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The severity of NAFLD is associated with the risk of urolithiasis

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ABSTRACT

Background and aims: Population-based studies suggest a strong association between the presence of nonalcoholic fatty liver disease (NAFLD) and an increased risk of urolithiasis. However, the available information on the association of the severity of NAFLD with urolithiasis is limited. We hypothesised a link between the severity of NAFLD and the risk of urolithiasis.

Methods: We recruited 1527 adult patients with NAFLD who completed a comprehensive health checkup. The severity of NAFLD was measured with AST to platelet ratio (APRI score). Logistic regression analysis was used to detect the association of APRI score with the risk of urolithiasis among NAFLD patients. ROC analysis was used to assess the diagnostic value of APRI score for identifying urolithiasis among NAFLD patients.

Results: Multivariate analysis showed three independent risk factors for urolithiasis: obesity (OR 2.06 95%CI 1.35–3.13), APRI score (OR 1.29 95%CI 1.05–1.59), and serum uric acid (OR 1.07 95%CI 1.05–1.09), suggesting an independent association between the noninvasive staging of liver fibrosis and the risk of urolithiasis in NAFLD patients. A three-variable model (obesity, APRI score, and serum uric acid) with an AUROC of 0.73 (95% CI 0.70–0.75) was significant in identifying urolithiasis.

Conclusions: The severity of NAFLD is associated with the risk of urolithiasis among NAFLD patients. Moreover, a three-variable model (obesity, APRI score, serum uric acid) could serve as a useful tool for identifying individuals at high risk for urolithiasis in these patients.

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Introduction

Nonalcoholic liver disease (NAFLD) is the most common form of chronic fatty liver diseases in the world, with an estimated prevalence of 19 ~ 46%, increasing rapidly due to the global epidemics of type 2 diabetes mellitus (T2DM) and obesity [1–3]. NAFLD can increase the risk of developing multi-diseases, ranging from liver fibrosis and cirrhosis to end-stage liver disease and hepatocellular carcinoma [4], and is increasingly regarded as a systematic metabolic condition rather than a disease of a single organ [5,6]. An increasing number of studies suggest that NAFLD not only contributes to liver injury but can also enhance the risk of developing extra-hepatic disorders, such as cardiovascular disease (CVD), urolithiasis and chronic kidney diseases [7–11].

Recently, the association of the presence of NAFLD with urolithiasis has attracted considerable scientific interests. There is growing evidence that NAFLD increases the risk of developing urolithiasis, which is a highly prevalent disease and constitutes a significant burden on the healthcare system worldwide [12–16]. A meta-analysis involving seven observational studies and 226,541 individuals reported a 1.73-fold increased risk of urolithiasis among NAFLD patients compared with healthy individuals [17]. The 2016 European Association of Urology guidelines recommended all patients with a renal tract calculus should receive a basic metabolic screen, suggesting the critical involvement of metabolic factors in the pathogenesis of urolithiasis [18]. Moreover, the potential association between NAFLD, metabolic factors and an increased risk of urolithiasis highlights the importance of screening for urolithiasis in patients with NAFLD [19,20].

Although several invasive scores for the staging of liver fibrosis, such as APRI score, have been well established, whether APRI score is linked to the risk for urolithiasis in NAFLD patients, however, has yet to be determined [21]. Given that preliminary studies have reported the link of the severity of NAFLD to the risk of chronic kidney disease, it is reasonable to hypothesise that the staging of liver fibrosis has an impact on the risk of urolithiasis and potentially serve as a marker for screening for urolithiasis in NAFLD [9].

To test the hypothesis that NAFLD severity is associated with an increased risk of urolithiasis, we undertook a retrospective study to determine the association of the risk of urolithiasis with the noninvasive staging of liver fibrosis (measured with APRI score), and further, to develop an diagnostic panel with an hypothetic AUROC of at least 0.6 for identifying individuals at increased risk for urolithiasis among NAFLD patients.

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Methods

Clinical and demographic characteristics of subjects were collected from the electronic health record in China-Japan union hospital of Jilin University. A total of 1527 adult patients with ultrasonography diagnosed NAFLD who completed a comprehensive health checkup between October 2015 and November 2017 were included. The exclusion criteria included: alcohol consumption of more than 30g or 20g per day respectively for males and females, positivity for the detection of hepatitis C virus antibodies or hepatitis B surface antigen, history of using hepatotoxic drugs, autoimmune liver diseases and other chronic hepatic diseases. This study was conducted according to the Helsinki declaration and was approved by the ethical committee of China-Japan Union Hospital of Jilin University. Accordingly, this study was designed to have a power of 90% to test the prespecified hypothesis that noninvasive staging of liver fibrosis would have an AUC of 0.6 for the detection of urolithiasis under the null hypothesis, at a one-sided type I error rate of 0.05. Assuming a prevalence of 8.5% for urolithiasis, a sample of 1176 subjects was needed in this study [17].

Information concerning demographics and lifestyle habits (smoking and drinking history) were retrospectively collected. Liver ultrasonography scanning was performed by experienced hepatologists, who were blinded to participants' details. Blood pressure was measured by a digital electronic sphygmomanometer. All serological examinations were made after an overnight fast using standardised methods. Hypertension was defined according to JNC 7 criteria [22]. Obesity was defined as a body mass index (BMI) value≥ 28 kg/m^2 [23]. Waist circumference was measured at the level of the umbilicus. Diabetes mellitus was diagnosed by the American Diabetes Association criteria [24]. Liver ultrasonography was used to diagnose nonalcoholic fatty liver disease according to practice guidance from the American Association for the study of Liver Diseases [25]. AST to Platelet Ratio Index (APRI score) was used for noninvasive staging of liver fibrosis. APRI score was calculated as follows: (AST/40)/PLT X 100. Urolithiasis was diagnosed using urinary system ultrasonography based on the guideline proposed by the American Urological Association [26].

Statistical analysis was as follows. First, clinical and biochemical characteristics were described. Continuous normally distributed variables are represented by mean ± SD. Continuous non-normal variables are summarised as median and range. Categorical variables are presented as numbers with percentages. Second, clinical characteristics and laboratory values are compared between those with and without urolithiasis. The Chi-squared test determined statistical differences in the distribution of categorical variables. Student's t-test compared the means of normally distributed variables between groups. The Mann-Whitney U test compared the differences of medians between groups for continuous non-normally distributed variables. Third, four logistic regression analyses were calculated for the odds ratio (OR) with 95% confidence interval (CI) of the associations between urolithiasis and clinical and demographic factors, and the APRI score. Model 1 adjusted for demographic characteristics (age, gender) and obesity; model 2 for demographic characteristics, obesity, diabetes, and CVD; model 3 for factors in model 2 and serum uric acid, and model 4 for the factors in model 3 and APRI score. Fourth, the diagnostic value of APRI score, as well as other risk factors for identifying urolithiasis was subsequently assessed using receiver operating characteristic (ROC) curves analysis. Moreover, a multivariable logistic regression model was also used to evaluate the area under the ROC (AUROC) of these independent risk factors of incident urolithiasis taken together. The optimal cutoff values for each factor were calculated by maximising the sum of sensitivity + specificity. The performance of various indicators for assessing the risk of urolithiasis was compared using the comparison of the AUROCs. A 2-tailed *p*-value less than 0.05 was considered statistically significant. All statistical analysis was performed using medcalc statistical software and R 3.5.1 for Windows [27].

Results

The demographic, clinical characteristics of the studied population are summarised in Table 1. Urolithiasis was present in 159 (10.4%), who were older, more likely to be obese, and had higher AST, uric acid, and APRI score. No significant differences existed between groups in the rate of diabetes mellitus, hypertension, CVD. These data were entered into a multivariate analysis using four different models to control for potential confounders. After logistic regression, all four models showed a consistent relationship between the severity of NAFLD (defined by APRI score) and an increased urolithiasis risk (Table 2). When adjusting for all potential confounding factors including demographic characteristics, medical comorbidities, serum uric acid, the final model (model 4) showed three independent risk factors: obesity, APRI score and uric acid to be related to an increased risk of urolithiasis (Table 2). Accordingly, the 3-variable model estimate was: c = (2.06 x obesity) + (1.01 x uric acid (1 or 0)) + (13.04 xAPRI) + 0.002. Although age differed between those with or without urolithiasis, multivariate analysis failed to show an independent association between age and the incidence of urolithiasis.

ROC analysis evaluated and compared the diagnostic value of several independent risk factors for

Table 1. Clinical and biochemical characteristics of NAFLD patients with and without urolithiasis.

		Urolithiasis among NAFLD patients		
	All patients (n = 1527)	No (n = 1368)	Yes (n = 159)	P value
Age (years)	58 (52,64)	57 (52,64)	62 (54.5,66)	< 0.001
Male (male, %)	861 (56.4%)	767 (56.1%)	94 (59.1%)	0.46
DM (n, %)	285 (18.7%)	254 (18.6%)	31 (19.5%)	0.64
Hypertension (n, %)	313 (20.5%)	283 (20.7%)	30 (18.9%)	0.59
CVD (n, %)	227 (14.9%)	204 (14.9%)	23 (14.5%)	0.88
Smoker (n, %)	221 (14.5%)	203 (14.8%)	18 (11.3%)	0.23
Obesity (n, %)	299 (19.6%)	232 (17.0%)	67 (42.1%)	< 0.001
AST (IU/L)	38 ± 5	38 ± 5	40 ± 5	< 0.001
ALT (IU/L)	38 ± 5	38 ± 59	38 ± 5	0.48
GGT (IU/L)	36 ± 9	36 ± 9	35 ± 8	0.35
PLT (x10^9/L)	250 ± 42	248 ± 41	241 ± 45	0.06
TG (mmol/L)	1.59 ± 0.64	1.59 ± 0.64	1.61 ± 0.65	0.70
HDL (mmol/L)	1.43 ± 0.34	1.43 ± 0.34	1.43 ± 0.36	0.91
LDL (mmol/L)	3.26 ± 0.41	3.26 ± 0.41	3.25 ± 0.41	0.75
Serum uric acid (umol/L)	254 ± 87	247 ± 84	307 ± 91	< 0.001
Sodium	139 ± 3	139 ± 3	139 ± 3	0.19
Chloride	104 ± 4	104 ± 4	105 ± 4	0.39
Bicarbonate	25 ± 3	25 ± 3	253 ± 3	0.36
APRI score	0.39 (0.34,0.45)	0.39 (0.34,0.45)	0.41 (0.36,0.48)	< 0.001

CVD cardiovascular disease, DM diabetes mellitus, SBP systolic blood pressure, DBP diastolic blood pressure, TG triglyceride, HDL high-density lipoprotein, LDL low-density lipoprotein. ALT alanine aminotransferase, AST aspartate aminotransferase. GGT gamma-glutamyl transpeptidase, PLT platelet. APRI aspartate transaminase-to-platelet ratio index. Data mean (SD), median (range) or n (%).

Table 2. Multivariate logistic regression analyses showing associations of APRI and other factors with incident urolithiasis among patients with NAFLD.

		Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
	Comparison	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Age	Per 5 unit increase	1.05 (0.95–1.16)	1.05 (0.95–1.16)	1.10 (1.00–1.28)	1.05 (0.90–1.16)
Gender	Male vs. Female	1.12 (0.80–1.58)	1.12 (0.80–1.58)	1.16 (0.82–1.65)	1.15 (0.81–1.63)
Diabetes	Yes vs. No		1.01 (0.65–1.53)	1.03 (0.66–1.57)	1.03 (0.66–1.58)
CVD	Yes vs. No		0.98 (0.60–1.55)	0.98 (0.59–1.56)	0.99 (0.60–1.57)
Obesity	Yes vs. No	**3.25 (2.18–4.82)**	**3.25 (2.18–4.82)**	**2.04 (1.33–3.10)**	**2.06 (1.35–3.13)**
Serum uric acid	Per 10 unit increase			**1.10 (1.05–1.16)**	**1.07 (1.05–1.09)**
APRI score	Per 0.1 unit increase				**1.29 (1.05–1.59)**

NOTE. Bold text indicates statistical significance. [a]Adjusting for demographic characteristics (age, gender) and obesity. [b]Adjusting for demographic characteristics, obesity, diabetes, and CVD. [c]Adjusting for demographic characteristics, obesity, diabetes, and CVD, serum uric acid. [d]Adjusting for demographic characteristics, obesity, diabetes, and CVD, serum uric acid, APRI score.

urolithiasis. The AUROC of obesity, APRI score, and serum uric acid for identifying urolithiasis, was 0.63 (95% CI 0.60–0.65), 0.58 (95% CI 0.56–0.61) and 0.69 (95% 0.66–0.71), respectively. Among that, the AUROC of serum uric acid was significantly higher than the AUROC of obesity and APRI score (P = 0.019, P = 0.003, respectively). The AUROC of these three variables taken together in the logistic regression model (model 4) for identifying urolithiasis was 0.73 (95% CI 0.70–0.75) (Figures 1 and 2).

Discussion

The major finding of this study is that the severity of NAFLD is related to a moderately increased risk of urolithiasis in patients with ultrasonography diagnosed NAFLD. Our logistic regression model identified three independent risk factors, obesity, APRI score, and serum uric acid for urolithiasis. This result confirmed the graded association of urolithiasis risk with liver fibrosis stage measured by APRI score in a population with NAFLD.

There is a growing body of evidence emerging that there is a potential relationship between NAFLD and an increased risk for urinary calculi [12–16]. Our findings are consistent with a population-based cross-sectional study of 3719 Chinese men, showing that NAFLD was associated with a higher incidence of urinary calculi, independently of age, education status, smoking habit, alcohol consumption, physical activity and BMI [16]. Also, the findings in our study were similar in a large cohort study involving 208,578 Korean adults who underwent a health checkup examination between January 2002 and December 2014, indicating that NAFLD was significantly associated with an increased incidence of urolithiasis [14]. Although the studies as mentioned above investigated the link between NAFLD and urolithiasis, the impact of severity of NAFLD on the risk of urolithiasis was not demonstrated. Traditional

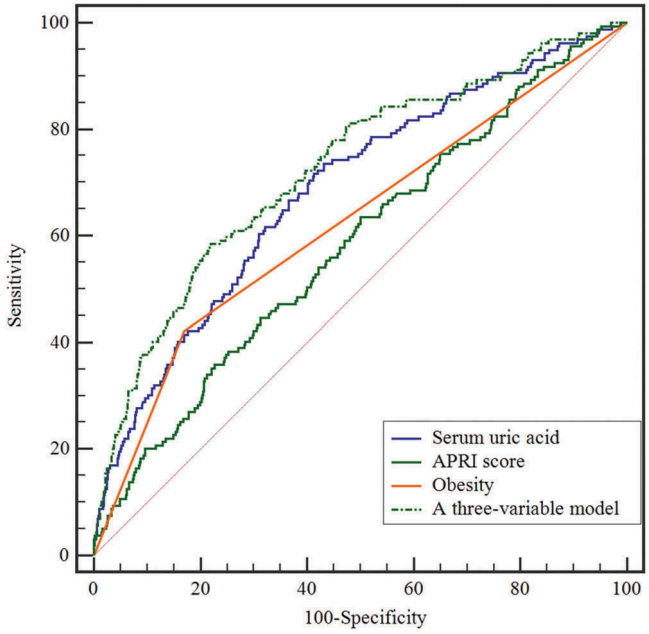

Figure 1. ROC curve analysis of obesity, APRI score, and serum uric acid, and a three-variable model for the detection of incident urolithiasis in NAFLD patients. The diagonal line represents detection achieved by chance alone (AUROC = 0.50); the ideal AUROC is 1.00. Delong test was used to compare AUROCs for various indexes.

	Obesity	Serum uric acid	APRI score	A three variables model
Obesity	AUC=0.63 (0.60-0.65)	P=0.019	P=0.130	P<0.001
Serum uric acid		AUC=0.69 (0.66-0.71)	P=0.003	P=0.004
APRI score			AUC=0.58 (0.56-0.61)	P<0.001
A three variables model				AUC=0.73 (0.70-0.75)

Figure 2. Comparison of the diagnostic value of obesity, APRI score, serum uric acid and a three-variable model for identifying incident urolithiasis among patients with NAFLD.

ultrasonography has a limitation in evaluating the fibrosis staging of liver because it is inaccurate for discriminating mild to moderate/severe fibrosis [28,29]. Therefore, APRI score, which is a well-established invasive score for liver fibrosis, was used to determine the staging of liver fibrosis in this study.

The underlying biological mechanism by which NAFLD may increase the risk for urolithiasis is poorly understood. The most obvious explanation for our findings is that NAFLD and urolithiasis share multiple common underlying metabolic risk factors, such as diabetes, hypertension, obesity, and metabolic syndrome [30,31]. In other words, a number of risk factors for NAFLD may also be involved in the development and progression of urolithiasis. Moreover, metabolic syndrome has been shown to alter urinary constituents, contributing to an increased risk of both uric acid and calcium oxalate stone formations [32–34]. Consequently, to some extent, urolithiasis is increasingly considered a component of the metabolic syndrome. In addition, insulin resistance, a vital factor in the pathogenesis of NAFLD, has been proposed to be a contributor to the

progression of urolithiasis by affecting urinary pH [35]. In detail, insulin resistance results in decreased ammoniagenesis in the renal tubule, leading to acidic urine which promotes uric acid stones formation [20,36,37]. Also, increasing evidence indicates the role of reactive oxygen species (ROS) production and oxidative stress development in renal stone formation. Initially, ROS could prevent stone formation by increasing the production of crystallisation inhibitors [38]. However, decreased antioxidant capacity may lead to ROS and urolithiasis. Moreover, antioxidants and inhibitors of ROS generating enzymes could decrease renal calcium oxalate crystal deposition, which is a surrogate marker of urolithiasis in animal models [39,40].

This study has some limitations. First, the causality of the association between the severity of NAFLD and urolithiasis could not be established, as this design of this study is cross-sectional. Although the positive correlation between the severity of NAFLD and urolithiasis still exists after adjusting for multiple potential confounding factors, prospective cohort study addressing the causal relationship between the severity of NAFLD and urolithiasis is still needed in future. Second, clinical data regarding symptoms of urolithiasis were not available. Third, the NAFLD was diagnosed with ultrasonography and its severity evaluated by APRI score, but not confirmed by liver biopsy. It is, however, not appropriate to perform liver biopsies in all NAFLD patients, particularly in a large sample of epidemiologic studies. Fourth, urea, creatinine and calcium were not performed. The impact of renal function and calcium into urolithiasis should be addressed in future studies.

Despite these limitations, this study has several strengths. First, this study has a relatively large sample size, ensuring sufficient power for detecting the potential role of APRI score, as well as other risk factors for identifying urolithiasis. Second, four multivariate logistic analyses were used for adjusting multiple potential confounders. Third, this study adopted a one-gate design, thus avoiding selection bias. Notably, a three-variable model (obesity, APRI score, serum uric acid) could serve as a useful tool in NAFLD patients for identifying subjects at high risk for urolithiasis. These cross-sectional findings, though not definitive, warrant further study. Future experimental and large-scale cohort studies are needed to confirm these findings and to elucidate the underlying biologic mechanisms.

This work represents an advance in biomedical science because our results suggest that the severity of NAFLD is associated with the risk of incident urolithiasis among NAFLD patients, independently of several traditional risk factors.

Summary table

What is known about this subject:

- NAFLD is the most common form of chronic liver diseases worldwide, and not only contributes to liver injuries but can also increase the risk of developing extra-hepatic diseases.
- The presence of NAFLD significantly increases the susceptibility of developing urolithiasis.

What this study adds:

- The severity of NAFLD is significantly linked to the risk of developing urolithiasis among patients with NAFLD.
- A three-variable model (obesity, APRI score, serum uric acid) could be used as a tool for discerning individuals at high risk for urolithiasis in patients with NAFLD.

Disclosure statement

No potential conflict of interest was reported by the authors.

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