ORIGINAL RESEARCH

Association Between Serum Uric Acid to Creatinine Ratio and Metabolic-Associated Fatty Liver Disease in Southeast China (TyG-BMI as a Potential Mediator)

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Purpose: Serum uric acid to creatinine ratio (SUA/Cr) has been associated with an increased risk of metabolic syndrome; however, limited evidence exists regarding the relationship between SUA/Cr and metabolic-associated fatty liver disease (MAFLD). This study aims to investigate the association between SUA/Cr, TyG-BMI (triglyceride glucose-body mass index), and MAFLD in Chinese adults.

Patients and Methods: The data were obtained from a health examination conducted at Nanping First Hospital. Spearman correlation analysis was employed to assess the association between SUA/Cr or TyG-BMI and various risk factors pertinent to MAFLD. A multivariate logistic regression model was utilized to investigate the relationship between SUA/Cr or TyG-BMI and MAFLD. Additionally, restricted cubic splines (RCS) and receiver operating characteristic (ROC) curve analyses were applied to explore the relationship between SUA/Cr and MAFLD. Mediation models were constructed to figure out the mediating role of TyG-BMI in the association between SUA/Cr and MAFLD.

Results: Spearman correlation analysis showed a significant association between SUA/Cr and multiple risk factors for MAFLD (such as BMI, SBP, DBP, TG, TC, ALT, AST, GGT, FPG, and HDL). Furthermore, SUA/Cr had a positive correlation with TyG-BMI ($P<0.05$). The logistic model demonstrated that elevated levels of SUA/Cr were significantly associated with an increased risk of MAFLD, even after adjusting for confounding factors (odds ratio [OR]: 1.390; 95% confidence interval [CI]: 1.255–1.538). The RCS curves revealed a consistent and monotonic increase in the relationship between SUA/Cr levels and the occurrence of MAFLD. Moreover, SUA/Cr exhibited moderate discriminatory ability in identifying individuals with MAFLD (AUC: 0.669). Mediation analysis indicated that approximately 52.05% of the positive association between SUA/Cr and MAFLD was mediated by TyG-BMI.

Conclusion: Our findings suggest a substantial association between elevated levels of SUA/Cr and an increased risk of MAFLD in the Chinese adult population, with TyG-BMI mediating this correlation.

Keywords: SUA/Cr, TyG-BMI, metabolic-associated fatty liver disease

Introduction

Fatty liver is a complex disease caused by a combination of genetic, dietary, and lifestyle factors.[1] The global prevalence of fatty liver is alarmingly high and continues to rise among the general population.[2,3] In 2020, the term "metabolic-associated fatty liver disease (MAFLD)" was proposed to encompass fatty liver disease related to systemic metabolic dysregulation.[4] MAFLD emphasizes the bidirectional interplay between fatty liver and metabolic alterations. Moreover, patients with MAFLD have an increased risk of fibrosis and mortality, along with a considerable burden of comorbidities and poorer prognosis.[5] Given that invasive pathological biopsy for diagnosing MAFLD are costly and prone to postoperative

complications, there is an urgent need for a concise and cost-effective approach utilizing laboratory biomarkers to predict the risk of MAFLD. Numerous studies have indicated that lifestyle interventions can significantly impact the clinical characteristics of patients with non-alcoholic fatty liver disease (NAFLD), including certain biochemical indicators such as insulin resistance (IR),[6] TG, HDL-C,[7] TyG, CRP.[8] However, due to the complex pathogenesis of MAFLD, there is still a need to identify novel biochemical predictors in order to effectively prevent its occurrence.

Uric acid is the end product of both exogenous and endogenous purine metabolism. Hyperuricemia can result from either excessive production or reduced excretion of SUA.[9] SUA has been reported to be associated with IR,[10] type 2 diabetes mellitus (T2DM),[11] MetS,[12] and CVD.[13] Recent research has demonstrated a correlation between SUA and uric acid-derived metabolites in NAFLD, where higher levels of SUA were positively correlated with NAFLD severity.[14] In addition, our previous study[15] revealed a positive association between SUA and the risk of MAFLD. Nevertheless, we acknowledge that kidney dysfunction can contribute to increased levels of SUA.[16] Therefore, SUA/Cr has emerged as a novel biomarker, which is considered superior to measuring only SUA. Previous studies have revealed significant associations between SUA/Cr and MetS,[17] as well as β-cell function in T2DM.[18] However, the association between SUA/Cr and the prevalence of MAFLD has not been investigated.

TyG-BMI index, proposed by Ko et al, is a measure of IR that assesses the body's sensitivity to insulin. It has been widely recognized as a simple, powerful, and clinically useful surrogate marker for early identification of IR.[19] Importantly, TyG-BMI shows a significant correlation with SUA,[10] and IR is significantly associated with the development of MAFLD.[20] Therefore, the objective of this study is to investigate the impact of SUA/Cr on MAFLD while also examining the potential mediating role of TyG-BMI in the association between SUA/Cr and MAFLD.

Methods

Study Design and Participants

We conducted a retrospective case-control study at the Health Examination Centre of Affiliated Nanping First Hospital, Fujian Medical University, from April 2015 to August 2017. The research design and study population are described in our team's previously published papers.[15] In addition, the following exclusion criteria were applied: (1) participants with more than 25 unanswered items in the questionnaire; (2) individuals with missing information on SUA and Cr.

The proposed diagnostic criteria for MAFLD are based on abdominal ultrasonography, in conjunction with one of the following three criteria: overweight/obesity, presence of T2DM, or evidence of metabolic dysregulation. The specific definition can be found in the article by Takumi et al.[21]

Clinical Examinations, Lifestyle Variables, and Biochemical Analysis

Upon enrollment in the study, all participants underwent structured interviews conducted by trained interviewers who used validated questionnaires to gather sociodemographic information (including age, sex, education level, etc) and lifestyle behaviors (such as smoking status, alcohol consumption, physical activity levels). In addition to that, skilled personnel employed calibrated instruments to measure body weight, height, and blood pressure values. For specific biochemical measurements like TG (mmol/L), TC (mmol/L), HDL-C (mmol/L), LDL-C (mmol/L), FPG (mmol/L), ALT (IU/L), AST(IU/L), GGT(IU/L), SUA (mg/dL), and creatinine (Cr; μmol/L) levels among others, please refer to Table 1.

Statistical Analysis

The statistical analyses were conducted using *SPSS* software (version 27.0) and *R* software (version 4.3.1). Normality of continuous biomarkers was assessed, and baseline characteristics were compared across MAFLD categories, presented as medians (IQRs) for continuous variables and proportions (*n* and %) for categorical variables. Baseline characteristics were compared using Chi-square tests or *Mann–Whitney U-test* analysis. Multivariate logistic regression models were employed to examine the association between SUA/Cr, TyG-BMI, and MAFLD, estimating *OR* with corresponding 95% *CI*. Model 1 represented the crude model; Model 2 adjusted for sex, age, education level, marital status, income, smoking status, alcohol consumption, tea drink status, physical activity, and BMI; Model 3 additionally adjusted for systolic pressure, diastolic pressure, TG, TC, HDL-C, LDL-C, ALT, AST, GGT, and FPG. The correlation between SUA/Cr or TyG-BMI and the potential risk factors of MAFLD was examined using *Spearman* correlation analysis. Additionally, RCS logistic regression

Table 1 General Characteristics of Cases and Controls Stratified by Sex, n (%)

Variables	MAFLD (n=649)	Control (n=1712)	χ^2 or Z	P-value
Sex			131.704	<0.001
Male	501(77.2)	875(51.1)		
Female	148(22.8)	837(48.9)		
Age (years)			30.054	<0.001
<50	399 (61.5)	1251 (73.1)		
≥50	250 (38.5)	461 (26.9)		
Education level			6.451	0.040
Primary school and less than	348 (53.6)	1010 (59.0)		
Junior middle and high school	257 (39.6)	583 (34.1)		
Junior college or above	44 (6.8)	119 (7.0)		
Marital status			18.911	<0.001
Single	58 (8.9)	272 (15.9)		
Married or other	591 (91.1)	1440 (84.1)		
Income (yuan/month)			5.185	0.075
<2000	34 (5.2)	99 (5.8)		
2000~3000	175 (27.0)	538 (31.4)		
≥3000	440 (67.8)	1075 (62.8)		
Smoking status			39.914	<0.001
Yes	206 (31.7)	334 (19.5)		
No	443 (68.3)	1378 (80.5)		
Alcohol consumption status			21.032	<0.001
Yes	288(44.4)	585(34.2)		
No	361(55.6)	1127(65.8)		
Tea drinking status			34.691	<0.001
Yes	194(29.9)	739(43.2)		
No	455(70.1)	973(56.8)		
Physical activity (time/week)			5.141	0.023
≤3	290(44.7)	677(39.5)		
>3	359(55.3)	1035(60.5)		
BMI (kg/m^2)*	25.46(24.03,27.04)	22.04(20.43,23.88)	−25.037	<0.001
Systolic pressure (mmHg)*	125.00(118.00,136.50)	116.00(108.00,116.00)	−14.431	<0.001
Diastolic pressure (mmHg)*	84.00(80.00,90.00)	78.00(70.00,84.00)	−15.302	<0.001
TG (mmol/L)*	1.91(1.31,2.79)	1.10(0.93,1.53)	−20.378	<0.001
TC (mmol/L)*	5.17(4.65,5.91)	4.95(4.42,5.48)	−6.563	<0.001
HDL-C (mmol/L)*	1.17(1.02,1.34)	1.37(1.18,1.48)	−14.605	<0.001
LDL-C (mmol/Ls)*	3.24(2.64,3.80)	3.07(2.60,3.56)	−3.873	<0.001
ALT (IU/L)*	27.00(19.00,38.00)	17.00(13.00,24.00)	−19.191	<0.001
AST (IU/L)*	23.00(20.00,29.00)	20.00(17.00,24.00)	−11.536	<0.001
GGT (IU/L)*	34.00(25.00,52.00)	20.00(15.00,30.00)	−18.727	<0.001
FPG (mmol/L)*	5.36(5.05,5.91)	5.13(4.86,5.44)	−10.665	<0.001
SUA (μmol/L)*	392.50(325.14,443.36)	315.62(265.22,378.87)	−16.230	<0.001
Cr (umol/L)*	84.58(73.90,93.78)	81.25(70.13,91.69)	−4.762	<0.001

Note: *Medians (P$_{25}$ and P$_{75}$).
Abbreviations: TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; GGT, g-glutamyltransferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FPG, fasting plasma glucose; SUA, serum uric acid; Cr, creatinine.

with 4 knots (5th, 35th, 65th, and 95th percentiles of SUA/Cr) was performed to evaluate non-linearity between SUA/Cr and MAFLD. Mediation analysis was performed to explore the mediating effect of TyG-BMI on the association between SUA/Cr and MAFLD. TyG index was calculated as Ln [TG (mg/dL) × FPG (mg/dL)/2], while TyG-BMI was calculated as Ln [TG (mg/dL) × FPG (mg/dL)/2] × BMI.[22] All P-values were two-tailed, and statistical significance was defined as $P < 0.05$.

Results

Study Population and Baseline Characteristics

The baseline characteristics of each group are summarized in Table 1. A total of 2361 subjects were included in this study. Compared to the control group, the MAFLD cases exhibited a higher proportion of males, an older age distribution, lower educational attainment, fewer individuals who were single, a higher prevalence of smoking and alcohol consumption, reduced tea intake and physical activity levels. Additionally, they had elevated BMI values as well as systolic and diastolic blood pressure readings. Furthermore, their triglyceride, total cholesterol, LDL-C, ALT, AST, GGT, FPG, SUA, and Cr levels were significantly higher while HDL-C level was lower.

Associations of SUA/Cr with the MAFLD

After adjusting for multiple variables, significant positive associations were observed between SUA/Cr and MAFLD (Table 2). In model 1, the *OR* of MAFLD for participants with SUA/Cr was 1.687 (95% CI: 1.547–1.839, $P < 0.001$). Even after controlling for confounding factors, the multivariate analysis showed a persistent positive correlation between SUA/Cr and MAFLD. In model 2 and model 3, the *ORs* were: 1.390 (95% CI: 1.255–1.538, $P < 0.001$) and 1.236 (95% CI: 1.2107–1.381, $P < 0.001$), respectively. In subgroup analyses, the association between SUA/Cr and MAFLD remained consistent across different BMI strata.

Associations Between TyG-BMI Levels and MAFLD

Following adjustment for potential confounding factors, the logistic regression model revealed that high levels of TyG-BMI were significantly associated with an increased risk of MAFLD (In model 1, $OR = 1.051$ (95% CI: 1.047–1.056, $P < 0.001$); In model 2, $OR = 1.052$ (95% CI: 1.042–1.061, $P < 0.001$); And in model 3, $OR = 1.044$ (95% CI: 1.022–1.065, $P < 0.001$)). The detailed results are presented in Table 3.

Spearman Correlation Between SUA/Cr or TyG-BMI and MAFLD Risk Factors

We observed a positive correlation between SUA/Cr or TyG-BMI and BMI, SBP, DBP, TG, TC, ALT, AST, GGT, FPG; as well as a negative correlation with HDL-C (rho = −0.245). In addition, TyG-BMI exhibited a positive association with Age. It is worth noting that TyG-BMI demonstrated a significant correlation with SUA/Cr (Table 4).

Table 2 Logistic Regression Analysis for Association of SUA/Cr with MAFLD, or (95% CI)

Variables	Total Population			BMI≤23 kg/m^2			BMI>23 kg/m^2		
	OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Model 1	1.687	1.547~1.839	<0.001	1.968	1.597~2.425	<0.001	1.363	1.229~1.512	<0.001
Model 2	1.390	1.255~1.538	<0.001	1.915	1.526~2.403	<0.001	1.271	1.137~1.422	<0.001
Model 3	1.236	1.107~1.381	<0.001	1.527	1.160~2.009	0.003	1.157	1.026~1.306	0.018

Notes: Model 1: crude model; Model 2: further adjusted for sex, age, education level, marital status, income, smoking status, alcohol drink status, tea drink status, physical activity, BMI; Model 3: further adjusted for systolic pressure, diastolic pressure, TG, TC HDL-C, LDL-C, ALT, AST, GGT, FPG.

Table 3 Logistic Regression Analysis for Association of TYG-BMI with MAFLD, or (95% CI)

Variables	Total Population			BMI≤23 kg/m^2			BMI>23 kg/m^2		
	OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Model 1	1.051	1.047~1.056	<0.001	1.078	1.061~1.095	<0.001	1.036	1.030~1.042	<0.001
Model 2	1.052	1.042~1.061	<0.001	1.098	1.074~1.124	<0.001	1.041	1.031~1.051	<0.001
Model 3	1.044	1.022~1.065	<0.001	1.147	1.074~1.225	<0.001	1.043	1.021~1.066	<0.001

Notes: Model 1: crude model; Model 2: further adjusted for sex, age, education level, marital status, income, smoking status, alcohol drink status, tea drink status, physical activity, BMI; Model 3: further adjusted for systolic pressure, diastolic pressure, TG, TC HDL-C, LDL-C, ALT, AST, GGT, FPG.

Table 4 Spearman Correlation of SUA/Cr or TYG-BMI with Potential Risk Factors of MAFLD

	SUA/Cr		TYG-BMI	
	rho	*P-value*	*rho*	*P-value*
Age	−0.031	0.137	0.290	<0.001
BMI	0.259	<0.001	0.920	<0.001
SBP	0.175	<0.001	0.439	<0.001
DBP	0.199	<0.001	0.459	<0.001
TG	0.302	<0.001	0.698	<0.001
TC	0.057	0.001	0.261	<0.001
HDL-C	−0.245	<0.001	−0.432	<0.001
LDL-C	0.037	0.076	0.160	<0.001
ALT	0.253	<0.001	0.450	<0.001
AST	0.163	<0.001	0.264	<0.001
GGT	0.312	<0.001	0.537	<0.001
FPG	0.052	0.011	0.345	<0.001
TYG-BMI	0.306	<0.001	/	/

RCS Analysis Between SUA/Cr and MAFLD

RCS regression was employed to assess the non-linear association between SUA/Cr levels and MAFLD. As depicted in Figure 1, the findings demonstrated a consistently increasing association between SUA/Cr level and MAFLD.

ROC Analysis of SUA/Cr for MAFLD

The ROC curves presented in Figure 2 demonstrate the predictive capability of SUA/Cr for MAFLD. The results indicate that SUA/Cr displays discriminative potential in identifying the presence of MAFLD, with an AUC value of
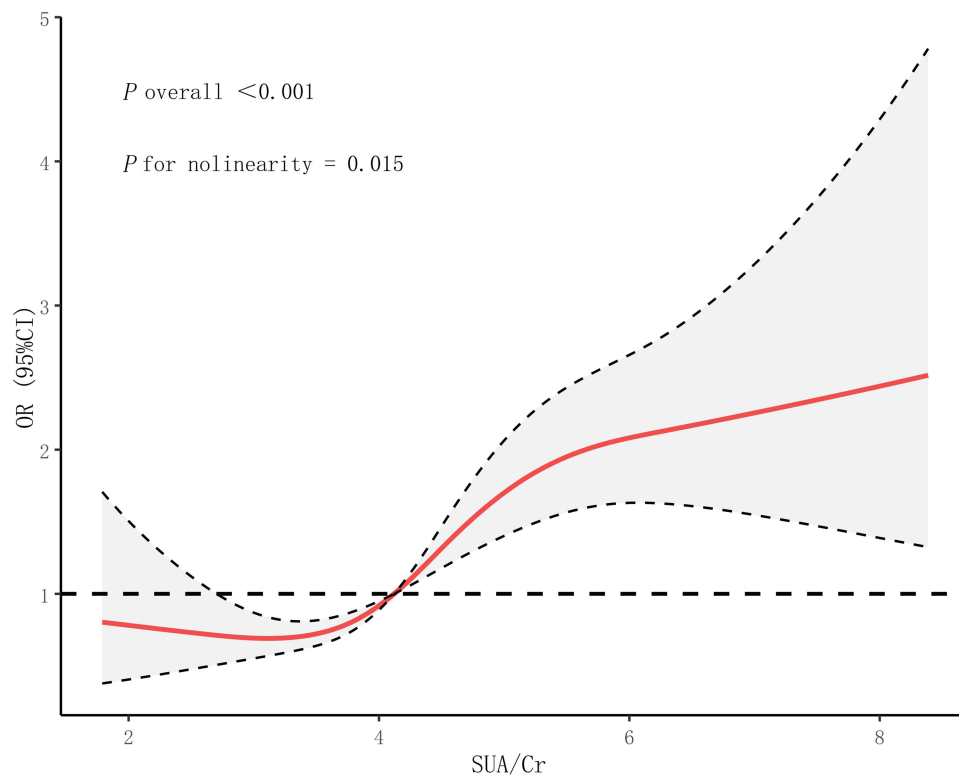

Figure 1 RCS of the association between SUA/Cr and MAFLD. Model adjusted for sex, age, education level, marital status, income, smoking status, alcohol consumption, tea drink status, physical activity, BMI.
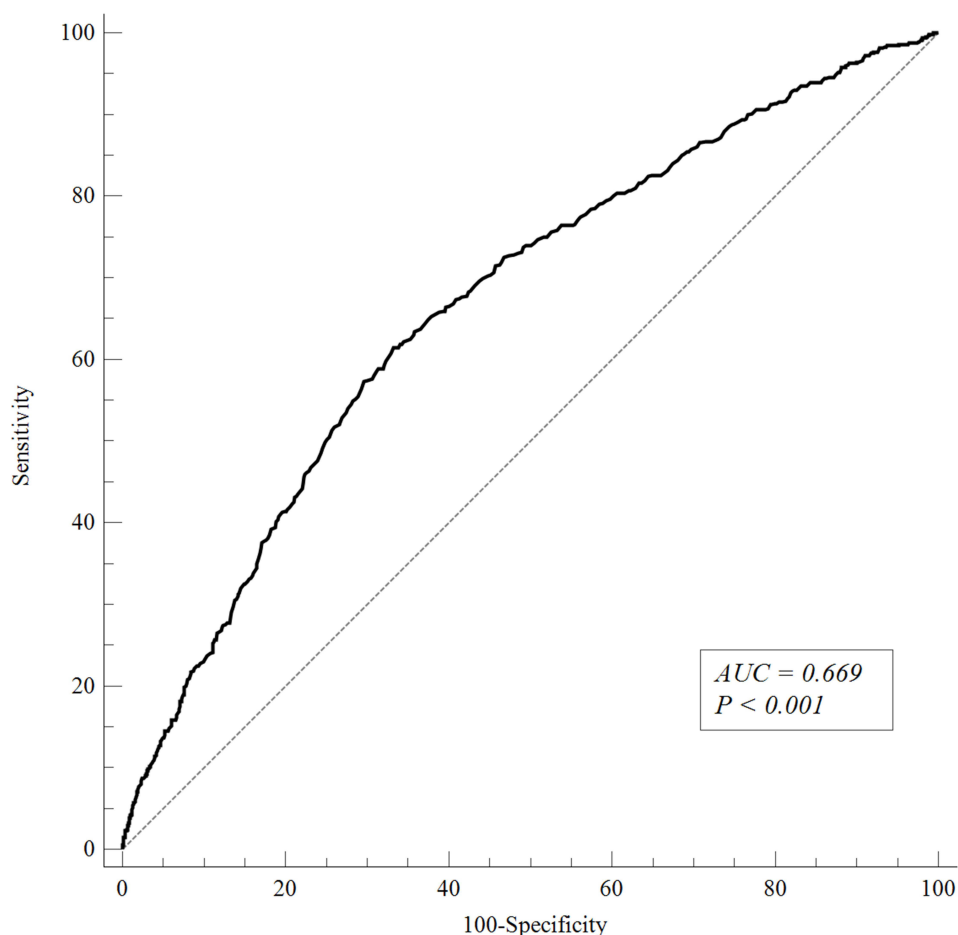
Figure 2 ROC curves of SUA/Cr for MAFLD.

0.669 (95% CI: 0.649–0.688, $P < 0.001$). The optimal cutoff value was determined to be 4.35, yielding a sensitivity of 61.48%, specificity of 66.76%, and Youden index of 0.282.

Mediated Effect of TyG-BMI on the Association Between SUA/Cr and MAFLD

The association of SUA/Cr and TyG-BMI with MAFLD is demonstrated in Table 2 and 3, while Table 4 reveals a positive association between TyG-BMI and SUA/Cr. These findings imply that the relationship between SUA/Cr and MAFLD might be partly elucidated by TyG-BMI. The results of mediation analyses are presented in Table 5.

Table 5 Mediation Analysis with TYG_BMI as Mediators Between SUA_Cr and MAFLD and NAFLD

TYG-BMI	MAFLD		NAFLD	
	OR (95% CI)[a]	*P-value*	OR (95% CI)[a]	*P-value*
Natural direct relationship	1.32(1.18~1.46)	<0.001	1.11(1.01~1.23)	0.039
Natural indirect relationship	1.35(1.27~1.44)	<0.001	1.17(1.13~1.22)	<0.001
Total relationship	1.78(1.58~2.01)	<0.001	1.31(1.18~1.45)	<0.001
Proportion, %[b]	52.05		58.14	

Notes: [a]Adjusted for age, sex, education, marital, income, smoking, drink alcohol, tea, exercise. [b]log (natural indirect relationship)/log(total relationship).

TyG-BMI serves as the most significant mediator for MAFLD, explaining around half of the relationship between SUA/Cr and MAFLD (mediation proportion: 52.05%). A sensitivity analysis conducted on NAFLD participants yielded consistent results (mediation proportion: 58.14%).

Discussion

MAFLD has affected approximately one-fourth of the global adult population, yet there remains a lack of research on the effects of elevated SUA/Cr levels on MAFLD. SUA/Cr has emerged as a new biomarker in the pathogenesis of MetS and its associated diseases.[23] Previous studies have demonstrated associations between SUA/Cr and metabolic syndrome,[24] hypertension,[25] and NAFLD.[26] Consequently, it is reasonable to postulate a correlation between SUA/Cr and MAFLD.

In this study, a positive association has been observed between SUA/Cr levels and the risk of MAFLD in Chinese adults. These findings provide compelling evidence for SUA/Cr as a crucial independent risk factor for MAFLD after adjusting for potential confounding factors. Furthermore, the results demonstrate that the relationship between SUA/Cr and MAFLD risk remains significant regardless of BMI status ($\leq 23 kg/m^2$ or $> 23 kg/m^2$. Notably, this study also reveals a non-linear correlation between SUA/Cr and MAFLD.

The positive associations between SUA/Cr and MAFLD in our study were consistent with previous epidemiological studies conducted by A Lum Han et al ($OR = 1.205$).[27] However, in our study, we adjusted for more potential confounding factors, which may have led to a more robust outcome. Other epidemiological studies have also suggested a positive relationship between SUA/Cr and MAFLD. A study of 228 subjects indicated that SUA/Cr was related to the severity of MAFLD.[28] A recent study in individuals with T2DM revealed that SUA/Cr was independently associated with a significantly higher risk of MAFLD.[29] Additionally, numerous previous studies support similar findings, suggesting that higher levels of SUA are positively associated with an increased risk of NAFLD.[30,31] Based on the results presented in our paper, it is evident that SUA/Cr is elevated in patients with MAFLD and can be utilized as a biomarker for monitoring this condition. We believe that SUA/Cr has the potential to serve as a predictive factor for the development of MAFLD.

The potential mechanisms underlying the relationship between SUA/Cr and MAFLD risk may be as follows: Firstly, SUA may accelerate chronic inflammatory processes by stimulating the production of proinflammatory mediators, which have been implicated in the pathogenesis of fatty liver.[32] Secondly, evidence also supports SUA as a potent antioxidant that can induce the generation of free radicals and oxidative stress,[33] both of which play crucial roles in the development of MAFLD.[34] Moreover, Evans J et al discovered that increased SUA levels could lead to liver fat accumulation through inhibition of intrahepatic IRS1 and Akt insulin signaling.[35] Furthermore, elevated SUA levels might promote IR by reducing the bioavailability of endothelial nitric oxide[36] and activating the NLRP3 inflammasome.[37]

The results of correlation analysis show a significant association between SUA/Cr and TyG-BMI. Additionally, our study reveals that elevated levels of TyG-BMI independently contribute to the risk of MAFLD. Therefore, a mediation analysis was conducted to explore whether TyG-BMI mediates the association between SUA/Cr and MAFLD. The findings from this study indicate that the relationship between SUA/Cr and MAFLD is partially mediated through TyG-BMI. Sensitivity analysis yielded consistent results in terms of mediation. Previous studies have also indicated that TyG-BMI can serve as an alternative biomarker for IR,[38] with a Korean study suggesting its potential use in clinical settings.[39] Although the causal relationship between SUA and IR remains unclear, elevated SUA levels may contribute to the exacerbation of IR to some extent. A study involving Chinese patients with T2DM demonstrated a significant correlation between SUA/Cr and islet β-cell function.[40] In addition, SUA has been shown to induce endothelial dysfunction and inhibit the bioavailability of nitric oxide, thereby increasing the risk of IR.[36] Consequently, higher levels of TyG-BMI may reflect greater IR potentially attributed to elevated SUA levels. It is well established that IR serves as the core pathological mechanism underlying MAFLD, preceding its diagnosis. Therefore, increased TyG-BMI can be considered an indicator of IR and may play an important role in the development of MAFLD. Previous research findings have also indicated that TyG-BMI could serve as a predictive biomarker for CVD[41] and MetS,[42] highlighting its potential physiological significance. Thus, it is plausible that TyG-BMI mediates the relationship between SUA/Cr and MAFLD mainly through IR.

Our previous research endeavors have unveiled that SUA elevates the risk of MAFLD.[15] Distinguishing itself from prior studies solely centered on SUA, this paper introduces several pivotal aspects: Firstly, SUA/Cr emerges as a comprehensive indicator of standardized SUA considering renal function, offering a more precise depiction of endogenous SUA levels compared to SUA alone. Secondly, this study goes beyond assessing the clinical relevance of SUA/Cr as a surrogate marker for MAFLD and delves into the intricate interplay between TyG-BMI, SUA/Cr, and MAFLD, thereby enriching the research landscape. Thirdly, a novel contribution lies in the mediation analysis that unravels the potential mediating role of TyG-BMI in the relationship between SUA/Cr and MAFLD, an aspect unexplored in previous literature.

The present study has several potential limitations. Firstly, the temporal sequence between SUA/Cr and MAFLD is still uncertain based on the results of this cross-sectional design. Therefore, further well-designed and large-scaled prospective studies are required to elucidate the relationship between SUA/Cr and MAFLD. Secondly, although ultrasonography is a noninvasive, safe, and widely available tool for diagnosing steatosis, it may potentially omit mild cases of steatosis. Thirdly, despite adjusting for numerous important covariates, there may still be unaccounted variables that could influence the results.

Conclusion

In summary, the present study demonstrates an independent correlation between SUA/Cr and an increased risk of MAFLD in Chinese adults, with TyG-BMI partially mediating this association. Although SUA is not currently included in the diagnostic criteria for MAFLD, our findings suggest that monitoring and controlling SUA/Cr levels should be considered during screening and treatment to prevent disease progression.

Ethics Approval

The investigation adhered to the ethical guidelines outlined in the 1975 Declaration of Helsinki. The study protocol (Ethics Number 2014096) obtained approval from the ethics committees of Fujian Medical University, and participants provided informed consent prior to their involvement.

Informed Consent

All participants provided informed consent.

Acknowledgments

Funding

Disclosure

The author(s) declare no conflicts of interest in this work.

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