

RESEARCH

Open Access



The triglyceride glucose-body mass index: a non-invasive index that identifies non-alcoholic fatty liver disease in the general Japanese population

Haofei Hu^{1,2,5†}, Yong Han^{3,4,5†}, Changchun Cao^{6*} and Yongcheng He^{7*} 

Abstract

Background: By identifying individuals at high risk for non-alcoholic fatty liver disease (NAFLD), interventional programs could be targeted more effectively. Some studies have demonstrated that triglyceride glucose-body mass index (TyG-BMI) showed an independent positive association with NAFLD. However, research on its diagnostic value in patients with suspected NAFLD is limited. In this study, we aimed to evaluate whether TyG-BMI was accurate in detecting NAFLD in the general Japanese population.

Methods: A cross-sectional study of 14,280 individuals who underwent a comprehensive health examination was conducted. Standard protocols were followed to collect anthropometric measurements, lab data, and ultrasonography features. All participants were randomly stratified into the development group (n = 7118) and validation group (n = 7162). The TyG-BMI was calculated. Following this, the diagnostic value of the TyG-BMI was evaluated based on the area under the receiver-operating characteristic curve (AUROC). Two cutoff points were selected and used to rule out or rule in the NAFLD, and the specificity, sensitivity, negative predictive value, and positive predictive value were explored, respectively. In order to verify the stability of the results, external verification was performed.

Results: There were 1272 and 1243 NAFLD participants in the development and validation groups, respectively. The area under the ROC curve (AUC) of TyG-BMI was 0.888 (95% CI 0.876–0.896) and 0.884 (95% CI 0.875–0.894) for the training and validation group, respectively. Using the low TyG-BMI (182.2) cutoff, NAFLD could be excluded with high accuracy (negative predictive value: 96.9% in estimation and 96.9% in validation). The presence of NAFLD could effectively be determined by applying the high cutoff of TyG-BMI (224.0), as the positive predictive value of the estimation and validation groups is 70.7% and 70.1%, respectively. As a result of applying this model, 9996 (70%) of the 14,280 participants would not have undergone ultrasonography, with an accurate prediction of 9308 (93.1%). AUC was 0.874

[†]Haofei Hu and Yong Han have contributed equally to this work

*Correspondence: caochangchun1015@163.com;
heyongcheng640815@126.com

⁶ Department of Rehabilitation, Shenzhen Dapeng New District Nan'ao People's Hospital, No. 6, Renmin Road, Dapeng New District, Shenzhen 518000, Guangdong, China

⁷ Department of Nephrology, Shenzhen Hengsheng Hospital, No. 20 Yintian Road, Baoan District, Shenzhen 518000, Guangdong, China
Full list of author information is available at the end of the article



for external validation using 183,730 Chinese non-obese participants. TyG-BMI was demonstrated to be an excellent diagnostic tool by both internal and external validation.

Conclusions: In conclusion, the present study developed and validated a simple, non-invasive, and cost-effective tool to accurately separate participants with and without NAFLD in the Japanese population, rendering ultrasonography for identifying NAFLD unnecessary in a substantial proportion of people.

Keywords: Non-alcoholic fatty liver disease, Triglyceride glucose-body mass index, Negative predictive value, Receiver operating characteristic, Positive predictive value

Introduction

A non-alcoholic fatty liver disease (NAFLD) is marked by hepatic steatosis without evidence of excessive alcohol use or other obvious factors that damage the liver [1]. In the 21st century, NAFLD remains an essential public health issue [2]. Globally, an estimated 20% of the general population is suffering from NAFLD, with a range from 6 to 35% based on multiple measurements [3]. There is a continuum of NAFLD, from simple steatosis to non-alcoholic steatohepatitis (NASH), with varying degrees of fibrosis that eventually progress to cirrhosis [4, 5]. NASH may cause cirrhosis and hepatocellular carcinoma, while simple steatosis presents as a benign condition with slow progression over many years [3, 6, 7]. The extrahepatic form of NAFLD is characterized by its ability to aggravate the cardiovascular disease, kidney disease, and diabetes, resulting in adverse health effects [8–10]. Even though the prevalence of NAFLD is increasing and its adverse effects are seen throughout multiple systems in the body, there are no effective treatments except for lifestyle changes along with regular physical activity [11]. It is therefore extremely important to identify patients whose risk of NAFLD is high at an early stage.

As far as diagnosis of NAFLD is concerned, liver biopsy has always been the gold standard [12]. However, due to its invasiveness and high cost, it could not become a widely accepted diagnosis. It is also unreasonable to perform routine liver biopsies as a screening or risk assessment test for the general population. In addition, a liver biopsy analysis with poor inter-observer variability and modest intra-observer variability has suboptimal reliability for measuring a treatment effect in clinical trials [13]. Clinical practitioners use liver ultrasound as a valuable tool in their practice for detecting fatty liver in the early stages. Ultrasonography (US), nevertheless, depends on the operator's experience and technological sophistication [14]. Besides, Steatosis less than 20% [15] or steatosis in morbidly obese individuals could not be detected by ultrasound [16]. In addition, the accuracy of US for hepatic steatosis assessment is affected by the presence of severe fibrosis [17]. Moreover, there is a drawback in that dietary and pharmacological interventions are unable to be qualitatively evaluated [18]. With the development of

ultrasonic transient elastography, the controlled attenuation parameters of the liver and the liver stiffness value can be used to assess the degree of hepatic steatosis and fibrosis quantitatively, but they are affected by the operator's skill level [19]. In addition, based on proton magnetic resonance spectroscopy (MRS) and magnetic resonance imaging (MRI), which can accurately determine the amount of liver fat content and the degree of fibrosis, and play the role of similar liver biopsy, but their cost is high, and difficult to obtain, so it has not been widely used clinically [20]. In recent years, serum non-invasive diagnostic markers or models have attracted widespread clinical attention due to their advantages of non-invasiveness, low cost, simple operation, strong reproducibility, and low requirements for operators, especially for early screening and evaluation of NAFLD [20]. Therefore, effective noninvasive methods should be used in clinical practice to identify NAFLD, track disease processes, and monitor treatment effects [21].

Overweight, obesity, and insulin resistance strongly correlate with NAFLD due to excessive fat accumulation, especially triglycerides in hepatocytes [22]. NAFLD is characterized by oxidative stress and inflammation. An increase in reactive oxygen species (ROS) can lead to lipid peroxidation by damaging both membrane structure and function. In addition to oxidizing key proteins for cell metabolism and function, it may also cause the oxidation of nucleic acids [23]. Since the liver has a limited ability for triglyceride accumulation, lipid deposition under overfeeding conditions, as in the case of NAFLD, determines the accumulation of high levels of fatty acids, generally saturated ones, which are associated with cell dysfunction [24]. Indeed, the excess of fatty acids induces high rates of β -oxidation, increasing the production of ROS in the mitochondrial respiratory chain, which causes cellular damage and oxidative stress [25]. Oxidative damage markers rise in response to this circumstance, Kupffer cells become active, pro-inflammatory pathways activate, and circulating immune cells are drawn into the body [26, 27].

An insulin resistance (IR) is characterized by decreased peripheral tissue insulin sensitivity, which is at the core of the pathogenesis of NAFLD by impairing glucose uptake

and oxidation [11, 28]. Triglyceride-glucose (TyG) is an index combining fasting blood glucose (FPG) with fasting triglyceride (TG) that could better reflect insulin resistance. It has been widely accepted and used in clinical applications due to its convenience and simple calculation [29–31]. Using a combination of body mass index (BMI) and TyG index, Er et al. found that the information imparted by a multitude of critical clinical indicators could be simultaneously reflected, such as blood lipids, blood glucose, and BMI, and could better reflect IR than the TyG index alone [32]. Given the importance of IR in NAFLD pathogenesis [11, 28], TyG-BMI has been linked to an increased incidence of NAFLD, according to certain studies [33–36]. As a result, we hypothesized that the TyG-BMI might be an effective marker in identifying NAFLD in the general population. However, as a non-invasive and simple model, applying TyG-BMI to identify and evaluate NAFLD still needs further research.

The objective of this study was to determine the diagnostic accuracy of the TyG-BMI in detecting NAFLD in the general Japanese population.

Methods and materials

Study population and design

In this study, the TyG-BMI was tested for its ability to detect NAFLD in the general Japanese population in a cross-sectional design. As a secondary analysis, we used data derived from a published article shared by Takuro Okamura et al. [37]. We obtained the data from the 'DATADRYAD' database (<https://datadryad.org/stash/>). This website permitted users to freely download the raw data. Dryad is a nonprofit membership organization that is committed to making data available for research and educational reuse now and into the future. According to Dryad Terms of Service, we cited the Dryad data package in the present study. (Dryad data package: Okamura, Takuro et al. Data from: ectopic fat obesity presents the greatest risk for incident type 2 diabetes: a population-based longitudinal study, Dryad, Dataset, <https://doi.org/10.5061/dryad.8q0p192>) [38]. From 2004 to 2015, the original study enrolled 20,944 participants ≥ 18 years of age who had at least two routine physical examinations at Murakami Memorial Hospital.

The database file contains the following variables: waist circumference (WC), gamma-glutamyltransferase (GGT), gender, total cholesterol (TC), age, diastolic blood pressure (DBP), smoking status, BMI, aspartate aminotransferase (AST), ethanol consumption, TG, alanine aminotransferase (ALT), high-density lipoprotein cholesterol (HDL-c), FPG, systolic blood pressure (SBP), hemoglobin A1C (HbA1c), comorbidity with fatty liver and the habit of exercise.

Exclusion criteria of the original study included: (1) participants diagnosed with type 2 diabetes ($n=323$) or with fasting plasma glucose (FPG) over 6.1 mmol/L ($n=808$); (2) participants with known liver disease, such as hepatitis B or C virus ($n=416$); (3) anyone who took medication ($n=2321$); (4) participants with heavy drinking habits (more than 40 g per day for women and more than 60 g per day for men) ($n=739$); (5) participants with a missed value of covariates, including abdominal ultrasonography, exercise, alcohol intake or laboratory variables ($n=863$) [37]. A total of 15,464 participants were included in the raw study for the final analysis. 1184 participants in the present study were further excluded for excessive alcohol consumption (in males >210 g/week and in females >140 g/week) [39]. Figure 1 showed the process of selecting participants. Finally, 14,280 subjects (7440 males and 6840 females) were included in this secondary analysis.

Murakami Memorial Hospital's Ethics Committee approved the research ethics, and all subjects provided informed consent in the original study [37].

Health check-ups and laboratory measurement

A standard and unified questionnaire was used by trained medical staff to gather basic health information about the subjects, including height, habit of exercise, weight, blood pressure (SBP and DBP), WC, age, smoking and drinking status. Biochemical analysis of blood samples was conducted after at least 8 h of fasting. Analysis indicators included HbA1c, ALT, FPG, TG, HDL-c, GGT, TC, and AST [37].

Definitions and calculations

$BMI = \text{weight} \text{ divided by } \text{height}^2$. $TyG = \text{Ln} [(FPG \text{ (mg/dL)} / 2) \times TG \text{ (mg/dL)}]$ [30]. $TyG-BMI = BMI \times TyG$ [32]. Ethanol consumption was evaluated by the mean ethanol intake of participants per week during the prior month. The smoking status was categorized into current smokers, ex-smokers, or non-smokers. According to World Health Organization 2020 guidelines on physical activity, regular exercise was defined as follows: adults should undertake 150–300 min of moderate-intensity, or 75–150 min of vigorous-intensity physical activity, or some equivalent combination of moderate-intensity and vigorous-intensity aerobic physical activity, per week [40].

Diagnosis of NAFLD by abdominal ultrasonography

An abdominal ultrasound was used to assess NAFLD, and gastroenterologists, without knowledge of the participants' personal information, reviewed the ultrasound images. The final diagnosis was made based on the evaluation of four ultrasound findings: liver brightness, liver,

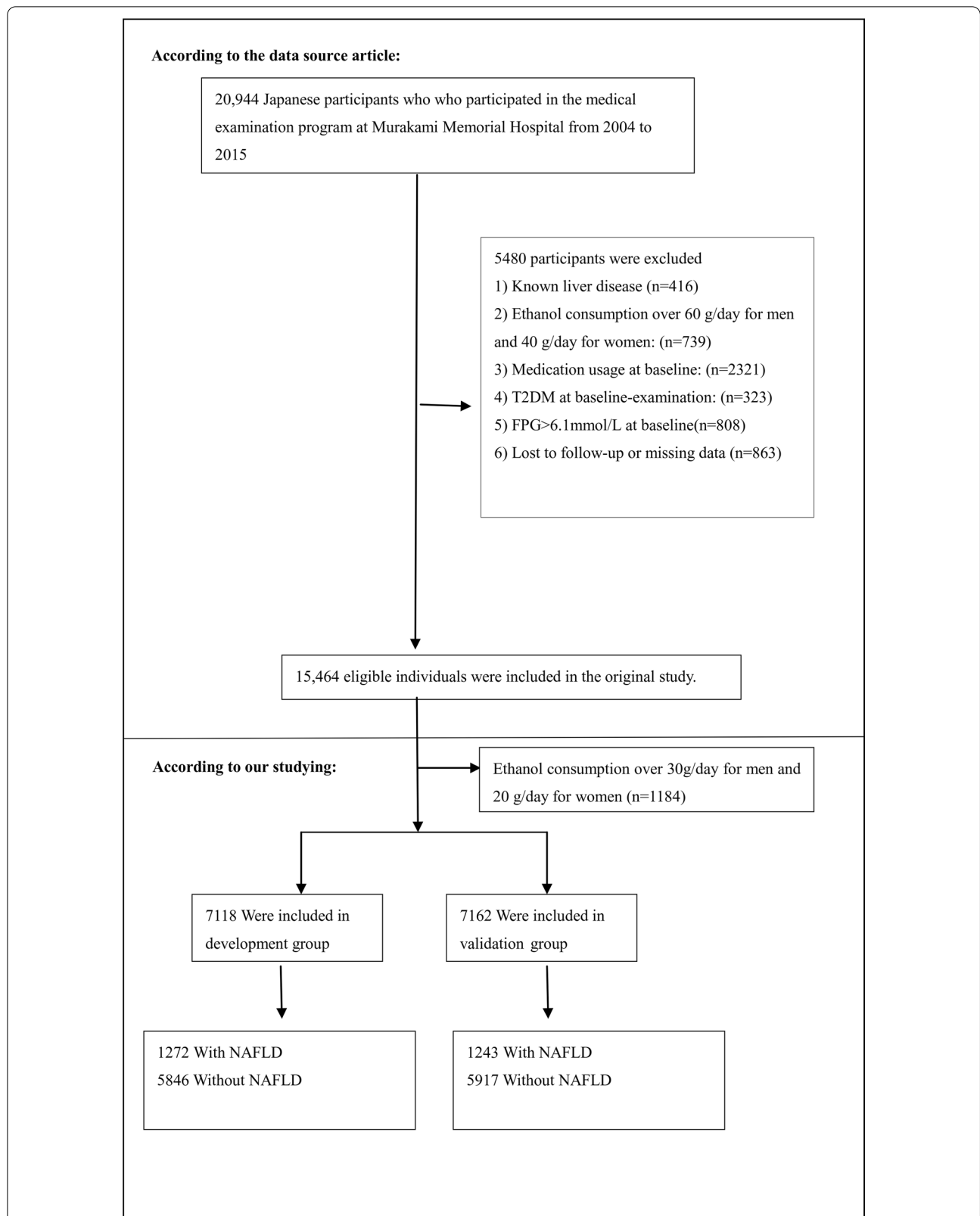


Fig. 1 Flowchart of study participants. The inclusion of participants. The eligibility of 15,464 participants was assessed in the original study. We excluded individuals with ethanol consumption over 30 g/day for men and 20 g/day for women (n = 1184). In the present study, 14,280 subjects were included in the final analysis

and kidney echo contrast, vessel blurring, and depth attenuation [41]. This was a new scoring system of ultrasonographic findings in apparently healthy Japanese adults. The AUC to diagnose NAFLD was 0.980. The sensitivity was 91.7% (95% CI 87.0–95.1), and the specificity was 100% (95% CI 95.4–100.0).

Statistical analysis

A random stratification process was used to divide participants into training and validation groups. For continuous variables, the mean (standard deviation) was given for normal distribution, the median (range) for non-normal distribution, and the number (%) for categorical variables. The authors used the student's *t*-test (normal distribution), the χ^2 (categorical variables), or the Mann–Whitney's *U*-test (non-normal distribution) to test for differences between development and validation groups. Stratified by the presence of NAFLD, the authors also showed the characteristics of the validation and training groups, respectively.

Using the area under the receiver operating characteristic (ROC) curve (AUC) and its 95% confidence intervals, the overall diagnostic accuracy of the TyG-BMI was determined in the development and validation groups, respectively. Using 500 bootstrap resamplings, the authors computed the AUC with a 95% CI with TyG-BMI to evaluate its discriminatory properties and validate its diagnostic accuracy [42].

Through the ROC curve, 2 cutoff points were selected according to the deciles of TyG-BMI and considering the specificity (SP), sensitivity (SE), negative predictive value (NPV), and positive predictive value (PPV) of the two cutoff points. The two cutoff points were used to rule out or rule in the NAFLD, respectively. The authors calculated specificity, sensitivity, NPV, PPV, positive likelihood ratios (PLR), and negative likelihood ratios (NLR) to determine the diagnostic accuracy of the two cutoff points. The authors also explored the cutoff points' diagnostic values for different NAFLD prevalence or different gender and age subgroups.

Moreover, the authors used a database of 183,730 general Chinese populations for external validation. The data were also taken from the DATADRYAD database (<https://datadryad.org/stash>), shared by Sun et al. [43]. Data from: association of low-density lipoprotein cholesterol within the normal range and NAFLD in the non-obese Chinese population: a cross-sectional and longitudinal study, Dryad, Dataset, <https://doi.org/10.5061/dryad.1n6c4>. All participants were non-obese people with a normal range of Low-density lipoprotein cholesterol (LDL-c), as described in the original article [43]. Decision curve analysis was performed to explore the clinical use of TyG-BMI for the diagnosis of NAFLD: the

proportion of people who showed a true positive result was first subtracted from those who showed a false positive result, then weighed against the relative risks of false-positive and false-negative results, and finally, obtained the net benefit of making a decision [44].

All results were reported according to the STARD statement [45]. All analyses were carried out using statistical packages from the R (<http://www.r-project.org>, The R Foundation) and EmpowerStats packages (<http://www.empowerstats.com>, X and Y Solutions, Inc, Boston, MA). *P* values less than 0.05 were considered statistically significant (two-sided).

Results

In the present study, 14,280 participants (52.1% men and 47.9% women) were eligible. Figure 1 depicted the subjects' selection and grouping process. The mean age of all participants was 43.53 ± 8.89 years. A total of 2515 (17.6%) participants were diagnosed with NAFLD. The mean BMI was 22.07 ± 3.14 kg/m². The mean FPG and TG were 92.74 ± 7.42 and 79.03 ± 56.07 mg/dL, respectively. The mean TyG and TyG-BMI were 8.01 ± 0.64 and 177.74 ± 34.53 , respectively.

Baseline characteristics of participants

Table 1 illustrated the eligible participants' basic demographic and clinical information. The authors randomly divided all participants into the development group (*n* = 7118) and the validation group (*n* = 7162). 1272 and 1243 participants were diagnosed with NAFLD in the development and validation groups, respectively. In all baseline characteristics, the development group did not differ statistically from the validation group (all *P* > 0.05).

By NAFLD status, Table 2 showed the characteristics of the 2 groups. The participants with NAFLD had higher BMI, WC, alcohol consumption, SBP, age, FPG, DBP, TG, HbA1c, ALT, TC, AST, BUN, GGT, and higher rates of males and ever or current smokers in the development and validation groups. In contrast, participants in the NAFLD group had lower levels of HDL-c.

TyG-BMI levels were distributed in a normal distribution, as shown in Fig. 2 and Additional file 1: Fig. S1. They ranged from 97.49 to 421.35 in the total population. The TyG-BMI values of all the participants from the NAFLD and non-NAFLD groups were shown in Fig. 3. As a result, the distribution level of TyG-BMI was higher in the NAFLD group than in the non-NAFLD group. Men were found to have a higher prevalence of NAFLD in age-stratified by 10 intervals than women, regardless of age group (Fig. 4). Meanwhile, the study also found that the prevalence of NAFLD increased stepwise in both male (except for those older than 50) and female (except for those older than 60) participants with increasing age

Table 1 Baseline characteristics of the development and validation groups

| Characteristic | Development group | Validation group | P-value |
|---------------------------|------------------------|------------------------|---------|
| N | 7118 | 7162 | |
| Age (years) | 43.533 ± 8.918 | 43.533 ± 8.864 | 0.964 |
| Alcohol consumption (g/w) | | | 0.893 |
| = 0 | 2364 (33.212%) | 2371 (33.105%) | |
| > 0 | 4754 (66.788%) | 4791 (66.895%) | |
| BMI (kg/m ²) | 22.046 ± 3.104 | 22.090 ± 3.168 | 0.398 |
| WC (cm) | 76.199 ± 9.026 | 76.193 ± 9.174 | 0.968 |
| ALT (U/L) | 17.000 (13.000–23.000) | 16.000 (12.000–23.000) | 0.161 |
| AST (U/L) | 17.000 (14.000–21.000) | 17.000 (14.000–21.000) | 0.727 |
| GGT (U/L) | 15.000 (11.000–21.000) | 15.000 (11.000–21.000) | 0.830 |
| HDL-c (mmol/L) | 1.462 ± 0.405 | 1.455 ± 0.399 | 0.285 |
| TC (mmol/L) | 5.125 ± 0.867 | 5.123 ± 0.869 | 0.901 |
| TG (mmol/L) | 0.723 (0.485–1.095) | 0.723 (0.485–1.106) | 0.291 |
| TyG-BMI | 177.386 ± 34.108 | 178.093 ± 34.940 | 0.222 |
| HbA1c (%) | 5.176 ± 0.321 | 5.180 ± 0.321 | 0.470 |
| FPG (mmol/L) | 5.145 ± 0.414 | 5.152 ± 0.410 | 0.308 |
| SBP (mmHg) | 113.878 ± 14.774 | 114.043 ± 14.892 | 0.506 |
| SBP (mmHg) | 71.031 ± 10.376 | 71.251 ± 10.407 | 0.204 |
| SEX, n (%) | | | 0.604 |
| Female | 3394 (47.682%) | 3446 (48.115%) | |
| Male | 3724 (52.318%) | 3716 (51.885%) | |
| Regular exerciser, n (%) | 1239 (17.407%) | 1237 (17.272%) | 0.831 |
| Smoking status, n (%) | | | 0.934 |
| Never-smoker | 4369 (61.380%) | 4382 (61.184%) | |
| Ever-smoker | 1284 (18.039%) | 1288 (17.984%) | |
| Current-smoker | 1465 (20.582%) | 1492 (20.832%) | |

Values are n (%) or mean ± SD or medians (quartiles)

HDL-c high-density lipoprotein cholesterol, *ALT* alanine aminotransferase, *FPG* fasting plasma glucose, *TC* total cholesterol, *DBP* diastolic blood pressure, *HbA1c* hemoglobina1c, *AST* aspartate aminotransferase, *BMI* body mass index, *TG* triglyceride, *SBP* systolic blood pressure, *GGT* gamma glutamyltransferase, *WC* Waist circumference, *TyG-BMI*: triglyceride glucose-body mass index

(Fig. 4). All participants were divided into four groups according to quartiles of TyGBMI, and we found that participants with a high TyGBMI had higher prevalence rates of NAFLD compared to the group with the lowest TyGBMI ($P < 0.0001$ for trend) (Additional file 2: Fig. S2).

Development phase

The median TyG-BMI was elevated among participants with NAFLD (214.5). For participants without NAFLD, the median level was 166.2 (Fig. 5A). The authors applied the ROC method to analyze the diagnostic accuracy of the TyG-BMI for detecting NAFLD in the development group. TyG-BMI had an AUC of 0.888 (95% CI 0.879, 0.897) (Fig. 6, Additional file 7: Table S1). Using 500 bootstrap resamplings, TyG-BMI had an average AUC of 0.886 (95% CI 0.876, 0.896). The AUROC remained high and almost unchanged in the development set (Additional file 3: Fig. S3).

Table 3 described the diagnostic accuracy of TyG-BMI in predicting NAFLD at decile intervals. In the development group, when the cut-off point of the TyG-BMI was set at 182.2 to discriminate NAFLD, it would meet the relatively high Youden's index (0.605) and the diagnostic accuracy of sensitivity (89.4%)/specificity (71.1%), PPV (40.2%)/NPV (96.9%), and LR+ (3.09)/LR− (0.15). Meanwhile, when the cut-off point of the TyG-BMI was set at 224.0, the diagnostic accuracy of sensitivity (38.1%)/specificity (96.6%), PPV (70.7%)/NPV (87.8%), and LR+ (11.09)/LR− (0.64). So a TyG-BMI < 182.2 could be used to rule out (SE = 89.4%, NPV = 96.9% LR− = 0.15) and a TyG-BMI ≥ 224.0 to rule in NAFLD (SP = 96.6%, PPV = 70.7%, LR+ = 11.1) (Table 3).

Using a low cutoff point (below 182.2), 4156 (71.1%) of the 5846 individuals without NAFLD were correctly identified, whereas 135 (3.3%) of 4289 individuals with a low cutoff point were incorrectly identified (Table 4).

Table 2 Baseline characteristics for the training and validation groups by NAFLD status

| Characteristic | Development group | | Validation group | |
|---------------------------|------------------------|------------------------|------------------------|------------------------|
| | Non-NAFLD | NAFLD | Non-NAFLD | NAFLD |
| N | 5846 | 1272 | 5919 | 1243 |
| Age (years) | 43.314 ± 9.050 | 44.537 ± 8.215 | 43.219 ± 8.923 | 45.027 ± 8.427 |
| Alcohol consumption (g/w) | | | | |
| = 0 | 1992 (34.075%) | 372 (29.245%) | 1997 (33.739%) | 374 (30.088%) |
| > 0 | 3854 (65.925%) | 900 (70.755%) | 3922 (66.261%) | 869 (69.912%) |
| BMI (kg/m ²) | 21.305 ± 2.581 | 25.448 ± 3.037 | 21.363 ± 2.633 | 25.551 ± 3.215 |
| WC (cm) | 74.090 ± 7.851 | 85.890 ± 7.636 | 74.117 ± 7.990 | 86.078 ± 7.920 |
| ALT (U/L) | 15.000 (12.000–20.000) | 27.000 (20.000–38.000) | 15.000 (12.000–20.000) | 27.000 (20.000–39.000) |
| AST (U/L) | 14.000 (11.000–18.000) | 20.000 (16.000–25.000) | 17.000 (14.000–20.000) | 21.000 (17.000–26.000) |
| GGT (U/L) | 14.000 (11.000–18.000) | 22.000 (16.000–32.250) | 14.000 (11.000–18.000) | 23.000 (16.000–33.000) |
| HDL-c (mmol/L) | 1.524 ± 0.402 | 1.181 ± 0.280 | 1.512 ± 0.394 | 1.186 ± 0.300 |
| TC (mmol/L) | 5.065 ± 0.859 | 5.397 ± 0.851 | 5.046 ± 0.847 | 5.488 ± 0.882 |
| TyG-BMI | 168.514 ± 27.726 | 218.162 ± 30.871 | 169.266 ± 28.289 | 220.124 ± 32.960 |
| TG (mmol/L) | 0.655 (0.452–0.937) | 1.231 (0.858–1.727) | 0.655 (0.452–0.960) | 1.264 (0.881–1.829) |
| HbA1c (%) | 5.148 ± 0.312 | 5.303 ± 0.329 | 5.155 ± 0.312 | 5.299 ± 0.339 |
| FPG (mmol/L) | 5.092 ± 0.405 | 5.386 ± 0.368 | 5.099 ± 0.400 | 5.404 ± 0.359 |
| SBP (mmHg) | 111.875 ± 14.020 | 123.082 ± 14.665 | 111.991 ± 14.031 | 123.811 ± 15.000 |
| DBP (mmHg) | 69.607 ± 9.894 | 77.572 ± 10.025 | 69.814 ± 9.830 | 78.097 ± 10.356 |
| SEX, n (%) | | | | |
| Female | 3153 (53.934%) | 241 (18.947%) | 3209 (54.215%) | 237 (19.067%) |
| Male | 2693 (46.066%) | 1031 (81.053%) | 2710 (45.785%) | 1006 (80.933%) |
| Regular exerciser, n (%) | 1040 (17.790%) | 199 (15.645%) | 1058 (17.875%) | 179 (14.401%) |
| Smoking status, n (%) | | | | |
| Never-smoker | 3777 (64.608%) | 592 (46.541%) | 3788 (63.997%) | 594 (47.788%) |
| Ever-somker | 966 (16.524%) | 318 (25.000%) | 964 (16.287%) | 324 (26.066%) |
| Current-smoker | 1103 (18.868%) | 362 (28.459%) | 1167 (19.716%) | 325 (26.146%) |

Values are n (%) or mean ± SD or medians (quartiles)

HDL-c high-density lipoprotein cholesterol, *BMI* body mass index, *ALT* alanine aminotransferase, *FPG* fasting plasma glucose, *TC* total cholesterol, *DBP* diastolic blood pressure, *HbA1c* hemoglobina1c, *AST* aspartate aminotransferase, *TG* triglyceride, *SBP* systolic blood pressure, *WC* waist circumference, *GGT* gamma-glutamyltransferase, *TyG-BMI* triglyceride glucose-body mass index

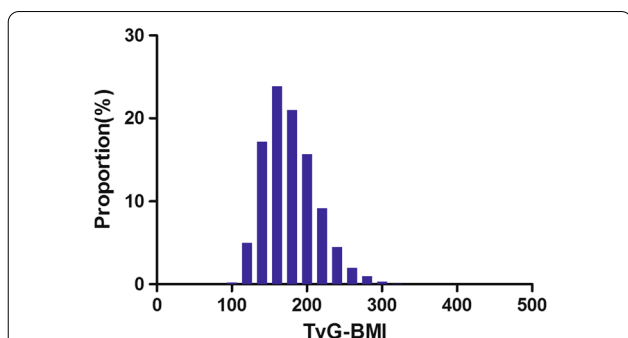
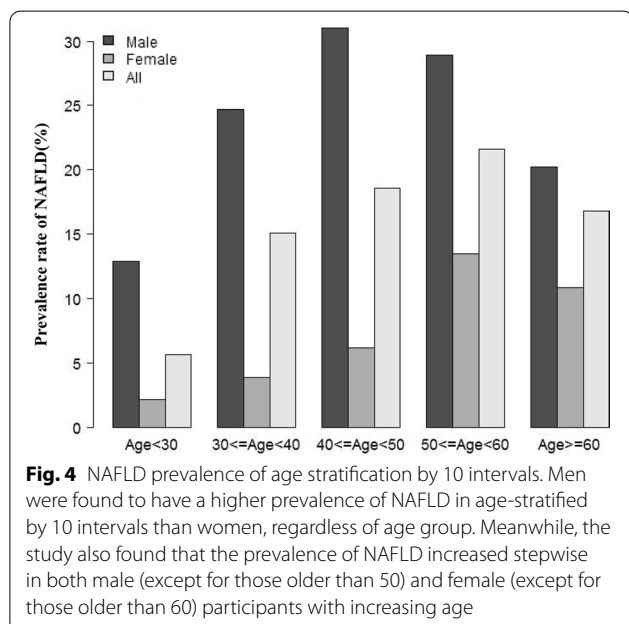
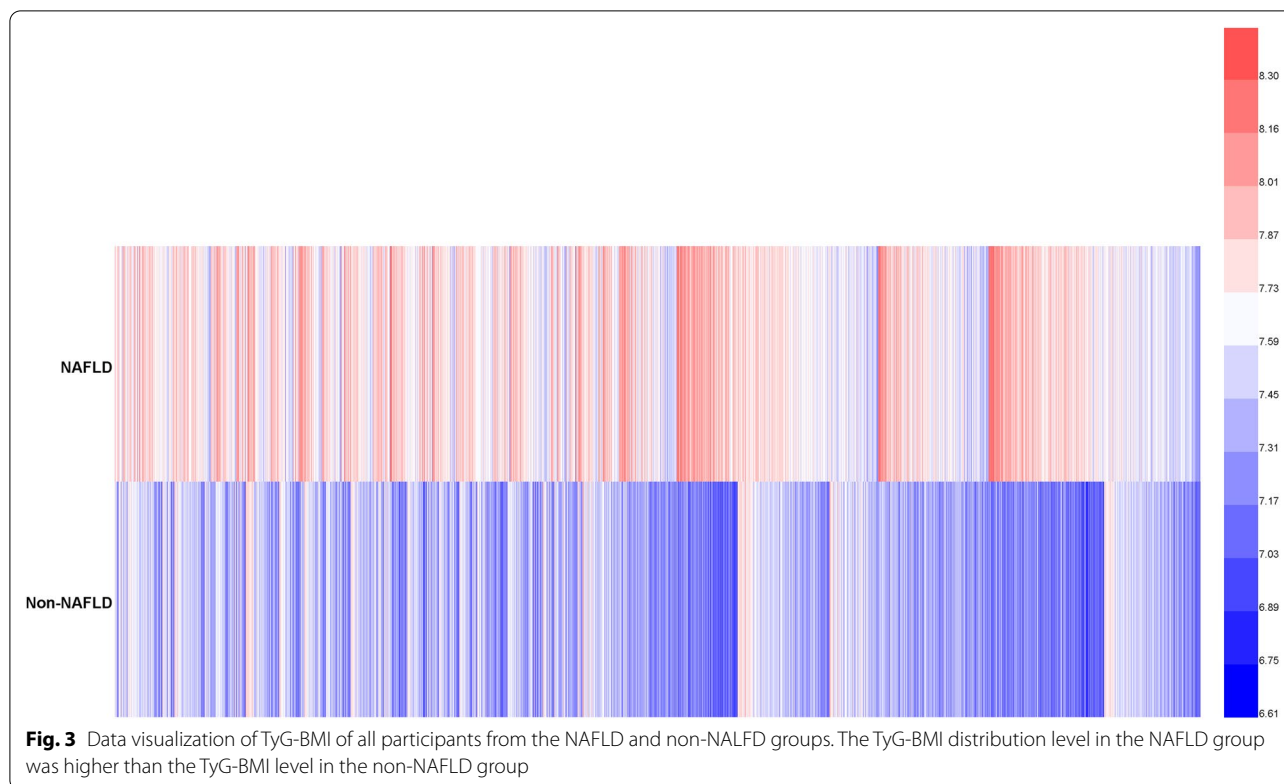


Fig. 2 Distribution of TyG-BMI. TyG-BMI presented a normal distribution ranging from 97.49 to 421.35 in the total population, with a mean level of 177.74

Thus, this low cutoff point could exclude the absence of NAFLD with high accuracy (NPV of 97%).

By applying the high cutoff point (above 224.0), 485 (38.1%) of 1272 participants with NALFD were correctly identified, whereas 201 (29%) of the 686 with the high cutoff point were incorrectly staged (Table 4). With this high cutoff point, it was possible to diagnose NALFD with high accuracy (71% PPV for detection).

Overall, in the development group, TyG-BMI predicted the absence or presence of NAFLD in $(4289 + 686)/7118 = 70\%$ of participants with a correct diagnosis in $4641/4975$ or 93% [or 65% ($4641/7118$) of the total]. The incorrect diagnosis rate in the development group was only $(135 + 201)/4975 = 6.75\%$. As a result, 4975 (70%) participants would have avoided abdominal ultrasonography if the model had been applied to the development group. Only 2143 (30%) of the 7118 participants with “indeterminate” status (TyG-BMI in the range



performance of the TyG-BMI in different gender and age strata for NAFLD was also evaluated using ROC analysis. TyG-BMI showed a larger AUC for distinguishing NAFLD in females, young, and middle-aged people (Table 5).

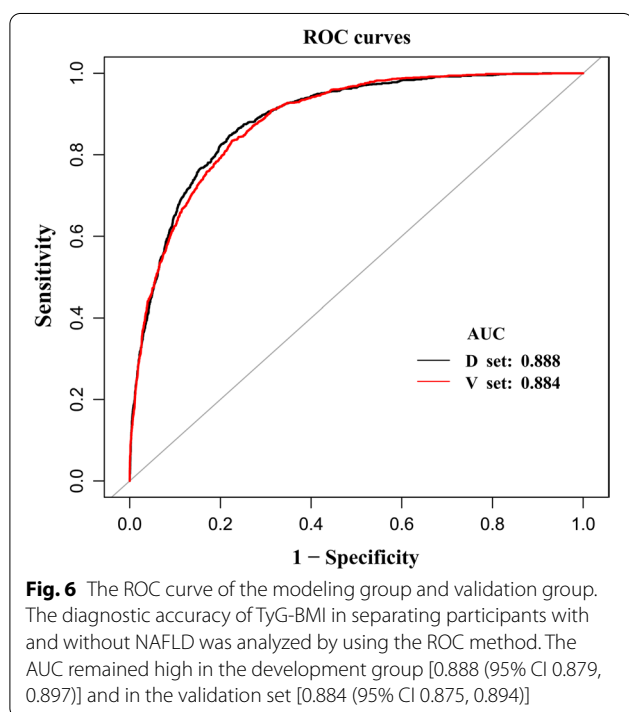
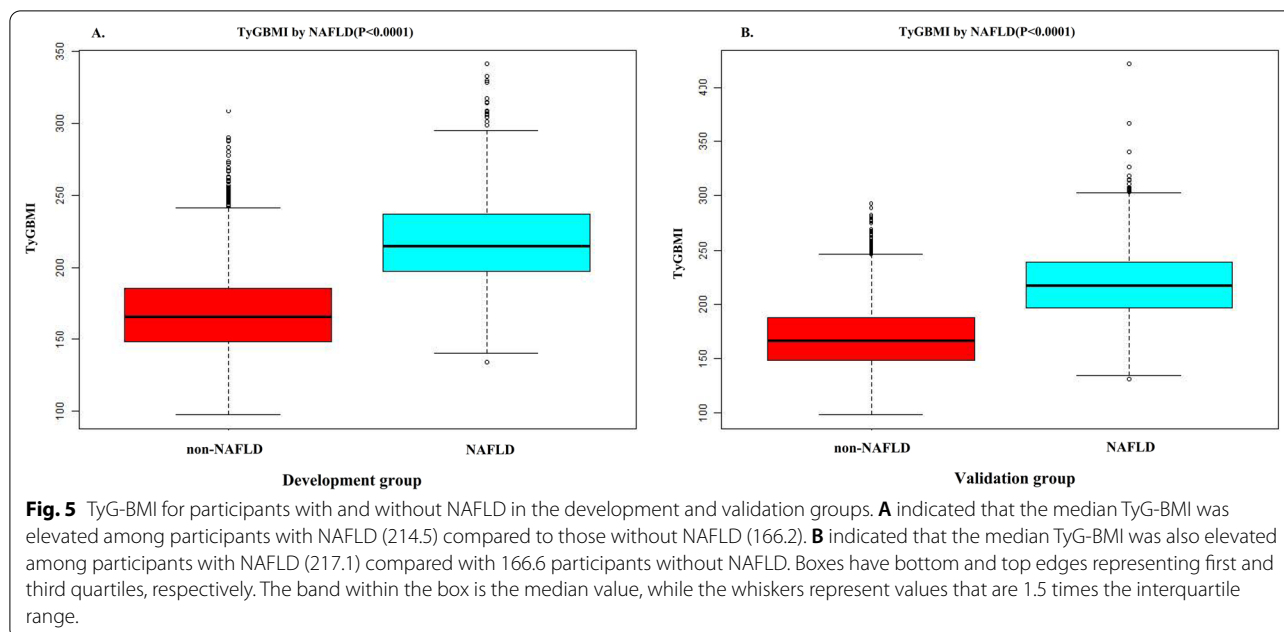
Validation Phase

In the validation group, the median TyG-BMI was also elevated among participants with NAFLD (217.1) compared with 166.6 among participants without NAFLD (Fig. 5B). The diagnostic accuracy of TyG-BMI in separating participants with and without NAFLD was analyzed by using the ROC method. The AUC remained high in the validation set [0.884 (95% CI 0.875, 0.894)] (Fig. 6, Additional file 7: Table S1), and also 500 bootstrap resamplings [0.886(95% CI 0.877, 0.897)] (Additional file 4: Fig. S4).

In the development group, when the cut-off point of the TyG-BMI was set at 182.2 to discriminate NAFLD, it would meet the relatively high Youden’s index (0.605) and the diagnostic accuracy of SE (89.2%)/SP (70.1%), PPV (38.5%)/NPV (96.9%), and LR+ (2.98)/LR– (0.15). Meanwhile, when the cut-off point of the TyG-BMI was set at 224.0, the diagnostic accuracy of sensitivity (41.8%)/specificity (96.3%), PPV (70.1%)/NPV (88.7%), and LR+ (11.18)/LR– (0.61). So a TyG-BMI < 182.2 could be

of 182.2–224.0) would need to undergo ultrasound imaging (Table 4).

Significant differences in NAFLD prevalence were found in age and gender stratification. The diagnostic



used to rule out (SE = 89.2%, NPV = 96.9% LR- = 0.15) and a TyG-BMI ≥ 224.0 to rule in NAFLD (SP = 96.3%, PPV = 70.1%, LR+ = 11.2) (Table 3).

By applying the low cutoff point (below 182.2), 4148 (70.1%) of the 5919 participants without NAFLD were correctly identified, whereas 134 (3.1%) of 4279 with a low cutoff point were incorrectly staged (Table 4). Thus,

this low cutoff point could also exclude the absence of NAFLD with high accuracy (NPV of 96.9%).

By applying the high cutoff point (greater than 224.0), 519 (41.8%) of the 1243 participants with NAFLD were correctly identified, whereas only 221 (29.9%) of the 742 participants with a high cutoff point were incorrectly staged (Table 4). It was possible to detect the presence of NAFLD with high accuracy using this high cutoff point (PPV of 70.1%).

Overall, in the validation group, the model identified the absence or presence of NAFLD in (4279 + 742 = 5021)/7162 = 70% of participants with a correct diagnosis in 4667/5021 = 93% [or 65.2% (4667/7162) of the total]. The incorrect diagnosis rate in the validation group was only (134 + 221)/5021 = 7.1%. Therefore, abdominal ultrasonography could have been avoided in 5021 (70%) of the participants if the model had been used in the validation group. Only 2141 (30%) of the 7162 participants identified as “indeterminate” (TyG-BMI in the range of 182.2–224) would receive ultrasonography.

The authors also found that TyG-BMI had a larger AUC to distinguish NAFLD in female and young and middle-aged people in the validation group (Additional file 7: Table S2).

Predictive values of the TyG-BMI for different prevalence of NAFLD

The worldwide prevalence of NAFLD ranges from 6 to 35% [3]. As a result, the authors calculated the positive and negative predictive values of the two cutoff

Table 3 Diagnostic accuracy of the TyG-BMI

| | Cut-off | No | SP (%) | SE (%) | PPV (%) | NPV (%) | PLR | NLR | Youden's index |
|-------------|---------|------|--------|--------|---------|---------|-------|-------|----------------|
| Development | ≥ 137.4 | 6405 | 12.2 | 99.9 | 19.8 | 99.9 | 1.14 | 0.006 | 0.121 |
| | ≥ 147.8 | 5705 | 24.2 | 99.5 | 22.2 | 99.6 | 1.31 | 0.020 | 0.237 |
| | ≥ 156.7 | 4998 | 35.9 | 98.5 | 25.1 | 99.1 | 1.54 | 0.042 | 0.344 |
| | ≥ 165.0 | 4264 | 48.2 | 97.1 | 29.0 | 98.7 | 1.87 | 0.060 | 0.453 |
| | ≥ 173.3 | 3541 | 60.0 | 94.3 | 33.9 | 98.0 | 2.36 | 0.094 | 0.543 |
| | ≥ 182.2 | 2829 | 71.1 | 89.4 | 40.2 | 96.9 | 3.09 | 0.149 | 0.605 |
| | ≥ 192.8 | 2113 | 81.2 | 79.6 | 48.0 | 94.8 | 4.25 | 0.251 | 0.608 |
| | ≥ 205.4 | 1396 | 90.2 | 64.9 | 59.1 | 92.2 | 6.64 | 0.389 | 0.551 |
| Validation | ≥ 224.0 | 686 | 96.6 | 38.1 | 70.7 | 87.8 | 11.09 | 0.641 | 0.347 |
| | ≥ 137.4 | 6447 | 12.1 | 99.8 | 19.3 | 99.7 | 1.14 | 0.013 | 0.119 |
| | ≥ 147.8 | 5719 | 24.4 | 99.6 | 21.7 | 99.7 | 1.32 | 0.017 | 0.240 |
| | ≥ 156.7 | 4998 | 36.3 | 99.0 | 24.6 | 99.4 | 1.55 | 0.029 | 0.353 |
| | ≥ 165.0 | 4304 | 47.8 | 97.6 | 28.2 | 98.9 | 1.87 | 0.050 | 0.454 |
| | ≥ 173.3 | 3599 | 59.1 | 94.3 | 32.6 | 98.0 | 2.30 | 0.097 | 0.534 |
| | ≥ 182.2 | 2883 | 70.1 | 89.2 | 38.5 | 96.9 | 2.98 | 0.154 | 0.593 |
| | ≥ 192.8 | 2171 | 80.0 | 79.2 | 45.5 | 94.8 | 3.97 | 0.260 | 0.592 |
| ≥ 205.4 | 1460 | 89.0 | 65.2 | 55.4 | 92.4 | 5.92 | 0.391 | 0.542 | |
| ≥ 224.0 | 742 | 96.3 | 41.8 | 70.1 | 88.7 | 11.18 | 0.605 | 0.381 | |

PPV positive predictive value, SP specificity, NPV negative predictive value, SE sensitivity, PLR positive likelihood ratio, NLR negative likelihood ratio, TyG-BMI triglyceride glucose-body mass index

Table 4 The diagnostic value of TyG-BMI obtained from the development and validation group

| | Low cutoff point (< 182.2) | Indeterminate (182.2–224.0) | High cutoff point (> 224.0) | Total |
|----------------|----------------------------------|-----------------------------|-----------------------------------|-------|
| Development | | | | |
| Total | 4289 | 2143 | 686 | 7118 |
| Non-NAFLD | 4156 | 1489 | 201 | 5846 |
| NAFLD | 135 | 652 | 485 | 1272 |
| Sensitivity | 89.4% | | 38.1% | |
| Specificity | 71.1% | | 96.6% | |
| PPV | 40.4% | | 70.7% | |
| NPV | 96.9% | | 87.8% | |
| PLR | 3.09 | | 11.09 | |
| NPR | 0.15 | | 0.64 | |
| Interpretation | Absence of NALFD (97% certainty) | | Presence of NAFLD (71% certainty) | |
| Validation | | | | |
| Total | 4279 | 2141 | 742 | 7162 |
| Non-NAFLD | 4148 | 1550 | 221 | 5919 |
| NAFLD | 134 | 590 | 519 | 1243 |
| Sensitivity | 89.2% | | 41.8% | |
| Specificity | 70.1% | | 96.3% | |
| PPV | 38.5% | | 70.1% | |
| NPV | 96.9% | | 88.7% | |
| PLR | 2.98 | | 11.18 | |
| NLR | 0.15 | | 0.61 | |
| Interpretation | Absence of NALFD (97% certainty) | | Presence of NAFLD (70% certainty) | |

PPV positive predictive value, NPV negative predictive value, PLR positive likelihood ratio, NLR negative likelihood ratio, TyG-BMI triglyceride glucose-body mass index

Table 5 Performance of the tests for diagnosis/exclusion of NAFLD by different subgroups

| Development group | AUROC (95% CI) | Cutoff | SE (%) | SP (%) | PPV (%) | NPV (%) | PLR | NLR |
|-------------------|------------------|--------|--------|--------|---------|---------|-------|-------|
| Sex | | | | | | | | |
| Male | 0.84 (0.83–0.86) | 182.2 | 91.1 | 55.4 | 43.9 | 94.2 | 2.04 | 0.16 |
| | | 224.0 | 39.3 | 94.6 | 73.5 | 80.3 | 7.25 | 0.64 |
| Female | 0.92 (0.92–0.93) | 182.2 | 82.2 | 84.6 | 28.9 | 98.4 | 5.32 | 0.21 |
| | | 224.0 | 32.8 | 98.3 | 59.3 | 95.3 | 18.79 | 0.68 |
| Age (years) | | | | | | | | |
| < 30 | 0.97 (0.94–0.99) | 182.2 | 92.3 | 88.1 | 33.3 | 99.4 | 7.77 | 0.087 |
| | | 224.0 | 53.8 | 99.0 | 77.8 | 97.1 | 54.38 | 0.49 |
| 30–40 | 0.91 (0.90–0.93) | 182.2 | 90.9 | 75.9 | 42.2 | 97.7 | 3.77 | 0.12 |
| | | 224.0 | 44.1 | 97.0 | 74.2 | 90.0 | 14.83 | 0.58 |
| 40–50 | 0.88 (0.87–0.90) | 182.2 | 89.8 | 70.1 | 42.1 | 96.8 | 3.10 | 0.14 |
| | | 224.0 | 38.8 | 96.2 | 70.1 | 87.1 | 10.34 | 0.64 |
| 50–60 | 0.85 (0.83–0.87) | 182.2 | 87.2 | 63.4 | 38.5 | 95.0 | 2.38 | 0.20 |
| | | 224.0 | 30.3 | 95.8 | 65.5 | 83.9 | 7.23 | 0.73 |
| > 60 | 0.82 (0.76–0.89) | 182.2 | 86.0 | 57.9 | 27.4 | 95.7 | 2.04 | 0.24 |
| | | 224.0 | 28.0 | 86.6 | 66.7 | 88.0 | 10.07 | 0.76 |

PPV positive predictive value, SP specificity, NPV negative predictive value, SE sensitivity, PLR positive likelihood ratio, NLR negative likelihood ratio, AUROC area under the receiver-operating characteristic curve

points using a range of prevalences of NAFLD ranging between 5 and 50%. The NPV of the low cutoff point to rule out NAFLD decreased as the prevalence of NAFLD increased, but it remained high ($\geq 87.8\%$, Table 6) when the prevalence of NAFLD was less than 30%. The PPV of the high cutoff point to diagnose NAFLD increased as the prevalence of NAFLD increased. It also remained high, particularly for the prevalence of 20% or more ($\geq 73.7\%$, Table 6). Thus, these two cutoff points may be helpful in diagnosing NAFLD in participants with different prevalences of NAFLD.

External validation

The external validation was performed on a database of 183,730 Chinese non-obese participants with a normal range of LDL-c. The mean age, BMI, TG, and FPG of the participants were 40.98 ± 14.06 years old, 21.43 ± 2.13 kg/m², 118.43 ± 90.39 mg/dL, and 92.76 ± 15.33 mg/dL, respectively (Additional file 7: Table S3). The AUC of the external validation was 0.874 (Additional file 5: Fig. S5). The NPV, sensitivity, and specificity rate of the low cutoff point to rule out NAFLD were 98.5%, 94.1%, and 60.0%, respectively. While the PPV, specificity, and sensitivity rate of the high cutoff point to diagnose NAFLD

Table 6 Diagnostic values of the cut-off points for different prevalences of NAFLD

| Prevalence of NAFLD (%) | Lower Cutoff Value (< 182.2) | | Higher Cutoff Value (> 224.0) | |
|-------------------------|------------------------------|------------------|-------------------------------|------------------|
| | PPV (95% CI) | NPV (95% CI) | PPV (95% CI) | NPV (95% CI) |
| 5 | 26.1 (21.1–31.8) | 98.3 (97.6–98.9) | 37.1 (27.9–47.2) | 96.7 (95.8–97.4) |
| 10 | 42.7 (35.2–50.6) | 96.5 (95.0–97.6) | 55.5 (43.0–67.2) | 93.4 (91.5–94.8) |
| 15 | 54.2 (45.3–62.9) | 94.6 (92.2–96.3) | 66.4 (52.6–78.0) | 89.8 (87.1–92.1) |
| 20 | 62.6 (53.0–71.4) | 92.5 (89.3–94.9) | 73.7 (59.3–84.5) | 86.2 (82.6–89.2) |
| 25 | 69.1 (59.1–77.6) | 90.3 (86.2–93.3) | 77.9 (63.4–88.0) | 82.4 (77.9–86.1) |
| 30 | 74.2 (64.1–82.3) | 87.8 (82.8–91.6) | 82.8 (68.2–91.8) | 78.5 (73.2–83.0) |
| 35 | 78.3 (68.2–86.0) | 85.2 (79.2–89.7) | 86.1 (71.7–94.2) | 74.3 (68.3–79.6) |
| 40 | 81.7 (71.7–88.9) | 82.3 (75.3–87.6) | 88.2 (73.9–95.5) | 70.1 (63.2–76.1) |
| 45 | 84.6 (74.7–91.2) | 79.1 (71.2–85.3) | 90.2 (76.1–96.7) | 65.6 (58.1–72.4) |
| 50 | 87.0 (77.3–93.1) | 75.6 (66.7–82.8) | 91.8 (78.0–97.6) | 60.1 (52.9–68.5) |

PPV positive predictive value, NPV negative predictive value

were 64.0%, 97.9%, and 23.6%, respectively (Table 7). The external validation revealed that TyG-BMI's ability to diagnose NAFLD could be promoted to some extent.

Clinical use of the model

The decision curve analysis of the TyG-BMI was demonstrated in Fig. 7 in the training and validation groups. As it could see from the graph, the black line represented the net benefit when no participants had been diagnosed

with NALFD. In contrast, the light gray line represented the net benefit when everyone had been diagnosed with NALFD. A model's diagnostic utility was defined as the distance between the "no treatment line" (black line) and the "all treatment line" (light gray line) in its curve. In terms of clinical application, the further the model curve was from the black and light gray lines, the better. Specifically, in the training cohort, the net benefit was equal to performing 50 additional NAFLD screenings (such

Table 7 Diagnostic value of the TyG-BMI from the external verification data

| | Low cutoff point (< 182.2) | Indeterminate (182.2–224.0) | High cutoff point (> 224.0) | Total |
|----------------|------------------------------------|-----------------------------|-----------------------------------|--------|
| Total | 96453 | 77897 | 9380 | 183730 |
| Non-NAFLD | 94958 | 59911 | 3374 | 158243 |
| NAFLD | 1495 | 17986 | 6006 | 25487 |
| Sensitivity | 94.1% | | 23.6% | |
| Specificity | 60.0% | | 97.9% | |
| PPV | 27.5% | | 64.0% | |
| NPV | 98.5% | | 88.8% | |
| PLR | 2.35 | | 11.05 | |
| NLR | 0.098 | | 0.78 | |
| Interpretation | Absence of NALFD (98.5% certainty) | | Presence of NAFLD (64% certainty) | |

PPV positive predictive value, NPV negative predictive value, PLR positive likelihood ratio, NLR negative likelihood ratio, TyG-BMI triglyceride glucose-body mass index

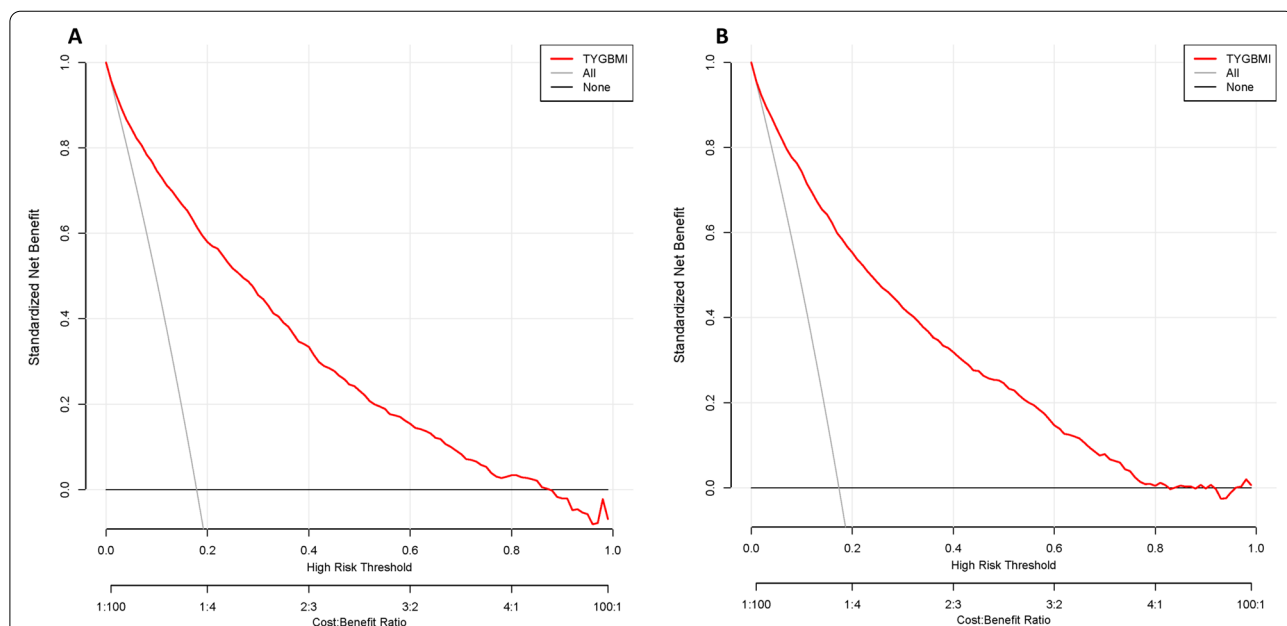


Fig. 7 The decision curve analysis of TyG-BMI for NAFLD in the training group (A) and validation group (B). TyG-BMI had good clinical application value for diagnosing or excluding NAFLD in the training and validation groups. When none of the participants are considered to develop NAFLD, the black line represents the net benefit. When all participants are considered to develop NAFLD, the light gray line represents the net benefit. A model's diagnostic utility is defined as the distance between the "no treatment line" (black line) and the "all treatment line" (light gray line) in its curve. It is better to use TyG-BMI in clinical settings when the model curve is farther from the black line and light gray line

as abdominal ultrasonography) per 100 Japanese adults if the threshold probability was 30% in the model when without a significant change in the prevalence of NAFLD (Fig. 7A). Similar results could be obtained in the internal and external validation participants (Fig. 7B, Additional file 6: Fig. S6).

Discussion

This cross-sectional study aimed to develop and validate a non-invasive index that uses routinely measured and readily accessible clinical and laboratory variables to discriminate between the presence or absence of NAFLD. This index, called the “TyG-BMI”, accurately distinguished the populations with or without NAFLD. The absence or presence of NAFLD was diagnosed in 9996 (70%) of the 14,280 patients using values below or above the lower or upper cutoff points. Of these 9996 individuals, 9308 (93.1%) were diagnosed correctly. Only 4284 participants (30%) of the 14,280 participants with TyG-BMI in the range of 182.2–224 were considered “indeterminate”. According to this, 70 percent (9996 out of 14,280) of participants in the whole population were able to avoid ultrasonography by applying the TyG-BMI. Both internal and external validations demonstrated that TyG-BMI was highly accurate in diagnosing patients. In addition, the authors summarized the positive and negative predictive values of the two cutoff points using a wide range of prevalence of NAFLD, ranging from 5 to 50%. TyG-BMI’s clinical application was demonstrated by the decision curve analysis.

A number of non-invasive and simple models have been developed to detect and evaluate NAFLD [18, 46]. Due to their calculation based on anthropometric and biochemical parameters, these could be easily obtained in clinical practice. Hepatic steatosis has been identified and managed with these models because they are cost-effective, practical, and reliable [46]. Several studies have shown that the fatty liver index (FLI), which is derived from a population of fewer than 8000 individuals in an Italian municipality [47], is acceptable for detecting NAFLD [48]. Based on a survey of nearly 10,000 Korean patients, the hepatic steatosis index (HSI) has also been shown to be an accurate and simple method for predicting NAFLD [49]. A few other indicators may be used to determine central lipid accumulation, including lipid accumulation product (LAP) and visceral adiposity index (VAI) [50, 51]. The underlying cause of NAFLD is a complex combination of environmental factors, heredity, and dietary habits [52]. Several dietary habits contribute to the development of NAFLD, such as excessive calorie consumption, fructose consumption, and physical inactivity [53]. Moreover, Western and Asian countries differ significantly in genetic backgrounds, dietary habits, and

lifestyles [54]. It is possible, however, that these indices may not be appropriate for Asian populations since they were most originally designed for western populations. Furthermore, most centers do not have external validation of these models, making it challenging to apply the proposed scoring system daily.

In a Japanese population, Wang et al. developed a novel model called the TyG-BMI index that could help predict NAFLD [34]. After adjusting for confounding variables, according to the study, NAFLD was positively associated with TyG-BMI (OR: 3.90 per SD increase; 95% CI 3.54 to 4.29). Analysis of ROC showed that the TyG-BMI was more effective at predicting NAFLD risk than other traditional indicators [TyG-BMI (AUC): 0.886; TyG (AUC): 0.808; TG (AUC): 0.797; BMI (AUC): 0.858; FPG (AUC): 0.711], especially among young and middle-aged individuals and individuals who aren’t obese. With the AUROC of 0.886 (95% CI 0.876, 0.896) in general populations and 0.88–0.97 in young and middle-aged people, and 0.84 in non-obese people (Additional file 7: Table S4), the results of the present study were consistent with Wang et al. [34]. However, hepatic steatosis commonly occurs in obese individuals. We consider the reasons for this phenomenon as follows. After further analysis of the baseline information of subjects for BMI stratification, we found that there were more non-obese women than men in this study. Sex differences in non-obese NAFLD have also been noted in some previous studies [55, 56]. There is a general tendency for females to have more subcutaneous and visceral fat [57, 58], and the BMI alone does not provide a complete picture of this information [56]. According to recent studies, people with non-obese NAFLD are more likely to develop metabolic diseases [59].

Wang et al. [59] carried out a receiver operating characteristic analysis that showed that the TyG-BMI could better predict the risk of NAFLD than other traditional indicators and obtained the optimal threshold for TyG-BMI. However, the performance of TyG-BMI has not been validated in an external population in the study of Wang et al. [34]. In addition, they did not explore two cut-off values of TyG-BMI to identify or exclude NAFLD and the corresponding positive and negative predictive values. It is essential to point out that although the optimal threshold had the largest Youden index, it is not associated with the greatest positive or negative predictive value. Therefore, a diagnostic and exclusion model of a disease requires 2 cut-off values, and the optimal threshold is not the best choice. To address this question, the present study developed and validated a simple, non-invasive, and cost-effective tool, TyG-BMI, to accurately separate participants with and without NAFLD in the Japanese population. A total of 2 cut-off values of TyG-BMI were found in this study, one for excluding

NAFLD and the other for diagnosing NALFD. The cut-off was 182.2 for the sensitivity of 0.894 and 224.0 for the specificity of 0.966 in the derivation cohort, leading to a negative predictive value of 0.969, a positive predictive value of 0.707, and an area under the ROC curve of 0.888 (95% CI 0.876–0.896). The results demonstrated that, as a result of applying this model, 9996 (70%) of the 14,280 participants would not have undergone ultrasonography, with an accurate prediction of 9308 (93.1%). Thereby facilitating the more accurate identification and selection of candidates for clinical intervention and reducing the number of unnecessary ultrasonography. Therefore, this model has good clinical application prospects.

In 2019, Mohammad et al. [36] developed triglyceride glucose index and related parameters (triglyceride glucose-waist circumference and triglyceride glucose-body mass index) to identify NAFLD in individuals with overweight/obesity in Iran. They found that TyG-WC showed the largest AUC for detection of NAFLD [0.693, 95% confidence interval (CI) 0.617–0.769], followed by TyG-index [0.676, 95% CI 0.598–0.754] and TyG-BMI (0.675, 95% CI 0.598–0.752). Another study [33] focuses on the association between TyG-BMI and NAFLD in the non-obese Chinese population with normal blood lipid levels. In their study, TyG-BMI had a good prediction value (0.85 area under ROC; 95% CI 0.84–0.86) for NAFLD incidence. The AUROCs of the two studies were a bit smaller than the present study. Besides, the AUROC of TyG-BMI was less than TyG for detecting NAFLD in the study of Mohammad E. et al.[36]. Several factors might explain the difference: (1) the study populations differed. The present study was performed on the general Japanese, while the above two studies focused on Iranian with overweight/obesity or the non-obese Chinese population with normal blood lipid levels. (2) The diagnosis method of NAFLD was different. There was a difference between ultrasonography and transient elastography. (3) The prevalence of NAFLD varied significantly by gender, age, dietary habits, and ethnicity [54].

Japanese dietary pattern is also different from Chinese dietary pattern. In the Japanese diet, the total energy is lower, and essential fatty acids (e.g., N-3 fatty acids) are higher because of more seafood consumption compared to the Chinese diet. NAFLD is a multifactorial disease related to a complex living environment, heredity, and dietary habits [52]. In patients with NAFLD, dietary n-3 polyunsaturated fatty acids (PUFAs) can reduce hepatic inflammation, fibrosis, and steatosis, lower plasma TG levels, and improve hepatic fatty acid metabolism [60]. Different dietary habits affected the prevalence of NAFLD in Chinese and Japanese populations, and the prevalence could affect the effectiveness of TyG-BMI in diagnosing NAFLD. However, our results validated in the

Chinese population suggest that the AUC was 0.874. The results indicate that TyG-BMI has an excellent ability to identify NAFLD in both Chinese and Japanese people.

Applying the TyG-BMI index, the results of the present study suggested that ultrasonography would only be needed to identify NAFLD in 30 percent of participants, i.e., those considered “indeterminate” (TyG-BMI in the range of 182.2–224). Most importantly, since most persons seen in clinical practice were not suffering from NAFLD [82.4% (11,765/14280) of the study cohort], the lower cutoff point was exceptionally accurate in ruling it out. In both estimation and validation, the NPV was 97% and 97%, respectively, and ranged from 75.6 to 98.3% for a prevalence of NAFLD of 5–50%. Among 14,280 patients, 8568 (60%) had a negative diagnosis of NAFLD through TyG-BMI (TyG-BMI below 182.2), and thus, using the TyG-BMI would have prevented the need for ultrasound. Of these 8568 participants diagnosed as not having NAFLD by TyG-BMI, 8304 (97%) were confirmed by ultrasound to have non-NAFLD indeed.

It should be pointed out that, clinically, US is the preferred imaging test for individuals with suspected NAFLD [61], with a typical appearance of a hyperechoic liver. In a recent meta-analysis, ultrasound showed 85% sensitivity and 94% specificity in diagnosing moderate-to-severe steatosis compared to histology [14]. In contrast, US could not detect steatosis of less than 20% [15] or steatosis in individuals with morbid obesity [16]. Moreover, ultrasound cannot determine how severe NAFLD steatosis is [17]. Using computed-assisted US hepatic/renal ratios and US hepatic attenuation rates, it is possible to detect NAFLD early [17, 62]. Compared to the conventional US, both measurements are excellent in detecting hepatic steatosis, with a sensitivity of 95% and specificity of 100%. However, the NPV is still low (72% for US H/R ratio and 67% for US hepatic attenuation rate) [17, 63]. In addition, by standardizing it with a tissue-mimicking phantom, this quantitative US model can improve its reliability and reproducibility, while these findings are needed to verify in further studies [63]. Above all, it is still recommended by current guidelines that US be used to diagnose moderate and severe steatosis [64]. Vibration-controlled transient elastography (TE) is one of the available non-invasive assessment tools for NAFLD. By generating vibrations of low frequency and mild amplitude, elastic shear waves propagate through liver tissues and are used for measuring stiffness [65]. With newer models, liver fibrosis can now be measured by liver stiffness measurement (LSM), and liver steatosis can be measured by controlled attenuation parameter (CAP) [66]. There are several benefits of TE, including its low cost, fast procedure time, immediate result availability, good reproducibility, and ability to be performed in

an outpatient setting [67]. Several cross-sectional studies have investigated how it helps diagnose NAFLD and assess its severity [63, 65, 68]. In conclusion, the quantitative US model and transient elastography will become a good non-invasive method for diagnosing NAFLD in the future, as an essential improvement of traditional ultrasonography.

Lipotoxicity in hepatocytes and immune-mediated inflammation play a crucial role in the development and progression of NAFLD. Hepatocellular injury caused by the lipotoxicity of accumulated lipids and free fatty acids (FFAs) is characterized by oxidative stress, endoplasmic reticulum stress, mitochondrial dysfunction, apoptosis, and subsequent expression of pro-inflammatory cytokines and inflammatory factors [69]. Apoptotic and immune pathways are activated as a consequence of cellular injury, which represents a distinctive feature of NASH pathophysiology. The lipotoxic lipids can activate both the intrinsic- and extrinsic-mediated (death receptor) apoptotic pathway in hepatocytes through the transcriptional up-regulation of proapoptotic and down-regulation of antiapoptotic proteins [70]. It is believed that apoptosis or other forms of hepatocyte cell death play a crucial role in promoting immune responses associated with the progression of NAFLD to a more severe stage, e.g., fibrosis and cirrhosis development [71].

Since oxidative stress is a significant feature of NAFLD, antioxidant therapy is of great value for NAFLD [23]. The Mediterranean diet, Silymarin and berberine could play an antioxidant role, thereby protecting liver cells [72–74]. In humans, only a small amount of oral antioxidants are absorbed because they are easily destroyed by acids and enzymes. Consequently, the development of effective methods for efficiently delivering antioxidants is urgently needed. Nano-antioxidants, created as a sponge-like polymer, act as a protective vehicle to prevent antioxidants from being degraded in the human gut and promote improved absorption in the digestive tract. A nanocapsule binds itself to the intestinal wall and releases antioxidants right into the intestinal cells, where they are absorbed directly into the bloodstream. Numerous antioxidant units are connected in a branched pattern to form nano-antioxidants. It could provide numerous possible sites to couple with an active species and have enhanced free radical scavenging potency [75].

The current study has some strengths, as follows: (1) the present study included a sizable sample size and diverse individuals, making it simple to publicize outside of the study. (2) TyG-BMI is determined using objective clinical and easily accessible lab variables routinely measured during health checkups, without requiring any other tests. (3) The authors explored two cutoff points used to identify or exclude NAFLD and used a wide range of

prevalence of NAFLD varying from 5 to 50% to study the changes in positive and negative predictive values. (4) Using our decision curve analysis, TyG-BMI's clinical effectiveness was demonstrated, and individuals with low-risk NAFLD would not require additional screening (such as ultrasonography). (5) The authors validated the results both internally and externally to make sure they were reliable.

Despite TyG-BMI's good performance, the study still has some potential limitations. First, due to its imperfect sensitivity, ultrasonography is not a gold standard in diagnosing NAFLD. The liver biopsy in asymptomatic people was typically not available in this considerable population-based investigation. Besides, patients with BMI on extreme ends of the spectrum may skew the ratio and can lead to decrease sensitivity and predictive value for the NAFLD. In the future, we could design our studies to diagnose NAFLD with more appropriate methods, such as the quantitative US model and transient elastography. We could also compare TyG-BMI against liver biopsy, a definitive test to establish the diagnosis of NAFLD. Second, the authors did not receive information about the severity of hepatic steatosis, so we could not evaluate the ability of TyG-BMI to quantify hepatic steatosis. Third, in this study, the development and validation of the diagnostic value of TyG-BMI for NAFLD were conducted in Asians. The diagnostic effect of NAFLD in non-Asian populations may be limited. However, some other western-derived indices for diagnosing NAFLD, such as FLI, Framingham steatosis index (FSI), and LAP, have been validated in Asians. And they were valuable indices for identifying the presence of NAFLD [76–79]. So, we tend to believe that the TyG-BMI index could help predict NAFLD in populations other than Asians. Fourth, this was a cross-sectional study, and we could not explore the predictive value of TyGBMI for the occurrence of NAFLD in the future.

Conclusion

TyG-BMI, constructed from routine clinical and laboratory variables, is able to accurately diagnose NAFLD, thus rendering ultrasonography unnecessary for the vast majority of populations. TyG-BMI, therefore, could be used to identify candidates for hepatic ultrasound and those who need lifestyle modifications.

Abbreviations

Ref: Reference; FPG: Fasting blood glucose; PPV: Positive predictive value; TG: Triglyceride; NPV: Negative predictive value; US: Ultrasonography; MRS: Magnetic resonance spectroscopy; MRI: Magnetic resonance imaging; HDL-c: High-density lipoprotein cholesterol; BMI: Body mass index; PLR: Positive likelihood ratio; WC: Waist circumference; NLR: Negative likelihood ratio; GGT: Gamma-glutamyl transferase; LR: Likelihood ratios; OR: Odds ratio; ROC: Receiver operating characteristic; AST: Aspartate aminotransferase; AUC: Area

under the curve; TyG index: Triglyceride-glucose index; TC: Total cholesterol; SP: Specificity; DBP: Diastolic blood pressure; SN: Sensitivity; IR: Insulin resistance; AUROC: Area under the receiver-operating characteristic curve; VAI: Visceral adiposity index; LAP: Lipid accumulation product; ALT: Alanine aminotransferase; LDL-c: Low density lipoprotein cholesterol; HIS: Hepatic steatosis index; PUFAs: Polyunsaturated fatty acids; H/R ratio: Hepatic/renal ratio; TE: Transient elastography; LSM: Liver stiffness measurement; CAP: Controlled attenuation parameter; FFAs: Free fatty acids; NASH: Non-alcoholic steatohepatitis; CI: Confidence interval; SBP: Systolic blood pressure; TyG-BMI: Triglyceride glucose-body mass index; SD: Standard deviation; NAFLD: Non-alcoholic fatty liver disease; HbA1c: Hemoglobin A1c.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12967-022-03611-4>.

Additional file 1: Fig. S1 Distribution of TyG-BMI in the development(A) and validation groups(B)

Additional file 2: Fig. S2 Prevalence of NAFLD according to the quartiles of TyG-BMI

Additional file 3: Fig. S3 The ROC curve of the development group after using bootstrap resampling validation (times=500)

Additional file 4: Fig. S4 The ROC curve of the validation group after using bootstrap resampling validation (times=500)

Additional file 5: Fig. S5 The ROC curves of TyG-BMI in the external validation group

Additional file 6: Fig. S6 The decision curve analysis of TyG-BMI for NAFLD in the external validation group

Additional file 7: Table S1 The optimal cutoff point of 189 for the TyG-BMI in diagnosing NAFLD. **Table S2** Performance of the tests for diagnosis/exclusion of NAFLD by different subgroups in the validation group.

Table S3 Baseline characteristics of the external verification. **Table S4** Performance of the tests for diagnosing NAFLD by BMI subgroups in the development group

Acknowledgements

As this is a secondary analysis, the data and method descriptions are primarily derived from the following studies: Okamura T, Hashimoto Y, Hamaguchi M, et al. Ectopic fat obesity presents the greatest risk for incident type 2 diabetes: a population-based longitudinal study. *Int J Obes (Lond)*. 2019 Jan; 43(1):139–148. <https://doi.org/10.1038/s41366-018-0076-3>. We are grateful to all the authors of the study.

Author contributions

Haofei Hu and Yong Han drafted and analyzed the manuscript as well as conceived and designed the research. Changchun Cao took part in the discussion. Yongcheng HE revised the manuscript. Final approval of the manuscript was obtained from all authors. All authors read and approved the final manuscript.

Funding

This study was partly supported by the Discipline Construction Ability Enhancement Project of the Shenzhen Municipal Health Commission (SZXJ2017031) and the Shenzhen Science and Technology Innovation Committee (JCYJ20210324133412033).

Availability of data and materials

Data can be downloaded from the 'DATADRYAD' database (<https://datadryad.org/stash>).

Declarations

Ethics approval and consent to participate

In the previously published article [37], Takuro Okamura et al. stated the study was conducted according to the Declaration of Helsinki, and the Ethics Committee of Murakami Memorial Hospital approved the original research.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

All subjects provided informed consent [37].

Author details

¹Department of Nephrology, The First Affiliated Hospital of Shenzhen University, Shenzhen 518000, Guangdong, China. ²Department of Nephrology, Shenzhen Second People's Hospital, Shenzhen 518000, Guangdong, China. ³Department of Emergency, Shenzhen Second People's Hospital, Shenzhen 518000, Guangdong, China. ⁴Department of Emergency, The First Affiliated Hospital of Shenzhen University, Shenzhen 518000, Guangdong, China. ⁵Shenzhen University Health Science Center, Shenzhen 518071, Guangdong, China. ⁶Department of Rehabilitation, Shenzhen Dapeng New District Nan'ao People's Hospital, No. 6, Renmin Road, Dapeng New District, Shenzhen 518000, Guangdong, China. ⁷Department of Nephrology, Shenzhen Hengsheng Hospital, No. 20 Yintian Road, Baoan District, Shenzhen 518000, Guangdong, China.

Received: 28 June 2022 Accepted: 24 August 2022

Published online: 05 September 2022

References

- Rinella ME. Nonalcoholic fatty liver disease: a systematic review. *JAMA*. 2015;313:2263–73.
- Raj H, Durgja H, Palui R, Kamalanathan S, Selvarajan S, Kar SS, Sahoo J. SGLT-2 inhibitors in non-alcoholic fatty liver disease patients with type 2 diabetes mellitus: a systematic review. *World J Diabetes*. 2019;10:114–32.
- Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther*. 2011;34:274–85.
- Calzadilla BL, Adams LA. The natural course of non-alcoholic fatty liver disease. *Int J Mol Sci*. 2016;17:774.
- Soon G, Wee A. Updates in the quantitative assessment of liver fibrosis for nonalcoholic fatty liver disease: histological perspective. *Clin Mol Hepatol*. 2021;27:44–57.
- Söderberg C, Stål P, Askling J, Glaumann H, Lindberg G, Marmur J, Hultcrantz R. Decreased survival of subjects with elevated liver function tests during a 28-year follow-up. *Hepatology*. 2010;51:595–602.
- Sanyal AJ, Harrison SA, Ratziu V, Abdelmalek MF, Diehl AM, Caldwell S, Shiffman ML, Aguilar SR, Jia C, McColgan B, et al. The Natural history of advanced fibrosis due to nonalcoholic steatohepatitis: data from the simtuzumab trials. *Hepatology*. 2019;70:1913–27.
- Byrne CD, Targher G. NAFLD: a multisystem disease. *J Hepatol*. 2015;62:S47–64.
- Adams LA, Anstee QM, Tilg H, Targher G. Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. *Gut*. 2017;66:1138–53.
- Ballestri S, Mantovani A, Nascimbeni F, Lugari S, Lonardo A. Extra-hepatic manifestations and complications of nonalcoholic fatty liver disease. *Future Med Chem*. 2019;11:2171–92.
- Wang XJ, Malhi H. Nonalcoholic fatty liver disease. *Ann Intern Med*. 2018;169:C65–80.
- Chalasanani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ. The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology*. 2012;55:2005–23.
- Davison BA, Harrison SA, Cotter G, Alkhoury N, Sanyal A, Edwards C, Colca JR, Iwashita J, Koch GG, Dittrich HC. Suboptimal reliability of liver biopsy evaluation has implications for randomized clinical trials. *J Hepatol*. 2020;73:1322–32.
- Hernaes R, Lazo M, Bonekamp S, Kamel I, Brancati FL, Guallar E, Clark JM. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. *Hepatology*. 2011;54:1082–90.
- Chalasanani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, Harrison SA, Brunt EM, Sanyal AJ. The diagnosis and management of nonalcoholic

- fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*. 2018;67:328–57.
16. Fedchuk L, Nascimbeni F, Pais R, Charlotte F, Housset C, Ratziu V. Performance and limitations of steatosis biomarkers in patients with nonalcoholic fatty liver disease. *Aliment Pharmacol Ther*. 2014;40:1209–22.
 17. Zhang B, Ding F, Chen T, Xia LH, Qian J, Lv GY. Ultrasound hepatic/renal ratio and hepatic attenuation rate for quantifying liver fat content. *World J Gastroenterol*. 2014;20:17985–92.
 18. Dasarathy S, Dasarathy J, Khiyami A, Joseph R, Lopez R, McCullough AJ. Validity of real time ultrasound in the diagnosis of hepatic steatosis: a prospective study. *J Hepatol*. 2009;51:1061–7.
 19. Zhou JH, Cai JJ, She ZG, Li HL. Noninvasive evaluation of nonalcoholic fatty liver disease: current evidence and practice. *World J Gastroenterol*. 2019;25:1307–26.
 20. Castera L, Friedrich-Rust M, Loomba R. Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease. *Gastroenterology*. 2019;156:1264–81.
 21. Cai J, Zhang XJ, Li H. Progress and challenges in the prevention and control of nonalcoholic fatty liver disease. *Med Res Rev*. 2019;39:328–48.
 22. Finck BN. Targeting metabolism, insulin resistance, and diabetes to treat nonalcoholic steatohepatitis. *Diabetes*. 2018;67:2485–93.
 23. Masarone M, Rosato V, Dallio M, Gravina AG, Aglitti A, Loguercio C, Federico A, Persico M. Role of oxidative stress in pathophysiology of non-alcoholic fatty liver disease. *Oxid Med Cell Longev*. 2018;2018:9547613.
 24. Alkhoury N, Dixon LJ, Feldstein AE. Lipotoxicity in nonalcoholic fatty liver disease: not all lipids are created equal. *Expert Rev Gastroenterol Hepatol*. 2009;3:445–51.
 25. Aronis A, Madar Z, Tirosh O. Mechanism underlying oxidative stress-mediated lipotoxicity: exposure of J774.2 macrophages to triacylglycerols facilitates mitochondrial reactive oxygen species production and cellular necrosis. *Free Radic Biol Med*. 2005;38:1221–30.
 26. Geering B, Stoeckle C, Conus S, Simon HU. Living and dying for inflammation: neutrophils, eosinophils, basophils. *Trends Immunol*. 2013;34:398–409.
 27. de Freitas CM, Lage NN, de Souza PA, Pereira RR, de Almeida LT, Da ST, de Brito MC, de Lima WG, Silva ME, Pedrosa ML, Da CGJ. Effects of açai on oxidative stress, ER stress, and inflammation-related parameters in mice with high fat diet-fed induced NAFLD. *Sci Rep*. 2019;9:8107.
 28. Khan RS, Bril F, Cusi K, Newsome PN. Modulation of insulin resistance in nonalcoholic fatty liver disease. *Hepatology*. 2019;70:711–24.
 29. Guerrero-Romero F, Simental-Mendía LE, González-Ortiz M, Martínez-Abundis E, Ramos-Zavala MG, Hernández-González SO, Jacques-Camarena O, Rodríguez-Morán M. The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemic-hyperinsulinemic clamp. *J Clin Endocrinol Metab*. 2010;95:3347–51.
 30. Sánchez-García A, Rodríguez-Gutiérrez R, Mancillas-Adame L, González-Nava V, Díaz GA, Solís RC, Álvarez-Villalobos NA, González-González JG. Diagnostic accuracy of the triglyceride and glucose index for insulin resistance: a systematic review. *Int J Endocrinol*. 2020;2020:4678526.
 31. Dikaiakou E, Vlachopapadopoulou EA, Paschou SA, Athanasouli F, Panagiotopoulos I, Kafetzi M, Fotinou A, Michalacos S. Triglycerides-glucose (TyG) index is a sensitive marker of insulin resistance in Greek children and adolescents. *Endocrine*. 2020;70:58–64.
 32. Er LK, Wu S, Chou HH, Hsu LA, Teng MS, Sun YC, Ko YL. Triglyceride glucose-body mass index is a simple and clinically useful surrogate marker for insulin resistance in nondiabetic individuals. *PLoS One*. 2016;11:e149731.
 33. Li Y, Zheng R, Li J, Feng S, Wang L, Huang Z. Association between triglyceride glucose-body mass index and non-alcoholic fatty liver disease in the non-obese Chinese population with normal blood lipid levels: a secondary analysis based on a prospective cohort study. *Lipids Health Dis*. 2020;19:229.
 34. Wang R, Dai L, Zhong Y, Xie G. Usefulness of the triglyceride glucose-body mass index in evaluating nonalcoholic fatty liver disease: insights from a general population. *Lipids Health Dis*. 2021;20:77.
 35. Zhang S, Du T, Li M, Jia J, Lu H, Lin X, Yu X. Triglyceride glucose-body mass index is effective in identifying nonalcoholic fatty liver disease in nonobese subjects. *Medicine*. 2017;96:e7041.
 36. Khamseh ME, Malek M, Abbasi R, Taheri H, Lahouti M, Alaei-Shahmiri F. Triglyceride glucose index and related parameters (triglyceride glucose-body mass index and triglyceride glucose-waist circumference) identify nonalcoholic fatty liver and liver fibrosis in individuals with overweight/obesity. *Metab Syndr Relat D*. 2021;19:167–73.
 37. Okamura T, Hashimoto Y, Hamaguchi M, Obora A, Kojima T, Fukui M. Ectopic fat obesity presents the greatest risk for incident type 2 diabetes: a population-based longitudinal study. *Int J Obesity*. 2019;43:139–48.
 38. Okamura TEA. Data from: ectopic fat obesity presents the greatest risk for incident type 2 diabetes: a population-based longitudinal study. 2018. Dryad, Dataset. <https://doi.org/10.5061/dryad.8q0p192>.
 39. Lee J, Ha J, Jo K, Lim DJ, Lee JM, Chang SA, Kang MI, Kim MH. High normal range of free thyroxine is associated with decreased triglycerides and with increased high-density lipoprotein cholesterol based on population representative data. *J Clin Med*. 2019;8:758.
 40. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, Carty C, Chaput JP, Chastin S, Chou R, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med*. 2020;54:1451–62.
 41. Hamaguchi M, Kojima T, Itoh Y, Harano Y, Fujii K, Nakajima T, Kato T, Takeda N, Okuda J, Ida K, et al. The severity of ultrasonographic findings in nonalcoholic fatty liver disease reflects the metabolic syndrome and visceral fat accumulation. *Am J Gastroenterol*. 2007;102:2708–15.
 42. Nalls MA, McLean CY, Rick J, Eberly S, Hutten SJ, Gwinn K, Sutherland M, Martinez M, Heutink P, Williams NM, et al. Diagnosis of Parkinson's disease on the basis of clinical and genetic classification: a population-based modelling study. *Lancet Neurol*. 2015;14:1002–9.
 43. Sun DQ, Wu SJ, Liu WY, Wang LR, Chen YR, Zhang DC, Braddock M, Shi KQ, Song D, Zheng MH. Association of low-density lipoprotein cholesterol within the normal range and NAFLD in the non-obese Chinese population: a cross-sectional and longitudinal study. *BMJ Open*. 2016;6:e13781.
 44. Fitzgerald M, Saville BR, Lewis RJ. Decision curve analysis. *JAMA*. 2015;313:409–10.
 45. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, Lijmer JG, Moher D, Rennie D, de Vet HC, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *BMJ*. 2015;351:h5527.
 46. Machado MV, Cortez-Pinto H. Non-invasive diagnosis of non-alcoholic fatty liver disease. A critical appraisal. *J Hepatol*. 2013;58:1007–19.
 47. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, Tiribelli C. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. *Bmc Gastroenterol*. 2006;6:33.
 48. Motamed N, Faraji AH, Khonsari MR, Maadi M, Tameshkel FS, Keyvani H, Ajdarkosh H, Karbalaie Niya MH, Rezaie N, Zamani F. Fatty liver index (FLI) and prediction of new cases of non-alcoholic fatty liver disease: a population-based study of northern Iran. *Clin Nutr*. 2020;39:468–74.
 49. Lee J, Kim D, Kim HJ, Lee C, Yang JI, Kim W, Kim YJ, Yoon J, Cho S, Sung M, Lee H. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. *Digest Liver Dis*. 2010;42:503–8.
 50. Kahn HS. The “lipid accumulation product” performs better than the body mass index for recognizing cardiovascular risk: a population-based comparison. *BMC Cardiovasc Disord*. 2005;5:26.
 51. Amato MC, Giordano C, Galia M, Criscimanna A, Vitabile S, Midiri M, Galluzzo A. Visceral adiposity index: a reliable indicator of visceral fat function associated with cardiometabolic risk. *Diabetes Care*. 2010;33:920–2.
 52. Oyarzún JE, Andia ME, Uribe S, Núñez PP, Núñez G, Montenegro G, Bridi R. Honeybee pollen extracts reduce oxidative stress and steatosis in hepatic cells. *Molecules*. 2020;26:6.
 53. Dongiovanni P, Valenti L. A Nutrigenomic approach to non-alcoholic fatty liver disease. *Int J Mol Sci*. 2017;18:1534.
 54. Lin Y, Gong X, Li X, Shao C, Wu T, Li M, Li F, Ma Q, Ye J, Zhong B. Distinct cause of death profiles of hospitalized non-alcoholic fatty liver disease: a 10 years' cross-sectional multicenter study in China. *Front Med*. 2020;7:584396.
 55. Sheng G, Xie Q, Wang R, Hu C, Zhong M, Zou Y. Waist-to-height ratio and non-alcoholic fatty liver disease in adults. *Bmc Gastroenterol*. 2021;21:239.
 56. Zou Y, Sheng G, Yu M, Xie G. The association between triglycerides and ectopic fat obesity: an inverted U-shaped curve. *PLoS One*. 2020;15:e243068.
 57. Palmer BF, Clegg DJ. The sexual dimorphism of obesity. *Mol Cell Endocrinol*. 2015;402:113–9.
 58. Swainson MG, Batterham AM, Hind K. Age- and sex-specific reference intervals for visceral fat mass in adults. *Int J Obes*. 2020;44:289–96.

59. Kwon YM, Oh SW, Hwang SS, Lee C, Kwon H, Chung GE. Association of nonalcoholic fatty liver disease with components of metabolic syndrome according to body mass index in Korean adults. *Am J Gastroenterol*. 2012;107:1852–8.
60. Liu L, Hu Q, Wu H, Wang X, Gao C, Chen G, Yao P, Gong Z. Dietary DHA/EPA ratio changes fatty acid composition and attenuates diet-induced accumulation of lipid in the liver of ApoE (–/–) mice. *Oxid Med Cell Longev*. 2018;2018:6256802.
61. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol*. 2016;64:1388–402.
62. Xia MF, Yan HM, He WY, Li XM, Li CL, Yao XZ, Li RK, Zeng MS, Gao X. Standardized ultrasound hepatic/renal ratio and hepatic attenuation rate to quantify liver fat content: an improvement method. *Obesity*. 2012;20:444–52.
63. Xiao G, Zhu S, Xiao X, Yan L, Yang J, Wu G. Comparison of laboratory tests, ultrasound, or magnetic resonance elastography to detect fibrosis in patients with nonalcoholic fatty liver disease: a meta-analysis. *Hepatology*. 2017;66:1486–501.
64. Zhu J, He M, Zhang Y, Li T, Liu Y, Xu Z, Chen W. Validation of simple indexes for nonalcoholic fatty liver disease in western China: a retrospective cross-sectional study. *Endocr J*. 2018;65:373–81.
65. Zhang X, Wong GL, Wong VW. Application of transient elastography in nonalcoholic fatty liver disease. *Clin Mol Hepatol*. 2020;26:128–41.
66. de Lédinghen V, Wong GL, Vergniol J, Chan HL, Hiriart JB, Chan AW, Chermak F, Choi PC, Foucher J, Chan CK, et al. Controlled attenuation parameter for the diagnosis of steatosis in non-alcoholic fatty liver disease. *J Gastroenterol Hepatol*. 2016;31:848–55.
67. Liu SY, Wong VW, Wong SK, Wong GL, Lai CM, Lam CC, Shu SS, Chan HL, Ng EK. A prospective 5-year study on the use of transient elastography to monitor the improvement of non-alcoholic fatty liver disease following bariatric surgery. *Sci Rep*. 2021;11:5416.
68. Kwok R, Tse YK, Wong GL, Ha Y, Lee AU, Ngu MC, Chan HL, Wong VW. Systematic review with meta-analysis: non-invasive assessment of non-alcoholic fatty liver disease—the role of transient elastography and plasma cytokeratin-18 fragments. *Aliment Pharmacol Ther*. 2014;39:254–69.
69. Reccia I, Kumar J, Akladios C, Virdis F, Pai M, Habib N, Spalding D. Non-alcoholic fatty liver disease: a sign of systemic disease. *Metabolism*. 2017;72:94–108.
70. Malhi H, Gores GJ. Molecular mechanisms of lipotoxicity in nonalcoholic fatty liver disease. *Semin Liver Dis*. 2008;28:360–9.
71. Parthasarathy G, Revelo X, Malhi H. Pathogenesis of nonalcoholic steatohepatitis: an overview. *Hepatol Commun*. 2020;4:478–92.
72. Eftekhari A, Hasanzadeh A, Khalilov R, Hosainzadegan H, Ahmadian E, Eghbal MA. Hepatoprotective role of berberine against paraquat-induced liver toxicity in rat. *Environ Sci Pollut Res Int*. 2020;27:4969–75.
73. Biccirè FG, Bucci T, Menichelli D, Cammisotto V, Pignatelli P, Carnevale R, Pastori D. Mediterranean diet: a tool to break the relationship of atrial fibrillation with the metabolic syndrome and non-alcoholic fatty liver disease. *Nutrients*. 2022;14:1260.
74. Mandegary A, Saeedi A, Eftekhari A, Montazeri V, Sharif E. Hepatoprotective effect of silymarin in individuals chronically exposed to hydrogen sulfide; modulating influence of TNF- α cytokine genetic polymorphism. *Daru*. 2013;21:28.
75. Watal G, Watal A, Rai PK, Rai DK, Sharma G, Sharma B. Biomedical applications of nano-antioxidant. *Methods Mol Biol*. 2013;1028:147–51.
76. Kim JH, Kwon SY, Lee SW, Lee CH. Validation of fatty liver index and lipid accumulation product for predicting fatty liver in Korean population. *Liver Int*. 2011;31:1600–1.
77. Huang X, Xu M, Chen Y, Peng K, Huang Y, Wang P, Ding L, Lin L, Xu Y, Chen Y, et al. Validation of the fatty liver index for nonalcoholic fatty liver disease in middle-aged and elderly Chinese. *Medicine*. 2015;94:e1682.
78. Chen LW, Huang PR, Chien CH, Lin CL, Chien RN. A community-based study on the application of fatty liver index in screening subjects with nonalcoholic fatty liver disease. *J Formos Med Assoc*. 2020;119:173–81.
79. Jung TY, Kim MS, Hong HP, Kang KA, Jun DW. Comparative assessment and external validation of hepatic steatosis formulae in a community-based setting. *J Clin Med*. 2020;9:2851.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

