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Research article

Clinical value of γ-glutamyl transpeptidase to platelet ratio and triglyceride measurement in the diagnosis of nonalcoholic fatty liver disease: A cross-sectional study

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ABSTRACT

Objective: In clinical practice, there are few effective biomarkers for identifying non-alcoholic fatty liver disease (NAFLD). The aim of this study is to investigate the diagnostic value of γ-glutamyl transpeptidase to platelet ratio (GPR) combined with triglyceride (TG) in NAFLD.
Methods: A total of 14,415 individuals participated in the annual physical examination. Multivariate logistic regression analysis was conducted to investigate the exposure factors associated with NAFLD. Spearman's analysis was performed to assess the correlation among the exposure factors of NAFLD. Furthermore, the diagnostic efficacy of the combination of GPR and TG in NAFLD was analyzed using the receiver operating characteristic curve (ROC).
Results: The results of the multivariate logistic regression analysis showed that BMI (OR = 1.619), Systolic Blood Pressure (SBP) (OR = 1.014), Diastolic Blood Pressure (DBP) (OR = 1.028), GPR (OR = 12.809), and TG (OR = 2.936) were all risk factors for NAFLD, while HDL-C (OR = 0.215) was a protective factor. Spearman correlation analysis revealed significant positive correlations between GPR and SBP, DBP, BMI, TG ($p < 0.01$), but a negative correlation between GPR and HDL-C ($p < 0.01$). TG was only positively correlated with GPR ($p < 0.001$). ROC curve analysis demonstrated that the area under the curve (AUC) of GPR combined with TG for diagnosis of NAFLD was 0.855 (95 % CI: 0.819–0.891), sensitivity was 83.45 % and specificity was 73.56 %.
Conclusion: This study indicated that high levels of GPR and TG were risk factors for NAFLD and demonstrated good clinical value in diagnosing NAFLD.

1. Introduction

Liver-related diseases remain the main killer worldwide [1]. Among which, non-alcoholic fatty liver disease (NAFLD), a prevalent condition affecting over a quarter of the global population, has emerged as a burgeoning global public health concern [2]. Recent years

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have witnessed a substantial epidemiological investigation revealing a staggering prevalence rate of 32.9 % for NAFLD in China [3]. The progression of NAFLD encompasses a spectrum of pathological changes, ranging from simple hepatic steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and ultimately hepatocellular carcinoma, imposing a substantial burden on the health and economic well-being of affected individuals [4]. A retrospective study conducted in the United States revealed that NAFLD accounted for 59 % of hepatocellular carcinoma cases and NASH is emerging as the primary cause of liver transplantation [5,6]. Timely diagnosis and intervention are therefore crucial in enhancing the prognosis of NAFLD patients.

Liver biopsy (LB) is widely recognized as the most dependable approach for evaluating liver disease and injury [7]. Nevertheless, its extensive implementation in clinical practice is impeded by the substantial expenses linked to the procedure, potential complications, and the likelihood of sampling inaccuracies [8,9]. Despite the recent recognition by experts of the diagnostic efficacy of blood biomarkers in detecting NAFLD [10], there is still a scarcity of efficacious biomarkers that can be readily utilized in clinical settings. Consequently, there is an urgent clinical imperative to investigate and identify biomarkers for NAFLD.

The pathological accumulation of triglycerides and other lipids in liver cells is a defining characteristic of fatty liver [11]. However, the expression of dyslipidemia in NAFLD can vary due to the complex biological pathways involved in lipid metabolism [12]. Currently, there is limited research in clinical practice on the use of triglyceride and other lipid indicators for diagnosing NAFLD. Lemoine et al. [13] found that the GPR index is more accurate than aspartate transaminase-to-platelet ratio index (APRI) and fibrosis-4 (FIB-4) in distinguishing liver fibrosis in patients with chronic hepatitis B in the West African population. Another study on liver biopsies of patients with chronic hepatitis B demonstrated a significant correlation between the GPR index and liver inflammation, particularly in HBeAg-positive patients, with high diagnostic accuracy [14]. Recent research has shown that the GPR index is an effective indicator for assessing the degree of liver fibrosis [15]. However, there is limited data on the role of GPR combined with triglycerides in NAFLD, necessitating further investigation. In this cross-sectional study, we aim to investigate whether the combination of GPR and triglycerides can serve as a non-invasive biomarker for diagnosing NAFLD.

2. Materials and methods

2.1. Study population

The data utilized in this study was obtained from the Advanced Medical Examination Center of the Second Affiliated Hospital of Guangzhou Medical University. The duration of data collection encompassed the period from Jan 1, 2022, to Oct 31, 2023. The inclusion criteria for participants consisted of individuals between the ages of 18 and 70 who had undergone abdominal ultrasound examinations, laboratory tests, and possessed complete basic physiological data. On the other hand, the exclusion criteria encompassed pregnant or lactating women, individuals with a history of heavy alcohol consumption ($\geq$30 g/d for males, $\geq$20 g/d for females) [16], those with a history of abdominal surgery (e.g., liver resection, pancreatic resection, splenectomy, etc.), individuals with liver and gallbladder tumors, those with hepatitis, and individuals with liver cysts. The study ultimately included a total of 14,415 participants, comprising 7459 males and 6956 females (Fig. 1).

2.2. Clinical and laboratory data collection

The specialized nursing staff collected general information and measured basic physiological indicators of the study subjects, such as name, gender, age, weight, height, systolic blood pressure, and diastolic blood pressure. To ensure accurate results, all subjects were required to fast for 8 h prior to having 4 mL of venous blood drawn from the elbow in the morning. The blood samples were then tested for various indicators, including fasting blood glucose (Glu), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), uric acid (UA), alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (GGT), and others, utilizing a fully automated biochemical analyzer (cobas8000, Roche, Germany). Additionally, a XN-2000AB fully automated analyzer was used to conduct blood routine tests, which encompassed white

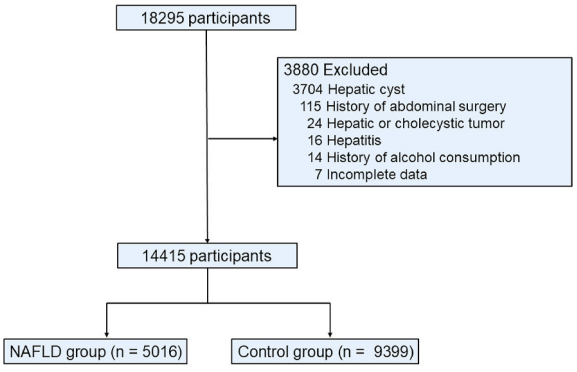

Fig. 1. Flow diagram describing the selection process of the study participants.

blood cell (WBC), platelet (Plt), neutrophil (Neut), lymphocyte (Lymph), and monocyte (Mono) measurements. Liver ultrasound examinations were conducted by professional ultrasound doctors using an ultrasound diagnostic instrument (HS60, Samsung, South Korea) equipped with a convex array probe operating at a frequency of 3.5 MHz. The subjects were examined in the supine and lateral positions while in a fasting state in the morning for routine liver ultrasound examination.

2.3. Definition

Abdominal ultrasound examinations are conducted by proficient ultrasound physicians, who were not provided with any prior knowledge of the participants' clinical data. The diagnosis of hepatic steatosis, a condition characterized by excessive fat accumulation in the liver, requires the identification of at least two abnormal findings in the abdominal ultrasound examination. These abnormal findings include [17,18]: (1) diffusely increased echogenicity liver significantly higher than kidneys or spleen; (2) occurrence of posterior beam attenuation; (3) loss of echogenicity in the portal vein wall. After ruling out alcohol abuse and other liver diseases, the diagnosis of NAFLD was made using abdominal ultrasound. The study subjects were then divided into two groups, the NAFLD group (n = 5822) and the healthy control group (n = 10975), based on the results of the abdominal color Doppler ultrasound examination. According to the hospital's laboratory technical standards, the reference ranges for various laboratory tests are as follows: ALT (7–40 U/L), AST (13–35 U/L), GGT (10–60 U/L), CHOL (3~5.18 mmol/L), TG (0.55–1.7 mmol/L), HDL-C (0.94–1.54 mmol/L), LDL-C (1.5–3.37 mmol/L), Glu (3.9–6.1 mmol/L), UA (210–420 μmol/L), WBC (3.5–9.5 $\times 10^9$/L), Plt (125–350 $\times 10^9$/L), Neut (1.8–6.3 $\times 10^9$/L), Lymph (1.1–3.2 $\times 10^9$/L), and Mono (0.1–0.6 $\times 10^9$/L).

The calculation formulas used in the study were as follows: body mass index (BMI) was calculated by dividing weight (in kilograms) by height (in meters) squared (kg/m^2). GPR = (GGT/upper limit of normal reference value)/platelet count $\times$ 100 [13].

2.4. Statistical analysis

SPSS (version 17.0, IBM, USA) is utilized for conducting statistical analysis in this study. Normally distributed metric data is represented by the mean and standard deviation ($\bar{x} \pm s$), and the independent sample *t*-test is employed for comparing groups. Non-normally distributed metric data is represented by M (P25, P75), and the Mann-Whitney *U* test is used for between-group comparisons. The Chi-square ($\chi 2$) test is employed for comparing count data. Multiple factor logistic regression analysis is utilized for analyzing risk factors, with the odds ratio (OR) and its 95 % confidence interval (CI) used to represent relative risk. Spearman analysis is employed to examine the correlation between risk factors. Receiver operating characteristic curve (ROC curve) analysis is used to assess the diagnostic value of GPR for NAFLD. A statistically significant difference is defined as a p-value <0.05.

3. Result

3.1. The demographic characteristics of the study participants

In the physical examination, a total of 14,415 participants were included, out of which 5016 cases (34.80 %) were diagnosed with NAFLD. The average age of the participants was 48.29 $\pm$ 14.27 years. Among the NAFLD group, there were 3502 males (46.95 %) with the mean age of 46.52 $\pm$ 14.02 years old, and 1514 females (21.77 %) with an average age of 52.39 $\pm$ 14.00 years old. The average age of males in the NAFLD group was found to be significantly lower than that of females ($P < 0.05$) (Table 1).

3.2. Comparison of clinical parameters between the two groups of participants

The anthropometric and laboratory parameters of the participants are shown in Table 2. In comparison to the healthy control group, the NAFLD group exhibited elevated levels of BMI, SBP, DBP, ALT, AST, GGT, TC, TG, HDL-C, LDL-C, Glu, UA, WBC, PLT, NEUT, Lymph, Mono, and GPR values ($P < 0.05$). The mean levels of BMI, TC, and LDL-C in the NAFLD group exceeded the upper limit of the reference values, while the mean levels of SBP, DBP, TG, and HDL-C were within the high range of the reference values.

3.3. Multivariate logistic regression analysis of exposure factors in NAFLD

The present study employed multiple logistic regression analysis to investigate the potential associations between exposure factors and the risk of NAFLD. Factors that exhibited statistically significant differences in Table 2 and had mean levels surpassing the reference range or falling within the high normal range were included as independent variables in the regression equation. The occurrence of NAFLD served as the dependent variable, while BMI, SBP, DBP, GPR, TC, TG, HDL-C, and LDL-C were considered as

Table 1
Baseline characteristics of the subjects in the two groups.

Variable	NAFLD	Control	*t/Z*	*P*-value
N (%)	5016 (34.80)	9399 (65.20)	–	–
Male/Female (%)	3502 (46.9)/1514 (21.8)	3957 (53.1)/5442 (78.2)	1006.20	0.000
Age (years)	48.29 $\pm$ 14.27	42.12 $\pm$ 14.69	24.25	0.000

Table 2
Comparison of anthropometric and laboratory parameters between NAFLD group and Control group.

Variable	NAFLD group (n = 5016)	Control group (n = 9399)	t/Z	*p*
BMI (kg/m^2)	25.84 ± 3.01	21.98 ± 2.60	22.67	0.000
SBP (mmHg)	131.67 ± 17.73	119.01 ± 15.85	15.15	*0.000*
DBP (mmHg)	81.00 ± 10.94	72.93 ± 10.28	15.56	*0.000*
ALT (U/L)	24.00 (17.50, 34.75)	17.00 (12.5, 23.00)	−11.84	0.000
AST (U/L)	21.43 (18.00, 25.83)	19.55 (16.33, 23.00)	−4.81	0.000
GGT (U/L)	26.00 (18.00, 41.00)	17.00 (12.00, 23.00)	−8.43	0.000
TC (mmol/L)	5.30 ± 1.09	4.81 ± 0.99	8.03	0.000
TG (mmol/L)	1.63 (1.23, 2.33)	0.88 (0.65, 1.27)	−19.25	0.000
HDL-C (mmol/L)	1.25 ± 0.38	1.44 ± 0.35	−9.21	0.000
LDL-C (mmol/L)	3.47 ± 0.95	3.07 ± 0.91	7.38	0.000
Glu (mmol/L)	5.62 ± 1.50	4.97 ± 0.62	9.72	0.000
UA (μmol/L)	398.69 ± 96.93	347.58 ± 91.95	9.38	0.000
WBC (10^9/L)	7.04 ± 1.68	6.32 ± 1.57	7.60	0.000
PLT (10^9/L)	263.36 ± 62.43	253.27 ± 55.38	2.96	0.003
NEUT (10^9/L)	3.93 ± 1.17	3.43 ± 1.16	7.44	0.000
Lymph (10^9/L)	2.33 ± 0.66	2.23 ± 0.65	2.56	0.011
Mono (10^9/L)	0.52 ± 0.18	0.47 ± 0.18	5.47	0.000
GPR	0.21 (0.14, 0.35)	0.11 (0.08, 0.17)	−9.64	0.000

Abbreviations: BMI: body mass index. SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure. ALT: alanine aminotransferase. AST: aspartate aminotransferase. GGT: γ-glutamyl transferase. TC: total cholesterol. TG: triglycerides. HDL-C: high-density lipoprotein cholesterol. LDL-C: low-density lipoprotein cholesterol. Glu: fasting blood glucose. UA: uric acid. WBC: white blood cell. PLT: platelet. NEUT: neutrophil. Lymph: lymphocyte. Mono: monocyte. GPR: Gamma-glutamyl transpeptidase to platelet ratio.

independent variables. Binary logistic regression analysis was conducted, and the results revealed that the odds ratio (OR) values for BMI (OR = 1.619), SBP (OR = 1.014), DBP (OR = 1.028), GPR (OR = 12.809), and TG (OR = 2.936) were all greater than 1 ($P < 0.05$), indicating a positive association with NAFLD risk. Conversely, the OR value for HDL-C (OR = 0.215) was less than 1 ($P < 0.05$), suggesting a negative association with NAFLD risk (Fig. 2).

3.4. Correlation analysis for exposure factors associated with NAFLD

To further investigate the correlation of various exposure factors in NAFLD, a Spearman correlation analysis was conducted on the variables that exhibited statistical differences as presented in Fig. 2. The results revealed that blood pressure was positively correlated with BMI and GPR ($P < 0.0001$), and negatively correlated with HDL-C ($P < 0.01$). GPR demonstrated positive correlation with SBP, DBP, BMI, and TG ($P < 0.01$), but negative correlation with HDL-C ($P < 0.05$). TG levels were solely found to have a positive correlation with GPR ($P < 0.001$). Furthermore, HDL-C displayed a negative correlation with blood pressure, BMI, and GPR ($P < 0.01$) (Fig. 3).

3.5. Diagnostic value of GPR combined with TG in NAFLD

Based on the findings presented in Figs. 2 and 3, a notable correlation can be observed between GPR and TG, with both variables exhibiting the highest odds ratio in NAFLD. To assess the diagnostic efficacy of GPR and TG in identifying NAFLD, ROC curves were

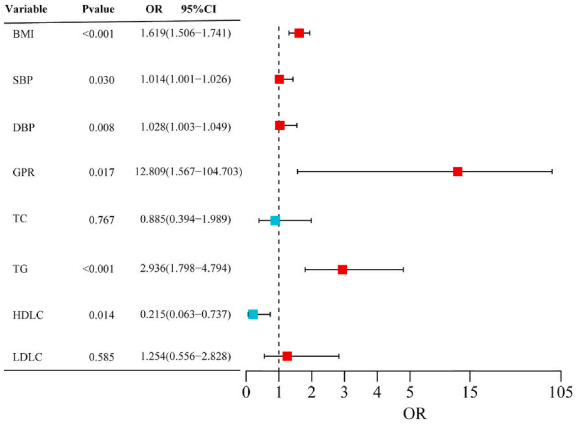

Fig. 2. Multivariate logistic regression analysis for factors associated with NAFLD. The small blue box represents the OR value is less than 1, and the red box represents the OR value is greater than 1. OR, Odds ratio.

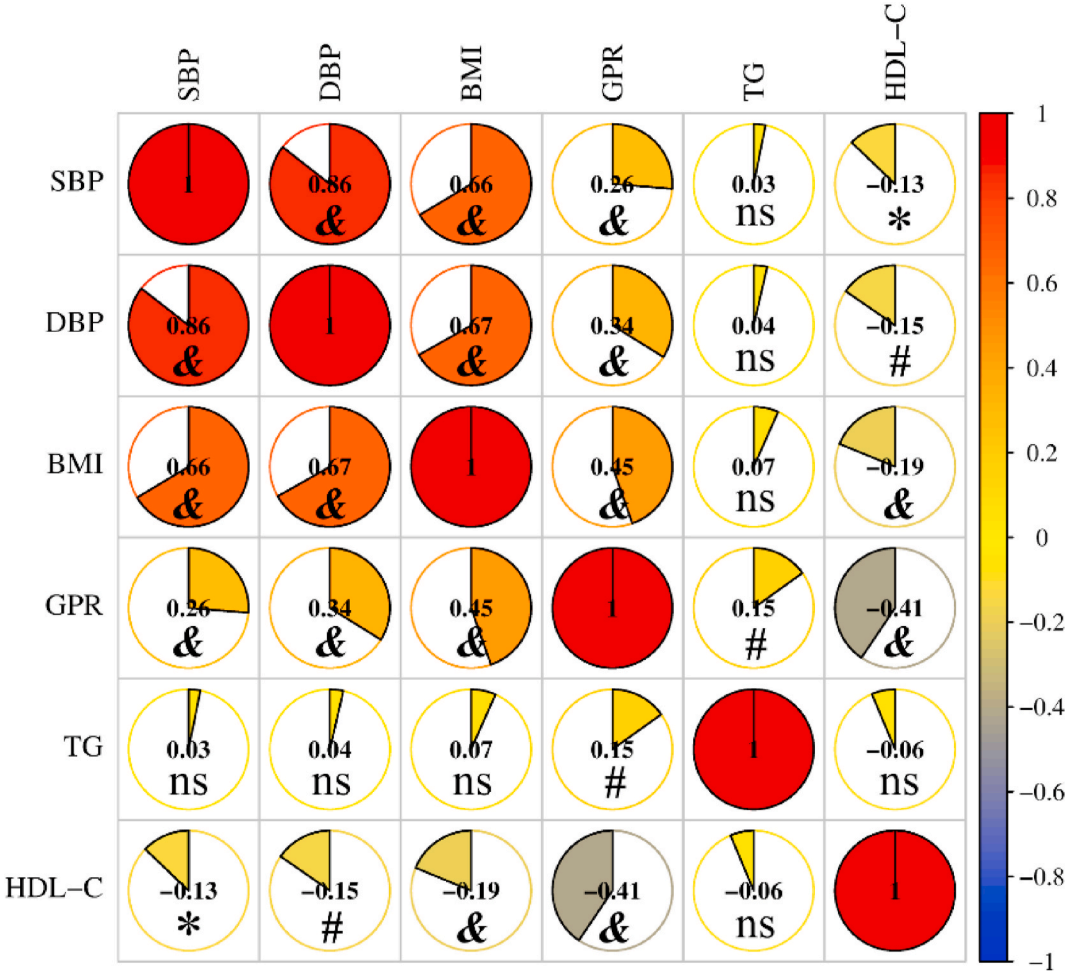

Fig. 3. Spearman correlation analysis of exposure factors in NAFLD. Red represents positive correlation, blue represents negative correlation, and the area of the pie chart represents correlation coefficient. The stronger the correlation, the darker the color, and the larger the area of the pie chart. *P < 0.01, #P < 0.001, & P < 0.0001, ns P > 0.05.

constructed, employing NAFLD as the state variable and GPR and TG as the test variables. The results revealed that the area under the curve (AUC) for GPR was 0.745 (95 % CI: 0.700–0.790), the AUC for TG was 0.811 (95 % CI: 0.770–0.851), and the AUC for the combination of GPR and TG was 0.855 (95 % CI: 0.819–0.891), the cut-off value was 0.5076. The sensitivity and specificity of the two indicators combined for diagnosing NAFLD were 83.45 % and 73.56 % respectively (Fig. 4).

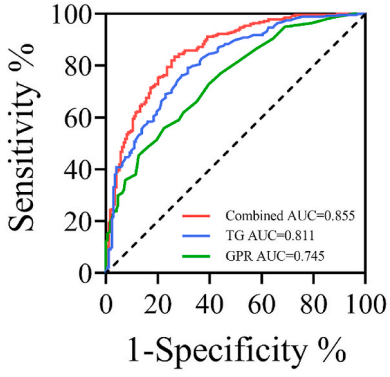

Fig. 4. ROC curves of GPR and TG for predicting NAFLD. ROC, receiver operating characteristic; AUC: Areas under the curve.

4. Discussion

This study conducted a retrospective analysis of various clinical indicators among the individuals undergoing health examinations at the Second Affiliated Hospital of Guangzhou Medical University in the year 2022. The findings revealed that the GPR and TG values in NAFLD individuals were significantly higher than those in the healthy control group, and were risk factors for the increased risk of NAFLD. Moreover, the combination of these two indicators exhibited promising diagnostic efficacy in predicting NAFLD.

Approximately 25 % of the global population was affected by NAFLD, and this prevalence was continuing to increase. NAFLD has emerged as a significant health condition that poses a threat to people's physical health [2]. A previous retrospective study of people who participated in physical examination showed that the prevalence of NAFLD in Guangzhou, China in 2020 was 24.12 % [16]. Our study utilized the most recent physical examination data, and the results showed that the current prevalence of NAFLD in Guangzhou was significantly increased (34.80 %), the incidence rate was found to be twice as high in males compared to females, and the average age of males (46.52 $\pm$ 14.02) was observed to be lower than that of females (52.39 $\pm$ 14.00). This disparity could potentially be attributed to the occurrence of the COVID-19 pandemic in Guangzhou during that period. As a result, a significant portion of the population opted to remain indoors, leading to a decrease in outdoor engagements and alterations in lifestyle patterns. In addition, the difference in prevalence rates between men and women might be related to diet, sedentary behavior and estrogen levels [19]. Our study demonstrated that the BMI, SBP, DBP, ALT, AST, GGT, TC, TG, LDL-C, Glu, UA, WBC, PLT, NEUT, Lymph, and Mono levels in NAFLD patients were significantly higher than those in the healthy control group, while the HDL-C level was lower than that in the healthy group. These results were consistent with previous research studies on the subject [16,20]. Additional multivariate logistic regression analysis was conducted, and the results showed that BMI, SBP, DBP, and TG were all risk factors for NAFLD, while HDL-C was identified as a protective factor. It is evident from this information that the management of body weight, the reduction of blood pressure, and the lowering of blood lipid levels play a critical role in mitigating the prevalence of NAFLD.

The structure of liver tissue is intricate, and the development of NAFLD is a continuous and chronic pathological process. In the early stages of the disease, the morphological changes are not apparent, thereby resulting in inconspicuous imaging manifestations. Liver biopsy is considered the definitive method for diagnosing NAFLD, but cannot be widely applied in clinical practice [16,21]. Hence, it is imperative to seek a straightforward and cost-effective non-invasive assessment, and blood testing is widely used due to its simplicity, safety, convenience, and affordability. Dyslipidemia is common metabolic features of NAFLD, among which the changes in TG have been proven to be the significant factors in the development and regression of NAFLD [22]. The accumulation of triglycerides within the liver can result in hepatocellular injury, which in turn can exacerbate NAFLD by further elevating triglyceride levels [23]. Kim et al. [24] confirmed that baseline serum TG levels have an advantage in predicting the course of NAFLD compared to hyperglycemia and hypertension. A Mendelian randomization study showed that the accumulation of triglycerides plays an important role in the development of NASH [25]. Our study showed that TG levels were significantly higher than that of healthy controls and were an independent risk factor for NAFLD.

GPR, as a novel biomarker, was initially used to predict fibrosis in patients with chronic hepatitis B [13]. A recent multicenter retrospective study has shown that GPR can predict advanced fibrosis, cirrhosis, and evaluate inflammatory activity in patients with chronic hepatitis B [26]. GPR consists of two simple serological markers, γ-glutamyl transferase (GGT) and platelet count. GGT is a microsomal enzyme widely distributed in human tissues [27], mainly derived from hepatocytes and cholangiocytes, and used for the diagnosis of hepatobiliary diseases [28]. Numerous liver and gallbladder disorders, such as viral hepatitis, NAFLD, and alcoholic liver disease, have the potential to induce liver cell injury, resulting in elevated levels of GGT [29,30]. Platelets, which are tangible components of blood, can be affected by liver injury or active hepatitis, leading to a decrease in platelet count [31]. Platelet count has been shown to be associated with the severity of liver disease [32,33]. The research by Wei Cao et al. [34] shows that the platelet levels of NASH patients are higher than those of non-NASH patients. Our study also indicates that the platelet levels of NAFLD patients are higher. Hence, the utilization of GPR holds significant clinical implications in the prediction of liver inflammation and fibrosis. Calvopina et al. [15] conducted a liver biopsy study involving 54 children diagnosed with cystic fibrosis related liver disease. The findings of the study demonstrated that GPR exhibited favorable diagnostic efficacy in evaluating the severity of liver fibrosis in pediatric patients with cystic fibrosis. Research by Xiang-An Zhao et al. [26] demonstrated that GPR could serve as an accurate predictive indicator for liver inflammation and fibrosis in patients with chronic hepatitis B. Our study demonstrates that GPR levels were significantly elevated in NAFLD patients compared to healthy controls, suggesting that high levels of GPR was an independent risk factor for NAFLD. Spearman analysis revealed a positive correlation between GPR and BP, BMI, and TG, while a negative correlation was observed with HDL-C.

The role of GPR and triglycerides in NAFLD remains unclear. Further ROC curve analysis in this study found that the area under the curve for GPR in diagnosing NAFLD was 0.745, while that for TG was 0.811, and GPR combined with TG had the largest AUC value (0.855), and its sensitivity (83.45 %) and specificity (73.56 %) were both higher high. This suggests that GPR combined with TG has good clinical efficacy in the diagnosis and prediction of NAFLD.

In addition, it is important to acknowledge the limitations of this study. Firstly, our study is a single-center retrospective observational study, which may introduce selection bias. Secondly, all participants in our study were sourced from a healthy physical examination center, which means that we were unable to differentiate the severity of NAFLD and obtain data from liver biopsy or FibroScan. However, we recognized that additional factors, such as dietary habits, physical activity, and genetic predispositions, could also influence the outcomes. Future studies should incorporate these variables to further elucidate their impact on the diagnosis and progression of NAFLD. Moving forward, it is imperative that we conduct a large sample cohort study to further investigate the predictive role of GPR and TG in the development of inflammation and fibrosis in different age groups of individuals with NAFLD. This will provide more robust clinical evidence for the prevention of NAFLD. Overall, our study showed that both GPR and TG were independent

risk factors for NAFLD and had the potential to serve as reliable clinical indicators for predicting NAFLD.

Ethics approval

This study was reviewed and approved by Clinical Research and Application institutional Review Board of The Second Affiliated Hospital of Guangzhou Medical University with the approval number: 2023-hg-ks-18.

Consent to participate

All participants were informed that consent to participate in the study and publish their data would be assumed on completion and submission of the study questionnaire/survey.

Consent for publication

Written consent for publication was got from all participated patients.

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Data availability statement

The raw data supporting the conclusions of this article are made available on supplementary file.

CRediT authorship contribution statement

Haohong Zhan: Writing – review & editing, Writing – original draft, Methodology, Investigation. **Xiaoli Nong:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Senzhi Zhu:** Writing – original draft, Supervision. **Ting Luo:** Visualization, Software, Formal analysis, Data curation. **Tian Li:** Writing – original draft, Validation. **Mingjing Cao:** Formal analysis, Data curation. **Qi Li:** Validation, Formal analysis. **Zhuosen He:** Validation, Formal analysis. **Junyan Hu:** Writing – review & editing, Supervision, Resources. **Xi Liu:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e36193.

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