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Assessment of the diagnostic accuracy of noninvasive scoring tools in predicting moderate-to-severe steatohepatitis *via* ultrasonography in asymptomatic healthy subjects admitted to family medicine outpatient clinics

A. MERT

Family Practice Department, State Hospital, Üsküdar, Istanbul, Turkey

Abstract. – OBJECTIVE: Efficacies of the noninvasive scoring tools in screening and diagnosing nonalcoholic fatty liver disease (NAFLD) remain controversial. Aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio, AST-to-platelet ratio index (APRI), and fibrosis-4 (FIB-4) index are the most frequently used parameters for differentiating moderate and severe steatohepatitis. In this context, the objective of this study is to evaluate the diagnostic accuracy of noninvasive tools in predicting moderate-to-severe steatohepatitis *via* ultrasonography in asymptomatic healthy subjects admitted to family medicine outpatient clinics.

PATIENTS AND METHODS: The population of this retrospective study consisted of healthy individuals tested within the scope of a medical check-up program between January and July 2021. All participants included in the study underwent relevant laboratory tests and liver ultrasonography (US). Steatohepatitis was graded using the US images as normal (grade 0), mild (grade 1), moderate (grade 2), and severe (grade 3). The participants with grade 0 and 1 steatohepatitis were categorized as Group 1, whereas those with grade 2 and 3 steatohepatitis (NAFLD) were categorized as Group 2. Any relationship between the aminotransferase/alanine aminotransferase (AST/ALT), AST-to-platelet ratio index (APRI), and fibrosis-4 index (FIB-4) parameters and the diagnostic powers thereof were analyzed based on the collected data.

RESULTS: The mean age of the study sample (n=408) was 46.1±12.7 years. There were 352 (86.3%) and 56 individuals in Groups 1 and 2, respectively. Platelet-to-lymphocyte ratio (PLR) and AST/ALT values were significantly higher, whereas APRI values were significantly lower in Group 1 than in Group 2 (p=0.004, p<0.001, and p<0.001, respectively). There were significant correlations between the presence of NAFLD and PLR values of ≤90.78 [area under the curve (AUC)=0.619, 95% confidence interval (CI): 0.570-0.666, p=0.007], AST/ALT values of ≤0.91 (AUC=0.802, 95% CI: 0.760-0.840, p<0.001), and APRI values of >0.22 (AUC=0.687, 95% CI: 0.640-0.732, p<0.001).

CONCLUSIONS: The composite noninvasive indices, including PLR, AST/ALT, and APRI, can be beneficial in predicting NAFLD in healthy individuals.

Key Words:
Fatty liver, Nonalcoholic steatohepatitis, Liver fibrosis, Ultrasound, Transaminases, Family practice.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a common public health problem worldwide[1,2]. Individuals with type 2 diabetes mellitus, obesity, and metabolic syndrome are more susceptible to NAFLD[3]. The prevalence of NAFLD reported in the literature[1,4,5] varies depending on ethnic differences and clinical characteristics.

Individuals with NAFLD feature a progressive disease spectrum, ranging from fatty infiltration to nonalcoholic steatohepatitis and hepatic fibrosis[1,2]. Liver fibrosis might lead to cirrhosis and its sequelae, such as hepatic failure and hepatocellular carcinoma1. The risks for the potential complications associated with NAFLD exponentially increase with the severity of hepatic fibrosis[2]. Early identification of individuals with NAFLD might help physicians to tailor the necessary treatment modalities to optimize the outcome of liver fibrosis[4,6,7].

There are several invasive and noninvasive tools for diagnosing NAFLD. Liver biopsy is the gold standard for diagnosing and quantifying NAFLD and determining the extent of liver fibrosis; however, it is invasive, expensive, and not devoid of severe complications[1,3,8]. Among noninvasive tools, ultrasonography (US) is one of the

Corresponding Author: Alpaslan Mert, MD; e-mail: alpaslanmrt@gmail.com

most accessible and familiar methods to screen the liver in terms of NAFLD[6]. There are also scoring tools, including aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio, AST-to-platelet ratio index (APRI), and fibrosis-4 (FIB-4) index, that utilize the demographic and laboratory characteristics of the tested individuals. In that way, it is possible to assess the severity of fibrosis in patients with NAFLD[1,3,8,9]. These scoring tools may predict the progression of liver fibrosis and identify the individuals that will benefit the most from a liver biopsy in the context of NAFLD[9,10]. However, although they are easy to calculate, a range of indeterminate/intermediate risks associated with the predefined cut-off values used in these scoring tools may render the interpretation of the individual results difficult[9]. Therefore, it is necessary to evaluate the diagnostic accuracies and the advantages and disadvantages of each scoring tool.

Population-based screening programs in diagnosing NAFLD in healthy individuals face some criticism4. The studies5,6 have failed to find a more straightforward and accessible noninvasive diagnostic tool with high accuracy to diagnose NAFLD. In the end, the screening and diagnostic modalities used in the context of NAFLD remain controversial.

In light of the foregoing, this study was carried out to investigate the presence and severity of steatohepatitis in asymptomatic individuals who participated in a medical check-up program *via* US and evaluate the diagnostic accuracy of several noninvasive scoring tools and indices in predicting moderate-to-severe steatohepatitis.

Patients and Methods

Study Design

This retrospective study was approved by the Local Ethical Committee (Approval Date and Number: 01.10.2021 and 46). The study was conducted in accordance with the principles of the Declaration of Helsinki. The written informed consent could not be taken from the participants due to the study's retrospective design and the data's unanimity.

Population and Sample

The study consisted of all consecutive healthy individuals aged 18 or older (n=440) tested within the scope of a medical check-up program in the Family Medicine Outpatient Clinics of Hurrem Sultan Hospital between January and July 2021. Individuals with incomplete demographic or clinical data, a chronic liver disease, including hepatitis B, hepatitis C, autoimmune hepatitis, chronic alcohol usage during the last 12 months (≥30 gr/day for males and ≥20 gr/day for females), a history of liver surgery, active malignancy, and use of medications implicated for the elevated transaminases were excluded from the study[2]. The participants with focal fatty infiltration and fatty sparing findings indicated by the US in the liver were excluded from the study. In the end, the study sample consisted of 408 individuals (Figure 1).

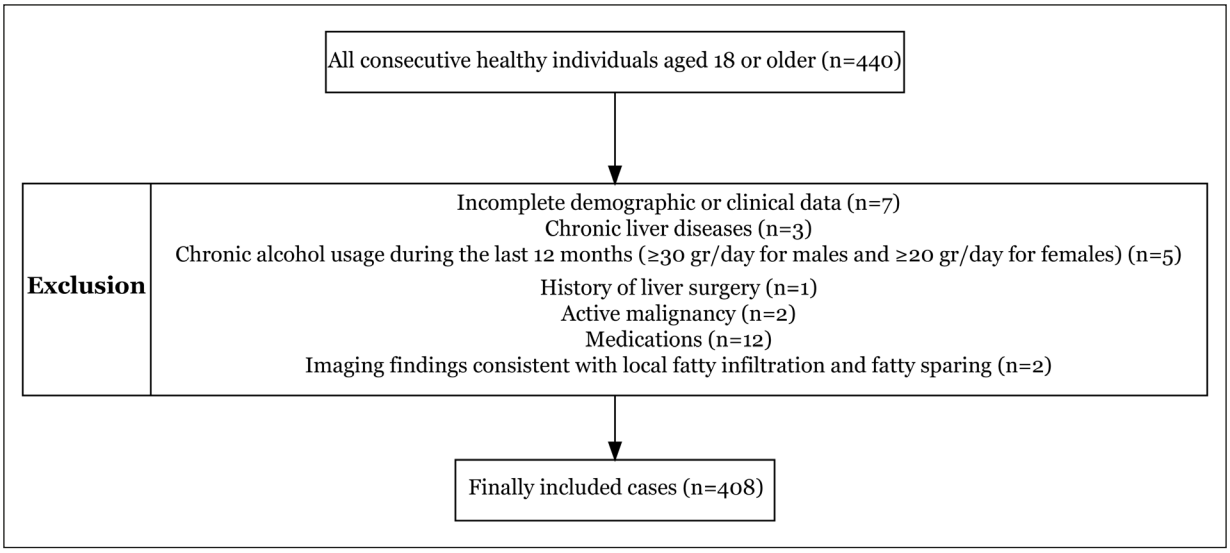

Figure 1. Flowchart of the study.

NAFLD Diagnosis

Steatohepatitis was graded between grades 0 and 3 based on the US images[11]. Grade 0 indicated normal steatohepatitis, i.e., normal liver US imaging in terms of the echogenicity of the parenchyma and visualization of the diaphragm and intrahepatic vessels. Grade 1 indicated mild steatohepatitis, i.e., slightly increased echogenicity of the liver parenchyma. Grade 2 indicated moderate steatohepatitis, i.e., markedly increased echogenicity of the liver parenchyma associated with slightly decreased visualization of the diaphragm and intrahepatic blood vessels. Lastly, Grade 3 indicated severe steatohepatitis, i.e., severely increased echogenicity of the liver parenchyma, absence or severely decreased visualization of the diaphragm, intrahepatic blood vessels, and posterior part of the right liver lobe. Accordingly, individuals with a) moderate (grade 2) to severe (grade 3) steatohepatitis as indicated by the US, b) no history of excessive alcohol intake in the past 12 months, and c) no hepatitis B or hepatitis C infection were diagnosed with NAFLD[12].

Data Collection

All participants' anamnesis was taken. All participants underwent physical examination followed by laboratory tests and liver US. Patients' demographic characteristics (age and gender), laboratory test results, and imaging findings were obtained from the subjects' medical files and the hospital information system. All data were recorded in a predetermined electronic worksheet. In addition to the laboratory tests, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), AST/ALT, APRI, and FIB-4 index were calculated as defined previously[1,2].

Study Groups

The individuals were categorized into two groups according to their steatohepatitis grades. Accordingly, participants with grade 0 and 1 steatohepatitis constituted Group 1, whereas those with grade 2 and 3 steatohepatitis constituted Group 2.

The study's primary outcome was the results of the comparative analysis of the groups with and without NAFLD based on several parameters, including AST/ALT ratio, APRI, and FIB-4, and the secondary outcome was the diagnostic values of the indices in predicting moderate-to-severe steatohepatitis.

Statistical Analysis

The collected data were expressed using descriptive statistics. Accordingly, continuous variables with normal distribution were expressed as mean±standard deviation values. Continuous variables without normal distribution were expressed as median and minimum-maximum values. Categorical variables were expressed as numbers (n) and percentage (%) values. The Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson-Darling tests were used to analyze the normal distribution characteristics of the numerical variables.

The independent samples t-test and the Mann-Whitney U test were used to compare two independent groups featuring numerical variables with and without normal distribution, respectively. Pearson's Chi-squared and Fisher's exact tests were used to compare the differences between categorical variables in 2x2 tables. On the other hand, the Fisher-Freeman-Halton test was used to compare the differences between categorical variables in RxC tables.

The receiver operating characteristic (ROC) curve analysis with the DeLong method and the Youden index was used to determine the optimal cut-off values of NLR, PLR, AST/ALT, APRI, and FIB-4 parameters in predicting the development of NAFLD (grade 2 or 3 steatohepatitis). The areas under the ROC curves (AUC) and the corresponding 95% confidence interval (CI) values were calculated. Specificity, sensitivity, positive and negative predictive values, and positive and negative likelihood ratios were calculated for the parameters with AUC value based on the optimal cut-off values determined for each parameter.

Jamovi project 2.2.5.0 (Jamovi, version 2.2.5.0, 2022, retrieved from https://www.jamovi.org) and JASP 0.16.1 (Jeffreys' Amazing Statistics Program, version 0.16.1, 2022, retrieved from https://jasp-stats.org) software packages were used in the statistical analyses. Probability (p) statistics of ≤ 0.05 indicated statistical significance.

Results

The mean age of the study sample (n=408), 59.1% of which was female, was 46.1±12.7 years. There were 225 (55.1%), 127 (31.1%), 50 (12.3%), and six (1.5%) participants with grades 0, 1, 2, and 3 steatohepatitis, respectively. Accordingly, 352 (86.3%) participants with either grade 0 or 1 liver, and 56 (13.7%) participants with either

grade 2 or 3 steatohepatitis, thus NAFLD, were categorized into Groups 1 and 2, respectively.

There was a significant difference between Group 1 and Group 2 in gender (p=0.027). The rate of male participants was significantly higher in Group 2 than in Group 1 (55.4% vs. 38.6%). There was no significant difference between the groups in age (p=0.052) and smoking status (p=0.369).

The results of the laboratory investigations for these groups can be found in Table I.

The results of the laboratory tests are given in Table II. Accordingly, white blood cell and lymphocyte counts, serum glucose, ALT, AST, triglyceride, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), C-reactive protein (CRP), and hemoglobin A1c (HbA1c) levels were significantly higher in Group 1 than in Group 2 (p<0.05 for all cases) (Table II).

Based on the cut-off values of the laboratory parameters, we found significant differences between the groups (p<0.05) (Table II). Accordingly, the likelihood of having hyperglycemia and hypertriglyceridemia was significantly higher among the participants in Group 2 than in Group 1 (p<0.001 and p=0.025, respectively). Similarly, ALT, CRP, and HbA1c levels were significantly higher in Group 2 than in Group 1 (p<0.001 for all cases). On the other hand, the rate of participants with higher HDL levels was significantly higher in Group 1 than in Group 2 (p=0.021). There was no significant difference between Group 1 and Group 2 in other laboratory parameters (Table II).

There were significant differences between the groups in PLR, AST/ALT, and APRI values (p<0.05) (Table III).

The median value of PLR and AST/ALT were significantly higher in Group 1 than in Group 2 (p=0.004 and p<0.001, respectively). Similarly, there was a significant difference between the groups in APRI calculations (p<0.001). On the other hand, there was no significant difference between the groups in NLR and FIB-4 values (p>0.05) (Table III).

The ROC curve analysis revealed ≤1.38, ≤90.78, ≤0.91,>0.22, and >0.69 as the optimal cut-off values for NLR, PLR, AST/ALT, APRI, and FIB-4 values in predicting the development of NAFLD, respectively. Among these parameters, PLR, AST/ALT, and APRI predicted moderate-to-severe steatohepatitis with statistical significance (p<0.05) (Table IV). Accordingly, there was a significant correlation between the

Table I. Laboratory investigations of the study groups.

	Grouping based on steatohepatitis scores		
	Group 1 (n=352)	Group 2 (n=56)	p
White blood cell count (x10^9/L)§	6.8 [4.0-26.9]	7.3 [5.0-14.0]	0.029*
Neutrophil count (x10^9/L)§	3.6 [1.7-24.5]	3.9 [2.3-9.9]	0.108*
Lymphocyte count (x10^9/L)§	2.3 [0.9-4.7]	2.6 [1.1-4.2]	0.019*
Red cell distribution width (%)§	13.3 [11.7-23.1]	13.5 [12.3-18.3]	0.052*
Platelet count (x10^9/L)§	244.0 [113.0-568.0]	240.5 [153.0-417.0]	0.523*
Platecrit (%)§	0.3 [0.1-0.6]	0.2 [0.2-0.4]	0.412*
Mean platelet volume (fL)§	10.3 [8.4-13.2]	10.4 [9.1-12.2]	0.901*
Glucose (mg/dL)§	99.0 [67.0-372.0]	110.0 [83.0-309.0]	<0.001*
ALT (IU/L)§	16.0 [5.0-115.0]	33.5 [10.0-89.0]	<0.001*
AST (IU/L)§	18.0 [10.0-147.0]	23.0 [11.0-54.0]	<0.001*
Triglyceride (mg/dL)§	109.0 [30.0-1285.0]	165.5 [59.0-401.0]	<0.001*
Cholesterol (mg/dL)†	220.5±47.0	221.7±40.4	0.840**
High density lipoprotein (mg/dL)†	54.2±13.4	45.9±10.2	<0.001**
Low density lipoprotein (mg/dL)†	150.5±37.5	155.7±31.8	0.274**
Very low-density lipoprotein (mg/dL)§	22.1 [6.0-117.8]	30.9 [11.8-80.2]	<0.001*
C-reactive protein (mg/dL)§	2.0 [0.1-64.4]	3.8 [0.8-27.6]	<0.001*
Rheumatoid factor (IU/mL)§	5.2 [0.4-127.1]	4.7 [0.1-20.6]	0.187*
Thyroid stimulating factor (µIU/mL)§	1.9 [0.0-49.0]	1.8 [0.0-27.7]	0.892*
HbA1c (%)§	5.7 [4.7-11.7]	6.1 [5.1-11.4]	<0.001*

†: mean±standard deviation, §: median [min-max]. ALT: alanine aminotransferase, AST: aspartate aminotransferase, HbA1c: glycated hemoglobin. Group 1: participants with US hepatic steatosis scores of 0 and 1, Group 2: participants with US hepatic steatosis scores of 2 and 3. *: Mann-Whitney U test. **: Independent Samples t-test.

Table II. Comparison of the patients according to the abnormal laboratory parameters.

		Grouping based on steatohepatitis scores		
		Group 1 (n=352)	Group 2 (n=56)	p*
White blood cell count‡	Low	2 (0.6)	0 (0.0)	
	Normal	340 (96.6)	53 (94.6)	0.553
	High	10 (2.8)	3 (5.4)	
Neutrophil count‡	Low	8 (2.3)	0 (0.0)	
	Normal	340 (96.6)	54 (96.4)	0.178
	High	4 (1.1)	2 (3.6)	
Lymphocytosis‡		2 (0.6)	1 (1.8)	0.359
Platelet count‡	Low	5 (1.4)	0 (0.0)	
	Normal	344 (97.7)	56 (100.0)	0.999
	High	3 (0.9)	0 (0.0)	
Mean platelet volume‡	Normal	278 (79.0)	47 (83.9)	0.499
	High	74 (21.0)	9 (16.1)	
Glycemia status	Hypoglycemia‡	3 (0.9)	0 (0.0)	
	Normoglycemia‡	247 (70.2)	23 (41.1)	<0.001
	Hyperglycemia‡	102 (29.0)	33 (58.9)	
High ALT‡		9 (2.6)	11 (19.6)	<0.001
High AST‡		1 (0.3)	2 (3.6)	0.051
Hypertriglyceridemia‡		54 (15.3)	16 (28.6)	0.025
Hypercholesterolemia‡		229 (65.1)	39 (69.6)	0.603
High density lipoprotein‡	High	299 (84.9)	40 (71.4)	0.021
C-reactive protein‡	High	56 (15.9)	21 (37.5)	<0.001
Rheumatoid factor‡	High	17 (4.8)	2 (3.6)	0.999
Thyroid stimulating factor‡	Low	3 (0.9)	2 (3.6)	
	Normal	337 (95.7)	51 (91.1)	0.100
	High	12 (3.4)	3 (5.4)	
HbA1c‡	High	35 (9.9)	19 (33.9)	<0.001

‡: n (%). Group 1: participants with US hepatic steatosis scores of 0 and 1, Group 2: participants with US hepatic steatosis scores of 2 and 3. ALT: alanine aminotransferase, AST: aspartate aminotransferase, HbA1c: glycated hemoglobin. *: Pearson Chi-Square, Fisher's Exact/Fisher Freeman Halton test.

presence of NAFLD and PLR values of ≤90.78 (AUC=0.619, 95% CI: 0.570-0.666, p=0.007), AST/ALT values of ≤0.91 (AUC=0.802, 95% CI: 0.760-0.840, p<0.001), and APRI values of >0.22 (AUC=0.687, 95% CI: 0.640-0.732, p<0.001). Additionally, the AUC value of AST/ALT was relatively higher than those of PLR and APRI (Table IV).

The grouping according to the cut-off values of PLR, AST/ALT, and APRI revealed that PLR had the highest diagnostic accuracy in detecting moderate-to-severe steatohepatitis (Table V). The AST/ALT values of ≤0.91 predicted moderate-to-severe steatohepatitis with a sensitivity of 82.1% and a specificity of 65.9%. The overall diagnostic accuracy of the AST/ALT parameter was 68.1%.

Table III. Comparison of the scores of the indices between the groups.

	Grouping based on steatohepatitis scores		
	Group 1 (n=352)	Group 2 (n=56)	p*
NLR§	1.6 [0.6-21.0]	1.5 [0.9-3.7]	0.616
PLR§	107.3 [40.8-389.0]	90.1 [46.8-238.6]	0.004
AST/ALT§	1.1 [0.4-2.5]	0.7 [0.4-1.5]	<0.001
APRI§	0.18 [0.0-1.3]	0.24 [0.1-0.9]	<0.001
FIB-4§	0.8 [0.2-3.1]	0.8 [0.3-2.6]	0.415

§: median [min-max]. Group 1: participants with US hepatic steatosis scores of 0 and 1, Group 2: participants with US hepatic steatosis scores of 2 and 3. NLR: neutrophil/lymphocyte, PLR: platelet/lymphocyte, AST/AST: aspartate aminotransferase/alanine aminotransferase, APRI: AST to platelet ratio index, FIB-4: fibrosis-4. *: Mann-Whitney U test.

Table IV. The Receiver Operating Characteristics (ROC) curve analysis of the indices predicting scores 2 or 3 steatohepatitis.

	AUC	Sensitivity	Specificity	Cut-off	95% CI	p
NLR	0.521	48.21	63.35	≤1.38	0.471-0.570	0.616
PLR	0.619	53.57	74.43	≤90.78	0.570-0.666	0.007
AST/ALT	0.802	82.14	65.91	≤0.91	0.760-0.840	<0.001
APRI	0.687	58.93	71.87	>0.22	0.640-0.732	<0.001
FIB-4 index	0.534	67.86	40.63	>0.69	0.484-0.583	0.411

AUC: Area under the Curve, NLR: neutrophil/lymphocyte, PLR: platelet/lymphocyte, AST/AST: aspartate aminotransferase/alanine aminotransferase, APRI: AST to platelet ratio index, FIB-4: fibrosis-4.

Discussion

Our findings showed that the composite noninvasive indices, including PLR, AST/ALT, and APRI as the noninvasive scoring tools, can predict NAFLD (moderate-to-severe steatohepatitis) in healthy subjects.

The efficacies of several noninvasive scoring tools in predicting hepatic steatohepatitis in different patient groups have been investigated in the literature[1-3,8]. However, there is still controversy on whether these assessment tools reflect the changes in the fibrogenesis process and can differentiate different stages or types of hepatic steatohepatitis[13,14]. Only a few studies[4,15] evaluated the efficacies of noninvasive scoring tools in predicting hepatic steatohepatitis addressed asymptomatic individuals. Anand et al[4] investigated the efficacies of FIB-4, NAFLD fibrosis score (NFS), and APRI in the family members of NAFLD-diagnosed patients based only on US data. They found that the FIB-4, NFS, and APRI scores were significantly lower in healthy family members with normal liver imaging than in the family members with fatty liver. However, they did not assess the steatohepatitis grades in their study. In a study[15] conducted with an asymptomatic Hispanic community in Texas diagnosed with NAFLD based only on US data, the individuals with steatohepatitis had significantly higher NFS and APRI scores than those without steatohepatitis. On the other hand, their FIB-4 scores were comparable.

In comparison, in this study, the APRI scores of participants with moderate-to-severe steatohepatitis were significantly lower than those with normal liver imaging or mild steatohepatitis, whereas their FIB-4 scores were comparable. Foschi et al[16] found moderate correlations between the grade of liver stiffness and several biomarkers, including AST/ALT, APRI, FIB-4, and gamma-glutamyl transferase (GGT), in the context of individuals with and without elevated liver enzymes. However, they could not determine the diagnostic abilities of these biomarkers. As a reason, demographic and clinical data are insufficient to suspect advanced hepatic fibrosis in an asymptomatic individual. In comparison, predefined cut-off values of the scoring tools for the presence or absence of moderate-to-severe

Table V. The diagnostic performance of the calculated indices in predicting scores of 2 or 3 steatohepatitis.

	US hepatic steatosis grades		Sensitivity [95% CI]	Specificity [95% CI]	Accuracy	PPV	NPV
	Score 0 or 1	Score 2 or 3					
PLR							
>90.78	262 (74.4)	26 (46.4)	53.6%	74.4%	71.6%	25.0%	91.0%
≤90.78	90 (25.6)	30 (53.6)					
AST/ALT							
>0.91	232 (65.9)	10 (17.9)	82.1%	65.9%	68.1%	27.7%	95.9%
≤0.91	120 (34.1)	46 (82.1)					
APRI							
≤0.22	253 (71.9)	23 (41.1)	58.9%	71.9%	70.1%	25.0%	91.7%
>0.22	99 (28.1)	33 (58.9)					

US: ultrasound, CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value, PLR: platelet/lymphocyte, AST/AST: aspartate aminotransferase/alanine aminotransferase, APRI: AST to platelet ratio index.

hepatic fibrosis were not addressed in this study[15]. The discrepancies between the studies on the efficacies of the biomarkers used to predict the presence or severity of NAFLD may be attributed to the methods used to analyze these biomarkers.

It is generally accepted that FIB-4, NFS, and APRI have higher efficacies in detecting hepatic fibrosis than other noninvasive biomarkers[9,17-19]. Rigor et al[9] reported that all FIB-4, NFS, and APRI helped rule out advanced hepatic fibrosis associated with NAFLD in a Portuguese cohort. Similar outcomes have been reported by others[5]. Nevertheless, the outcomes of the studies on the diagnostic accuracies of these biomarkers remain controversial due to the methodological heterogeneities between the studies and the differences between the characteristics of the samples investigated in these studies.

In a study conducted with NAFLD patients, whose diagnoses were confirmed by biopsy, Petta et al[20] found a significant correlation between liver stiffness measurements *via* transient elastography and FIB-4 and NFS scores. Based on these findings, they recommended the combined use of several noninvasive assessment tools in diagnosing severe liver fibrosis in NAFLD patients. Nevertheless, the diagnostic accuracies of both markers were roughly 70%, with a diagnostic margin of error of 10%. Another study[10] recommended the sequential use of noninvasive assessment tools for predicting advanced fibrosis in NAFLD patients, thereby avoiding liver biopsy. In comparison, in this study, the noninvasive assessment tools were applied to the study group only once. Further prospective studies with multi-facet analyses might be beneficial in finding the most appropriate approach to predict hepatic fibrosis.

The FIB-4 or APRI scores were deemed optimal for determining the presence or severity of advanced fibrosis in NAFLD patients[17,21]. Some studies[21] reported that the diagnostic accuracies of the noninvasive assessment tools were reduced in populations with no cases of advanced hepatic fibrosis. Similarly, no significant relationship was found between the FIB-4 scores and moderate-to-severe steatohepatitis in the healthy participants. A NAFLD cohort study[22] conducted in Malaysia found the FIB-4 parameter superior to AST/ALT, APRI, and NFS parameters in predicting advanced hepatic fibrosis. The differences between the efficacies of the noninvasive assessment tools in predicting severe steatohepatitis may be attributed to the differences between the reference method used to determine the diagnostic accuracies of these tools. In addition, while some studies[2,3,8,10,14,17,20,22] included biopsy-proven NAFLD patients, others[1,4,5,7,18] included clinically diagnosed NAFLD patients.

AST/ALT ratio is another parameter used to detect steatohepatitis in different patient groups[17-19]. Siddiqui et al[17] and Durazzo et al[19] reported that AST/ALT was inferior to FIB-4, APRI, or NFS regardless of the fibrosis stage in NAFLD patients. In contrast, others[18] reported different diagnostic accuracies of AST/ALT in predicting advanced fibrosis in NAFLD patients. In comparison, in this study, a significant correlation was found between the AST/ALT ratio and moderate-to-severe steatohepatitis development. AST/ALT values of $\leq$0.91 predicted moderate-to-severe steatohepatitis with an accuracy rate of 68.1%, lower than those obtained with FIB-4 and APRI parameters. These results indicate that it is not easy to compare the diagnostic accuracy rates of AST/ALT, FIB-4, and APRI based merely on the findings of retrospective studies.

Some[6] argued that liver US alone might be inefficient in assessing liver diseases. In contrast, others suggested[4,23] that brighter liver echo texture compared to the renal cortex and intra-hepatic vascular blurring indicated NAFLD in the US and reported up to 52.3% success rate in diagnosing asymptomatic participants with grades 1 to 3 steatohepatitis. In comparison, participants with grade 2 or 3 steatohepatitis were considered to have NAFLD in this study. Hence, more standardized criteria are needed to obtain clinically significant results.

The components of metabolic syndrome, particularly dyslipidemia, and obesity, have been the most frequently investigated risk factors for steatohepatitis[13,24,25]. Metabolic (dysfunction)-associated fatty liver disease (MAFLD) has been proposed as a new NAFLD subcategory[5,9,14]. Hyperlipidemia, type 2 diabetes mellitus, and hypertension are the most frequent comorbidities reported[14] in NAFLD patients. In comparison, there was a significant difference between participants with and without NAFLD in the rate of dyslipidemia. Accordingly, it was found that participants with moderate-to-severe steatohepatitis were more likely to have laboratory results supporting dyslipidemia. However, given that the sample of this study consisted only of participants attending a medical check-up program, the participants were not categorized according to whether they had dyslipidemia.

The relationship between PLR and NAFLD has been investigated in several studies[26-29]. However, the results of these studies on the prognostic value of PLR in predicting the presence of NAFLD are controversial. The findings of this study revealed a significant correlation between PLR and moderate-to-severe steatohepatitis in healthy subjects. Further studies are needed to shed more light on this matter.

Limitations

The study's primary limitation was its retrospective single-center design, which might prevent the generalizability of its results to other clinical settings. US has major advantages such as noninvasiveness, easy application, and availability in many facilities. However, using US as the sole reference method for comparing the noninvasive steatohepatitis scoring tools may be another study limitation due to operator dependency and inter-observer variability. Therefore, supplementing the US-based findings with computed tomography and liver biopsy would increase their reliability in cases where the invasiveness of these methods is not a concern. Thirdly, the NFS scores of some subjects could not be calculated due to missing serum albumin measurements, which may be deemed another limitation of the study.

Conclusions

In conclusion, the study findings indicated that PLR, AST/ALT, and APRI parameters help discriminate moderate-to-severe steatohepatitis from normal and mild cases in healthy individuals. Further large-scale studies to be conducted in different settings are needed to corroborate this study's findings.

Ethics Approval

The protocol of this retrospectively designed study was approved by the Local Ethical Committee of Hürrem Sultan Hospital (Approval Date and Number: 01.10.2021 and 46). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent

The written informed consent could not be taken from the participants due to the study's retrospective design and the data's anonymity.

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Conflict of Interest

The authors have no relevant financial or non-financial interests to disclose.

Data Availability

The article's data will be shared on reasonable request by the corresponding author.

Authors' Contributions

Conceptualization, A.M.; Methodology, A.M.; Formal Analysis, A.M.; Writing – Original Draft Preparation, A.M.; Writing – Review and Editing, A.M.

ORCID ID

Alpaslan Mert: 0000-0002-5230-7069

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