RESEARCH ARTICLE

WILEY

Serum uric acid to creatinine ratio is associated with higher prevalence of NAFLD detected by FibroScan in the United States

Rusha Wang[1] | Feiben Xue[1] | Liping Wang[1] | Guangxia Shi[1] | Guoqing Qian[1] | Naibin Yang[1] | Xueqin Chen[2]

[1]Department of Infectious Diseases, Ningbo First Hospital, Ningo University, Ningbo, China

[2]Department of Traditional Chinese Medicine, Ningbo First Hospital, Ningbo University, Ningbo, China

Correspondence
Xueqin Chen, Department of Traditional Chinese Medicine, Ningbo First Hospital, Ningbo University, Liuting Street NO.59, Haishu District, Ningbo, Zhejiang 315010, China.
Email: cxq2316@163.com

Naibin Yang and Guoqing Qian, Department of Infectious Diseases, Ningbo First Hospital, Ningbo University, NO.59 Liuting Street, Haishu District, Ningbo, Zhejiang 315010, China.
Emails: mafld2021@163.com(N.Y.); guoqing.qian@foxmail.com(G.Q.)

Abstract

Background: The association between the serum uric acid (sUA) to creatinine ratio (sUA/Cr) and non-alcoholic fatty liver disease (NAFLD) has not been sufficiently clarified. In this study, we investigated the relationship between sUA/Cr and NAFLD among participants in the United States.

Methods: We performed a cross-sectional study based on data from the National Health and Nutrition examination Survey (NHANES) 2017–2018. A measured controlled attenuation parameter (CAP) value of ≥274 dB/m detected by Fibroscan was used to identify hepatic steatosis. SUA/Cr was calculated as sUA divided by serum creatinine. Multivariate logistic regression analysis was used to estimate the association between sUA/Cr and NAFLD. The adjusted odds ratio (OR) of sUA/Cr for NAFLD was estimated, and subgroup analysis stratified by sex was also conducted. The nonlinear relationship between sUA/Cr and NAFLD was further described using smooth curve fittings and threshold-effect analysis.

Results: We found that sUA/Cr was positively correlated with NAFLD status after fully adjustment for confounding factors. In subgroup analysis stratified by sex, the positive interaction between sUA/Cr and NAFLD status only existed in women but not in men. Moreover, the nonlinear association between sUA/Cr and NAFLD status was an inverted U-shaped curve with an inflection point at 9.7 among men.

Conclusions: Our study identified that sUA/Cr was positively associated with the risk of NAFLD among individuals in the United States. Moreover, the correlation between sUA/Cr and NAFLD differed according to sex.

KEYWORDS
inflammation, NAFLD, NHANES, serum uric acid to creatinine ratio, steatosis

1 | INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the predominant cause of chronic liver disease all over the world.[1] The number of people with NAFLD is predicted to increase from 83.1 million in 2015 to 100.9 million in 2030 in the United States.[2] NAFLD comprises two major histological phenotypes, nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH), which can further progress to fibrosis, cirrhosis, and hepatocellular carcinoma.[3,4] More importantly, strong evidence has revealed that NAFLD is a multisystem disease that plays an important role in liver-associated complications and extrahepatic organ dysfunction. NAFLD is closely related to type 2 diabetes mellitus (T2DM), metabolic syndrome (MetS), cardiovascular diseases (CVD), and chronic kidney diseases (CKD).[5] In the last decade, given the rapid increase in the prevalence of NAFLD, this condition has imposed a considerable health and economic burden. Hence, it is essential to discover related risk factors and develop suitable biomarkers for the prediction, early diagnosis, and management of the disease.

Serum uric acid (sUA) is a metabolite of purine nucleotides, mainly excreted through the kidney.[6] Recently, sUA and uric acid–derived metabolic and inflammatory markers have been reported to be associated with various conditions, such as T2DM,[7,8] hypertension,[9,10] MetS,[11,12] CVD[13], dyslipidemia,[14] thyroiditis,[15] NAFLD,[16] and liver dysfunction.[17] NAFLD is characterized with deteriorated metabolism and increased inflammatory burden. Similar to NAFLD, hyperuricemia is closely linked to metabolic dysregulation, including T2DM, obesity, and insulin resistance (IR).[18] Since kidney function affects the elimination of sUA, we used the sUA to creatinine ratio (sUA/Cr), an indicator of renal function-standardized sUA in this study. Previous studies[19–21] have shown that sUA/Cr is a better predictor of CKD incidence in patients with T2DM than sUA alone, and sUA/Cr correlated with

β-cell function and a higher risk of MetS in patients with T2DM. However, the relationship between sUA/Cr and NAFLD is yet to be clarified.

Here, we performed a cross-sectional study based on the data from National Health and Nutrition Examination Survey (NHANES) 2017–2018 to explore the correlation between sUA/Cr and NAFLD status detected by Fibroscan in the US. We further investigated this association after stratification by sex.

2 | MATERIALS AND METHODS

2.1 | Participants

The National Health and Nutrition examination Survey (NHANES) is a large-scale investigation conducted to assess the health and nutrition status of the American people. We selected data from the 2017 to 2018 cycle for this research. More details about the design of this survey can be found at the website: https://www.cdc.gov/nchs/nhanes/. The National Center for Health Statistics (NCHS) ethics review board approved all methods used in the investigation. All participants signed an informed consent form.

After excluding participants who lacked mobile examination center (MEC) exam data ($n = 550$), without transient elastography data ($n = 2717$, ineligible, not done, or not available), participants with partial exam unqualified ($n = 493$, including 257 individuals with a fasting time <3 h, 129 individuals missing 10 measurements and 107 individuals with interquartile range(IQR)/median liver stiffness measurement (LSM) values ≥30%), participants with hepatitis B ($n = 27$), hepatitis C ($n = 86$) or significant alcohol intake ($n = 752$), and participants without available sUA or Cr data ($n = 332$), a total of 4297 subjects were included in the final analysis (Figure 1).
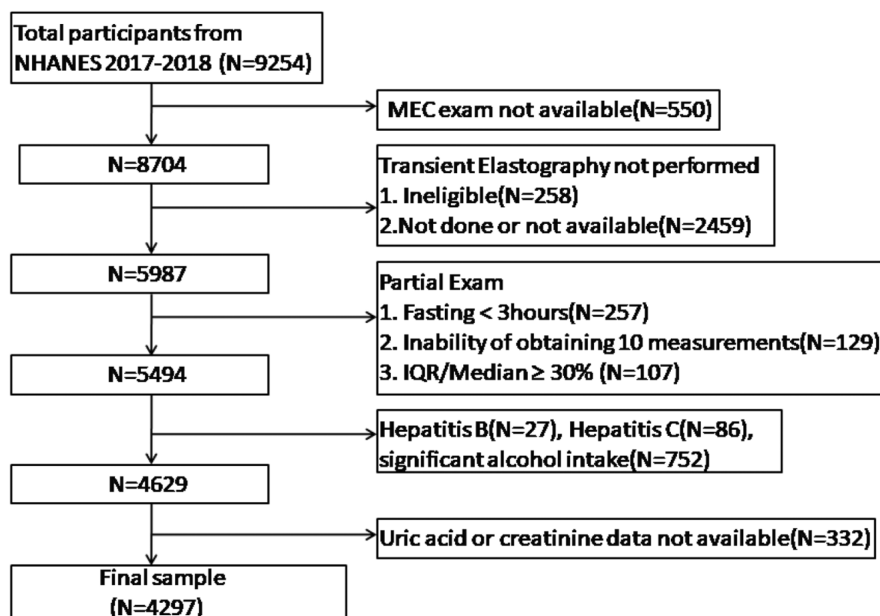

FIGURE 1 Flowchart of subjects included in this study

2.2 | Variables

The sUA/Cr was calculated as sUA divided by serum creatinine. The sUA/Cr and NAFLD status were regarded as independent and dependent variable, respectively. Vibration-controlled transient elastography (Fibroscan) was used to quantify liver steatosis through CAP. NAFLD status was defined according to the following criteria: CAP values ≥274 dB/m without hepatitis B or C virus infection and significant alcohol intake. Significant alcohol consumption was defined as ongoing or recent alcohol consumption of >three standard drinks per day in men and >two standard drinks per day in women.[22,23] Hyperuricemia was defined as serum uric acid levels ≥420 μmol/L(7 mg/dL)and ≥360 μmol/L(6 mg/dL) in men and women, respectively.

The specific measurement methods of sUA, serum creatinine, CAP, and related covariates can be acquired in http://www.cdc.gov/nchs/nhanes/.

2.3 | Statistical analysis

We used R version 3.4.3 (http://www.R-project.org) and EmpowerStats software (http://www.empowerstat.com) for all statistical analysis. The sample weights proposed by NCHS were considered. A p value <0.05 was considered statistically significant. Weighted multivariate logistic regression analysis was conducted to assess the association between sUA/Cr and NAFLD status. Three regression models were established. For Model 1, no covariates were adjusted; for model 2, age, sex, and race were adjusted; for model 3, age, sex, race, BMI, diabetes status, SBP, DBP, ALT, AST, GGT, glycohemoglobin, HDL-cholesterol, totalcholesterol, triglyceride, PLT, and serum albumin were adjusted. The confounding factors were screened and confirmed according to previous studies on the relationship of sUA/Cr and NAFLD. We used the weighted linear regression model to analyze the differences among continuous valuables and the weighted chi-square test for categorical valuables. Additionally, a subgroup analysis stratified by sex was performed. Smooth curving fittings and generalized additive models were used to explore the potential nonlinear relationships between sUA/Cr and NAFLD status. When nonlinearity was found, the inflection point was further calculated using a recursive algorithm and a weighted two-piecewise linear regression model was built.

3 | RESULTS

The description of the weighted characteristics of the 4297 participants according to sUA/Cr quartiles (Q1:0.41–5.27; Q2:5.28–6.32; Q3:6.33–7.59; Q4: 7.60–27.60) is presented in Table 1. Dramatic differences were shown between baseline characteristics and sUA/Cr quartiles. Compared with the Q1 group, participants in the higher quartile groups were younger, more likely to be women, smoked less, had higher BMI, waist circumference, total cholesterol, triglyceride,

fast insulin, AST, ALT, serum albumin, platelet count, CAP value and had lower HDL-cholesterol.

Multivariate regression analyses of the significantly related variables were performed to evaluate the ORs of NAFLD, and the results are presented in Table 2. On the one hand, we observed evident differences between sUA/Cr and NAFLD status in three models (mode 1: OR = 1.28, 95% CI: 1.23–1.3, $p < 0.0001$; model 2: OR = 1.30, 95% CI: 1.25–1.35, $p < 0.0001$; model 3: OR = 1.11, 95% CI: 1.03–1.19, $p = 0.0056$). On the other hand, compared with the lowest level of sUA/Cr (Q1), higher sUA/Cr levels (Q2–Q4) were associated with a higher incidence of NAFLD after adjusting for all covariates in model 3 (P for trend = 0.0016). In subgroup analyses stratified by sex, a positive interaction between sUA/Cr and NAFLD status only existed in women rather than men after controlling for confounding factors. For every unit increase in sUA/Cr value, the NAFLD risk was 1.21-fold higher(OR = 1.21, 95% CI: 1.09–1.33, $p = 0.0001$) among women.

By using smooth curve fittings and generalized additive models, we further confirmed the nonlinear relationship between sUA/Cr and NAFLD status (Figure 2,3). The sUA/Cr was positively associated with CAP values and the prevalence of NAFLD (Figure 2). The nonlinear relationship stratified by sex is presented in Table 3. In men, an inflection point was calculated at 9.7 fitted by the two-piecewise linear regression model. For a sUA/Cr value >9.7, a unit increase in sUA/Cr correlated with a 50% decrease in NAFLD risk (95% CI: 0.3–0.9). In contrast, when the sUA/Cr value was lower than 9.7, every unit increase in sUA/Cr was associated with a 10% increase in NAFLD risk (95% CI: 1.0–1.2).

4 | DISCUSSION

In the current study, we demonstrated that elevated sUA/Cr level was positively correlated with a higher prevalence of NAFLD. In the subgroup analysis stratified by sex, we revealed that a positive relationship existed only in women rather than men, with adjustment for confounders. More importantly, the nonlinear interaction between sUA/Cr and NAFLD status was an inverted U-shaped curve with an inflection point at 9.7 among men. From our perspective, this study is the largest sample size and population-based study on the correlation between sUA/Cr and NAFLD status.

Our findings are consistent with those of previous studies showing that serum uric acid levels were significantly associated with NAFLD prevalence.[24,25] A study based on the NHANES 1988–1994 in the United States also identified similar results between elevated uric acid level and ultrasound-diagnosed NAFLD in non-diabetic adults.[26] However, the effect of kidney function on the sUA level has been neglected in many studies, and sUA/Cr, a renal function-normalized index, might be a better biomarker.[20] Another study based on a Chinese population with normal sUA levels indicated that sUA/Cr was positively related to NAFLD incidence, and the area under the curve of C-peptide (AUC$_{cp}$)

TABLE 1 Weighted characteristic of the participants according to quartiles of serum uric acid to creatinine ratio

Characteristics	Q1(0.41–5.27) N = 1073	Q2(5.28–6.32) N = 1074	Q3(6.33–7.59) N = 1072	Q4(7.60–27.60) N = 1078	p-value
Age (years)	54.00 (12.00–80.00)	50.00 (12.00–80.00)	46.50 (12.00–80.00)	39.00 (12.00–80.00)	<0.001
Men: n(%)	557 (51.91%)	530 (49.35%)	500 (46.64%)	484 (44.90%)	0.007
Race/Ethnicity: n(%)					<0.001
Mexican American	116 (10.81%)	128 (11.92%)	142 (13.25%)	209 (19.39%)	
Hispanic	72 (6.71%)	96 (8.94%)	106 (9.89%)	116 (10.76%)	
Non-Hispanic White	401 (37.37%)	414 (38.55%)	349 (32.56%)	274 (25.42%)	
Non-Hispanic Black	359 (33.46%)	242 (22.53%)	206 (19.22%)	160 (14.84%)	
Non-Hispanic Asian	64 (5.96%)	137 (12.76%)	215 (20.06%)	238 (22.08%)	
Other race	61 (5.68%)	57 (5.31%)	54 (5.04%)	81 (7.51%)	
Diabetes status					0.330
YES	100 (9.72%)	120 (11.49%)	91 (8.80%)	109 (10.67%)	
NO	909 (88.34%)	908 (86.97%)	919 (88.88%)	889 (86.99%)	
Not available	20 (1.94%)	16 (1.54%)	24 (2.32%)	24 (2.35%)	
Smoked at least 100 cigarettes in life (%)					<0.001
YES	443 (41.29%)	333 (31.01%)	309 (28.82%)	246 (22.82%)	
NO	559 (52.10%)	617 (57.45%)	578 (53.92%)	556 (51.58%)	
Not available	71 (6.62%)	124 (11.55%)	185 (17.26%)	276 (25.60%)	
Ever have 4/5 or more drinks every day					<0.001
YES	113 (10.53%)	96 (8.94%)	77 (7.18%)	75 (6.96%)	
NO	741 (69.06%)	687 (63.97%)	628 (58.58%)	546 (50.65%)	
Not available	219 (20.41%)	291 (27.09%)	367 (34.24%)	457 (42.39%)	
SBP	122.80 (82.00–215.33)	122.67 (87.33–218.67)	122.67 (86.67–188.67)	122.80 (87.33–218.00)	0.697
DBP	70.00 (0.00–122.00)	70.00 (4.00–124.67)	70.00 (0.00–118.00)	70.00 (0.00–110.00)	0.024
BMI(Kg/m2)	26.30 (14.80–66.20)	27.00 (15.10–62.10)	27.50 (15.00–63.40)	29.10 (13.20–86.20)	<0.001
Waist circumference (cm)	93.50 (56.40–164.10)	95.40 (59.30–154.50)	96.25 (57.0–166.0)	99.00 (58.50–156.30)	<0.001
Total Cholesterol (mg/dL)	176.00 (91.00–384.00)	178.00 (86.00–366.00)	183.00 (84.0–352.0)	178.00 (79.0–428.0)	0.014
Triglyceride (mg/dL)	73.00 (10.00–708.00)	78.00 (14.00–2684.0)	94.00 (16.00–1213.0)	98.00 (13.00–1407.0)	<0.001
Glycohemoglobin(%)	5.60 (4.20–14.30)	5.50 (4.10–15.20)	5.50 (4.30–13.90)	5.50 (4.10–14.20)	0.010
FSG (mmol/L)	5.66 (3.72–18.10)	5.69 (2.94–21.10)	5.88 (4.00–25.00)	6.00 (3.66–21.60)	0.161
Fast insulin(mIU/L)	8.63 (0.71–485.10)	9.64 (0.71–267.22)	12.43 (1.73–321.64)	13.90 (0.71–136.96)	<0.001
HOMA-IR	4.08 (0.15–122.03)	4.08 (0.15–154.39)	4.08 (0.39–130.94)	4.08 (0.15–123.52)	0.002
AST (IU/L)	18.00 (6.00–272.00)	19.00 (7.00–198.00)	19.00 (7.00–182.00)	19.00 (8.00–178.00)	<0.001
ALT (IU/L)	15.00 (3.00–139.00)	16.00 (4.00–420.00)	17.00 (4.00–213.00)	18.00 (5.00–175.00)	<0.001
GGT (IU/L)	18.00 (4.00–708.00)	18.00 (2.00–269.00)	20.00 (4.00–646.00)	20.00 (4.00–650.00)	<0.001
Serum albumin (g/L)	40.00 (25.00–50.00)	41.00 (24.00–50.00)	41.00 (29.00–54.00)	41.00 (26.00–52.00)	<0.001
Platelet count (109/L)	228.00 (71.00–662.00)	234.00 (57.00–562.00)	242.00 (8.00–535.00)	253.00 (54.0–818.0)	<0.001
HDL-Cholesterol (mg/dL)	54.00 (10.00–147.00)	53.00 (24.00–122.00)	51.00 (22.00–178.00)	48.00 (22.0–126.0)	<0.001
LDL-Cholesterol (mg/dL)	104.00 (36.00–275.00)	108.96 (32.00–225.00)	108.96 (21.0–269.0)	108.96 (25.0–359.0)	0.331
CAP (dB/M)	238.00 (100.0–400.0)	247.00 (100.0–400.0)	261.5 (100.0–400.0)	273.00 (100.00–400.00)	<0.001
LSM (kPa)	4.90 (1.70–75.00)	4.80 (2.00–72.00)	4.80 (2.20–75.00)	5.00 (1.60–75.00)	0.001
Hyperuricemia: n (%)	71 (6.62%)	96 (8.94%)	203 (18.94%)	456 (42.30%)	<0.001
eGFR (mL/min/1.73m^2)	84.10 (3.12–187.89)	96.12 (21.14–179.50)	103.7 (37.11–194.85)	116.65 (49.78–219.41)	<0.001

TABLE 1 (Continued)

Characteristics	Q1(0.41–5.27) N = 1073	Q2(5.28–6.32) N = 1074	Q3(6.33–7.59) N = 1072	Q4(7.60–27.60) N = 1078	p-value
Kidney dysfunction: n (%)	621 (57.88%)	432 (40.22%)	311 (29.01%)	151 (14.01%)	<0.001
Slight	418 (38.96%)	363 (33.80%)	273 (25.47%)	143 (13.27%)	
Moderate	172 (16.03%)	68 (6.33%)	38 (3.54%)	8 (0.74%)	
Severe	31 (2.89%)	1 (0.09%)	0 (0.00%)	0 (0.00%)	
SUA/Cr	4.60 (0.41–5.27)	5.78 (5.28–6.32)	6.90 (6.32–7.59)	8.63 (7.60–27.60)	<0.001

Note Median (Min–Max) was for continuous variables. P-value was calculated by the weighted linear regression model. % was for categorical variables. P value was calculated by weighted chi-square test.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; DBP, diastolic blood pressure; FSG, fast serum glucose; GGT, gamma glutamyl transpeptidase; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment- insulin resistance; LSM, liver stiffness measurement; SBP, systolic blood pressure.

TABLE 2 Correlation between serum uric acid to creatinine ratio and NAFLD status

	Model 1:OR (95% CI) p value	Model 2: OR (95% CI) p value	Model 3:OR (95% CI) p value
Serum UA to creatinine ratio	1.28(1.23,1.3) **<0.0001**	1.30(1.25,1.35) **<0.0001**	1.11(1.03,1.19) **0.0056**
Serum UA to creatinine ratio (Quartile)			
Q1	Reference	Reference	Reference
Q2	1.31 (1.09, 1.57) **0.0036**	1.51 (1.25, 1.83) **<0.0001**	1.26 (0.88, 1.78) 0.2031
Q3	1.75 (1.46, 2.09) **<0.0001**	2.32 (1.91, 2.82) **<0.0001**	1.42 (0.99, 2.04) 0.0558
Q4	2.32 (1.95, 2.77) **<0.0001**	3.63 (2.97, 4.43) **<0.0001**	1.80 (1.24, 2.62) **0.0019**
P for trend	**<0.0001**	**<0.0001**	**0.0016**
Subgroup analysis stratified by sex			
Men	1.06 (1.02, 1.11) **0.0082**	1.16 (1.10, 1.22) **<0.0001**	1.03 (0.92, 1.15) 0.6165
Women	1.32 (1.26, 1.39) **<0.0001**	1.39 (1.32, 1.47) **<0.0001**	1.21 (1.09, 1.33) **0.0001**

Model 1: No covariates were adjusted. Model 2: Sex, age, and race were adjusted. Model 3: Sex, age, race, BMI, diabetes status, SBP, DBP, ALT, AST, GGT, glycohemoglobin, HDL-cholesterol, total cholesterol, triglyceride, PLT, and serum albumin were adjusted. In the subgroup analysis stratified by sex, the model is not adjusted for sex.

partly mediated the association.[27] The study recruited only 282 individuals, and this result may have been biased with this small sample size. However, this conclusion was supported by a survey conducted in South Korea.[28] The method they used to diagnose NAFLD was abdominal computed tomography (CT). Considering the radioactivity of CT and the high cost of magnetic resonance spectroscopy (MRS), ultrasonography is the most widely used tool to detect fatty liver disease in routine clinical practice. However, it has limited sensitivity and cannot reliably diagnose steatosis at <20%. Fibroscan is an increasingly applied modality for measuring CAP values. A recent study demonstrated that CAP cutoff values ≥274 dB/m identified participants with hepatic steatosis with a sensitivity of 90% compared to liver biopsy.[29]

Similar to our results, other epidemiological studies have provided evidence that there is a gender difference in the prevalence of NAFLD. NAFLD prevalence has been shown to be significantly higher in postmenopausal women but not in premenopausal women.[30–32] However, an independent study indicated high sUA levels correlated with NAFLD risk in all women, regardless of menstrual status[33]. In addition, a large retrospective study conducted in Japan from 2009 to 2012 showed

that the prevalence of NAFLD has increased in general, especially in males.[34] Males had higher prevalence of NAFLD than females within the same age[35] and male sex was a risk factor for fatty liver.[36] The outcomes varied, possibly due to the regions, differing lifestyles between countries and different research methods.

Several studies have proposed possible explanations for the association between uric acid and NAFLD. Exposure to UA resulted in mitochondrial dysfunction and lipogenesis increase in hepatocytes.[37] UA induced pro-inflammatory endocrine imbalance in adipose tissue and acted as pro-oxidant, leading to oxidant stress.[38,39] The intracellular and mitochondrial oxidative stress caused by UA induces disturbances in the Krebs cycle, leading to increased fat synthesis and impaired fatty acid oxidation. Moreover, oxidant stress may be a critical factor in the pathogenesis of NAFLD.[40] The effect of metabolic factors, including visceral obesity, insulin resistance, and diabetes control, on NAFLD might be indirectly mediated through sUA/Cr[41]. The accumulation of visceral adipose tissue stimulates UA synthesis through *de novo* purine synthesis via the pentose phosphate pathway.[42] Reduced glomerular filtration rates results in elevated sUA levels; therefore, sUA/Cr is a more reliable predictor of
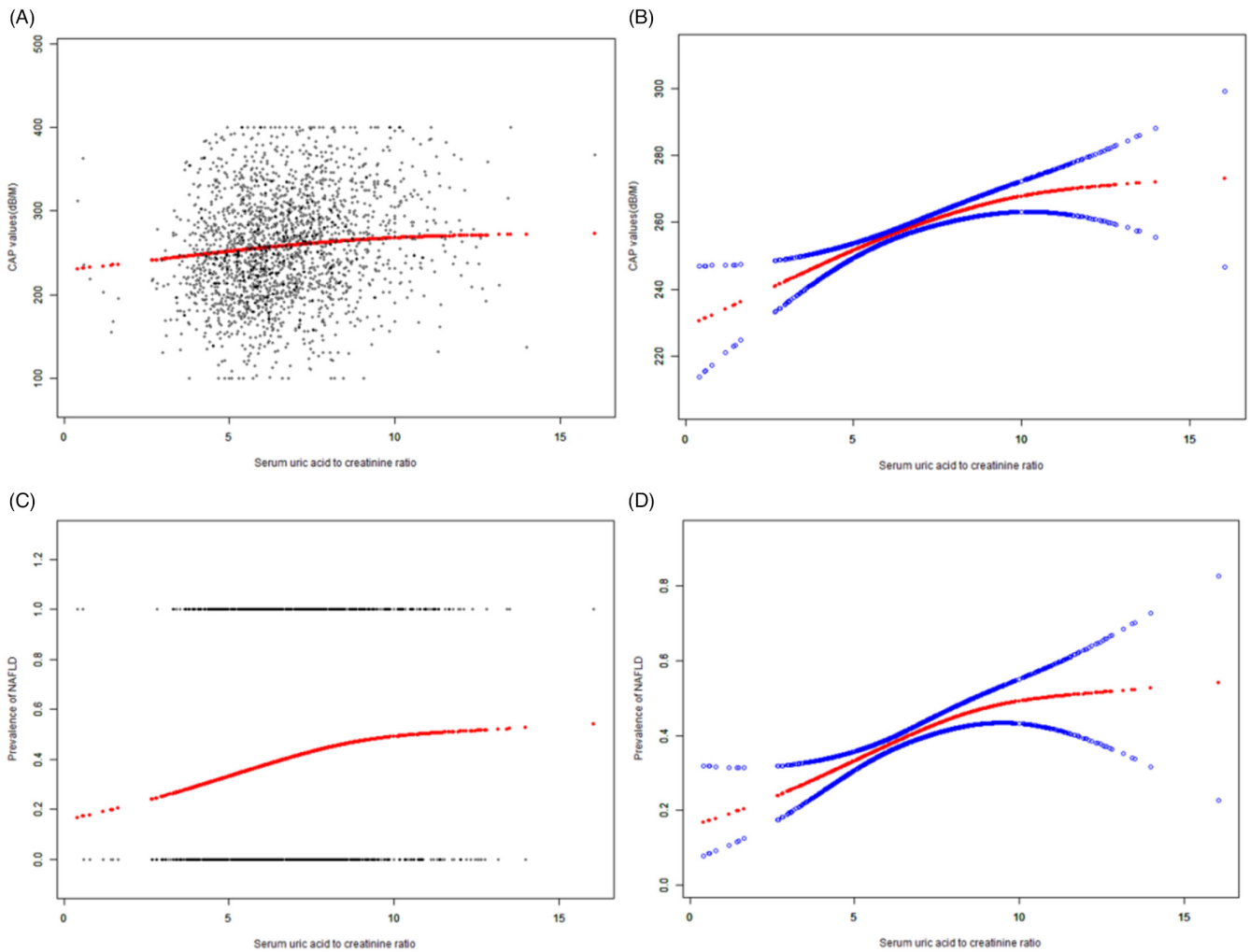
(A)

(B)

(C)

(D)

FIGURE 2 Associations between serum uric acid to creatinine ratio and CAP values or prevalence of NAFLD. (A) and (C): Each black point represents a sample. (B) and (D): Solid redline represents the smooth curve fit between variables. Blue bands represent the 95% of confidence interval from the fit. Adjusted for: sex, age, race, BMI, diabetes status, SBP, DBP, ALT, AST, GGT, glycohemoglobin, HDL-cholesterol, total cholesterol, triglyceride, and serum albumin
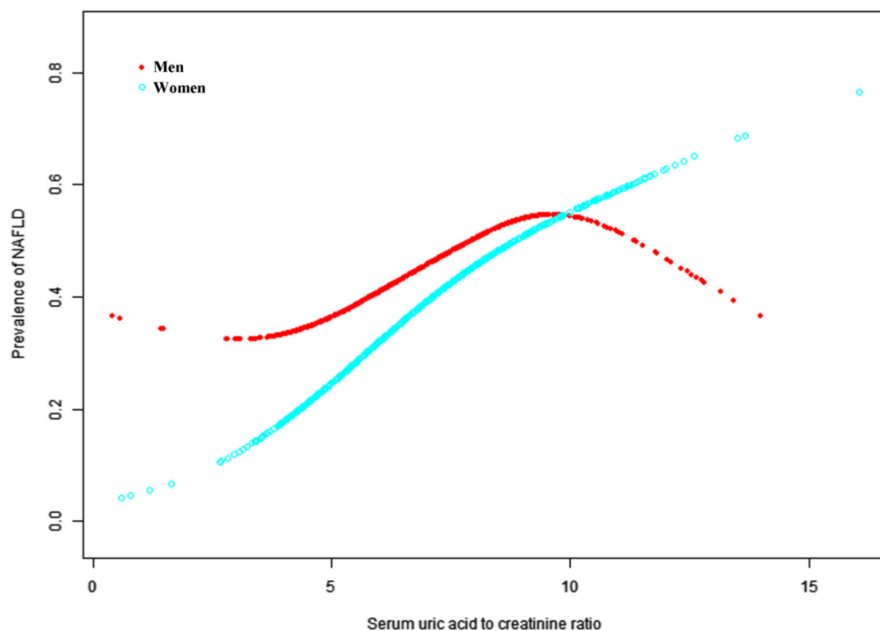
FIGURE 3 Association between sUA/Cr and prevalence of NAFLD stratified by sex. Adjusted for: age, race, BMI, diabetes status, SBP, DBP, ALT, AST, GGT, glycohemoglobin, HDL-cholesterol, total cholesterol, triglyceride, and serum albumin

TABLE 3 Threshold effect analysis of serum uric acid to creatinine ratio and prevalence of NAFLD using the two-piecewise linear regression model

prevalence of NAFLD	Adjusted OR (95% CI), *p*-value
All participants	
Fitting by the standard linear model	1.1 (1.0, 1.2) <0.001
Fitting by the two-piecewise linear model	
Inflection point	9.9
Serum uric acid to creatinine ratio <9.9	1.2 (1.1, 1.3) <0.001
Serum uric acid to creatinine ratio >9.9	0.8 (0.5, 1.1) 0.132
Log likelihood ratio	0.034
Men	
Fitting by the standard linear model	1.0 (0.9, 1.1) 0.679
Fitting by the two-piecewise linear model	
Inflection point	9.7
Serum uric acid to creatinine ratio <9.7	1.1 (1.0, 1.2) 0.126
Serum uric acid to creatinine ratio >9.7	0.5 (0.3, 0.9) 0.014
Log likelihood ratio	0.008

Sex, age, race, BMI, diabetes status, SBP, DBP, ALT, AST, GGT, glycohemoglobin, HDL-cholesterol, total cholesterol, triglyceride, and serum albumin were adjusted. In the analysis for sex, the model was not adjusted for sex.

NAFLD, reducing the confounding effect caused by kidney dysfunction. However, the detailed mechanism of NAFLD development and the role of uric acid require further investigation.

Given the nationally representative and large sample size, our findings can be considered representative of the US. It should be noted that our research had several limitations. First, the nature of this cross-sectional research restrained further exploration of the causal effect of sUA/Cr on NAFLD. Therefore, more mechanistic and longitudinal studies are required to elucidate the detailed relationship between sUA/Cr and NAFLD. Second, although we adjusted for several important covariates, other potential factors such as physical activities, drug use, and menstrual status might have introduced bias. Third, self-reported confounding factors may have been influenced by a self-report bias.

5 | CONCLUSION

We found that higher sUA/Cr was significantly associated with added odds of NAFLD in the general US population. sUA/Cr is a potential biomarker for recognizing patients with NAFLD and indicates worsening disease progression in clinical practice. However, the utility of sUA/Cr, which is superior to other canonical risk factors, requires further validation and optimization.

AUTHOR CONTRIBUTIONS

ORCID

Naibin Yang https://orcid.org/0000-0001-7439-723X

REFERENCES

1. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology.* 2016;64:73-84.
2. Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. *Nat Med.* 2018;24:908-922.
3. European Association for the Study of the L, European Association for the Study of D, European Association for the Study of O. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol.* 2016;64:1388-1402.
4. Rinella ME, Sanyal AJ. Management of NAFLD: a stage-based approach. *Nat Rev Gastroenterol Hepatol.* 2016;13:196-205.
5. Byrne CD, Targher G. NAFLD: a multisystem disease. *J Hepatol.* 2015;62:S47-S64.
6. Mandal AK, Mount DB. The molecular physiology of uric acid homeostasis. *Annu Rev Physiol.* 2015;77:323-345.
7. Aktas G, Kocak MZ, Bilgin S, Atak BM, Duman TT, Kurtkulagi O. Uric acid to HDL cholesterol ratio is a strong predictor of diabetic control in men with type 2 diabetes mellitus. *Aging Male.* 2020;23:1098-1102.
8. Haque T, Rahman S, Islam S, Molla NH, Ali N. Assessment of the relationship between serum uric acid and glucose levels in healthy, prediabetic and diabetic individuals. *Diabetol Metab Syndr.* 2019;11:49.
9. Aktas G, Khalid A, Kurtkulagi O, et al. Poorly controlled hypertension is associated with elevated serum uric acid to HDL-cholesterol ratio: a cross-sectional cohort study. *Postgrad Med.* 2022;134:297-302.
10. Ali N, Mahmood S, Islam F, et al. Relationship between serum uric acid and hypertension: a cross-sectional study in Bangladeshi adults. *Sci Rep.* 2019;9:9061.
11. Kocak MZ, Aktas G, Erkus E, Sincer I, Atak B, Duman T. Serum uric acid to HDL-cholesterol ratio is a strong predictor of metabolic syndrome in type 2 diabetes mellitus. *Rev Assoc Med Bras.* 1992;2019(65):9-15.
12. Ali N, Miah R, Hasan M, et al. Association between serum uric acid and metabolic syndrome: a cross-sectional study in Bangladeshi adults. *Sci Rep.* 2020;10:7841.

13. Kleber ME, Delgado G, Grammer TB, et al. uric acid and cardiovascular events: a mendelian randomization study. *J Am Soc Nephrol.* 2015;26:2831-2838.

14. Ali N, Rahman S, Islam S, et al. The relationship between serum uric acid and lipid profile in Bangladeshi adults. *BMC Cardiovasc Disord.* 2019;19:42.

15. Kurtkulagi O, Tel BMA, Kahveci G, et al. Hashimoto's thyroiditis is associated with elevated serum uric acid to high density lipoprotein-cholesterol ratio. *Rom J Intern Med.* 2021;59:403-408.

16. Kosekli MA, Kurtkulagii O, Kahveci G, et al. The association between serum uric acid to high density lipoprotein-cholesterol ratio and non-alcoholic fatty liver disease: the abund study. *Rev Assoc Med Bras.* 1992;2021(67):549-554.

17. Molla NH, Kathak RR, Sumon AH, et al. Assessment of the relationship between serum uric acid levels and liver enzymes activity in Bangladeshi adults. *Sci Rep.* 2021;11:20114.

18. Wan X, Xu C, Lin Y, et al. Uric acid regulates hepatic steatosis and insulin resistance through the NLRP3 inflammasome-dependent mechanism. *J Hepatol.* 2016;64:925-932.

19. Al-Daghri NM, Al-Attas OS, Wani K, et al. Serum uric acid to creatinine ratio and risk of metabolic syndrome in saudi type 2 diabetic patients. *Sci Rep.* 2017;7:12104.

20. Gu L, Huang L, Wu H, Lou Q, Bian R. Serum uric acid to creatinine ratio: A predictor of incident chronic kidney disease in type 2 diabetes mellitus patients with preserved kidney function. *Diab Vasc Dis Res.* 2017;14:221-225.

21. Li M, Gu L, Yang J, Lou Q. Serum uric acid to creatinine ratio correlates with beta-cell function in type 2 diabetes. *Diabetes Metab Res Rev.* 2018;34:e3001.

22. Boyle M, Masson S, Anstee QM. The bidirectional impacts of alcohol consumption and the metabolic syndrome: cofactors for progressive fatty liver disease. *J Hepatol.* 2018;68:251-267.

23. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American association for the study of liver diseases. *Hepatology.* 2018;67:328-357.

24. Li S, Fu Y, Liu Y, et al. Serum uric acid levels and non-alcoholic fatty liver disease: a two-sample bidirectional mendelian randomization study. *J Clin Endocrinol Metab.* 2022. doi:10.1210/clinem/dgac190. Online ahead of print.

25. Cui Y, Liu J, Shi H, Hu W, Song L, Zhao Q. Serum uric acid is positively associated with the prevalence of nonalcoholic fatty liver in non-obese type 2 diabetes patients in a Chinese population. *J Diabetes Complications.* 2021;35:107874.

26. Sirota JC, McFann K, Targher G, Johnson RJ, Chonchol M, Jalal DI. Elevated serum uric acid levels are associated with non-alcoholic fatty liver disease independently of metabolic syndrome features in the United States: liver ultrasound data from the National Health and Nutrition Examination Survey. *Metabolism.* 2013;62:392-399.

27. Ma C, Liu Y, He S, et al. c-peptide: a mediator of the association between serum uric acid to creatinine ratio and non-alcoholic fatty liver disease in a Chinese population with normal serum uric acid levels. *Front Endocrinol (Lausanne).* 2020;11:600472.

28. Seo YB, Han AL. Association of the serum uric acid-to-creatinine ratio with nonalcoholic fatty liver disease diagnosed by computed tomography. *Metab Syndr Relat Disord.* 2021;19:70-75.

29. Eddowes PJ, Sasso M, Allison M, et al. Accuracy of fibroscan controlled attenuation parameter and liver stiffness measurement in assessing steatosis and fibrosis in patients with nonalcoholic fatty liver disease. *Gastroenterology.* 2019;156:1717-1730.

30. Moon SS. Relationship between serum uric acid level and nonalcoholic fatty liver disease in pre- and postmenopausal women. *Ann Nutr Metab.* 2013;62:158-163.

31. Hamaguchi M, Kojima T, Ohbora A, Takeda N, Fukui M, Kato T. Aging is a risk factor of nonalcoholic fatty liver disease in premenopausal women. *World J Gastroenterol.* 2012;18:237-243.

32. Zhou H, Zhang C, Ni J, Han X. Prevalence of cardiovascular risk factors in non-menopausal and postmenopausal inpatients with type 2 diabetes mellitus in China. *BMC Endocr Disord.* 2019;19:98.

33. Chen Y, Huang Q, Ai P, et al. Association between Serum Uric Acid and Non-Alcoholic Fatty Liver Disease according to Different Menstrual Status Groups. *Can J Gastroenterol Hepatol.* 2019;2019:2763093-2763093.

34. Eguchi Y, Hyogo H, Ono M, et al. Prevalence and associated metabolic factors of nonalcoholic fatty liver disease in the general population from 2009 to 2010 in Japan: a multicenter large retrospective study. *J Gastroenterol.* 2012;47:586-595.

35. Hu X, Huang Y, Bao Z, et al. Prevalence and factors associated with nonalcoholic fatty liver disease in Shanghai work-units. *BMC Gastroenterol.* 2012;12:123-123.

36. Han L, Zhang Y, Yue C, Huang Y, Wu Y, Chen J. Preliminary study on risk factors for morbidity of nonalcoholic fatty liver disease in high-income male population. *J Healthcare Eng.* 2022;2022:9331284-9331210.

37. Lanaspa MA, Sanchez-Lozada LG, Choi YJ, et al. Uric acid induces hepatic steatosis by generation of mitochondrial oxidative stress: potential role in fructose-dependent and -independent fatty liver. *J Biol Chem.* 2012;287:40732-40744.

38. Choi YJ, Shin HS, Choi HS, et al. Uric acid induces fat accumulation via generation of endoplasmic reticulum stress and SREBP-1c activation in hepatocytes. *Lab Invest.* 2014;94:1114-1125.

39. La Grotta R, de Candia P, Olivieri F, et al. Anti-inflammatory effect of SGLT-2 inhibitors via uric acid and insulin. *Cell Mole Life Sci.* 2022;79:273.

40. Spahis S, Delvin E, Borys JM, Levy E. Oxidative stress as a critical factor in nonalcoholic fatty liver disease pathogenesis. *Antioxid Redox Signal.* 2017;26:519-541.

41. Sookoian S, Pirola CJ. The serum uric acid/creatinine ratio is associated with nonalcoholic fatty liver disease in the general population. *J Physiol Biochem.* 2022. doi:10.1007/s13105-022-00893-6. Online ahead of print.

42. Santos RD. Elevated uric acid, the metabolic syndrome and cardiovascular disease: cause, consequence, or just a not so innocent bystander? *Endocrine.* 2012;41:350-352.