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Clinical Characteristics, Risk Factors, and Predictors of Nonobese Fatty Liver Disease: A Cross-Sectional Study

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Purpose: This study aimed to investigate the risk factors and predictors of non-obese fatty liver disease in the Chinese population.
Patients and Methods: A total of 6,014 adults who underwent physical examinations at Union Hospital of Huazhong University of Science and Technology from March 2019 to March 2023 were included in this study. Fatty liver disease was diagnosed based on at least two of the following criteria: diffuse echo patterns relative to the liver, spleen, and kidney; ultrasonic beam attenuation; and poor intrahepatic visual details. The associations between non-obese fatty liver and gender, age, total bilirubin(TBIL), direct bilirubin-(DBIL), alanine aminotransferase(ALT), aspartate aminotransferase(AST), glutamine transferase(GGT), alkaline phosphatase(ALP), triglycerides(TG), total cholesterol(TC), high-density lipoprotein cholesterol(HDLC), low-density lipoprotein cholesterol(LDLC), urea nitrogen(BUN), creatinine(Cr), uric acid(UA), Central nervous system sensitivity PTFQI, TSHI, TT4RI, TFQI, Peripheral sensitivity, free thyroxine(FT_4), thyroid-stimulating hormone(TSH), triiodothyronine(FT_3), fasting blood glucose(FBG), systolic blood pressure-(SBP), diastolic blood pressure(DBP), body mass index(BMI) were analyzed via binary logistic regression. Correlation between non-obese fatty liver and high blood lipids, hypertension, hyperuricemia, diabetes, thyroid dysfunction were analyzed using the Pearson and Spearman methods. ROC curve was used to evaluate the diagnostic effect of the indicator.
Results: Compared with the normal group, age, proportion of males, ALT, AST, GGT, ALP, TG, TC, BUN, Cr, UA, TSHI, TT4RI, FT_3/FT_4, TSH, FT_3, FBG, SBP, DBP and BMI in the disease group were significantly higher. The prevalence of non-obese fatty liver was associated with hyperlipidemia, hypertension, hyperuricemia and diabetes. Gender, age, DBIL, ALT, ALP, TG, HDL-C, LDL-C, BUN, UA, FBG, DBP, BMI were independent risk factors for non-obese fatty liver.FT_3/FT_4 may be considered as a predictor of nonobese fatty liver.
Conclusion: Risk factors for non-obese fatty liver may include sex, age, TG, TC, BMI, etc. Hyperlipidemia, hypertension, hyperuricemia and diabetes mellitus are related to non-obese fatty liver. FT_3/FT_4 may be a predictor of non-obese fatty liver disease.
Keywords: Fatty liver, Non-obese type, Risk Factors, Forecasting, Clinical Features

Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the most prevalent liver disorders, characterized by hepatic steatosis in the absence of excessive alcohol consumption.[1] It is frequently associated with symptoms such as general fatigue, dull pain in the liver region, discomfort or a sensation of fullness in the right upper abdomen, loss of appetite, nausea, and other nonspecific manifestations. A common clinical finding is hepatomegaly, often accompanied by splenomegaly; some patients may also present with mild jaundice.[2] NAFLD typically coexists with conditions such as type 2 diabetes mellitus, dyslipidemia, metabolic syndrome, and obesity.[3] Historically, research on FLD has focused mainly on obese

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individuals, as obesity is a significant risk factor that facilitates identification and study. In contrast, locating non-obese individuals with NAFLD is challenging and requires advanced screening methods, increasing research costs and complicating investigations. Consequently, studies on non-obese fatty liver disease are limited. However, recent findings indicate that a considerable number of cases occur in non-obese populations. The definition of obesity among Asians differs from other ethnic groups due to genetic, lifestyle, dietary habits, and other factors. This distinction is evident in varying body mass index (BMI) cut-off values: for Asians, the recommended BMI thresholds for overweight and obesity are 23 to 25 kg/m² and ≥25 kg/m²; for other races, they are 25 to 30 kg/m² and >30 kg/m². Therefore, this paper suggests that the definition of non-obesity should align with BMI criteria set by different countries. For this study focusing on Chinese subjects, it follows the guidelines for preventing overweight and obesity in Chinese adults: a BMI of 18.5 ≤ BMI < 24.0 kg/m² is considered non-obese.[4] A meta-analysis of 55,936 lean/non-obese subjects showed that the combined prevalence rates of NAFLD in lean or non-obese people was 10.2% (95% CI: 7.6%-13.6%) and 15.7% (95% CI: 12.5%-19.6%), respectively, with an increasing trend in recent years.[5] This suggests that the health risks associated with this demographic should not be overlooked.

Studies have shown that the strongest risk factors for NAFLD are T2DM, obesity, sex, and Hispanic ethnicity, with demographic factors including age, ethnicity, and genetic factors associating with risk of disease progression[6,7] However, the relevance of these factors in patients with non-obese fatty liver disease has not been thoroughly investigated. This study aims to explore the influencing and predictive factors associated with non-obese fatty liver disease, with the goal of enhancing medical services for affected patients.

Material and Methods

Study Design and Subjects

This study was a cross-sectional analysis based on a population undergoing physical examinations at the Union Hospital of Huazhong University of Science and Technology. A total of 6,014 subjects, with an average age of 46.81 ± 12.18 years, were retrospectively selected from the Hospital Information System (HIS) between March 2019 and March 2023, comprising 2,752 men and 3,262 women. The severity of fatty liver observed in this study was predominantly mild. According to established diagnostic criteria, out of 1,298 patients assessed for fatty liver disease, 887 exhibited mild fatty liver, while 234 presented with moderate fatty liver and 13 with severe fatty liver.[8]

The exclusion criteria were as follows: (1) incomplete clinical data; (2) patients classified as obese or lean with a BMI <18.5 kg/m² or BMI ≥24.0 kg/m²; (3) individuals with other established liver diseases: including viral hepatitis (hepatitis B, hepatitis C); (4) recent use of thyroid disease drugs or anti-hyperglycemic drugs, because these drugs may affect the biochemical indicators of the liver.[9–11] This can obscure or exaggerate biochemical indicators of fatty liver and interfere with the assessment of fatty liver risk factors; (5) severe liver dysfunction or renal insufficiency, which can lead to complications and physiological changes that affect the onset, progression, and prognosis of FLD.[12,13] This may mask the effects directly related to fatty liver itself; (6) pregnant women. This study has been approved by the Ethics Committee of Huazhong University of Science and Technology, and an informed consent was signed with the physical examination clients before the physical examination, including the use analysis of the results and the principle of confidentiality of personal information. Finally, 6014 subjects were included in the study (2752 male subjects, 45.8%).

Definition

Peripheral sensitivity was calculated using the formula FT_3 (pmol/L)/FT_4 (pmol/L). Central sensitivity TFQI=cdf fT_4 - (1-cdf TSH); TSHI = TSH (mIU/L) + 0.1345 * FT_4 (pmol/L); TT4RI =FT_4 (pmol/L) * TSH (mIU/L). Diagnostic criteria of NAFLD uses the Chinese medical association in 2010 liver disease, NAFLD diagnostic criteria, namely NAFLD was diagnosed with at least two of the three exceptions, the relative to the liver spleen and kidney diffuse echo, the structure of the ultrasonic beam attenuation and intrahepatic poor visual details.[14]

According to the guidelines for prevention and control of overweight and obesity in Chinese adults, BMI < 18.5 kg/m^2 was considered as underweight, BMI ≥ 24.0 kg/m^2 was considered as overweight, and BMI ≥ 28 kg/m^2 was

considered as obesity.[4] Therefore, FLD cases with 18.5 ≤ BMI < 24.0 kg/m^2 were defined as non-obese FLD cases in this study.

Metabolic syndrome in this study primarily encompasses thyroid dysfunction, diabetes, hypertension, and hyperuricemia. These conditions are extensively documented in the literature and may be associated with fatty liver disease.[15–18] According to the standard of Union Hospital, the reference ranges for FT_3, FT_4 and TSH were 2.63–5.70 pmol/L, 9.00–19.18 pmol/L and 0.35–4.94 mIU/L, respectively. Any values falling outside of these ranges would indicate thyroid dysfunction. Diabetes was defined as a fasting blood glucose level ≥7.0 mmol/L or any use of antidiabetic drugs with a previously reported history of diabetes. Hypertension was defined as systolic blood pressure ≥140mmHg or diastolic blood pressure ≥90mmHg, along with any use of antihypertensive medication. Hyperuricemia was defined as uric acid levels ≥357μmol/L while hyperlipidemia was defined as TC≥5.2 mmol/L, LDL-C≥3.4 mmol/L, HDL-C < 1.0 mmol/L or TG≥1.7 mmol/L.

Statistical Analysis

Statistical analyses were performed using SPSS version 26.0. For normally distributed data, continuous variables were expressed as mean ± SD; for skewed data, continuous variables were expressed as median (quartile); and for categorical variables, the data were expressed as frequencies (n) and percentages (%). One-way ANOVA was used to compare data between groups. Spearman/Pearson correlations were used to analyze the correlations between non-obese FLD and Metabolic syndrome. The factors influencing non-obese FLD were analyzed through binary logistic regression analyses. All significance tests were two-tailed, with P<0.05 as the threshold for statistical significance. ROC curve was used to evaluate the diagnostic effect of the indicator. AUROC values were used to evaluate the predictive performance of the predictor.

Results

Baseline Demographic and Clinical Characteristics of Subjects

All subjects with normal BMI (n = 6014) were categorized into the normal group and the disease group based on FLD presence. Compared with the normal group, the disease group had a higher proportion of males, an older average age, and significantly higher levels of ALT, AST, GGT, ALP, TG, TC, LDLC, BUN, Cr, UA, TSHI, TT4RI, FT_3/FT_4 ratio, FT_3, FBG, SBP, DBP and TSH. In addition, BMI was also significantly increased. In contrast, TBIL, DBIL, HDLC and FT_4 levels were significantly decreased. (Table 1).

Table 1 Baseline Clinical Characteristics of All Subjects

	The Normal Group	The Disease Group	Test Statistic	P value
Gender (male cases, proportion %)	1945(41.2)	807(62.2)	179.646[c]	<0.001
Age ($\overline{X} \pm s$, year)	45.91±12.243	50.04±11.390	−11.414[a]	<0.001
TBIL [M(QR),μmol/L]	13.900(6.1)	13.200(6.5)	−3.266[b]	0.001
DBIL [M(QR),μmol/L]	4.500(2.3)	4.200(2.3)	−5.372 [b]	<0.001
ALT [M(QR),U/L]	17.00(11)	24.00(17)	−19.673 [b]	<0.001
AST [M(QR), U/L]	22.00(8)	24.00(10)	−8.818 [b]	<0.001
GGT [M(QR), U/L]	15.00(10)	23.00(20)	−22.343 [b]	<0.001
ALP [M(QR), U/L]	61.00(25)	70.00(25)	−14.572 [b]	<0.001
TG [M(QR), mmol/L]	0.94(0.60)	1.44(1.02)	−25.836 [b]	<0.001
TC ($\overline{X} \pm s$, mmol/L)	4.8971±0.93129	5.1794±0.97841	−9.668 [a]	<0.001
HDL-C ($\overline{X} \pm s$, mmol/L)	1.5610±0.37684	1.3271±0.32523	22.162 [a]	<0.001
LDL-C ($\overline{X} \pm s$, mmol/L)	2.7964±0.76697	3.0852±0.80861	−11.439 [a]	<0.001

(*Continued*)

Table 1 (Continued).

	The Normal Group	The Disease Group	Test Statistic	P value
BUN [M(QR), mmol/L]	4.6400(1.62)	4.7400(1.48)	−2.785 [b]	0.005
Cr [M(QR), μmol/L]	63.15(20.6)	70.40(22.0)	−9.772 [b]	<0.001
UA [M(QR), μmol/L]	292.750(106.6)	348.300(128.1)	−18.445 [b]	<0.001
PTFQI ($\overline{X} \pm s$)	0.04614±0.37850	0.04947±0.38452	−0.293 [a]	0.769
TSHI [M(QR)]	3.54622(1.23697)	3.61330(1.24340)	−1.988 [b]	0.047
TT4RI [M(QR)]	23.17937(16.427)	24.02442(16.20734)	−2.092 [b]	0.036
FT_3/FT_4 ($\overline{X} \pm s$)	0.34523±0.04564	0.35375±0.04319	−6.206 [a]	<0.001
FT_4 [M(QR), pmol/L]	13.200(1.8)	13.100(1.8)	−2.216 [b]	0.027
TSH [M(QR), uIU/mL]	1.7576(1.2330)	1.81830(1.2440)	−2.509 [b]	0.012
FT_3 [M(QR), pmol/L]	4.500(0.7)	4.600(0.6)	−4.784 [b]	<0.001
FBG [M(QR), mmol/L)	4.80(0.60)	5.00(0.78)	−13.152 [b]	<0.001
SBP [M(QR), mmHg]	112(21)	120(23)	−14.025 [b]	<0.001
DBP [M(QR), mmHg]	70(13)	74(14)	−13.548 [b]	<0.001
BMI [M(QR)]	21.5(2.4)	23.0(1.2)	−30.323 [b]	<0.001
TFQI ($\overline{X} \pm s$)	−0.00035±0.36840	0.00206±0.37461	−0.209 [a]	0.835

Notes: a, *T* Test Statistic; b, Mann–Whitney *U*-Test Statistic; c, Chi-Square Test Statistic.
Abbreviations: TBIL, total bilirubin; DBIL, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, glutamine transferase; ALP, alkaline phosphatase; TG, triglycerides; TC, total cholesterol; HDL-C, high -density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BUN, urea nitrogen; Cr, creatinine; UA, uric acid; FT_4, free thyroxine; TSH, thyroid-stimulating hormone; FT_3, triiodothyronine; FBG, fast blood glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

Baseline Characteristics of Clinical Subjects Stratified by FT_3/FT_4 Quartiles

Based on the quartiles of FT_3 and FT_4, 6,014 subjects were categorized into four groups: Q1 (≤0.317), Q2 (0.317–0.345), Q3 (0.345–0.375), and Q4 (≥0.375). Table 2 shows that groups with a higher FT_3/FT_4 ratio had elevated clinical indicators such as ALT, AST, GGT, ALP, TG, Cr, UA, TSH, FT_3, SBP, DBP, BMI, and male proportion ($P < 0.05$). Additionally, an increase in the FT_3/FT_4 ratio was associated with higher values for these indices. Conversely, levels of DBIL, TC, HDLC, PTFQI, TFQI and FT_4 decreased as the FT_3/FT_4 ratio declined ($P < 0.05$). Shockingly, these indicators correspond almost exactly to the difference indicators between the disease group and the normal group in Table 1. (Table 2).

Table 2 Baseline Characteristics of Clinical Subjects Stratified by FT_3/FT_4 Quartiles

Features	Quartile of FT_3/FT_4				Test statistic	P value
	Q1	Q2	Q3	Q4		
Gender (male cases, proportion %)	490(32.6)	636(42.3)	773(50.7)	853(57.7)	212.307[c]	<0.001
Age ($\overline{X} \pm s$, year)	47.10±12.689	46.44±12.219	46.94±11.964	46.74±11.840	0.789[a]	0.500
TBIL [M(QR),μmol/L]	13.900(6.1)	13.700(6.3)	13.700(6.4)	13.700(5.9)	4.082[b]	0.253
DBIL [M(QR),μmol/L]	4.600(2.3)	4.400(2.4)	4.500(2.4)	4.300(2.3)	10.353[b]	0.016
ALP [M(QR),U/L]	16.00(11)	18.00(13)	19.00(13)	21.00(15)	181.966[b]	<0.001
AST [M(QR), U/L]	22.00(8)	22.00(10)	23.00(10)	23.00(10)	75.441[b]	<0.001
GGT [M(QR), U/L]	15.00(9)	16.00(13)	17.00(12)	19.00(15)	154.501[b]	<0.001
ALP [M(QR), U/L]	60.00(25)	63.00(23)	64.00(24)	65.00(25)	68.861[b]	<0.001
TG [M(QR), mmol/L]	0.93(0.60)	0.98(0.63)	1.06(0.74)	1.16(0.81)	144.664[b]	<0.001
TC ($\overline{X} \pm s$, mmol/L)	5.0013±0.95161	4.9733±0.92219	4.9422±0.93438	4.9149±0.98505	2.647[a]	0.047
HDL-C ($\overline{X} \pm s$, mmol/L)	1.5786±0.40170	1.5258±0.36975	1.4848±0.36847	1.4523±0.36226	31.765[a]	<0.001
LDL-C ($\overline{X} \pm s$, mmol/L)	2.8511±0.79998	2.8689±0.76513	2.8616±0.77527	2.8532±0.8006	0.172[a]	0.915

(*Continued*)

Table 2 (Continued).

Features	Quartile of FT_3/FT_4				Test statistic	P value
	Q1	Q2	Q3	Q4		
BUN [M(QR), mmol/L]	4.70(1.58)	4.62(1.59)	4.62(1.54)	4.7200(1.62)	2.453[b]	0.484
Cr [M(QR), μmol/L]	62.00(18.8)	63.90(21.2)	66.05(22.0)	67.80(21.7)	53.698[b]	<0.001
UA [M(QR), μmol/L]	284.9(101.7)	300.7(109.8)	312.2(120.2)	322.0(121.4)	115.714[b]	<0.001
PTFQI($\overline{X} \pm s$)	0.20193±0.37414	0.09198±0.35617	0.02073±0.36251	−0.12942±0.34846	221.726[a]	<0.001
TSHI[M(QR)]	3.6085(1.2425)	3.56885(1.1838)	3.5568(1.23121)	3.4975(1.33895)	2.729[b]	0.435
TT4RI[M(QR)]	23.92138(17.44960)	23.42736(15.86013)	23.34243(15.94923)	22.5940(16.5018)	1.628[b]	0.653
TFQI[M(QR)]	0.15764±0.36314	0.04414±0.34503	−0.02813±0.35238	−0.17559±0.33730	29.049[a]	<0.001
FT_4[M(QR), pmol/L]	14.0(1.7)	13.4(1.5)	13.0(1.5)	12.300(1.4)	1451.706[b]	<0.001
TSH [M(QR), ulU/mL]	1.6735(1.2422)	1.7511(1.1994)	1.7882(1.2343)	1.8533(1.3352)	34.239[b]	<0.001
FT_3 [M(QR), pmol/L]	4.100(0.5)	4.400(0.5)	4.700(0.5)	4.900(0.5)	2208.317[b]	<0.001
FBG [M(QR), mmol/L)	4.82(0.70)	4.80(0.63)	4.81(0.70)	4.80(0.64)	10.725[b]	0.013
SBP [M(QR), mmHg]	112(22)	112(23)	114(22)	115(21)	31.977[b]	<0.001
DBP [M(QR), mmHg]	70(13)	70(14)	72(13)	72(14)	34.502[b]	<0.001
BMI [M(QR)]	21.6(2.5)	21.9(2.2)	22.10(2.2)	22.20(2.4)	73.166[b]	<0.001

Notes: a. Single-factor analysis of variance test statistic; b. Kruskal–Wallis test statistic; c. Chi-square test statistic.
Abbreviations: TBIL, total bilirubin; DBIL, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, glutamine transferase; ALP, alkaline phosphatase; TG, triglycerides; TC, total cholesterol; HDL-C, high -density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BUN, urea nitrogen; Cr, creatinine; UA, uric acid; FT_4, free thyroxine; TSH, thyroid-stimulating hormone; FT_3, triiodothyronine; FBG, fast blood glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

Association Between Metabolic Syndromes and Non-Obese FLD

In all subjects, non-obese FLD was positively correlated with hyperlipidemia, hypertension, hyperuricemia and diabetes, the chi-square values were 237.784, 101.021, 259.430, and 72.683 respectively (P<0.05), whereas it was negatively correlated with Thyroid dysfunction. (Table 3)

Table 3 Correlation of Non-Obese FLD with Metabolic Syndromes

	The Normal Group	The Disease Group	Test Statistic	P value
	Frequency (percentage)	Frequency (percentage)		
Normal blood lipids	2733(58.0)	439(33.8)	237.784	<0.001
High blood lipids	1983(42.0)	859(66.2)		
Euthyroid function	4429(93.9)	1224(94.3)	0.267	0.605
Thyroid dysfunction	287(6.1)	74(5.7)		
Normal blood pressure	4308(91.3)	1059(81.6)	101.021	<0.001
Hypertension	408(8.7)	239(18.4)		
Normal uric acid	3592(76.2)	692(53.3)	259.430	<0.001
Hyperuricemia	1124(23.8)	606(46.7)		
Normoglycemia	4633(98.2)	1219(93.9)	72.683	<0.001
Diabetes	83(1.8)	79(6.1)		

Logistics Regression Analysis of Non-Obese FLD

In this study, we used binary logistic regression model to analyze the independent influencing factors of non-obese FLD. The dependent variable was whether the patient had non-obese FLD (with 1, without 0), and the statistically significant factors in the univariate analysis of Table 1 were used as independent variables, including gender, age, ALT, AST, GGT, ALP, TG, TC, LDLC, BUN, Cr, UA, TSHI, TT4RI. FT_3/FT_4, FBG, SBP, FT_3, DBP, TSH, BMI, TBIL, DBIL, HDLC, FT_4. Results showed that gender, age, DBIL, AST, ALP, TG, HDL-C, LDL-C, BUN, UA, FBG, DBP, and BMI were independent risk factors for non-obese FLD (P<0.05). (Table 4)

Table 4 Binary Logistic Regression Analysis of Non-Obese FLD

Variables of interest	B	P	OR	95% CI for OR
Gender (male 1 female 2)	0.249	0.040	1.283	1.011, 1.629
Age	0.013	<0.001	1.013	1.006, 1.021
DBIL(μmol/L)	−0.128	0.011	0.880	0.798, 0.971
ALT (U/L)	0.011	<0.001	1.011	1.007, 1.016
ALP (U/L)	0.006	0.003	1.006	1.002, 1.010
TG (mmol/L)	0.355	<0.001	1.426	1.236, 1.645
HDL-C (mmol/L)	−0.585	0.006	0.557	0.368, 0.842
LDL-C(mmol/L)	0.437	0.034	1.548	1.035, 2.317
BUN (mmol/L)	−0.098	0.003	0.907	0.850, 0.968
UA (μmol/L)	0.004	<0.001	1.004	1.003, 1.005
FBG (mmHg)	0.127	<0.001	1.136	1.070, 1.206
DBP (mmHg)	0.011	0.038	1.011	1.001, 1.022
BMI	0.730	<0.001	2.075	1.933, 2.228
Constant quantity	−20.759	<0.001		

Abbreviations: DBIL, direct bilirubin; ALT, alanine aminotransferase; ALP, alkaline phosphatase; TG, triglycerides; HDL-C, high -density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BUN, urea nitrogen; UA, uric acid; FBG, fast blood glucose; DBP, diastolic blood pressure; BMI, body mass index.

Assessment of the Predictive Value of FT_3/FT_4 for Non-Obese FLD

ROC curve results showed that the area under the ROC curve of FT_3/FT_4 was 0.558 [95% CI = (0.541–0.575), P < 0.001], suggesting that FT_3/FT_4 had diagnostic value for patients with non-obese fatty liver. The optimal cut-off value of FT_3/FT_4 was 0.3387, and the sensitivity and specificity were 63.4% and 53.3%, respectively. (Figure 1)

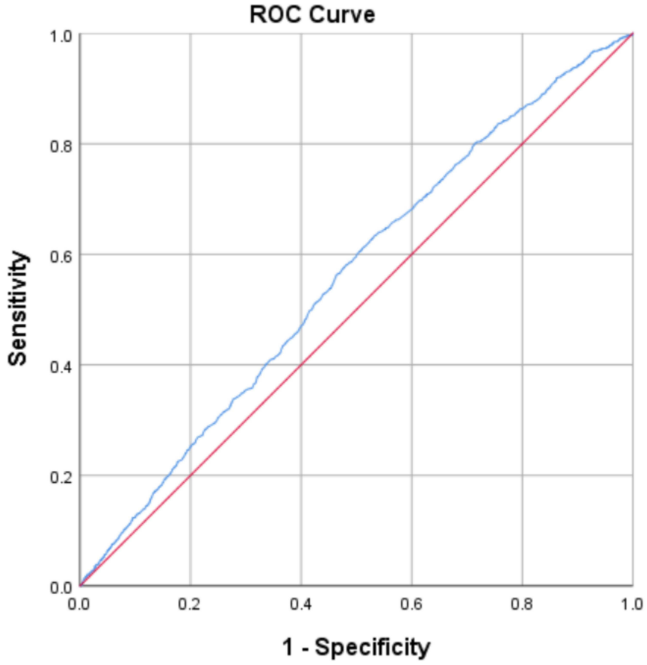

Figure 1 Receiver Operating Characteristic (ROC) curve illustrating the predictive performance of FT_3/FT_4 for non-obese fatty liver disease (FLD). The area under the curve (AUC) is 0.558 (95% CI: 0.541–0.575), indicating a predictive ability. The curve demonstrates the balance between sensitivity (true positive rate) and 1-specificity (false positive rate) across various threshold settings. The diagonal red line represents the performance of a random classifier, while the blue line indicates the performance of FT_3/FT_4. Data were obtained from our research, with P < 0.001.

Discussion

Fatty liver disease is a prevalent condition, particularly among obese individuals; however, recent studies have highlighted the significance of non-obese fatty liver as well. A meta-analysis encompassing 10,530,308 subjects from 24 countries revealed that the prevalence of non-obese fatty liver disease (FLD) in the general population varies significantly —ranging from 25% or less in certain countries (eg, Malaysia and Pakistan) to over 50% in others (eg, Austria, Mexico, and Sweden), within the NAFLD population, 19.2% (95% CI: 15.9–23.0) of people were lean and 40·8% (95% CI: 36.6–45.1) were non-obese.[19] Another study reported non-obese FLD prevalence was highest in Hispanic and Asian (35.1% and 35.6%, respectively) followed by white (30.0%) and was lowest amongst black (11.6%).[20] In the Chinese population: a meta-analysis involving 25 studies with a total of 229,091 participants indicated that the prevalence of lean FLD among Chinese subjects was estimated at 8.98% (95% CI: 5.55–13.13), whereas the prevalence of non-obese FLD stood at 13.77% (95% CI: 11.13–16.63). Notably, this prevalence has shown a gradual increase over recent years.[21] Given these findings, it is crucial to investigate the influencing factors and predictive determinants associated with non-obese FLD.

The development of fatty liver in non-obese individuals is frequently attributed to the synergistic interplay of multiple biological mechanisms. Studies show that insulin resistance is crucial in the development of non-alcoholic fatty liver disease, even in non-obese individuals. This condition reduces hepatic glucose uptake and increases free fatty acid (FFA) release, leading to fat accumulation in the liver.[22–24] Research also indicates that some lean patients with NAFLD have a genetic predisposition. Key loci associated with higher NAFLD risk, increased severity, and faster progression to advanced fibrosis include: PNPLA3, TM6SF2, GCKR, and MBOAT7.[25] Another study published in *Nature Communications* found that Golgi membrane protein 73 (GP73), a Rab GTPase-activating protein, regulates the export of very low-density lipoprotein-apolipoprotein B (VLDL-ApoB) from the liver through its GAP activity. Consequently, the transport of lipids such as triglycerides and cholesterol from the liver to systemic circulation is impeded, which further promotes the development of non-obese NAFLD.[26] In this study, we found that compared with the normal group, age, proportion of males, ALT, AST, GGT, ALP, TG, TC, BUN, Cr, UA, TSHI, TT4RI, peripheral sensitivity, TSH, FT_3, FBG, SBP, DBP and BMI in the disease group were significantly higher. Among them, the peripheral sensitivity FT_3/FT_4 index was used as an indicator to evaluate peripheral DIO activity, and its ratio represented peripheral thyroid hormone metabolism, which was used to evaluate thyroid hormone sensitivity.[27] Thyroid hormone has an important impact on fat metabolism, including fat synthesis, decomposition and oxidation. Reduced sensitivity around thyroid hormone may lead to the occurrence of insulin resistance, which in turn leads to the weakened response of adipose tissue to insulin, and promotes fat synthesis and accumulation.[28,29] In addition, thyroid hormone has a regulatory effect on the inflammatory response of adipose tissue, and its reduced sensitivity may lead to an increase in the inflammatory response of adipose tissue, and then trigger non-obese fatty liver disease.[30] Therefore, the peripheral sensitivity quartile was used as the grouping index to further compare the differences in indicators among the groups, and it was found that the subjects with higher FT_3/FT_4 ratio had higher clinical indicators. Such as ALT, AST, GGT, ALP, TG, Cr, UA, TSH, FT_3, SBP, DBP, BMI and the number of males ($P< 0.05$). In addition, there were also some lower clinical indicators, such as DBIL, TC, HDL-C, PTFQI, TFQI, FT_4 ($P< 0.05$). These indicators correspond well with the difference indicators between the fatty liver group and the non-fatty liver group, suggesting that FT_3/FT_4 may be used as a predictor of non-obese fatty liver, which can be further studied.

The results of this study also showed that gender, age, DBIL, AST, ALP, TG, HDL-C, BUN, UA, FBG and BMI were significantly correlated with non-obese FLD ($P<0.05$). Men are more likely to have non-obese fatty liver disease, which may be related to differences in body fat distribution, hormone levels, and liver metabolism in men. The liver of male patients has poor fat uptake and metabolic processing capacity, so it is more likely to accumulate fat and lead to the occurrence of fatty liver.[31] Secondly, with the increase of age, the metabolic capacity of the liver gradually declines, while the repair ability of liver cells is also weakened, and the decline in metabolic function of the whole body makes the liver more vulnerable to injury and inflammation.[32] Liver function indexes such as DBIL, ALT and ALP can reflect the degree of liver injury and inflammation. In addition, blood biochemical indicators such as TG, HDL-C and BUN also showed a correlation with non-obese fatty liver disease.[33] High TG levels may reflect abnormal fat metabolism, leading

to fat accumulation in the liver. The increase of urea nitrogen may be related to the decrease of liver metabolic function and abnormal protein metabolism. High FBG may reflect insulin resistance and abnormal glucose metabolism, leading to liver fat accumulation. Another study also showed an independent non-linear association between FBG and NAFLD in non-obese Chinese people with normal lipid levels, and an increase in FBG may indicate an increased risk of NAFLD.[34] An increase in BMI was positively associated with the development of non-obese fatty liver, possibly because obesity leads to excessive accumulation of fat in the liver, similar to findings from other studies.[35]

Moreover, our findings indicate a significant correlation among hyperlipidemia, hypertension, hyperuricemia, diabetes mellitus, and non-obese FLD. Hyperlipidemia leads to an increase in triglycerides and cholesterol in the blood, and these fatty substances are easily deposited in the liver, resulting in the occurrence of fatty liver. And hyperlipidemia can also cause inflammation, further aggravating liver damage.[36] Second, high blood pressure leads to a decrease in the blood supply to the liver, which reduces the metabolic function of the liver. This lack of blood supply can lead to a lack of oxygen and damage to the liver, which in turn promotes the development of fatty liver disease.[37] In addition, high uric acid can also lead to fat accumulation and increased inflammation in the liver by activating inflammatory pathways within liver cells.[38] In diabetics, insulin resistance causes blood sugar to rise, which encourages the liver to make more fat. Insulin resistance also affects the oxidation and clearance of fatty acids, further exacerbating the development of fatty liver.[39] It is worth noting that, although diabetes and hypertension are considered risk factors in both obese and non-obese fatty liver disease, their mechanisms of action as well as their relative contributions in non-obese individuals may differ from those in obese individuals and require further investigation.

This study has several limitations. Firstly, the cross-sectional design restricts the ability to establish causality. The observed associations between identified risk factors and non-obese fatty liver disease do not definitively indicate whether these factors precede and cause the disease or are merely correlated with it. Secondly, the study's failure to account for alcohol consumption represents a significant oversight. Alcohol is a well-established risk factor for FLD, and its exclusion may have confounded the results, thereby influencing the identification of independent risk factors. Future studies should explore the impact of alcohol consumption on these identified associations. Despite these limitations, this study offers valuable insights for developing screening strategies and early intervention programs targeting non-obese FLD within the Chinese population. Our findings suggest that FT_3/FT_4 levels may serve as potential predictors of non-obese fatty liver disease. For individuals exhibiting elevated FT_3/FT_4 levels, early intervention could mitigate the risk of developing non-obese FLD and enhance prognosis. Furthermore, calculating FT_3/FT_4 is straightforward and cost-effective, making it a promising indicator for assessing non-obese FLD. Further longitudinal follow-up studies are warranted to determine whether FT_3/FT_4 can be utilized as an early screening tool to prevent initial stages of liver disease in patients.

Conclusion

In this study, we found that risk factors for non-obese fatty liver may include male proportion, age, TG, TC, BMI. Groups with these indicators characteristics should pay special attention to the occurrence of non-obese fatty liver, and based on certain intervention measures in advance. Hyperlipidemia, hypertension, hyperuricemia and diabetes mellitus are related to FLD. In the treatment of fatty liver, attention should be paid to the intervention of metabolic syndrome, including the control of blood lipid, blood pressure, uric acid and blood glucose levels. FT_3/FT_4 may be a predictor of non-obese fatty liver disease, which needs to be confirmed by further studies.

Abbreviations

TBIL, total bilirubin; DBIL, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, glutamine transferase; ALP, alkaline phosphatase; TG, triglycerides; TC, total cholesterol; HDL-C, high -density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BUN, urea nitrogen; Cr, creatinine; UA, uric acid; FT_4, free thyroxine; TSH, thyroid-stimulating hormone; FT_3, triiodothyronine; FBG, fast blood glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

Ethical Approval and Informed Consent

Ethics approval and consent to participate this study was approved by the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology ([2022]0422) and performed in accordance with the Declaration of Helsinki. Informed consent was obtained from participants prior to their physical examinations, which included provisions regarding the analysis of results and confidentiality principles concerning personal information. All data analyses were performed based on anonymized data. Avoid including any information that might identify participants in the analysis.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Xiaomei Zhang and Shi Wang are co-first authors, Gong Rui and Sun Shiran are co-corresponding authors.

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Disclosure

The authors report no conflicts of interest in this work.

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