. Because of the cross-sectional fashion of this retrospective study, the researchers were unable to identify causal relationships or long-term clinical outcomes. Prospective studies with a longer follow-up period are needed to confirm the results.

CONCLUSION

MASLD is a common disease has become an important healthcare concern. An effective monitoring indicator is urgently needed for early detection of MASLD. We think that using hematological biomarkers will be beneficial for the simple and rapid detection of suspected patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Selçuk University Local Ethics Committee (Date: 18.07.2023, Decision No: 2023/352).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Ludwig J. Nonalcoholic steatohepatitis:Mayo Clinic experiences with a hitherto unnamed disease. Mayo Clin Proc 1980;55(7):434-8.
2. Eslam M, Sanyal AJ, George J;International Consensus Panel. MAFLD:A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. Gastroenterology. 2020;158(7):1999-2014.e1.
3. Rinella ME, Lazarus JV, Ratziu V, et al. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. Ann Hepatol. 2023:101133.
4. Shah J, Okubote T, Alkhouri N. Overview of Updated Practice Guidelines for Pediatric Nonalcoholic Fatty Liver Disease. Gastroenterol Hepatol (N Y) 2018;14:407–14.
5. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease:Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328–57.
6. Anderson EL, Howe LD, Jones HE, Higgins JP, Lawlor DA, Fraser A. The Prevalence of Non-Alcoholic Fatty Liver Disease in Children and Adolescents:A Systematic Review and Meta-Analysis. PLoS One 2015;10:e0140908.
7. Shaunak M, Byrne CD, Davis N, Afolabi P, Faust SN, Davies JH. Nonalcoholic fatty liver disease and childhood obesity. Arch Dis Child. 2021;106:3– 8.
8. Gokce S, Atbinici Z, Aycan Z, Çınar HG, Zorlu P. The relationship between pediatric non-alchololic fatty liver disease and cardiovasculer risk factors and increased risk of atherosclerosşs in obese children. Pediatr Cardiol 2013;34:308–15.
9. Akcam M, Boyaci A, Pirgon O, Koroglu M, Dundar BN. Importance of the liver ultrasound scores in pubertal obese children with nonalcoholic fatty liver disease. Clin Imaging 2013;37:504–8
10. Powell EE, Wong VW, Rinella M. Non-alcoholic fatty liver disease. Lancet. 2021;397:2212–24.
11. Türkiye Karaciğer Araştırmaları Derneği. Alkol dışı yağlı karaciğer hastalığı (NAFLD) klinik rehberi. Ankara;2021. s. 11-51.
12. Söderberg C, Stål P, Askling J, et al. Decreased survival of subjects with elevated liver function tests during a 28-year follow-up. Hepatology 2010;51:595–602.

13. Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. Nat. Med. 2018;24:908–922.
14. Schuster S, Cabrera D, Arrese M, Feldstein AE. Triggering and resolution of inflammation in NASH. Nat Rev Gastroenterol Hepatol 2018;15(6):349–64.
15. Qin B, Ma N, Tang Q, et al. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) were useful markers in assessment of inflammatory response and disease activity in SLE patients. Mod Rheumatol 2016;26(3):372–6.
16. Lee J, Vali Y, Boursier J, et al. Prognostic accuracy of FIB-4, NAFLD fibrosis score and APRI for NAFLD-related events:A systematic review. Liver Int. 2021;41(2):261-70.
17. Shah AG, Lydecker A, Murray K, et al. Comparison of Noninvasive Markers of Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. Clinical Gastroenterology and Hepatology. 2009;7(10):1104–12.
18. Yajima Y, Ohta K, Narui T, Abe R, Suzuki H, Ohtsuki M. Ultrasonografical diagnosis of fatyy liver:Significance of the liver-kidney contrast. Tohoku J Exp Med 1983;139:43-50.
19. Rumack CM. Diagnostic Ultrasound. In:Rumack CM, Editor. St Louis:Mosby;1998.pp.
20. Targher G, Bertolini L, Padovani R, et al. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. Diabetes Care 2007;30(5):1212-8.
21. Alkhouri N, Tamimi TA, Yerian L, Lopez R, Zein NN, Feldstein AE. The inflamed liver and atherosclerosis:a link between histologic severity of nonalcoholic fatty liver disease and increased cardiovascular risk. Dig Dis Sci 2010;55(9):2644-50.
22. Mirbagheri SA, Rashidi A, Abdi S, Saedi D, Abouzari M. Liver:an alarm for the heart? Liver Int 2007;27(7):891-4
23. Budak YU, Polat M, Huysal K. The use of platelet indices, plateletcrit, mean platelet volume and platelet distribution width in emergency non-traumatic abdominal surgery:a systematic review. Biochem Med (Zagreb). 2016;26(2):178-93.
24. Totani L, Evangelista V. Platelet-leukocyte interactions in cardiovascular disease and beyond. Arterioscler Thromb Vasc Biol 2010;30:2357-61.
25. Kilciler G, Genc H, Tapan S, Ors F, et al. Mean platelet volume and its relationship with carotid atherosclerosis in subjects with non-alcoholic fatty liver disease. Ups J Med Sci. 2010;115(4):253-9.
26. Karasu Z, Tekin F, Ersoz G, et al. Liver fibrosis is associated with decreased peripheral platelet count in patients with chronic hepatitis B and C. Dig Dis Sci. 2007;52(6):1535–9.
27. Yoneda M, Fujii H, Sumida Y, et al. Platelet count for predicting fibrosis in nonalcoholic fatty liver disease. J Gastroenterol. 2011;46(11):1300–6.
28. Neuschwander-Tetri BA, Clark JM, Bass NM, et al. Clinical, laboratory and histological associations in adults with nonalcoholic fatty liver disease. Hepatology. 2010;52(3):913–24.
29. Cao W, Zhao C, Shen C, Wang Y. Cytokeratin 18, alanine aminotransferase, platelets and triglycerides predict the presence of nonalcoholic steatohepatitis. PLoS One. 2013;8(12) e82092.
30. Çiftci A, Yilmaz B, Köklü S, et al. Serum levels of nitrate, nitrite and advanced oxidation protein products (AOPP) in patients with nonalcoholic fatty liver disease. Acta Gastroenterol Belg. 2015;78(2):201-205.
31. Milovanovic Alempijevic T, Stojkovic Lalosevic M, Dumic I, et al. Diagnostic Accuracy of Platelet Count and Platelet Indices in Noninvasive Assessment of Fibrosis in Nonalcoholic Fatty Liver Disease Patients. Can J Gastroenterol Hepatol. 2017;2017:6070135.
32. Celikbilek M, Gürsoy S, Deniz K, Karaman A, Zararsiz G, Yurci A. Mean platelet volume in biopsy-proven non-alcoholic fatty liver disease. Platelets. 2013;24(3):194-9.
33. Farkas N, Szabo A, Lorand V, et al. Clinical usefulness of measuring red blood cell distribution width in patients with systemic sclerosis. Rheumatol (Oxford) 2014;53:1439–45.
34. Ferrucci L, Guralnik JM, Woodman RC, et al. Proinflammatory state and circulating erythropoietin in persons with and without anemia. Am J Med 2005;118:1288.
35. Hampole CV, Mehrotra AK, Thenappan T, Gomberg-Maitland M, Shah SJ. Usefulness of red cell distribution width as a prognostic marker in pulmonary hypertension. Am J Cardiol 2009;104:868-72.
36. Kim HM, Kim BS, Cho YK, et al. Elevated red cell distribution width is associated with advanced fibrosis in NAFLD. Clin Mol Hepatol 2013;19:258–65.
37. Juarez-Hernandez E, Chávez-Tapia NC, Brizuela-Alcántara DC, et al. Association Between Serum Hemoglobin Levels and Non Alcoholic Fatty Liver Disease in a Mexican Population. Ann Hepatol, 2018;17(4):577-84.
38. Chung GE, Yim JY, Kim D, et al. Associations between hemoglobin concentrations and the development of incidental metabolic syndrome or nonalcoholic fatty liver disease. Dig Liver Dis. 2017;49(1):57-62.
39. Wang S, Zhang G, Zhang Z, et al., Association between white blood cell count and non-alcoholic fatty liver disease in urban Han Chinese:a prospective cohort study. BMJ Open 2016;6(6):e010342.
40. Lee YJ, Lee HR, Shim JY, Moon BS, Lee JH, Kim JK. Relationship between white blood cell count and nonalcoholic fatty liver disease. Dig. Liver Dis. 2010;42:888–94.
41. Yu YY, Cai JT, Song ZY, Tong YL, Wang JH. The associations among Helicobacter pylori infection, white blood cell count and nonalcoholic fatty liver disease in a large Chinese population. Medicine 2018;97:e13271.
42. Chung GE, Yim JY, Kim D, et al. Associations between white blood cell count and the development of incidental nonalcoholic fatty liver disease. gastroenterol. Res. Pract. 2016;2016:7653689.
43. Jaeschke H. Reactive oxygen and mechanisms of inflammatory liver injury:present concepts. J Gastroenterol Hepatol 2011;26(Suppl 1):173-9.
44. Zhou Y, Tian N, Li P, He Y, Tong L, Xie W. The correlation between neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio with nonalcoholic fatty liver disease: a cross-sectional study. Eur J Gastroenterol Hepatol. 2022;34(11):1158-64.
45. Van Rooyen DM, Larter CZ, Haigh WG, et al. Hepatic free cholesterol accumulates in obese, diabetic mice and causes nonalcoholic steatohepatitis. Gastroenterology 2011;141:1393–403.
46. Gong P, Liu Y, Gong Y, et al. The association of neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and lymphocyte to monocyte ratio with post-thrombolysis early neurological outcomes in patients with acute ischemic stroke. J Neuroinflammation. 2021;18:51.
47. Vukicevic P, Klisic A, Neskovic V, et al. New markers of platelet activation and reactivity and oxidative stress parameters in patients undergoing coronary artery bypass grafting. Oxid Med Cell Longev. 2021;2021:8915253.
48. Emre AR, Yasar KA, Atakan Y, Orhan C, Murathan K. Relationship between white blood count to mean platelet volume ratio and clinical outcomes and severity of coronary artery disease in patients undergoing primary percutaneous coronary intervention. Cardiovasc Ther. 2020;2020:9625181.
49. Guetl K, Raggam RB, Muster V, et al. The White blood cell count to mean platelet volume ratio for the prediction of chronic limb-threatening ischemia in lower extremity artery disease. J Clin Med. 2019;8(10):1593.
50. Chen M, Wang B, Huang J, Zhao J, Chen J, Chen G. The role of platelet-related parameters for the prediction of NAFLD in OSAHS patients. BMC Pulm Med. 2022;22(1):487.
51. Sun T, Shen H, Guo Q, et al. Association between Neutrophil Percentage-to-Albumin Ratio and All-Cause Mortality in Critically Ill Patients with Coronary Artery Disease. Biomed Res. Int. 2020:2020;8137576.
52. Ferro M, Babă DF, de Cobelli O, et al. Neutrophil percentage-to-albumin ratio predicts mortality in bladder cancer patients treated with neoadjuvant chemotherapy followed by radical cystectomy. Futur Sci OA 2021;7:FSO709.
53. Liu CF, Chien LW. Predictive Role of Neutrophil-Percentage-to-Albumin Ratio (NPAR) in Nonalcoholic Fatty Liver Disease and Advanced Liver Fibrosis in Nondiabetic US Adults:Evidence from NHANES 2017–2018. Nutrients 2023;5(8):1892.
54. Zhou WJ, Yang J, Zhang G, Hu ZQ, Jiang YM, Yu F. Association between red cell distribution width-to-platelet ratio and hepatic fibrosis in nonalcoholic fatty liver disease:A cross-sectional study. Medicine 2019;98(30).

55. Ziegler-Heitbrock L. The CD14+ CD16+ blood monocytes:their role in infection and inflammation. J Leukocyte Biol 2007;81(3):584-92.
56. Akboga MK, Balci KG, Maden O, et al. Usefulness of monocyte to HDL-cholesterol ratio to predict high SYNTAX score in patients with stable coronary artery disease. Biomark Med. 2016;10(4):375–83.
57. Zhang Y, Li S, Guo YL, et. al. Is monocyte to HDL ratio superior to monocyte count in predicting the cardiovascular outcomes:evidence from a large cohort of Chinese patients undergoing coronary angiography. Annals of Medicine 2016;48(5):305-12.
58. Yozgat A, Ekmen N, Kasapoglu B, Unsal Y, Sokmen F, Kekilli M. Monocyte/HDL ratio in non-alcoholic hepatic steatosi. Arq Gastroenterol 2021;58:439–42.
59. Huang H, Wang Q, Shi X, Chen Y, Shen C, Zhang J, Xu C. Association between monocyte to high-density lipoprotein cholesterol ratio and nonalcoholic fatty liver disease:a cross-sectional study. Mediat Inflamm. 2021;2021:6642246.
60. Wang L, Dong J, Xu M, Li L, Yang N, Qian G. Association between monocyte to high-density lipoprotein cholesterol ratio and risk of non-alcoholic fatty liver disease:a cross-sectional study. Front Med (Lausanne). 2022;9:898931.
61. Ekstedt M, Hagstrom H, Nasr P, et al.Fibrosis stage is the strongest predictor for disease specific mortality in NAFLD after up to 33 years of follow-up. Hepatology 2014;61(5):1547-54.
62. Lemoine M, Shimakawa Y, Nayagam S, et al. The gamma-glutamyl transpeptidase to platelet ratio (GPR) predicts significant liver fibrosis and cirrhosis in patients with chronic HBV infection in West Africa. Gut. 2016;65:1369–76.
63. Schiavon LL, Narciso-Schiavon JL, Ferraz ML, Silva AE, Carvalho-Filho RJ. The gamma-glutamyl transpeptidase to platelet ratio (GPR) in HBV patients:just adding up? Gut. 2016;66(6):1169-70.
64. Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003;38(2):518-26.
65. Kruger FC, Daniels CR, Kidd M, Swart G, Brundyn G, Kotze M. APRI:A simple bedside marker for advanced fibrosis that can avoid liver biopsy in patients with NAFLD/NASH. S Afr Med J 2011:6;477-80.
66. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006;43:1317-25.
67. Sumida Y, Yoneda M, Hyogo H, et al. Validation of FIB-4 index in a Japanese fatty liver disease population BMC Gastroenterol 2012;12;1-9.