Nutrition & Metabolism

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Clinical characteristics of lean and non-lean non-alcoholic fatty liver disease: a cross-sectional study

Mengyan Xu[1†], Rui Gong[2†], Jiao Xie[2], Sanping Xu[2*] and Shi Wang[3*]

Abstract

Introduction Non-alcoholic fatty liver disease (NAFLD) affects more than a quarter of the global population and has become the world's number one chronic liver disease, seriously jeopardizing public life and health. Despite the new terminology of metabolic dysfunction-associated steatotic liver disease (MASLD) has been proposed, the mechanisms underlying the heterogeneity across BMI stratification in non-alcoholic fatty liver disease (NAFLD) remain unclear. The aim of this study was to reveal the differences in metabolic and fibrotic characteristics between lean (BMI < 23 kg/m^2) and non-lean NAFLD in an Asian population.

Methods The current study collected NAFLD patients from the physical examination population. Patients were divided into two groups by BMI to compare their clinical parameters, including lean (BMI < 23 kg/m^2) and non-lean (BMI ≥ 23 kg/m^2) and fibrosis subgroups (with a threshold of LSM = 8 kPa) and analyzed for risk factors by logistic regression models.

Results Of the 11,577 NAFLD patients who participated in the study, there were 916 lean and 10,661 non-lean. The non-lean group was younger than the lean group (median age 50 vs. 52 years, $P < 0.001$) and had a significantly higher prevalence of hypertension (28.0% vs. 18.3%), diabetes mellitus (10.1% vs. 6.1%), and liver fibrosis (9.1% vs. 5.1%) (all $P < 0.001$). Analysis of metabolic indexes showed that TyG, TyG-BMI, TG/HDL-C and APRI were higher in the non-lean group (all $P < 0.001$). Gender stratification revealed that ALT was significantly higher in the male non-lean group, while HDL-C was lower in the female non-lean group (1.35 vs. 1.47 mmol/L). Multiple regression suggested that the risk of fibrosis was independently associated with CAP values and fasting glucose, BMI, direct bilirubin, globulin, and age in the non-lean group, whereas the risk was mainly driven by GGT and ALP in the lean group.

Conclusions Non-lean NAFLD patients showed more significant metabolic disturbances and risk of liver fibrosis. Although metabolic indicators (TyG, FIB-4) have limited predictive value for liver fibrosis, they are strongly associated with metabolic risk in MASLD.

Keywords Non-alcoholic fatty liver disease, Lean, Fibrosis

†Mengyan Xu and Rui Gong have contributed equally to this work.

*Correspondence:
Sanping Xu
xusanpinghao@aliyun.com
Shi Wang
wangshi505213@163.com
Full list of author information is available at the end of the article

Introduction

NAFLD is a metabolic disorder characterized by liver injury and closely related to insulin resistance and genetic susceptibility, which may progress to non-alcoholic steatohepatitis or even cirrhosis [1]. According to a recent systematic evaluation and meta-analysis, the global prevalence of NAFLD has increased from 25.3% in 1990–2006 to 38% in 2016–2019 [2], making it the most common chronic liver disease and the leading cause of abnormal liver biochemical indices on health examination globally, which is a serious risk to the public's life and health [3, 4].

It has been shown that BMI is directly related to the development of NAFLD [5]. Normal BMI was previously defined as between 18.5 and 24.9 kg/m^2. Compared to other races, Asians have more visceral fat deposition at the same BMI [6]. Therefore, the World Health Organization recommends that people of Asian origin reduce the BMI thresholds for overweight and obesity (a BMI of 23–27.5 kg/m^2 is defined as overweight, and a BMI > 27.5 kg/m^2 is defined as obese) [5–7]. A recent study from the Global NAFLD/NASH Registry reported that nearly 8% of NAFLD patients had a lean BMI, and the cohort was older and had a lower metabolic syndrome component relative to overweight/obese patients, but was equally at risk for advanced fibrosis [8, 9]. Previous studies have repeatedly reported that patients with lean NAFLD have the same or even more severe liver lesions and higher all-cause mortality rates than obese patients [10–12], while the clinical and metabolic characteristics of lean NAFLD patients have not been adequately investigated, and there is a need for cross sectional studies are necessary to obtain the clinical characteristics and risk factors of NAFLD patients with different BMI.

Non-alcoholic fatty liver disease (NAFLD) is closely associated with metabolic syndrome and type 2 diabetes mellitus (T2DM), and contributes to the development of cardiovascular disease (CVD) and chronic kidney disease.[13] However, the term "non-alcoholic fatty liver disease" fails to comprehensively characterize this condition. Consequently, the International Fatty Liver Expert Panel proposed in 2020 to rename NAFLD as metabolic dysfunction-associated fatty liver disease (MAFLD) [14]. Subsequently in 2023, three major multinational liver associations recommended replacing NAFLD with metabolic dysfunction-associated steatotic liver disease (MASLD) and substituting non-alcoholic steatohepatitis (NASH) with metabolic dysfunction-associated steatohepatitis (MASH) [15]. Research by Hannes et al. further demonstrated that 99% of NAFLD patients meet MASLD diagnostic criteria, indicating the epidemiological data of NAFLD remain applicable to MAFLD populations [16].

Insulin resistance (IR) is a criterion for measure metabolic syndrome (MetS), and hyper-insulinemic euglycemic clamp (HEC), the gold standard for measuring insulin resistance, is less frequently utilized in clinical practice because of its cumbersome measurement. In primary care settings, insulin concentrations are not routinely tested, which makes the calculation of homeostatic model assessment for insulin resistance (HOMA-IR) difficult [17]. In view of this, the triglyceride-glucose index (Ty-G), the TyG-BMI index, and the ratio of triglycerides to high-density lipoprotein cholesterol (TG/HDL-C) have been proposed for easy estimation of the degree of insulin resistance, and these indices are of great value in metabolic-related diseases [18–20]. The predictive role of metabolic syndrome-related indices in NAFLD and its hepatic fibrosis has been studied in the literature, however, lean NAFLD has not been compared with non-lean NAFLD. Therefore, in this paper, a cross-sectional study was conducted on the metabolic indicators of lean NAFLD and non-lean NAFLD, aiming to obtain the clinical and metabolic characteristics of patients with lean NAFLD.

Methods

Study group

The population selected from March 1, 2020 to March 31, 2023 who underwent health checkups at the Health Management Center of Wuhan Union Hospital. Inclusion criteria: people diagnosed with NAFLD by abdominal ultrasound and liver transient elastography. Exclusion criteria: 1. Patients with excessive alcohol consumption (> 60 g/d for men; > 40 g/d for women); 2. Accompanied by other diseases of the liver such as viral hepatitis, drug-induced liver disease, autoimmune liver disease, cirrhosis, and hepatocellular carcinoma, etc.; 3. Combined malignant tumors, autoimmune diseases and other patients who need long-term treatment.

Data collection and organization

History taking and physical examination was performed on all patients. Sex and age, height and weight of each medical examiner were collected, BMI was calculated, and patients' pulse, and blood pressure were taken. All participants underwent abdominal ultrasound and liver transient elastography.

Before performing blood tests, all subjects were asked to fast for 8 h and venous blood was collected. The examination items included hemoglobin (Hb); platelet count (PLT); total protein (TP); albumin (ALB); globulin (ALG); total bilirubin (TB); direct bilirubin (DB); alanine aminotransferase (ALT); aspartate aminotransferase (AST); glutamyl-transpeptidase (GGT); alkaline phosphatase (ALP); triglyceride (TG); total cholesterol (TC); and high-density lipoprotein cholesterol (HDL-TC); low-density lipoprotein cholesterol (LDL-TC);

urea nitrogen (UN); creatinine (Cr); uric acid (UA); fasting blood glucose (FBG); glycosylated hemoglobin (HbA1c).

The results of abdominal ultrasound (Mindray-DC90) and liver transient elastography (Fibrotouch C-FT7000) are used to diagnose fatty liver and liver fibrosis. Fatty liver was diagnosed when two of the following criteria were met: 1. liver echoes were enhanced in the near field and weakened in the far field; 2. controlled attenuation parameter (CAP) ≥ 240 db/m. Liver fibrosis was diagnosed by liver stiffness measurement (LSM). Significant liver fibrosis was not excluded when LSM ≥ 8 kPa, and excluded when LSM < 8 kPa. For Asian populations, NAFLD patients were divided into a lean group (BMI < 23 kg/m^2) and a non-lean group (BMI ≥ 23 kg/m^2).

Hypertension and diabetes mellitus were assessed. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, self-reported hypertension, or regular oral antihypertensive medication. Diabetes was defined as fasting blood glucose ≥ 7.0 mmol/L; or glycosylated hemoglobin ≥ 6.5% and self-reported diabetes mellitus or regular use of hypoglycemic medication or insulin.

Statistical methods

Statistical analysis was performed using SPSS 27.0 software. Normally distributed data are expressed as mean ± standard deviation (SD) and compared between groups using Student's t-test. Non-normally distributed data are presented as median (M) with interquartile range (P25, P75) and analyzed by Mann–Whitney U test. Categorical variables are reported as number of cases (percentage) and compared via Chi-square test. For the complex interactions between various metabolic indicators, we performed an interaction test between variables and then stratified the analysis by gender, age and comorbidities. A univariate analysis of all indicators was performed first. Variables with $P < 0.1$ in univariate analysis, along with clinically or literature-supported predictors, were included in the multivariate model (forward likelihood ratio method, α_entry = 0.05, α_removal = 0.1).

Results

Comparison of clinical and metabolic characteristics between lean and non-lean NAFLD patients

Based on the above inclusion and exclusion criteria, 11,577 study subjects were obtained, including 916 (7.9%) with lean NAFLD (BMI < 23 kg/m^2) and 10,661 (92.1%) with non-lean NAFLD (BMI ≥ 23 kg/m^2). Of the 916 lean NAFLD subjects, 474 were male and 442 were female, and their median age was 52 years, of the 10,661 non-lean NAFLD subjects, 8117 were male and 2544 were female, and their median age was 50 years. Among the lean subjects, 18.3% were hypertensive and 6.1% were diabetic, among the non-lean subjects, 28% were hypertensive and 10.1% were diabetic (Table 1).

Compared with female lean NAFLD subjects, non-lean NAFLD subjects exhibited significantly higher levels of PLT count, ALT, GGT, TG, LDL-C, UA, FBG, HbA1c, along with significantly lower levels of ALB and HDL-C, with statistically significant differences ($P < 0.05$). In male NAFLD subjects, non-lean individuals demonstrated significantly elevated levels of Hb, GLB, ALT, AST, GGT, TG, TC, LDL-C, UA, FBG, and HbA1c, alongside significantly reduced levels of ALB and HDL-C, compared to lean counterparts ($P < 0.05$) (Table 2).

Metabolic syndrome and transient elastography results related indicators were introduced into this study to compare the difference between lean NAFLD and non-lean patients (Table 2). Both in male and female patients, TyG, TyG-BMI, TG/HDL were higher in non-lean NAFLD patients than in lean patients with statistical significance ($P < 0.05$). In female patients, CAP and LSM were higher in non-lean subjects than in lean subjects; in male subjects, CAP was greater in non-lean NAFLD than in lean NAFLD, and the difference was statistically significant ($P < 0.05$).

Subjects were categorized into 8 groups by gender, age, presence of hypertension and presence of diabetes. Differences between groups were examined separately using binary logistic regression analysis.

Table 1 Comparison of lean and non-lean general conditions

	Lean (n = 916)	Non-lean, (n = 10,661)	Z/×2	P
Sex, male (%)	474 (51.7%)	8117 (76.10%)	262.181	< 0.001
Age, M(P25, P75)	52 (42,59)	50 (41,57)	−3.921	< 0.001
Hypertension, n (%)	168 (18.3%)	2989 (28.0%)	39.985	< 0.001
Diabetes, n (%)	56 (6.10%)	1078 (10.1%)	15.260	< 0.001
Hepatic fibrosis, n (%)	47 (5.13%)	970 (9.1%)	16.571	< 0.001

Table 2 Baseline values for lean and non-lean NAFLD patients between genders

	Female				Male			
	lean (n = 442)	non-lean (n = 2544)	Z/×2	*P*	lean (n = 474)	non-lean (n = 8117)	Z/×2	*P*
Age	54 (46, 60)	54 (46, 59)	0.545	0.928	50 (40, 59)	49 (40, 56)	1.52	0.02
Hb, g/L	133.5 (128, 139)	134 (128, 140)	0.958	0.318	153 (147, 159.25)	155 (149, 162)	2.095	< 0.001
PLT, $\times 10^9$/L	233 (201, 271.25)	242 (205, 281)	1.421	0.035	222.5 (189, 263)	226 (192, 262)	0.86	0.451
TP, g/L	73.7 (70.8, 76.6)	73.2 (70.4, 76)	1.04	0.23	73.35 (70.1, 76.5)	73.2 (70.4, 76.2)	0.696	0.719
ALB, g/L	46.8 (44.9, 48.6)	45.8 (44.2, 47.6)	3.097	< 0.001	47.75 (45.98, 49.63)	47.4 (45.7, 49.2)	1.918	0.001
GLB, g/L	26.9 (24.58, 23.9)	27.3 (25, 29.6)	1.251	0.087	25.5 (23.2, 27.53)	25.8 (23.5, 28.1)	1.397	0.04
TB, μmol/L	12.6 (10.5, 15.43)	12 (9.8, 14.9)	1.875	0.002	13.55 (11, 18.1)	13.9 (11.1, 17.6)	0.848	0.468
CB, μmol/L	3.7 (2.8, 4.8)	3.6 (2.8, 4.6)	0.716	0.685	4.3 (3.2, 5.8)	4.4 (3.4, 5.7)	0.883	0.416
ALT, U/L	19 (14, 25)	21 (16, 29)	2.15	< 0.001	25.5 (19, 35)	31 (22, 45)	3.574	< 0.001
AST, U/L	22 (19, 27.25)	23 (19, 28)	1.081	0.193	24 (20, 29)	26 (21.5, 32)	2.729	< 0.001
GGT, U/L	16 (13, 23)	18 (14, 27)	2.081	< 0.001	27 (19, 41)	32 (23, 51)	3.178	< 0.001
ALP, U/L	69 (56, 85)	70 (57.25, 86)	1.012	0.258	69.5 (59, 82.25)	69 (59, 81)	0.637	0.813
TG, mmol/L	1.26 (0.9.1.85)	1.42 (1.03, 2.04)	2.49	< 0.001	1.49 (1.08, 2.29)	1.76 (1.24, 2.64)	2.721	< 0.001
TC, mmol/L	5.12 (4.58, 5.87)	5.17 (4.56, 5.82)	0.638	0.81	4.96 (4.31, 5.63)	5.03 (4.43, 5.67)	1.411	0.037
HDL-C, mmol/L	1.47 (1.22, 1.71)	1.35 (1.16, 1.57)	3.203	< 0.001	1.22 (1.04, 1.42)	1.13 (0.97, 1.3)	3.356	< 0.001
LDL-C, mmol/L	3.04 (2.53, 3.6)	3.09 (2.58, 3.62)	0.889	0.409	2.89 (2.42, 3.51)	3.04 (2.53, 3.57)	1.924	0.001
BUN, mmol/L	4.63 (3.86, 5.52)	4.66 (3.91, 5.57)	0.499	0.965	4.87 (4.17, 5.68)	4.99 (4.27, 5.85)	1.22	0.102
Cr, μmol/L	57.2 (51.58, 62.1)	55.9 (50.7, 61.7)	1.085	0.189	75.95 (68.5, 83.73)	76.8 (69.9, 84.5)	1.086	0.189
UA, μmol/L	279.4 (244.75, 323.2)	297.25 (257.9, 345.68)	2.46	< 0.001	383.45 (315.4, 435.45)	403.7 (351.3, 464.75)	2.718	< 0.001
FBG, mmol/L	4.96 (4.66, 5.31)	5.1 (4.72, 5.54)	2.005	0.001	4.97 (4.6, 5.36)	5.08 (4.7, 5.6)	2.084	< 0.001
BMI, kg/m^2	22.2 (21.5, 22.6)	25.8 (24.4, 27.5)	19.405	< 0.001	22.2 (21.7, 22.6)	26.6 (25.1, 28.4)	21.162	< 0.001
HbA1c, %	5.5 (5.2, 5.7)	5.6 (5.3, 5.9)	2.66	< 0.001	5.4 (5.2, 5.7)	5.5 (5.3, 5.8)	1.815	0.003
CAP, db/m	253 (246, 260.25)	264 (251, 282)	6.468	< 0.001	256 (248, 262)	274 (255, 290)	8.93	< 0.001
LSM, kPa	5.5 (4.8, 6.3)	5.6 (4.8, 6.5)	1.52	0.02	5.6 (4.7, 6.4)	5.7 (4.9, 6.6)	1.251	0.087
TyG	8.53 (8.16, 9.96)	8.67 (8.34, 9.09)	2.66	< 0.001	8.68 (8.33, 9.14)	8.89 (8.51, 9.34)	3.219	< 0.001
TyG-BMI	187.74 (178.4, 197.79)	225.05 (210.12, 244.61)	13.814	< 0.001	191.86 (183.19, 202.35)	236.9 (219.36, 259.32)	15.473	< 0.001
TG/HDL-C	0.83 (0.55, 1.43)	1.06 (0.69, 1.67)	3.007	< 0.001	1.26 (0.81, 2.06)	1.56 (1, 2.57)	3.057	< 0.001
FIB-4	1.12 (0.84, 1.55)	1.11 (0.8, 1.48)	1.142	0.147	1 (0.75, 1.46)	1 (0.73, 1.35)	1.313	0.064
APRI	0.23 (0.18, 0.32)	0.24 (0.19, 0.32)	0.63	0.822	0.27 (0.2, 0.35)	0.29 (0.23, 0.38)	2.386	< 0.001
AST/ALT	1.18 (0.95, 1.45)	1.07 (0.86, 1.33)	2.931	< 0.001	0.93 (0.71, 1.16)	0.81 (0.65, 1.04)	3.229	< 0.001
Hypertension, n (%)	77 (17.46%)	717 (28.18%)	22.348	< 0.001	91 (19.2%)	2272 (28%)	17.363	< 0.001
Diabetes, n (%)	15 (3.4%)	222 (8.73%)	14.656	< 0.001	41 (8.65%)	856 (10.55%)	1.722	0.216

Continuous variables were shown as mean ± SD or median (interquartile range), and categorical variables were expressed as counts (percentage)

Hb hemoglobin, *PLT* platelet, *TP* total protein, *ALB* albumin, *GLB* globulin, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *TB* total bilirubin, *DB* direct bilirubin, *GGT* gamma-glutamyl transpeptidase, *ALP* alkaline phosphatase, *Cr* creatinine, *BUN* blood urea nitrogen, *UA* Uric Acid, *FBG* fasting blood glucose, *TG* triglyceride, *CHOL* cholesterol, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HbA1c* glycosylated hemoglobin, *TyG* triglyceride and glucose index, *TyG-BMI* triglyceride glucose-body mass index, *FIB-4* fibrosis-4 score, *APRI* aspartate aminotransferase to platelet ratio index, *CAP* controlled attenuation parameter, *LSM* liver stiffness measurement

In women < 50 years of age, ALB, HDL-C, UA, HbA1c, and hypertension differed among the different types of NAFLD patients. In women ≥ 50 years of age, TB, ALT, HDL-C, diabetes, and hypertension differed among the different types of NAFLD patients (Fig. 1).

In men < 50 years of age, hypertension, uric acid, high-density lipoprotein, ALT, and age differed between lean and non-lean NAFLD patients. In men ≥ 50 years of age, Hb, ALT, BUN, HDL-C, UA levels and hypertension prevalence differed in lean and non-lean NAFLD patients (Fig. 2).

In subjects with hypertension, non-lean and lean NAFLD patients differed in age, Hb, ALB, ALT and UA levels; and in subjects without hypertension, lean and non-lean NAFLD patients differed in Hb, ALB, ALT, HDL-C, BUN, UA levels and diabetes prevalence (Fig. 3).

In subjects with diabetes mellitus, lean and non-lean NAFLD differed in age, ALB and Cr levels. In subjects

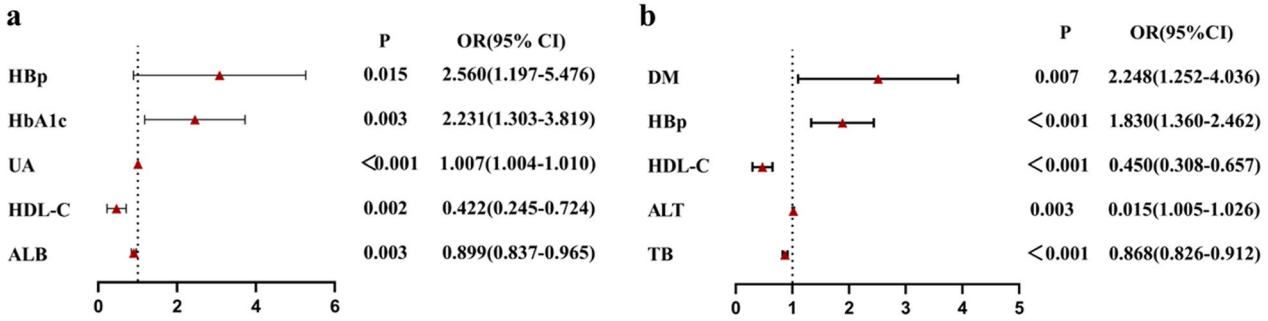

Fig. 1 **a** Multivariate logistic regression analysis for female < 50 years of age; **b** Multivariate logistic regression analysis for female ≥ 50 years of age

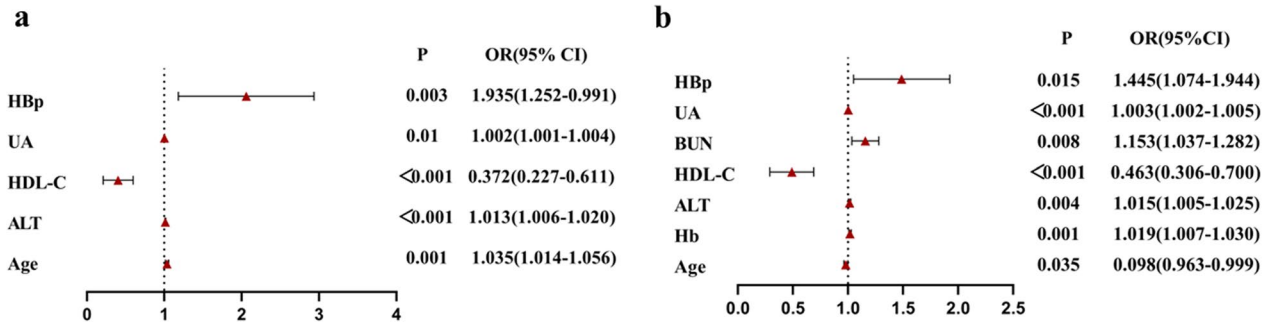

Fig. 2 **a** Multivariate logistic regression analysis for male < 50 years of age; **b** Multivariate logistic regression analysis for male ≥ 50 years of age

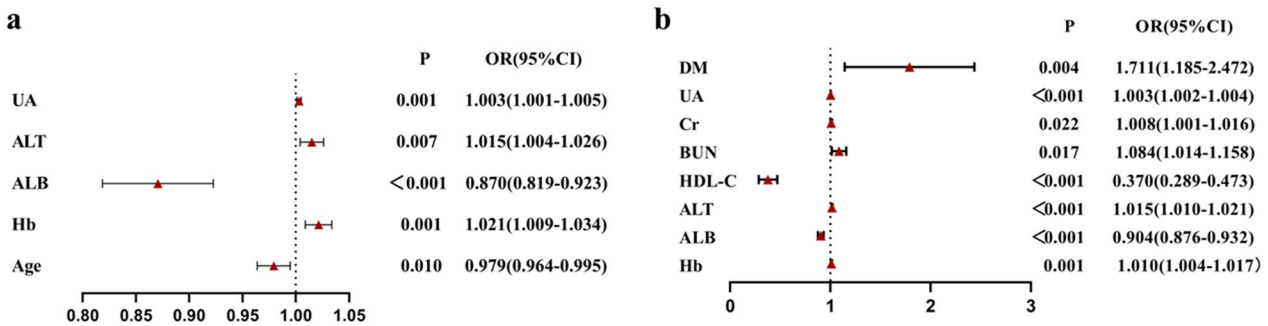

Fig. 3 **a** Multivariate logistic regression analysis for subjects with hypertension; **b** multivariate logistic regression analysis for subjects without hypertension

without diabetes mellitus, lean and non-lean NAFLD differed significantly in age, Hb, ALT, ALB, HDL-C, BUN, Cr, UA, FBG, HbA1c levels and prevalence of hypertension (Fig. 4).

Comparison of the degree of liver fibrosis between lean and non-lean NAFLD patients

For lean NAFLD patients, there was no significant difference in sex ratio, CAP, and BMI among subjects with fibrosis, but had younger age and were higher in ALT, AST, γ-GT, ALP, TG, and UA than those with LSM < 8 kPa ($P < 0.05$) (Table 3). For non-lean NAFLD subjects, there was a significant difference in the male-to-female ratio in subjects with significant fibrosis not excluded ($P < 0.05$), and age, Hb, TP, GLB, TB, CB, ALT, AST, γ-GT, ALP, TG, UA, FPG, and HBA1c% were significantly higher than those in subjects with LSM < 8 kPa ($P < 0.05$), and there was also a significant difference in BMI and CAP were significantly different ($P < 0.05$) (Table 4).

Numerous studies have shown that liver fibrosis cannot be ruled out when the LSM ≥ 8 kPa, and that a complete

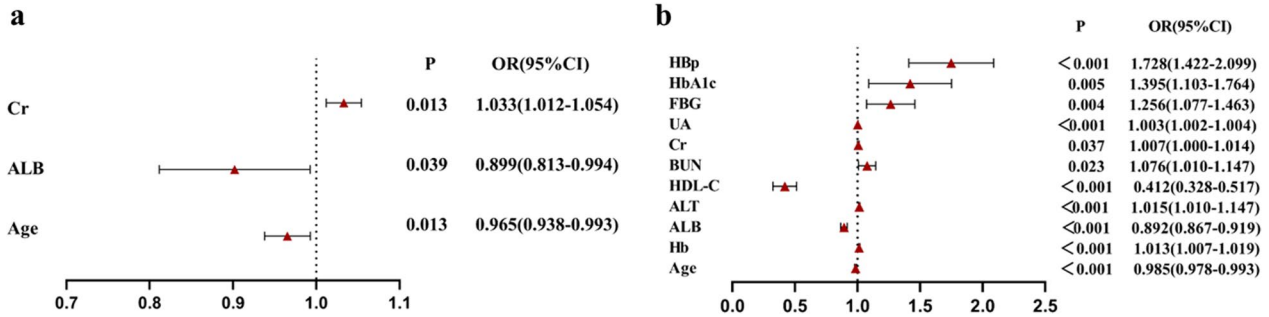

Fig. 4 **a** Multivariate logistic regression analysis for subjects with diabetes; **b** Multivariate logistic regression analysis for subjects without diabetes

Table 3 Liver fibrosis in lean and non-lean NAFLD patients

	LSM < 8 kPa	LSM ≥ 8 kPa
Lean (n = 916), n (%)	869 (94.87)	47 (5.13)
Non-lean (n = 10,661), n (%)	9691 (90.90)	970 (10.01)
X^2	16.571	$p < 0.001$

liver biopsy is needed to clarify the state of liver fibrosis [21, 22]. On this basis, subjects were divided into two groups, and independent risk factors affecting hepatic fibrosis were analyzed using multivariate logistic regression with statistically different data from univariate analysis as the independent variables. PLT, GGT, and ALP were the independent influencing factors for lean NAFLD, while GGT and ALP were risk factors. Age, PLT, ALG, TB, DB, ALT, HDL-C, FBG, BMI, and CAP were the independent influencing factors for liver fibrosis in non-lean NAFLD, while age, ALG, DT, ALT, FBG, BMI, and CAP were risk factors (Fig. 5).

Discussion

Non-alcoholic fatty liver disease (NAFLD) has emerged as the predominant cause of chronic liver disease worldwide, with a notable gender disparity in its epidemiological distribution [23, 24]. In the Asian region, the epidemiological characteristics of NAFLD are marked by a higher prevalence non-obese NAFLD (BMI < 25 kg/m^2). Despite maintaining normal BMI parameters, lean NAFLD patients present metabolic profiles and hepatic fibrosis progression patterns similar to those observed in obese populations, challenging conventional obesity-centric diagnostic paradigms [6, 25, 26]. This paradoxical presentation highlights the complex pathophysiology of NAFLD in Asian populations, where traditional anthropometric standards may not adequately reflect metabolic risk.

In 2023, international liver associations recommended replacing the term NAFLD with metabolic dysfunction-associated steatotic liver disease (MASLD). These two entities share substantial overlap in pathogenic mechanisms, both being characterized by hepatic fat accumulation as a core feature and closely linked to metabolic disturbances such as insulin resistance, obesity, and dyslipidemia. The diagnosis of MASLD emphasizes the centrality of metabolic dysfunction, requiring the presence of at least one cardiometabolic risk factor (e.g., elevated BMI, hypertension, or type 2 diabetes mellitus) [10, 14]. In contrast, the traditional definition of NAFLD primarily focuses on excluding alternative etiologies of liver injury, particularly alcohol consumption. Thus, MASLD represents an evolved and refined conceptualization of NAFLD, aiming to strengthen the role of metabolic abnormalities in disease phenotyping and prognostic evaluation.

Although the MASLD nomenclature has been progressively adopted in international guidelines, our study's protocol design and data collection period (March 2020–March 2023) predate these updated recommendations. Furthermore, as this investigation focuses on BMI stratification's impact on NAFLD phenotypes, retaining the NAFLD diagnostic framework ensures methodological consistency. The MASLD criteria may include subjects with low BMI but concurrent metabolic abnormalities, and maintaining the original NAFLD classification prevents potential bias from retrospective reclassification.

In this study, patients with NAFLD were divided into lean (BMI < 23 kg/m^2) and non-lean (BMI ≥ 23 kg/m^2) groups according to the WHO recommendations for Asians. In a population-based study conducted in Hong Kong, PNPLA3 gene polymorphisms had a more significant effect on liver fat in lean individuals than in overweight and obese individuals. In addition, lean individuals in Asia have a significantly higher probability of carrying this risk allele compared to overweight and obese individuals, which may explain the similar prevalence of NAFLD as in the West even

Table 4 Baseline values for lean and non-lean NAFLD patients between LSM < 8 kPa and LSM ≥ 8 kPa groups

	Lean				Non-lean			
	LSM < 8 kPa	**LSM ≥ 8 kPa**	**t/×2/Z**	***P***	**LSM < 8 kPa**	**LSM ≥ 8 kPa**	**t/×2/Z**	***P***
N (male/female)	869 (449/420)	47 (25/22)	0.041	0.839	9691 (7349, 2342)	970 (768, 202)	5.421	0.02
Age	52 (42, 59)	50.67 ± 11.636	− 1.599	0.11	50 (41, 57)	53 (44, 60)	− 7.866	< 0.001
Hb, g/L	143 (133, 154)	143.17 ± 14.952	− 0.083	0.934	152 (141, 159)	154 (144, 162)	− 4.985	< 0.001
PLT, $\times 10^9$/L	231 (195.5, 270)	234.37 ± 58.217	− 3.393	0.001	230 (196, 267)	223 (181, 262)	− 4.727	< 0.001
TP, g/L	73.487 ± 4.277	73.487 ± 4.276	− 0.952	0.342	73.1 (70.4, 76.1)	74.1 (71, 77.2)	− 6.005	< 0.001
ALB, g/L	47.278 ± 2.752	47.278 ± 2.752	1.1	0.272	47.1 (45.3, 48.9)	47 (45, 48.9)	− 1.02	0.308
GLB, g/L	26.1 (23.8, 28.5)	26.3 (23.8, 29.9)	− 1.231	0.218	26 (23.8, 28.4)	27 (24.8, 29.5)	− 7.934	< 0.001
TB, μmol/L	13.2 (10.8, 17)	12.2 (9.4, 16.3)	− 1.364	0.172	13.4 (10.7, 17)	13.8 (10.975, 17.3)	− 2.203	0.028
CB, μmol/L	4 (3, 5.25)	4.404 ± 1.98	− 0.295	0.768	4.2 (3.2, 5.4)	4.4 (3.4, 5.7)	− 3.404	0.001
ALT, U/L	21 (16, 31)	25 (19, 40)	− 2.684	0.007	27 (20, 40)	39 (26, 65)	− 17.07	< 0.001
AST, U/L	23 (19, 28)	27 (22, 35)	− 3.642	< 0.001	24 (21, 30)	31 (24, 41)	− 19.059	< 0.001
GGT, U/L	21 (15,32)	33 (20, 58)	− 4.226	< 0.001	28 (19, 44)	38.5 (26, 61)	− 13.652	< 0.001
ALP, U/L	69 (58, 83)	71.77 ± 21.182	− 2.643	0.008	69 (58, 82)	73 (61, 87)	− 6.569	< 0.001
TG, mmol/L	1.37 (0.96, 2.065)	1.53 (1.15, 2.58)	− 1.991	0.046	1.65 (1.16, 2.46)	1.9 (1.34, 2.923)	− 7.633	< 0.001
TC, mmol/L	5.04 (4.425, 5.75)	5.1319 ± 0.983	− 1.182	0.237	5.07 (4.46, 5.69)	5.07 (4.45, 5.8)	− 1.129	0.259
HDL-C, mmol/L	1.33 (1.12, 1.57)	1.3732 ± 0.353	− 1.457	0.145	1.18 (1.01, 1.39)	1.11 (0.96, 1.3)	− 7.409	< 0.001
LDL-C, mmol/L	2.98 (2.46, 3.55)	3.041 ± 0.813	− 1.872	0.061	3.05 (2.54, 3.57)	3.07 (2.54, 3.64)	− 0.637	0.524
BUN, mmol/L	4.76 (4, 5.506)	4.879 ± 1.191	− 0.845	0.398	4.92 (4.18, 5.78)	4.96 (4.16, 5.843)	− 0.834	0.405
Cr, μmol/L	65.4 (56.85, 76.95)	67.133 ± 14.189	− 0.616	0.538	73 (62.9, 82)	73 (62.675, 81.6)	− 0.243	0.808
UA, μmol/L	321.2 (267.8, 393.05)	335.756 ± 91.291	− 2.311	0.021	379.4 (316.9, 443.9)	394.7 (334.3, 464.075)	− 5.428	< 0.001
FBG, mmol/L	4.94 (4.605, 5.34)	5.11 (4.61, 5.8)	− 1.48	0.139	5.04 (4.7, 5.5)	5.395 (4.86, 6.2)	− 12.017	< 0.001
BMI, kg/m^2	22.2 (21.6, 22.6)	22.1 (21.6, 22.7)	− 0.422	0.673	26.3 (24.9, 28)	27.6 (25.8, 30.1)	− 14.689	< 0.001
HbA1c, %	5.4 (5.2, 5.7)	5.5 (5.2, 5.9)	− 1.432	0.152	5.5 (5.3, 5.8)	5.7 (5.4, 6.2)	− 11.077	< 0.001
CAP, db/m	254 (247, 261)	255 (245, 270)	− 0.336	0.737	270 (253, 287)	287 (268, 306)	− 17.777	< 0.001
LSM, kPa	5.5 (4.7, 6.2)	9.8 (8.4, 12)	− 11.564	< 0.001	5.5 (4.8, 6.3)	9.7 (8.6, 11.6)	− 51.444	< 0.001
TyG	8.588 (8.239, 9.044)	8.919 ± 0.752	− 2.253	0.024	8.822 (8.448, 9.264)	9.054 (8.63, 9.51)	− 10.257	< 0.001
TyG-BMI	190.837 ± 15.517	191.922 (183.589, 201.599)	− 0.985	0.325	232.708 (215.63, 253.549)	252.492 (228.37, 279.66)	− 17.01	< 0.001
TG/HDL-C	1.033 (0.649, 1.698)	1.271 (0.775, 2.114)	− 2.068	0.039	1.404 (0.885, 2.295)	1.728 (1.091, 2.948)	− 8.667	< 0.001
FIB-4	1.063 (0.787, 1.482)	1.355 (1.027, 2.07)	− 3.776	< 0.001	1.011 (0.737, 1.353)	1.206 (0.858, 1.694)	− 10.956	< 0.001
APRI	0.247 (0.194, 0.331)	0.368 (0.26, 0.5)	− 4.838	< 0.001	0.275 (0.213, 0.355)	0.355 (0.263, 0.518)	− 18.002	< 0.001
AST/ALT	1.053 (0.822, 1.333)	1 (0.819, 1.333)	− 0.713	0.476	0.875 (0.692, 1.118)	0.771 (0.621, 1)	− 9.413	< 0.001

Defined LSM ≥ 8 kPa as liver fibrosis not excluded group

Continuous variables were shown as mean ± SD or median (interquartile range), and categorical variables were expressed as counts (percentage)

Hb hemoglobin, *PLT* platelet, *TP* total protein, *ALB* albumin, *GLB* globulin, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *TB* total bilirubin, *DB* direct bilirubin, *GGT* gamma-glutamyl transpeptidase, *ALP* alkaline phosphatase, *Cr* creatinine, *BUN* blood urea nitrogen, *UA* Uric Acid, *FBG* fasting blood glucose, *TG* triglyceride, *CHOL* cholesterol, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HbA1c* glycosylated hemoglobin, *TyG* triglyceride and glucose index, *TyG-BMI* triglyceride glucose-body mass index, *FIB-4* fibrosis-4 score, *APRI* aspartate aminotransferase to platelet ratio index, *CAP* controlled attenuation parameter, *LSM* liver stiffness measurement

though Asians have a lower metabolic burden [27]. High-risk PNPLA3 rs738409 variants are associated with increased risk of NAFLD, more severe liver histology (e.g., presence of steatohepatitis and fibrosis), and future development of hepatocellular carcinoma and cirrhotic complications [28].

Male NAFLD subjects far outnumbered female subjects in both lean and non-lean groups, and the mean age of males was lower than that of females. They also exhibited worse metabolic profile compared to females, regardless of lean or non-lean NAFLD status. These findings suggest that males generally present with higher prevalence of MetS, predisposing them to hepatic injury and fibrosis progression. This divergence may be attributed to sex-specific adipose distribution patterns: males predominantly develop visceral adiposity and central obesity, whereas females, despite higher overall adiposity, it often presents as subcutaneous fat and pear-shaped

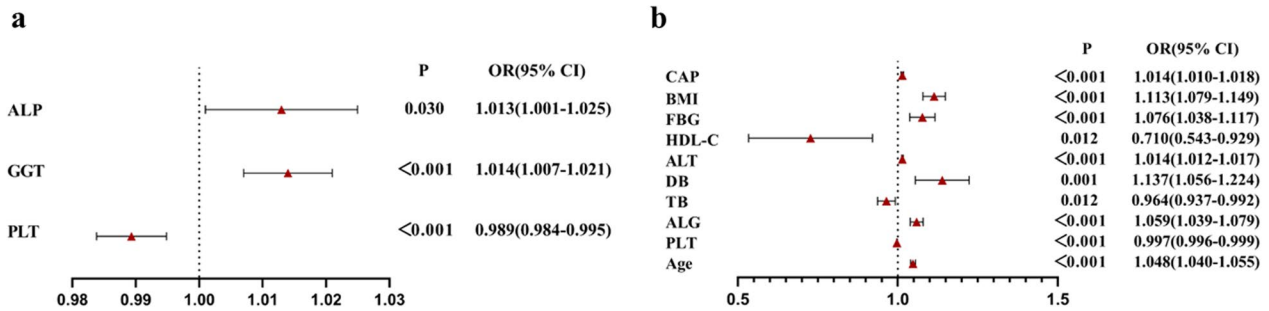

Fig. 5 **a** Logistic regression analysis of liver fibrosis in lean NAFLD subjects; **b** Logistic regression analysis of liver fibrosis in non-lean NAFLD subjects

buttock obesity [29, 30]. Consequently, males exhibit a higher susceptibility to obesity-related chronic diseases. Using 50 years as a cutoff, there were 1986 female patients older than 50 years old and 1000 female patients younger than 50. It has been suggested that postmenopausal women have a significantly higher incidence of NAFLD and a greater risk of developing non-alcoholic steatohepatitis (NASH) [31–33]. The underlying reason for this maybe the enhanced insulin sensitivity in premenopausal females, mediated by estrogen's protective effects, correlates with a lower incidence of metabolic disorders compared to age-matched males. However, this metabolic advantage diminishes post-menopause or upon progression of insulin resistance to hyperglycemia and type 2 diabetes [34, 35]. Importantly, prolonged suboptimal glycemic control serves as an independent risk factor for NAFLD in females.

NAFLD is recognized as an independent risk factor for cardiovascular disease (CVD) morbidity and mortality, which are the leading cause of mortality in adults with NAFLD [36, 37]. Compared to lean NAFLD patients, the lipid profile of non-lean subjects showed significant atherogenic features: higher levels of triglycerides, LDL cholesterol, and reduced levels of HDL cholesterol [38, 39]. A meta-analysis that included several cohort studies showed that the risk of lethal and non-lethal CVD increases further with the severity of liver disease in patients with NAFLD, especially in NASH with high fibrosis [40]. Metabolic dysfunction and atherogenic dyslipidemia due to insulin resistance are the main pathophysiologic mechanisms underlying the development of MASLD [41]. Multiple mechanisms (lipotoxicity [42], intestinal dysbiosis [43], and pro-inflammatory diet [44]) cause chronic inflammation in the liver and chronic inflammation throughout the body [45], ultimately leading to adverse outcomes such as hepatic fibrosis, atherosclerosis, and tumors. Meanwhile in non-lean NAFLD subjects, the prevalence of hypertension reached 28%, which was much higher than that in lean NAFLD subjects (18.3%, $P<0.001$), suggesting that the accumulation of visceral fat drives the hyperactivation of the renin–angiotensin–aldosterone system (RAAS) system as well as chronic inflammation in the liver ultimately contributes to the development of CVD [37]. In addition, blood pressure stratification helped predict the progression of NAFLD [46, 47]. Numerous epidemiological evidence also suggests that NAFLD not only promotes accelerated coronary atherosclerosis, but also affects all other anatomical structures of the heart, increasing the risk of diastolic dysfunction and hypertrophy of the left ventricle, calcification of the heart valves, and cardiac arrhythmias [36, 48].

Non-alcoholic fatty liver disease and type 2 diabetes mellitus (T2DM) share a common pathophysiological basis in insulin resistance, with strong bidirectional associations observed clinically [49]. Epidemiological studies demonstrate that the percentage of patients with NAFLD who also have T2D ranges between 30 and 80% [50, 51]. A meta-analysis of data form longitudinal studies reveals a significantly increased risk of T2DM in the NAFLD population, with a random-effects model showing a combined hazard ratio (HR) of 2.22 (95% confidence interval [CI] 1.84–2.60), which is 2.22-fold elevated compared to the non-NAFLD population [52]. Dysglycemia exacerbates insulin resistance, activates oxidative stress pathways, and induces hepatic steatosis and hepatocyte apoptosis. Excessive circulating lipids further promote hepatic fat deposition, creating a vicious cycle of metabolic dysfunction [53, 54]. Notably, the risk of diabetes development was histologically progression-dependent: patients with progressive NASH exhibited the highest susceptibility to diabetes compared to patients with early stages of non-alcoholic steatohepatitis (NASH) [2, 55]. A critical caveat lies in the potential confounding effect of diabetes-related weight loss or sarcopenic obesity in lean NAFLD subjects, which may introduce bias in anthropometric-metabolic correlations.

In non-lean NAFLD patients, serum UA levels were much higher than in lean NAFLD subjects, consistent with previous studies [56, 57]. Uric acid is produced

through purine catabolism and hyperuricemia is a risk factor for gout and urolithiasis [58]. Elevated serum uric acid leads to a reduction in lipocalin, which promotes insulin resistance-mediated visceral adipose accumulation (VAT), and bi-directional effects between hyperuricemia and insulin resistance, and between insulin resistance and visceral adipose accumulation [59–61], which accelerates the development of NAFLD [62].

Liver fibrosis, a consequence of chronic hepatic injury coupled with sustained inflammatory activation and fibrogenesis, is recognized as the primary driver of progression from chronic liver disease to cirrhosis [63]. Accumulating evidence supports the diagnostic accuracy of transient elastography for detecting advanced fibrosis and cirrhosis in most NAFLD patients, though its sensitivity for early-stage fibrosis remains suboptimal. Based on Vincent et al.'s 2010 criteria [22], this study defined LSM < 8 kPa as the threshold to exclude significant fibrosis (negative predictive value ≥ 91% for ≥ F2 fibrosis). Patients exceeding this threshold require confirmatory assessments to guide anti-fibrotic interventions [22]. Although previous meta-analyses have demonstrated that obese NAFLD (BMI ≥ 25 kg/m^2) patients have significantly higher metabolism-related serologic markers than non-obese (BMI < 25 kg/m^2) patients [64], the extent of hepatic pathology in lean and non-lean NAFLD patients has generated much controversy.

In a study of 1090 patients with biopsy-proven NAFLD followed up for 133 months, non-obese NAFLD (BMI < 25 kg/m^2) patients were found to have more severe liver lesions and shorter survival compared with obese NAFLD patients (BMI ≥ 25 kg/m^2). Instead, in another study of 307 patients with biopsy-proven NAFLD, serum cytokeratin-18 levels, liver stiffness measurements and histologic fibrosis stage were significantly lower in non-obese NAFLD patients [65]. Kim et al. identified a distinct metabolic phenotype in lean MASLD: dysregulated triglycerides (TG) and branched-chain amino acid (BCAA) metabolism exacerbate mitochondrial dysfunction via AMPK pathway suppression, driving ALT elevation and hepatocyte injury [66]. Concurrently, insulin resistance activates sterol regulatory element-binding protein 1c (SREBP-1c) and carbohydrate-responsive element-binding protein (ChREBP), enhancing de novo lipogenesis (DNL). This metabolic milieu is further compounded by bile acid dysmetabolism and cholestasis, manifesting as elevated alkaline phosphatase (ALP) and GGT [67]. In contrast, non-lean NASLD is characterized by higher fasting glucose, lower HDL-C, increased metabolic syndrome prevalence, and greater fibrosis risk [68]. A 2024 study also showed that lean MASLD patients have higher levels of nonalcoholic cirrhosis, while non-lean patients are more likely to have comorbidity chronic kidney disease and heart disease [69]. Prior studies link increased mean platelet volume (MPV)—a marker of platelet activation—to fibrosis severity independent of BMI [70].

Interestingly, although it has been shown that FIB-4 has some diagnostic performance in advanced liver fibrosis compared to APRI [71]. However, in the present study, when comparing lean and non-lean groups who could not rule out liver fibrosis, the FIB—4 value of 1.355 (1.027, 2.07) in lean patients was higher than that of 1.206 (0.858, 1.694) in non-lean patients, and lean patients were in the low risk range for FIB-4 [72], which seems to indicate that the predictive power of FIB—4 in obese or overweight patients does not match the predictive ability of LSM [73]. It seems that a single blood index, whether it is a traditional liver fibrosis predictor or a predictor of metabolic function, cannot accurately assess liver lesions in patients with NAFLD [74], and a combination of imaging tools is needed to screen for liver fibrosis.

There are several limitations to this study. In terms of experimental design, this paper was a cross-sectional study and did not include negative controls, so it was not possible to explore the causal relationship between disease occurrence and metabolic indicators, and it also lacked normal indicators for the population in the region as a control reference. Meanwhile, since the included population was mainly from health management center, the population in economically disadvantaged areas might be neglected, suggesting a certain selection bias. Regarding the diagnosis of the subjects, only ultrasound and liver elastography were used in this experiment, and liver biopsy was not performed. In addition, the present trial did not assess the effects of body fat distribution (e.g., waist and hip circumference) and lifestyle, which may underestimate the differences in metabolic risk. In view of this, future multicenter, prospective studies that incorporate liver biopsy techniques in the course of the study are necessary to obtain more accurate results.

In summary, non-lean NAFLD patients showed more significant risk of metabolic disorders and liver fibrosis, which is highly consistent with recent studies of metabolism-hepatic axis injury mechanisms in the framework of MASLD. It is worth noting that despite the lower BMI in lean NAFLD, the metabolic TyG, TyG-BMI, and TG/LDL-C indices were still significantly higher than the healthy threshold, suggesting that metabolic syndrome is still a core driver of hepatic steatosis even with a normal BMI, and thus the MASLD definition is more able to summarize the metabolic characteristics of lean NAFLD patients. Traditional predictors of liver fibrosis and metabolic-related markers are suggestive of NAFLD and liver fibrosis in the initial screening, but further imaging is needed to confirm the diagnosis.

Abbreviations

FBG	Fasting blood glucose
TG	Triglyceride
HDL-C	High-density lipoprotein cholesterol
BMI	Body mass index
GGT	Glutamyl-transpeptidase
OR	Odds ratio
AST	Aspartate aminotransferase
TyG index	Triglyceride-glucose index
TC	Total cholesterol
IR	Insulin resistance
VAI	Visceral adiposity index
ALT	Alanine aminotransferase
LDL-C	Low density lipoprotein cholesterol
LSM	Liver stiffness measurement
CAP	Controlled attenuation parameter
NASH	Non-alcoholic steatohepatitis
TyG-BMI	Triglyceride glucose-body mass index
NAFLD	Non-alcoholic fatty liver disease
HbA1c	Glycosylated hemoglobin
BUN	Blood urea nitrogen
Cr	Creatinine
UA	Uric acid
ALP	Alkaline phosphatase
FIB-4	Fibrosis 4 scores
APRI	Aspartate aminotransferase-to-platelet ratio index
MAFLD	Metabolic dysfunction-associated fatty liver disease
MASLD	Metabolic dysfunction-associated steatotic liver disease
CVD	Cardiovascular disease
DM	Diabetes mellitus

Author contributions

X.M.Y. and G.R.: conceived and designated the study; X.M.Y.: performed the data analysis and wrote the article. X.J and G.R.: revised the article; S.X.P. and W.S.: performed the supervision, and manuscript revision. All authors have read and approved the manuscript.

Funding

This study was supported by China Health Promotion Foundation Fatty Liver Prevention and Control Special Fund.

Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by the Wuhan Union Hospital Ethics Committee and the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (IORG No: ([2022]0422)) and performed in accordance with the Declaration of Helsinki. The data are anonymous, and the requirement for informed consent was therefore waived.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Gastroenterology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China. [2]Health Management Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China. [3]Department of Breast and Thyroid Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China.

Received: 4 January 2025 Accepted: 4 April 2025
Published online: 12 May 2025

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