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ORIGINAL RESEARCH

Association Between Different Metabolic Markers and Metabolic Syndrome in an Outpatient Hyperuricemia Population: A Cross-Sectional Study

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Background: Hyperuricemia (HUA) is often associated with metabolic syndrome (MetS). However, the role of different metabolic markers in the screening of MetS in out-patients with hyperuricemia is unclear. The study aims to investigate the relationship between different metabolic indexes and MetS.

Methods: A total of 399 hyperuricemia patients from Tianjin Medical University General Hospital from 2022 to 2023 were included in this study. We collected demographic, anthropometric, and biochemical data on each subject. And calculate serum uric acid-to-creatinine ratio (SUA/Cr), serum uric acid to high-density lipoprotein cholesterol (UHR), triglyceride to high-density lipoprotein cholesterol (THR), and triglyceride and glucose (TyG) index. Binary logistic regression modeling was performed to explore the association between different metabolic markers and MetS.

Results: Out of the 399 subjects, 28.3% had MetS. UHR, THR, and TyG index were significantly higher in the MetS group than those in the control group ($p<0.05$), which were associated with an increased risk of MetS. However, SUA/Cr was not associated with MetS ($p>0.05$). TyG index had a stronger relationship with the risk of MetS (OR 5.476, 95% CI 2.210–13.569, $p<0.001$). The cut-off with the biggest Youden index of the TyG index was 9.13 and the area under the curve (AUC) was 0.719.

Conclusion: A high TyG index is associated with an increased risk of MetS in HUA patients. These findings might help screen MetS in individuals with HUA and could be more standardized management of patients with high uric acid in outpatient clinics.

Keywords: metabolic syndrome, serum uric acid-to-creatinine ratio, serum uric acid to high-density lipoprotein cholesterol, triglyceride to high-density lipoprotein cholesterol, TyG index

Introduction

Metabolic syndrome (MetS) is a collection of hypertension, diabetes, obesity, high levels of triglyceride (TG), and low levels of high-density lipoprotein cholesterol (HDL-c).¹ According to a report of 31 provinces in China, there were nearly 454 million adults who had MetS in mainland China, with the prevalence of MetS being 13.3% in those aged 35–64 years.² MetS has become an increasingly common disease in the world.

Hyperuricemia (HUA) is an increase in the level of serum uric acid (SUA) due to excessive or insufficient urinary excretion of uric acid, or both. Recently, the prevalence of HUA has been increasing, and it is higher in males than in females, higher in urban than in rural, and higher in coastal than inland.³ Insulin resistance (IR) is one of the most important pathogens in T2DM patients and HUA. Studies have found that the hyper-insulinemic environment could lead to uric acid excretion decreasing and production increasing, which in turn leads to uric acid accumulation.⁴ There was a bidirectional relationship between SUA levels and MetS risk, with higher SUA levels associated with an increased risk

of MetS.^{5–7} In addition, patients with Hyperuricemia are often seen in outpatient clinics. Therefore, it is important to predict the incidence of MetS in a Hyperuricemia population.

However, there was conflicting result. The study indicated that SUA has no apparent association with MetS,⁸ which may be related to the fact that levels of endogenous uric acid depend on renal clearance function. Therefore, renal function-normalized uric acid (SUA/Cr) has been as a standard SUA and a new biomarker, which is regarded as a superior indicator of net uric acid production.⁹ Some studies have found that SUA/Cr is associated with metabolic diseases, which is a predictor for total mortality.^{10,11} Moreover, high uric acid can also cause target organ damage. The recent results of the URRAH (Uric Acid Right for Heart Health) project have shown that SUA is related to cardiovascular (CV) and chronic kidney disease (CKD).¹² Increasing SUA levels are associated with higher cardiovascular mortality (CVM) risk irrespective of the presence of MetS, and a cardiovascular SUA threshold may improve risk stratification.¹³ However, its association with MetS in hyperuricemia patients is unclear.

Studies have confirmed that UHR was associated with some diseases, such as nonalcoholic fatty liver disease (NAFLD), diabetic kidney injury (DKI), and MetS.^{11,14,15} THR is a useful marker for evaluating IR and arteriosclerosis disease¹⁶ and is associated with cerebrovascular disease, diabetes, and MetS.^{17–19} However, their association with MetS in hyperuricemia patients is unclear. In addition, the TyG index is a new indicator of insulin resistance (IR),²⁰ but its relationship with HUA is unclear. Therefore, our study compares four metabolic markers with the prevalence of MetS.

Methods

Study Design and Populations

The cross-sectional study collected data from the endocrine clinics of Tianjin Medical University General Hospital between March 2022 and March 2023, which totaled 950 patients (Figure 1). Subjects with the following conditions were excluded: (1) Incomplete information; (2) Use drugs that affect uric acid excretion (diuretics, SGLT-2i, aspirin, and benzbromarone); (3) Autoimmune diseases, acute and chronic diseases Infected persons; (4) Tumor diseases and blood system diseases. After excluding, a total of 399 patients were enrolled.

Data Collection

The anthropometric indices and demographic characteristics were extracted from electronic medical records, including gender, age, history of diabetes and hypertension, duration of hyperuricemia, complications of hyperuricemia (gout and

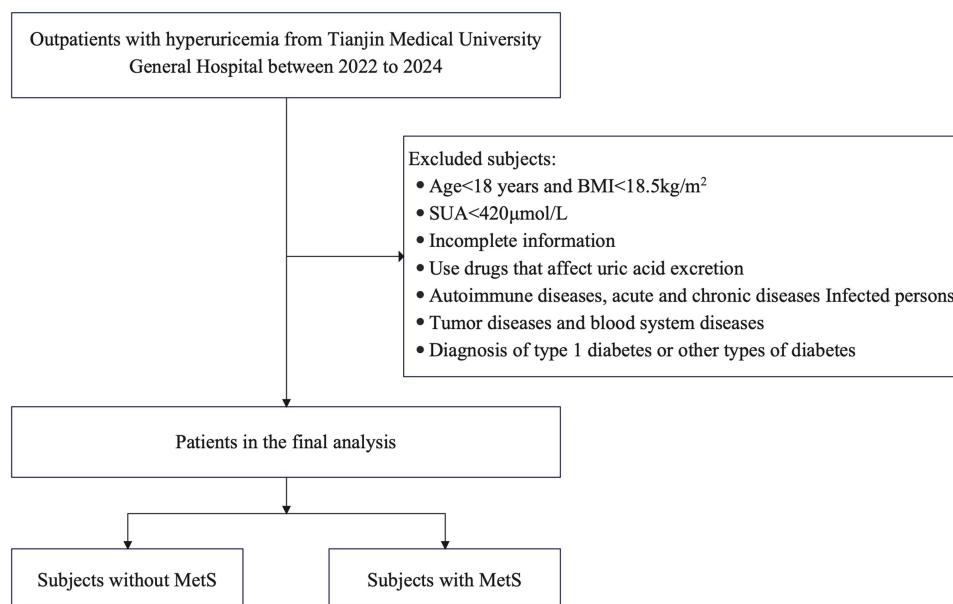


Figure 1 Flowchart of the cross-sectional study.

renal calculi), weight, and height. Fasting plasma glucose (FPG), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), alanine aminotransferase (ALT), aspartate aminotransferase (AST), glutamyl transpeptidase (GGT), creatinine (Cr), and uric acid (UA) were measured by an autoanalyzer.

Definition

Body mass index (BMI) was calculated by body weight in kilograms divided by height in square meters. Moreover, SUA/Cr is the ratio of serum uric acid to creatinine, UHR is the ratio of serum uric acid to high-density lipoprotein cholesterol, THR is the ratio of triglyceride to high-density lipoprotein cholesterol, TyG = Ln [fasting plasma glucose (mg/dL) × TG (mg/dL)/2].²¹ Hyperuricemia was defined differently in males and females; serum uric acid level >420 μmol/L (>7.0 mg/dL) in males and >360 μmol/L (>6.0 mg/dL) in females.²²

According to the Chinese Diabetes Society Criteria,²³ the patients were defined as having MetS if they had three or more of the following: (1) BMI≥25 kg/m²; (2) were receiving treatment for hypertension or had a diastolic blood pressure (DBP)≥90mm/Hg or (and) a systolic blood pressure (SBP)≥140mm/Hg; (3) had been diagnosed with diabetes or had an FPG concentration ≥6.1 mmol/L; (4) were female and had HDL-c levels<1.0 mmol/L, were male and had HDL-c concentration<0.9 mmol/L, or/and had TG levels≥1.7 mmol/L.

Statistical Analysis

Statistical analyses were performed with SPSS version 29.0 (IBM Corp., Armonk, NY). Kolmogorov-Smirnov (K-S) method was used to test the normality of the data for continuous variables ($P>0.05$ was significant), which were expressed as the mean ± standard deviation (SD) or the median with an interquartile range (25%, 75%). Categorical variables were presented as percentages (%). The independent sample *t*-test and one-way analysis of variance were used for the comparison of normally distributed variables among groups. Mann-Whitney *U*-test and Kruskal-Wallis *H*-test were used for comparison between non-normally distributed variables between groups. Categorical variables were expressed as percentages and compared between groups using the Chi-square test or Fisher's exact test. Binary logistic regression tests were used to analyze the associations between different metabolic indexes and MetS. The receiver operating characteristics (ROC) curve was constructed to evaluate the predictive value of different induces for MetS, and the maximum Youden index determined the optimal cut-off point. A P -value <0.05 (two-sided) was regarded as statistically significant.

Results

Characteristics of Study Participants

The clinical and biochemical characteristics of the subjects are shown in Table 1. Compared with non-MetS, participants with MetS were older than non-MetS ($p=0.003$).

Participants with MetS presented with higher BMI, UHR, THR, TyG index, and higher levels of TG, FPG, ALT, and AST ($p<0.05$). They also showed lower levels of HDL than the non-MetS individuals ($p<0.001$). The prevalence of type 2 diabetes (T2DM) or hypertension was higher in the MetS group ($p<0.001$).

The general characteristics of the study participants are summarized in Tables 2–4, according to the quartiles of UHR, THR, and TyG index. In Table 2, the patients in the Q4 group were younger than those in the Q1-Q3 group ($p<0.05$). BMI of Q3-Q4 was higher than that of Q1-Q2 ($p<0.05$). SUA/Cr is significant among groups for every UHR additional unit ($p<0.05$). The levels of GGT (glutamyl transpeptidase) in the Q4 group were higher than those in the Q1-Q3 group ($p<0.05$). However, there were no significant differences in duration, UAE (urinary albumin excretion), eGFR, FPG, AST, and the incidence of MetS ($p>0.05$).

In Table 3, the levels of TC and LDL in Q3 were higher than those in the Q1-Q2 group ($p<0.05$). TyG index is significant among groups for every THR additional unit ($p<0.05$). The levels of GGT in the Q4 group were higher than those in the Q1-Q2 group ($p<0.05$). Moreover, the incidence of MetS in the Q2-Q4 group was higher than in the Q1 group ($p<0.001$, Figure 2A). However, there were no significant differences in age, gender, SUA, Cr, UAE, and eGFR

Table 1 General Characteristics of the Study Population

Variables	Non-MetS (n=286)	MetS (n=113)	p
Age (years)	37 (29,45)	40 (34,51)	0.003
Gender (male, %)	253 (88.5%)	98 (86.7%)	0.631
Duration (years)	3.0 (1.0,5.0)	2.5 (1.0,5.0)	0.698
Hypertension (yes, %)	18 (6.3%)	43 (38.1%)	<0.001
Diabetes (yes, %)	7 (2.4%)	38 (33.6%)	<0.001
Gout (yes, %)	202 (70.6%)	80 (70.8%)	0.974
Renal calculi (yes, %)	31 (10.8%)	10 (8.8%)	0.555
BMI (kg/m^2)	27.25 (24.50,29.97)	29.39 (27.04,32.53)	<0.001
SUA ($\mu\text{mol}/\text{L}$)	524 (469,585)	499 (467,579)	0.212
Cr ($\mu\text{mol}/\text{L}$)	76 (69,84)	76 (69,82)	0.536
SUA/Cr ($\mu\text{mol}/\text{L}$)	6.94 (6.11,7.85)	6.96 (6.00,7.71)	0.699
UHR (mmol/L)	0.48 (0.42,0.55)	0.50 (0.43,0.60)	0.018
THR (mmol/L)	1.78 (1.36,2.46)	2.27 (1.80,3.21)	<0.001
TyG (mg/dL^2) ²	9.02 (8.72,9.34)	9.31 (9.10,9.59)	<0.001
UAE ($\text{mg}/24\text{h}$)	583.94 (452.51,780.86)	631.50 (492.80,871.47)	0.066
eGFR ($\text{mL}/\text{min}/1.73\text{m}^2$)	110.15±22.55	106.01±21.43	0.095
TG (mmol/L)	1.99 (1.58,2.74)	2.23 (1.99,3.05)	<0.001
TC (mmol/L)	4.94±1.04	5.08±1.11	0.225
LDL (mmol/L)	3.25±0.80	3.35±0.81	0.258
HDL (mmol/L)	1.09 (1.01,1.23)	1.02 (0.89,1.16)	<0.001
FPG (mmol/L)	5.1 (4.8,5.4)	5.7 (5.1,6.6)	<0.001
ALT (U/L)	33 (23,50)	41 (33,53)	0.001
AST (U/L)	23 (18,30)	25 (21,32)	0.008
GGT (U/L)	31 (19,54)	30 (17,49)	0.132

Abbreviations: MetS, metabolic syndrome; BMI, body mass index; SUA, serum uric acid; Cr, creatinine; UAE, urinary albumin excretion; eGFR, estimated glomerular filtration rate; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SUA/Cr, serum uric acid-to-creatinine ratio, UHR, serum uric acid to high-density lipoprotein cholesterol; THR, triglyceride to high-density lipoprotein cholesterol; TyG, triglyceride and glucose; FPG, Fasting plasma levels of glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, glutamyl transpeptidase.

Table 2 Characteristics of the Patients According to UHR Quartiles

Variables	Q1 (n=102)	Q2 (n=101)	Q3 (n=101)	Q4 (n=95)	p
Age (years)	41 (36,52)	40 (30,51)	38 (31,50)	34 (28,39)*#&	<0.05
Gender (male, %)	78 (78.0%)	85 (85.0%)	91 (91.9%)*	97 (97.0%)*#	<0.05
Duration (years)	2.0 (1.0,5.0)	2.3 (1.0,5.0)	3.0 (1.0,5.0)	3.0 (2.0,5.0)	0.091
Hypertension (yes, %)	17 (17.0%)	15 (15.0%)	21 (21.2%)	8 (8.0%)	0.071
Diabetes (yes, %)	14 (14.0%)	17 (17.0%)	9 (9.1%)	5 (5.0%)*#	<0.05
Gout (yes, %)	67 (67.0%)	66 (66.0%)	70 (70.7%)	79 (79.0%)	0.168
Renal calculi (yes, %)	11 (11.0%)	8 (8.0%)	12 (12.1%)	10 (10.0%)	0.803
BMI (kg/m^2)	27.02 (24.65,29.39)	25.95 (24.22,29.27)	28.57 (26.04,31.72)*#	29.41 (27.47,32.19)*#	<0.05
SUA($\mu\text{mol}/\text{L}$)	459 (437,488)	498 (456,536)*	535 (493,571)*#	625 (571,695)*#&	<0.05
Cr($\mu\text{mol}/\text{L}$)	74 (66,80)	75 (69,83)	76 (68,82)	81 (71,89)*	<0.05
SUA/Cr($\mu\text{mol}/\text{L}$)	6.25 (5.64,7.27)	6.68 (5.90,7.40)	7.07 (6.36,7.79)*#	7.66 (6.94,8.95)*#&	<0.05
UHR (mmol/L)	0.37 (0.34,0.40)	0.45 (0.43,0.47)*	0.52 (0.51,0.54)*#	0.63 (0.61,0.70)*#&	<0.001
THR (mmol/L)	1.52 (1.12,1.85)	1.79 (1.44,2.20)*	2.18 (1.71,2.91)*#	2.39 (1.87,3.89)*#	<0.05
TyG (mg/dL^2) ²	9.00 (8.71,9.23)	9.07 (8.81,9.35)	9.20 (8.90,9.46)*	9.23 (8.94,9.59)*	<0.05
UAE ($\text{mg}/24\text{h}$)	570.97 (434.20,833.30)	582.16 (461.71,774.18)	601.20 (478.44,773.60)	648.13 (461.10,884.34)	0.542

(Continued)

Table 2 (Continued).

Variables	Q1 (n=102)	Q2 (n=101)	Q3 (n=101)	Q4 (n=95)	p
eGFR (mL/min/1.73m ²)	107.27±22.18	107.59±23.46	110.95±21.50	110.15±22.08	0.568
TG (mmol/L)	1.93 (1.53,2.37)	2.00 (1.65,2.39)	2.21 (1.83,2.93)*	2.31 (1.82,3.65)*#	<0.05
TC (mmol/L)	5.20±1.09	4.67±1.09*	5.09±0.97#	4.96±1.06	<0.05
LDL (mmol/L)	3.34±0.85	3.10±0.79*	3.45±0.79#	3.25±0.75	<0.05
HDL (mmol/L)	1.25 (1.17,1.36)	1.11 (1.02,1.21)*	1.02 (0.96,1.09)*#	0.98 (0.89,1.04)*#	<0.001
FPG (mmol/L)	5.3 (4.9,5.8)	5.2 (4.8,5.9)	5.2 (4.9,5.6)	5.1 (4.8,5.5)	0.376
ALT (U/L)	34 (23,45)	34 (23,45)	39 (27,54)	40 (29,63)*	<0.05
AST (U/L)	23 (18,30)	23 (18,29)	25 (20,32)	24 (18,30)	0.105
GGT (U/L)	29 (17,52)	26 (17,47)	27 (19,44)	39 (24,62)*#&	<0.05
MetS (yes, %)	26 (26.0%)	20 (20.0%)	34 (34.3%)	33 (33.0%)	0.089

Notes: Compared with Q1 group, *p<0.05; compared with Q2 group, #p<0.05; compared with Q3 group, &p<0.05.

Abbreviations: MetS, metabolic syndrome; BMI, body mass index; SUA, serum uric acid; Cr, creatinine; UAE, urinary albumin excretion; eGFR, estimated glomerular filtration rate; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SUA/Cr, serum uric acid-to-creatinine ratio, UHR, serum uric acid to high-density lipoprotein cholesterol, THR, triglyceride to high-density lipoprotein cholesterol; TyG, triglyceride and glucose; FPG, Fasting plasma levels of glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, glutamyl transpeptidase.

Table 3 Characteristics of the Patients According to THR Quartiles

Variables	Q1 (n=100)	Q2 (n=101)	Q3 (n=98)	Q4 (n=100)	p
Age (years)	37 (28,46)	37 (29,46)	38 (31,50)	40 (33,48)	0.204
Gender (male, %)	85 (85.0%)	86 (85.1%)	86 (87.8%)	94 (94.0%)	0.169
Duration (years)	2.8 (1.0,4.4)	2.5 (1.0,5.0)	2.0 (1.0,5.0)	3.0 (2.0,5.0)	0.324
Hypertension (yes, %)	11 (11.0%)	24 (23.8%)	16 (16.3%)	10 (10.0%)	0.026
Diabetes (yes, %)	3 (3.0%)	15 (14.9%)*	15 (15.3%)*	12 (12.0%)*#	<0.05
Gout (yes, %)	73 (73.0%)	69 (68.3%)	65 (66.3%)	75 (75.0%)	0.507
Renal calculi (yes, %)	11 (11.0%)	11 (10.9%)	10 (10.2%)	9 (9.0%)	0.965
BMI (kg/m ²)	27.66(24.56,29.78)	26.89(24.57,30.01)	28.41(25.82,31.91)	28.44(25.86,31.46)	0.007
SUA (μmol/L)	518(465,570)	519(469,588)	499 (458,579)	533 (471,600)	0.395
Cr (μmol/L)	77 (69,84)	76 (69,85)	75 (70,82)	76 (68,86)	0.659
SUA/Cr (μmol/L)	6.80 (5.98,7.86)	6.93 (6.17,7.77)	6.97 (5.98,7.78)	7.05 (6.10,7.92)	0.899
UHR (mmol/L)	0.43 (0.36,0.49)	0.48 (0.41,0.54)	0.51 (0.44,0.57)*#	0.55 (0.48,0.63)*#&	<0.05
THR (mmol/L)	1.20 (0.97,1.36)	1.72 (1.63,1.80)*	2.20 (2.03,2.42)*#	3.87 (3.15,4.83)*#&	<0.001
TyG (mg/dL) ²	8.62 (8.45,8.78)	9.02 (8.89,9.15)*	9.18 (9.06,9.35)*#	9.66 (9.45,9.91)*#&	<0.05
UAE (mg/24h)	641.83 (493.11,833.06)	554.30 (444.35,802.13)	604.73 (462.95,818.14)	620.80 (455.61,780.18)	0.470
eGFR (mL/min/1.73m ²)	108.89±25.46	108.24±21.46	109.95±19.76	108.76±22.50	0.959
TG (mmol/L)	1.42 (1.18,1.64)	1.93 (1.80,2.06)*	2.25 (2.07,2.62)*#	3.84 (3.11,4.63)*#&	<0.001
TC (mmol/L)	4.67±1.04	4.74±1.01	5.09±1.02*	5.41±1.01*	<0.001
LDL (mmol/L)	3.11±0.81	3.18±0.81	3.51±0.78*	3.33±0.76*	<0.05
HDL (mmol/L)	1.23 (1.09,1.32)	1.14 (1.04,1.21)*	1.02 (0.96,1.08)*#	0.97 (0.89,1.06)*#	<0.05
FPG (mmol/L)	5.1 (4.7,5.4)	5.3 (5.0,5.8)*	5.3 (4.8,5.7)*	5.1 (4.8,5.7)	<0.05
ALT (U/L)	31 (21,45)	33 (25,45)	41 (29,57)*	41 (30,61)*	<0.05
AST (U/L)	22 (18,29)	21 (18,29)	27 (21,32)*#	24 (21,31)	<0.05
GGT (U/L)	25 (18,46)	25 (17,45)	31 (19,53)	41 (23,59)*#	<0.05
MetS (yes, %)	5 (5.0%)	33 (32.7%)*	36 (36.7%)*	39 (39.0%)*	<0.001

Notes: Compared with Q1 group, *p<0.05; compared with Q2 group, #p<0.05; compared with Q3 group, &p<0.05.

Abbreviations: MetS, metabolic syndrome; BMI, body mass index; SUA, serum uric acid; Cr, creatinine; UAE, urinary albumin excretion; eGFR, estimated glomerular filtration rate; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SUA/Cr, serum uric acid-to-creatinine ratio, UHR, serum uric acid to high-density lipoprotein cholesterol, THR, triglyceride to high-density lipoprotein cholesterol; TyG, triglyceride and glucose; FPG, Fasting plasma levels of glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, glutamyl transpeptidase.

Table 4 Characteristics of the Patients According to TyG Index Quartiles

Variables	Q1 (n=102)	Q2 (n=96)	Q3 (n=100)	Q4 (n=101)	p
Age (years)	35 (27,43)	37 (30,45)	39 (31,53)*	40 (34,50)*	0.013
Gender (male, %)	2.0 (1.0,4.0)	3.0 (1.0,5.0)	3.0 (1.0,5.0)	3.0 (1.0,6.0)	0.541
Duration (years)	2.0 (1.0,4.0)	3.0 (1.0,5.0)	3.0 (1.0,5.0)	3.0 (1.0,6.0)	0.541
Hypertension (yes, %)	10 (9.8%)	22 (22.9%)	17 (17.0%)	12 (11.9%)	0.050
Diabetes (yes, %)	3 (2.9%)	6 (6.3%)	13 (13.0%)*	23 (22.8%)*#	<0.05
Gout (yes, %)	73 (71.6%)	65 (67.7%)	72 (72.0%)	73 (72.3%)	0.885
Renal calculi (yes, %)	12 (11.8%)	10 (10.4%)	9 (9.0%)	10 (9.9%)	0.932
BMI (kg/m^2)	27.66 (24.39,30.58)	27.76 (24.80,30.26)	27.69 (25.38,30.48)	28.47 (25.45,31.95)	0.242
SUA ($\mu\text{mol}/\text{L}$)	515 (468,572)	530 (468,586)	518 (468,591)	516 (466,585)	0.907
Cr ($\mu\text{mol}/\text{L}$)	77 (69,82)	77 (70,85)	76 (71,83)	74 (65,84)	0.528
SUA/Cr ($\mu\text{mol}/\text{L}$)	6.78 (6.13,7.83)	6.78 (6.00,7.75)	7.04 (6.14,7.79)	7.03 (6.10,7.97)	0.667
UHR (mmol/L)	0.45 (0.38,0.53)	0.48 (0.42,0.54)	0.49 (0.42,0.56)	0.53 (0.45,0.61)*	<0.001
THR (mmol/L)	1.25 (0.97,1.42)	1.78 (1.64,1.96)*	2.20 (1.80,2.52)*#	3.85 (3.02,4.80)*##&	<0.05
TyG (mg/dL^2) ²	8.63 (8.48,8.76)	8.99 (8.93,9.04)*	9.25 (9.16,9.33)*#	9.66 (9.51,9.90)*##&	<0.001
UAE ($\text{mg}/24\text{h}$)	637.38 (476.49,885.54)	560.48 (447.81,772.92)	561.82 (453.07,814.20)	634.60 (448.90,779.57)	0.412
eGFR ($\text{mL}/\text{min}/1.73\text{m}^2$)	110.38±24.17	108.88±22.37	107.26±20.03	108.92±22.86	0.807
TG (mmol/L)	1.42 (1.19,1.64)	1.96 (1.80,2.06)*	2.30 (2.11,2.68)*#	3.82 (3.05,4.62)*##&	<0.001
TC (mmol/L)	4.69±1.06	4.58±0.95	5.18±0.94	5.45±1.06	<0.001
LDL (mmol/L)	3.15±0.88	3.17±0.73	3.48±0.75*#	3.34±0.81	<0.05
HDL (mmol/L)	1.16 (1.04,1.28)	1.10 (1.02,1.20)	1.07 (0.97,1.23)*	1.01 (0.93,1.08)*##&	<0.05
FPG (mmol/L)	4.9 (4.7,5.2)	5.1 (4.9,5.5)*	5.5 (5.0,6.0)	5.4 (4.9,6.2)*	<0.05
ALT (U/L)	30 (20,43)	38 (28,53)*	37 (24,49)	41 (30,61)*	<0.05
AST (U/L)	21 (18,27)	25 (18,31)	25 (18,31)	24 (21,33)*	<0.05
GGT (U/L)	23 (17,41)	34 (19,52)	24 (18,43)	41 (25,61)*##	<0.001
MetS (yes, %)	7 (6.9%)	21 (21.9%)*	40 (40.0%)*#	45 (44.6%)*#	<0.05

Notes: Compared with Q1 group, * $p<0.05$; compared with Q2 group, # $p<0.05$; compared with Q3 group, ^ $p<0.05$.

Abbreviations: MetS, metabolic syndrome; BMI, body mass index; SUA, serum uric acid; Cr, creatinine; UAE, urinary albumin excretion; eGFR, estimated glomerular filtration rate; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SUA/Cr, serum uric acid-to-creatinine ratio, UHR, serum uric acid to high-density lipoprotein cholesterol, THR, triglyceride to high-density lipoprotein cholesterol; TyG, triglyceride and glucose; FPG, Fasting plasma levels of glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, glutamyl transpeptidase.

($p>0.05$). The incidence of hypertension, gout, and renal calculi showed no significant difference among the four groups ($p>0.05$).

In Table 4, the patients of the Q4 group were older than those in Q1 ($p<0.05$). The levels of LDL in Q3 were higher, and the levels of HDL in Q4 were lower than those in the Q1-Q3 group ($p<0.05$). The level of THR is significant among groups for every TyG index additional unit ($p<0.05$). The levels of GGT in the Q4 group were higher than those in the Q1 and Q3 groups ($p<0.05$). Moreover, the incidence of MetS in the Q3-Q4 group was higher than in the Q1-Q2 group ($p<0.05$, Figure 2B). However, there were no significant differences in gender, SUA, Cr, UAE, and eGFR ($p>0.05$). The incidence of hypertension, gout, and renal calculi showed no significant difference among the four groups ($p>0.05$).

Association Among THR, TyG Index, and MetS

Tables 5 and 6 showed the relationship between THR, TyG index, and MetS. As shown in the tables, we found that a unit increase in THR (OR=1.345, 95% CI=1.155–1.566), TyG index (OR=5.070, 95% CI=3.002–8.564) were significantly associated with the prevalence of MetS ($p<0.001$).

After adjusting for age, gender, duration, BMI, TC, LDL, FPG, SUA, Cr, eGFR, UAE, ALT, AST, GGT, hypertension, diabetes, gout, and Renal calculi, THR (OR=1.757, 95% CI=1.383–2.232) was still associated with an increased risk of MetS ($p<0.001$). After adjusting for age, gender, duration, BMI, TC, LDL, HDL, SUA, Cr, eGFR, UAE, ALT, AST, GGT, hypertension, diabetes, gout and Renal calculi, TyG index (OR=5.476, 95% CI=2.210–13.569) was still associated with an increased risk of MetS ($p<0.001$).

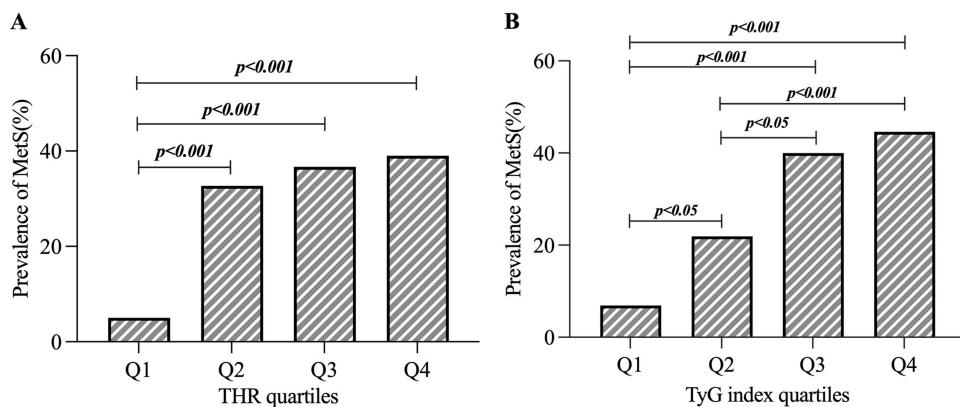


Figure 2 Comparison of metabolic syndrome (MetS) prevalence between triglyceride to high-density lipoprotein cholesterol (THR, **A**) and triglyceride and glucose (TyG, **B**) index level.

In addition, we constructed three models to explore the associations of the THR and TyG index quartiles with MetS using binary logistic regression analyses. Model 1 was unadjusted, model 2 was adjusted for age, gender, and duration; model 3 further adjusted for TC, LDL, ALT, AST, GGT, diabetes, hypertension, gout, and renal calculi. However, there were differences between the THR and the TyG groups, after adjusting FPG in the THR group and HDL in the TyG group. The result is shown in Figure 3.

Receiver-Operating Characteristics (ROC) Curve Analysis

The diagnostic ability of THR and TyG index for MetS was found by the ROC curve. The differences between the area under the curve of THR and TyG index were all significant ($p<0.001$). (Figure 4). The area under ROC curve (AUC) of THR and TyG index for MetS was 0.677, and 0.719 respectively (all $p<0.001$). TyG index had a larger area under the ROC curve compared to THR, and the cut-off with the biggest Youden index of TyG index was 9.13 with a sensitivity of 74.3% and a specificity of 63.3%. Moreover, Figure 5 shows that the probability of developing MetS will also increase as the level of the TyG index increases.

Table 5 Association Between THR and MetS

	p	OR (95% CI)
Model 1	<0.001	1.345 (1.155–1.566)
Model 2	<0.001	1.323 (1.133–1.546)
Model 3	<0.001	1.757 (1.383–2.232)

Notes: Model 1: Crude model; Model 2: Model 1+adjust for age, gender, duration and BMI; Model 3: Model 2+adjust for TC, LDL, FPG, SUA, Cr, eGFR, UAE, ALT, AST, GGT, hypertension, diabetes, gout and renal calculi.

Table 6 Association Between TyG Index and MetS

	p	OR (95% CI)
Model 1	<0.001	5.070 (3.002–8.564)
Model 2	<0.001	4.846 (2.781–8.443)
Model 3	<0.001	5.476 (2.210–13.569)

Notes: Model 1: Crude model; Model 2: Model 1+adjust for age, gender, duration and BMI; Model 3: Model 2+adjust for TC, LDL, HDL, SUA, Cr, eGFR, UAE, ALT, AST, GGT, hypertension, diabetes, gout and renal calculi.

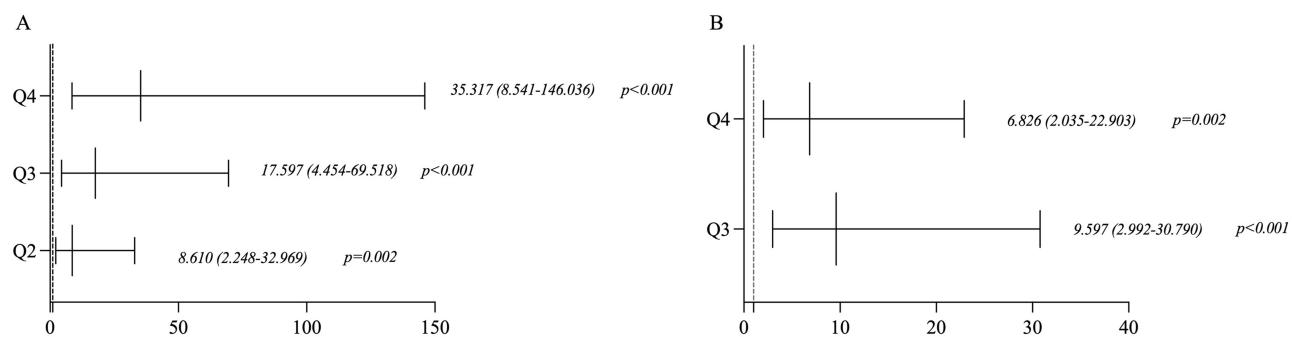


Figure 3 Association among THR (A), TyG index (B), and MetS.

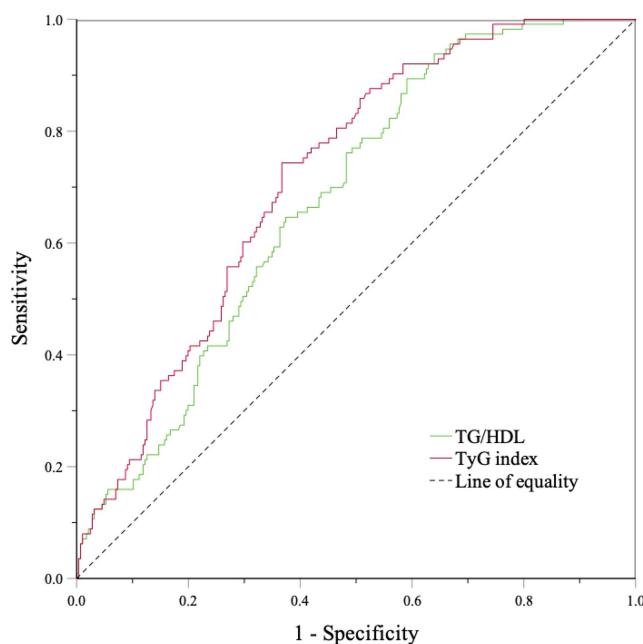


Figure 4 The ROC curve of MetS for diagnosing.

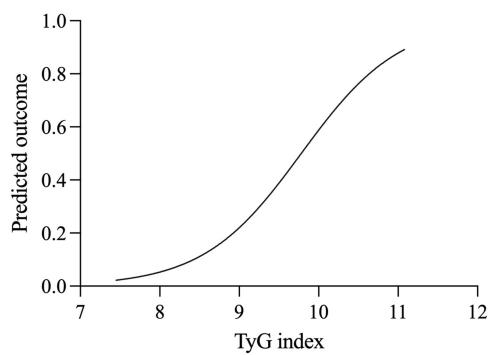


Figure 5 The predicted outcome of the TyG index in MetS.

Discussion

We conducted this cross-sectional study to investigate the role of different metabolic markers in screening metabolic syndrome in out-patients with hyperuricemia. Our study involved a population of 399 patients in endocrine clinics. We

discovered the prevalence of MetS to be 28.3% and the TyG index was positively associated with MetS in HUA patients, compared with another index.

HUA is a purine metabolism disorder associated with excessive secretion or decreased clearance of UA in the body.²⁴ High levels of SUA can induce oxidative stress in vascular endothelial cells, activate inflammatory cells and pathways, stimulate the expression of inflammatory transmitters, and increase the production of reactive oxygen species (ROS), which all lead to long-term chronic inflammation, and aggravate lipid metabolism disorder and IR in further.²⁵ HUA is related to IR, so it is important to explore the relationship between different metabolic markers and MetS.

The role of UA in the prevalence of MetS was always unclear, which may be due to renal clearance dysfunction. Individuals with lower eGFRs are more likely to have higher UA concentrations.²⁶ For this reason, renal function-normalized UA will be more exact to reflect net UA production.²⁷ The study of Zhong et al has shown that elevated values of SUA/Cr were associated with MetS, and the positive relationship remained in those individuals with normal UA levels.⁹ Based on the 2015 CHARLES database, the study found that SUA/Cr was significantly and positively associated with MetS risk in Chinese individuals aged ≥ 45 years.²⁸ The recent study by She et al found that SUA/Cr levels were significantly associated with MetS and its components in Chinese adults with overweight/obesity.²⁹ However, there was no significant association between SUA/Cr and MetS in our study, which may be due to the small sample size and different participants.

As we all know, elevated SUA levels have often been related to cardiovascular risk factors such as obesity, hypertriglyceridemia, hypertension, and hyperglycemia, which the collection called MetS.³⁰ Obesity is an important contributing factor in the incidence and development of hypertension.³¹ A study has found that elevated SUA marks a pre-inflammatory state and impacts the role of HDL-c on carotid atherosclerosis.³² The study has confirmed that people with low HDL are more than 4 times more likely to develop MetS than people with normal HDL, and people with a high UHR are 2.9 times more likely to have MetS.¹⁴ In a retrospective study by Kocak et al, more than 10.6% of UHR had a high sensitivity and specificity for the prediction of MetS in 100 patients with type 2 diabetes.³³ In our study, the patients with MetS had higher levels of UHR, but there was no significant association between UHR quartiles and MetS.

In the MetS, hypertriglyceridemia, which is part of arteriosclerosis dyslipidemia, leads to lower levels of high-density lipoprotein (HDL-c) cholesterol and smaller, Low-density lipoprotein (LDL) particles, this leads to a high risk of myocardial infarction.^{34,35} Meanwhile, HDL prevents arteriosclerosis by delivering excess cholesterol to the liver, inhibiting LDL oxidation, stimulating prostacyclin secretion, and reducing platelet aggregation.³⁶ The atherogenic link between high triglyceride and HDL-c is due to high plasma concentrations of triglyceride and Low-density lipoprotein that produce small, dense LDL during lipid exchange and lipolysis. Thus, lipid ratios, such as THR and TC/HDL, are widely used for cardiovascular disease risk assessment.³⁷

At the same time, insulin resistance is associated with increased production of Very Low-density lipoprotein cholesterol (VLDL-c) in the liver, chemical transformation of HDL particles, and rapid excretion by the kidneys, leading to changes in blood lipids, as TG increases and HDL decreases. Clinical studies have shown that THR can predict the MetS and assess the risk of later cardiovascular events.^{35,38} A four-year follow-up of 15,198 subjects showed a positive association between THR and HUA risk, an independent predictor of elevated UA.³⁹ However, no studies demonstrate the relationship between THR and MetS in HUA patients. In our study, THR was associated with MetS, but less than the TyG index.

In the end, IR is one of the pathogenesis in many metabolic diseases, and SUA levels are also closely related to IR.⁴⁰ The study of Xie et al found that UA induces hepatic fat accumulation via the ROS/ JNK/AP-1 pathway, which HUA may induce insulin resistance and aggravate hyperlipidemia.⁴¹ The TyG index is a new, easy-to-use clinical measure, which is regarded as a simple and reliable alternative clinical marker of IR.⁴² Many studies have demonstrated that the TyG index was associated with HUA in different metabolic diseases, such as hypertension,⁴³ nonalcoholic fatty liver disease (NAFLD),²⁰ and diabetic kidney (DKD).⁴⁴ The study of Luo et al found that the TyG index was positively associated with SUA in non-obese T2DM patients, which might be better than HOMA-IR.⁴⁵ Gisela Unger et al suggested that the TyG index and THR are closely related to the IR, which is the basis of MetS, it can be used as an evaluation index of MetS.⁴⁶ In our study, we found that the TyG index was closely related to the risk of MetS in hyperuricemia patients. The risk of developing MetS will also increase as the level of the TyG index increases. Furthermore, the study of

Chen et al has shown that an elevated TyG index is independently associated with an increased risk of eGFR decline in hypertensive patients.⁴⁷ In our study, eGFR levels in HUA patients were normal, which the relationship between TyG index and decreased renal function in HUA needs further investigation.

This study had some limitations. Firstly, this was a cross-sectional study with small sample size, and it was impossible to determine cause-and-effect relationships between MetS and indicators, nor to explore gender differences. Secondly, some variables such as dietary habits and lifestyle were missing, which may affect UA and Cr levels. Thirdly, only a single measurement of SUA and Cr and MetS components in the study may introduce bias. Fourthly, MetS was defined according to the Chinese Diabetes Society Criteria in 2004, it was not possible to test the predictive power of different indicators in abdominal obesity. Finally, a future longitudinal study with a larger sample size is needed to explore this association further.

Conclusion

In conclusion, the TyG index was closely related to the risk of MetS in HUA patients, and the higher the risk of MetS, the higher the value of the TyG index level was. TyG index is a powerful indicator for identifying MetS in out-patients. A future longitudinal study with a larger sample size is needed to explore this association further.

Data Sharing Statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics Statement

All procedures performed in studies were by the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The ethical approval for this study was provided by the Ethical Committee of Tianjin Medical University General Hospital (Approval number: IRB2020-YX-027-01). Informed consent was obtained from all participants.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no potential conflicts of interest relevant to this article.

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