

The Negative Association Between Non-alcoholic Fatty Liver Disease Severity and Gouty Nephropathy in a Non-diabetic Gouty Population: A Cross-Sectional Study

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Research article

Keywords: Non-alcoholic fatty liver disease, gouty nephropathy, non-diabetes

Posted Date: August 18th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-60574/v1>

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Abstract

Background: Nonalcoholic fatty liver (NAFLD) and chronic kidney disease (CKD) share common pathogenic mechanisms and risk factors, but the specific relationship between NAFLD and gouty nephropathy has not been well understood. We aim to evaluate the association between NAFLD and gouty nephropathy in a non-diabetic gouty population.

Methods: The retrospective cross-sectional study was performed on 1049 non-diabetic gouty participants, who were hospitalized between 2014 and 2020, across 4 districts in Shandong, China. Demographic and clinical characteristics of the study population were collected. The odds ratios (OR) and corresponding 95% confidence intervals (CI) in relation to the NAFLD severity determined by ultrasonography were obtained by multiple logistic regression analysis.

Results: An unexpectedly inverse relationship was found between NAFLD severity and the risk of gout nephropathy. Multivariate logistic regression analysis demonstrated that higher degree of NAFLD severity is independently associated with lower risk of gouty nephropathy, after adjusted for age, sex, smoking, gout duration, and metabolic risk factors including obesity, hypertension, hyperglycemia, hyperuricemia and dyslipidemia, with OR 0.392 (95 % CI 0.248–0.619, $P < 0.001$), 0.379 (95 % CI 0.233–0.616, $P < 0.001$) and 0.148 (95 % CI 0.043–0.512, $P = 0.003$) in participants with mild, moderate, and severe NAFLD, respectively, compared to those without NAFLD. We also observed a weakened association of serum uric acid (SUA) with metabolic risk factors and NAFLD under circumstances of gouty nephropathy ($r = -0.054$, $P = 0.466$).

Conclusions: The presence and severity of NAFLD was negatively associated with the risk of gouty nephropathy in the non-diabetic gouty populations. Further investigation of NAFLD will provide insights into the pathogenesis of gouty nephropathy.

Trials registration: Chinese Clinical Trials Registry ChiCTR2000035185. Registered 2 August 2020.

Background

Gout is a disorder of purine metabolism characterized by hyperuricemia, recurrent acute arthritis, and tophi deposition[1, 2], which is associated with many comorbidities including hypertension, cardiovascular diseases (CVDs), and renal disorders[3-5]. Excessive uric acid (UA), usually in the form of monosodium urate (MSU) crystals, precipitates in synovial cavities and other anatomic location to induce severe inflammation and debilitating pain. The most serious complication of hyperuricemia is considered to be gouty nephropathy, which results from the deposits of UA in the kidney[3, 4]. Specially, acute gouty nephropathy is caused by precipitation of UA crystals in renal interstitium and tubules, usually collecting ducts, while chronic gouty nephropathy is characterized by the deposition of MSU crystals primarily involving the collecting ducts in the medulla[6]. The obstruction could be further exacerbated by the inflammatory response, endothelial dysfunction, and activation of the renin-angiotensin system that it initiates[7-10]. Particularly, by recruiting interleukin (IL)-1 β -secreting macrophages, activating Nod-like

receptor protein 3 inflammasomes in macrophages, and promoting chemokine secretion in proximal tubular cells[11], hyperuricaemia constantly aggravates the renal damage. However, the clinical risk factors for gouty nephropathy remain controversial and are insufficiently studied at present.

The relationship between nonalcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD) has attracted much attention, since they share similar risk factors and pathogenic mechanisms, such as insulin resistance (IR), diabetes mellitus (DM), hyperlipidemia and obesity[12-18]. While numbers of previous studies indicated the presence and severity of NAFLD was a potential contributory risk factor for the development and progression of CKD, recent studies suggested no adverse association between NAFLD hepatic steatosis and renal function both in general populations and diabetic individuals[19-22]. Some researchers argued that NAFLD itself is not an independent risk factor for CKD, while it is the comorbidities of NAFLD such as obesity, hypertension, and hyperuricemia that are independently associated with CKD[23]. Some also argue that NAFLD was associated with early stages of CKD, but not the late stages of CKD[22]. In addition, although it is reasonable to assume that NAFLD may promote renal damage, it is still uncertain if NAFLD is associated with a specific type of kidney disease[16]. Given that most of the studies were focused on patients with DM[24, 25], the specific relationship between NAFLD and gouty nephropathy has been poorly studied.

To bridge the evidence gap between NAFLD and gouty nephropathy, we conducted a hospital-based cross-sectional study in Shandong, China. We aimed to investigate whether the probable advanced NAFLD evaluated by ultrasound is independently associated with gouty nephropathy in non-diabetic gouty populations, the results of which may provide a novel theoretical basis and therapeutic target for the prevention and treatment of gouty nephropathy.

Methods

Design and study participants

We reported the retrospective cross-sectional study according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[26]. Data were collected from 1545 non-diabetic gouty patients hospitalized between 2014 and 2020, across 4 districts in Shandong, China, by a trained staff group. All patients were diagnosed with the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) gout diagnostic criteria[27]. The diagnosis of gouty nephropathy was based on the diagnosis of primary gout[28], with one or more of the following parameters: Urinary protein > 150 mg/dl; urine white blood cells > 5/high power field (HPF); urine red blood cells > 3/HPF; serum creatinine > 115 μ mol/l; blood uric acid/creatinine ratio > 2.5. Additionally, an ultrasound or ureterography revealing renal calculus or a shrunken kidney was also considered. The exclusion criteria include the following: (1) age < 18 years or > 80 years; (2) with secondary hyperuricaemia; (3) receiving medical treatment for current chronic glomerulonephritis other than gouty nephropathy; (4) with DM, severe CVDs, heart failure, or cancer; (5) with ethanol intake per week that is more than 140 g in men and 70 g in women[29]; (6) with specific diseases that could result in fatty liver,

such as viral hepatitis and drug-induced liver disease; (7) with positive for hepatitis B or C viruses other types of liver diseases, including primary biliary cirrhosis, autoimmune hepatitis[30]. Patients with missing information on severity of NAFLD, or inadequate variables to calculate eGFR were also excluded.

The protocol was designed according to the Declaration of Helsinki and was approved by the ethics committee of the Qingdao University affiliated hospital, and all participants provided written informed consent. The study was registered on <http://www.chictr.org.cn/> under number ChiCTR2000035185.

Anthropometric and biochemical measurements

The characteristics of the study population included age, sex, height, weight, waist circumference (WC), gout duration, blood pressure, serum uric acid (SUA), fasting plasma glucose (FPG), fasting insulin, lipid profiles [triglycerides (TG), total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-c), high-density lipoprotein-cholesterol (HDL-c) and free fatty acid (FFA)], liver enzymes [alanine transaminase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transpeptidase (GGT)], renal function biomarkers [serum creatinine (SCr), blood urea nitrogen (BUN), Cystatin C (Cys C)], smoking and drinking history, and medical history.

Height and weight were measured with patients standing without shoes and with lightweight clothing. WC was measured in the horizontal plane midway between the lowest ribs and the iliac crest, as suggested by the World Health Organization and the International Diabetes Federation. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2), and $\text{BMI} > 29.9$ was used to define obesity[31]. Blood pressure was reported as the means of three consecutive measurements with an interval of five minutes, and hypertension was defined by systolic blood pressure (SBP) $\geq 140\text{mmHg}$, or diastolic blood pressure (DBP) $\geq 90\text{mmHg}$, or self-reported previous diagnosis of hypertension by physicians.

Blood samples were obtained between 6:00-9:00 a.m. after fasting for at least 8 h. Venipuncture was performed in the median cubital vein, and centrifugation and dispensing were completed within 1 h. All samples were cold-chained, stored and transported to a central laboratory for testing within 2-4 h. Biochemical parameters including FPG, lipids, liver and renal function biomarkers were performed with a Beckman Coulter AU 680 (Brea, USA). Hyperglycaemia was defined as a FPG $\geq 100\text{ mg/dL}$ (5.56 mmol/L). Hyperuricemia was defined as SUA $> 420\text{ }\mu\text{mol/L}$ in male and $> 360\text{ }\mu\text{mol/L}$ in female. High LDL-c was defined as $\geq 140\text{ mg/dL}$ (3.63 mmol/L). Low HDL-c was defined as $< 40\text{ mg/dL}$ (1.04 mmol/L) in male, and < 50 (1.30 mmol/L) mg/dL in female. High TG was defined as $\geq 150\text{ mg/dL}$ (1.70 mmol/L). High TC was defined as $\geq 200\text{ mg/dL}$ (5.18 mmol/L)[32]. IR was evaluated by homeostasis model assessment index of insulin resistance (HOMA-IR): $\text{HOMA-IR} = (\text{fasting insulin} [\text{milli international units per liter}] * (\text{FPG} [\text{millimoles per liter}]) / (22.5))$ [33]. The estimated glomerular filtration rate (eGFR) was calculated according to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula[34], and CKD stages were classified according to the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative guidelines (KDOQI)[35]. The diagnosis of fatty liver was based on the results of

abdominal ultrasound (Philips, Amsterdam, Holland). including hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring[30], which was performed by the two experienced physicians who were blinded to their clinical data. Specially, it was divided into four groups by ultrasound as no NAFLD, mild NAFLD, moderate NAFLD, and severe NAFLD[36].

Statistical analysis

The SPSS version 22.0 software (SPSS IBM Corporation, Armonk, NY, USA) and SATA (version 12.0, StataCorp, Lakeway Dr., TX, USA) was used to perform statistical analyses. Normally distributed continuous variables are presented as mean \pm standard deviation (SD), while non-normally distributed continuous variable are presented as median (interquartile range, IQR), and categorical variables are presented as frequency (%). We compared different groups by Chi-square and one-way ANOVA on normal and continuous variables, respectively. When observe values did not approximate to the normal distribution, the Kruskal-Wallis test were replaced. The correlations between the levels of SUA and risk factor variables were calculated with the Spearman's correlation test. The odds ratios (OR) and the corresponding 95% confidence intervals (CI) for gouty nephropathy concerning NAFLD severity were obtained by multiple logistic regression analysis. All statistical analyses were two-sided, and p-values less than 0.05 were considered to be statistically significant.

Results

We initially enrolled 1545 individuals and a total of 1049 were in final analysis after exclusion criteria (Fig. 1). We excluded participants who were missing laboratory results (n =32) and ultrasound results (62), had a history of DM (129), severe CVDs or cancer (17), excessive consumption (male \geq 140 g/week, female \geq 70 g/week) of pure alcohol (n = 117), self-reported viral hepatitis (including hepatitis B and hepatitis C virus) (n = 53), was using medications associated with secondary NAFLD or autoimmune liver disease (n = 21), and was considered as secondary hyperuricaemia (8).

Baseline Characteristics of participants with gout

Clinical characteristics of the individuals stratified by the presence of gouty nephropathy were shown in Table 1, and stratified by the severity of NAFLD in Table 2. As shown in Table 1, among the 1049 hospitalized non-diabetic gouty patients, 17.4% were found to have gouty nephropathy. Participants with gouty nephropathy were older and had longer gout duration, more prone to be smokers, with lower BMI, higher SBP, higher FPG and SUA levels, than those without gouty nephropathy. Of note, participants with gouty nephropathy were more likely to have lower prevalence and severity of NAFLD by ultrasound, with lower levels of ALT and AST, than those without gouty nephropathy ($P < 0.001$). Meanwhile, insignificant differences in sex, DBP, HOMA-IR, and lipid profiles (including LDL-c, HDL-c, TG, TC and FFA) between the groups were detected.

The trend analysis of demographic and biochemical features among different categories of NAFLD severity was presented in Table 2. As we can see, participants with higher severity of NAFLD seem to be

younger, more likely to be smokers, with higher BMI and abdominal obesity, higher FPG and HOMA-IR, higher levels of SUA, LDL-c, TG, TC and FFA, and lower levels of HDL-c, than those with less severe or without NAFLD. Of note, preserved renal function were observed in individuals with more severe NAFLD, reflected by lower prevalence of gouty nephropathy, lower levels of indicators of renal damage (SCr, BUN and Cys C), as well as higher levels of eGFR and Ccr, compared to those with less severe or without NAFLD ($P < 0.001$).

Association of ultrasound-diagnosed NAFLD with gouty nephropathy

We further determined the renal function based on eGFR and Ccr levels with respect to the degree of NAFLD severity by box plot (Fig. 2 A and B). As we can see, as the severity of NAFLD increased, the levels of eGFR and Ccr were higher ($P < 0.001$), with the lowest eGFR levels seen in individuals with non-NAFLD and highest eGFR levels seen in those with severe NAFLD. Box plots were also performed to demonstrated the relationship between liver function and eGFR categories (Fig. 2 C and D). Consistently, with the decline of eGFR in gouty participants, we observed that the levels of liver enzymes including ALT and AST decreased ($P < 0.001$).

As shown in Table 3, the risk of gouty nephropathy was significantly associated with NAFLD severity in the logistic regression analyses. In unadjusted analysis, the OR was 0.336 (95 % CI 0.218–0.517, $P < 0.001$), 0.320 (95 % CI 0.205–0.510, $P < 0.001$) and 0.321 (95 % CI 0.218–0.517, $P = 0.001$), respectively, in participants with mild, moderate, and severe NAFLD compared to those without NAFLD. On further adjustment for age, sex and smoking, NAFLD severity was still significantly associated with the risk of gouty nephropathy, with OR 0.394 (95 % CI 0.254–0.612, $P < 0.001$), 0.388 (95 % CI 0.245–0.614, $P < 0.001$) and 0.152 (95 % CI 0.046–0.499, $P = 0.002$) in participants with mild, moderate, and severe NAFLD compared to those without NAFLD. When further adjusted for metabolic parameters, including obesity, hypertension, hyperglycemia, hyperuricemia, and hyperlipidemia, the association of NAFLD severity with gouty nephropathy was still significant, with OR 0.392 (95 % CI 0.248–0.619, $P < 0.001$), 0.379 (95 % CI 0.233–0.616, $P < 0.001$) and 0.148 (95 % CI 0.043–0.512, $P = 0.003$) in participants with mild, moderate, and severe NAFLD, respectively, compared to those without NAFLD.

Risk factors for gouty nephropathy in the multiple logistic regression analysis

The complex nature of the variables that determine the gouty nephropathy risk was further studied in a forest plot. As shown in Fig. 3, gouty nephropathy was introduced as a dependent variable in the multiple factors logistic regression analysis, using old age (more than 60 years), long gout duration (more than 10 years), smoking, obesity, hypertension, hyperglycemia, hyperuricemia, high LDL-c, low HDL-c, high TG and high TC level, as well as NAFLD severity as independent variables. In addition to the severity of NAFLD, we observed the old age, hypertension, and hyperglycemia were significant risk factors for gouty nephropathy. However, sex, long gout duration, smoking, obesity, hyperuricemia, and dyslipidemia were insignificantly associated with gouty nephropathy in the non-diabetic gouty participants.

Association of SUA with metabolic syndrome and NAFLD in participants with gout

In the present study, we also examined the association between SUA and both metabolic syndrome and NAFLD severity in the gouty population. To detect different clinical significance of hyperuricaemia for metabolic disorders in patients with and without renal insufficiency, we divided the participants into two groups based on the presence of gouty nephropathy, and separately analyzed the association of SUA with both metabolism-related parameters and NAFLD severity. The Spearman correlation coefficients between SUA and metabolism-related parameters were given in Table 4. SUA was significantly associated with BMI ($r = 0.200$, $P < 0.001$), WC ($r = 0.187$, $P < 0.001$), DBP ($r = 0.098$, $P = 0.004$), HOMA-IR ($r = 0.131$, $P = 0.004$), LDL-c ($r = 0.151$, $P < 0.001$), TG ($r = 0.230$, $P < 0.001$), TC ($r = 0.160$, $P < 0.001$) and degree of NAFLD severity ($r = 0.240$, $P < 0.001$) in participants without gouty nephropathy. However, this association weakened and became insignificant in participants with gouty nephropathy.

Discussion

This retrospective cross-sectional study outlines the association between the presence and severity of NAFLD and the risk of gouty nephropathy in non-diabetic gouty patients. Interestingly, we detected a significant negative association between NAFLD severity and the risk of gouty nephropathy, which is an unexpected finding because the severity of hepatic steatosis in NAFLD is associated with increased CKD risk in previous studies[37]. Moreover, this association was independent of age, sex, smoking, gout duration, and metabolic risk factors (e.g. obesity, hypertension, hyperglycemia, hyperuricemia and dyslipidemia). We also observed a weakened association of SUA with NAFLD and metabolic risk factors under gouty nephropathy. Therefore, our study suggests a complicated correlation between co-existing NAFLD and the development of renal dysfunction in non-diabetic gouty patients, which might be linked to the surrounding mellitus. Further investigation of NAFLD will provide insights into the pathogenesis of gouty nephropathy.

Up till now, numbers of studies have explored the relationship between NAFLD and CKD risk in different populations. While numbers of previous studies indicated that the presence of NAFLD was a potential contributory risk factor for the development and progression of CKD, recent studies suggested no adverse association between NAFLD hepatic steatosis and renal function both in general populations and diabetic individuals[19-22]. Some experts argued that NAFLD itself is not an independent risk factor for CKD, while the comorbidities of NAFLD such as obesity, hypertension, hyperglycemia and hyperuricemia are independently associated with renal dysfunction[23]. Some also argue that NAFLD was associated with early stages of CKD, but not the late stages of CKD[22]. However, most of previous studies had a much higher prevalence of diabetes in their study samples[24, 25], raising the possibility of selection bias given the strong association between diabetes and CKD. Additionally, although it is reasonable to assume that NAFLD may promote renal damage, it is still uncertain if NAFLD is associated with a specific type of kidney disease[16]. Anyhow, despite that gouty nephropathy and diabetic kidney disease (DKD) have many risk factors in common, they are actually distinct entities with differing risk profiles. Given that none of the studies have been focused on the specific relationship between NAFLD and gouty nephropathy, we conducted this retrospective cross-sectional study to explore the association between

the presence and severity of NAFLD and the risk of gouty nephropathy in Chinese gouty individuals without diabetes.

Inverse associations of NAFLD severity as well as liver enzymes, with the risk of gouty nephropathy were observed in non-diabetic gouty individuals in this study. Similar to our findings, latest evidence showed that in CKD population, the prevalence of NAFLD was significantly higher in patients with preserved renal function, and they had more severe liver fibrosis than advanced CKD patients[38]. Similarly, inverse associations of NAFLD as well as liver disease biomarkers with the risk of ischemic stroke have also been reported in a large-scale case-cohort study[39]. Another research addressing the risk of composite cardiovascular endpoints also presented an inverse association of NAFLD in general population with old age, and a positive association in younger individuals[40], suggesting a complex relationship between NAFLD and CVD risk. Additionally, complicated associations between liver dysfunction and the risk of mortality have also been reported, with the observation that low ALT levels indicated a higher all-cause, CVD-related, and cancer-related mortality[41]. Some researchers further argued that ALT levels may exhibit a U-shaped association with cardiovascular and total mortality, and that the low ALT could be considered as a biomarker of an exaggerated hepatic aging process[42, 43].

NAFLD and CKD share similar pathological mechanisms, therefore they are speculated to have some links. The aforementioned mechanisms included the role of obesity, insulin resistance, the renin-angiotensin system, and dysregulation of glucose metabolism and lipogenesis in the development of both disorders[17, 44, 45]. In this study, in line with the concept that NAFLD is the hepatic manifestation of the metabolic syndrome, the presence of NAFLD is associated with obesity and components of metabolic syndrome. However, the association of renal dysfunction and components of metabolic syndrome, such as obesity, insulin resistance and hyperlipidemia, became insignificant in this non-diabetic gouty population. We concluded several responsible mechanisms regarding the negative association between NAFLD severity and risk of gout nephropathy as follows:

(I) Lower degree of oxidative stress in gouty nephropathy. The intensity of antioxidant protection system and OS factors in patients with NAFLD has been shown depending on the form of CKD[46]. While the intensity of OS increases in the form of chronic pyelonephritis and DKD, in the comorbidity of NAFLD with gouty nephropathy and in conditions of asymptomatic hyperuricemia, the degree of OS is significantly lower due to the strong antioxidant properties of UA[46]. Notably, UA is considered as a double-edged sword in the context of human health, as it has both anti- and pro-oxidant properties depending on the surrounding environment[47-49]. In a physiological milieu, UA serves as an antioxidant, and when homeostasis is perturbed, divergent effects are observed depending on the clinical context[50]. Moreover, the effect of reducing hydroxyl and superoxide radicals is concentration-dependent, such that increasing serum concentrations of UA intensifies scavenging of reactive oxygen species (ROS)[51-53]. UA also has the ability to form stable complexes with iron ions, which can dramatically inhibit Fe³⁺-catalyzed ascorbate oxidation and lipid peroxidation[54]. Consistently, inverse relationship between UA and cardiovascular and mortality risk has also been seen in patients with ESRD on hemodialysis[50, 55-57], which was considered to be due to antioxidant properties of UA.

(II) Weakened association between UA and metabolic risks under renal insufficiency. An interesting observation was that although the independent association of serum UA with metabolic syndrome was recognized[58], this association no longer existed in participants with advanced CKD after adjustment for other metabolic risk factors and renal eGFR[59]. It was also showed that when there are more late stages of CKD, the relationship of NALFD and CKD attenuates during multivariate analysis[22]. In this study, we further confirmed that in subjects with gouty nephropathy, hyperuricemia is no longer associated with the high prevalence of obesity, insulin resistance, hyperlipidemia or NAFLD severity, compared with those without gouty nephropathy. Consistently, researchers also observed a weak predictor of CVD in people at low risk of atherosclerotic CVD, while UA is recognized as a significant independent predictor of CVD among high-risk individuals[60]. This renal function-dependent association might be related to the different properties and effects of UA on metabolic disorders under different physicochemical conditions[50]. Another possible explanation for this phenomenon is that it is the generation of oxygen radicals by xanthine oxidase (XO) in the process of generating UA, rather than hyperuricaemia per se, that causes endothelial dysfunction, oxidative stress and eventually multiple metabolic disorders[61].

(III) Monocyte-associated immunosuppression in ESRD. Despite prolonged and severe hyperuricaemia, gouty arthritis is considered to be rare in patients with ESRD[62, 63]. Further exploration indicated that monocytes from gouty patients with ESRD produced significantly lower amounts of proinflammatory cytokines such as IL-1 β , IL-6 and TNF- α , in response to stimuli of MSU crystals than did monocytes from healthy subjects, which may be partly account for the infrequent gout episodes in chronic renal failure patients[64]. Similarly, in gouty patients with severe renal dysfunction, the monocyte-associated immunosuppression, with reduced secretion of proinflammatory cytokines in response to MSU crystals, might be partly account for the less severity of NAFLD.

(IV) Frequent use of xanthine oxidase (XO) inhibition provides the potential to attenuate liver damage. Recent evidence indicated that XO inhibition could attenuate diet-induced steatohepatitis in mice[65, 66]. Specially, febuxostat, with its non-purine structure, selectively inhibits both the oxidized and reduced form of XO[67], has been shown to significantly decrease hepatic XO activity and UA levels in the NAFLD model mice, accompanied by attenuation of insulin resistance, lipid peroxidation, and classically activated M1-like macrophage accumulation in the liver[65]. Experts further found that in NAFLD patients with hyperuricemia, treatment with febuxostat for 24 weeks significantly decreased the serum levels of liver enzymes, alanine aminotransferase and aspartate aminotransferase. In our cross-sectional study, more frequents uses of febuxostat were found in gouty patients with nephropathy compared with those without. Therefore, the more frequent use of febuxostat in gouty patients with nephropathy may partly account for the lower severity of NAFLD and lower levels of liver enzymes.

To the best of our knowledge, the current study is the first to evaluate the relationships between the presence and severity of NAFLD and risk of gouty nephropathy in hospitalized gouty population without diabetes. Even though previous studies have reported positive associations of NAFLD with CVD and CKD, no study have investigated the separate association with gouty nephropathy. Our present study also has several limitations. Firstly, owing to the cross-sectional study design, we are unable to draw conclusions

about the causality of NAFLD and gout nephropathy. Secondly, liver biopsy is the best diagnostic tool for quantification of NAFLD, and it is most sensitive and specific for providing important prognostic information. However, because it is an invasive procedure, it cannot be easily implemented in normal people. Thus, our NAFLD diagnosis was based on ultrasound imaging. It has been shown that only when liver fatty of > 33 % on liver biopsy can radiological imaging optimal for detecting steatosis[68]. Third, eGFR was estimated by age and creatinine regardless of the influence of some drugs. Some drugs, including trimethoprim and cimetidine, inhibit creatinine secretion, thereby reducing creatinine clearance and elevating the serum creatinine level without affecting the GFR[69]. However, no history of above drug uses was observed in the participants. Finally, patients of different races and ethnics were not included in this study, making it difficult to avoid selection bias. In the future, randomized studies with larger cohorts of patients and longer follow-up and histologically confirmed NAFLD are needed to verify a causal relationship between NAFLD and gouty nephropathy.

Conclusions

In conclusion, in this retrospective cross-sectional study of non-diabetic gouty individuals, NAFLD was independently associated with a lowered risk for gouty nephropathy, and this association was independent of age, sex, gout duration, and metabolic risk factors (obesity, hypertension, hyperglycemia, hyperuricemia and dyslipidemia). We also observed a weakened association of UA with NAFLD and metabolic risk factors under gouty nephropathy. Our study suggests a complicated correlation between co-existing NAFLD and the development of renal dysfunction in non-diabetic gouty patients, which might be linked to the surrounding mellitus. Although prospective studies are still needed to figure out the causal relationship, our findings provide novel insights into the potential roles of NAFLD in the pathogenesis of gouty nephropathy.

Abbreviations

ACR/EULAR: American College of Rheumatology/European League Against Rheumatism; ALT: alanine transaminase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; Ccr: creatinine clearance; CI: confidence intervals; CKD: chronic kidney disease; CVD: cardiovascular disease; Cys C: Cystatin C; DBP: diastolic blood pressure; DKD: diabetic kidney disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; FFA: free fatty acid; FPG: fasting plasma glucose; GGT: gamma-glutamyl transpeptidase; HDL-c: high-density lipoprotein-cholesterol; HOMA-IR: homeostasis model assessment index of insulin resistance; IR: insulin resistance; LDL-c: low-density lipoprotein-cholesterol; NAFLD: Nonalcoholic fatty liver; OR: odds ratios; ROS: reactive oxygen species; SBP: systolic blood pressure; SCr: serum creatinine; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology; SUA: serum uric acid; TC: total cholesterol; TG: triglycerides; WC: waist circumference; XO: xanthine oxidase.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of Affiliated Hospital of Medical College Qingdao University, and conducted in accordance with good clinical practice. All participants gave their informed consent to participate.

Consent for publication

All participants gave their informed consent to publication.

Availability of data and materials

The datasets generated and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflict of interest.

Funding

Chen Y. received funding support from NSFC (National Natural Science Foundation of China) with grant number 81600601. Wang YG. received funding support from MOST (Ministry of Science and Technology of the People's Republic of China) with grant number 2020ZX09201-018. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author contributions

Chen and YG. Wang did the study design. Y. Zhou and YH. Wang contributed to the data collection. Y. Zhou, JW. Chi and WS. Lv analyzed the study data. Y. Zhou and MZ. Xing wrote the manuscript and created the figures. JW. Chi, WS. Lv, and Y. Chen reviewed and edited the manuscript. Y. Zhou and YH. Wang contributed to the figures and tables editing. All authors reviewed the manuscript, approved the final draft and agreed to submit it for publication.

Acknowledgments

We thank the data provided by the authors of included in this study.

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Tables

Table 1. Clinical characteristics of study population stratified by the presence of gouty nephropathy in Chinese gouty patients.

Characteristics	Gouty nephropathy N=183	No gouty nephropathy N=866	P-value
Age, y	58.01±14.84	48.84±14.38	< 0.001
Men, %	177 (96.7%)	849 (98.0%)	0.409
BMI, kg/m ²	26.39±3.97	27.95±3.89	< 0.001
Duration of Gout, y	10.46±7.45	7.71±6.57	< 0.001
FPG, mmol/l	5.25±1.04	5.02±0.87	0.005
HOMA-IR	4.30±3.39	4.14±4.30	0.722
BP, mmHg			
Systolic	140.02±22.61	135.67±17.05	0.015
Diastolic	86.04±14.40	84.62±11.36	0.212
Lipid Profile, mmol/l			
LDL-c	2.82±0.75	2.93±0.79	0.102
HDL-c	1.11±0.28	1.12±0.27	0.674
TG	1.77±1.30	1.98±1.46	0.066
TC	4.73±1.01	4.84±1.03	0.198
FFA	0.42±0.18	0.44±0.16	0.286
Liver Enzymes, IU/l			
ALT	29.78±26.03	47.93±48.04	< 0.001
AST	21.08±12.96	25.33±18.53	< 0.001
GGT	45.63±44.17	53.59±53.25	0.064
SUA, umol/l	504.33±132.39	479.47±122.79	0.014
eGFR, ml/min/1.73m ²	58.22±27.94	98.19±24.04	< 0.001
Ccr, ml/min	69.32±40.97	125.16±48.93	< 0.001
Smoking, %	101 (55.2%)	418 (48.3%)	0.030
Hypertension, %	128 (69.9%)	397 (45.8%)	< 0.001
NAFLD Severity, %			
Any NAFLD	69 (37.7%)	562 (64.9%)	< 0.001
Mild NAFLD	31 (16.9%)	246 (28.4%)	< 0.001

Moderate NAFLD	28 (15.3%)	233 (26.9%)	< 0.001
Severe NAFLD	10 (5.5%)	83 (9.6%)	< 0.001
Febuxostat Use	142 (77.6%)	391 (45.2%)	< 0.001
Allopurinol Use	8 (8.3%)	52 (6.0%)	0.439

Data are presented as the mean±SD for continuous variables or percentage for categorical variables.

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; Ccr, creatinine clearance; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FFA, free fatty acid; FPG, fasting plasma glucose; GGT, gamma-glutamyl transpeptidase; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment index of insulin resistance; LDL-C, Low density lipoprotein cholesterol; SBP, Systolic blood pressure; SUA, serum uric acid; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

Table 2. Clinical characteristics of study population stratified by the degree of NAFLD in Chinese gouty patients.

Characteristics	Non-NAFLD (N=418)	Mild NAFLD (N=277)	Moderate NAFLD (N=261)	Severe NAFLD (N=93)	P-value
Age, y	56.36±14.04	50.02±13.28	46.48±13.98	36.18±11.60	< 0.001
Men, %	408 (97.6%)	271 (97.8%)	254 (97.3%)	93 (100%)	0.215
BMI, kg/m ²	25.66±3.51	27.86±2.98	29.38±3.73	31.74±3.67	< 0.001
WC, cm	95.36±45.49	98.46±9.11	101.23±10.20	107.34±10.46	0.003
FPG, mmol/l	5.05±0.90	5.06±0.92	5.09±0.92	5.04±0.90	0.939
HOMA-IR	3.04±2.76	4.03±3.86	4.61±5.05	6.00±4.43	< 0.001
BP, mmHg					
Systolic	135.90±19.92	135.45±17.57	137.35±16.97	139.09±15.04	0.285
Diastolic	83.44±12.25	85.05±12.16	85.95±11.32	87.69±11.02	0.004
Lipid Profile, mmol/l					
LDL-c	2.76±0.74	2.96±0.76	3.00±0.82	3.20±0.79	< 0.001
HDL-c	1.14±0.30	1.14±0.27	1.09±0.23	1.08±0.24	0.046
TG	1.51±1.23	2.04±1.32	2.25±1.58	2.76±1.58	< 0.001
TC	4.60±0.99	4.89±1.03	4.95±1.02	5.22±0.94	< 0.001
FFA	0.40±0.16	0.44±0.17	0.45±0.16	0.53±0.19	< 0.001
Liver Enzymes, IU/l					
ALT	30.32±29.47	47.11±52.58	52.75±44.62	79.90±57.45	< 0.001
AST	20.87±15.08	25.77±22.72	25.79±13.39	34.26±18.37	< 0.001
GGT	47.53±53.39	56.28±62.14	52.92±40.49	59.93±34.93	0.070
SUA, umol/l	468.30±118.70	465.04±116.75	500.21±129.02	563.37±127.85	< 0.001
Renal Function Parameters					

Gouty nephropathy, %	114 (27.3)	31 (11.2)	29 (11.1)	9 (9.7%)	< 0.001
eGFR, ml/min/1.73m ²	82.58±29.97	94.27±25.94	96.27±26.20	106.78±29.81	< 0.001
Ccr, ml/min	93.27±45.00	118.16±42.48	131.11±53.44	169.26±50.39	< 0.001
SCr, umol/l	100.99±54.29	85.81±26.53	85.90±22.81	84.74±22.60	< 0.001
BUN, mmol/l	6.84±3.84	5.57±2.23	5.40±1.90	5.10±1.34	< 0.001
Cys C, mg/l	1.33±0.54	1.04±0.26	1.07±0.29	0.99±0.13	< 0.001
Smoking, %	223 (53.3%)	138 (49.8%)	129 (49.4%)	31 (33.3%)	0.010
Hypertension, %	231 (55.3%)	132 (47.7%)	119 (45.6%)	43 (46.2%)	0.050
Febuxostat Use, %	231 (55.3%)	140 (50.5%)	125 (47.9%)	37 (39.8%)	0.030
Allopurinol Use, %	27 (6.5%)	17 (6.1%)	12 (4.6%)	4 (4.3%)	0.716

Data are presented as the mean±SD for continuous variables or percentage for categorical variables.

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; Ccr, creatinine clearance; Cys C, Cystatin C; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FFA, free fatty acid; FPG, fasting plasma glucose; GGT, gamma-glutamyl transpeptidase; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment index of insulin resistance; LDL-C, Low density lipoprotein cholesterol; SBP, Systolic blood pressure; SCr, serum creatinine; SUA, serum uric acid; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

Table 3 Odds of prevalent gout nephropathy in patients with different ultrasonographic severity of NAFLD as compared to patients with non-NAFLD.

Regression models	OR	95% CI	P value
<i>Unadjusted model</i>			
Non-NAFLD	1		
Mild NAFLD	0.336	0.218-0.517	< 0.001***
Moderate NAFLD	0.320	0.205-0.510	< 0.001***
Severe NAFLD	0.321	0.161-0.641	0.001**
<i>Model 1</i>			
Non-NAFLD	1		
Mild NAFLD	0.394	0.254-0.612	< 0.001***
Moderate NAFLD	0.388	0.245-0.614	< 0.001***
Severe NAFLD	0.152	0.046-0.499	0.002**
<i>Model 2</i>			
Non-NAFLD	1		
Mild NAFLD	0.392	0.248-0.619	< 0.001***
Moderate NAFLD	0.379	0.233-0.616	< 0.001***
Severe NAFLD	0.148	0.043-0.512	0.003**

Significance: *P < 0.05; **P < 0.01; ***P < 0.001.

Model 1, unadjusted; Model 2, adjusted for age, sex and smoking; Model 3, further adjusted for gout duration, obesity, hypertension, hyperglycemia, hyperuricemia, and hyperlipidemia.

Abbreviations: CI, confidence interval; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio.

Table 4 Correlation analysis between serum uric acid and metabolism-related parameters.

Variable	Serum uric acid					
	Total		No gouty nephropathy		Gouty nephropathy	
	Coefficient	P value	Coefficient	P value	Coefficient	P value
BMI, kg/m ²	0.150	< 0.001***	0.200	< 0.001***	-0.020	0.791
WC, cm	0.153	< 0.001***	0.187	< 0.001***	0.023	0.766
SBP, mmHg	0.033	0.280	0.050	0.142	-0.072	0.336
DBP, mmHg	0.088	0.005**	0.098	0.004**	0.026	0.731
HOMA-IR	0.120	0.005**	0.131	0.004**	0.079	0.504
LDL-c, mmol/L	0.122	< 0.001***	0.151	< 0.001***	0.009	0.910
HDL-c, mmol/L	-0.042	0.181	-0.024	0.473	-0.111	0.145
TG, mmol/L	0.184	< 0.001***	0.230	< 0.001***	0.022	0.768
TC, mmol/L	0.131	< 0.001***	0.160	< 0.001***	0.015	0.843
Hypertension	0.057	0.066	-0.073	0.032*	-0.061	0.411
NAFLD severity	0.176	< 0.001***	0.247	< 0.001***	-0.054	0.466

Significance: *P < 0.05; **P < 0.01; ***P < 0.001.

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein-cholesterol; HOMA-IR, homeostasis model assessment index of insulin resistance; LDL-c, low-density lipoprotein-cholesterol; NAFLD, nonalcoholic fatty liver disease; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

Figures

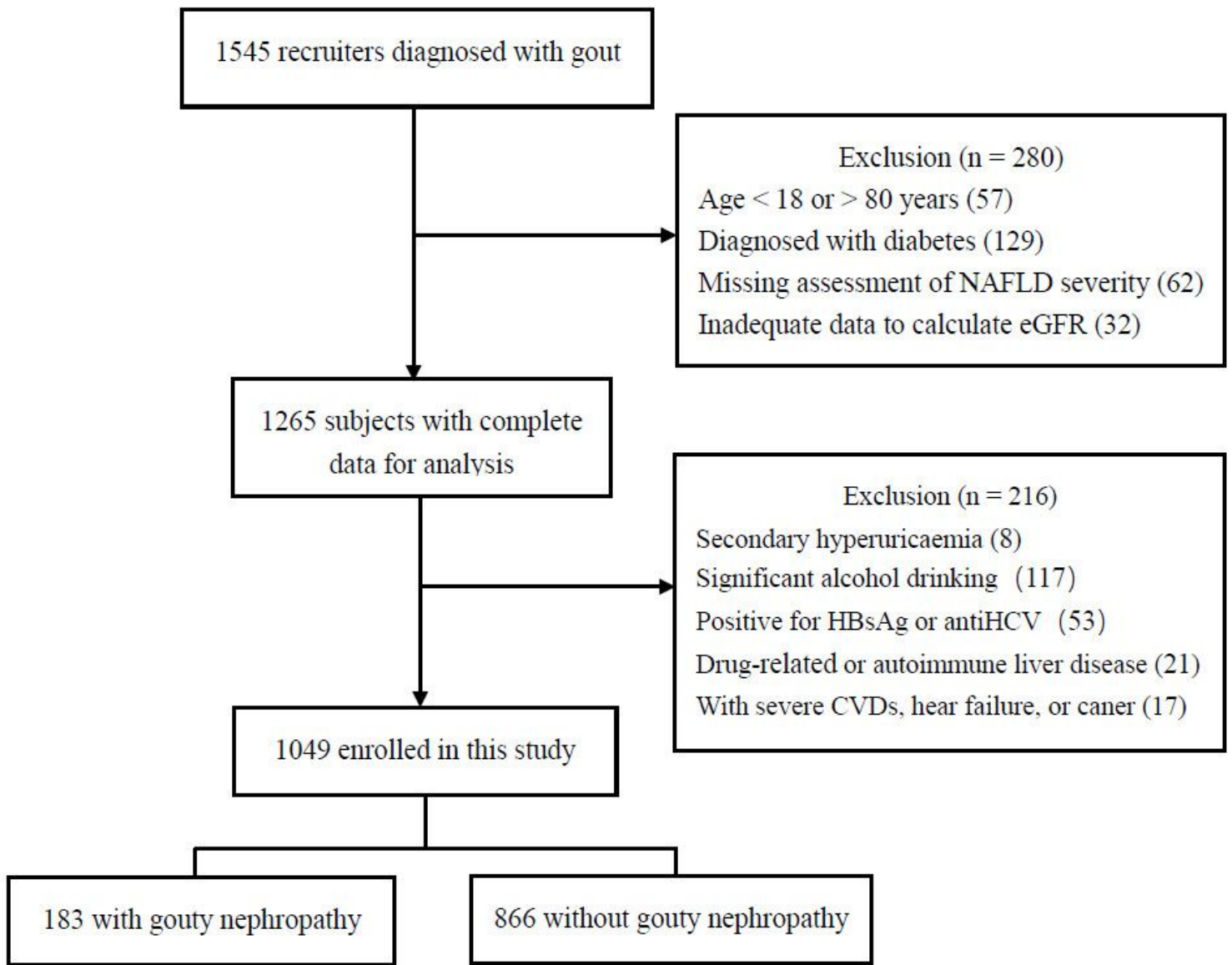


Figure 1

Flow chart of patient selection. Abbreviations: CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; NAFLD, nonalcoholic fatty liver disease.

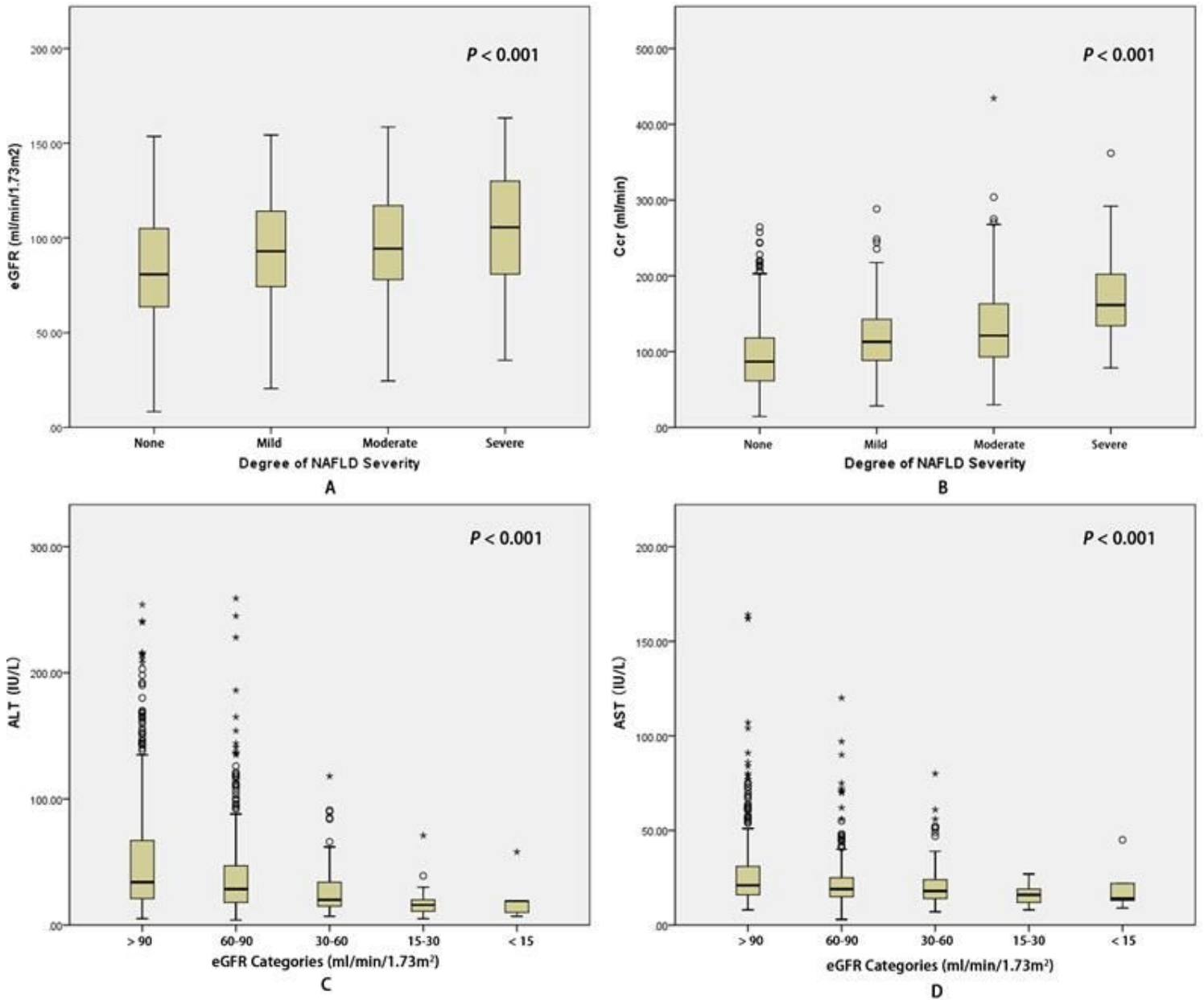


Figure 2

The box plots of eGFR and Ccr levels stratified by degree of NAFLD severity, and serum transaminases levels stratified by eGFR categories. A. eGFR levels stratified by degree of NAFLD severity; B. Ccr levels stratified by degree of NAFLD severity; C. ALT levels stratified by eGFR categories; D. AST levels stratified by eGFR categories. Data are presented as medians, 25th and 75th percentiles (boxes), and 10th and 90th percentiles (whiskers). Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; Ccr, creatinine clearance; eGFR, estimated glomerular filtration rate; NAFLD, non-alcoholic fatty liver disease.

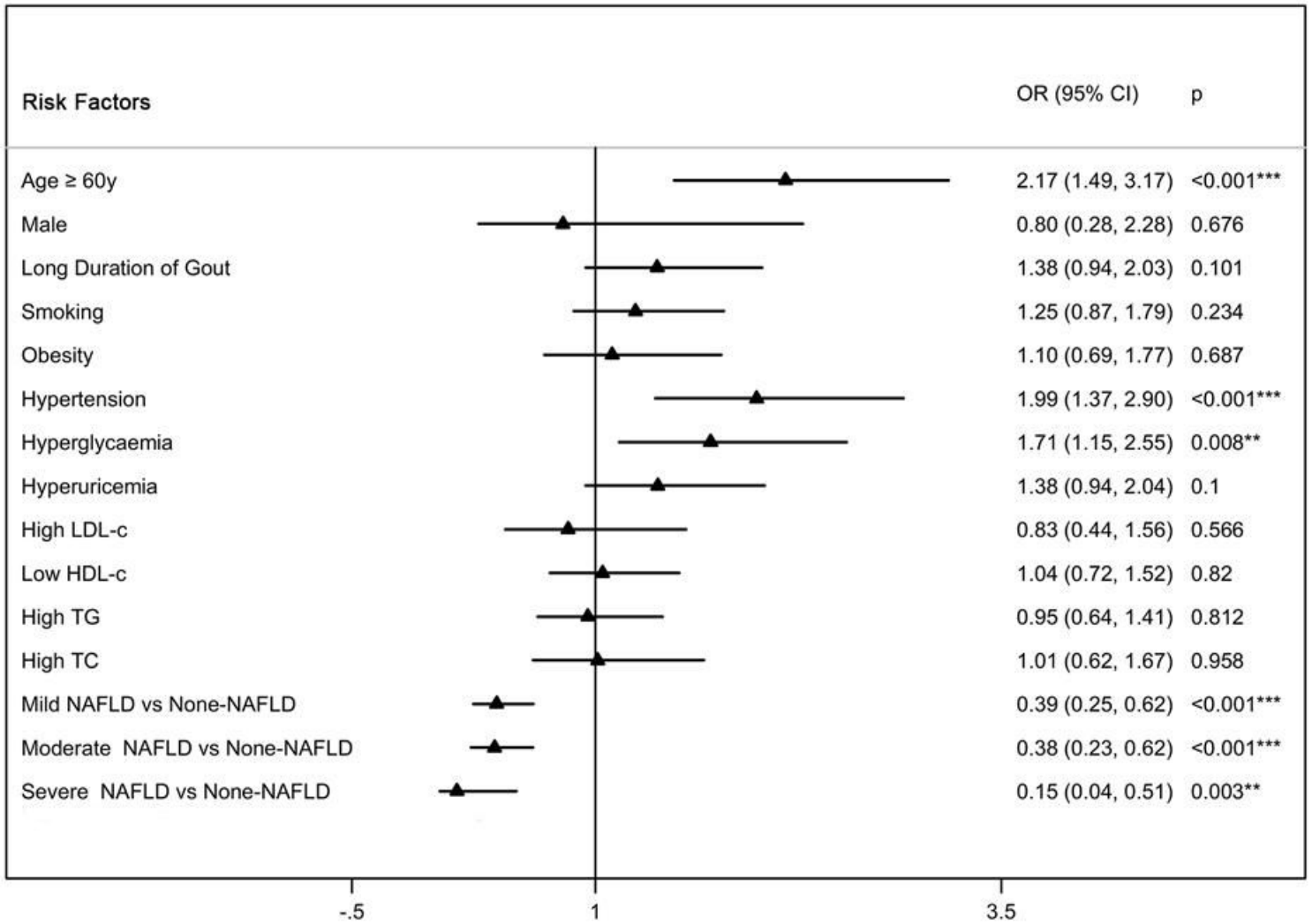


Figure 3

Multivariate logistic regression analysis of risk factors for gouty nephropathy. Obesity was defined as BMI > 29.9 kg/m². Hypertension was defined by systolic blood pressure ≥ 140mmHg or diastolic blood pressure ≥ 90mmHg, or self-reported previous diagnosis of hypertension by physicians. Hyperglycaemia was defined as a fasting glucose ≥ 100 mg/dL (5.56 mmol/L). Hyperuricemia was defined as serum uric acid > 420 μmol/L in male and > 360 μmol/L in female. High LDL-c was defined as ≥ 140 mg/dL (3.63 mmol/L). Low HDL-c was defined as < 40 mg/dL (1.04 mmol/L) in male, and < 50 mg/dL (1.30 mmol/L) in female. High TG was defined as ≥ 150 mg/dL (1.70 mmol/L). High TC was defined as ≥ 200 mg/dL (5.18 mmol/L). Abbreviations: HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; NAFLD, non-alcoholic fatty liver disease; TG, triglyceride; TC, total cholesterol.