Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

Association of Uric Acid to Creatinine Ratio with Metabolic Dysfunction-Associated Fatty Liver in Non-Obese Individuals Without Type 2 Diabetes Mellitus

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Introduction: Metabolic dysfunction-associated fatty liver disease (MAFLD) is the most common chronic liver disease, which is usually associated with type 2 diabetes mellitus (T_2DM) and obesity. However, the incidence of MALFD in non-obese individuals without T_2DM is increasing, and the pathogenesis is unclear. Serum uric acid to creatinine ratio (sUA/Cr) can reflect overall metabolic status. This study aims to observe the association between sUA/Cr and MAFLD in non-obese individuals without T_2DM.

Methods: A total of 21,996 individuals were included in this study. The subjects were divided into four subgroups: non-obese patients without T_2DM, obese patients without T_2DM, non-obese patients with T_2DM, and obese patients with T_2DM. Logistic regression analyzed the correlation between sUA/Cr and MAFLD subgroups. Receiver operating characteristics analyzed the predictive value of sUA/Cr for MAFLD subgroups. The stratified analyses by sex and age were performed.

Results: Non-obese MAFLD individuals without T_2DM had higher sUA/Cr levels than their counterparts. sUA/Cr was significantly correlated positively with MAFLD in non-obese patients. Similar results were observed in both males and females and in populations at all age stages (all $p<0.01$). sUA/Cr was capable of discriminating MAFLD in non-obese individuals without T_2DM (AUC: 0.667), especially for patients over 60 years old (AUC: 0.704).

Conclusion: The sUA/Cr ratio was correlated with MAFLD in non-obese patients without T_2DM. The predictive value of sUA/Cr for MAFLD was observed. Hence, the sUA/Cr ratio might be given more concern for the risk of MAFLD in non-obese individuals without T_2DM.

Keywords: uric acid, creatinine, metabolic dysfunction-associated fatty liver disease, non-obesity, type 2 diabetes mellitus

Introduction

Metabolic dysfunction-associated fatty liver disease (MAFLD) is defined as a condition of excessive fat deposition in the liver, accompanied by obesity, metabolic disorders, or type 2 diabetes (T_2DM).[1] MAFLD is recognized as a common chronic liver disease, the prevalence of which is about 39% all over the world.[2] The latest consensus suggests that MAFLD should be divided into three subgroups according to different diagnostic modalities, including obesity, non-obesity, and T_2DM subgroups.[3] The risk of MAFLD is often highlighted in obese and diabetic patients, but not in non-obese individuals due to deceptive body mass index (BMI) and euglycemia.[4] However, the prevalence of non-obese MAFLD ranges from 5% to 45%.[5] Further research indicated that non-obese MAFLD might be a distinct pathophysiological entity, with half progressing into NASH, which has a higher mortality rate and accelerated disease progression despite a more benign metabolic profile.[6–8] Hence, it is important to identify the risk of MAFLD in non-obese normoglycemic patients at an early stage.

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Uric acid (UA) is a product of purine metabolism taking part in lipid and glucose metabolism.[9,10] Serum uric acid to creatinine ratio (sUA/Cr) can reflect the level of sUA while excluding the influence of kidney diseases. Research conducted by She D et al suggested that sUA/Cr was significantly associated with metabolic syndrome.[11] UA was also found to be associated with sarcopenia, which is presented in many cases of MAFLD.[12,13] Previous evidence suggested serum uric acid (sUA) plays a critical role in the incidence and development of MAFLD, and the high level of sUA is correlated with BMI.[14] However, the association of sUA with non-obese MAFLD in normo-glycemic individuals is unclear. Considering that the sUA/Cr ratio represents a comprehensive metabolic situation excluding the influence of renal function, this study explored the association of sUA/Cr with non-obese MAFLD in individuals without T_2DM. The stratified analyses by age and sex were performed.

Materials and Methods

Study Design and Participants

The participants consisted of 24,714 Chinese adults from the China–Japan Friendship Hospital from January 2019 to June 2022. The study was approved by the Ethics Committee of the China–Japan Friendship Hospital Clinical Research Ethics Committee in compliance with the Declaration of Helsinki. Informed consent was waived because of the retrospective nature of our study. The data are anonymous.

Inclusion Criteria

1. Individuals who were ≥18 years old.

2. Participants were diagnosed with MAFLD as follows, which meet conditions (1) and (2) simultaneously.[3]

(1) Diagnosis of hepatic steatosis by ultrasound.[10] The inclusion of at least two of the three following conditions was required: ① hypoechogenicity in the far field of the liver; ② hyperechogenicity in the near field of the liver or bright liver, as well as signs of it being stronger than the kidney cortex; and ③ a blurry intrahepatic tubular structure.

(2) Patients who complied with one of the following three conditions were included: ① Obesity: Body mass index (BMI) ≥23 kg/m^2. ② Non-obesity: BMI < 23 kg/m^2 combining ≥2 abnormal metabolic indexes including 1) Waist circumference (WC) ≥90 cm in males or 80 cm in females; 2) Blood pressure (BP) ≥130/85 mmHg or taking antihypertensive agents; 3) Plasma triglycerides (TG) ≥1.70 mmol/L or taking lipid-lowering agents; 4) Plasma high-density lipoprotein cholesterol (HDL-C) <1.0/1.3 mmol/L for males and females or specific drug treatment; 5) Prediabetes (fasting glucose levels (FPG) 5.6–6.9 mmol/L or 2h postprandial plasma glucose (2h-PPG) 7.8–11.0 mmol/L or HbA1c 5.7%–6.4%); 6) insulin resistance (IR) score ≥2.5; 7) Plasma high-sensitivity C-reactive protein (hs-CRP) >2 mg/L. ③ Type 2 diabetes mellitus (T_2DM): The diagnostic criteria were based on international standards.[15]

Exclusion Criteria

1. Cushing's syndrome, viral liver disease, and medication history (eg glucocorticoids), which lead to special conditions of liver steatosis. 2. Suffering from serious cardiac-cerebral vascular disease, kidney failure, and malignant tumors. 3. Pregnancy and lactation. 6. Medication history of SGLT-2 inhibitors, GLP-1 receptors agonists, and antihyperuricemic agents.

According to inclusion and exclusion criteria, 21,996 participants were included in the final retrospective cross-sectional analysis (Figure 1).

Data Collection

The subjects were examined in the morning after overnight fasting. The examination included demographic data (age, gender, physical activity, and medication history) using a self-reported questionnaire, and anthropometry (weight, height, WC, and BP). Measurements were replicated three times, and the means were recorded. The abdominal ultrasound examination was performed on the participants by two experienced sonographers. Elbow venous blood was taken to determine the levels of fasting lipids (TG, total cholesterol (TC), HDL-C, and low-density lipoprotein cholesterol (LDL-C), liver enzymes (alanine transaminase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT)),

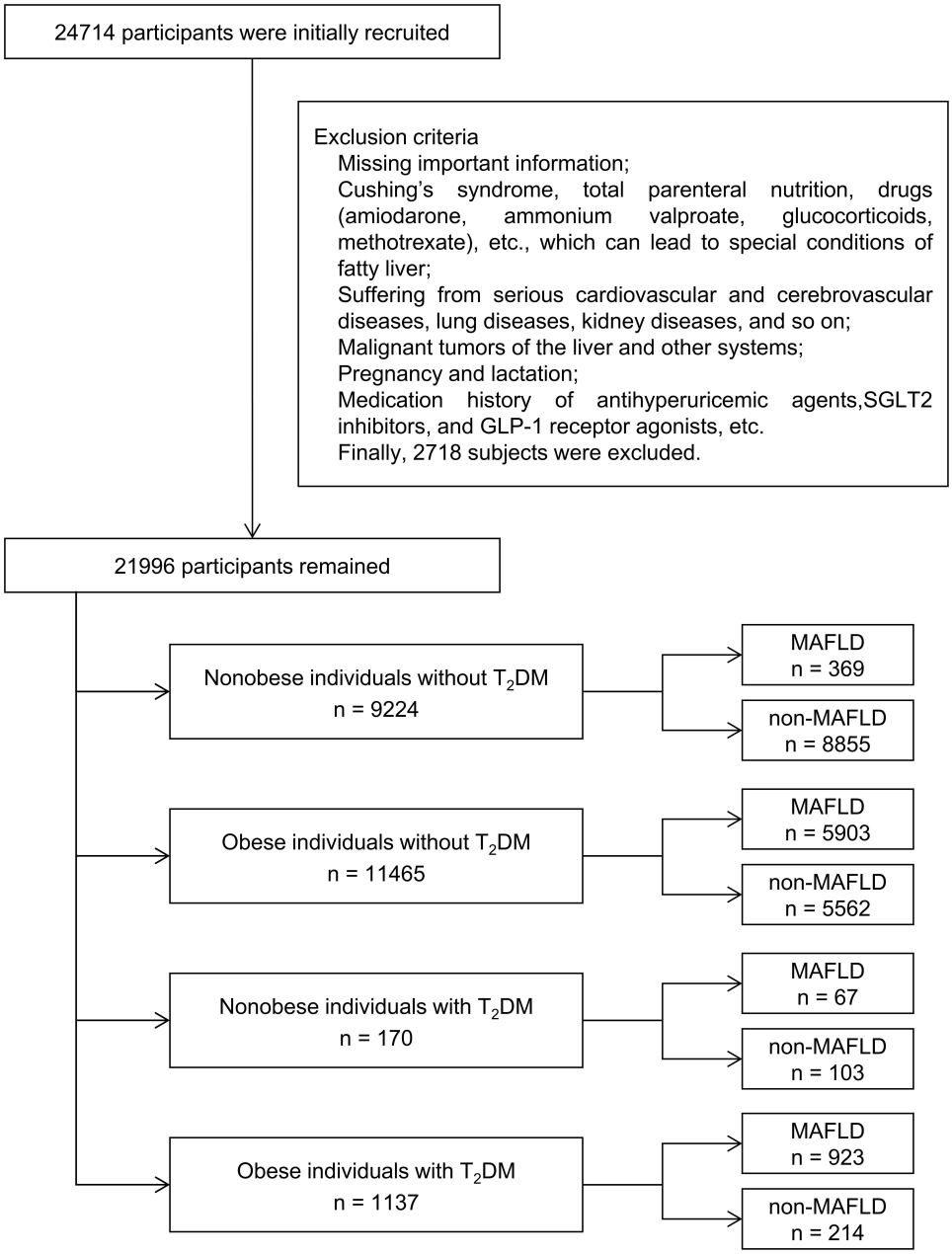

Figure 1 Flow chart of the study subjects.
Abbreviations: MAFLD, metabolic dysfunction-associated fatty liver disease; BMI, body mass index; T_2DM, type 2 diabetes mellitus.

FPG, UA, and Cr. Dyslipidemia was defined as TC ≥ 5.2 mmol/L or TG ≥ 1.7 mmol/L or LDL-C ≥3.4 mmol/L or HDL-C <1.0 mmol/L for men and <1.3 mmol/L for women.[16]

Abnormal liver function was defined as AST ≥ 42 IU/L or ALT ≥ 40 IU/L or GGT ≥ 52 IU/L.

Statistical Analysis

The data analysis was processed using SPSS 26.0 statistical software. Continuous variables were expressed as mean ± standard deviation ($\bar{x} \pm S$) and Student's *t*-test was performed to compare subgroups. Categorical variables were presented as a percentage (%) and analyzed by the chi-square test. To evaluate the association of sUA/Cr with MAFLD, logistic regression was used, and the results were expressed by odds ratios (ORs) with 95% confidence intervals (CI). To assess the predictive value of sUA/Cr, we examined the receiver operating characteristic (ROC) and

calculated the areas under the curves (AUCs) using MedCalc 20.022 statistical software. The optimal cutoff points and the Youden index with sensitivity and specificity were shown. $P<0.01$ was considered statistically significant.

Results

Clinical Characteristics of the Study Population

In total, 21,996 subjects were analyzed in this study. There were 8855 non-obese individuals without T_2DM who did not have MAFLD and 369 non-obese individuals without T_2DM who had MAFLD (Table 1). MAFLD patients (n=7262) had higher UA, Cr, SUA/Cr, BMI, FPG, percentages of abnormal liver function, dyslipidemia, and hypertension than those in non-MAFLD participants (n=14,734) (all $P<0.01$) (Table 1). The sUA/Cr ratio in MAFLD patients was higher than non-MAFLD individuals in males (5.44±1.26 vs 4.88±1.08) and females (5.84±1.43 vs 4.84±1.12), and at all age stages (18–39 years old: 5.73±1.29 vs 4.90±1.10; 40–59 years old: 5.41±1.29 vs 4.77±1.09; ≥60 years old: 5.43±1.41 vs 4.88±1.19) (all $P<0.01$) (Figure 2).

Table 1 Baseline and Clinical Characteristics of Participants with and without Metabolic Dysfunction-Associated Fatty Liver Disease (n=21,996)

	MAFLD (n =7262)	Non-MAFLD (n =14,734)	*p*
Male [n (%)]	5465 (75.3%)	6121 (41.5%)	0.000
Female [n (%)]	1797 (24.7%)	8613 (58.5%)	
Obesity without T_2DM [n (%)]	5903 (81.3%)	5562 (37.7%)	0.000
Non-obesity without T_2DM [n (%)]	369 (5.1%)	8855 (60.1%)	0.000
Obesity with T_2DM [n (%)]	923 (12.7%)	214 (1.5%)	0.000
Non-obesity with T_2DM [n (%)]	67 (0.9%)	103 (0.7%)	0.075
Age (years)	44.16±11.66	38.72±11.02	0.000
BMI (kg/m^2)	27.13±3.31	22.39±2.89	0.000
UA (μ mol/L)	380.79±88.34	306.84±81.58	0.000
Cr (μ mol/L)	70.20±17.48	64.03±14.31	0.000
sUA/Cr	5.54±1.31	4.86±1.10	0.000
FPG (mmol/L)	5.89±1.54	5.19±0.67	0.000
TG (mmol/L)	2.10±1.57	1.09±0.69	0.000
TC (mmol/L)	5.36±0.99	5.10±0.92	0.000
HDL-C (mmol/L)	1.22±0.34	1.46±0.34	0.000
LDL-C (mmol/L)	3.04±0.74	2.72±0.70	0.000
Dyslipidemia [n (%)]	5900 (81.2%)	7364 (50.0%)	0.000
ALT (mmol/L)	37.77±28.21	20.01±17.46	0.000
AST (mmol/L)	25.13±11.82	20.59±8.25	0.000
GGT (IU/L)	38.83±34.92	20.74±20.39	0.000
Abnormal liver function [n (%)]	2658 (36.6%)	1127 (7.6%)	0.000
Tbil (μ mol/L)	12.93±5.20	13.15±5.49	0.004
SBP (mm Hg)	129.60±16.39	117.13±15.33	0.000
DBP (mm Hg)	77.99±11.45	69.64±10.34	0.000
Hypertension [n (%)]	3626 (49.9%)	3091 (21.0%)	0.000
WC (cm)	96.14±9.10	82.33±9.37	0.000
Smoking history [n (%)]	1748 (24.1%)	1417 (9.6%)	0.000

Notes: Data were expressed as mean ± standard deviation and analyzed by student's *t* test for continuous variables or expressed as number (percentage) and analyzed by chi-square test for categorical variables.

Abbreviations: MAFLD, metabolic dysfunction-associated fatty liver disease; T_2DM, type 2 diabetes mellitus; BMI, body mass index; UA, uric acid; Cr, creatinine; sUA/Cr, serum uric acid to creatinine ratio; FPG, fasting plasma glucose; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; TBil, total bilirubin; SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference.

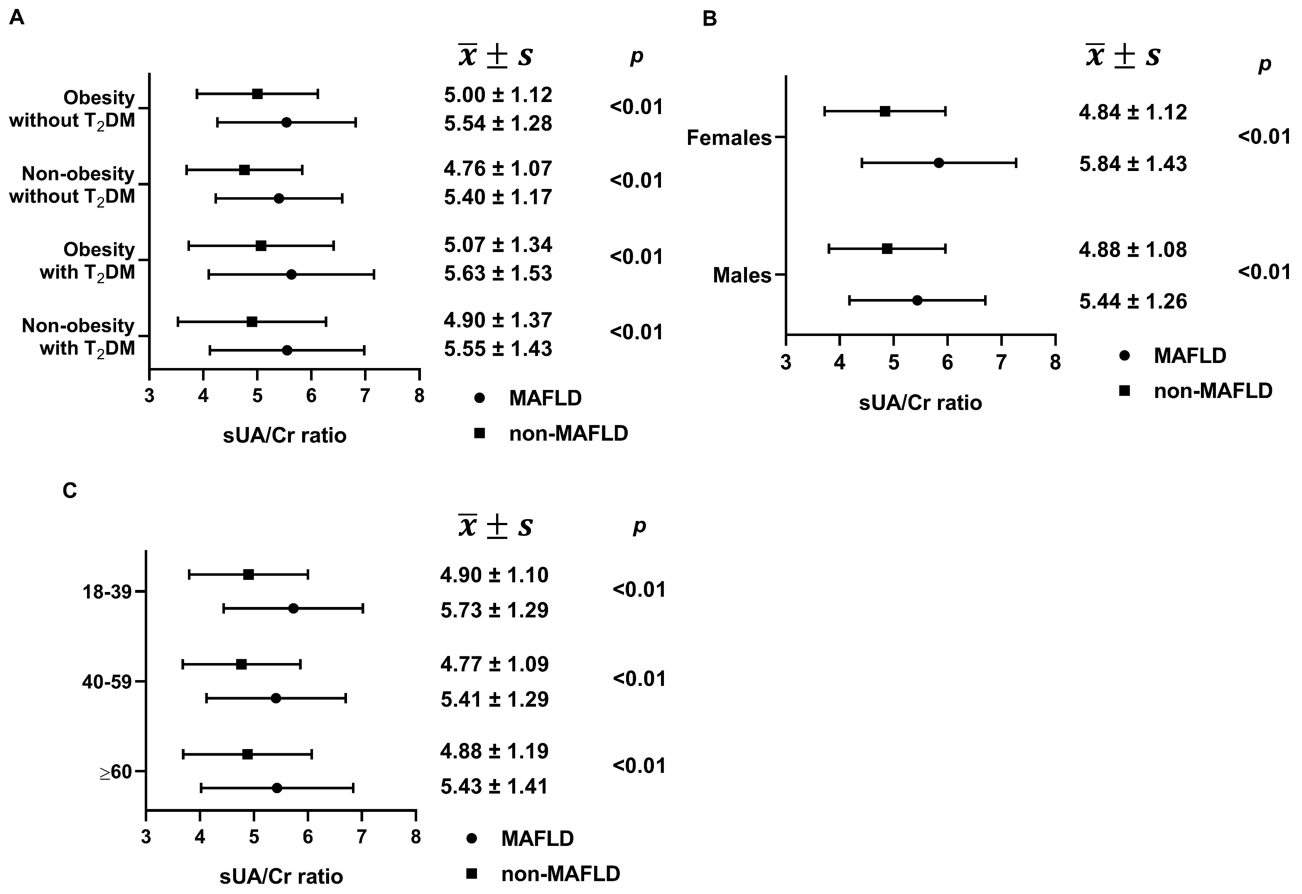

Figure 2 The serum uric acid to creatinine ratio value in metabolic dysfunction-associated fatty liver disease and its subgroups. (**A**) sUA/Cr values in different subgroups. (**B**) sUA/Cr values in different sex groups. (**C**) sUA/Cr values in different age groups (years). Data were expressed as mean ± standard deviation ($\bar{x} \pm S$) and analyzed by student's *t* test.

Abbreviations: MAFLD, metabolic dysfunction-associated fatty liver disease; sUA/Cr, serum uric acid to creatinine ratio; T_2DM, type 2 diabetes mellitus.

The Correlation Between sUA/Cr and MAFLD in Non-Obese Patients Without T_2DM

The sUA/Cr ratio in non-obese MAFLD patients without T_2DM was higher than that in corresponding controls (5.40 ±1.17 vs 4.76±1.07, $P<0.01$). sUA/Cr was correlated to MAFLD in non-obese individuals without T_2DM (OR=1.587, 95% CI: 1.461–1.723). The correlation was stronger than that in obese patients without T_2DM (OR=1.456, 95% CI: 1.409–1.504), obese patients with T_2DM (OR=1.318, 95% CI:1.177–1.475), and non-obese patients with T_2DM (OR=1.400, 95% CI:1.110–1.766) (all $P<0.01$) (Figure 3). Similar results were observed after adjustment for age, sex, BMI, dyslipidemia, and abnormal liver function (non-obese patients without T_2DM: OR =1.490, 95% CI: 1.359–1.634, $P<0.01$; obese patients without T_2DM: OR=1.294, 95% CI: 1.247–1.344, $p<0.01$; obese patients with T_2DM: OR=1.120, $P=0.074$; non-obese patients with T_2DM: OR=1.380, $P=0.013$) (Figure 4).

Multivariate Correlation Analysis Stratified by Sex and Age

After correcting for confounders (age, BMI, dyslipidemia, and abnormal liver function), sUA/Cr was correlated to MAFLD in non-obese patients without T_2DM (adjusted OR=1.428, 95% CI: 1.231–1.657, $P<0.01$) and obese patients without T_2DM (adjusted OR=1.243, 95% CI: 1.188–1.302, $P<0.01$) in males. No correlation was observed between sUA/Cr and MAFLD in obese patients with T_2DM (OR=1.102, $P=0.182$) or non-obese patients with T_2DM (OR=1.257, $p=0.167$). Similar results were obtained in females (non-obese patients without T_2DM: adjusted OR=1.498, 95% CI: 1.332–1.686, $P<0.01$; obese patients without T_2DM: adjusted OR=1.417, 95% CI: 1.327–1.514. $P<0.01$; obese patients with T_2DM; adjusted OR=1.157, $P=0.277$; non-obese patients with T_2DM: adjusted OR=1.525, $P=0.046$) (Figures 3 and 4).

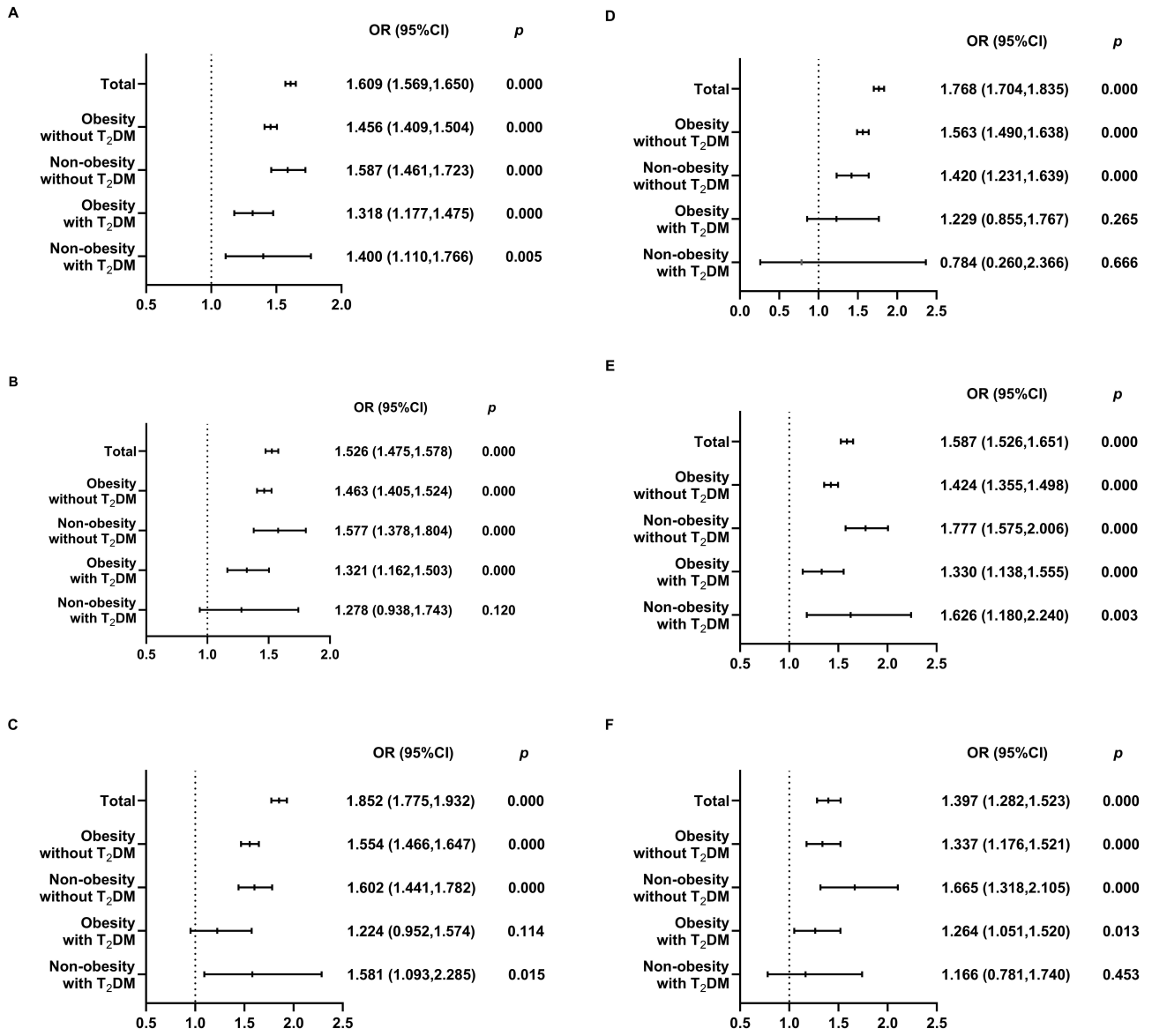

Figure 3 The univariate correlation analysis between serum uric acid to creatinine ratio and metabolic dysfunction-associated fatty liver diseases. (**A**) Univariate ORs of sUA/Cr in MAFLD and its subgroups. (**B**) Univariate ORs of sUA/Cr in MAFLD and its subgroups in males. (**C**) Univariate ORs of sUA/Cr in MAFLD and its subgroups in females. (**D**) Univariate ORs of sUA/Cr in MAFLD and its subgroups aged 18–39 years old. (**E**) Univariate ORs of sUA/Cr in MAFLD and its subgroups aged 40–59 years old. (**F**) Univariate ORs of sUA/Cr in MAFLD and its subgroups aged ≥60 years old.

Abbreviations: MAFLD, metabolic dysfunction-associated fatty liver disease; sUA/Cr, serum uric acid to creatinine ratio; T_2DM, type 2 diabetes mellitus; OR, odds ratio; CI, confidence interval.

The positive association of sUA/Cr with MAFLD in non-obese patients without T_2DM was observed at all age stages (18–39 years old: OR=1.420, 95% CI: 1.231–1.639; 40–59 years old: OR=1.777, 95% CI: 1.575–2.006; ≥60 years old: OR=1.665, 95% CI: 1.318–2.105, all $P<0.01$). Similar results were obtained after correcting for sex, BMI, dyslipidemia, and abnormal liver function (18–39 years old: OR=1.253, 95% CI: 1.072–1.464; 40–59 years old: OR=1.647, 95% CI: 1.443–1.880; ≥60 years old: OR=1.610, 95% CI: 1.249–2.075, all $P<0.01$) (Figures 3 and 4).

The Predictive Value of sUA/Cr for MAFLD in Non-Obese Patients Without T_2DM

It was found that sUA/Cr had a better predictive value for MAFLD in non-obese patients without T_2DM (AUC: 0.667, sensitivity: 58.27%, specificity: 67.42%) than obese patients without T_2DM (AUC: 0.626, sensitivity: 55.24%, specificity:

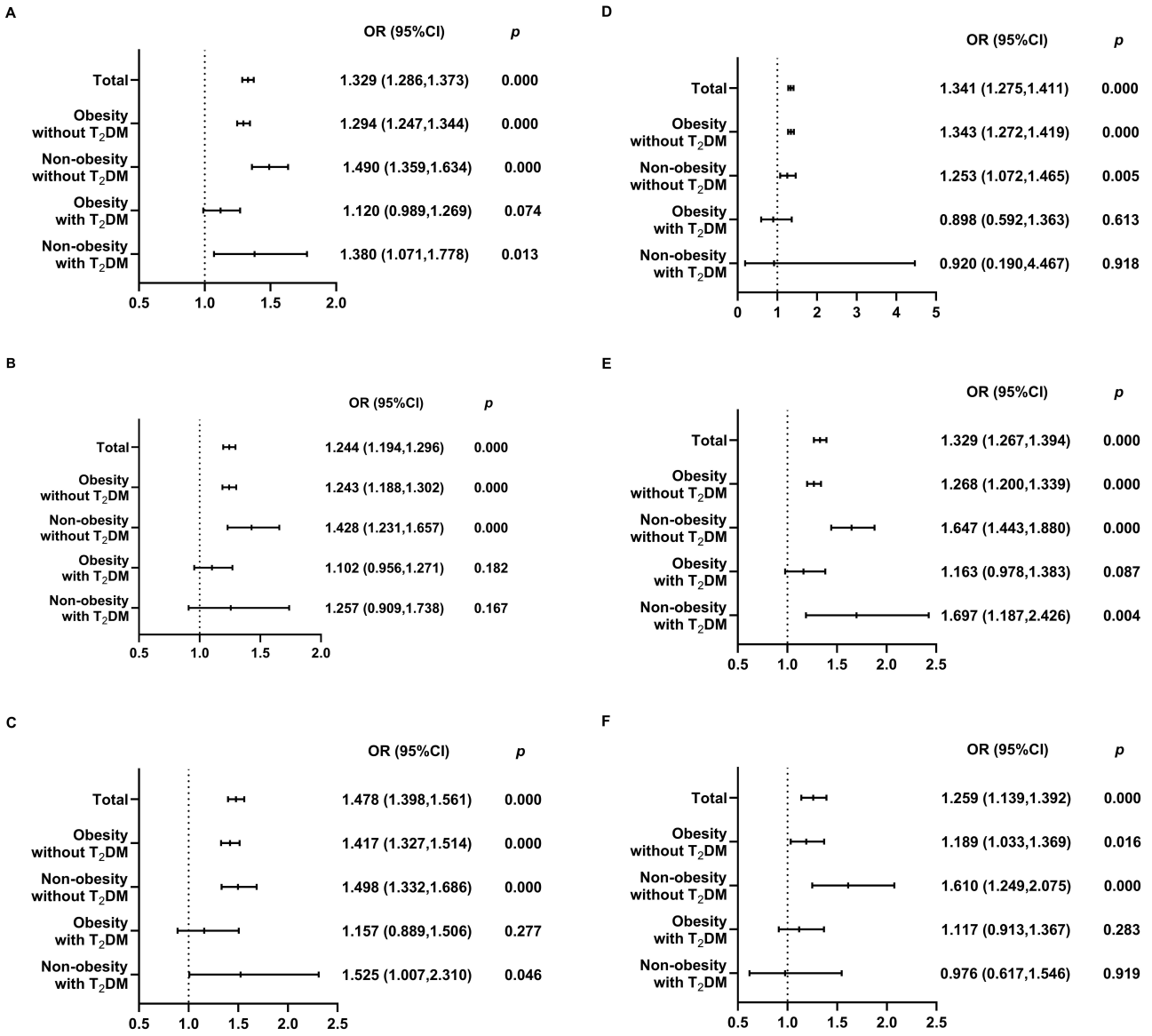

Figure 4 The multivariate correlation analysis between serum uric acid to creatinine ratio and metabolic dysfunction-associated fatty liver diseases. (**A**) Multivariate ORs of sUA/Cr in MAFLD and its subgroups. (**B**) Multivariate ORs of sUA/Cr in MAFLD and its subgroups in males. (**C**) Multivariate ORs of sUA/Cr in MAFLD and its subgroups in females. (**D**) Multivariate ORs of sUA/Cr in MAFLD and its subgroups aged 18–39 years. (**E**) Multivariate ORs of sUA/Cr in MAFLD and its subgroups aged 40–59 years. (**F**) Multivariate ORs of sUA/Cr in MAFLD and its subgroups aged ≥60 years.

Abbreviations: MAFLD, metabolic dysfunction-associated fatty liver disease; sUA/Cr, serum uric acid to creatinine ratio; T_2DM, type 2 diabetes mellitus; OR, odds ratio; CI, confidence interval.

63.16%) based on ROC analysis ($P<0.01$), but not non-obese patients with T_2DM (AUC: 0.633, sensitivity: 77.61%, specificity: 47.57%, $P>0.01$) or obese patients with T_2DM (AUC: 0.620, sensitivity: 72.91%, specificity: 48.60%, $P>0.01$).

With stratification for sex, both in males and females, sUA/Cr had the ability to predict MAFLD in non-obese patients without T_2DM (AUCs: male: 0.671, sensitivity: 81.29%, specificity: 48.17%; female: 0.665, sensitivity: 50.00%, specificity: 75.81%) and obese patients without T_2DM (AUCs: male: 0.621, sensitivity: 53.21%, specificity: 64.44%; female: 0.659, sensitivity: 67.43%, specificity: 56.59%) (all $P<0.01$). No statistically significant difference in AUCs was observed between the two groups either in males or in females (all $P>0.01$).

Stratified by age, sUA/Cr could discriminate for MAFLD at all age stages in non-obese patients without T_2DM (all $P<0.01$). Moreover, the ability of sUA/Cr to discriminate for MAFLD increased with aging (AUCs: 18–39 years old:

0.637, sensitivity: 65.62%, specificity: 59.19%; 40–59 years old: 0.698, sensitivity: 79.59%, specificity: 51.03%; ≥60 years old: 0.704, sensitivity: 57.78%, specificity: 75.17%; all $P<0.01$) (Table 2 and Figure 5).

Discussion

MAFLD is the hepatic manifestation of metabolic dysfunction, and the association with UA abnormalities has been studied but the results were controversial. The study conducted by Xing Y et al showed an association between sUA/Cr and MAFLD in patients with type 2 diabetes, which was in accordance with the univariate analysis results in this study.[17] However, the difference between the two studies in that the association was not observed in this study after adjusting for age, BMI, dyslipidemia, and abnormal liver function. Therefore, the difference in confounders adjusted might contribute to the distinguished results. In addition, the larger sample size of this study may lead to a more representative result. Moreover, this study set a more stringent threshold for statistical significance at p<0.01 rather than p<0.05 in Xing Y's study.

Table 2 Receiver Operating Characteristics Analysis of Serum Uric Acid to Creatinine Ratio in Predicting the Risk of Metabolic Dysfunction-Associated Fatty Liver Disease in Different Groups

	Varibles	AUC	95% CI	*p* value	Cutoff Points	Youden Index	Sensibility (%)	Specificity (%)
MAFLD								
	Overall	0.660	(0.654,0.666)	<0.0001	5.038	0.2400	62.56	61.44
	Male	0.639	(0.630,0.647)	<0.0001	5.035	0.2085	60.24	60.61
	Female	0.714	(0.705,0.723)	<0.0001	5.223	0.3230	64.27	68.03
	Age 18–39	0.692	(0.684,0.700)	<0.0001	5.096	0.2860	66.73	61.86
	Age 40–59	0.652	(0.642,0.662)	<0.0001	5.038	0.2323	58.69	64.54
	Age ≥60	0.626	(0.601,0.652)	<0.0001	5.212	0.2080	52.53	68.28
Obesity without T_2DM								
	Overall	0.626	(0.617,0.634)	<0.0001	5.249	0.1840	55.24	63.16
	Male	0.621	(0.611,0.632)	<0.0001	5.238	0.1765	53.21	64.44
	Female	0.659	(0.643,0.675)	<0.0001	5.123	0.2403	67.43	56.59
	Age 18–39	0.648	(0.635,0.660)	<0.0001	5.130	0.2170	65.63	56.07
	Age 40–59	0.617	(0.603,0.630)	<0.0001	5.038	0.1793	58.21	59.72
	Age ≥60	0.599	(0.563,0.635)	<0.0001	5.356	0.1841	45.48	72.93
Non-obesity without T_2DM								
	Overall	0.667	(0.657,0.676)	<0.0001	5.102	0.2569	58.27	67.42
	Male	0.671	(0.652,0.690)	<0.0001	4.578	0.2946	81.29	48.17
	Female	0.665	(0.654,0.676)	<0.0001	5.395	0.2581	50.00	75.81
	Age 18–39	0.637	(0.624,0.649)	<0.0001	4.912	0.2482	65.62	59.19
	Age 40–59	0.698	(0.680,0.715)	<0.0001	4.589	0.3062	79.59	51.03
	Age ≥60	0.704	(0.652,0.752)	<0.0001	5.298	0.3295	57.78	75.17
Obesity with T_2DM								
	Overall	0.620	(0.591,0.648)	<0.0001	4.719	0.2151	72.91	48.60
	Male	0.612	(0.580,0.644)	<0.0001	4.719	0.2036	70.08	50.28
	Female	0.603	(0.537,0.666)	0.0755	4.885	0.2858	80.10	48.48
	Age 18–39	0.588	(0.502,0.671)	0.2802	5.409	0.2097	70.97	50.00
	Age 40–59	0.612	(0.575,0.648)	0.0001	4.971	0.1957	63.37	56.20
	Age ≥60	0.615	(0.557,0.672)	0.0018	5.341	0.2461	51.89	72.73
Non-obesity with T_2DM								
	Overall	0.633	(0.556,0.706)	0.0019	4.632	0.2518	77.61	47.57
	Male	0.590	(0.485,0.689)	0.1323	4.926	0.2167	58.33	63.33
	Female	0.675	(0.556,0.780)	0.0049	4.632	0.3773	93.55	44.19
	Age 18–39	0.583	(0.317,0.818)	0.5779	5.482	0.4000	100.00	40.00
	Age 40–59	0.718	(0.611,0.809)	0.0001	4.926	0.3851	70.59	67.92
	Age ≥60	0.547	(0.421,0.669)	0.5090	4.645	0.1898	81.48	37.50

Abbreviations: MAFLD, metabolic dysfunction-associated fatty liver disease; T_2DM, type 2 diabetes mellitus; AUC, area under curve; CI, confidence interval.

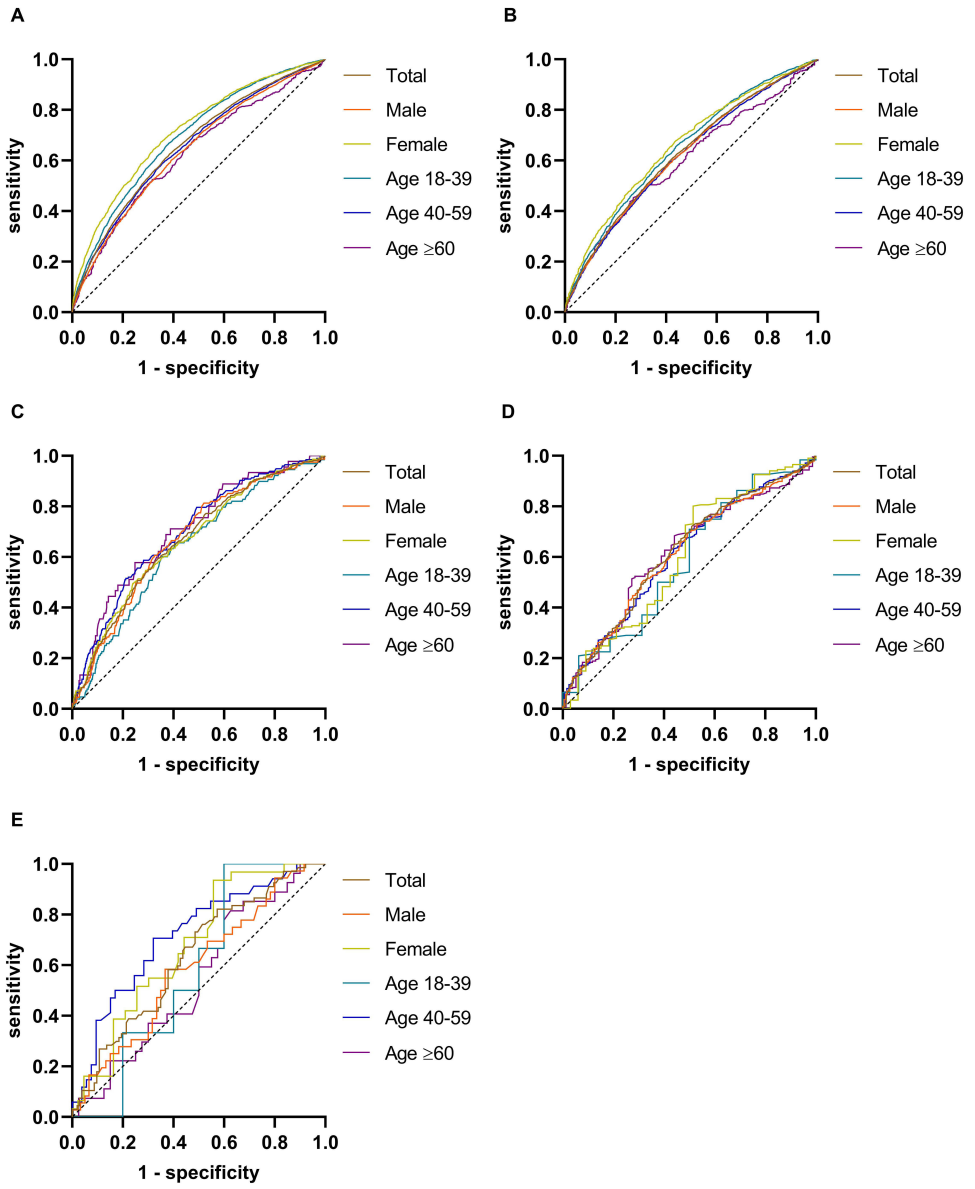

Figure 5 Receiver operating characteristics analysis of serum uric acid to creatinine ratio in predicting the risk of MAFLD in different groups. (**A**) ROC of overall MAFLD. (**B**) ROC of obesity without T_2DM. (**C**) ROC of non-obesity without T_2DM. (**D**) ROC of obesity with T_2DM. (**E**) ROC of non-obesity with T_2DM.
Abbreviations: ROC, receiver operating characteristics; MAFLD, metabolic dysfunction-associated fatty liver disease; T_2DM, type 2 diabetes mellitus.

UA is the final metabolic product of purine and is excreted by the kidney (~70%) and intestine (~30%).[18] Previous studies showed that UA played a key role in lipid metabolism[19] and was associated with a variety of metabolism-related diseases, such as metabolic syndrome,[20] diabetes,[21] and NAFLD.[22] The level of serum Cr is commonly used to measure renal clearance function, which can be affected by the number of muscles and meat intake.[23] Serum UA/Cr is a composite index of renal function-normalized sUA, reflecting endogenous UA levels more precisely than sUA.[24]

Consistent with this study, Seo YB et al found that the level of sUA/Cr was correlated with NAFLD.[25] IR and compensatory hyperinsulinemia progressing to defective lipid metabolism and hepatic triglyceride accumulation are commonly considered as the core pathogenesis mechanism for MAFLD.[26] Furthermore, elevated sUA might lead to IR via reducing endothelial nitric oxide (NO) bioavailability,[27] downregulating the production of insulin sensitizers, and activating the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome [21,22].

As reported, 60%~70% of NAFLD patients are complicated with T_2DM.[28] However, this study revealed that the association of sUA/Cr with MAFLD was observed in patients without T_2DM, but not those with T_2DM, which suggested that in addition to IR and β-cell dysfunction, abnormal UA metabolism may play a critical role in the pathogenesis of MAFLD. Liu N et al indicated that UA could react with some special free radicals and produce stronger free radicals, which induce severe endoplasmic reticulum stress and mitochondrial oxidative stress and interfere with tricarboxylic acid cycle, contributing to the increase in fat synthesis, the impairment of fatty acid oxidation, and development of hepatic steatosis.[29]

This study also found that in patients without T_2DM, the association of sUA/Cr with MAFLD was stronger in non-obese individuals than in obese individuals. This study doubts that the well-acknowledged association of obesity with MAFLD may mask the effect of UA on MAFLD. In non-obese individuals, the effect of sUA on MAFLD might be more obvious. Moreover, Eun Kyung Choe et al suggested that the prevalence of NAFLD was significantly higher in sarcopenic subjects than in nonsarcopenic subjects, regardless of obesity.[30] A higher level of sUA led to sarcopenia and patients with low muscle mass and muscle strength were at a higher risk of NAFLD.[31–33] IR is a common pathophysiology of sarcopenia and NAFLD because both liver and muscle are target organs for insulin.[34,35] The loss of muscle mass leads to glucose intolerance and promotes gluconeogenesis by reducing the quantity of the main cellular target for insulin. When IR occurs in myocytes, muscle mass is depleted by the reduction in protein synthesis and the increase in catabolism.[36,37] Finally, IR and sarcopenia become a vicious cycle. Furthermore, further studies found that non-obese MAFLD patients had a distinct metabolic profile with an increased rate of PNPLA3 risk allele carriage, which may involve specific metabolic pathways and need further exploration.[38,39]

Strengths

There are some strengths in this study. First, this study is aimed at the association of sUA/Cr with MAFLD in non-obese and obese individuals with or without T_2DM, and the results have certain practical application value. The findings highlight the significance of focusing on the level of sUA/Cr, even though UA is excluded from the diagnostic standards of MAFLD. Furthermore, this study provides new insights into understanding the pathogenesis of MAFLD in addition to IR and obesity, especially for non-obese individuals without T_2DM. The study had a large sample size of 21,996 subjects, and the results obtained are relatively representative.

Limitations

This study does possess some limitations. Firstly, the severity of MAFLD was not classified due to the limitation of ultrasound and the different emphasis in this study. Besides, considering the large sample size of this retrospective study, we did not administer questionnaires regarding physical activity and diet, or measure muscle mass to identify sarcopenia, which may be associated with fatty liver and HUA.[40,41] In our future cohort studies, we will document physical activity and diet habit, and measure body muscle mass to further explore the risk factors of MAFLD. Finally, this study was a single-center study at a risk of selection bias, but the large sample size compensated for this to some extent.

Conclusions

This large-scale cross-sectional study demonstrated the association of sUA/Cr with non-obese MAFLD in patients without T_2DM. Besides, sUA/Cr was capable of discriminating for MAFLD in non-obese individuals without T_2DM, especially for those over 60 years old. These findings contribute to understanding the effect of sUA on MAFLD and suggest that non-obese individuals without T_2DM should pay more attention to sUA/Cr to prevent MAFLD.

Abbreviations

MAFLD, metabolic dysfunction-associated fatty liver disease; T_2DM, type 2 diabetes mellitus; sUA/Cr, serum uric acid to creatinine ratio; NAFLD, non-alcoholic fatty liver disease; IR, insulin resistance; BMI, body mass index; UA, uric acid; WC, waist circumference; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; LDL-C, low-density lipoprotein

cholesterol; TC, total cholesterol; TG, triglyceride; TBil, total bilirubin; FPG, fasting plasma glucose; OR, odds ratio; CI, confidence intervals; AUC, area under the curve; ROC, receiver operating characteristic; NLRP3, NOD-like receptor family pyrin domain containing 3.

Data Sharing Statement

All data relevant to the study are included in the article. Data can be provided upon request to credible investigators on verification for patient confidentiality.

Ethics Approval and Consent to Participate

This retrospective study was approved by the ethical review board of the China–Japan Friendship Hospital, No. 2, East Yinghua Road, Chaoyang District, Beijing, 100029, China (Number of Ethics documents: 2018-110-K79-1). The requirement for informed consent was waived owing to the retrospective study design. The data are anonymous.

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Disclosure

The authors have no relevant financial or non-financial interests to disclose.

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