Original Article

DOI: 10.4274/haseki.galenos.2023.8559
Med Bull Haseki 2022;60:1-6

Comparison of the Diagnostic Accuracy of the Gamma-Glutamyl Transpeptidase to Platelet Ratio and Systemic Inflammation Response Index in Non-Alcoholic Fatty Liver Disease

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Abstract

Aim: The aim of this study was to evaluate the diagnostic usability of the systemic inflammation response index (SIRI) and the gamma-glutamyl transpeptidase to platelet ratio (GPR) in non-alcoholic fatty liver (NAFL).

Methods: This is a case-control study that was conducted with patients who came to a hospital for a check-up between July 2020 and July 2021, in the internal medicine outpatient clinic of a tertiary care university hospital. The existence and severity of NAFL were confirmed with ultrasonography, and patients were divided into two groups, mild and advanced, according to the severity of NAFL. Body mass index (BMI), alanine aminotranspherase (ALT), aspartate aminotranspherase (AST), gamma-glutamyl transpeptidase (GGT), complete blood count parameters, and erythrocyte sedimentation rates (ESR) were compared between groups.

Results: In total, 665 patients were enrolled in the study, and in 347 (52.3%) of them, the existence of NAFL was confirmed. Of the patients who had NAFL, 184 had mild (grade1), whereas 163 had advanced (grade 2 and 3) steatosis. The differences were significant in age and gender distribution, BMI, ESR, ALT, AST values, GPR, AST to platelet ratio (APRI), and fibrosis-4 (FIB-4) scores between the NAFL and control groups. Univariate regression analyses revealed an increased risk for the development of NAFL in BMI, ALT, AST, ESR, GPR, APRI, and FIB-4 variables. Age, BMI, GPR, and ALT were found to be independent risk factors for the development of NAFL in multivariate analyses. Gamma-glutamyl transpeptidase to platelet ratio was found to be the most effective parameter for predicting the existence of NAFL.

Conclusion: The gamma-glutamyl transpeptidase to platelet ratio is a new and simple marker for predicting the existence of NAFL.

Keywords: Gamma-glutamyl transpeptidase, inflammation, non-alcoholic fatty liver disease, platelet count

Introduction

Non-alcoholic fatty liver (NAFL) is a major reason for chronic liver disease and has a remarkable prevalence of 25-45% (1). In NAFL, chronic inflammation occurs, and it has an important role in the development of NAFL. Hepatocytes can store some fat, but when the amount increases above cell tolerance limits, inflammation starts (2). Non-alcoholic fatty liver has been linked to the severity of inflammation (3).

A liver biopsy result is the gold standard in the diagnosis of NAFL, but liver biopsy has its own risks and is an invasive procedure (4). Because of this, there is a need for novel, easily applicable, and non-invasive diagnostic approaches to NAFL. The relationship between NAFL and inflammatory markers was investigated previously; a fibrosis index score based on four factors fibrosis-4 (FIB-4), red cell diameter width (RDW) to platelet count ratio (RPR), and aspartate aminotransferase (AST) to platelet ratio index (APRI) were inspected (5-8).

The efficiency of the gamma-glutamyl transpeptidase to platelet ratio (GPR) to demonstrate the severity of fibrosis in the liver as a novel marker, was investigated in chronic hepatitis B, autoimmune hepatitis, cystic fibrosis, and drug-induced liver injury cases (9-13). A novel marker: systemic inflammation response index (SIRI), was reported to be effective in demonstrating the prognosis of the patients who had hepatocellular cancer (14). To our

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Received: 30.06.2022 **Accepted:** 01.02.2023

knowledge, the effectiveness of these novel markers in the diagnosis and demonstration of the severity of NAFL had not previously been reported in the literature.

The purpose of this study was to assess the diagnostic performance of GPR and SIRI in NAFL diagnosis and to demonstrate the severity of the disease. These two markers will also be compared with the previously reported markers used in the NAFL.

Materials and Methods

Compliance with Ethical Standards

This observational retrospective study was conducted with patients who came for check-ups between July 2020 and July 2021 to the internal medicine outpatient clinic of a tertiary care university hospital. This study was approved by the Lokman Hekim University Non-Invasive Clinical Research Ethics Committee (approval no: 2021154, date: 23.12.2021). All of the patients who took part in the study provided informed written consent. This study was conducted according to the Declaration of Helsinki directives.

Inclusion Criteria

Patients who had complete information about the inspected variables for the study-alanine aminotransferase (ALT), AST, gamma-glutamyl transpeptidase (GGT), complete blood count, and ultrasonography for the abdomen-in the hospital computer database were included.

Exclusion Criteria

Patients with liver diseases, malignancies, or who consumed more than 20 g of alcohol per day were excluded from the study, as were patients under the age of 18.

Patients were evaluated with hepatobiliary ultrasonography, which was performed by a 12-year-experienced radiologist with a GE Voluson 730 ultrasonography device (GE Medical Systems, Kretztechnik GmbH, Austria). Patients in whom fatty liver disease was detected were divided into two subgroups: mild (grade 1) and advanced (grade 2 and 3). Body mass index (BMI), AST, ALT, and erythrocyte sedimentation rate (ESR) data of all participants were recorded, and comparisons were made between groups according to the existence of NAFL and the severity of NAFL in patients with NAFL.

Criteria to determine the existence of fatty liver in an ultrasonographic evaluation

• Patients with no fatty liver; the liver's echogenicity is lower than that of the kidneys.

• Patients who have a fatty liver; In mild fatty liver, the echogenity of the liver is increased, periportal vascularity can be differentiated, and diaphragmatic echogenity is distinct compared with liver echogenity.

In advanced fatty liver, the echogenity of the liver is remarkably increased, and periportal vascularity and/or diaphragmatic echogenity cannot be distinguished from liver echogenity (15).

Calculations used in the study

Body mass index was calculated by dividing body weight in kilograms by the square of the height in meters. Calculations were made according to the following formulas;

RPR=RDW (%)/Platelet count ($\times 10^9$/L),

GPR=GGT (U/L)/Platelet count ($\times 10^9$/L),

FIB-4=age (years) ×AST (U/L)/[platelet count (10^9/L)×(ALT (U/L)1/2],

APRI=AST (U/L)/platelet count (10^9/L),

NLR=neutrophil count (10^9/L)/lymphocyte count (10^9/L)

SIRI=neutrophil count (10^9/L)×monocyte (10^9/L)/ lymphocyte count (10^9/L).

Laboratory Data

After a 12-hour fast, blood samples were collected. Whole blood counts were analyzed on a Sysmex XN-1000 (USA) device. Alanine aminotranspherase, GGT, and AST were analyzed by a Roche Hitachi Cobas 501 (Switzerland) device. Erythrocyte sedimentation rates were determined using a Biosed 100 (Italy) device.

Statistical Analysis

The SPSS for Windows 25.0 statistical software package (SPSS Inc., Armonk, NY, USA) was used for statistical analysis of the data. Data distributions or normality tests were evaluated by the Shapiro-Wilk test. Data for normally distributed variables were shown as the mean and standard deviation. The comparisons between groups were evaluated by a One-Way ANOVA and an independent t-test. P-values below 0.05 were considered significant. The risk factors for NAFL were investigated by univariate and multivariate logistic regression analyses. In the receiver operator characteristics (ROC) curve, the area under the curve was used to determine the diagnostic power in predicting NAFL.

Results

A total of 665 patients were included in the study, with 338 (50.8%) males and 327 (49.5%) females. The mean age of participants was 48.28±15.09 (males; 45.01±14.20, females; 51.67±15.26). Non-alcoholic fatty liver was confirmed in 347 (52.3%) participants. In the study group who had NAFL, age, gender, BMI, ESR, ALT, AST, GPR, APRI, and FIB-4 parameters were significantly different from those in the group without NAFL (Table 1).

Table 1. Demographic characteristics and laboratory data of participants with and without non-alcoholic fatty liver

Parameter	NAFL (+) (n=347)	NAFL (-) (n=318)	p-value
Age (years, mean±SD)	51.53±12.62	44.74±16.71	**<0.001**†
Gender (male/female ratio)	191/156	147/171	**0.023**‡
Body mass index (mean±SD)	29.12±4.48	25.41±3.88	**<0.001**†
Erythrocyte sedimentation rate (mm/hour)	18.41±13.66	15.80±12.83	**0.014**†
Red-cell diameter width (%)	13.58±1.86	13.36±1.72	0.119†
ALT (IU/L)	29.22±22.72	20.01±14.22	**<0.001**†
AST (IU/L)	22.15±17.48	18.04±6.39	**<0.001**†
Platelet count (×10^9/L)	273.66±71.92	264.56±66.44	0.092†
GPR	0.13±0.13	0.08±0.07	**<0.001**†
NLR	2.10±1.62	2.17±1.54	0.569†
APRI	8.86±8.04	7.22±3.20	**0.001**†
FIB-4	0.88±0.6	0.78±0.49	**0.016**†
SIRI	1.51±2.0	1.43±1.63	0.587†
RPR	0.05±0.02	0.05±0.02	0.485†

†Student's t-test, ‡Chi-square test SD: Standard deviation, NAFL: Non-alcoholic fatty liver, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GPR: Gamma-glutamyl transpeptidase to platelet ratio, NLR: Neutrophil to lymphocyte ratio, APRI: Aspartate aminotransferase to platelet ratio index, FIB-4: Fibrosis index score based on four factors, SIRI: Systemic inflammation response index, RPR: Red cell diameter width to platelet count ratio

Table 2. Comparison of demographic characteristics and laboratory parameters according to severity of non-alcoholic fatty liver

Parameter	Mild NAFL (n=184)	Advanced NAFL (n=163)	p-value
Age (years, mean±SD)	50.84±14.07	52.31±10.72	0.277†
Gender (male/female ratio)	97/87	94/69	0.388‡
Body mass index (mean±SD)	28.02±3.93	30.37±4.75	**<0.001**†
Erythrocyte sedimentation rate (mm/hour)	18.97±15.36	17.77±11.44	0.425†
Red-cell diameter width (%)	13.65±1.77	13.50±1.96	0.455†
ALT (IU/L)	24.27±19.71	34.80±24.59	**<0.001**†
AST (IU/L)	21.03±21.25	23.41±11.80	0.205†
Platelet count (×10^9/L)	275.09±74.95	272.05±68.54	0.695†
GPR	0.11±0.11	0.16±0.15	**0.001**†
NLR	2.29±1.99	1.88±1.0	**0.019**†
APRI	8.49±9.54	9.29±5.93	0.359†
FIB-4	0.92±0.74	0.85±0.40	0.268†
SIRI	1.62±2.37	1.38±1.47	0.263†
RPR	0.05±0.02	0.05±0.02	0.383†

†Student's t-test, ‡Chi-square test SD: Standard deviation, NAFL: Non-alcoholic fatty liver, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GPR: Gamma-glutamyl transpeptidase to platelet ratio, NLR: Neutrophil to lymphocyte ratio, APRI: Aspartate aminotransferase to platelet ratio index, FIB-4: Fibrosis-4, SIRI: Systemic inflammation response index, RPR: Red cell diameter width to platelet count ratio

Table 3. Univariate and multivariate regression analysis of risk factors for development for non-alcoholic fatty liver

Parameter	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
ESR	1.54 (1.48-1.61)	**<0.001**	1.01 (0.99-1.02)	0.483
Age	1.84 (1.71-1.96)	**<0.001**	0.95 (0.93-0.98)	**<0.001**
ALT	1.62 (1.57-1.68)	**<0.001**	0.97 (0.95-1.00)	**0.027**
AST	1.59 (1.52-1.66)	**<0.001**	1.00 (0.95-1.06)	0.979
BMI	2.68 (2.47-2.89)	**<0.001**	0.84 (0.80-0.89)	**<0.001**
GPR	1.59 (1.54-1.65)	**<0.001**	0.30 (0.00-0.59)	**0.021**
APRI	1.56 (1.50-1.62)	**0.001**	0.98 (0.85-1.13)	0.774
FIB-4	1.55 (1.48-1.62)	**0.016**	2.36 (0.84-6.60)	0.103

OR: Odd's ratio, CI: Confidence interval, ESR: Erythrocyte sedimentation rate, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BMI: Body mass index, GPR: Gamma-glutamyl transpeptidase to platelet ratio, APRI: Aspartate aminotransferase to platelet ratio index, FIB-4: Fibrosis-4

Of the patients who had NAFL, 184 had mild (grade 1) steatosis, whereas 163 had advanced (grade 2 and 3). Differences in ALT, BMI, GPR, and NLR parameters were significant between the groups who had mild and advanced NAFL (Table 2).

In univariate regression analysis, BMI, ALT, AST, ESR, GPR, APRI, and FIB-4 were found to be risk factors in the development of NAFL. Multivariate regression analysis of these parameters revealed that age, BMI, GPR, and ALT were independent risk factors for the development of NAFL (Table 3).

The ROC analysis was performed to determine the efficiency of inflammatory markers used to diagnose NAFL, and GPR was found to be the most effective marker (Figure 1). The optimal cut-off value for GPR in predicting the existence of NAFL was 0.9 (66% sensitivity, 62% specificity).

Discussion

This study documented that GPR values were the most effective markers for the diagnosis in people who had NAFL. Gamma-glutamyl transpeptidase has an important role in the metabolism of the main anti-oxidant in the human body known as glutathione. In the presence of conditions such as inflammation and increased oxidative stress, GGT levels are reported to be increased in the body (16,17). Increased fat deposition in the hepatocytes starts an inflammation and this results in an increase in GGT levels. Increased GGT activity reflects increased oxidative stress in NAFL (18,19). Decreased platelet counts are related to fibrosis of the liver (20). Gamma-glutamyl transpeptidase and platelet values, each also

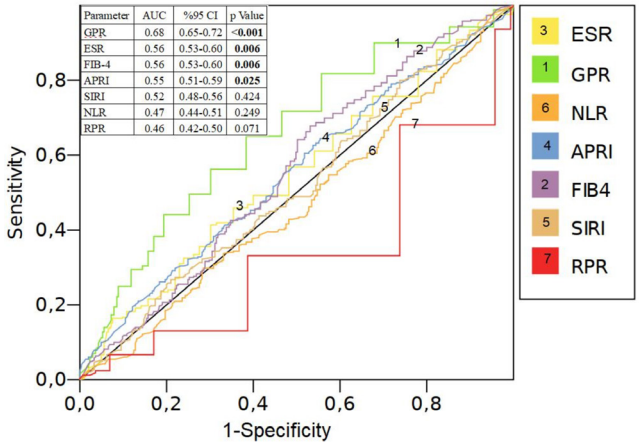

Figure 1. Receiver operating characteristic curve analysis to determine efficiency of markers used to diagnose NAFL
NAFL: Non-alcoholic fatty liver, ESR: Erythrocyte sedimentation rate, GPR: Gamma-glutamyl transpeptidase to platelet ratio, NLR: Neutrophil to lymphocyte ratio, APRI: Aspartate aminotranspherase to platelet ratio, FIB-4: Fibrosis-4, SIRI: Systemic inflammation response index, RPR: Red cell distribution width to platelet count

an inflammatory marker, were used to calculate GPR, a novel inflammatory predictor reported for the first time in 2016 in chronic hepatitis B virus (HBV) infections (21); GPR was also used in other studies inspecting autoimmune hepatitis, cystic fibrosis, and drug-induced liver injuries and was found to be superior to other inflammatory markers in demonstrating the existence of fibrosis (7-13). A study of 131 patients with chronic HBV infection who also had NAFL found that GPR was better than APRI at predicting liver fibrosis (12). The efficiency of GPR in patients who have NAFL but no chronic liver diseases has not been clearly evaluated before. The presented study showed that GPR was related to both the existence and severity of NAFL. The relationship between GPR and NAFL was preserved after multivariate regression analysis, considering the other parameters used in this study. The gamma-glutamyl transpeptidase to platelet ratio is becoming increasingly popular as a marker. Recently, in a new study, the normal reference ranges of GPR in the Chinese population were evaluated (22). This reference level will be useful for future research.

A study reported an association between age, BMI, and the existence of NAFL, independent of laboratory parameters (5). In a previous study, a positive correlation was found between ESR and obesity, and ESR was found to be increasing as BMI increased (23). Congruently, ESR is expected to be elevated in patients as their BMI increases. Obesity is a risk factor for NAFL, and the prevalence of NAFL is reported to be increased in obese individuals (24). Concordant with the aforementioned issues, this presented study reveals associations between age, BMI, ESR, and NAFL.

In one study, the FIB-4 and APRI markers were found to be effective in detecting NAFL (25); in another, the FIB-4 marker was found to be the most effective in demonstrating the presence of NAFL (5). In this study, although FIB-4 and APRI were associated with NAFL, GPR was found to be the most efficient marker in the diagnosis of NAFL.

Study Limitations

There are some limitations to this study. The diagnosis of NAFL was not confirmed with liver biopsies, but ultrasonography was used as a diagnostic tool. Since the study design was retrospective, detailed information about the concomitant diseases of patients and data about the measurement of waist circumference could not be found on every patient's record and thus could not be used. There are some strength parts in this study too. First, the number of participants was relatively high. Second,

participants who had no liver disease were evaluated. This group was not assessed before.

Conclusion

In the study, GPR and SIRI were evaluated in determining NAFL for the first time, but only GPR was found to be efficient. The gamma-glutamyl transpeptidase to platelet ratio is an easy, simple, and rapidly evaluated marker. Further studies, in which the existence of NAFL was confirmed with liver biopsies, are necessary to evaluate the efficiency of GPR in NAFL.

Ethics

Ethics Committee Approval: This study was approved by the Lokman Hekim University Non-Invasive Clinical Research Ethics Committee (approval no: 2021154, date: 23.12.2021).

Informed Consent: All of the patients who took part in the study provided informed written consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: R.A., M.B.K., Design: R.A., M.B.K., Data Collection or Processing: R.A., M.B.K., Analysis or Interpretation: R.A., M.B.K., Literature Search: R.A., M.B.K., Writing: R.A., M.B.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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