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The gamma-glutamyl transpeptidase to platelet ratio (GPR) and the gamma-glutamyl transpeptidase to albumin (GAR) versus fibroscan as indicators of hepatic fibrosis in Non-Alcoholic Fatty Liver Disease Patients

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Running head: GPR &GAR as indicators of fibrosis in NAFLD.

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Abstract:

Background: Identifying patients at risk with Non-alcoholic fatty liver disease (NAFLD) related fibrosis is crucial. Many noninvasive fibrosis markers were developed recently in chronic hepatitis C and B patients, but a few were evaluated in NAFLD.

Aim: to assess the accuracy of the gamma-glutamyl transpeptidase and the other non-invasive markers gamma-glutamyl transpeptidase-to-platelet ratio and gamma-glutamyl transpeptidase-to-albumin ratio (GPR and GAR) versus fibroscan as indicators of hepatic fibrosis in NAFLD patients.

Patients and Methods: A total of 100 NAFLD patients were examined by abdominal ultrasound and then fibroscan to assess liver steatosis and fibrosis. They were grouped into the early fibrosis group and the advanced fibrosis group. Demographic data and laboratory investigation were collected. GPR and GAR were calculated. The correlation between them and liver stiffness measurement (LSM) was reported. The accuracy of predicting liver fibrosis was assessed.

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Results: There was a significant positive correlation between GPR and GAR and the degree of fibrosis. GPR (P <0.001*) and GAR (P <0.001*) were independent predictors for advanced hepatic fibrosis by multiple linear regression analysis. Fibrosis score was used as the dependent variable, with the other studied biomarkers as independent variables. The AUCs of GPR and GAR were 0.790 and 0.949 in assessing liver fibrosis, respectively.

Conclusion: GPR and GAR were positively correlated with hepatic fibrosis and may be used as a novel, simple, accurate, and low-cost parameter for diagnosing hepatic fibrosis in NAFLD patients.

Keywords: gamma-glutamyl transpeptidase-to-platelet ratio, gamma-glutamyl transpeptidase-to-albumin ratio, liver fibrosis, nonalcoholic fatty liver disease.

Introduction:

Non-alcoholic fatty liver disease (NAFLD) is a significant public health problem. It is defined as hepatic steatosis in more than 5% of hepatocytes without important ongoing or recent alcohol consumption or other known liver disease causes. [1] NAFLD covers a spectrum ranging from simple steatosis to steatohepatitis and cirrhosis [2].
Available data suggest that Egypt has one of the highest prevalences of metabolic associated fatty liver disease (MAFLD) (formerly known as nonalcoholic fatty liver disease [NAFLD]), affecting more than one-third of the population, compared to a global prevalence of about 25%. [3,4] Specific studies suggest that the prevalence range of MAFLD in Egypt is approximately 47.5%, with 56.7% having fibrosis [5]
The mortality rate in NAFLD patients is increased compared with the general population. Cardiovascular disease, malignancy, or liver-related mortality are the leading causes of mortality in NAFLD patients [6].
Patients with nonalcoholic steatohepatitis (NASH) and F2–4 fibrosis are at higher risk for liver-related events and mortality and are considered "at-risk" NASH. [7]
Over the past 40 years, our understanding of NAFLD has evolved to broadly define a link to metabolic dysregulation as the driving force in the pathogenesis of the disease. [8-11].

The gold standard for diagnosis of NAFLD is liver biopsy. In recent years, non-invasive tools for measuring liver fibrosis and liver steatosis, such as transient elastography, controlled attenuation parameters, or magnetic resonance-based methods, have been developed, and their utility in the setting of NAFLD is being extensively investigated [12,13].

Lemoine and colleagues presented a marker of liver fibrosis, the gamma-glutamyl transpeptidase to platelet ratio (GPR), as a more accurate non-invasive marker than either the aspartate aminotransferase to platelet ratio index (APRI) or the fibrosis index based on four factors (FIB-4) for diagnosing liver fibrosis in patients with chronic hepatitis B virus (HBV) infection in West Africa, and a simple and inexpensive alternative to transient elastography and liver biopsy **[14].**

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HE et al. concluded that, like the APRI score and FIB-4 index, GGT/Alb ratio is a simple and practical noninvasive model for diagnosing liver fibrosis and can provide a reference for diagnosing liver fibrosis degree in patients with chronic HBV infection [15].

Also, Li et al. reported that GAR is a more accurate non-invasive index than APRI and FIB-4 to stage significant fibrosis and cirrhosis in chronic hepatitis B (CHB) patients and represents a novel non-invasive alternative to liver biopsy [16].

However, the role of GGT and its other noninvasive markers in assessing hepatic fibrosis in patients with NAFLD must be well studied. This study evaluated the accuracy of the gamma-glutamyl transpeptidase and the other non-invasive markers (GPR and GAR) versus fibroscan as indicators of hepatic fibrosis in NAFLD patients.

Patients and Method:

This study was an observational cross-sectional trial. This study was conducted on 100 patients recruited from the Tropical Medicine and infectious diseases department clinic, Tanta university hospital, from January 2022 to January 2023.

Patients with liver steatosis were included, determined by abdominal ultrasound with the characteristic of "bright liver," NAFLD was diagnosed by transient elastography (fibroscan) by controlled attenuation parameter (CAP) determination of liver steatosis more than 240 dB/min.

The following conditions were excluded: Chronic Hepatitis B infection**,** Chronic hepatitis D Infection**,** Chronic hepatitis C infection**,** HIV**,** Drug-induced liver disease**,** Autoimmune liver disease**,** Renal failure**.,** Endocrinal disorders, e.g., hypothyroidism and hyperthyroidism, Febrile patients, Any stress condition**,** Alcoholism**,** phenobarbital, and phenytoin intake.

All patients signed the informed consent, and all clinical procedures were by the Helsinki Declaration 1975, as revised in 1983. The ethics committee of the faculty of medicine at Tanta University permitted the study protocol (35175/1/22).

All patients were subjected to Full history taking and general examination. Anthropometric measurements were taken (height, weight, waist circumference, hip circumference, waist-hip ratio (WHR), and BMI).

Laboratory investigations include Complete blood picture, liver function tests, prothrombin time, INR, blood glucose, and total lipid profile.

- GGT measurement and calculation of the gamma-glutamyl transpeptidase to platelet ratio (GPR) and the gamma-glutamyl transpeptidase to albumin ratio (GAR)

  GPR = [(GGT/upper limit of normal GGT) × 100]/platelet count(10^9/L)

  GAR=GGT (IU/L) / albumin (g/L)

  Fatty liver evaluation

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Liver US (Toshiba, Japan) scanning was performed to assess fatty liver

Fibroscan: The Controlled Attenuation Parameter (CAP) and Liver Stiffness Measurement (LSM) were obtained for all participants to assess liver steatosis and fibrosis grades.

Transient elastography (TE) was performed under fasting conditions. The same operator measured LSM and CAP according to the manufacturer's protocol. L probe was used in obese patients. The value of the LSM was represented in kilopascal (kPa). The value of the CAP is expressed in db/m. LSM and CAP were detected in the same region of liver parenchyma (between 25 and 65mm in depth). Up to 10 valid measurements were obtained on each patient. [17]

The hepatic steatosis degree is diagnosed by CAP value. normal: CAP ≤ 239 db/m, mild hepatic steatosis: 240-264 db/m, moderate hepatic steatosis: 265- 294 db/m, severe hepatic steatosis: CAP ≥ 295 db/m. The fibrosis degree is assessed according to the value of LSM. Significant fibrosis is determined if LSM (F3 ≥ 9.8 kpa). A fibrosis score of 3 or 4 was defined as advanced fibrosis.

Statistical analysis.

All statistical analyses were performed using SPSS version 16.0 (IBM Corp, Chicago, IL, USA). Data were expressed in mean ± standard deviation (SD) for normally distributed continuous data, median (interquartile range) for non-normally distributed continuous data, and percentage for categorical data. The comparison of the two groups used an independent t-test and Mann–Whitney U for normally distributed and skewed variables, respectively. Categorical data were compared using the Chi-square ($\chi 2$) test. The diagnostic accuracy of the noninvasive scoring systems was calculated using the area under the receiver operating characteristics (AUROC) curve, and the 95% confidence interval (CI) was determined. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated based on the cut-off values in the previously published reports.

Results

A total number of 100 patients with liver steatosis was determined by abdominal ultrasound.
Then, NAFLD was diagnosed by CAP determination of liver steatosis of more than 240 dB/min. Seventy-eight patients (78%) had early fibrosis (early fibrosis group), and 22 patients (22%) had advanced fibrosis (advanced fibrosis group)
The demographic and characteristic data are presented in **Table 1**.

Table1. Demographic data of the studied groups.

Variable	Early Fibrosis Group (n= 78)	Advanced Fibrosis Group (n= 22)	p-value
Gender			0.246
Female	50 (64.1%)	17 (77.3%)	
Male	28 (35.9%)	5 (22.7%)	
Age	45.36 ± 8.76	47.27 ± 9.44	0.689

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height	162.97 ± 7.20	160.14 ± 6.33	0.123
weight	90.94 ± 20.62	108.97 ± 21.16	0.001*
Waist	106.92 ± 11.89	118.82 ± 17.95	0.001*
Hip	124.05 ± 15.16	127.36 ± 15.87	0.217
BMI	34.37 ± 8.01	42.64 ± 8.93	<0.001*
WHR	0.86 ± 0.06	0.93 ± 0.04	<0.001*
DM			0.194
- **No**	70 (89.7%)	22 (100.0%)	
- **Yes**	22 (10.3%)	0 (0.0%)	
Hypertension			0.469
- **No**	58 (74.4%)	18 (81.8%)	
- **Yes**	20 (25.6%)	4 (18.2%)	
History of regimen:			0.246
- **No**	54 (69.2%)	18 (81.8%)	
- **Yes**	24 (30.8%)	4 (18.2%)	

Abbreviation: n, number of cases/participants; BMI, Body mass index; WHR, waist-hip ratio

The mean age was (45.36 ± 8.76) in the early fibrosis group and (47.27 ± 9.44) in the advanced fibrosis group. A statistically significant difference was detected between both groups regarding weight, waist, BMI, and WHR ratio (p <0.001*).

The clinical and laboratory data of the early fibrosis group were compared with data of the advanced fibrosis group, as shown in **Table 2.**

Table 1. ***Clinical and laboratory data of the studied patients.***

Variable	Early Fibrosis Group (n= 78)	Advanced Fibrosis Group (n= 22)	p-value
Steatosis grade			**<0.001***
S0	**8 (10.3%)**	**0 (0.0%)**	
S1	**20 (25.6%)**	**4 (18.2%)**	
S2	**28 (35.9%)**	**0 (0.0%)**	
S3	**22 (28.2%)**	**18 (81.8%)**	
fibrosis score	**5.11 ± 0.92**	**9.18 ± 1.38**	**<0.001***
steatosis score	**280.18 ± 37.75**	**323.27 ± 42.07**	**<0.001***
SBP	**123.33 ± 15.97**	**134.55 ± 14.05**	**0.003***
DBP	**72.31 ± 11.72**	**82.73 ± 12.41**	**<0.001***
ALT	**43.84 ± 24.61**	**60.30 ± 28.15**	**<0.001***
AST	**45.26 ± 20.54**	**63.18 ± 20.99**	**<0.001***
Bilirubin	**0.84 ± 0.23**	**0.87 ± 0.27**	**0.786**
albumin	**4.22 ± 0.35**	**3.95 ± 0.18**	**0.001***
INR	**1.08 ± 0.32**	**1.00 ± 0.00**	**0.720**
Fasting sugar	**100.10 ± 9.62**	**106.36 ± 12.45**	**0.358**

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HbA1C	**5.73 ± 1.07**	**5.92 ± 0.14**	**0.234**
TG	**164.97 ± 52.97**	**152.91 ± 47.74**	**0.751**
cholesterol	**212.87 ± 46.61**	**178.09 ± 38.17**	**0.147**
LDL	**167.24 ± 59.79**	**145.58 ± 53.72**	**0.264**
HDL	**36.78 ± 10.56**	**38.95 ± 11.71**	**0.650**
VLDL	**29.90 ± 15.56**	**23.36 ± 8.36**	**0.340**
GGT	**20.56 ± 3.69**	**26.62 ± 2.70**	**<0.001***
HB	**12.22 ± 1.18**	**11.62 ± 0.69**	**0.029***
WBC	**7.21 ± 1.85**	**7.38 ± 2.01**	**0.880**
Lymphocyte (%)	**29.50 ± 11.26**	**33.64 ± 6.57**	**0.078**
neutrophil (%)	**59.10 ± 8.47**	**55.82 ± 5.53**	**0.026***
Platelets	**274.92 ± 58.44**	**259.64 ± 76.03**	**0.211**
GPR	**0.08 ± 0.03**	**0.11 ± 0.03**	**<0.001***
GAR	**4.92 ± 1.03**	**6.78 ± .91**	**<0.001***

Data presented as mean + SD. (P < 0.05 is significant).

Abbreviation: n, number of cases/participants; FBS, Fasting blood sugar; HbA1c, Glycated hemoglobin; TC, Total cholesterol; TG, Triacylglycerol; HDL-c, High-density lipoprotein–cholesterol; LDL-c, Low-density lipoprotein–cholesterol; VLDL-c, Very low-density lipoprotein–cholesterol; ALT, Alanine aminotransferase; AST, Aspartate Aminotransferase; ALP, Alkaline phosphatase; GGT, Gamma-glutamyl Transferase; INR, International normalized ratio; HB, Hemoglobin; WBCs, White blood cells; GPR, Gamma-glutamyl transferase to platelets ratio; GAR, Gamma-glutamyl transferase to albumin ratio.

Patients with advanced fibrosis had significantly higher levels according to fibrosis score and steatosis score, ALT, AST, and GGT (P <0.001). Still, lower levels of albumin (P = 0.001) and systolic and diastolic blood pressure were significantly increased in the advanced fibrosis group.

Table 3 demonstrates that both GPR and GAR values were positively correlated with fibrosis grade and steatosis grade scores by bivariate correlation analysis.

There was a significant positive correlation between GPR and GAR and the degree of fibrosis, while there was a non-significant negative correlation between GPR and the degree of steatosis. A significant positive correlation between GAR and grade of steatosis was noticed.

Table (3): Bivariate correlations between GPR and GAR and grades of steatosis and fibrosis.

Table 3. ***Bivariate correlations between GPR and GAR and grades of steatosis and fibrosis.***

		GPR	**GAR**
Steatosis grade	**r**	-0.036	0.226
	P value	0.725	0.024*
Fibrosis grade	**r**	0.417	0.645

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P value	<0.001*	<0.001*

GPR (B 3.424, P <0.001*) and GAR (B 0.175, P <0.001*) were the independent predictors for advanced hepatic fibrosis by multiple linear regression analysis. Fibrosis score was used as the dependent variable, with the other studied biomarkers as independent variables, as shown in Table 4.

Table 4. Potential predictors of advanced hepatic fibrosis by multiple linear regression analysis.

	Unstandardized Coefficients		**Standardized Coefficients**	**t**	**P value**
	B	**Std. Error**	**Beta**		
GPR	3.424	1.470	0.332	2.329	<0.01*
GAR	0.175	0.075	0.307	2.323	<0.01*
Albumin	-0.496	0.243	-0.202	-2.037	<0.05 *
GGT	0.023	0.023	0.121	0.995	0.324
ALT	0.004	0.011	0.043	0.348	0.729
Dependent variable: Fibrosis score					

The receiver operating characteristic (ROC) curve (**Table 5, Fig 1**) showed that GAR has the largest area under the curve (0.949, 95% CI 0.905- 0.992) followed by GGT (0.921, 95% CI 0.864 - 0.978), then GPR (0.790, 95%CI0.700-0,880).
Using a cut-off of more than 5.897, GAR showed a 90.9% sensitivity and 94.8% specificity for differentiating early and advanced fibrosis. ROC curve results for GPR demonstrated that using >0.079 as a cut-off will have a 100% sensitivity and 61.5%. In contrast, with a cut-off value of >23, GGT showed a 90.9% sensitivity and 89.7% for differentiating early and advanced fibrosis.

Table 5. ***Performance of GPR and GAR as predictors of advanced hepatic fibrosis (ROC curve analysis)***

Variable	AUC	SE	95% CI [b]	p-value	Cut-off	Sens	spec	PPV	NPV	Accuracy
GAR	0.949	0.0222	0.905 to 0.992	<0.001*	>5.897	90.91	94.87	83.3	97.4	94.0
GPR	0.790	0.0459	0.700 to 0.880	<0.001*	>0.079	100.00	61.54	42.3	100.0	70.0
albumin	0.723	0.0646	0.596 to 0.849	<0.001*	≤3.8	36.36	100.00	100.0	84.8	86.0
ALT	0.769	0.0520	0.667 to 0.871	<0.001*	>43	72.73	71.79	42.1	90.3	72.0
AST	0.781	0.0459	0.691 to 0.871	<0.001*	>38	100.00	58.97	40.7	100.0	68.0
GGT	0.921	0.0291	0.864 to 0.978	<0.001*	>23	90.91	89.74	71.4	97.2	90.0

*AUC: area under the ROC curve; CI: confidence interval of AUC; NPV: negative predictive value; PPV: positive predictive value; SE: standard error of AUC; Sens: sensitivity; spec: specificity; * significant at p<0.05.*

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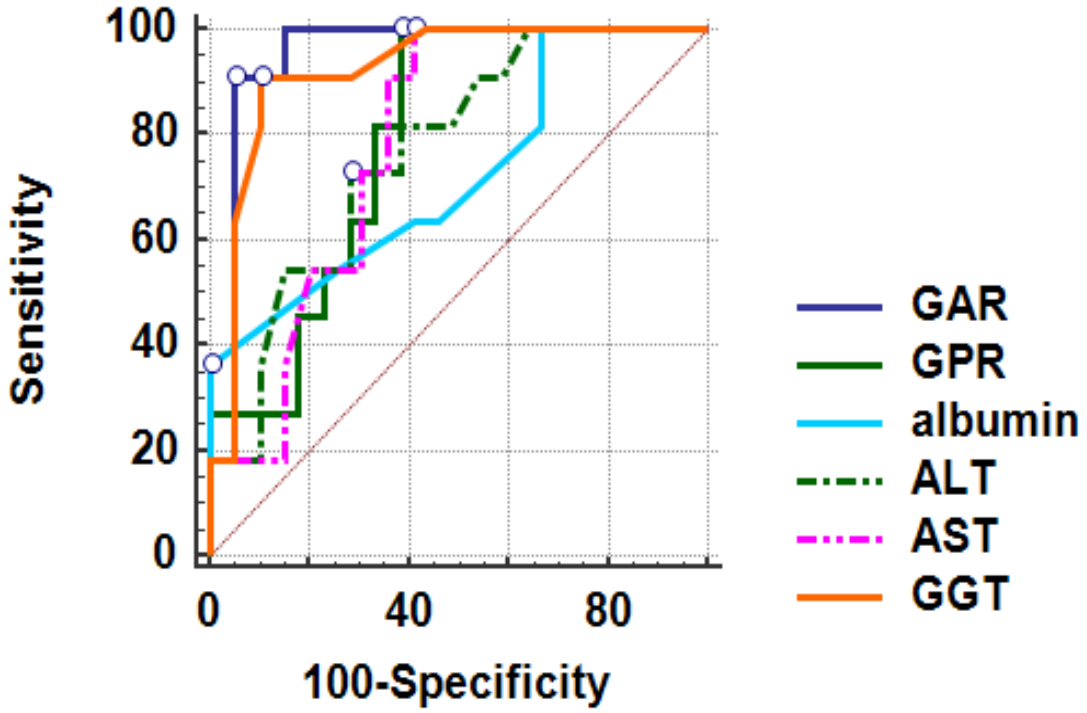

Figure 1. ***Fig 1: Receiver operating characteristic (ROC) curve of GPR, GAR value, albumin, ALT, AST, and GGT for differentiating early and advanced fibrosis groups.***

Discussion

The prevalence of NAFLD is rising worldwide, and liver fibrosis is a risk of complications leading to decompensation and HCC. Identifying patients with advanced fibrosis (at-risk patients) is essential to treat them. Novel noninvasive biomarkers are emerging for the assessment of NAFLD-related fibrosis.

The Egyptian guidelines for MAFLD recommended that excluding high-risk of significant fibrosis is acceptable using simple, noninvasive biomarkers and scores of fibrosis. Also, considerable fibrosis can be confirmed by liver stiffness measurement by Vibration-controlled transient elastography (VCTE) and/or sequential combination with serum biomarkers/scores [18].

In this study, we compared the diagnostic performance of GGT and other noninvasive blood parameters (GPR & GAR) versus transient elastography for assessing liver fibrosis in NAFLD. We found that Patients with advanced fibrosis were significant with higher levels according to fibrosis score and steatosis score, ALT, AST, and GGT ($P < 0.001$) but lower levels of albumin, and this agrees with a study done by Chen et al., which demonstrated that GGT elevation was associated with metabolic syndrome(MetS), hepatic steatosis, and fibrosis in patients with non-alcoholic fatty liver disease [19].
Also, Zain et al. demonstrated that the risk of advanced fibrosis increased 13-fold when serum GGT level was above ULN and 5-fold with diabetes mellitus [20]. In addition, the results of another study suggest that GGT is a new non-invasive marker that can be used to predict advanced histological liver damage. [21].

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In this work, we found that the values of both GPR and GAR were positively correlated with fibrosis.

Many studies have suggested that GPR can evaluate liver fibrosis in patients with chronic hepatitis B and NAFLD [22-24].

In 2016, Lemoine et al. proposed GPR as a marker of the fibrosis stage in patients with chronic hepatitis B [14].

Li et al. evaluated GPR as a predictive marker of fibrosis compared to liver biopsy in patients with HBV and NAFLD (HBV-NAFLD). In this study, GGT levels were higher in patients with HBV-NAFLD than in patients with HBV alone. Additionally, it showed higher GPR results in patients with advanced fibrosis and a correlation between fibrosis levels and GPR in patients who had only NAFLD and did not have chronic hepatitis B [23].

Khare et al. found that in patients with chronic hepatitis B, significant fibrosis could be ruled out by noninvasive blood parameters (APRI, FIB-4, and GPR) with negative predictive values above 93%. The results showed that GPR, APRI, and FIB-4 were highly correlated with LSM [25].

Also, Luo et al. suggested that serological markers could evaluate hepatic fibrosis. They reported that GPR correlates well with LSM in assessing liver fibrosis and can be used as a noninvasive index to evaluate liver fibrosis in patients with concomitant CHB and NAFLD [22].

Meanwhile, GAR is a more accurate noninvasive index than APRI and FIB-4 to stage significant fibrosis and cirrhosis in CHB patients and represents a novel noninvasive alternative to liver biopsy [16].

In this study, the Receiver operating characteristic (ROC) curve showed that GAR has the largest area under the curve (0.949, 95% CI 0.905- 0.992) followed by GGT (0.921, 95% CI 0.864 - 0.978), then GPR (0.790, 95%CI0.700-0,880).

This result is consistent with a previous study, which reported that The AUCs of APRI, FIB-4, and GPR were 0.766 · 0.826 and 0.805 respectively [22].

GPR had high negative predictive values (NPVs) for ruling out significant fibrosis (91%), severe fibrosis (98%), and cirrhosis (100%), respectively, but low positive predictive values (PPVs) for diagnosing substantial fibrosis (65%), severe fibrosis (39%), and cirrhosis (30%), respectively [23].

Also, Li et al. found that the area under the receiver operating characteristic curve (AUROC) of GAR was significantly higher than that of APRI and FIB-4 to predict ≥F2 (0.82, 0.70, and 0.68, respectively), ≥F3 (0.86, 0.76, and 0.75, respectively), and F4 (0.88, 0.75, and 0.73, respectively), respectively. [16]

In conclusion, our study found that GPR and GAR were positively correlated with hepatic fibrosis and may be novel, simple, accurate, and low-cost parameters for diagnosing hepatic fibrosis in NAFLD patients.

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The limitations of the study are the small sample size. So, extensive studies are needed. Also, our study relied on imaging and Fibroscan assessment for NAFLD and not on liver biopsy, which is the gold standard for diagnosis.

Footnotes.

Peer-Reviewers: Nevin Ibrahim Fouad (prof of internal medicine), Lobna Abo Ali (professor of tropical medicine), Mohamed Emara (professor of gastroenterology, hepatology, and infectious diseases), and Ahmed Fathy (professor of internal medicine).

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Ethics Approval and Consent to Participate: All procedures followed were by the ethical standards of the responsible committee on human experimentation (Institutional Review Board (IRB)" (35175/1/22) of Tanta University and with the Helsinki Declaration of 1964 and later versions.

Consent for publication: All patients included in this research gave written informed permission to publish the data contained within this study.

Availability of data and materials: The datasets used or analyzed during the current study are available from the corresponding author upon reasonable request.

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Authors' contributions: **SS,** writing the research, selecting research cases, preparing the figures for case demonstration, and reviewing the study. **RB** assessed patients for initial diagnosis**. SS** and **WE were** considered in case selection and carried out cases on workstations. "All authors read and approved the final manuscript."

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