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Predictive value of triglyceride glucose index in non-obese non-alcoholic fatty liver disease

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ABSTRACT

Objectives A large number of patients with non-obese non-alcoholic fatty liver disease (NAFLD) in China remain undiagnosed and untreated due to insufficient awareness and ineffective pharmacotherapy. Therefore, a convenient, predictive marker and diagnostic tools are imperative. This study aimed to investigate the ability of the triglyceride glucose index (TyG) in predicting non-obese NAFLD.

Design An observational cross-sectional study.

Setting Department of Health Management, large urban academic medical centre and DRYAD database data.

Participants This study included 456 patients with non-obese NAFLD and matched 456 non-fatty liver controls according to age, sex and body mass index (BMI).

Primary and secondary outcome measures The receiver operating characteristic (ROC) curve was used to evaluate the predictive role of the TyG index in non-obese NAFLD. Based on the TyG index, a clinical prediction model for non-obese NAFLD was constructed, then the prediction model was verified by the DRYAD database (n=11 562).

Results TyG in non-obese NAFLD was higher than that in controls (9.00 (8.66–9.40) vs 8.46 (8.10–8.83), p<0.001). Logistic regression analysis showed that TyG was an independent risk factor for non-obese NAFLD (OR=9.03, 95% CI: 5.46 to 14.94, p<0.001). ROC analysis showed that the area under the curve (AUC) was 0.78, the sensitivity was 82.5%, the specificity was 60.5%. Based on the TyG index, sex, age and BMI, the AUC of the predictive model for non-obese NAFLD was 0.78 (95% CI: 0.75 to 0.81, p<0.001). Using the DRYAD database to verify the prediction model, the AUC of the verification group was 0.85 (95% CI: 0.84 to 0.86, p<0.001).

Conclusions The high level of the TyG may be an independent risk factor for non-obese NAFLD. The prediction model for non-obese NAFLD based on the TyG index has good clinical prediction value.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ By enrolling participants from a diverse background, the study enhances the generalisability of the findings to a broader population.
⇒ The Chinese population was verified with other group data to enhance the credibility.
⇒ The cross-sectional design used in this study does not confirm a causal relationship.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) affects approximately 25% of adults worldwide[1–3] and is gradually becoming the leading cause of liver disease. NAFLD is prone to develop into non-alcoholic steatohepatitis, cirrhosis and hepatocellular carcinoma due to long-term disorders of liver lipid metabolism and inflammatory stimulation.[4 5] Previous studies have shown that NAFLD is more common in the obese population.[6–8] In practice, there is also about 40% of NAFLD in non-obese people (normal or below normal weight and waist circumference)[9] which is classified as non-obese NAFLD. This non-obese NAFLD is more common in Asian people.[10 11] The study also revealed that non-obese NAFLD, similar to its obese counterpart, carries a substantial risk for both atherosclerotic cardiovascular disease and liver fibrosis.[12–14] However, non-obese NAFLD is more likely to be ignored because it lacks the dominant characteristics of obesity. Therefore, early identification of non-obese NAFLD through simple and effective diagnostic tools in daily practice is clinically beneficial.

Patients with non-obese NAFLD can have different risk factors, such as genetic predispositions, environmental factors or distinct metabolic pathways that contribute to liver disease progression. Non-obese NAFLD significantly affects the patient's metabolism,[15] while metabolic impairment has been reported to be more severe in non-obese NAFLD than in obese NAFLD.[16] However, NAFLD is closely related to insulin resistance (IR). NAFLD accumulates a large amount of fat in the liver and produces excess glucose and triglycerides (TG), leading to metabolic disorders.[17 18] Likewise, IR is involved in the critical aspects of NAFLD pathogenesis,[6 19] and the two reinforce each other. Triglyceride glucose index (TyG) is considered a good

marker of IR,[20] which has been widely accepted and used in clinical practice due to its easy access and simple calculation. Obese NAFLD is correlated with high levels of TyG,[21] while TyG has some predictive ability of obese NAFLD.[22 23] It has also been suggested that non-obese NAFLD may have a stronger correlation with IR, non-obese NAFLD should be more concerned[16 24]; however, clinical evidence of TyG and non-obese NAFLD is limited, so this study aimed to investigate the relationship and predictive value of TyG with non-obese NAFLD.

SUBJECTS AND METHODS

Subjects

The individuals include 456 patients with non-obese NAFLD and 456 non-fatty liver disease controls matched propensity-wise according to age, sex and body mass index (BMI) from June 2022 to December 2022 in the Department of Health Management of Daping Hospital. The NAGALA data from the DRYAD database (https://doi.org/10.5061/dryad.8q0p192)[25] was also used to validate the prediction model.

Patient and public involvement

In our research, patients and the public were not directly involved in the study.

Inclusion criteria

1. 18 years≤ age <85 years.
2. According to the Redefinition and Disposition of Obesity in the Asia-Pacific Region, 18 kg/m^2 <BMI < 23.9 kg/m^2.
3. Diagnosis of the non-obese non-alcoholic fatty liver based on: according to the guidelines proposed by the Asia-Pacific Working Group, patients who had fatty liver and did not drink excessive alcohol[26] (men>140 g/week, women>70 g/week),[24] did not have a history of hepatitis virus carriage, no use of hepatotoxic drugs and relevant diagnostic criteria in the Guidelines for the Prevention and Treatment of Non-alcoholic Fatty Liver Disease (2018 Update) were diagnosed as NAFLD. Fatty liver was assessed by ultrasound scan for the presence of hepatic steatosis.
4. Physical examination, laboratory tests and other appropriate indicators were completed in our physical examination centre.

Exclusion criteria

1. Previous alcoholic fatty liver, viral fatty liver, autoimmune liver disease, other chronic liver diseases.
2. Previous history of liver virus carriage, use of fatty or hepatotoxic drugs, taking diabetes or dyslipidemic drugs, etc.
3. Previous diagnosis of malignant tumours, severe heart, liver, kidney and other vital organ diseases and various acute and chronic inflammatory diseases.
4. Other systemic conditions, such as hypothyroidism, vitamin B12 or folic acid deficiency, niacin deficiency, severe anaemia, hyponatraemia, hypocalcaemia, neurosyphilis, HIV infection, alcohol and drug abuse, etc.
5. Age, sex, blood pressure (BP), BMI, fasting glucose (FPG), TG, alanine transaminase (ALT) or missing liver ultrasound data.

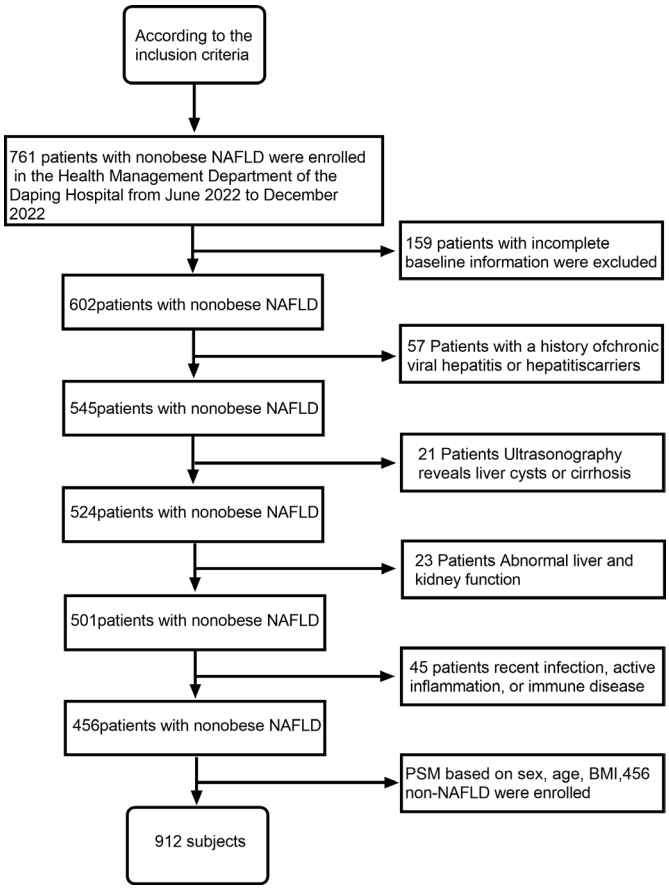

Figure 1 Flow chart of study selection for the non-obese NAFLD group. BMI, body mass index; NAFLD, non-alcoholic fatty liver disease; PSM, propensity score matching

Health check-ups and laboratory measurement

All subjects' gender, age, BMI and current and past medical history (diabetes) were collected at the time of physical examination, and 5 mL of fasting venous blood was organised early in the morning on the day of physical examination to test FPG, total cholesterol (TC), TG, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, liver function and other biochemical parameters (figure 1). The TyG=Ln (fasting triacylglycerol (mg/dL) × FPG (mg/dL)/2).[27]

Statistical analysis

All statistical analyses were performed using SPSS V.26.0. Normally distributed measures were expressed as mean±SD (x±s), non-normally distributed variables were expressed as M (P25~P75), and categorical data were expressed as (cases (%)); t-test was used to compare independent samples between two groups for normal and Mann-Whitney U test was used to compare non-normal measures; χ^2 test was used to compare between groups

Table 1 Study population characteristics

Basic information	CN (n=456)	n-NAFLD (n=456)	X² or Z	P value
Age (years)	48.00 (37.25–54.00)	47.00 (38.00–55.00)	0.02	0.985
Female (%)	124 (27.19)	100 (21.92)	3.41	0.065
BMI (kg/m2)	22.98 (22.38–23.49)	23.07 (22.30–23.51)	0.08	0.936
Diabetes mellitus (%)	8 (1.75)	20 (4.39)	5.31	0.021
TC (mmol/L)	5.07 (4.51–5.69)	5.40 (4.70–6.06)	4.60	<0.001
TG (mmol/L)	1.19 (0.85–1.74)	1.93 (1.43–2.63)	13.51	<0.001
HDL-C (mmol/L)	1.38 (1.23–1.60)	1.27 (1.12–1.44)	6.93	<0.001
LDL-C (mmol/L)	3.07 (2.67–3.53)	3.29 (2.85–3.82)	4.66	<0.001
ALT (IU/L)	16.8 (12.80–21.98)	24.9 (17.9–35.38)	10.90	<0.001
AST/ALT	1.32 (1.08–1.65)	0.99 (0.76–1.27)	11.45	<0.001
AST (IU/L)	22.4 (19.13–25.90)	24.55 (20.5–28.88)	5.45	<0.001
FPG (mmol/L)	4.73 (4.44–5.07)	4.91 (4.59–5.52)	5.79	<0.001
SBP (mm Hg)	118 (110–131)	124 (115–137)	5.28	<0.001
DBP (mm Hg)	73.5 (66.00–79.00)	77 (71.00–85.00)	6.60	<0.001
URIC (μmol/L)	353.30 (297.35–411.28)	382.50 (323.40–442.65)	4.92	<0.001

Note: The n-NAFLD group includes first-diagnosed, untreated diabetics.
ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CN, Control groups; DBP, diastolic blood pressure; FPG, fasting glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; n-NAFLD, non-obese non-alcoholic fatty liver disease; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; URIC, uric acid.

for categorical data. The binary logistic regression was used to analyse the risk factors associated with non-obese NAFLD; the TyG was plotted to evaluate the receiver operating characteristic (ROC) curve of subjects with NAFLD and the area under the ROC curve was calculated to find the optimal critical value. The prediction model was constructed by incorporating gender, age, BMI and TyG, and the clinical utility value of the prediction model was tested. All hypothesis tests were two-sided and statistically significant at p<0.05. Statistical analyses were conducted using the SPSS statistical package V.26 (IBM SPSS Statistics for Windows, Armonk, New York, USA) and R software V.4.3.0 (R Foundation for Statistical Computing).

RESULTS

Basic clinical and laboratory characteristics

A total of 912 subjects were enrolled in this study. There were no significant differences in age, BMI and gender between the non-obese NAFLD and control groups. The prevalence of diabetes, FPG, TG, TyG, uric acid, alanine Transaminase (ALT), aspartate transaminase (AST), systolic BP (SBP) and diastolic BP (DBP) levels in the NAFLD group was higher than in the non-NAFLD group. In contrast, the HDL-C level was lower than that in the non-NAFLD group, and the differences were statistically significant (table 1; online supplemental file 1).

TyG was an independent risk factor for non-obese NAFLD

To clarify whether TyG was a risk factor for non-obese NAFLD, three logistic regression models were constructed with whether NAFLD occurred as the dependent variable, according to different correction confounders. The confounders of model 1 included adjusting for sex, age and BMI. Model 2 using stepwise logistic regression included sex, BMI, URIC, TG, ALT, AST/ALT and SBP. Model 3 using lasso regression with a penalty coefficient λ with minimal partial likelihood error, log(λ) = 0.001924542, (figure 2A,B). 13 independent variables sex, age, BMI, URIC, FPG, ALT, AST, AST/ALT, HDL-C, TC, TG, SBP and DBP were selected. TyG was an independent risk factor for non-obese NAFLD in the three models, and the difference was statistically significant (p<0.05). Non-obese NAFLD had a higher TyG than control subjects (9.00 (8.66–9.40) vs 8.46 (8.10–8.83), p<0.001) (figure 2C). The logistic regression analysis of TyG quartiles also revealed a significant increase in the risk of non-obese fatty liver disease with increasing TyG levels (table 2). The prevalence rate of non-obese NAFLD in quartiles corresponding to the control group was higher as the level of TyG increased in patients with non-obese fatty liver compared with controls, with a prevalence rate of 16.74% in quartile 1 and 79.48% in TyG quartile 4 (figure 2D).

TyG subgroup analysis

To further clarify the effect of the TyG on non-obese NAFLD, we analysed its risk by binary logistic regression differentiating by gender and age. We found that after correcting for BMI, URIC, ALT, AST/ALT and DBP, high TyG had a higher risk of developing non-obese NAFLD in different gender and age groups, and the risk was more significant in young-aged subjects (figure 3A,B). The area

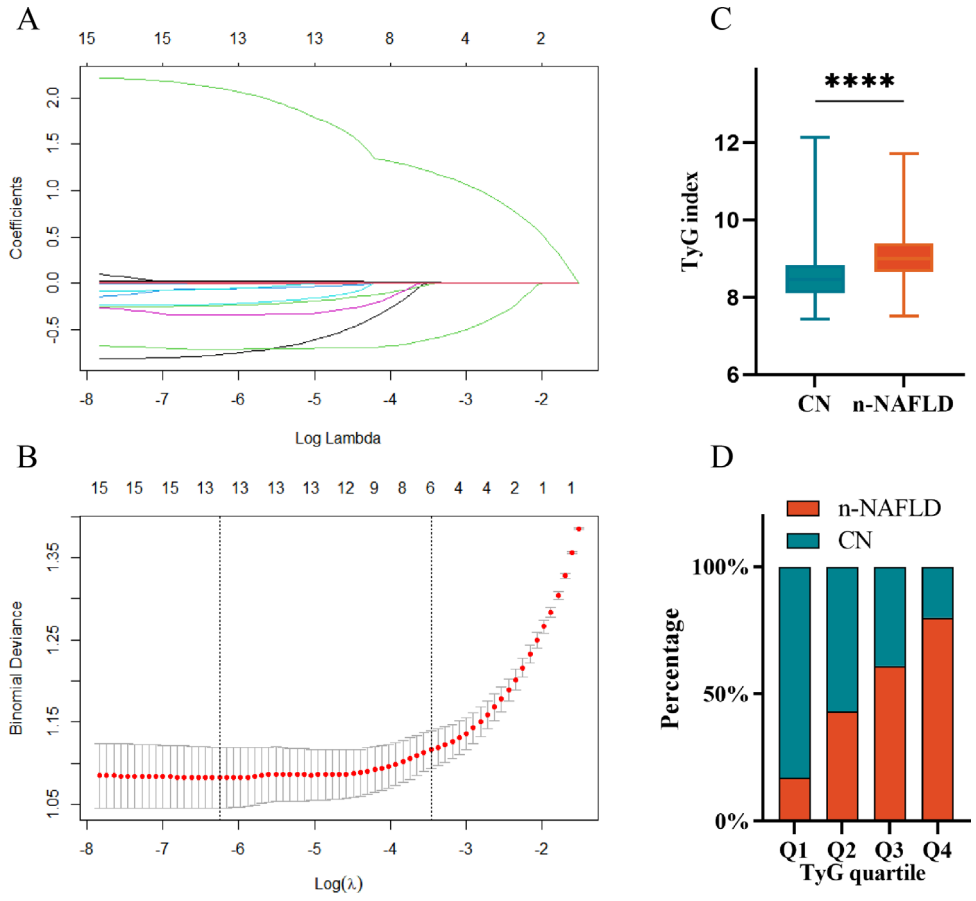

Figure 2 Lasso regression analysis identifying key predictors and comparison of TyG index quartiles and prevalence rates between non-obese NAFLD and control groups. (A) Lasso regression coefficient curves; (B) Lasso regression cross-validation curves to screen for best predictors; (C) Comparison of TyG index between non-obese NAFLD and control groups; (D) TyG index quartiles of the number of people with prevalence rates in non-obese NAFLD and control groups. n-NAFLD, non-obese non-alcoholic fatty liver disease; CN, control groups; TyG, triglyceride glucose index.

under the curve (AUC) of TyG ROC curve analysis was 0.77 and 0.78 in men and women, respectively, and there was no statistical significance between them. Those results indicated that TyG could predict non-obese NAFLD in different genders (figure 3C). The AUC was 0.80, 0.76 and 0.75 in young, middle-aged and older adults, respectively, indicating that TyG had predictive ability for non-obese NAFLD in different age groups (figure 3D).

Table 2 Logistic regression analyses for the association between TyG and risk of non-obese NAFLD in different models

	ORs (95% CI)			
	Crude model	**Model 1**	**Model 2**	**Model 3**
TyG index	5.96 (4.45, 8.00)	6.48 (4.78, 8.80)	6.18 (4.46, 8.58)	9.03 (5.46,14.94)
TyG (Quartile)				
Quartile 1	Ref	Ref	Ref	Ref
Quartile 2	3.395 (2.38, 4.84)	3.51 (2.44, 5.03)	3.11 (2.15, 4.49)	2.71 (1.81, 4.07)
Quartile 3	5.75 (3.87, 8.51)	6.02 (4.03, 8.98)	5.19 (3.45, 7.82)	4.13 (2.58, 6.61)
Quartile 4	14.95 (8.88, 25.18)	16.1 (9.50, 27.37)	15.08 (8.25, 27.55)	14.39 (6.13, 33.77)
P-trend	<0.001	<0.001	<0.001	<0.001

Model 1 adjusted for sex, age, BMI.
Model 2 adjusted for sex, age, BMI, diabetes, URIC, FPG.
Model 3 adjusted for sex, age, BMI, diabetes, URIC, FPG, ALT, AST, HDL-C, TC, TG, LDL-C, SBP and DBP.
ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NAFLD, non-alcoholic fatty liver disease; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; TyG index, triglyceride glucose index; URIC, uric acid.

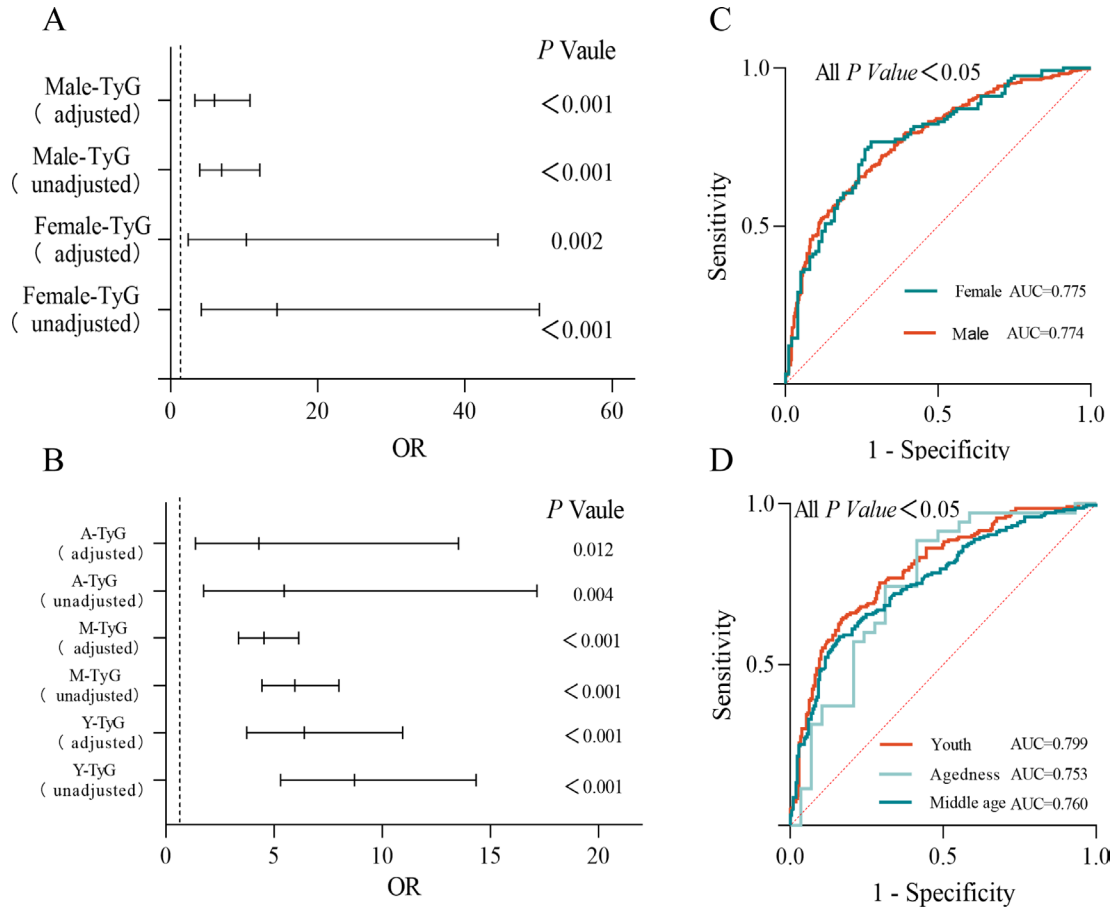

Figure 3 Logistic regression and ROC curve analysis of TyG index across gender and age groups. (A) Logistic regression analysis of TyG index by gender; (B) logistic regression analysis of TyG index by youth, middle age and old age; (C) ROC curves of TyG index by gender; (D) ROC curves of TyG index by youth, middle age and old age. A, agedness; M, middle age; Y, youth. Age classification of subgroups: young adults: ages 18–39 years. Middle-aged adults: ages 40–64 years. Older adults: ages 65 years and above. AUC, area under the curve; ROC, receiver operating characteristic; TyG, triglyceride glucose index.

Efficacy of TyG in predicting patients with non-obese NAFLD

TyG ROC curve analysis showed that the AUC was 0.775, the sensitivity was 82.5%, the specificity was 60.5% and the Youden index was 0.43 (p<0.05). This further indicated that the TyG index could predict non-obese NAFLD (figure 4A). For clinical application, we try to construct a prediction model nomogram. We found there was no statistical difference in the AUC of the

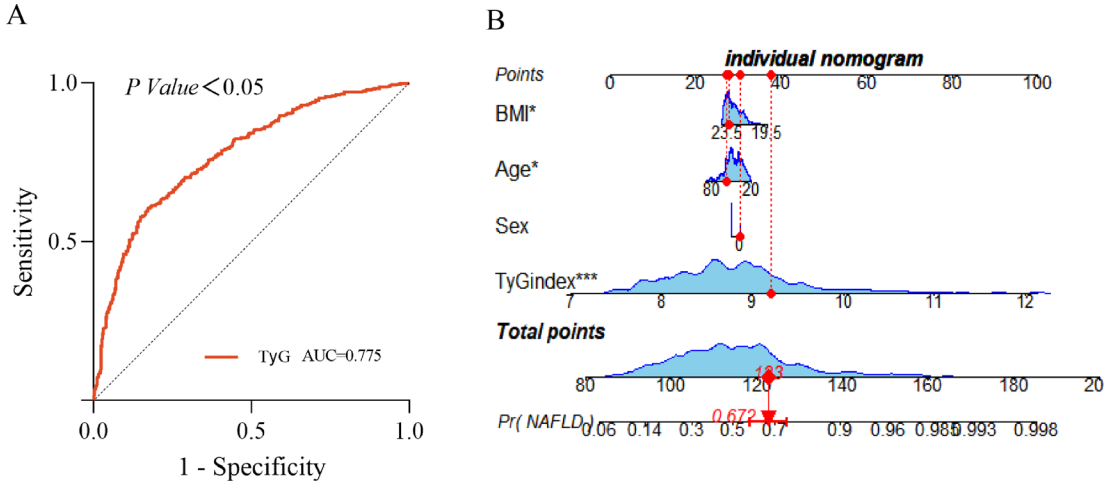

Figure 4 TyG index ROC curve and prediction model nomogram. (A) TyG ROC curve. (B) Prediction model nomogram. AUC, area under the curve; BMI, body mass index; NAFLD, non-alcoholic fatty liver disease; ROC, receiver operating characteristic; TyG, triglyceride glucose index.

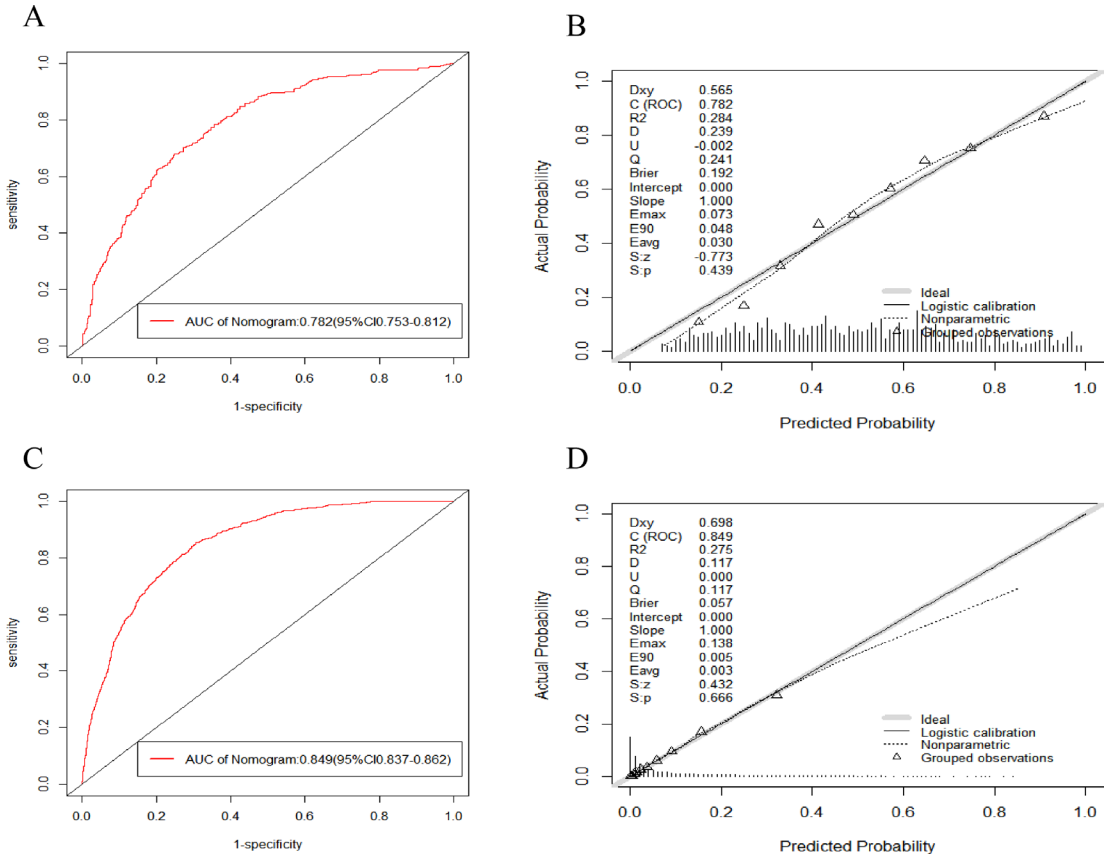

Figure 5 ROC curves and correction curves of the nomogram prediction model for both the overall and validation groups. (A) ROC curve of nomogram prediction model; (B) ROC curve of a nomogram prediction model in the validation group; (C) correction curve of nomogram prediction model; (D) correction curve of a nomogram prediction model in the validation group. AUC, area under the curve; ROC, receiver operating characteristic.

three models, but Model 1 was simpler and more convenient in clinical practice, so we constructed the prediction model based on Model 1 and its column diagram was shown in figure 4B. The AUC of the nomogram was 0.78 in the modelling group and 0.85 in the validation group (figure 5A,C). The Brier scores were 0.19 in the modelling group and 0.06 in the validation group. The calibration curves were drawn (figure 5B,D). The Hosmer-Lemeshow goodness of fit test in the modelling group and the validation group indicated the predicted probability was in good agreement with the actual possibility ($p>0.05$). To evaluate the clinical utility of the prediction model, a clinical Decision Curve Analysis was drawn with a threshold between 5% and 70% and a net benefit rate above the two lines within the threshold probability range (figure 6A,B). The probability of benefit from the model in patients with non-obese NAFLD was greater than the two extreme cases which were positive net benefit. The Clinical Impact Curve was consistent with the actual patients when the threshold probability was more significant than 0.8 (figure 6C,D). More patients were predicted within the threshold probability range than actual patients, suggesting that the prediction model had high clinical practicability.

DISCUSSION

In recent years, some studies have found that the TyG can better identify IR which may be related to the TyG taking into account both blood glucose and lipid. The TyG can more comprehensively reflect the body's metabolic state.[22 28 29] It is consistent with the results of our study (online supplemental figure 1). We found that the TyG may be more valuable in the diagnosis of non-obese NAFLD than previous obese NAFLD,[24] which may be due to our strict matching of controls or due to differences in metabolic levels among subjects in different regions. Due to our propensity matching (number of caliper for propensity score matching is 0.02) for the age, sex and BMI level of the issues for reducing data bias and confounding variables, we found a significant difference in TyG levels between the control group and the non-obese non-alcoholic fatty liver group. It is more clinically relevant than previous studies, as participants in those studies were not completely non-obese.[30 31] The present study assessed the independent effect of TyG on the risk of non-obese NAFLD and explored the predictive value of TyG for non-obese NAFLD.

In this cross-sectional study, when TyG was divided into quartiles, the highest quartile of TyG showed a more

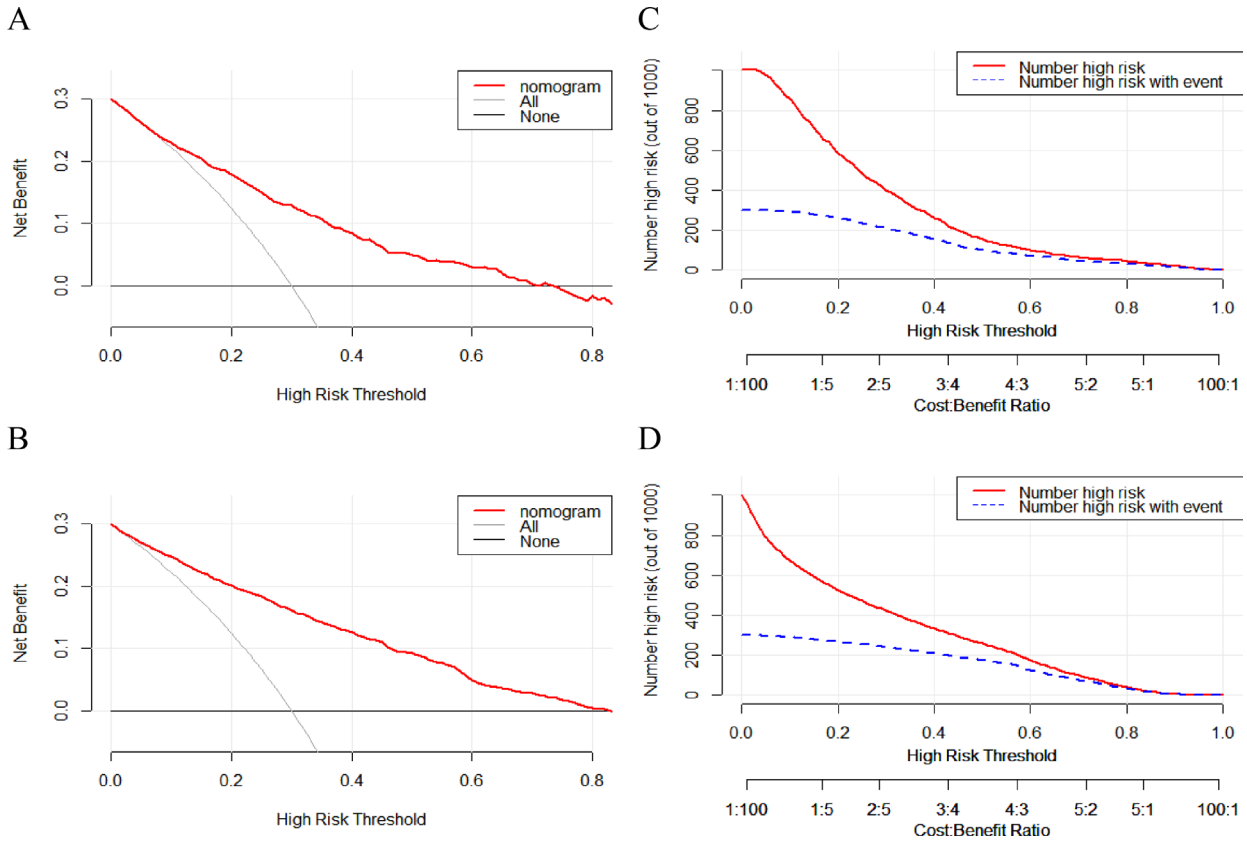

Figure 6 Clinical decision and impact curves of the prediction model for overall and validation groups. (A) Clinical Decision Curve Analysis of the prediction model; (B) clinical Decision Curve Analysis of the prediction model in the validation group; (C) clinical impact curve of the prediction model; (D) Clinical impact curve of the prediction model in the validation group.

significant OR compared with other quartiles, and it was also found that the prevalence rate of non-obese NAFLD in the highest quartile reached 79.48%. Logistic regression analysis showed that the risk of non-obese fatty liver significantly increased with the increase of TyG level, and the risk of the fourth quartile was about 20 times higher than that of the first quartile, which indicated that high TyG was an independent risk factor for non-obese NAFLD. Subgroup analysis showed that young women had a higher risk of TyG-associated non-obese NAFLD, which was different from the previous conclusion[31] that the risk of TyG-associated NAFLD was higher in middle-aged people. In general, the subcutaneous fat and visceral fat content in women was higher than that in men,[29] consistent with the finding that high TyG in women was associated with a higher risk of non-obese NAFLD. We advocate that non-obese individuals with higher TyG need more aerobic exercise and dietary interventions because they can increase muscle glucose transport activity, insulin can stimulate muscle glycogen synthesis, reduce de novo lipogenesis and IR in the liver, and thus reduce the risk of NAFLD.[32]

The validation of the nomogram prediction model with DRYAD data (online supplemental file 2) showed that this model has good clinical utility. The nomogram of the prediction model showed that lower BMI was associated with higher risk, which was inconsistent with the previous study.[33] This is mainly due to the population difference between our two study groups and may also be due to genetic and environmental factors.[34] Consistent with our subgroup analysis and the study,[13] younger age may have increased the disease risk, due to lack of exercise,[35] increased fat intake, IR and postprandial lipid metabolism dysfunction[36] and genetic susceptibility. [37 38]Clinical significance of the prediction model: The non-obese NAFLD disease model can be used to personalise the risk stratification of non-obese subjects. The high-risk individuals can receive targeted lifestyle interventions to reduce the risk. Unlike the current strategy of performing B-ultrasound examination in all topics,[1] this prediction model has the advantages of low cost, good overall performance and ease of implementation. Moreover, the subject can be avoided from monitoring B-ultrasound multiple times, thereby reducing the burden and cost.

The study has the following limitations: IR may be a key factor leading to non-obese NAFLD with high TyG,[16] but IR could not be excluded in this study, which may cause particular bias in the results. The prevalence of non-obese NAFLD varies by region and race, which may not apply to people from other areas. This study, a cross-sectional design, is unable to confirm the causal relationship between non-obese NAFLD and TyG. The diagnosis of NAFLD in this study was based on abdominal ultrasound, but the gold standard for diagnosing NAFLD was liver

biopsy,[39] and the sensitivity of ultrasound was limited.[40] This study is suitable for the risk assessment of non-obese NAFLD in the general population, but it cannot further distinguish non-alcoholic steatohepatitis.

In conclusion, the risk of NAFLD increased with the increase in TyG level in non-obese subjects, especially in young women. TyG is not only an independent risk factor for patients with non-obese NAFLD but also has a good ability to predict non-obese NAFLD. This study provides a simple, inexpensive and convenient biomarker and prediction model for NAFLD in the non-obese physical examination population.

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Contributors JD and LQF designed the study. XPZ and FS executed the study and collected clinical information. FS and XG conducted the statistical analysis. XPZ and FS are co-first authors. HL and YJS prepared the figure. XPZ and ZYL drafted the manuscript. JD and LQF revised the manuscript. All authors contributed to the article and approved the submitted version. XPZ are responsible for the overall content as the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Ethics Committee of the Army Medical Center of PLA, Daping Hospital and the waiver of the requirement for informed consent was approved by the Ethics Committee (Ethics Approval Number: 2023-82).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The authors are open to sharing statistical codes and study data. Relevant data have been deposited in Dryad with the following DOI: https://doi.org/10.5061/dryad.8q0p19.

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