Higher Serum Uric Acid Level Predicts Non-alcoholic Fatty Liver Disease: A 4-Year Prospective Cohort Study

Fengjiang Wei1†, Jiaxin Li2†, Chen Chen3, Kai Zhang3, Li Cao3, Ximo Wang2*, Jun Ma4*, Shuzhi Feng3* and Wei-Dong Li1*

1Department of Genetics, College of Basic Medical Sciences, Tianjin Medical University, Tianjin, China, 2Tianjin Medical University, Tianjin, China, 3Tianjin Medical University General Hospital, Tianjin, China, 4Department of Health Statistics, College of Public Health, Tianjin Medical University, Tianjin, China

Background: Non-alcoholic fatty liver disease (NAFLD) has become a serious disease affecting people’s health in the world. This article studies the causal relationship between NAFLD and serum uric acid (SUA) levels.

Methods: During the 4 years of follow-up in a fixed cohort that was established in 2014, 2,832 follow-up subjects without NAFLD were finally included in this study. The study population was divided into four groups according to baseline SUA levels. Cox hazard regression model and Kaplan–Meier survival curves analysis were used to predict risk factors of NAFLD. The receiver operating characteristic curve analyses were used to determine SUA cutoffs for predicting NAFLD.

Results: The cumulative prevalence rates of NAFLD were 33.97% (962/2,832), 38.93% (758/1,947) in males and 23.05% (204/885) in females. The results showed that males had a higher incidence of NAFLD \( \chi^2 = 68.412, P = 0.000 \). The Cox regression analysis disclosed that the hazard ratios of NAFLD [95% confidence interval (CI)] were 1.431 (95% CI, 1.123–1.823), 1.610 (95% CI, 1.262–2.054), and 1.666 (95% CI, 1.287–2.157) across the second to the fourth quartile of SUA adjusted for other confounders. The SUA cutoffs, sensitivity, specificity, and area under the curve (AUC) (95% CI) were ≥288.5 µmol/L, 75.5%, 46.5%, 0.637(0.616–0.658), respectively, for total; ≥319.5 µmol/L, 65.8%, 48.4%, 0.590 (0.564–0.615), respectively, for males; and ≥287.5 µmol/L, 51.0%, 75.6%, 0.662 (0.619–0.704), respectively, for females. Kaplan–Meier survival curves revealed that individuals with higher SUA level had an increased risk of NAFLD in comparison to lower SUA level (\( P = 0.000 \)).

Conclusion: Serum uric acid is positively correlated with NAFLD, and elevated SUA level can be used as an independent predictor for NAFLD.

Keywords: non-alcoholic fatty liver disease, hyperuricemia, serum uric acid, risk factor, cohort study
INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a very common chronic liver disease. The prevalence of NAFLD in the general population ranges from 20 to 30%, but its prevalence in the middle-aged population of Western countries can reach 46%, and to 42% in Asian countries (1–6). As a component of metabolic syndrome (MetS), NAFLD is closely related to obesity, insulin resistance (IR), type 2 diabetes mellitus (T2DM), cardiovascular disease, and other chronic diseases (7, 8).

Serum uric acid (SUA) maintains balance in the body through a series of precise regulation mechanisms. Previously, numerous studies have suggested that the level of SUA will increase with the development of chronic metabolic diseases such as cardiovascular disease (9, 10), T2DM (11), and MetS (12–14). Studies in European or Korean populations have shown that SUA is associated with the occurrence and progression of NAFLD. A meta-analysis involving 55,573 participants indicated that the level of SUA was still related to NAFLD except for the confounding factors of sex, age, and MetS (15). A study that included 6,967 participants has the same conclusion (16). But in a cohort study involving 7,564 atomic bomb survivors, this association was found to be not statistically significant (17). In a cross-sectional study including 129 children and adolescents, the association between SUA and NAFLD was not observed (18). In a Chinese prospective cohort study (PMMJS) among 841 NAFLD males, they arrived to the conclusion that the level of SUA was negatively correlated with the remission rate of NAFLD (19). A cross-sectional study of 541 patients with type 2 diabetes showed that the association between SUA and NAFLD was found only in males, but not in females (20). The reason for different conclusions may be different sample size, population, definitions of hyperuricemia, lifestyle, and eating habits.

However, the causal relationship between hyperuricemia and NAFLD is controversial. Therefore, we established a prospective cohort study in the Chinese population to determine the causal relationship between SUA level and NAFLD except for the confounding factors of sex, age, and MetS. We set up a follow-up cohort from April 2014 through October 2018. A total of 24,102 participants were enrolled in our cohort; after excluding the data that at least 1 year without a physical examination or with no test for SUA or one of the covariate variables, 4,418 subjects (3,222 men and 1,196 women) completed all inspections and measurements. Excluding 1,586 subjects (1,275 men and 311 women) with NAFLD at baseline examination, 2,832 subjects remained (1,947 men and 885 women, with an average age of 64.54 ± 14.66 years and 59.32 ± 15.83 years, respectively) in the study (Figure 1). Exclusion criteria were as follows: (1) already have NAFLD disease; (2) intake of alcohol >140 g/wk for males and 70 g/wk for females; (3) with a history of chronic liver disease.

MATERIALS AND METHODS

Participants

We set up a follow-up cohort from April 2014 through October 2018. A total of 24,102 participants were enrolled in our cohort; after excluding the data that at least 1 year without a physical examination or for SUA or one of the covariate variables, 4,418 subjects (3,222 men and 1,196 women) completed all inspections and measurements. Excluding 1,586 subjects (1,275 men and 311 women) with NAFLD at baseline examination, 2,832 subjects remained (1,947 men and 885 women, with an average age of 64.54 ± 14.66 years and 59.32 ± 15.83 years, respectively) in the study (Figure 1). Exclusion criteria were as follows: (1) already have NAFLD disease; (2) intake of alcohol >140 g/wk for males and 70 g/wk for females; (3) with a history of chronic liver disease.
RESULTS
The Univariate Analyses of Characteristics
The univariate analyses of factors associated with NAFLD are shown in Table 1. There was no significant difference in mean age, eGFR, TBIL, DBIL, GLB, BUN, and TC between the two groups. Gender, BMI, SBP, DBP, SUA, ALT, TP, ALB, SCR, FBG (fasting plasma glucose), HbA1c, TGs, HDL-C, and LDL-C were associated with NAFLD in univariate analysis (P < 0.05). The NAFLD group had higher BMI, SBP, DBP, ALT, TP, ALB, SCR, TGs, FBG, LDL-C, and HbA1c and lower HDL-C. The results showed that the NAFLD group had higher SUA level (Table 1).

Association of SUA Level With Prevalence Rate of NAFLD
The cumulative prevalence rates of NAFLD after 4 years' follow-up was 33.97% (962/2,832): 38.93% (758/1,947) in males and 23.05% (204/885) in females, respectively (Table 2). Males had a higher incidence of NAFLD ($\chi^2 = 49.860$, $P = 0.000$). The prevalence rates of HUA (Hyperuricemia) identified by baseline SUA levels were 11.2% (318/2,832), 13.7% (266/1,947) in males, 6.1% (52/855) in females, respectively. The prevalence rates of HUA were higher in males ($\chi^2 = 68.412$, $P = 0.000$). The study population was divided into four quartiles by their SUA levels. As shown in Table 2, the overall prevalence of NAFLD was 18.51, 31.48, 40.06, and 45.62%, respectively, from the first quintile to the fourth in total. The results showed that the prevalence of NAFLD was significantly different among four quartiles ($\chi^2 = 130.843$, $P = 0.000$). The cumulative prevalence rates of NAFLD have a similar tendency in males and females. The results showed that SUA level was related to the prevalence of NAFLD.

The Cox Regression Analysis of SUA Levels for Incidence NAFLD
The Cox regression analysis was performed to evaluate association between SUA and NAFLD. Fourteen variables including gender, age, BMI, SBP, DBP, ALT, TP, SCR, ALB, FBG, HbA1c, TGs, HDL-C, and LDL-C were set as the independent variables, and with or without NAFLD as the dependent variable (Table 3). As shown in Table 3, among total study population, during the 4-year follow-up period from the index date, using the lowest SUA quintiles as reference, the crude HRs of NAFLD (95% CI) were 1.803 (95% CI, 1.453–2.239), 2.418 (95% CI, 1.964–2.978), and 2.864 (95% CI, 2.335–3.513) across the second to the fourth quartile of SUA in model 1 (unadjusted baseline values of variables); the HRs of NAFLD (95% CI) were 1.667 (95% CI, 1.342–2.094), 2.159 (95% CI, 1.729–2.696), and 2.487 (95% CI, 1.986–3.116) across the second to the fourth quartile of SUA in model 2 (model 1 adjusted for age and gender); the HRs of NAFLD (95% CI) were 1.431 (95% CI, 1.123–1.823), 1.610 (95% CI, 1.287–2.157) across the second to the fourth quartile of SUA in model 3 (model 2 further adjusted for other confounders). The sex-specific association analysis between HUA and NAFLD has a similar tendency in females (Table 4, Models 4–6) and males (Table 5, Models 7–9). Notably, HUA was found to be an independent risk factor for NAFLD.
TABLE 1 | The univariate analyses of demographic and laboratory characteristics of patients with or without NAFLD.

| Variable                  | NAFLD       | t/χ² | P   |
|---------------------------|-------------|------|-----|
| Gender (male/female)      | 1,189/681   |      |     |
| Age (y)                   | 63.02 ± 15.67 | 0.555 | 0.579 |
| BMI (kg/m²)               | 23.02 ± 2.69 | −22.571 | 0.000 |
| eGFR (mL/min per 1.73 m²) | 88.79 ± 18.51 | −0.510 | 0.610 |
| SBP (mm Hg)               | 134.67 ± 20.95 | −5.085 | 0.000 |
| DBP (mm Hg)               | 73.38 ± 11.70 | −6.664 | 0.000 |
| SUA (µmol/L)              | 302.93 ± 77.09 | −11.839 | 0.000 |
| ALT (IU/L)                | 14.87 ± 9.07 | −7.643 | 0.000 |
| TBIL (µmol/L)             | 13.30 ± 5.43 | −1.294 | 0.196 |
| DBIL (µmol/L)             | 4.73 ± 1.65 | 0.243 | 0.808 |
| TP (g/L)                  | 73.08 ± 3.84 | −2.096 | 0.036 |
| ALB (g/L)                 | 46.24 ± 2.44 | −3.477 | 0.001 |
| GLB (g/L)                 | 26.84 ± 3.41 | 0.074 | 0.941 |
| BUN (µmol/L)              | 5.23 ± 1.45 | −0.847 | 0.397 |
| SCR (µmol/L)              | 77.41 ± 17.74 | −3.615 | 0.000 |
| FBG (µmol/L)              | 5.38 ± 1.04 | −3.735 | 0.000 |
| HbA1c(%)                  | 5.81 ± 0.68 | −2.951 | 0.003 |
| TC (mmol/L)               | 5.00 ± 0.94 | −0.887 | 0.375 |
| TGs (mmol/L)              | 1.12 ± 0.57 | −13.694 | 0.000 |
| HDL-C (mmol/L)            | 1.52 ± 0.42 | 0.310 | 0.552 |
| LDL-C (mmol/L)            | 2.98 ± 0.83 |      |     |

BMI, body mass index; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; SUA, serum uric acid; ALT, alanine aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; TP, plasma total protein; GLB, globulin; ALB, albumin; BUN, blood urea nitrogen; SCR, serum creatinine; FBG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; TGs, plasma levels of triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Kaplan–Meier Survival Curves for NAFLD Among SUA Quartiles

As shown in Figure 2, Kaplan–Meier survival curves illustrate the differences in prevalence of NAFLD between different SUA quartiles. Among the total study population (Figure 2A), Kaplan–Meier survival curves revealed that individuals with higher SUA level had an increased risk of NAFLD in comparison to lower SUA level (P = 0.000). Similar results were found among males (Figure 2B) and females (Figure 2C). The log-rank test showed significance for all the SUA quartiles, the first quartile showed the lowest disease hazard for NAFLD, and the fourth quartile showed the highest disease hazard. The log-rank test showed that in the third quartile vs. the fourth quartile in total and males (Figures 2A,B), and the first quartile vs. the second quartile, as well as the second quartile vs. the third quartile in females (Figure 2C), there were no significant differences. However, other quartiles displayed significant difference. The above results showed that there is a dose-effect relationship between hyperuricemia and NAFLD; NAFLD onset significantly changed with SUA quartiles.

TABLE 2 | Association of SUA level with prevalence rate of NAFLD.

| Quartiles | NAFLD | Total | Prevalence rates (%) | χ² | P   |
|-----------|-------|-------|----------------------|----|-----|
| No        | Yes   |       |                      |    |     |
| Quartile 1 | 568 | 129  | 697                  | 18.51 |
| Quartile 2 | 492 | 226  | 718                  | 31.48 |
| Quartile 3 | 425 | 284  | 709                  | 40.06 | 0.000 |
| Quartile 4 | 385 | 323  | 708                  | 45.62 |
| Quartile 4 | 258 | 230  | 488                  | 47.15 |

Quartiles of SUA were defined as follows: first quartile, <258 µmol/L; second quartile, 258–310 µmol/L; third quartile, 310–362 µmol/L; and fourth quartile, ≥362 µmol/L. Total, Quartiles based on serum uric acid levels: first quartile, <258 µmol/L; second quartile, 258–310 µmol/L; third quartile, 310–362 µmol/L; and fourth quartile, ≥362 µmol/L.

TABLE 3 | The Cox regression analysis of SUA levels for incidence NAFLD during 4 years of follow-up among 2,832 subjects without NAFLD at the entry examination (total).

| Model | N | HR | 95% CI | P   |
|-------|---|----|--------|-----|
| Model 1: unadjusted baseline values of variables | | | | |
| Quartile 1 | 697 | — — | — | 0.000 |
| Quartile 2 | 718 | 1.803 | 1.453–2.329 | 0.006 |
| Quartile 3 | 709 | 2.418 | 1.964–2.978 | 0.000 |
| Quartile 4 | 708 | 2.864 | 2.335–3.513 | 0.000 |
| SUA as a continuous variable (µmol/L) | 2.832 | 1.004 | 1.004–1.005 | 0.005 |

Model 2: model 1 adjusted for age and gender

| Model | N | HR | 95% CI | P   |
|-------|---|----|--------|-----|
| Quartile 1 | 697 | — — | — | 0.000 |
| Quartile 2 | 718 | 1.667 | 1.342–2.094 | 0.000 |
| Quartile 3 | 709 | 2.159 | 1.729–2.696 | 0.000 |
| Quartile 4 | 708 | 2.487 | 1.986–3.116 | 0.000 |
| SUA as a continuous variable (µmol/L) | 2.832 | 1.004 | 1.003–1.005 | 0.005 |

Model 3: model 2 further adjusted for other confounders

| Model | N | HR | 95% CI | P   |
|-------|---|----|--------|-----|
| Quartile 1 | 697 | — — | — | 0.000 |
| Quartile 2 | 718 | 1.431 | 1.123–1.823 | 0.004 |
| Quartile 3 | 709 | 1.610 | 1.262–2.054 | 0.000 |
| Quartile 4 | 708 | 1.666 | 1.287–2.157 | 0.000 |
| SUA as a continuous variable (µmol/L) | 2.832 | 1.002 | 1.001–1.003 | 0.000 |

Model 1 (baseline): Quartiles based on SUA levels: first quartile, <258 µmol/L; second quartile, 258–310 µmol/L; third quartile, 310–362 µmol/L; and fourth quartile, ≥362 µmol/L. Model 2: model 1 adjusted for age and gender. Model 3: model 2 was further adjusted for BMI, SBP, DBP, ALT, TP, ALB, SCR, FBG, HbA1c, TGs, HDL-C, LDL-C. P < 0.05 was considered statistically significant.
TABLE 4 | The Cox regression analysis of SUA levels for incidence NAFLD during 3 years of follow-up among 885 subjects without NAFLD at the entry examination (females).

| Model | N  | HR  | 95% CI | P     |
|-------|----|-----|--------|-------|
| Model 4: unadjusted baseline values of variables |   |     |        |       |
| Quartile 1 | 219 | —   | —      | 0.000 |
| Quartile 2 | 222 | 1.502 | 0.922–2.447 | 0.103 |
| Quartile 3 | 222 | 2.091 | 1.317–3.319 | 0.002 |
| Quartile 4 | 222 | 3.459 | 2.240–5.341 | 0.000 |
| SUA as a continuous variable (µmol/L) | 885 | 1.006 | 1.005–1.008 | 0.000 |
| Model 5: model 1 adjusted for age |   |     |        |       |
| Quartile 1 | 219 | —   | —      | 0.000 |
| Quartile 2 | 222 | 1.435 | 0.880–2.340 | 0.148 |
| Quartile 3 | 222 | 1.933 | 1.215–3.078 | 0.005 |
| Quartile 4 | 222 | 3.001 | 1.929–4.670 | 0.000 |
| SUA as a continuous variable (µmol/L) | 885 | 1.005 | 1.004–1.007 | 0.000 |
| Model 6: model 2 further adjusted for other confounders |   |     |        |       |
| Quartile 1 | 219 | —   | —      | 0.009 |
| Quartile 2 | 222 | 1.425 | 0.803–2.529 | 0.226 |
| Quartile 3 | 222 | 1.954 | 1.150–3.322 | 0.013 |
| Quartile 4 | 222 | 2.495 | 1.481–4.202 | 0.001 |
| SUA as a continuous variable (µmol/L) | 885 | 1.004 | 1.002–1.007 | 0.001 |

Model 4 (baseline): Quartiles based on SUA levels: first quartile, <222 µmol/L (<P25); second quartile, 222–257 µmol/L (P25<P75); third quartile, 257–301 µmol/L (P75<P90); and fourth quartile, ≥301 µmol/L (≥P90). Model 5: model 1 adjusted for age. Model 6: model 2 was further adjusted for BMI, SBP, DBP, ALT, TP, SCR, ALB, FBG, HbA1C, TGs, HDL-C, LDL-C. *P < 0.05 was considered statistically significant.

ROC Curve of the SUA Level as a Predictor of NAFLD

Receiver operating characteristic analysis was used and calculated specificity and sensitivity of the prediction. The best cutoff value of SUA level to predict the incidence of NAFLD was ≥288.5 µmol/L, the AUC (95% CI) was 0.637 (0.616–0.658) with a sensitivity of 75.5% and specificity of 46.5% in total, as seen in Figure 3A. The best cutoff value was ≥319.5 µmol/L; the AUC (95% CI) was 0.590 (0.564–0.615) with a sensitivity of 65.8% and specificity of 48.4% in males, as seen in Figure 3B. The best cutoff value was ≥287.5 µmol/L; the AUC (95% CI) was 0.662 (0.619–0.704) with a sensitivity of 51.0% and specificity of 75.6% in females, as seen in Figure 3C.

DISCUSSION

Non-alcoholic fatty liver disease has a higher prevalence in the Western world, and which is becoming an emerging health threat in Asia (25). We prospectively followed 2,832 subjects who were free from NAFLD at baseline examination from April 2014 through October 2018. Our results show that SUA level can be used as an independent predictor of NAFLD in a fixed cohort Chinese population.

In cross-sectional and prospective studies, SUA level was a risk factor for NAFLD. In a study including 242 male patients with NAFLD [102 with non-alcoholic steatohepatitis (NASH) and 140 with simple steatosis (SS)], the study found that SUA was associated with early liver damage in patients with NAFLD, and SUA levels were significantly higher in subjects with NASH than those of SS (26). More recently, a cross-sectional and longitudinal population study showed that SUA is related to the occurrence and development of NAFLD. Additionally, the pathogenic effect of SUA levels on fatty liver is more significant in female population than in males (27). In a meta-analysis of 11 studies that were done in various countries, including China, Korea, Japan, India, and United States, they found a significant association between SUA and NAFLD. The risk of NAFLD was increased almost 2-fold in the highest SUA group compared to the lowest group (28). As expected, we performed the Cox regression analysis, and our results showed that the HRs of NAFLD (95% CI) were 1.431 (95% CI, 1.123–1.823), 1.610 (95% CI, 1.262–2.054), and 1.666 (95% CI, 1.287–2.157) across the second to the fourth quartile of SUA vs. the first quartile after adjusting for other confounders. The sex-specific association analysis between HUA and NAFLD has a similar tendency in males and females. Our findings suggest that elevated SUA levels promote the development of NAFLD, and which is consistent with the previous hypothesis that SUA might be an important contributor to the development of NAFLD.

In our studies, the Kaplan–Meier survival curves revealed that individuals with higher SUA level had an increased risk of NAFLD in comparison to lower SUA level (P < 0.001). HUA predicted higher incidences of NAFLD in a dose-dependent manner; NAFLD onsets significantly differed across SUA quartiles. Our results are consistent with other studies.
conducted on Chinese population. In study of two distinct ethnic groups, Uyghur and Han in northwest China, the major findings were that SUA concentrations and NAFLD were correlated in both populations, but Uyghurs had a higher prevalence of NAFLD. This finding may indicate that some related factors such as lifestyle, dietary habits, and genetic susceptibility play a more important role in the pathogenesis of NAFLD in Uyghurs than in Hans (29). In a Chinese cross-sectional study including 8,925 subjects, the results also demonstrated the effect of SUA on NAFLD (30). In the Cardiometabolic Risk in Chinese study, they found strong positive associations between elevated
SUA levels and NAFLD risk in the non-hypertensive Chinese adults, independent of other metabolic changes (31). Another prospective study that followed 6,890 men and women found a positive correlation between SUA and NAFLD (32).

The pathogenesis of NAFLD is very complex, and its specific causes are not fully explained. The occurrence and development of NAFLD are the result of genetic and environmental factors. Several major hexose–uric acid transporters, including SLC2A9 and ABCG2, are highly expressed in the liver and kidney (33, 34). In our previous studies, we found that the plasma uric acid level was dynamically coupled with the HbA1c level, depending on different stages of normal, impaired glucose tolerance, and diabetes. It seems uric acid is a regulator, or at least regulated, by the plasma glucose level (35). The first pathogenic mechanism was metabolic disturbances. Oxidative stress and lipid peroxidation were the main causes of fatty liver (36), whereas SUA was the main antioxidant in vivo, which was significantly associated with the degree of steatosis and the greater odds of advanced lobular inflammation of NAFLD (37). Another pathogenic mechanism was IR. Hyperuricemia is a component of MetS; the increase in SUA level could promote oxidative stress and reactive oxygen species level. Because of the above reasons, it would cause IR and abnormal blood glucose metabolism in the body and then cause the occurrence of NAFLD (38). Lanaspa et al. (39) found that uric acid can directly stimulate hepatic fat accumulation. This is a good supplement to the pathogenesis of NAFLD caused by SUA.

CONCLUSION

In summary, we conducted a follow-up study in the Chinese population, and the results showed that after excluding other confounding factors there was a causal relationship between SUA level and NAFLD. Serum uric acid can be used as an independent predictor of NAFLD. There was a dose–effect relationship between hyperuricemia and NAFLD; NAFLD onsets significantly changed with SUA quartiles. Further studies on the mechanism of NAFLD caused by SUA will not only broaden our comprehension of the NAFLD mechanisms, but also assist in the eventual development of new prevention and treatment strategies for the NAFLD.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Human Ethics Committee of Tianjin Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

W-DL conceived and designed the study. W-DL and FW wrote the manuscript. JM, SF, FW, CC, KZ, LC, JL, and XW collected subjects and clinical data. FW and JL analyzed the data. All authors have reviewed the manuscript.

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