Relationship Between Serum Uric Acid Levels and Non-alcoholic Fatty Liver Disease in the Non-Obese Chinese Population: A Secondary Analysis Based on A Cross-Sectional Study

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Research

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is linked to some metabolic disorders. Herein, we explored the relationship of levels of serum uric acid （SUA）with NAFLD in a population of non-obese Chinese.

Methods: This was a cross-sectional study that involved 183,903 Chinese men and women with an average age of 40.98 years who underwent physical examinations at a health screening center at Wenzhou People's Hospital. We defined NAFLD by ultrasound detection of steatosis. We employed univariate analysis along with multivariate Cox proportional hazards analyses to investigate the relationship of SUA level with NAFLD. Moreover, we employed the receiver operating characteristic curve to establish the SUA cutoffs of estimating NAFLD.

Results: Overall, 25,501 participants (13.9%) had NAFLD. The NAFLD ORs were 1.47 (95% CI 1.35 to 1.59), 2.01 (95% CI 1.85 to 2.18) and 2.77 (95% CI 2.55 to 3.02) compared with Q1.AUC values for SUA ratios was 0.728. The optimal SUA level cut-off value for identification of NAFLD was 287.5, with a specificity and a sensitivity of 60.7% and 73.9%, respectively.

Conclusion: High Serum uric acid levels shows positive correlation with NAFLD. SUA constitutes a cheap, simple, non-invasive, as well as a beneficial biomarker that could be utilized to forecast NAFLD in the non-obese Chinese population.

Background

Non-alcoholic fatty liver disease (NAFLD) is becoming more and more prevalent due to higher life standards of people and changes in their diet habits. According to epidemiological surveys, Over the past twenty years, the prevalence of NAFLD has ranged from 24 to 42 percent in western countries and from 5 to 30 percent in Asian countries. [1–3]. Clinically, the diagnosis of NAFLD is defined as the daily alcohol consumption of ≤ 20g per day and ≤ 30g per day in women and men, respectively, and other causes of the disease, including steatogenic drugs, autoimmune, viral, etc., have been excluded [3, 4]. NAFLD is defined by excessive triglyceride accumulation in hepatocytes in excess of 5%. This fat deposition could result in numerous diseases, ranging from simple steatosis to hepatocellular carcinoma, cirrhosis, NASH (non-alcoholic steatohepatitis), as well as liver failure [5]. Mostly, NAFLD is known as a hepatic manifestation of the metabolic syndrome. NAFLD has been shown to be associated to several factors such as hypertension, hyper- uricemia, insulin resistance, dyslipidemia, diabetes, as well as obesity [3, 6–8].

In humans, SUA (serum uric acid) is the final compound of purine catabolism. Elevated SUA levels have been frequently documented to be linked to insulin resistance, atherosclerosis, hypertension, cardiovascular disease, renal disease and obesity [9–12]. Recently evidence from multiple studies has shown that higher level of SUA is often linked to NAFLD [13, 14]. In a meta-analysis involving 100,725

participants, positive correlation was found between elevated levels of SUA and NAFLD, in addition to confounding factors such as gender and age[15].

Nevertheless, the underlying relationship between hyperuricemia and NAFLD remains controversial. Hence, we conducted a cross-sectional secondary study to determine the underlying connection between SUA levels and NAFLD.

Methods

Study population

The methods and the study population presented here are an extension of a previously reported prospective study [16], carried out from January 2010 to December 2014 at the Wenzhou People's Hospital, Wenzhou city, China.. This involved a total of 339,101 patients. Considering that not all the subjects complied with the criteria, only 183903 individuals were enrolled into the cross-sectional study. The exclusion criteria for the study subjects consisted of: excess alcohol consumption of > 140 g per week and > 70 g per week for men and women, respectively, or with a history of viral hepatitis, autoimmune hepatitis history or a history of any other recognized cause of chronic liver disease; a LDL-c of > 3.12 mmol/L and a BMI of ≥ 25 kg/m2; were under hypertensive medication, under diabetic medications, or taking lipid-lowing medications; and lost to follow-up subjects or subjects with missing data. The ethics committee of the Wenzhou People's Hospital provided approval of the study. Informed consent was obtained before the study, as previously reported in the literature [16].

Data Source

Our data was downloaded from the 'DATADRYAD' data resource, and the original data of this website is free to download. We performed secondary analyses on these data taking into consideration the rights of the original author. The Dryad data package was cited when we utilized the data (Dryad data package: Sun DQ, Wu SJ, Liu WY, Wang LR, Chen YR, Zhang DC, Braddock M, Shi KQ, Song D,Zheng MH (2016) Data from: Association of low-density lipoprotein cholesterol within the normal range and NAFLD in the non-obese Chinese population: a cross-sectional and longitudinal study. The variables analyzed were: sex, UA (uric acid), age, AST (aspartate transaminase), low and HDLc, ALT (alanine aminotransferase), BMI, TG, albumin, FPG (fasting plasma glucose), fasting total cholesterol (TC), creatinine, GGT (γ-glutamyl transpeptidase), and blood urea nitrogen.

Ultrasonographic Diagnosis Of Nafld

The NAFLD diagnosis was on the basis of the diagnostic criterion of the Chinese Liver Disease Association[17].

Statistical analysis

In this study, we used EmpowerStats for analysis, and the R statistical package was used to represent the categorical variables and continuous variables with percentage or frequency, which were respectively expressed as mean ± standard deviation (normal distribution) or a median/quartile (skewed distribution). Chi-square test, Kruskal Wallis H test along with one-way ANOVA were employed to determine the statistical difference. We employed the univariate linear regression to assess the relationship of SUA level and NAFLD. $P < 0.05$ signified statistical significance. All the analyses were carried out using the R statistical software package (http://www.R-project.org, The R Foundation), as well as Empower-Stats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA).

Results

Baseline features

The average age of the study subjects was 40.98 ± 14.06 years old, with approximately 49.62% being male. The baseline features are listed in Table 1. 25501 (13.86%) non-obese subjects developed NAFLD. The SUA stratification groups defined by four groups were group Q1: 4-215, group Q2: 216–272, group Q3: 273–340 and group Q4: 341–889. In contrast with subjects in the lowest tertile of the SUA, the following indicators were elevated: Age; HDL-c; BUN; Sex; GGT; LDL-c; FPG; BMI; AST; ALT; ALB; SUA; GLB; CR; TC; TG. The NAFLD incidence significantly increased across the SUA tertiles (3.53% vs. 7.94% vs. 15.92% vs. 27.96% for tertile 1, 2, 3, and 4, respectively).

Table 1
Baseline Features of the study subjects

SUA	Q1	Q2	Q3	Q4	*P*-value
Number	45684	45862	46260	46069	
Age(years, mean ± sd)	38.88 ± 11.24	40.37 ± 13.59	42.02 ± 14.98	42.63 ± 15.68	< 0.001
GGT (U/L, mean ± sd)	18.49 ± 13.98	22.88 ± 21.85	30.29 ± 28.01	41.64 ± 45.10	< 0.001
ALT (U/L, mean ± sd)	15.91 ± 12.58	18.28 ± 17.38	21.69 ± 18.34	24.77 ± 20.98	< 0.001
AST (U/L, mean ± sd)	20.49 ± 8.21	21.66 ± 10.74	23.29 ± 11.63	25.03 ± 13.25	< 0.001
ALB (U/L, mean ± sd)	43.76 ± 2.72	44.28 ± 2.74	44.93 ± 2.79	45.48 ± 2.85	< 0.001
GLB (g/L, mean ± sd)	29.66 ± 3.77	29.59 ± 3.86	29.21 ± 3.87	29.13 ± 3.94	< 0.001
BUN (mmol/L, mean ± sd)	3.96 ± 1.09	4.28 ± 1.16	4.56 ± 1.24	4.83 ± 2.89	< 0.001
CR (mmol/L, mean ± sd)	65.76 ± 13.37	72.55 ± 17.64	83.59 ± 20.24	92.63 ± 25.86	< 0.001
SUA(μmol/L, mean ± sd)	179.57 ± 26.83	243.43 ± 16.35	305.13 ± 19.55	403.24 ± 55.36	< 0.001
FPG(mmol/L, mean ± sd)	5.05 ± 0.77	5.12 ± 0.87	5.21 ± 0.89	5.24 ± 0.86	< 0.001
TG(mmol/L, mean ± sd)	0.96 ± 0.46	1.12 ± 0.66	1.39 ± 0.89	1.87 ± 1.49	< 0.001
HDL-c(mmol/L,mean ± sd)	1.59 ± 0.35	1.50 ± 0.35	1.39 ± 0.34	1.31 ± 0.33	< 0.001
LDL-c(μmol/L,mean ± sd)	2.14 ± 0.47	2.22 ± 0.47	2.30 ± 0.47	2.34 ± 0.46	< 0.001
BMI (kg/m^2, mean ± sd)	20.54 ± 1.99	21.03 ± 2.09	21.74 ± 2.05	22.41 ± 1.88	< 0.001
TC(mmol/L, mean ± sd)	4.46 ± 0.78	4.51 ± 0.78	4.55 ± 0.79	4.65 ± 0.82	< 0.001

Cr, creatinine; GGT, γ-glutamyl transpeptidase; TC, total cholesterol; AST, aspartate aminotransferase; BUN, blood urea nitrogen; SUA, serum uric acid; TG, triglyceride; GLB: globulin; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; BMI, body mass index; ALB, albumin; NAFLD, non-alcoholic fatty liver disease; ALT, alanine aminotransferase.

SUA	Q1	Q2	Q3	Q4	*P*-value
Sex (n%)					< 0.001
Female	42652 (93.36%)	32857 (71.64%)	13968 (30.19%)	3150 (6.84%)	
Male	3032 (6.64%)	13005 (28.36%)	32292 (69.81%)	42919 (93.16%)	
NAFLD(n%)					< 0.001
No	44070 (96.47%)	42220 (92.06%)	38895 (84.08%)	33189 (72.04%)	
Yes	1614 (3.53%)	3642 (7.94%)	7365 (15.92%)	12880 (27.96%)	

Cr, creatinine; GGT, γ-glutamyl transpeptidase; TC, total cholesterol; AST, aspartate aminotransferase; BUN, blood urea nitrogen; SUA, serum uric acid; TG, triglyceride; GLB: globulin; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; BMI, body mass index; ALB, albumin; NAFLD, non-alcoholic fatty liver disease; ALT, alanine aminotransferase.

Univariate Analyses

The univariate analyses data are displayed in Table 2, and demonstrated that age, AST, FPG, sex, GGT, BMI, BUN, ALT, GLB, CR, ALB, TC, TG, HDL-c, LDL-c, BMI along with SUA were positively correlated to NAFLD.

Table 2
Univariate Analysis data

NAFLD	Statistics (mean ± sd)	OR(95% CI) *P*-value
SEX		
Female	92643 (50.38%)	1.0
Male	91260 (49.62%)	4.22 (4.09, 4.35) <0.0001
Age	40.98 ± 14.06	1.03 (1.03, 1.03) <0.0001
GGT	29.25 ± 32.00	1.02 (1.02, 1.02) <0.0001
ALT	20.51 ± 18.17	1.04 (1.03, 1.04) <0.0001
AST	22.80 ± 11.41	1.03 (1.03, 1.03) <0.0001
ALB	44.63 ± 2.85	1.07 (1.06, 1.07) <0.0001
GLB	29.39 ± 3.87	1.01 (1.01, 1.01) <0.0001
BUN	4.41 ± 1.79	1.17 (1.16, 1.18) <0.0001
CR	78.67 ± 22.32	1.01 (1.01, 1.02) <0.0001
SUA	283.13 ± 88.90	1.33 (1.29, 1.39) <0.0001
GLU	5.15 ± 0.85	1.69 (1.66, 1.71) <0.0001
TG	1.34 ± 1.02	2.71 (2.66, 2.75) <0.0001
HDL	1.45 ± 0.36	0.11 (0.10, 0.11) <0.0001
LDL	2.25 ± 0.47	2.54 (2.46, 2.61) <0.0001
BMI	21.43 ± 2.13	2.08 (2.06, 2.11) <0.0001
TC	4.54 ± 0.79	1.64 (1.61, 1.67) <0.0001

The Relationship Of Sua Level With Nafld

We employed univariate linear regression to explore the relationship of SUA levels with NAFLD. Table 3. displayed the non-adjusted as well as adjusted models. In the crude model, SUA exhibited a positive relationship with NAFLD (OR = 2.01, 95% CI: 2.0 to 2.02, P < 0.01). In the minimally adjusted model (adjusted age, sex), no remarkable differences were reported (OR = 2.33, 95%CI: 2.28 to 2.36, P < 0.001). In Fully adjusted model (adjusted sex; BUN; LDL; age; BMI; GGT; TC; AST; GLU; GLB; CR; TG; ALB; HDL; and ALT), no remarkable differences were reported (OR = 1.39, 95%CI: 1.28 to1.46, P < 0.001).

Table 3
Relationship between SUA and NAFLD in different models

Variable	Crude model	Minimally adjusted model (OR, 95%CI, *P*)	Fully adjusted model (OR, 95%CI, *P*)
SUA (per 0.1 change)	2.01 (2.0, 2.02) < 0.0001	2.33 (2.28, 2.36) < 0.0001	1.39 (1.28, 1.46) < 0.0001
SUA (quartile)			
Q1	1.0	1.0	1.0
Q2	2.36 (2.22, 2.50) < 0.0001	1.97 (1.86, 2.10) < 0.0001	1.47 (1.35, 1.59) < 0.0001
Q3	5.17 (4.89, 5.47) < 0.0001	3.46 (3.25, 3.67) < 0.0001	2.01 (1.85, 2.18) < 0.0001
Q4	10.60 (10.04, 11.18) < 0.0001	6.44 (6.05, 6.85) < 0.0001	2.77 (2.55, 3.02) < 0.0001
Crude model: other covariants were adjusted.			
Minimally adjusted model: age and sex were adjusted.			
Fully adjusted model: sex; age; GGT; ALT; AST; ALB; GLB; BUN; CR; GLU; TG; HDL-c; LDL-c; BMI and TC were adjusted.			

Non-linear Association Analysis

Herein, we investigated the non-linear association linking SUA to NADFLD since SUA constitutes a continuous variable as indicated in Fig. 1. Consequently, the connection linking SUA to NAFLD was non-linear (after adjusting GLB, sex, BMI, BUN, age, ALT, ALB, GGT, HDL, CR AST, GLU, TG, LDL, and TC).

The SUA level predictive value for the risk of NAFLD

A ROC curve analysis was employed to compare the predictive values (Fig. 2). It showed that the AUCs for SUA was 0.728. The optimal SUA level threshold value for the identification of NAFLD was 287.5, with a specificity of 60.7% and a sensitivity of 73.9%.

Discussion

Our study demonstrated that SUA levels are associated with NAFLD in a non obese chinese population.. The NAFLD prevalence increased with increments in SUA level. Besides, there were remarkably elevated risks for NAFLD in individuals with high SUA level in the non-obese Chinese population.

NAFLD is among the most frequent causes of chronic liver disease globally. In a recent study, NAFLD has been shown to be the primary cause of chronic liver disease, as well as cirrhosis [18]. Moreover, NAFLD is an independent predisposing factor of not only hepatocellular carcinoma along with cirrhosis, but also of cardiovascular disease, as well as type 2 diabetes [19]. Studies have shown that the predisposing factors for the progression of include insulin resistance, oxidative stress, as well as systemic inflammation [20, 21].

Previous studies have documented the relationship between elevated levels of SUA and NAFLD in the population. Yanru Chen et al reported that high levels of SUA were associated with NAFLD in women and were remarkably also associated with menstrual status [22]. Fengjiang Wei reported that SUA is positively linked to NAFLD and could be applied as an independent indicator of NAFLD[23]. Another contemporary cross-sectional and longitudinal study established a relationship between SUA and the onset and progress of NAFLD.. In addition, the pathogenic influence of SUA on NAFLD is more remarkable in females as compared to males [9]. Alihan Oral et al documented that the UA level was remarkably and independently linked to hepatocellular steatosis, as well as the NAFLD stage in individuals with biopsy-proven NAFLD [8].

The pathogenesis of NAFLD has not yet been fully elucidated. The onset and the progress of NAFLD are caused by a combined effect of genetic and environmental factors. The specific mechanism of the positive relationship of SUA with NAFLD is still unclear, and there are several theories at present. Uric acid stimulates inflammation by producing P38 mitogen-activated protein kinase (MAPK), cyclocyte 2 (COX-2), and chemotaxis to monocyte chemotaxis protein 1. Moreover, Uric acid enhances the lipogenesis of fructose by increasing ketohexokinase (KHK) expression, leading to triglyceride accumulation in liver cells. The presence of insulin resistance in NAFLD may increase serum uric acid by decreasing the rate of uric acid clearance in the proximal renal tubules [24, 25]. Hyperuricemia is a component of metabolic syndrome, and elevated levels of SUA can enhance oxidative stress and increased levels of reactive oxygen species. Another possible explanation for the relationship of SUA levels with NAFLD is the presence of pancreatic hyperleptinemia. Some studies have also shown the role of leptin in hyperuricemia[26]. Multiple studies have documented that leptin triggers oxidative stress in endothelial cells, which increases the SUA level [27]. In addition, leptin participation in sodium tube reabsorption could result in an increase in blood SUA level[28]. The NLRP3 inflammatory complex plays an important role in obesity, insulin resistance, abnormal lipid metabolism, and liver cell steatosis [29]. Increased uric acid levels can cause a significant up-regulation of NLRP3 levels in mouse liver cells[30]. When the level of uric acid increases, the expression of aldose reductase in human liver cells is up-regulated, and then glucose is transferred to the polyol pathway, leading to the production, metabolism and fat accumulation of endogenous fructose[31].

The relationship of SUA level with NAFLD implies that uric acid has a vital role in the occurrence and progress of NAFLD. Uric acid is considered as a natural scavenger of peroxynitrite, as well as peroxynitrite derived free radicals [32]. For a long time, animal experiments and clinical studies have recognized the increase of systemic oxidative stress in NAFLD patients[33]. The increase in SUA may show a

compensatory mechanism that counteracts the increase in NAFLD-related oxidative stress. NAFLD has been shown to increase the risk of cardiovascular disease[34]. Simultaneously, uric acid can stimulate the proliferation of vascular smooth muscle, as well as mediate vascular endothelial dysfunction [35], which could result in vascular inflammation and arterial damage, hence elevating the risk of cardiovascular disease. On this basis, treatment by lowering SUA may have a beneficial effect on reducing cardiovascular disease risk in individuals with NAFLD.

There are several potential limitations to our study that need to be noted. Firstly, dietary factors which might affect SUA levels such asmeat, and fructose intake were not adjusted for the study.,. Secondly, for all the included studies, NAFLD was confirmed by ultrasonography, and there was no histological diagnosis of fatty liver. Although liver ultrasonography is not the gold standard, it is the first-line diagnostic imaging approach for NAFLD. Liver ultrasonography has the characteristics of non-invasiveness and safety. Thirdly, the subjects of this study are mostly residents of Wenzhou, China and the relationship of NAFLD with SUA levels may be different due to different lifestyles and dietary habits in other places. Finally, the association of NAFLD with SUA may be impacted by other unmeasured confounders.

Conclusion

In summary, high SUA levels showed positive correlation with NAFLD in a non-obese Chinese population.. SUA is a simple, cheap, non-invasive, as well as useful clinical biomarker that could be employed to predict NAFLD. NAFLD prevention is critical for the general health of the population. In addition, serum uric acid can used be a prospective NAFLD therapeutic target.

Abbreviations

Cr: creatinine; GGT: γ-glutamyl transpeptidase; TC: total cholesterol; AST: aspartate aminotransferase; BUN: blood urea nitrogen; SUA: serum uric acid; TG: triglyceride; GLB: globulin; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; FPG: fasting plasma glucose; BMI:body mass index; ALB: albumin; NAFLD: non-alcoholic fatty liver disease; ALT: alanine aminotransferase.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

GSQ contributed to the drafting of the manuscript. RK and LJS analysed and interpreted the data. YSA contributed to the conception and critical revision of the manuscript, analysis and interpretation of the

data and approved the final version of the submitted manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

Data can be downloaded from the ‘DATADRYAD’ database (www. Datadryad.org).

Ethics approval and consent to participate

This study was a second analysis of existing data; the data were anonymous,

and the requirement for informed consent was therefore waived.

Consent for publication

Not applicable.

Competing interests

Authors declare that they have no competing interests

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Figures

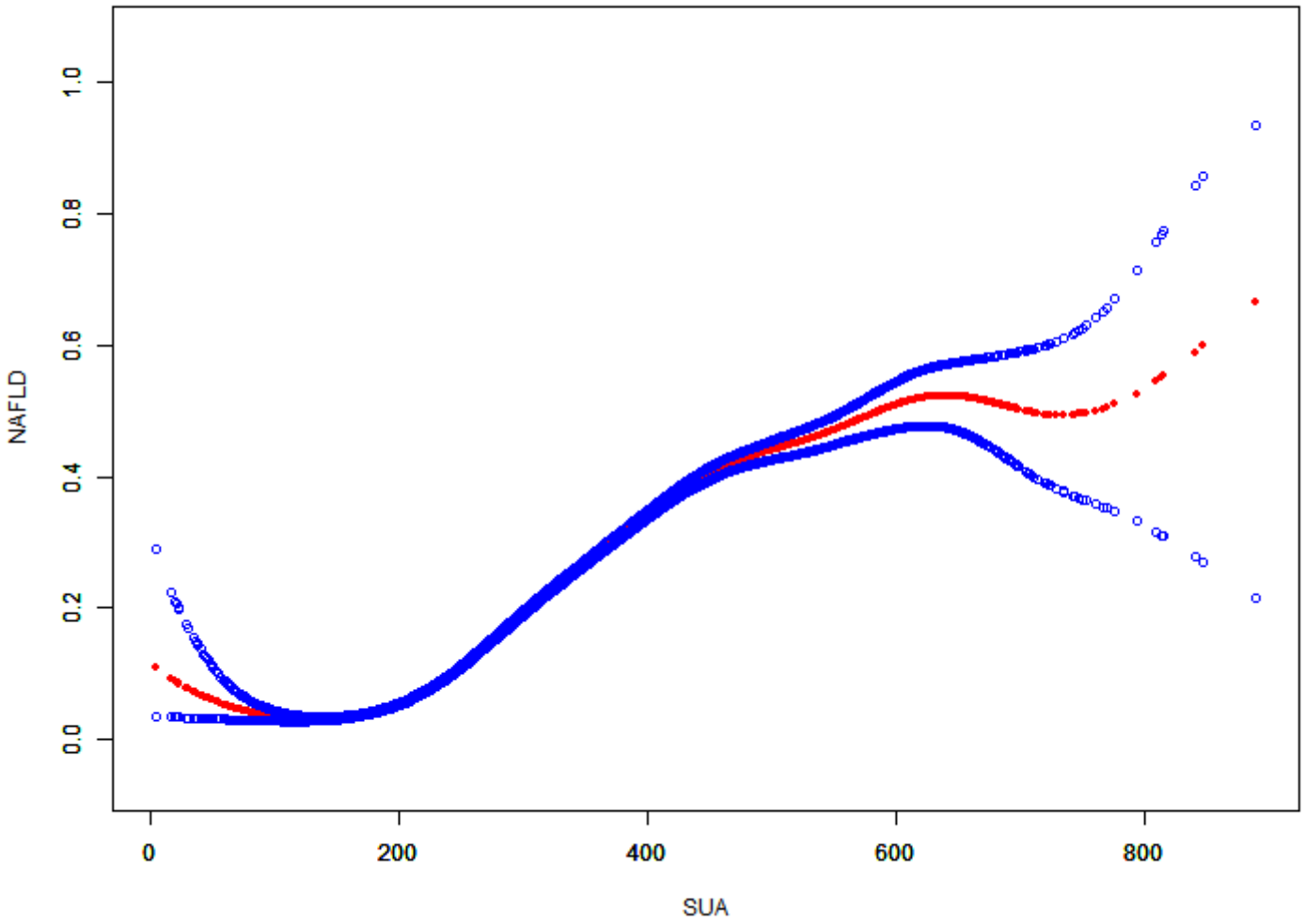

Figure 1

The relationship between SUA level and NAFLD. A nonlinear association of SUA with NAFLD was detected after adjusting for sex, age, GGT, ALT, AST, ALB, GLB, BUN, CR, GLU, TG, HDL, LDL, BMI and TC.

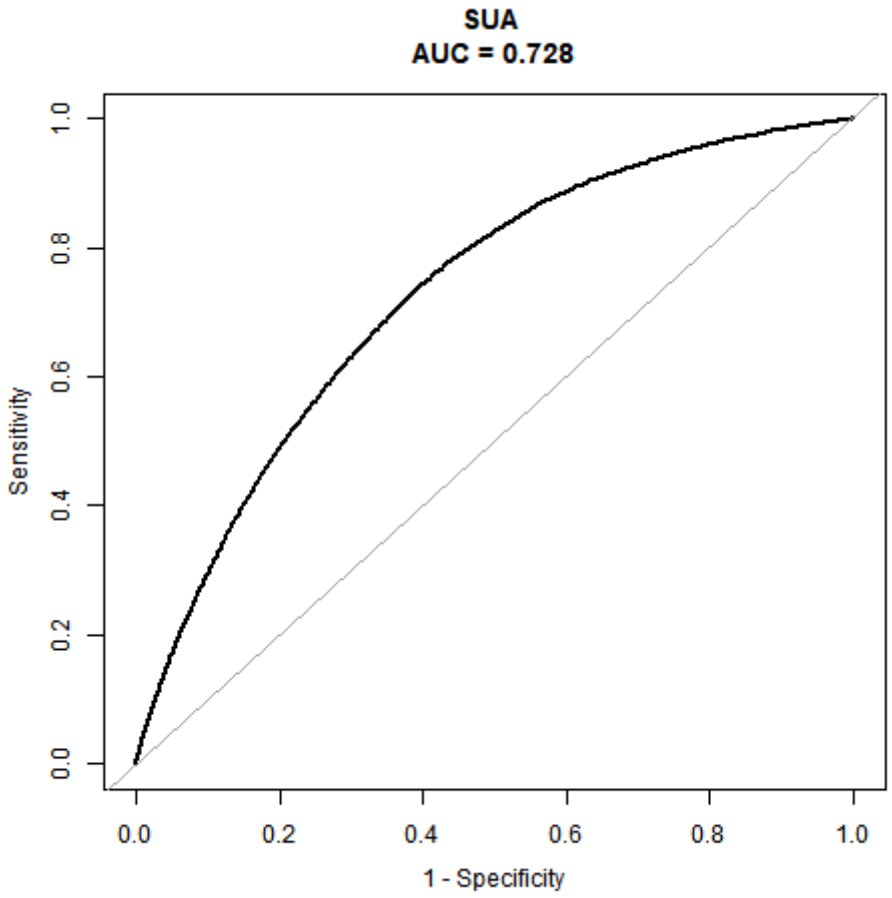

Figure 2

Receivers Operating Characteristic (ROC) Curve for detecting NAFLD based on the Serum Uric Acid