Research Square

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# Aspartate aminotransferase/alanine aminotransferase ratio is associated with hyperuricemia in type 2 diabetic populations: a cross-sectional study

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## Abstract

# Background

Aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio has been shown to be associated with type 2 diabetes and its complications. The aim of this paper is to investigate the relationship between AST/ALT ratio and hyperuricemia in a type 2 diabetes population.

# Methods

There were 1997 subjects, 597 of whom had hyperuricemia. Multivariate binary logistic regression analysis was applied to explore the correlation between AST/ALT ratio and hyperuricemia. Stratified by gender and body mass index (BMI), the predictive value of different subgroups was compared.

# Results

The risk of hyperuricemia in patients with type 2 diabetes mellitus (T2DM) is negatively correlated with AST/ALT ratio. In unadjusted models, each standard deviation (SD) increase in AST/ALT ratio was associated with a 64% reduction in the risk of hyperuricemia (95% CI: 0.27,0.48; P < 0.001). After adjusting for sex, gender, body mass index (BMI), fasting blood glucose (FBG) and glycosylated hemoglobin (HbA1c), the adjusted odds ratio (OR) and 95% confidence interval (CI) of model 4 was 0.54 (0.35,0.82).

# Conclusion

AST/ALT ratio is associated with the risk of hyperuricemia in patients with T2DM, especially in overweight and young adults.

## INTRODUCTION

Hyperuricemia is the deposition of urates in the body due to excessive secretion or excretion of uric acid [1], which is thought to be associated with a variety of diseases including diabetes, metabolic syndrome, and cardiovascular disease [2–3]. The overall prevalence of hyperuricemia in China is 13.3% [4], which has become another common metabolic disease after diabetes mellitus [5]. Uric acid is the end product of purine breakdown. Xanthine oxidase, a key enzyme in uric acid production, is most expressed in the liver, and some studies have confirmed that fatty liver disease and hyperuricemia are mutually causative [6]. Krishnan E et al. demonstrated in a 15-year follow-up that hyperuricemia in the 20s is an indicator of future diabetes and prediabetes [7], and that diabetic patients with hyperuricemia are at elevated risk of

developing diabetic complications [8]. Meanwhile, type 2 diabetes mellitus (T2DM) and nonalcoholic fatty liver disease (NAFLD) are also strongly linked [9].

Routine tests for liver function include glutamic oxalacetic transaminase and glutamic alanine transaminase, which tend to be elevated in cases of liver injury. In 1957 De Ritis proposed an index reflecting simultaneous changes in aspartate aminotransferase (AST) and alanine aminotransferase (ALT): the Aspartate aminotransferase/alanine aminotransferase ratio (AST/ALT ratio), named after him as the De Ritis ratio [10]. AST/ALT ratio was usually considered as an essential predictor of severe hepatic fibrosis (bridging/cirrhosis) in the past [11], and in recent years its significance in pathological processes such as systemic inflammatory response, insulin resistance, and its proven association with diabetic vascular complications and neuropathy has been gradually discovered [12–14]. However, no discussion exists for ARR versus hyperuricemia in patients with T2DM, and the mechanism is unknown.

The aim of this cross-sectional study was to investigate the relationship between AST/ALT ratio and hyperuricemia in a diabetic population and to discuss the possible mechanisms.

## MATERIALS AND METHODS

## Study population

In this retrospective study, we collected 2317 hospitalization records from 2017 to 2022 from the Department of Endocrinology and Metabolism, General Hospital of Tianjin Medical University. All patients were discharged with a diagnosis of type 2 diabetes. This study was approved by the hospital ethics committee and informed consent was not required because the data were derived from electronic medical records and did not show true information of the patients. Exclusion criteria: (1) patients with missing AST values; (2) patients with ALT deficiency; (3) patients with unknown hyperuricemia status. Finally, 1997 patients were enrolled. (Fig. 1)

## Data collection

The patient's height and weight were measured on admission by a corrected standard measuring device. Body mass index (BMI) is the calculate of weight (kg) divided by the square of height ($m^2$). Estimate glomerular filtration rate (eGFR) was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [15]. Patients' systolic and diastolic blood pressures were recorded by averaging after two measurements using a standard sphygmomanometer in a quiet environment in the morning. We also collected patients' age, gender, duration of diabetes, status of smoking, family history of diabetes (FH of DM), fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), albumin (ALB), Aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl-transferase (GGT), lactate dehydrogenase (LDH), total bilirubin (TBIL), total cholesterol (TC), total triglycerides (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), and uric acid(UA) values.

## Definitions

Diabetes was diagnosed by fasting blood glucose value ≥ 7.0 mmol/L, 2-hour postprandial blood glucose value ≥ 11.1 mmol/L, HbA1c ≥ 6.5%, previous confirmation of diabetes, or application of antidiabetic drugs [16].

Hyperuricemia is defined as a blood uric acid level of more than 420 μmol/L on two different days, in both men and women [5].

BMI was used as a cut point at 18.5, 24 and 28, respectively. BMI < 18.5 is underweight, normal weight is BMI between 18.5 and 23.9, overweight is BMI between 24.0 and 27.9, and obese is BMI ≥ 28 [17].

# Statistical analysis

All analyses were performed using IPB SPSS for Windows (version 27.0, Armonk, NY, USA) and R software (version 4.4.1). Continuous and categorical variables are expressed as mean ± SD and percentage, respectively, and continuous variables with skewed distribution are expressed as median and quartiles. Student' s *t*-test was used for continuous variables conforming to normal distribution. Continuous variables that did not conform to a normal distribution were analyzed using the Mann–Whitney *U* test. Categorical data were analyzed using $\chi 2$ test. The relationship between the variables was represented by Spearman correlation coefficient (r). the relationship between AST/ALT ratio and hyperuricemia was determined by binary logistic regression analysis, calculating odd ratios (ORs) and corresponding 95% confidence intervals (CIs). logistic regression analysis adjusted for the following variables: model 1 was unadjusted. Model 2 was adjusted for age and gender; model 3 was adjusted for BMI based on model 2; and model 4 was adjusted for FBG and HbA1c based on model 3. The ability of AST/ALT ratio to predict hyperuricemia was evaluated by ROC curve. Restricted cubic spline (RCS) was used to analyze the dose-response relationship between AST/ALT ratio and the risk of HUA

## RESULTS

# Baseline characteristics of the study participants

The basic characteristics of the subjects are shown in Table 1. A total of 1997 subjects were included in this study. Among the patients with hyperuricemia, 62.5% were male, 20.4% were smokers, and 24.3% had a family history of diabetes. BMI ($P < 0.001$), TG($P < 0.001$), TBIL($P < 0.001$), UA ($P < 0.001$) and GGT ($P < 0.001$) in the hyperuricemia group were significantly higher than those in the non-hyperuricemia group. Interestingly, although AST/ALT ratio ($P < 0.001$) was lower in the hyperuricemia group, ALT($P < 0.001$) and AST($P < 0.001$) were significantly higher in the hyperuricemia group than in the non-hyperuricemia group.

Table 1
Baseline characteristics of the study participants

| Variables | HUA | Non-HUA | P-value |
|---|---|---|---|
| No. of participants | 597 | 1400 | |
| Age (years) | 51.12 ± 16.94 | 57.75 ± 14.14 | < 0.001 |
| Duration of DM (years) | (6,20) | (6,20) | 0.518 |
| Male, % | 62.5 | 48.0 | < 0.001 |
| Smoker, % | 20.4 | 30.9 | < 0.001 |
| FH of DM, % | 24.3 | 48.5 | < 0.001 |
| FBG (mmol/L) | 7.32 ± 3.03 | 8.38 ± 3.25 | < 0.001 |
| HbA1c (%) | 8.08 ± 2.10 | 8.49 ± 2.51 | 0.001 |
| BMI (kg/m²) | 32.93 ± 33.62 | 26.76 ± 4.38 | < 0.001 |
| SBP (mmHg) | 136.65 ± 20.51 | 136.12 ± 18.02 | 0.576 |
| DBP (mmHg) | 83.88 ± 13.39 | 83.74 ± 47.09 | 0.944 |
| ALB (g/L) | 39.68 ± 4.51 | 41.29 ± 4.51 | < 0.001 |
| ALT (U/L) | 40.15 ± 40.05 | 25.07 ± 30.53 | < 0.001 |
| AST (U/L) | 29.31 ± 27.23 | 21.77 ± 20.71 | < 0.001 |
| GGT (U/L) | 54.81 ± 70.78 | 35.73 ± 53.24 | < 0.001 |
| LDH (U/L) | 186.79 ± 65.37 | 199.18 ± 61.02 | < 0.001 |
| TBIL (umol/L) | 12.30 ± 6.42 | 10.71 ± 5.77 | < 0.001 |
| TC (mmol/L) | 5.08 ± 1.58 | 5.09 ± 1.53 | 0.848 |
| TG (mmol/L) | 3.05 ± 3.03 | 2.23 ± 2.25 | < 0.001 |
| HDL-c (mmol/L) | 0.99 ± 0.29 | 1.13 ± 0.33 | < 0.001 |
| LDL-c (mmol/L) | 3.05 ± 1.19 | 3.04 ± 1.10 | 0.970 |
| eGFR | 96.98 ± 30.80 | 99.81 ± 21.15 | 0.043 |

Data was presented as mean ± SD, weighted median (25th percentile, 75th percentile) or n (%).

DM, diabetes mellitus; FH of DM, Family history of DM; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; LDH, Lactate dehydrogenase; TBIL, Total bilirubin; TC, total cholesterol; TG, total triglycerides; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; eGFR, Estimate glomerular filtration rate; UA, uric acid.

| Variables | HUA | Non-HUA | P-value |
|---|---|---|---|
| (mL/min/1.73m²) | | | |
| UA (umol/L) | 459.97 ± 95.69 | 306.68 ± 81.93 | < 0.001 |
| AST/ALT ratio | 0.88 ± 0.40 | 1.03 ± 0.46 | < 0.001 |
| Data was presented as mean ± SD, weighted median (25th percentile, 75th percentile) or n (%). | | | |
| DM, diabetes mellitus; FH of DM, Family history of DM; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; LDH, Lactate dehydrogenase; TBIL, Total bilirubin; TC, total cholesterol; TG, total triglycerides; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; eGFR, Estimate glomerular filtration rate; UA, uric acid. | | | |

**Correlation of AST/ALT** ratio **with clinical variables**

In all subjects, AST/ALT ratio was positively correlated with subject's age ($r = 0.233$, $P < 0.001$), gender ($r = 0.188$, $P < 0.001$), LDH ($r = 0.092$, $P < 0.001$) and HDL-c ($r = 0.158$, $P < 0.001$). AST/ALT ratio was negatively correlated with FBG ($r = -0.061$, $P = 0.010$), BMI ($r = -0.079$, $P < 0.001$), TBIL ($r = -0.079$, $P < 0.001$), ALT ($r = -0.340$, $P < 0.001$), UA ($r = -0.118$, $P < 0.001$), eGFR ($r = -0.183$, $P < 0.001$) and ALB ($r = -0.169$, $P < 0.001$). Meanwhile, AST/ALT ratio was not significantly correlated with smoking status, family history of diabetes mellitus, SBP, TC, and LDL-c levels. (Table 2)

Table 2
Univariate correlations between AST/ALT ratio and metabolic variables

| Variables | AST/ALT ratio | |
|---|---|---|
| | r | p |
| Age (years) | 0.233 | < 0.001 |
| Duration of DM (years) | 0.233 | < 0.001 |
| Male, % | 0.188 | < 0.001 |
| Smoker, % | -0.039 | 0.081 |
| FH of DM, % | 0.015 | 0.511 |
| FBG (mmol/L) | -0.061 | 0.010 |
| HbA1c (%) | -0.041 | 0.075 |
| BMI (kg/m²) | -0.079 | < 0.001 |
| SBP (mmHg) | -0.001 | 0.981 |
| DBP (mmHg) | -0.048 | 0.035 |
| ALB (g/L) | -0.169 | < 0.001 |
| ALT (U/L) | -0.340 | < 0.001 |
| AST (U/L) | -0.023 | 0.309 |
| GGT (U/L) | -0.093 | < 0.001 |
| LDH (U/L) | 0.092 | < 0.001 |
| TBIL (umol/L) | -0.079 | < 0.001 |
| TC (mmol/L) | -0.001 | 0.953 |
| TG (mmol/L) | -0.084 | < 0.001 |
| HDL-c (mmol/L) | 0.158 | < 0.001 |
| LDL-c (mmol/L) | -0.013 | 0.559 |
| eGFR (mL/min/1.73m²) | -0.183 | < 0.001 |
| UA (umol/L) | -0.118 | < 0.001 |

DM, diabetes mellitus; FBG, fasting blood glucose; FH of DM, Family history of DM; HbA1c, glycosylated hemoglobin; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; LDH, Lactate dehydrogenase; TBIL, Total bilirubin; TC, total cholesterol; TG, total triglycerides; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; eGFR, Estimate glomerular filtration rate; UA, uric acid.

**Relation between AST□ALT□AST/ALT** ratio **and hyperuricemia**

The correlation between AST/ALT and the risk of prevalence of hyperuricemia is demonstrated in Table 3. Regardless of the model used, AST/ALT ratio was significantly associated with the risk of hyperuricemia. In model 1, each unit increase in the AST/ALT ratio was associated with a 64% reduction in the risk of hyperuricemia (unadjusted; 95% CI: 0.27 to 0.48; $P < 0.001$). This apparent correlation persisted even after adjusting for age, gender, BMI and FBG, HbA1c levels. In fully adjusted model 4, the OR (95% CI) per unit increase in subjects' AST/ALT was 0.54 (0.34–0.93; $P < 0.01$). In addition, in the fully adjusted model, the fully adjusted odds ratio (95% CI) for tertile 3 versus tertile 1 was 0.53 (0.37 to 0.77; $P = 0.001$ for trend).

Table 3

Odds ratios (95% CI) for association of AST、ALT、AST/ALT ratio with the prevalence of hyperuricemia.

| | N | OR (95%CI) | | | |
|---|---|---|---|---|---|
| | | **Model 1** | **Model 2** | **Model 3** | **Model 4** |
| AST | | | | | |
| Tertile1 | 742 | Ref. | Ref. | Ref. | Ref. |
| Tertile2 | 613 | 1.37* (1.07,1.76) | 1.41** (1.10,1.83) | 1.48** (1.12,1.96) | 1.73** (1.21,2.46) |
| Tertile3 | 642 | 2.68*** (2.12,3.39) | 2.44*** (1.91,3.10) | 2.19*** (1.67,2.88) | 2.54*** (1.80,3.59) |
| P for trend | | < 0.001 | < 0.001 | < 0.001 | < 0.001 |
| AST (continuous) | 1997 | 1.02*** (1.01,1.02) | 1.01*** (1.01,1.02) | 1.01*** (1.01,1.02) | 1.01** (1.01,1.02) |
| ALT | | | | | |
| Tertile1 | 750 | Ref. | Ref. | Ref. | Ref. |
| Tertile2 | 610 | 1.69*** (1.30,2.18) | 1.67*** (1.29,2.16) | 1.54** (1.16,2.05) | 1.75** (1.21,2.51) |
| Tertile3 | 637 | 3.65*** (2.87,4.65) | 2.90*** (2.25,3.72) | 2.36*** (1.77,3.14) | 2.76*** (1.93,3.97) |
| P for trend | | < 0.001 | < 0.001 | 0.001 | 0.002 |
| ALT (continuous) | 1997 | 1.02*** (1.01,1.02) | 1.01*** (1.007,1.014) | 1.01*** (1.005,1.013) | 1.01*** (1.004,1.013) |
| AST/ALT ratio | | | | | |
| Tertile1 | 668 | Ref. | Ref. | Ref. | Ref. |
| Tertile2 | 671 | 0.51*** (0.41,0.65) | 0.62*** (0.49,0.79) | 0.68** (0.52,0.89) | 0.63** (0.45,0.87) |

AST (U/L): T1 ≤ 16, 17 ≤ T2 ≤ 22, T3 ≥ 23; ALT (U/L): T1 ≤ 16, 17 ≤ T2 ≤ 27, T3 ≥ 28; AST/ALT ratio: T1 ≤ 0.78, 0.79 ≤ T2 ≤ 1.07, T3 ≥ 1.08. Model 1: unadjusted. Model 2: adjusted for age and gender; Model 3: adjusted for Model 2 plus BMI; Model 4: adjusted for Model 3 plus FBG, HbA1c.

*P < 0.05, **P < 0.01, ***P < 0.001. OR, odds ratio; CI, confidence interval; BMI, body mass index; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

| | N | OR (95%CI) | | | |
|---|---|---|---|---|---|
| | | Model 1 | Model 2 | Model 3 | Model 4 |
| Tertile3 | 658 | 0.35*** | 0.47*** | 0.57*** | 0.53*** |
| | | (0.28,0.45) | (0.37,0.61) | (0.43,0.77) | (0.37,0.77) |
| P for trend | | < 0.001 | < 0.001 | < 0.001 | 0.001 |
| AST/ALT ratio | 1997 | 0.36*** | 0.52*** | 0.64** | 0.54** |
| (continuous) | | (0.27,0.48) | (0.39,0.69) | (0.47,0.88) | (0.35,0.82) |

AST (U/L): T1 ≤ 16, 17 ≤ T2 ≤ 22, T3 ≥ 23; ALT (U/L): T1 ≤ 16, 17 ≤ T2 ≤ 27, T3 ≥ 28; AST/ALT ratio: T1 ≤ 0.78, 0.79 ≤ T2 ≤ 1.07, T3 ≥ 1.08. Model 1: unadjusted. Model 2: adjusted for age and gender; Model 3: adjusted for Model 2 plus BMI; Model 4: adjusted for Model 3 plus FBG, HbA1c.

*P < 0.05, **P < 0.01, ***P < 0.001. OR, odds ratio; CI, confidence interval; BMI, body mass index; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

## Subgroup analyses

We also performed subgroup analyses (Table 4). The association between AST/ALT ratio and the incidence of hyperuricemia was stratified by BMI, age, gender and Smoking status. As shown in Table 4, in the following subgroups (model 4): age < 60 (P < 0.01), female(P < 0.05), BMI ≥ 24 (P < 0.01) and non-smoker(P < 0.01), higher AST/ALT ratio levels were associated with lower incidence of hyperuricemia.

Table 4
Subgroup analysis for the association of AST/ALT ratio with the prevalence of hyperuricemia.

| Subgroup | N | OR (95%CI) | | | |
|---|---|---|---|---|---|
| | | Model 1 | Model 2 | Model 3 | Model 4 |
| Gender | | | | | |
| Male | 1045 | 0.44*** (0.30,0.64) | 0.70 (0.48,1.01) | 0.86 (0.55,1.32) | 0.67 (0.37,1.22) |
| Female | 946 | 0.37*** (0.23,0.58) | 0.39*** (0.25,0.62) | 0.49** (0.30,0.80) | 0.48* (0.25,0.89) |
| Smoker | | | | | |
| NO | 1428 | 0.32*** (0.23,0.45) | 0.49*** (0.35,0.68) | 0.59** (0.41,0.84) | 0.47** (0.28,0.80) |
| YES | 554 | 0.44** (0.24,0.82) | 0.75 (0.41,1.36) | 1.06 (0.55,2.06) | 0.83 (0.39,1.78) |
| BMI | | | | | |
| < 24 | 388 | 0.72 (0.39,1.33) | 0.74 (0.40,1.37) | — | 0.34 (0.11,1.02) |
| ≥ 24 | 1366 | 0.30*** (0.21,0.44) | 0.56** (0.39,0.82) | — | 0.52** (0.33,0.82) |
| Age | | | | | |
| < 60 | 1036 | 0.22*** (0.15,0.34) | 0.26*** (0.17,0.41) | 0.48** (0.30,0.78) | 0.38** (0.21,0.70) |
| ≥ 60 | 955 | 0.89 (0.63,1.25) | 0.89 (0.63,1.26) | 0.80 (0.53,1.20) | 0.66 (0.36,1.20) |

Model 1: unadjusted. Model 2: adjusted for age and gender; Model 3: adjusted for Model 2 plus BMI; Model 4: adjusted for Model 3 plus FBG, HbA1c. When not involved.

*P < 0.05, **P < 0.01, ***P < 0.001. OR, odds ratio; CI, confidence interval; BMI, body mass index; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin.; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

## The predictive value of AST/ALT ratio for hyperuricemia

The predictive ability of AST/ALT ratio for hyperuricemia was assessed using ROC curve analysis (Fig. 2). ROC curve analysis showed that the area under curve (AUC) was 0.630 (95%CI: 0.60–0.66, P < 0.001), indicating that AST/ALT ratio had a certain predictive value for hyperuricemia. When 0.692 was used as the best cut-off value, the sensitivity was 0.839 and the specificity was 0.635, indicating that this index was more sensitive in identifying positive samples.

# Non-Linear Association Between AST/ALT ratio and hyperuricemia

Restricted cubic spline (RCS) was used to analyze the dose-response relationship between AST/ALT ratio and the risk of hyperuricemia. Taking the median of AST/ALT ratio as the reference point (OR = 1), after adjusting for age, gender, BMI, HbA1c and FBG, the results showed that there was a significant nonlinear association between AST/ALT ratio and hyperuricemia (nonlinear test P < 0.001). When AST/ALT ratio was less than 1.0, the risk of HUA increased significantly with the decrease of AST/ALT. When AST/ALT ratio ≥ 1.0, the risk plateaued. (Fig. 3)

# DISCUSSION

This study is the first to investigate the relationship between AST/ALT ratio and hyperuricemia in patients with type 2 diabetes and found a nonlinear relationship between the two. When AST/ALT ratio is < 1, the risk of hyperuricemia increases with the decrease of the ratio. This confirms that the AST/ALT ratio may be a predictor of hyperuricemia.

Globally, the prevalence and incidence of hyperuricemia will both increase substantially from 2000 to 2023, remain higher in high-income and urban Settings, and increase with age [18]. The liver is a key organ involved in biotransformation in the body, and all types of exogenous and endogenous substances can cause liver damage [19]. Elevated aminotransferase activity is considered to be an indicator marker of hepatotoxicity [20]. The liver is the site of origin with the highest expression of xanthine oxidase protein, the main enzyme responsible for uric acid formation [21]. Therefore, it can be assumed that the liver is chronically exposed to relatively high levels of uric acid concentration. When the body is at risk of developing hyperuricemia, the liver cells are also able to perceive the increase in uric acid concentration in the surrounding environment earlier, although at this time the uric acid level is still in the normal range.

As mentioned earlier, liver enzymes such as AST, ALT, and GGT are elevated when there is liver damage. AST/ALT ratio, however, is widely used as a noninvasive indicator to predict the risk of serious liver outcomes in the general population for various liver diseases, including NAFLD, and to detect advanced liver fibrosis/cirrhosis. [22–23] During a mean follow-up of 12.9 years (range = 4 to 21) in 5518 participants, higher serum UA levels were associated with higher mean ALT levels [24]. Similarly, National adolescent data from the US National Health and Nutrition Examination Survey (NHANES) also found that ALT levels should be closely monitored while UA was monitored [25]. These findings suggest that,

also as a marker of liver injury, perhaps ALT elevation is more pronounced and of greater concern. Our data show that both AST and ALT are risk factors for hyperuricemia, but their ratio is inversely proportional to the risk of hyperuricemia, which may be related to the more obvious changes in ALT. In addition, the ALT/AST ratio may be more accurate in identifying hepatic steatosis than ALT or AST alone [26].

In recent years, the AST/ALT ratio has received much attention. Some studies have found that a lower AST/ALT ratio is associated with increased insulin resistance in people with normal ALT ranges [26]. Similarly, the risk of diabetes increased rapidly when AST/ALT ratio was ≤ 1.18 in the cross-sectional study of Chinese population [27]. In addition, high ALT values are associated with hepatic insulin resistance [28]. Insulin resistance (IR) and hyperuricemia are also closely related and play a key role in each other's occurrence and development. Multiple surrogate indicators of insulin resistance were evaluated in non-diabetic Yi residents in Yunnan province, and it was found that multiple indicators were correlated with the occurrence of hyperuricemia [29]. Elevated serum uric acid, in turn, can promote insulin resistance. Excessive uric acid levels can lead to hepatic fat accumulation through activation of NOD-like receptor family containing 3 (NLRP3) inflammatory vesicles and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. [30–31] Meanwhile, insulin resistance (IR) present in patients with type 2 diabetes may amplify this effect[6]. Thus, the underlying elevated uric acid caused liver cell destruction, inducing the development of NAFLD, which in turn led to elevated ALT. This "vicious cycle" reflects the complex interplay among liver dysfunction, insulin resistance, and hyperuricemia [32]. Our study also revealed liver damage in patients with hyperuricemia, whose GGT values were significantly higher than those in subjects without hyperuricemia ($P < 0.001$). Thus, the correlation between AST/ALT and hyperuricemia in our study may be due to insulin resistance mediated.

The conversion of xanthine to uric acid is accompanied by the production of large amounts of reactive oxygen species (ROS). [33] Excess ROS production leads to oxidative stress. Whereas uric acid has both oxidative and antioxidant effects, hyperuricemia promotes the development of many diseases by utilizing the oxidative effect of uric acid. [34] It is well known that HDL-c has a variety of metabolic protective functions, while inflammation and oxidative stress can change the quantity and quality of HDL-c, leading to decreased levels and abnormal functions of HDL-c [35]. In our study, subjects with T2DM alone had higher HDL-c levels than those with hyperuricemia ($P < 0.001$). Correlation analysis showed that AST/ALT ratio was positively correlated with HDL-c ($P < 0.001$). Therefore, it is reasonable to speculate that oxidative stress plays a mediating role in the occurrence and development of AST/ALT ratio with hyperuricemia. However, further studies are needed.

The prevalence of hyperuricemia increased from 6.7% to 11.2% in women and from 12.3% to 18.6% in men worldwide [18]. The risk of hyperuricemia increases rapidly in women. Stratified analysis showed that the AST/ALT ratio was more meaningful in women. Previous studies have shown that female patients have more severe hepatic steatosis [36]. Moreover, the serum glutamine/glutamine ratio is

significantly higher in women than in men [37]. Thus, it may be more suggestive of hyperuricemia, but the mechanisms involved are not clear.

Excessive accumulation of adipose tissue in overweight individuals disrupts adipocytokine regulation, triggers the release of inflammatory cytokines, and leads to increased uric acid production [25]. In addition, hyperuricemia may be associated with the process of adipogenesis and/or catabolism. In terms of lipogenesis, fatty acid synthesis in adipocytes leads to increased triglyceride accumulation and purine synthesis, which in turn leads to elevated UA levels. They complement each other and have a dramatic impact on individual health. AST/ALT ratio has more predictive value in people with BMI ≥ 24, which indicates that it is a new evaluation index for hyperuricemia in people with known high risk of hyperuricemia, which can better predict the risk of disease and guide early prevention.

There are still some shortcomings in our study. First, our study is an observational study, which can only show that there is a correlation between the two, but cannot explain for the causal relationship. Second, the lack of abdominal ultrasound findings in some of the patients prevented us from evaluating how much of a role nonalcoholic fatty liver disease played in the relationship between AST/ALT ratio and hyperuricemia. Finally, our study included only patients with T2DM and needs to be expanded to a wider population.

## CONCLUSIONS

This study is the first to investigate the relationship between AST/ALT ratio and hyperuricemia, and there is a nonlinear correlation between the two. It provides a new idea for disease prediction in diabetic patients with normal serum uric acid. In the future, it is recommended that healthcare practitioners provide timely guidance on the prevention of hyperuricemia to individuals with AST/ALT ratios below 1.

## Declarations

### Ethics approval and consent to participate

The Institutional Review Board of Tianjin Medical University General Hospital approved the study in accordance with the Declaration of Helsinki. Informed consent was not obtained because the patient information was extracted from electronic medical records at the Department of Endocrinology and Metabolism, and the patients' identities were kept anonymous, except for date of birth. (Approval number: IRB2020-YX-027-01).

### Consent for publication

All authors consent to publication.

## Competing interests

The authors declare no interest conflict.

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# Author Contribution

WM is responsible for Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing.CQH is responsible for Investigation; Methodology; Project administration; Writing – review & editing.CJQ is responsible for Conceptualization; Investigation; Methodology; Supervision; Writing – review & editing.

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# Data Availability

Data were obtained from the corresponding author.

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# Figures

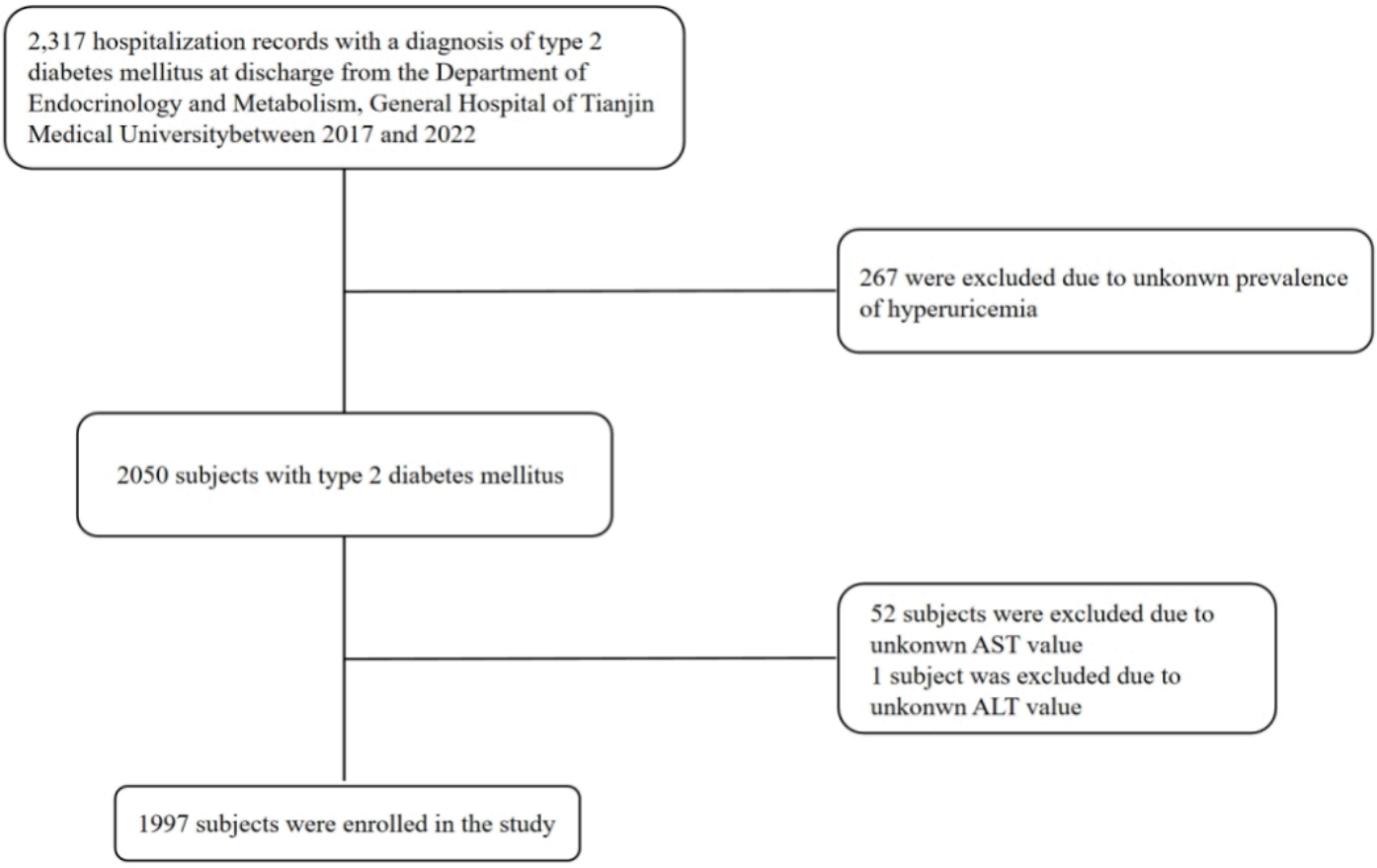



**Figure 1**

Flowchart of identification of study population. Based on the exclusion criteria, a total of 1997 patients with T2DM were included.

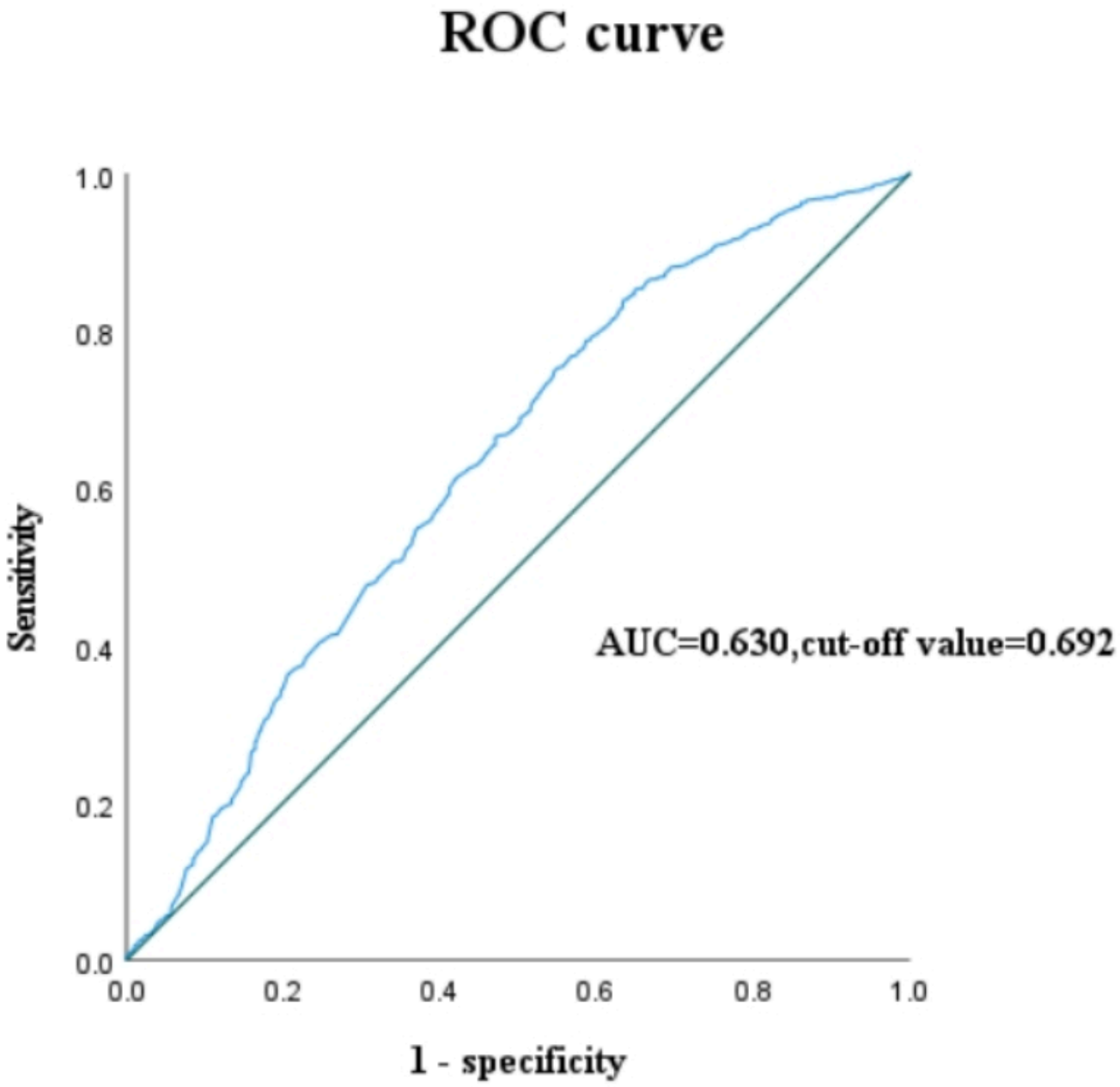



**Figure 2**

Receiver operating curve (ROC) for the analysis of AST/ALT ratio as the predictor of hyperuricemia in the study population. AUC indicates area under curve.

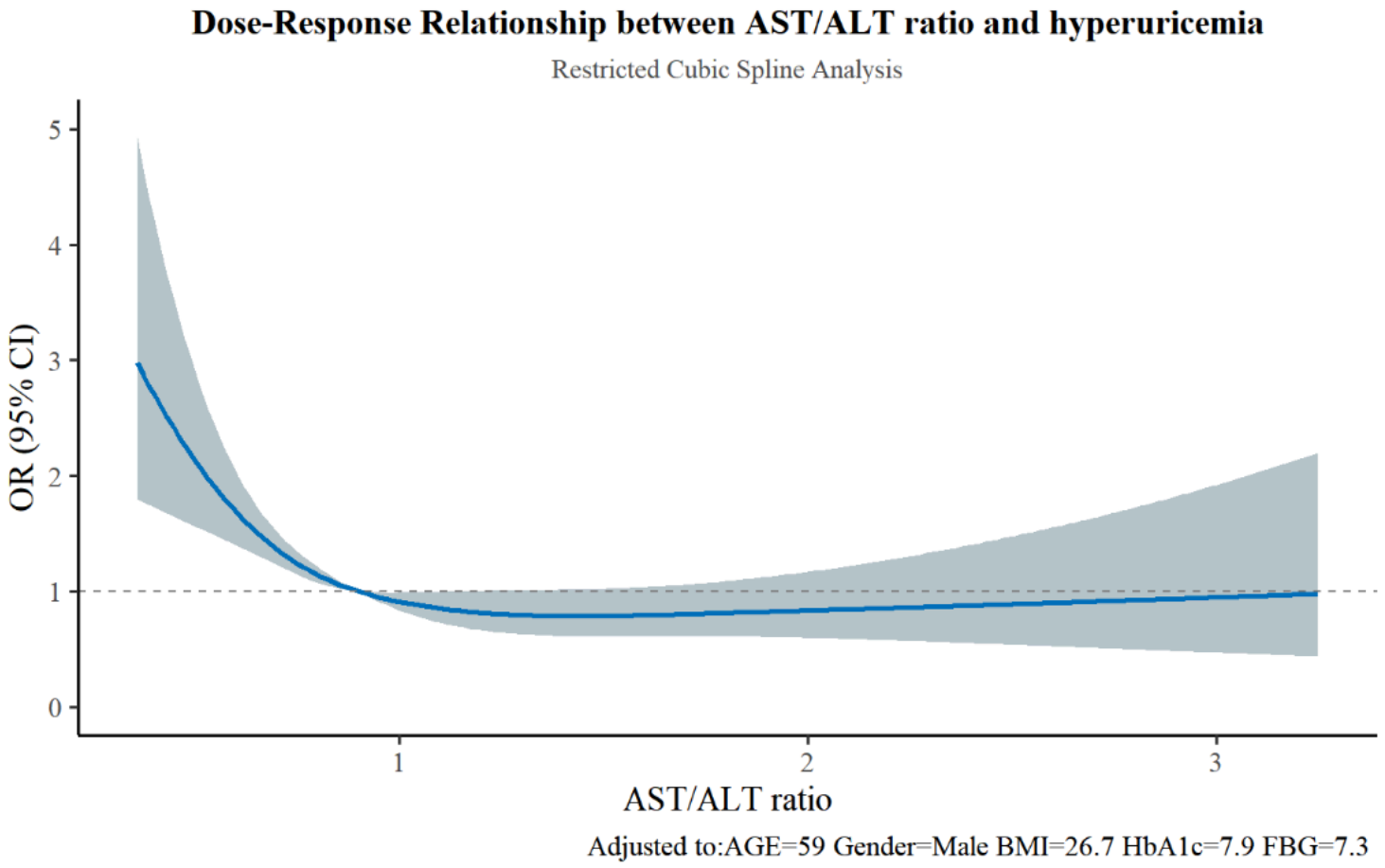



**Figure 3**

Dose–response relationship between AST/ALT ratio and hyperuricemia risk using restricted cubic spline analysis.