Zhu *et al.*
European Journal of Medical Research (2025) 30:137
https://doi.org/10.1186/s40001-025-02373-1

European Journal
of Medical Research

REVIEW

Open Access

Risk factor analysis and predictive model construction of lean MAFLD: a cross-sectional study of a health check-up population in China

Ruya Zhu[1], Caicai Xu[2], Suwen Jiang[1], Jianping Xia[1], Boming Wu[1], Sijia Zhang[1], Jing Zhou[1], Hongliang Liu[1], Hongshan Li[1*] and Jianjun Lou[2*]

Abstract

Aim Cardiovascular disease morbidity and mortality rates are high in patients with metabolic dysfunction-associated fatty liver disease (MAFLD). The objective of this study was to analyze the risk factors and differences between lean MAFLD and overweight MAFLD, and establish and validate a nomogram model for predicting lean MAFLD.

Methods This retrospective cross-sectional study included 4363 participants who underwent annual health checkup at Yuyao from 2019 to 2022. The study population was stratified into three groups: non-MAFLD, lean MAFLD (defined as the presence of fatty liver changes as determined by ultrasound in individuals with a BMI < 25 kg/m^2), and overweight MAFLD (BMI ≥ 25.0 kg/m^2). Subsequent modeling analysis was conducted in a population that included healthy subjects with < 25 kg/m^2 ($n = 2104$) and subjects with lean MAFLD ($n = 849$). The study population was randomly split (7:3 ratio) to a training vs. a validation cohort. Risk factors for lean MAFLD was identify by multivariate regression of the training cohort, and used to construct a nomogram to estimate the probability of lean MAFLD. Model performance was examined using the receiver operating characteristic (ROC) curve analysis and k-fold cross-validation ($k = 5$). Decision curve analysis (DCA) was applied to evaluate the clinical usefulness of the prediction model.

Results The multivariate regression analysis indicated that the triglycerides and glucose index (TyG) was the most significant risk factor for lean MAFLD (OR: 4.03, 95% CI 2.806–5.786). The restricted cubic spline curves (RCS) regression model demonstrated that the relationships between systolic pressure (SBP), alanine aminotransferase (ALT), serum urate (UA), total cholesterol (TCHO), triglyceride (TG), triglyceride glucose (TyG) index, high density lipoprotein cholesterol (HDLC), and MAFLD were nonlinear and the cutoff values for lean MAFLD and overweight MAFLD were different. The nomogram was constructed based on seven predictors: glycosylated hemoglobin A1c (HbA1c), serum ferritin (SF), ALT, UA, BMI, TyG index, and age. In the validation cohort, the area under the ROC curve was 0.866 (95% CI 0.842–0.891), with 83.8% sensitivity and 76.6% specificity at the optimal cutoff. The PPV and NPV was 63.3% and 90.8%, respectively. Furthermore, we used fivefold cross-validation and the average area under the ROC curve was 0.866 (Figure S3). The calibration curves for the model's predictions and the actual outcomes were in good agreement. The DCA findings demonstrated that the nomogram model was clinically useful throughout a broad threshold probability range.

*Correspondence:
Hongshan Li
lihongshan_1982@126.com
Jianjun Lou
jun020425@163.com

Conclusions Lean and overweight MAFLD exhibit distinct metabolic profiles. The nomogram model developed in this study is designed to assist clinicians in the early identification of high-risk individuals with lean MAFLD, including those with a normal BMI but at metabolic risk, as well as those with abnormal blood lipid, glucose, uric acid or transaminase levels. In addition, this model enhances screening efforts in communities and medical screening centers, ultimately ensuring more timely and effective medical services for patients.

Keywords Lean MAFLD, Overweight MAFLD, Risk factors, Health check-up population, Nomogram prediction model

Introduction

MAFLD, formerly known as nonalcoholic fatty liver disease (NAFLD), is a metabolic disorder involving multiple systems. MAFLD is strongly associated with metabolic syndrome (MetS) and the related complications, including obesity, hypertension, hyperlipidemia, chronic kidney disease, and cardiovascular disease [1–4]. The global adult prevalence of MAFLD ranges from 25.2% to 29.8% [5]. The adult prevalence of MAFLD in China ranges from 6.3% to 27% and is increasing [6–9]; MAFLD can progress from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma, ultimately leading to death, and is expected to become the main indication for liver transplantation, posing a serious risk to human health [9–11]. The prevalence and severity of MAFLD gradually increase as the prevalence of obesity increases [12]. The prevalence of MAFLD in the overweight population was 69.99% [13]. However, some patients with MAFLD have a normal or even low BMI. Compared with overweight NAFLD, lean NAFLD has significantly less metabolic dysfunction [14]. However, other studies have shown that metabolic dysfunction is more common in lean NAFLD [15–17]. Compared with overweight MAFLD, individuals with lean MAFLD have a worse prognosis and a more rapid progression to cirrhosis with hepatic and nonhepatic comorbidities [18]. Mortality is almost twofold higher for lean MAFLD compared with overweight MALFD [19]. Currently, the precise etiology and pathogenesis of lean MAFLD are unclear. The development of lean MAFLD is influenced by a multitude of factors, including hyperandrogenemia, excess accumulation of visceral fat, muscular atrophy, unhealthy dietary habits, gut microbiota dysbiosis, and genetic susceptibility [20–24]. Although patients with lean MAFLD typically do not exhibit the conventional risk factors associated with obesity, they may still experience issues, such as visceral fat accumulation. These, coupled with metabolic disorders, such as insulin resistance, dyslipidemia, and inflammatory responses, collectively contribute to the development of MAFLD. Furthermore, recent research suggests that the increased mortality in lean MAFLD patients compared to non-lean MAFLD patients could be partially attributed to shorter telomere length [25]. Therefore, comprehensive management and treatment strategies for patients with lean MAFLD should take into account these multiple factors to reduce disease risk and improve prognosis. However, lean MAFLD patients usually have a normal BMI, making early diagnosis difficult. Imaging tests such as FibroScan and magnetic resonance imaging–proton density fat fraction (MRI–PDFF) are accurate but impractical for routine screening. Moreover, no specific guidelines and diagnostic criteria are available for the early detection of lean MAFLD. Therefore, developing a simple, noninvasive, and effective clinical predictive model to accurately screen for lean MAFLD is crucial. The model will enable timely detection and intervention in the early stages of the disease to minimize the associated complications.

In the big data era, clinical predictive modeling based on data mining improves the diagnosis and monitoring of diseases. The nomogram predictive model is an intuitive scoring system that evaluates the correlation of variables with outcome events, allowing the calculation of risk probabilities for outcome events [26]. Some research mentions Nomogram prediction models regarding MAFLD or obese NAFLD [27, 28]. However, the nomogram prediction model has not been widely applied to lean MAFLD. In addition, the clinical data incorporated into the nomogram may differ due to the varying prevalence of lean MAFLD in different regions. Developing simple and practical methods for the early identification of lean MAFLD is important in guiding early intervention.

Materials and methods

Study design and participants

This study included 4363 participants who underwent medical checkups with complete liver ultrasound data at Yuyao People's Hospital, in Ningbo, China from June 13, 2019 to December 14, 2022. The diagnosis of MAFLD was based on evidence of hepatic steatosis on ultrasound and the following conditions: overweight or obesity, diabetes mellitus, and metabolic dysfunction. Diagnosis of metabolic dysfunction required at least two of the following criteria [29]: (1) male waist circumference ≥ 90 cm, female waist circumference ≥ 80 cm; (2) hypertension;

(3) TG) ≥ 1.70 mmol/L or on lipid-lowering therapy); (4) HDLC < 1.0 mmol/L in males, HDLC < 1.3 mmol/L in females; and (5) prediabetes. The exclusion criteria were as follows: (1) excessive alcohol consumption (140 g/week for men and 70 g/week for women); (2) serologic and virological diagnosis of hepatitis B, hepatitis C, or autoimmune liver disease; (3) drug-induced liver disease; (4) metabolic liver diseases, such as hepatolenticular degeneration; and (5) missing key biochemical indicators.

The study population was divided into three groups: non-MAFLD, lean MAFLD (BMI < 25 kg/m^2), and overweight MAFLD (BMI ≥ 25.0 kg/m^2). Normal TG levels were defined as < 1.7 mmol/L and hyperlipidemia was defined as TG ≥ 1.7 mmol/L.

Data collection

The following patient information was collected: gender, age, height, weight, blood pressure, and prior medical history. In addition, the following clinical information was collected from the electronic case system: fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), TG, total cholesterol (TCHO), HDLC, low-density lipoprotein cholesterol, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein, albumin, globulin, white blood cell ratio, direct bilirubin, indirect bilirubin, glutamyl transpeptidase (GGT), alkaline phosphatase, creatinine, urea, uric acid (UA), serum ferritin (SF), platelets (PLT), neutrophils, lymphocytes, mean red blood cell volume, and hemoglobin. TyG, platelet-to-lymphocyte ratio, and neutrophil-to-platelet ratio (NPR) were calculated. NPR was calculated as follows:

$$\begin{aligned} \mathrm{NPR} &= \mathrm{NE/PLT} \times 1000,\ \mathrm{TyG} \\ &= \mathrm{Ln}\left[\mathrm{TG}\left(\mathrm{mg/dl}\right)\right] \times \mathrm{FPG}\left(\mathrm{mg/dl}\right)/2]. \end{aligned}$$

Statistical analyses

First, irrelevant variables were deleted, and missing values were filled using stratified mean values. Statistical analyses were performed using SPSS software (version 26.0), RStudio software with the rms package, ggplot2 package, and sci package. To improve the robustness and reliability of our conclusions, the lean MAFLD and no-MAFLD populations were randomly divided into a training and a validation cohort at a 7:3 ratio. Continuous variables were expressed as means ± standard deviations or medians ± interquartile ranges. Categorical values were expressed using relative frequencies and proportions. Data that conformed to normal distribution and homogeneity of variance were compared with a one-way analysis of variance. Data that did not conform to normal distribution were compared using the Kruskal–Wallis H test with Bonferroni correction post hoc pairwise comparisons. To explore nonlinear data, restricted cubic spline curves (RCS) were applied followed by the construction of a two-piecewise linear regression model to calculate the turning point. For linear regression analyses, covariate diagnostics were performed to rule out covariates, with a variance inflation factor of > 10 indicating covariance between factors. A univariate logistic regression analysis combined with a multivariate logistic regression analysis (forward-LR) was performed to select the optimal predictive factors with a p value threshold of 0.05. Based on the regression results, seven parameters were selected to construct a nomogram to predict the probability of having lean MAFLD. We assess diagnostic accuracy of models using ROC analysis and k-fold cross-validation ($k = 5$), evaluate consistency between predicted and actual observed probabilities with a calibration curve, and determine the clinical utility of the nomogram model through DCA. Differences were considered to be statistically significant at $P < 0.05$.

In addition, Sample size calculation in this study was done through PASS 15.0 software. Given that the prevalence of lean MAFLD is approximately 20%, the confidence level was set at 0.95 and the width of the two-sided confidence interval was 0.05, which was calculated to require a sample size of 1022. In this research, the sample size actually collected was 4363. The statistical efficacy of the study was improved by increasing the sample size, thus reducing the effect of random error.

Results

Participant characteristics

A total of 4363 participants who met the inclusion and exclusion criteria participated in the study. The flow chart of the study design is shown in Fig. 1. The characteristics are shown in Table 1. This study included 849 (19.46%) patients with lean MAFLD, 1410 (32.32%) patients with overweight MAFLD, and 2104 (48.22%) patients with non-MAFLD. Participants with MAFLD had lower HDLC, elevated blood pressure, elevated UA, and elevated FPG compared with participants with non-MAFLD, indicating that more participants with MAFLD had MetS.

To improve the robustness and reliability of our conclusions, participants with lean MAFLD and non-MAFLD were randomly divided at a ratio of 7:3 into training (n = 2067) and validation (n = 886) cohort. The significantly different metabolic parameters in the validation and training data sets are shown in Table 2.

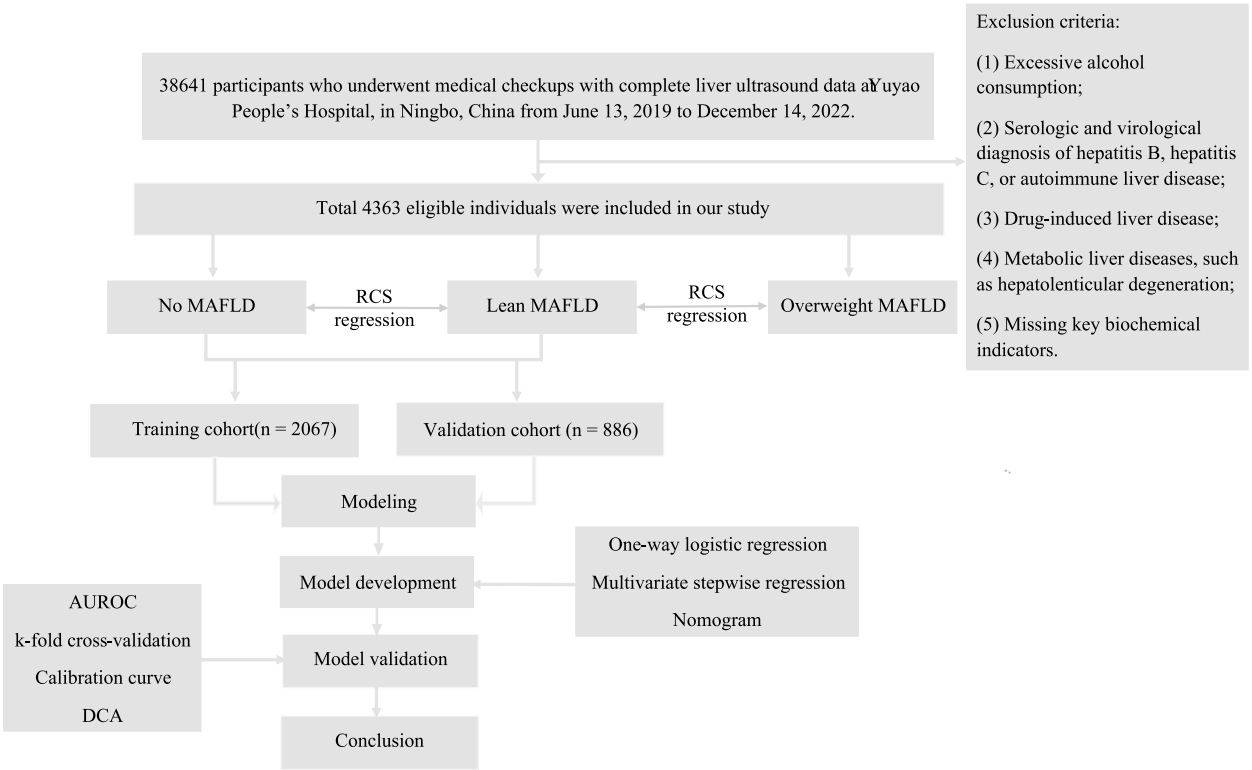

Fig. 1 Flow chart of the study design

The nonlinear relationship of MAFLD with risk factors

Multiple logistic regression analysis of risk factors

Multiple logistic regression analysis comparing the lean MAFLD and overweight MAFLD groups with the non-MAFLD group revealed age, BMI, HbA1c, TyG index, SBP, UA, and ALT were common risk factors for both the lean and overweight MAFLD groups. For every 1 mg/dl increase in TyG, the risk of lean MAFLD increased 4.03 times and the risk of overweight MAFLD increased 3.041 times (Table 3, Figs. 2 and 3).

Nonlinear associations between risk factors and MAFLD

The nonlinear relationship and risk differences between age, HbA1c, SBP, ALT, UA, TCHO, TG, and Tyg and lean and overweight MAFLD were investigated using RCS regression analysis. Figures 4 and 5, and Supplementary Figures S1 and S2, show significant nonlinear dose relationships between age, HbA1c, SBP, ALT, UA, TCHO, TG, and Tyg and MAFLD (non-linear test, $P < 0.05$) and a linear relationship between HbA1c and lean MAFLD ($P = 0.07$).

The risk of developing MAFLD was relatively low and stable when the age of the participant with lean MAFLD was below 45 years; however, the risk of developing MAFLD increased rapidly for participants older than 45 years. For participants with overweight MAFLD, the risk of developing MAFLD was lower when the participants were younger than 33 years, but the risk of overweight MAFLD increased significantly in participants between 33 and 44 years or above 44 years.

The cutoff values for HbA1c, SBP, ALT, UA, TCHO, TG, and TyG index were lower for participants with lean MAFLD (5.46% vs. 5.53%, 119 mmHg vs. 124 mmHg, 17 U/L vs. 19 U/L, 312 mmol/L vs. 335 mmol/L, 4.82 mmol/L vs. 4.86 mmol/L, 1.3 mmol/L vs. 1.5 mmol/L, and 4.05 mmol/L vs. 4.21 mmol/L, respectively). The cutoff value for HDLC was higher for participants with lean MAFLD (1.33 mmol/L vs. 1.30 mmol/L) (Figs. 4 and 5 and Supplementary Figures S1 and S2).

Nomogram for lean MAFLD

A nomogram was developed to predict lean MAFLD using a stepwise multivariate logistic regression (Supplementary Table 1), incorporating seven independent predictors: HbA1c, SF, ALT, UA, BMI, TyG index, and age (Fig. 6). Each variable has a corresponding score on the point scale axis of the nomogram. The probability of lean MAFLD is estimated by placing the total score of the covariates on a total point scale.

Table 1 Clinical features of the study participants

	Lean MAFLD	Overweight MAFLD	Non-MAFLD	*H* value	*P*	*P**	P#	P&
n	849 (19.46%)	1410 (32.32%)	2104 (48.22%)	245.11	< 0.001			
Male	656 (15.04%)	1209 (27.71%)	855 (19.6%)	831.52	< 0.001			
Age, yrs	49 (41, 56)	47 (39, 54)	42.0 (37, 52)	241.11	< 0.001	< 0.001	< 0.001	< 0.001
BMI, kg/m^2	23.63 (22.73, 24.30)	26.99 (25.87, 28.59)	21.74 (20.16, 23.51)	2734.61	< 0.001	< 0.001	< 0.001	< 0.001
SBP, mmHg	126 (116, 138)	133 (122, 143)	116 (107, 128)	715.13	< 0.001	< 0.001	< 0.001	< 0.001
ALT, U/L	24.00 (17.00, 35.00)	32.00 (22.00, 49.00)	15.00 (11.00, 20.00)	1396.72	< 0.001	< 0.001	< 0.001	< 0.001
AST, U/L	20.00 (17.00, 25.00)	23.00 (18.00, 30.00)	17.00 (15.00, 20.00)	747.37	< 0.001	< 0.001	< 0.001	< 0.001
TBIL, μmol/L	13.30 (10.00, 16.90)	13.00 (9.90, 16.48)	11.90 (9.20, 15.50)	45.33	< 0.001	0.528	< 0.001	< 0.001
DBIL, μmol/L	2.10 (1.70, 2.70)	2.20 (1.80, 2.80)	1.90 (1.60, 2.40)	135.73	< 0.001	0.07	< 0.001	< 0.001
IBIL, μmol/L	11.00 (8.10, 14.40)	10.70 (7.90, 13.80)	9.90 (7.50, 13.00)	32.04	< 0.001	0.187	< 0.001	< 0.001
GGT, U/L	36.00 (24.00, 57.00)	45.00 (30.00, 73.75)	18.00 (14.00, 28.00)	1353.30	< 0.001	< 0.001	< 0.001	< 0.001
ALP, U/L	72.50 (62.00, 86.00)	71.00 (61.00, 84.75)	62.00 (51.00, 75.00)	313.30	< 0.001	0.552	< 0.001	< 0.001
CR, μmol/L	70 (60, 78)	72 (64, 80)	60 (52, 72)	471.57	< 0.001	< 0.001	< 0.001	< 0.001
UA, μmol/L	375 (318, 436)	403 (345.25, 453)	289 (244.75, 350)	1144.95	< 0.001	< 0.001	< 0.001	< 0.001
TCHO, mmol/L	5.03 (4.48, 5.57)	5.03 (4.53, 5.69)	4.74 (4.24, 5.32)	122.37	< 0.001	0.255	< 0.001	< 0.001
TG, mmol/L	1.97 (1.43, 2.80)	2.15 (1.56, 2.97)	1.13 (0.86, 1.58)	1304.22	< 0.001	0.02	< 0.001	< 0.001
LDLC, mmol/L	2.82 (2.41, 3.26)	2.90 (2.51, 3.36)	2.54 (2.15, 2.97)	281.44	< 0.001	0.001	< 0.001	< 0.001
HDLC, mmol/L	1.20 (1.06, 1.37)	1.15 (1.04, 1.29)	1.41 (1.22, 1.62)	765.25	< 0.001	< 0.001	< 0.001	< 0.001
HbA1c, %	5.56 (5.40, 5.74)	5.62 (5.44, 5.80)	5.42 (5.25, 5.59)	473	< 0.001	< 0.001	< 0.001	< 0.001
GLU, mmol/L	4.94 (4.70, 5.24)	5.01 (4.76, 5.38)	4.75 (4.55, 4.99)	424.82	< 0.001	< 0.001	< 0.001	< 0.001
TyG	4.48 (4.15, 4.86)	4.60 (4.27, 4.93)	3.88 (3.60, 4.23)	1418.89	< 0.001	0.002	< 0.001	< 0.001
SF, ng/ml	235.88 (143.54, 363.32)	298.05 (186.77, 446.15)	95.38 (37.72, 201.82)	1085.87	< 0.001	< 0.001	< 0.001	< 0.001

p^*: Lean MAFLD group vs. overweight MAFLD group. $p^\#$: Overweight MAFLD group vs. NO MAFLD group. $p^\&$: Lean MAFLD group vs. non-MAFLD group

Data are n. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CR, serum creatinine; GGT, glutamyl transpeptidase; GLU, glucose; HB,, hemoglobin; HbA1c, glycosylated hemoglobin A1c; HDLC, high density lipoprotein cholesterol; IBIL, indirect bilirubin; LDLC, low density lipoprotein cholesterol; MCV, mean erythrocyte volume; NPR, neutrophil to platelet ratio, PLR, Platelet to lymphocyte ratio; SBP, systolic pressure; SF, serum ferritin; TBIL, total bilirubin; TCHO, total cholesterol; TG, triglyceride; TyG, triglyceride glucose index; UREA, urea; UA, uric acid

Accuracy of lean MAFLD diagnosis

In the training cohort, the area under the ROC was 0.869 (95% CI 0.852–0.885, P < 0.001), and the cutoff value was 0.22, and the sensitivity and specificity of the prediction model were 86.2% and 72%, respectively (Fig. 7A), the PPV and NPV were 54.7% and 93.3%, respectively. The area under the ROC curve for predicting MAFLD in the validation set was 0.866 (95% CI 0.842–0.890, P < 0.001), and the sensitivity and specificity were 83.8% and 76.6%, respectively (Fig. 7B), the PPV and NPV were 63.3% and 90.8%, respectively. Furthermore, we used fivefold cross-validation and the average area under the ROC curve as 0.866 (Supplement Figure S3). The calibration curve of the prediction model for lean MAFLD was extremely close to the diagonal line, and the training and validation sets were similar (Fig. 8A, B).

Clinical practicality

Decision curves were used to evaluate the clinical practicality of the developed nomogram model. Based on the decision curve analysis, the nomogram model yielded a net benefit for threshold probabilities from 5 to 92% in the training set and 5% to 78% in the validation set (Fig. 9A, B). Thus, when the predicted risk value is between 5 and 78%, further diagnosis can be beneficial. When the predictive risk value is less than 5% or greater than 78%, a MAFLD diagnosis may not be beneficial. Lean MAFLD risk can be classified as low (< 5%), moderate (5–78%), and high (> 78%) with the nomogram. Based on the risk assessment derived from the nomogram, the physician could make a treatment plan based on the patient's own situation. This personalized approach ensures that the treatment plan is both effective and adapted to the patient's specific situation while taking into account factors, such as age, comorbidities and other relevant clinical variables. Similarly, in patient management, nomogram provides continuous risk assessment to help physicians monitor conditions and make adjustments to treatment plans.

Table 2 Baseline characteristics of the training and validation sets

Variables	Training cohort ($n=2067$)			Validation test cohort ($n=886$)		
	Non-MAFLD	Lean MAFLD	*P*	Non-MAFLD	Lean MAFLD	*P*
Female	883 (59%)	126 (22%)	< 0.001	366 (60%)	67 (24%)	< 0.001
Male	613 (41%)	445 (78%)		242 (40%)	211 (76%)	
Age, yrs	42 (37, 50)	50 (42, 56)	< 0.001	42 (36, 50)	49 (41, 54)	< 0.001
BMI, kg/m^2	21.76 (20.18, 23.59)	23.61 (22.63, 24.26)	< 0.001	21.70 (20.19, 23.36)	23.64 (22.90, 24.36)	< 0.001
SBP, mmHg	116 (107, 128)	127 (118, 138)	< 0.001	116 (107, 127)	124 (115, 136)	< 0.001
ALT, U/L	15 (11, 20)	24 (17, 34)	< 0.001	14 (11, 20)	25 (18, 36)	< 0.001
AST, U/L	17.0 (15.0, 20.0)	21.0 (17.0, 25.0)	< 0.001	17 (15, 20)	20 (17, 25)	< 0.001
TBIL, μmol/L	12.0 (9.2, 15.5)	13.2 (9.9, 16.6)	< 0.001	11.9 (9.3, 15.3)	13.7 (10.2, 17.7)	< 0.001
DBIL, μmol/L	1.90 (1.60, 2.40)	2.10 (1.70, 2.65)	< 0.001	1.90 (1.60, 2.50)	2.20 (1.80, 2.78)	< 0.001
IBIL, μmol/L	10.0 (7.5, 13.1)	11.0 (8.1, 13.9)	< 0.001	9.8 (7.7, 12.9)	11.3 (8.5, 15.0)	< 0.001
GGT, U/L	18 (14, 27)	36 (24, 55)	< 0.001	19 (14, 29)	32 (23, 59)	< 0.001
ALP, U/L	62 (51, 75)	73 (62, 86)	< 0.001	62 (50, 76)	73 (62, 86)	< 0.001
CR, μmol/L	60 (52, 72)	70 (61, 78)	< 0.001	60 (52, 72)	70 (59, 79)	< 0.001
UA, μmol/L	291 (246, 353)	374 (321, 435)	< 0.001	289 (243, 348)	378 (313, 432)	< 0.001
TCHO, mmol/L	4.73 (4.26, 5.33)	4.99 (4.48, 5.57)	< 0.001	4.76 (4.19, 5.31)	5.05 (4.53, 5.58)	< 0.001
TG, mmol/L	1.12 (0.86, 1.58)	1.98 (1.42, 2.85)	< 0.001	1.14 (0.87, 1.57)	1.94 (1.43, 2.73)	< 0.001
LDLC, mmol/L	2.55 (2.15, 2.98)	2.79 (2.36, 3.28)	< 0.001	2.50 (2.14, 2.96)	2.86 (2.48, 3.21)	< 0.001
HDLC, mmol/L	1.41 (1.22, 1.62)	1.19 (1.06, 1.37)	< 0.001	1.41 (1.20, 1.63)	1.19 (1.07, 1.36)	< 0.001
HbA1c, %	5.42 (5.26, 5.59)	5.57 (5.41, 5.76)	< 0.001	5.42 (5.24, 5.59)	5.53 (5.37, 5.67)	< 0.001
GLU, mmol/L	4.77 (4.56, 5.00)	4.97 (4.73, 5.28)	< 0.001	4.73 (4.54, 4.95)	4.87 (4.65, 5.16)	< 0.001
TyG	3.87 (3.60, 4.23)	4.51 (4.15, 4.88)	< 0.001	3.90 (3.62, 4.22)	4.41 (4.16, 4.81)	< 0.001
SF, ng/ml	95 (38, 199)	248 (149, 374)	< 0.001	94 (38, 203)	224 (129, 335)	< 0.001

Data are *n*. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CR, serum creatinine; GGT, glutamyl transpeptidase; GLU, glucose; HB, hemoglobin; HbA1c, glycosylated hemoglobin A1c; HDLC, high density lipoprotein cholesterol; IBIL, indirect bilirubin; LDLC, low density lipoprotein cholesterol; MCV, mean erythrocyte volume; NPR, neutrophil to platelet ratio, PLR, Platelet to lymphocyte ratio; SBP, systolic pressure; SF, serum ferritin; TBIL, total bilirubin; TCHO, total cholesterol; TG, triglyceride; TyG, triglyceride glucose index; UREA, urea; UA, uric acid

Discussion

The risk factors for lean MAFLD were identified and a predictive model was established. The risk factors for lean MAFLD and overweight MAFLD, including age, BMI, HbA1c, TyG, SBP, UA, and ALT, were identified using regression analysis. Then, the cutoff values of lean MAFLD and overweight MAFLD were determined using RCS curves to understand the differences of these risk factors from other factors, such as glucolipid metabolism, and the relationship with the risk of MAFLD. Compared with overweight MAFLD, the cutoff values for HbA1c, SBP, ALT, UA, TCHO, TG, and TyG in lean MAFLD were relatively low, the protective factor, HDLC, had a higher cutoff value. Compared with overweight MAFLD, individuals with lean MAFLD have higher visceral fat content, accompanied by metabolic diseases, such as sarcopenia, dyslipidemia, hypertension, and hyperglycemia [15, 30–32]. These results support the view that glucolipid metabolism is different in lean MAFLD and overweight MAFLD. Patients with lean MAFLD have worse prognoses and their disease risk may be underestimated. Establishing a predictive model can help patients and doctors identify lean MAFLD and promptly intervene. Our nomogram provides physicians with a useful assessment tool to help inform them in the prevention or diagnosis of lean MAFLD.

MAFLD is a manifestation of metabolic syndrome in the liver, and the high prevalence of metabolic diseases has led to a significant increase in the incidence of MAFLD, surpassing viral hepatitis as the most prevalent chronic liver disease worldwide [33, 34]. The two main causes of mortality in patients with MAFLD are cardiovascular disease and extrahepatic malignant tumors [35–38]. In this study, MAFLD patients were older and had a higher prevalence of overweight, obesity, type 2 diabetes, hyperlipidemia, hypertension, and hyperuricemia compared with non-MAFLD patients. Notably, our findings align with previous studies [39–41].

MAFLD is strongly associated with a high BMI. Historically, the occurrence of MAFLD in overweight or obese populations was the focus of research and clinical efforts, and the incidence of MAFLD in non-obese individuals was overlooked. However, approximately 40% of the global MAFLD population are non-obese, and

Table 3 Multivariate logistic analyses of risk factors for MAFLD

Variables	Lean MAFLD versus Non-MAFLD		Overweight MAFLD versus Non-MAFLD	
	OR (95%CI)	*P*	OR (95%CI)	*P*
Age, yrs	1.041 (1.030–1.053)	< 0.001	1.042 (1.026–1.059)	< 0.001
Sex				
Female	Ref.		Ref.	
Male	1.225 (0.941–1.595)	0.132	1.529 (1.009–2.318)	0.045
BMI, kg/m^2	1.095 (1.036–1.158)	0.001	5.862 (5.101–6.735)	< 0.001
HbA1c, %	1.830 (1.285–2.606)	0.001	2.481 (1.588–3.877)	< 0.001
Tyg	4.03 (2.806–5.786)	< 0.001	3.041 (1.875–4.931)	< 0.001
SBP, mmHg	1.007 (1.00–1.013)	0.043	1.011 (1.002–1.021)	0.017
UA, μmol/L	1.005 (1.004–1.007)	< 0.001	1.006 (1.004–1.008)	< 0.001
HDLC, mmol/L	0.407 (0.255–0.650)	< 0.001	0.241 (0.116–0.504)	< 0.001
TCHO, mmol/L	1.056 (0.925–1.204)	0.420	1.082 (0.898–1.304)	0.407
HTG, mmol/L				
No	Ref.		Ref.	
Yes	0.883 (0.648–1.205)	0.433	1.410 (0.912–2.181)	0.122
ALT, U/L	1.034 (1.026–1.041)	< 0.001	1.040 (1.031–1.049)	< 0.001

ALT, alanine aminotransferase; BMI, body mass index; HbA1c, glycosylated hemoglobin A1c; HDLC, high density lipoprotein cholesterol ; HTG, hypertriglyceridemia ; MAFLD, metabolic dysfunction-associated fatty liver disease; OR, odds ratio; Ref, reference; SBP, systolic pressure; Tyg, triglyceride glucose index; TCHO, total cholesterol; UA, uric acid.

20% of individuals with MAFLD are lean. In Europe, the incidence of non-obese MAFLD is approximately 50%; in East Asia [19, 42], the prevalence of non-obese MAFLD is 38%, and the incidence ranges from 12 to 47% in Asia. In this study, 19.46% of participants were classified into the lean MAFLD group. The incidence of lean MAFLD may vary due to regional variations, ethnic distinctions, environmental factors, and dietary habits.

Gender and age significantly influenced MAFLD in this study; the likelihood of developing lean MAFLD increased by 4.1% per year. The RCS analysis revealed that the risk of developing lean MAFLD was relatively low before the age of 45 years but gradually escalated thereafter. Conversely, the prevalence of overweight MAFLD was higher between the ages of 33 and 44 years and continued to rise as the participants aged. Notably, within the 33 to 44 age bracket, the RCS curve for obese MAFLD displayed an 'inverted U' pattern, indicating a potential association with other factors that may elevate the risk of developing metabolic diseases, such as female pregnancy and hormonal fluctuations [43–45]. Aging-related mitochondrial dysfunction contributes to a decline in cellular fatty acid oxidation capacity. Consequently, fat deposition increases [46], particularly in elderly individuals [47]. Several studies showed that the incidence of MAFLD is higher in males compared to females [48]. However, female subcutaneous fat possesses a greater storage capacity, enabling the efficient conversion of excess energy into fat rather than allowing accumulation in the liver. Furthermore, female subcutaneous fat exhibits enhanced browning, which promotes metabolism, and high adiponectin-releasing capacity, which facilitates fatty acid oxidation and boosts insulin sensitivity [49]. These unique physiological traits may help reduce the likelihood of developing MetS and MAFLD. Conflicting results from other studies suggest that postmenopausal women exhibit a higher incidence of MAFLD and liver fibrosis, and elderly women experience a higher mortality rate from MAFLD than men. These differences may be due to hormonal fluctuations and menopausal status, which potentially impact the pathophysiology of MAFLD [50, 51]. Age- and gender-related differences in the development of MAFLD have profound implications for clinicians, enabling them to devise tailored preventive measures and treatment strategies for patients of varying ages and genders to minimize the risk of developing MAFLD.

Multiple studies demonstrated that patients with lean MAFLDs bear a heightened risk for glucose intolerance, hypertension, metabolic syndrome, cardiovascular mortality, and cancer compared with their overweight/obese counterparts [38, 52–54]. Consequently, relying solely on BMI as an initial screening indicator for MAFLD is inadequate. A subset of patients with normal BMI may present with uneven fat distribution, elevated visceral fat content, and transient fluctuations in body mass. Notably, visceral obesity increases the susceptibility of non-obese individuals to MAFLD. In clinical practice, several key variables have been identified as significant predictors of non-obese MAFLD, including waist-to-hip ratio, neck circumference, body fat analysis, FIB-4 index, GGT levels, cholesterol levels, and hemoglobin levels [42, 55–57]. In this study, the lean MAFLD group exhibited significantly higher age, BMI, SBP, ALT, AST, GGT, CR, UR, HbA1c, GLU, TyG, and SF compared with the non-MAFLD group. The multiple logistic regression analysis revealed that age, BMI, HbA1c, TyG, SBP, UA, HDLC, and ALT were independent risk factors specifically associated with lean MAFLD. Several studies have shown that patients with a higher TyG index have a higher risk of fatty liver, diabetes, stroke, cardiovascular disease and a worse prognosis, and that the TyG index can be a good

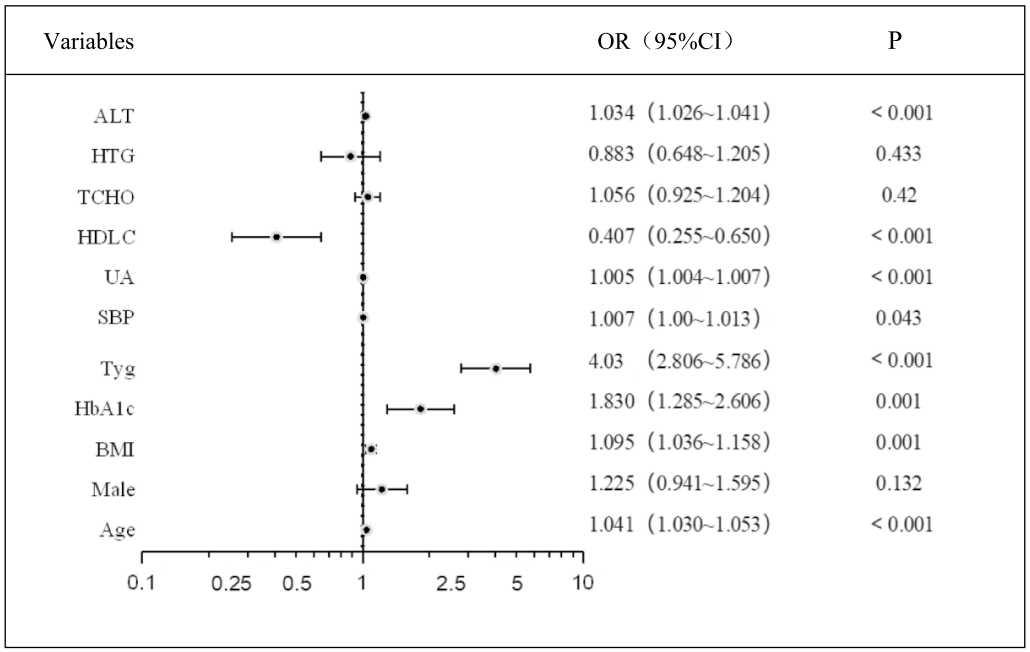

Fig. 2 Forest map of the multivariate logistic analyses for the lean MAFLD group vs. non-MAFLD group. Odds ratios (OR) comparing lean MAFLD group to healthy group using multivariate logistic regression. Age is year. ALT, alanine aminotransferase; BMI, body mass index; CI, confidence interval. HDLC, high density lipoprotein cholesterol; HTG, hypertriglyceridemia; SBP, systolic pressure; TCHO, total cholesterol; TyG, triglyceride glucose index; UA, uric acid; HbA1c, glycosylated hemoglobin A1c

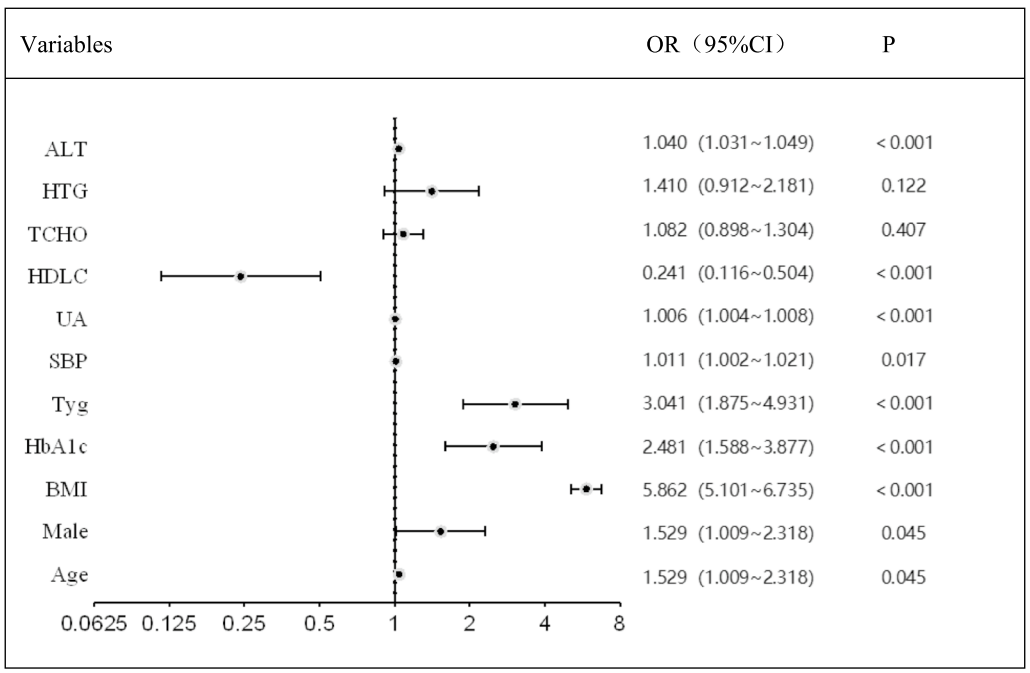

Fig. 3 Forest map of the multivariate logistic analyses for the overweight MAFLD vs. non-MAFLD group. Odds ratios (OR) comparing overweight MAFLD group to healthy group using multivariate logistic regression. Age is year. ALT, alanine aminotransferase; BMI, body mass index; CI, confidence interval. HDLC, high density lipoprotein cholesterol; HTG, hypertriglyceridemia; SBP, systolic pressure; TCHO, total cholesterol; TyG, triglyceride glucose index; UA, uric acid; HbA1c, glycosylated hemoglobin A1c

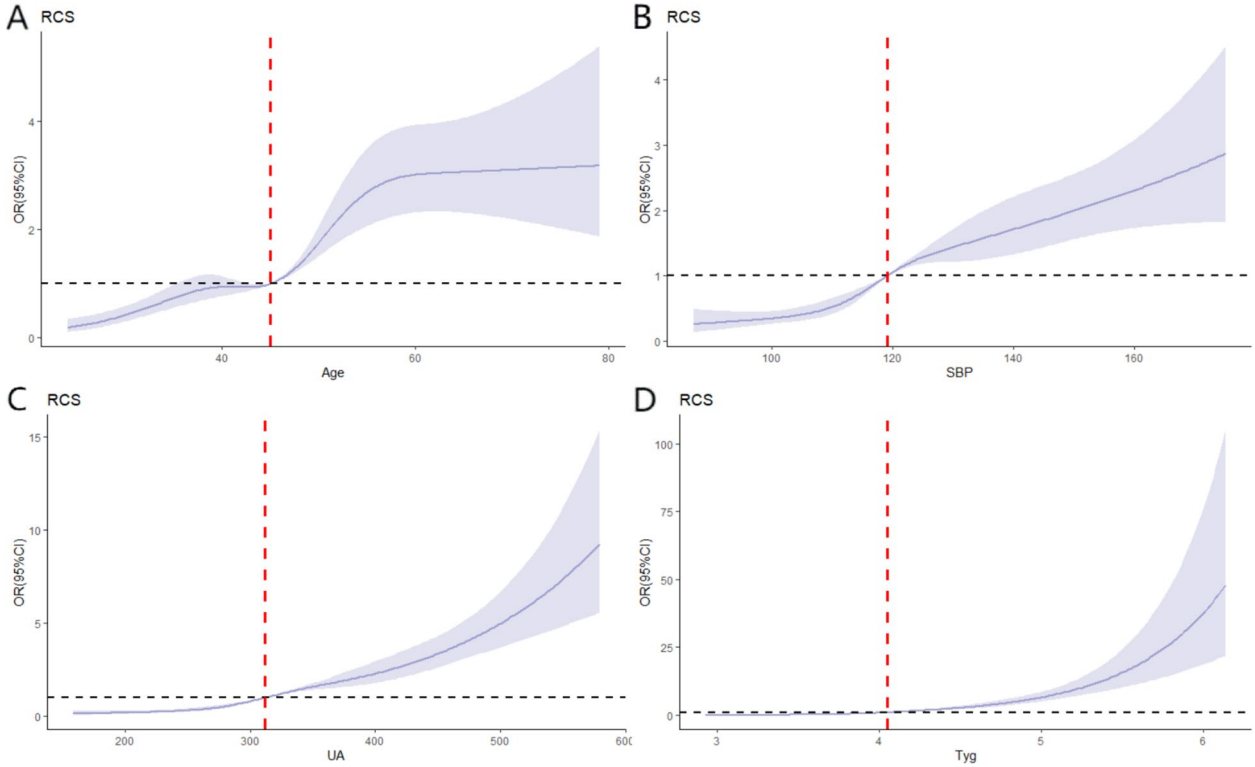

Fig. 4 Using the restricted cubic spline regression model to investigate the relationship between various indicators and the risk of lean MAFLD. **A** Using the restricted cubic spline regression model to investigate the relationship between age and the risk of lean MAFLD. **B** Using the restricted cubic spline regression model to investigate the relationship between SBP and the risk of lean MAFLD. **C** Using the restricted cubic spline regression model to investigate the relationship between UA and the risk of lean MAFLD. **D** Using the restricted cubic spline regression model to investigate the relationship between Tyg and the risk of lean MAFLD. Age is year. CI, confidence interval; SBP, systolic pressure; UA, uric acid; OR, odds ratio; Tyg, triglyceride glucose index

diagnostic and predictive tool for diseases related to insulin resistance and metabolic disorders [58–61]. The forest plot for the regression analysis results indicates that the risk of developing lean MAFLD increases 3.03-fold for every 1-unit increment in the TyG level compared with the non-MAFLD group. Compared with overweight MAFLD, the RCS plot revealed a comparatively lower cutoff value for TyG in the lean MAFLD group (4.05 vs. 4.21). A comparative analysis of multiple variable-based ROC curves revealed that the AUC predicted by TyG for lean MAFLD was 0.81, which surpassed the AUCs of other indicators, such as HbA1c, ALT, and BMI.

Prior studies established a close association between the incidence of lean MAFLD and gut microbiota composition, genetic susceptibility, environmental factors, and cholesterol metabolism disorders. The secretion of msRNA 23487 [62] by Escherichia coli and the reduced abundance of Bacteroides and Ruminococcaceae, intensify liver inflammation and fibrosis in individuals with lean MAFLD [22]. Downregulation of the histone variants macroH2A1.1 and macroH2A1.2 [63] elevated serum levels of miR-4488 [64], gradually upregulated GP73 [21]in hepatocytes, activated macrophages via Toll-like receptor (TLR) ligands, and suppressed bile acid signaling [65]; all of these effects may contribute to the onset and progression of lean MAFLD.

The deposition of ectopic fat within muscles and the liver contributes to the development of insulin resistance (IR) in individuals diagnosed with lean MAFLD. IR is intricately linked with MAFLD and correlates with the amount of visceral or abdominal adipose tissue. Moreover, IR leads to the onset of MetS [24, 66, 67]. Conventional techniques for the diagnosis of IR, such as the hyperinsulinemic–euglycemic clamp technique and the homeostasis model assessment of insulin resistance, often entail intricate procedures and considerable costs. Consequently, their implementation is limited in basic healthcare settings. The TyG index, a simplified indicator derived by logarithmic transformation of the product of triglycerides and glucose, effectively captures insulin resistance. Thus, this technique has recently emerged as a novel metric for assessing IR [68, 69]. The TyG index is associated with the extent of liver injury and the severity of coronary atherosclerosis in patients with MAFLD.

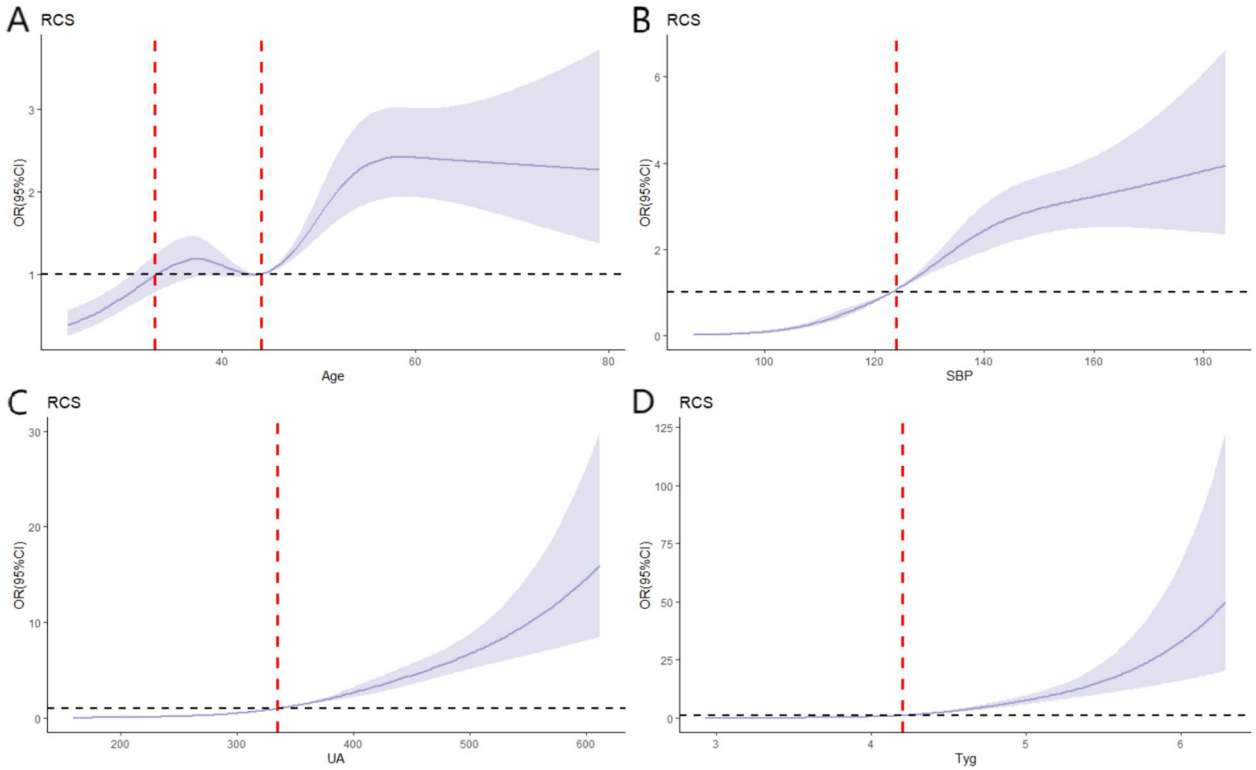

Fig. 5 Using the restricted cubic spline regression model to investigate the relationship between various indicators and the risk of overweight MAFLD. **A** Using the restricted cubic spline regression model to investigate the relationship between age and the risk of overweight MAFLD. **B** Using the restricted cubic spline regression model to investigate the relationship between SBP and the risk of overweight MAFLD. **C** Using the restricted cubic spline regression model to investigate the relationship between UA and the risk of overweight MAFLD. **D** Using the restricted cubic spline regression model to investigate the relationship between Tyg and the risk of overweight MAFLD. Age is year. CI, confidence interval; SBP, systolic pressure; UA, uric acid; OR, odds ratio; Tyg, triglyceride glucose index

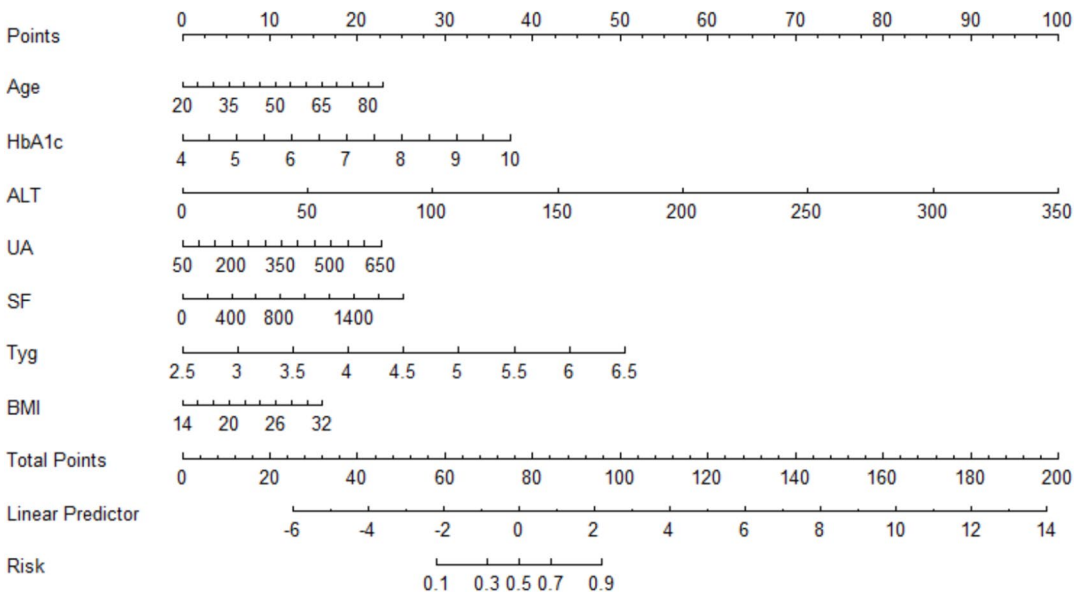

Fig. 6 Nomogram model for predicting lean MAFLD. The nomogram model is based on age, HbA1c, ALT, UA, SF, Tyg, and BMI. Each predictor has a score point, and the total of these seven factors indicates the risk of developing a lean MAFLD probability. Age is year. ALT, alanine aminotransferase; BMI, body mass index; SBP, systolic pressure; SF, serum ferritin; UA, uric acid; Tyg, triglyceride glucose index

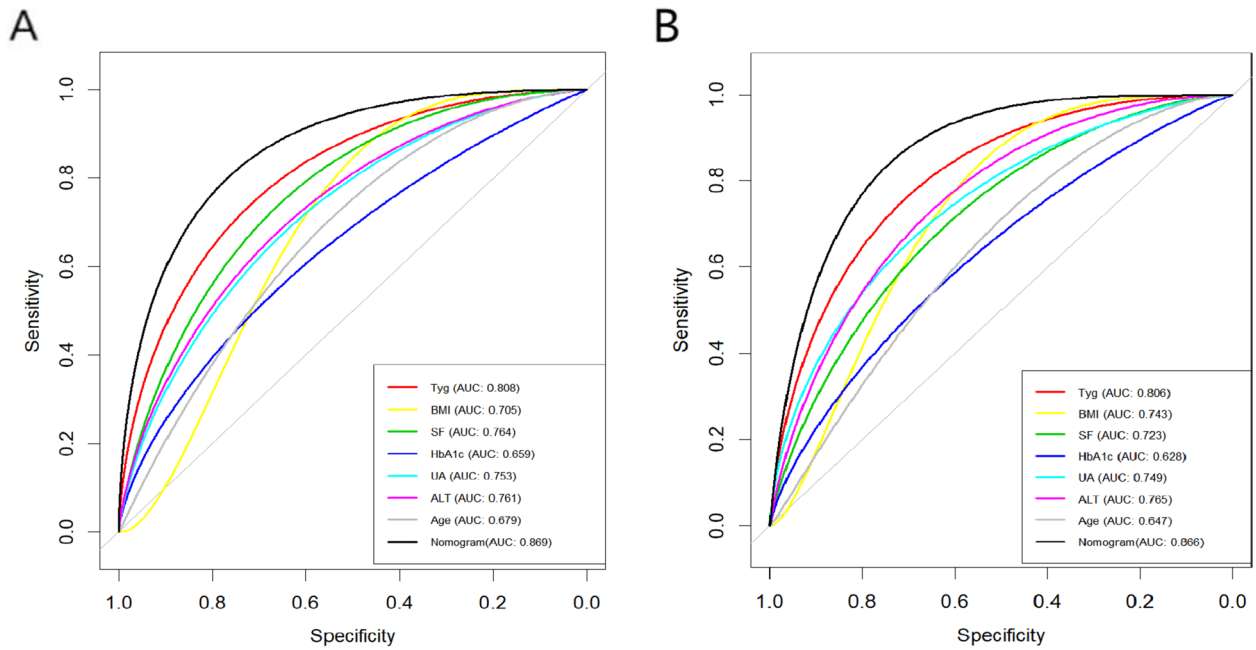

Fig. 7 ROC for predicting lean MAFLD in the training and validation cohort. **A** ROC for predicting lean MAFLD in the training cohort. The area under the ROC curve (AUC) of the model is 0.869 (95% CI 0.853–0.886, P < 0.001), with a sensitivity and specificity of 86.2% and 72%, respectively, the PPV and NPV were 54.7% and 93.3%, respectively. **B** ROC curves for predicting NAFLD in the validation set. The AUC of the model is 0.866 (95% CI 0.842–0.891, P < 0.001) with a sensitivity and specificity of 83.8% and 76.6%, respectively, the PPV and NPV were 63.3% and 90.8%, respectively; Age is year. ALT, alanine aminotransferase; BMI, body mass index; SBP, systolic pressure; SF, serum ferritin; UA, uric acid; Tyg, triglyceride glucose index. CI: confidence interval (1000 bootstrap resamples)

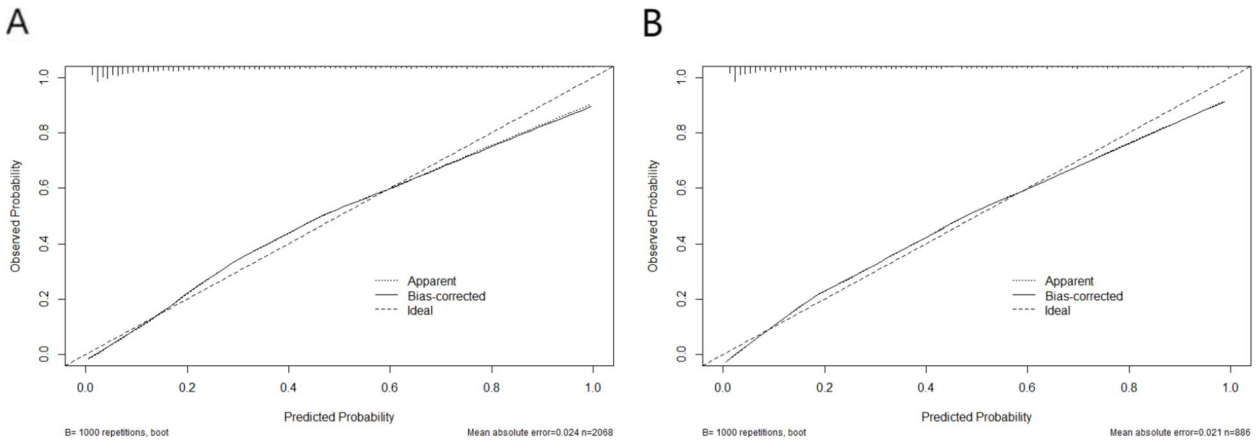

Fig. 8 Calibration curve of the model in the training and validation cohort. **A** Calibration curve of the model in the training cohort; **B** Calibration curve of the model in the validation cohort. The 45°line represents a perfect prediction by an ideal model, and the "Apparent" line reflects the fit between the predicted and actual values. The bias-corrected line shows exactly how the predicted values fit the actual values after correction (1000 bootstrap resamples)

Furthermore, the TyG index is an independent risk factor for diabetes, coronary heart disease, hypertension, stroke, and other associated adverse events [70, 71]. The high sensitivity of the TyG index in detecting metabolic disorders and MAFLD underscores its significance as a widely used biomarker [72, 73]. Individuals with lean MAFLD exhibit a higher incidence of cardiovascular events and an increased risk of all-cause mortality compared with individuals without lean MAFLD [18]. Thus, the development of predictive models with risk

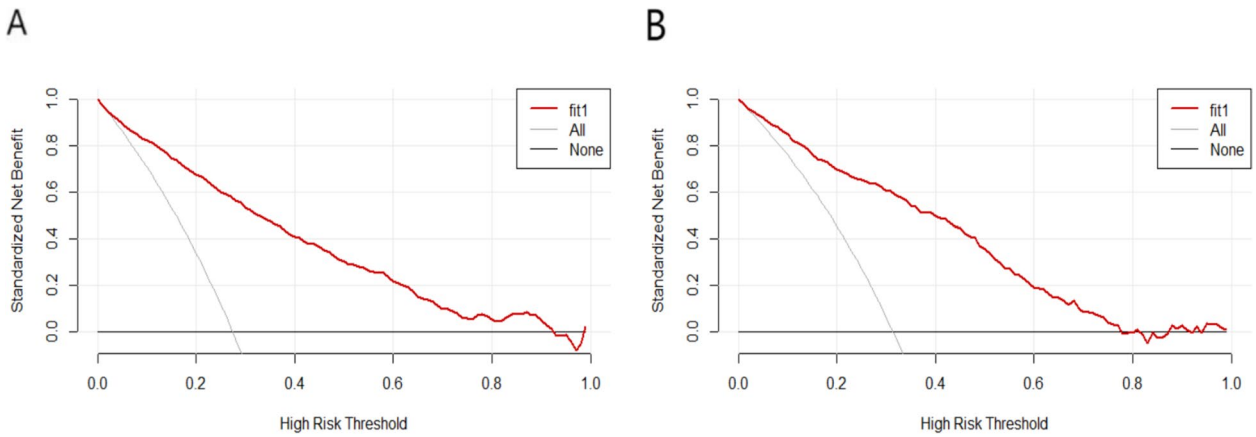

Fig. 9 The DCA of the nomogram for lean MAFLD risk in the training and validation cohort. **A** DCA of the nomogram for lean MAFLD risk in the training cohort; **B** DCA of the nomogram for lean MAFLD risk in the validation cohort. The red solid line is the prediction model; the gray solid line is all lean MAFLD patients, and the solid line horizontal line is the non-lean MAFLD patients. The graph depicts the expected net benefit of each patient relative to nomogram in predicting lean MAFLD risk. With the extension of the model curve, the net benefit increases. The *y*-axis represents net benefits, calculated by subtracting the relative harms (false positives) from the benefits (true positives). The *x*-axis measures the threshold probability (1000 bootstrap resamples)

factors specific to lean MAFLD is crucial for early identification, diagnosis, and intervention of this disease. The ultimate aim is to decrease the occurrence of cardiovascular events and other harmful outcomes in patients with MAFLD.

A nomogram is a graphical form used to illustrate and calculate the relationships between multiple variables. Nomograms are widely used in disease prognosis and can assist doctors in clinical decision-making. Prospective cohort studies predicted the risk of developing MAFLD after 2 or 3 years in a Chinese non-fat population [74, 75], which is helpful for timely intervention and reducing the incidence of NAFLD. In addition, taking into account regional differences in the prevalence of NAFLD. This study is a cross-sectional investigation of a southern Chinese population to predict the risk of lean MAFLD. Thus, we developed a nomogram prediction model for the occurrence of lean MAFLD based on multiple logistic regression analysis, including age, BMI, HbA1c, TyG, SBP, UA, and other indicators. The model has good predictive performance (area under the ROC = 0.866), and the DCA shows good consistency between the predicted and actual values. The nomogram diagram is a visualization of the logistic regression analysis, providing an accurate digital risk probability for each patient and assisting clinicians in making decisions for personalized healthcare. The nomogram prediction model has predictive value for lean MAFLD patients and can be used for clinical decision-making.

In conclusion, the harm of lean MAFLD is not limited to the liver, lean MAFLD can lead to diabetes, cerebrocardiovascular diseases, and metabolic syndrome-related diseases. Therefore, clinicians should pay attention to patients with MAFLD who have a normal BMI and patients who exhibit mild metabolic abnormalities, which may lead to MAFLD. The nomogram has a wide range of applications in medical, particularly for screening high-risk populations, including normal BMI individuals with metabolic risks and those with abnormal lipid, glucose, uric acid, or aminotransferase levels, to assess disease risk and provide personalized preventive advice. It also plays an important role in community and medical center screening to help identify at-risk populations. For patients predicted to be at high risk by the Nomogram model, more detailed screening, including liver ultrasound, should be performed to further confirm the presence of MAFLD. For patients predicted to be at low risk, a regular follow-up program can be instituted to follow-up on changes in their clinical variables and to adjust the screening strategy as needed.

However, the current study has several potential limitations. First, it is retrospective, single-centered and cross-sectional, which does not adequately represent the wider population, and in addition, the cross-sectional design fails to provide information on the dynamics of the disease over time, thus limiting the generalizability of the study. Second, previous diagnosis of MAFLD has relied on ultrasound, which may have led to some patients with mild MAFLD being missed, thus underestimating the true prevalence of the disease, and future studies should consider the use of a combination of more advanced imaging techniques, such as FibroScan and MRI–PDFF. These techniques can provide more precise quantitative information about

fat and help to more accurately assess the severity of MAFLD. Third, missing values were filled in with stratified means. This may affect the accuracy of the model. Fourth, the lack of external validation and the lack of lifestyle information in the data weakened the ability of the model to generalization, in addition to the fact that lifestyle information is essential for understanding the onset and progression of the disease. The lack of such information may prevent the study from fully exploring the association between MAFLD and lifestyle factors, thus weakening the depth and breadth of the findings.

Therefore, future studies should focus on strengthening multicenter collaboration, increasing sample size, and collecting more data from different clinical populations to cover a wider range of age, ethnicity, disease status, and other variables to improve the accuracy of findings and reduce bias. Meanwhile, cohort studies covering community and urban populations need to be established, with regular follow-up of cohort members to collect information on disease progression, treatment response and prognosis. This will make the study population more diverse and representative and improve the representativeness and breadth of the study. On this foundation, longitudinal studies should be carried out to gain an in-depth understanding of the occurrence and development of MAFLD and its relationship with related diseases through long-term follow-up and observation of the same group of people, so as to more accurately assess the risk of the disease and predict the course of the disease. In addition, the accuracy and reliability of the model is assessed through external validation, and the nomogram model is regularly updated as new data accumulate and clinical practice changes. It helps to improve the prevention, diagnosis and treatment of MAFLD, thereby reducing the risk and burden of related diseases.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-025-02373-1.

Additional file 1.

Acknowledgements
We would like to thank all the participants of this study and others who supported this study, including the funders.

Author contributions
Ruya Zhu, Hongshan Li and Jianjun Lou wrote the main manuscript text and prepared all figures. All authors reviewed the manuscript.

Funding
This work was supported by the Major Special Science and Technology Project of Ningbo City(#2022Z128), National Administration of Traditional Chinese Medicine–Zhejiang Provincial Administration of Traditional Chinese Medicine Joint Construction Technology Plan (GZY-ZJ-KJ-23092), the Zhejiang Provincial Natural Science Foundation of China under Grant No. LY23H290004, the Ningbo Natural Science Foundation, Project ID: 2022J242, Zhejiang Province Traditional Chinese Medicine Science and Technology Plan (2022ZB332), and the Project of NINGBO Leading Medical and Health Discipline, Project Number: 2022Z01.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study protocol complied with the principles of the Declaration of Helsinki. The Ethics Committee of the First Affiliated Yuyao People's Hospital approved this study (2024–01-001), confirming it as a retrospective study that meets the ethical requirements for waiver of informed consent. All data were collected in an electronic medical record system. All methods were performed in accordance with the relevant guidelines and regulations. There have been several researchers to check the accuracy and completeness of the data to avoid information bias. In addition, researchers anonymise or de-identify patient data to reduce the risk of data breaches.

Competing interests
The authors declare no competing interests.

Author details
[1]Liver Disease Department of Integrative Medicine, Ningbo No. 2 Hospital, Ningbo 315010, Zhejiang, China. [2]Chronic Liver Disease Center, The Affiliated Yangming Hospital of Ningbo University, Zhejiang 315400, China.

Received: 5 September 2024 Accepted: 10 February 2025
Published online: 25 February 2025

References

1. Eslam M, Sanyal AJ, George J, International Consensus Panel. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology. 2020;158(7):1999–2014.
2. Duell PB, Welty FK, Miller M, et al. Nonalcoholic fatty liver disease and cardiovascular risk: a scientific statement from the American heart association. Arterioscler Thromb Vasc Biol. 2022;42(6):168–85.
3. Katsiki N, Mikhailidis DP, Mantzoros CS. Non-alcoholic fatty liver disease and dyslipidemia: an update. Metabolism. 2016;65(8):1109–23.
4. Wang TY, Wang RF, Bu ZY, et al. Association of metabolic dysfunction-associated fatty liver disease with kidney disease. Nat Rev Nephrol. 2022;18(4):259–68.
5. Riazi K, Azhari H, Charette JH, et al. The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2022;7(9):851–61.
6. Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73–84.
7. Younossi Z, Tacke F, Arrese M, et al. Global perspectives on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Hepatology. 2019;69(6):2672–82.
8. Zhou F, Zhou J, Wang W, Zhang XJ, et al. Unexpected rapid increase in the burden of NAFLD in China from 2008 to 2018: a systematic review and meta-analysis. Hepatology. 2019;70(4):1119–33.
9. Li J, Zou B, Yeo YH, et al. Prevalence, incidence, and outcome of non-alcoholic fatty liver disease in Asia, 1999–2019: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2019;4(5):389–98.
10. Powell EE, Wong VW-S, Rinella M. Non-alcoholic fatty liver disease. The Lancet. 2021;397(10290):2212–24.
11. Huang DQ, El-Serag HB, Loomba R. Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol. 2020;18(4):223–38.
12. Polyzos SA, Kountouras J, Mantzoros CS. Obesity and nonalcoholic fatty liver disease: from pathophysiology to therapeutics. Metabolism. 2019;92:82–97.

13. Quek J, Chan KE, Wong ZY, et al. Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2023;8(1):20–30.
14. Tang A, Ng CH, Phang PH, Muthiah M, Noureddin M, et al. Comparative burden of metabolic dysfunction in lean NAFLD vs non-lean NAFLD—a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2023;21(7):1750–60.
15. Gao Y, Zhao T, Song S, et al. Lean nonalcoholic fatty liver disease and risk of incident type 2 diabetes mellitus: a literature review and meta-analysis. Diabetes Res Clin Pract. 2023;200: 110699.
16. Ahadi M, Molooghi K, Masoudifar N, et al. A review of non-alcoholic fatty liver disease in non-obese and lean individuals. J Gastroen Hepatol. 2020;36(6):1497–507.
17. Gao N, Deng J, Wang J, et al. The prevalence, comorbidities, influencing factors, and identifying factors of non-obese fatty liver disease. Front Med. 2022;9:1038475.
18. Huang S, Bao Y, Zhang N, et al. Long-term outcomes in lean and non-lean NAFLD patients: a systematic review and meta-analysis. Endocrine. 2023. https://doi.org/10.1007/s12020-023-03351-5.
19. Ye Q, Zou B, Yeo YH, et al. Global prevalence, incidence, and outcomes of non-obese or lean non-alcoholic fatty liver disease: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2020;5(8):739–52.
20. Chan W-K. Comparison between obese and non-obese nonalcoholic fatty liver disease. Clin Mol Hepatol. 2023;29(Suppl):58–67.
21. Peng Y, Zeng Q, Wan L, et al. GP73 is a TBC-domain Rab GTPase-activating protein contributing to the pathogenesis of non-alcoholic fatty liver disease without obesity. Nat Commun. 2021;12(1):7004.
22. Lee G, You HJ, Bajaj JS, et al. Distinct signatures of gut microbiome and metabolites associated with significant fibrosis in non-obese NAFLD. Nat Commun. 2020;11(1):4982.
23. Razouki ZA, Zhang X, Hwang JP, et al. Clinical factors associated with non-obese nonalcoholic fatty liver disease detected among US adults in the NHANES 2017–2018. J Clin Med. 2022;11(15):4260.
24. Shida T, Oshida N, Suzuki H, et al. Clinical and anthropometric characteristics of non-obese non-alcoholic fatty liver disease subjects in Japan. Hepatol Res. 2020;50(9):1032–46.
25. Alarabi M, Pan Z, Romero-Gómez M, et al. Telomere length and mortality in lean MAFLD: the other face of metabolic adaptation. Hepatol Int. 2024;18(5):1448–58.
26. Balachandran VP, Gonen M, Smith JJ, et al. Nomograms in oncology: more than meets the eye. Lancet Oncol. 2015;16(4):e173–80.
27. Cai X, Wang M, Liu S, et al. Establishment and validation of a nomogram that predicts the risk of type 2 diabetes in obese patients with non-alcoholic fatty liver disease: a longitudinal observational study. Am J Transl Res. 2022;14(7):4505–14.
28. Cai X, Zhu Q, Cao Y, et al. A prediction model based on noninvasive indicators to predict the 8-year incidence of type 2 diabetes in patients with nonalcoholic fatty liver disease: a population-based retrospective cohort study. Biomed Res Int. 2021. https://doi.org/10.1155/2021/5527460.
29. Eslam M, Sarin SK, Wong VW-S, et al. The Asian Pacific Association for the study of the liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease. Hep Intl. 2020;14(6):889–919.
30. Kuchay MS, Martínez-Montoro JI, Choudhary NS, et al. Non-alcoholic fatty liver disease in lean and non-obese individuals: current and future challenges. Biomedicines. 2021;9(10):1346.
31. Eslam M, El-Serag HB, Francque S, et al. Metabolic (dysfunction)-associated fatty liver disease in individuals of normal weight. Nat Rev Gastroenterol Hepatol. 2022;19(10):638–51.
32. Levelt E, Pavlides M, Banerjee R, et al. Ectopic and visceral fat deposition in lean and obese patients with type 2 diabetes. J Am Coll Cardiol. 2016;68(1):53–63.
33. Bence KK, Birnbaum MJ. Metabolic drivers of non-alcoholic fatty liver disease. Mol Metab. 2021;50: 101143.
34. Farrell GC. Non-alcoholic steatohepatitis: what is it, and why is it important in the Asia-Pacific region? J Gastroenterol Hepatol. 2003;18(2):124–38.
35. Liu Z, Lin C, Suo C, et al. Metabolic dysfunction–associated fatty liver disease and the risk of 24 specific cancers. Metabolism. 2022;127:154955.
36. Tanaka I, Nagase K, Tanase K, et al. Improvement in neurogenic detrusor overactivity by peripheral C fiber's suppression with cyclooxygenase inhibitors. J Urol. 2010;183(2):786–92.
37. Gutiérrez-Cuevas J, Santos A, Armendariz-Borunda J. Pathophysiological molecular mechanisms of obesity: a link between MAFLD and NASH with cardiovascular diseases. Int J Mol Sci. 2021;22(21):11629.
38. Ahmed OT, Gidener T, Mara KC, et al. Natural history of nonalcoholic fatty liver disease with normal body mass index: a population-based study. Clin Gastroenterol H. 2022;20(6):1374-1381.e1376.
39. Caussy C, Aubin A, Loomba R. The relationship between type 2 diabetes, NAFLD, and cardiovascular risk. Curr Diabetes Rep. 2021;21(5):1.
40. Lim S, Kim J-W, Targher G. Links between metabolic syndrome and metabolic dysfunction-associated fatty liver disease. Trends Endocrinol Metab. 2021;32(7):500–14.
41. Peterson JM, Sogabe M, Okahisa T, et al. Differences among patients with and without nonalcoholic fatty liver disease having elevated alanine aminotransferase levels at various stages of metabolic syndrome. PLoS ONE. 2020;15(8): e0238388.
42. Tan EX-X, Lee JW-J, Jumat NH, et al. Non-obese non-alcoholic fatty liver disease (NAFLD) in Asia: an international registry study. Metabolism. 2022;126: 154911.
43. Lee SM, Kim W. Nonalcoholic fatty liver disease-based risk prediction of adverse pregnancy outcomes: ready for prime time? Clin Mol Hepatol. 2022;28(1):47–9.
44. Westbrook RH, Dusheiko G, Williamson C. Pregnancy and liver disease. J Hepatol. 2016;64(4):933–45.
45. Lee SM, Jung YM, Choi ES, et al. Metabolic dysfunction-associated fatty liver disease and subsequent development of adverse pregnancy outcomes. Clin Gastroenterol H. 2022;20(11):2542–50.
46. Ipsen DH, Lykkesfeldt J, Tveden-Nyborg P. Molecular mechanisms of hepatic lipid accumulation in non-alcoholic fatty liver disease. Cell Mol Life Sci. 2018;75(18):3313–27.
47. Ogrodnik M, Miwa S, Tchkonia T, et al. Cellular senescence drives age-dependent hepatic steatosis. Nat Commun. 2017;8(1):15691.
48. Fresneda S, Abbate M, Busquets-Cortés C, et al. Sex and age differences in the association of fatty liver index-defined non-alcoholic fatty liver disease with cardiometabolic risk factors: a cross-sectional study. Biol Sex Diff. 2022;13(1):64.
49. Morán-Costoya A, Proenza AM, Gianotti M, et al. Sex differences in nonalcoholic fatty liver disease: estrogen influence on the liver-adipose tissue crosstalk. Antioxid Redox Signal. 2021;35(9):753–74.
50. Tobari M, Hashimoto E. Characteristic features of nonalcoholic fatty liver disease in Japan with a focus on the roles of age, sex and body mass index. Gut Liver. 2020;14(5):537–45.
51. Lonardo A, Nascimbeni F, Ballestri S, et al. Sex differences in nonalcoholic fatty liver disease: state of the art and identification of research gaps. Hepatology. 2019;70(4):1457–69.
52. Kechagias S, Nasr P, Blomdahl J, et al. Established and emerging factors affecting the progression of nonalcoholic fatty liver disease. Metabolism. 2020;111:154183.
53. Golabi P, Paik JM, Arshad T, et al. Mortality of NAFLD according to the body composition and presence of metabolic abnormalities. Hepatol Commun. 2020;4(8):1136–48.
54. Dao AD, Nguyen VH, Ito T, et al. Prevalence, characteristics, and mortality outcomes of obese and nonobese MAFLD in the United States. Hep Intl. 2022;17(1):225–36.
55. Shao C, Ye J, Li F, et al. Different predictors of steatosis and fibrosis severity among lean, overweight and obese patients with nonalcoholic fatty liver disease. Digest Liver Dis. 2019;51(10):1392–9.
56. Jiang D, Zhiyi H, Cailan X, et al. Analysis of the prevalence and influencing factors of non-obese fatty liver. J Clin Hepatobil Dis. 2021;37(11):2600–4.
57. Miaomiao F. Research progress of lean nonalcoholic fatty liver disease. Chin Med Clin Res. 2022;14(19):142–5.
58. Liang S, Wang C, Zhang J, et al. Triglyceride-glucose index and coronary artery disease: a systematic review and meta-analysis of risk, severity, and prognosis. Cardiovasc Diabetol. 2023;22(1):170.
59. Muhammad IF, Bao X, Nilsson PM, et al. Triglyceride-glucose (TyG) index is a predictor of arterial stiffness, incidence of diabetes, cardiovascular disease, and all-cause and cardiovascular mortality: a longitudinal two-cohort analysis. Front Cardiovasc Med. 2023;9:1035105.

60. Yang Y, Huang X, Wang Y, et al. The impact of triglyceride-glucose index on ischemic stroke: a systematic review and meta-analysis. Cardiovasc Diabetol. 2023;22(1):2.
61. Nayak SS, Kuriyakose D, Polisetty LD, et al. Diagnostic and prognostic value of triglyceride glucose index: a comprehensive evaluation of meta-analysis. Cardiovasc Diabetol. 2024;23(1):310.
62. Xin F-Z, Zhao Z-H, Liu X-L, et al. *Escherichia fergusonii* promotes nonobese nonalcoholic fatty liver disease by interfering with host hepatic lipid metabolism through its own msRNA 23487. Cell Mol Gastroenterol Hepatol. 2022;13(3):827–41.
63. Buzova D, Maugeri A, Liguori A, et al. Circulating histone signature of human lean metabolic-associated fatty liver disease (MAFLD). Clin Epigenetics. 2020;12(1):1.
64. Shen N, Tang L, Qian Y, et al. Serum miR-4488 as a potential biomarker of lean nonalcoholic fatty liver disease. Ann Transl Med. 2023;11(4):173–173.
65. Alharthi J, Pan Z, Gloss BS, et al. Loss of metabolic adaptation in lean MAFLD is driven by endotoxemia leading to epigenetic reprogramming. Metabolism. 2023;144:155583.
66. Tamura Y. Ectopic fat, insulin resistance and metabolic disease in non-obese Asians: investigating metabolic gradation. Endocr J. 2019;66(1):1–9.
67. Radu F, Potcovaru C-G, Salmen T, et al. The link between NAFLD and metabolic syndrome. Diagnostics. 2023;13(4):614.
68. Son D-H, Lee HS, Lee Y-J, et al. Comparison of triglyceride-glucose index and HOMA-IR for predicting prevalence and incidence of metabolic syndrome. Nutr Metab Cardiovasc Dis. 2022;32(3):596–604.
69. Tahapary DL, Pratisthita LB, Fitri NA, et al. Challenges in the diagnosis of insulin resistance: focusing on the role of HOMA-IR and tryglyceride/glucose index. Diabetes Metab Syndr Clin Res Rev. 2022;16(8):102581.
70. Rivière B, Jaussent A, Macioce V, et al. The triglycerides and glucose (TyG) index: a new marker associated with nonalcoholic steatohepatitis (NASH) in obese patients. Diabetes Metab. 2022;48(4):101345.
71. Zhao J, Fan H, Wang T, et al. TyG index is positively associated with risk of CHD and coronary atherosclerosis severity among NAFLD patients. Cardiovasc Diabetol. 2022;21(1):123.
72. Zhang R, Guan Q, Zhang M, et al. Association between triglyceride-glucose index and risk of metabolic dysfunction-associated fatty liver disease: a cohort study diabetes. Metab Syndr Obes Targ Ther. 2022;15:3167–79.
73. Furdela V, Pavlyshyn H, Shulhai A-M, et al. Triglyceride glucose index, pediatric NAFLD fibrosis index, and triglyceride-to-high-density lipoprotein cholesterol ratio are the most predictive markers of the metabolically unhealthy phenotype in overweight/obese adolescent boys. Front Endocrinol. 2023;14:1124019.
74. Cai X, Aierken X, Ahmat A, et al. A nomogram model based on noninvasive bioindicators to predict 3-year risk of nonalcoholic fatty liver in nonobese mainland chinese: a prospective cohort study. Biomed Res Int. 2020. https://doi.org/10.1155/2020/8852198.
75. Ji L, Cai X, Bai Y, Li T. Application of a novel prediction model for predicting 2-year risk of non-alcoholic fatty liver disease in the non-obese population with normal blood lipid levels: a large prospective cohort study from China. Int J Gen Med. 2021;14:2909–22.

Publisher's Note