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Original Article

Analysis of the interaction effects among the risk factors for hyperuricaemia in adults: a cross-sectional survey in Guilin, China

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Abstract: In recent years, the prevalence of hyperuricaemia has risen, especially in younger populations. This study was designed to explore the risk factors and their interactions of hyperuricaemia for establishing effective preventive measures to reduce the prevalence of hyperuricaemia. We conducted a cross-sectional survey of 6241 adults selected with a cluster sampling method. Survey items included a questionnaire survey, physical measurements, chemistry parameters, and liver Doppler ultrasonography. We analysed the metabolic characteristics of subjects with hyperuricaemia, and developed the CRT model to screen the risk factors for hyperuricaemia and the interactions among the risk factors. The non-conditional logistic regression model was used in combination with the additive model to quantitatively analyse the interactions among the risk factors. A total of 1035 individuals were found to have hyperuricaemia, and were included in the high uric acid (HUA) group (men: 755, women: 280), the overall prevalence of hyperuricaemia was 16.6%. The levels of systolic blood pressure, diastolic blood pressure, body mass index (BMI), uric acid, fasting plasma glucose (FPG), triglycerides (TG), total cholesterol, low-density lipoprotein cholesterol (LDL-C) and the prevalence of non-alcoholic fatty liver disease (NAFLD) were significantly higher in the HUA group than in the control group ($P < 0.01$). The CRT model selected 7 explanatory variables: age, gender, BMI, TG, LDL-C, FPG, and NAFLD; among these, TG, BMI, and NAFLD were most closely related to hyperuricaemia. The multivariate logistic regression analysis showed that the prevalence of hyperuricaemia was 3.957-fold higher in individuals with high TG and high BMI than in those with low TG and low BMI (OR = 3.957, CI: 3.129~5.004), and the attributable percent was 9.17%. The results suggested that individuals with hyperuricaemia had multiple metabolic abnormalities; age, gender, BMI, TG, LDL-C, FPG, and NAFLD were closely related to hyperuricaemia. Moreover, the positive interaction between high TG and high BMI was one of the most important risk factors for hyperuricaemia, and the co-presence of high TG and high BMI significantly increased the risk of hyperuricaemia.

Keywords: Hyperuricaemia, risk factor, interaction, classification and regression tree model

Introduction

Uric acid is the end-product of purine metabolism in the body. Environmental and genetic factors can cause pathological purine metabolism disorders, resulting in hyperuricaemia [1]. Hyperuricaemia and gout are two common conditions in economically developed regions [2], and their prevalence is also high in the elderly, with a severe impact on the quality of life [3]. In the past two decades, with social and economic development, improvement in living standards, and changes in lifestyle and diet in Asia, the prevalence of hyperuricaemia has risen [4], especially in younger populations. A persistent purine metabolism disorder can gradually lead to a series of conditions associated with high serum uric acid [5]. Moreover, hyperuricaemia is often associated with cardiovascular and cerebrovascular diseases [6] and with metabolic syndrome [7], and is closely related to insulin resistance. Hyperuricaemia and relevant complications have severe impacts on the quality of life and on physical and mental health [8], and have thus become global health-threatening public health problems [9]. Therefore, we must take effective measures to reduce the prevalence of hyperuricaemia.

Many risk factors are related to hyperuricaemia, and the mechanisms are not entirely clear. Studies have shown that intervention in high-risk populations makes good health and economic sense, and the effect of preventive measures is superior in high-risk populations than in the whole population. Epidemiological studies have shown that independent risk factors for hyperuricaemia include diet [10], the geographical environment, hypertension [11], coronary heart disease [12], insulin resistance [13], and glucose and lipid metabolism disorders [14]. Through effectively identifying risk factors and dietary or behavioural interventions in high-risk populations, we can reduce the costs associated with prevention and the prevalence of hyperuricaemia in the future, thus contributing to improved public health.

Previous epidemiological studies on hyperuricaemia focused on the effect of independent risk factors. These studies often screened the risk factors with a single multivariate linear regression, logistic regression, or COX regression model, but these methods have stringent restrictions and requirements of data type and distribution, and are vulnerable to the effect of collinearity, which affects statistical power to varying degrees. As a new data processing method, the tree classification model has many advantages over conventional analysis methods: it can quickly and effectively identify the main determinants of disease, overcome the effect of collinearity, and display the interactions among different levels of variables on a tree graph, thus facilitating advanced interaction analysis [15]. Interactions among risk factors may be an important mechanism of hyperuricaemia; thus, we used the classification and regression tree (CRT) model combined with a non-conditional logistic regression analysis to identify the risk factors closely related to the development and progression of hyperuricaemia, and the interactions among these risk factors to help healthcare professionals establish effective preventive measures to reduce the prevalence of hyperuricaemia.

Methods

Study population

We conducted a cross-sectional survey in individuals (all Han Chinese) sampled with a cluster sampling method from those who visited the medical centre of the Affiliated Hospital of Guilin Medical University for a health check-up between July 2012 and November 2012. Each subject consented and signed the informed consent. On the day of study enrolment, the subject completed a questionnaire survey and had physical measurements, laboratory tests, and ultrasound assessments. The exclusion criteria were as follows: severe heart, lung or brain disease; renal impairment; malignant tumour; recent use of drugs that may affect purine metabolism; and subjects unable to be evaluated due to incomplete data. Finally, 6241 individuals with complete data were included in the statistical analysis. These individuals were age 20 to 70 (mean: 46.26 ± 11.79), including 3271 men (mean age: 46.71 ± 12.09) and 2970 women (mean age: 45.76 ± 11.42). The study protocol was approved by the Ethics Committee of the Affiliated Hospital of Guilin Medical University (YXLL-2012-11).

Data collection

A unified epidemiological questionnaire survey was used to collect the basic information, lifestyle, family history, and history of disease (such as hypertension, high cholesterol, and diabetes) of the subjects.

Physical measurements

Trained and qualified staffs measured height and weight. The subjects were instructed to remove hats and shoes and stand upright for height measurements (increment: 0.01 m) and to remove their shoes and empty their bladders prior to weight measurements (increment: 0.1 kg). Body mass index (BMI) was determined by weight (kg)/height $(m)^2$. The subjects rested for 5 to 10 minutes before their blood pressure was taken in a sitting position; the subjects were instructed to refrain from smoking, drinking coffee, tea, or alcoholic beverages, or exercising strenuously before the blood pressure measurement. The blood pressure of the right brachial artery was measured twice, with 1 to 2 minutes between measurements. In case of a significant discrepancy between measurements, blood pressure was measured a third time, and the mean value (increment: 1 mmHg) was used for the analysis.

Laboratory tests

The subjects fasted overnight, and a fasting venous blood sample (5 mL) was taken on the

Table 1. Clinical characteristics of subjects in the high uric acid (HUA) group and the control group

Variables	HUA group n = 1035	Control group n = 5206	*t*-value	*P*-value
SBP (mmHg)	130.40 ± 17.37	124.33 ± 17.54	10.182	0.000
DBP (mmHg)	82.13 ± 11.69	77.12 ± 11.50	12.766	0.000
BMI (kg/m^2)	25.79 ± 3.02	23.80 ± 3.06	19.088	0.000
UA (μmol/L)	457.99 ± 58.84	298.44 ± 62.73	75.484	0.000
FPG (mmol/L)	5.60 ± 0.90	5.44 ± 1.01	4.832	0.000
TG (mmol/L)	2.34 ± 1.63	1.43 ± 1.04	23.134	0.000
TC (mmol/L)	5.15 ± 0.89	4.88 ± 0.87	9.205	0.000
LDL-C (mmol/L)	3.54 ± 0.85	3.12 ± 0.85	14.787	0.000
HDL-C (mmol/L)	1.26 ± 0.32	1.48 ± 0.39	-17.346	0.000

Variables are shown as mean ± standard deviation (SD) and number (n). *P*-values compare clinical and metabolic characteristics between the HUA group and control group, using the *t*-test. Abbreviations: n, number; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; UA, uric acid; FPG, fasting plasma glucose; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

next morning to determine the levels of uric acid (UA), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and fasting plasma glucose (FPG) with the Roche Cobas C501 automated biochemical analyser (Basel, Switzerland). Specifically, the uricase assay, the glycerol phosphate oxidase-peroxidase assay, cholesterol oxidase assay, the surfactant assay, the phosphotungstic acid-magnesium assay, and the glucose oxidase assay were used to determine the UA, TG, TC, LDL-C, HDL-C, and FPG levels, respectively.

Liver doppler ultrasonography

The experienced professional sonographers performed liver Doppler ultrasonography (probe frequency: 3.5 MHz) with the Mindray DC-6 Expert type II Doppler ultrasound machine (Shenzhen, China) and issued unified diagnostic reports.

Quality control

All investigators were trained and qualified healthcare professionals. Sphygmomanometers and weight scales were calibrated by the medical centre staff. The questionnaire was filled out by the investigator after a detailed inquiry of each subject. The data were double-entered, logically verified, cross-checked, and corrected in EpiData (v3.02, Odense, Denmark) to ensure data accuracy. Quality control measures were implemented for the on-site questionnaire survey, sampling, and data entry. The central laboratory of Affiliated Hospital of Guilin Medical University was responsible for the quality control of the laboratory tests.

Diagnosis and classification

Hyperuricaemia [10] was defined as fasting serum uric acid > 420 μmol/L (male) or > 360 μmol/L (female) with a normal non-purine-restricting diet. Hypertension was diagnosed according to Chinese and international guidelines: systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg, or a previous diagnosis of hypertension that is under control with antihypertensive drugs [16]. Dyslipidemia was defined as TC ≥ 6.22 mmol/L and/or HDL-C < 1.04 mmol/L. Non-alcoholic fatty liver disease (NAFLD) was diagnosed if the subject had no history of heavy drinking or specific conditions that may cause fatty liver (such as drug-induced liver disease and viral hepatitis) and if liver imaging findings indicated a diffuse fatty liver [17]. The values of age, BMI, TG, LDL-C, and FPG were assigned based on the cut-off points in the classification tree model.

Statistical analysis

SPSS (v18.0, Chicago, IL, USA) and MedCalc (v11.4.2.0, Mariakierke, Belgium) were used for data analysis. Normally distributed measurement data were expressed as the mean ± standard deviation ($x \pm s$), and the student-test was performed to compare the mean values between the two groups. The count data were expressed as rate (%), and the chi-square test was performed to compare the rate between the two groups. $P < 0.05$ was set as the significance level.

The classification tree model classifies and predicts dependent variables on the basis of independent variables. The chi-squared automatic interaction detector (CHAID) and the CRT model are two common classification tree methods. The CHAID method applies only to categorical variables, whereas the CRT method is suitable

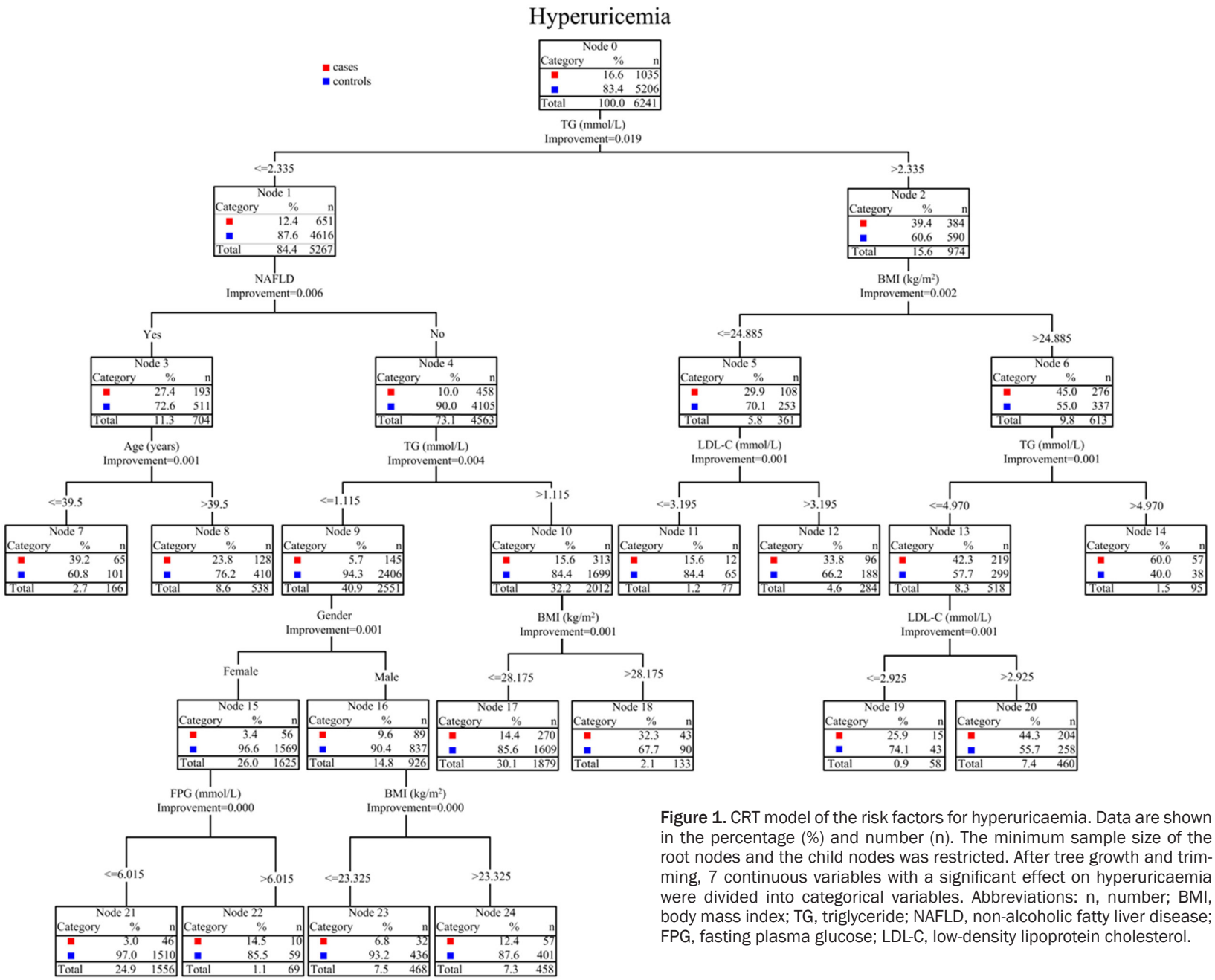

Figure 1. CRT model of the risk factors for hyperuricaemia. Data are shown in the percentage (%) and number (n). The minimum sample size of the root nodes and the child nodes was restricted. After tree growth and trimming, 7 continuous variables with a significant effect on hyperuricaemia were divided into categorical variables. Abbreviations: n, number; BMI, body mass index; TG, triglyceride; NAFLD, non-alcoholic fatty liver disease; FPG, fasting plasma glucose; LDL-C, low-density lipoprotein cholesterol.

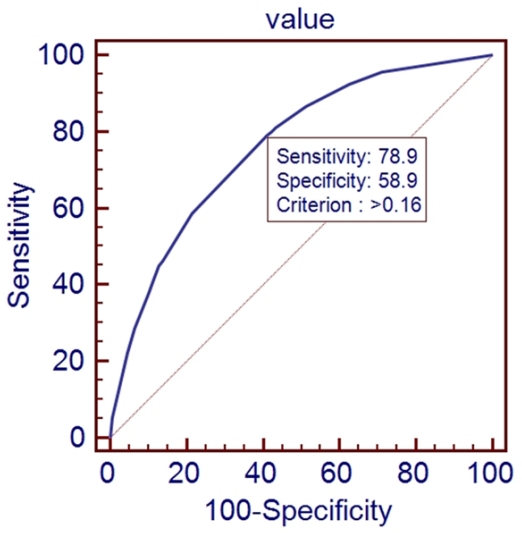

Figure 2. Evaluation of CRT model-ROC curve. The AUC value was 76.2%, the optimal cut-off point of 0.16 marked with a sensitivity of 78.94% and a specificity of 58.86%.

Table 2. Parameters of ROC curve

Parameters	ROC curve of CRT model
Cut-off criterion	0.16
Sensitivity % (95% CI)	78.94 (76.3~81.4)
Specificity % (95% CI)	58.86 (57.5~60.2)
AUC % (95% CI)	76.2 (75.1~77.2)*
Youden index %	37.8

Sensitivity, specificity, AUC and Youden index of ROC curve are shown as percentages (%), and numbers in parentheses are 95% CI. Abbreviations: ROC, receiver operating characteristic; CRT, classification and regression tree; CI, confidence interval; AUC, area under the curve. *$P < 0.01$.

for detecting the interactions between continuous, and categorical variables and automatically identifies the optimal cut-off values of continuous variables under the settings of tree growth restriction and significance level (P = 0.05). In the CRT model, the minimum sample size was 100 for parent nodes and 50 for child nodes. The chi-square test (independent variables vs. dependent variables) was used to split and merge samples to minimise the confounding factors and to continue to generate child nodes on the basis of the significance level of the chi-square value. Moreover, a receiver operating characteristic (ROC) curve was plotted according to the predictive ability of the CRT model, and the area under the curve (AUC) was used to evaluate the accuracy of the CRT model (0.5-1.0). A non-conditional logistic regression model is a common conventional method and is suitable for analysing the relationship between dichotomous variables, which can be used to identify the determinants (risk factors or protective factors) of hyperuricaemia and their impacts. Multivariate analysis was performed to further analyse the factors identified as "significant" by univariate logistics analysis to eliminate confounding factors and correct the impacts of these factors; in addition, the odds ratio (OR) value of the factors was used to quantitatively analyse the interactions among these factors to compensate for the shortcoming of the classification tree model. In this study, we used the CRT method to screen the risk factors for hyperuricaemia and the interactions among the risk factors, and we used the non-conditional logistic regression model combined with the addictive model to quantitatively analyse the interactions among the risk factors.

Results

Clinical characteristics of subjects in the high uric acid (HUA) group and the control group

In this study, a total of 1035 subjects with hyperuricaemia were included in the HUA group (men: 755, women: 280; mean age: 46.95 ± 12.18 years), the overall prevalence of hyperuricaemia was 16.6%, and 5206 subjects with normal uric acid levels were included in the control group (men: 2516, women: 2690; mean age: 46.12 ± 11.70 years). The prevalence of hyperuricaemia was significantly higher in the men (23.1%) than in the women (9.4%) (χ^2 = 209.782, $P < 0.01$). The levels of SBP, DBP, BMI, UA, FPG, TG, TC, and LDL-C were significantly higher in the HUA group than in the control group, whereas the HDL-C level was significantly lower in the HUA group than in the control group (**Table 1**). The prevalence of NAFLD was significantly higher in the HUA group (39.4%) than in the control group (14.8%) (χ^2 = 343.544, $P < 0.01$).

CRT model of the risk factors for hyperuricaemia

Subjects with hyperuricaemia was set as "1", and subjects without hyperuricaemia was set as "0"; gender, age, hypertension, BMI, TG, TC, LDL-C, HDL-C, FPG, and NAFLD were used as

Table 3. Variables and assignments in non-conditional logistic regression model

Variables	Assignments
Hyperuricaemia	No = 0; Yes = 1
Gender	Male = 0; Female = 1
Age (years)	≤ 39.5 = 0; > 39.5 = 1
BMI (kg/m^2)	≤ 24.885 = 0; > 24.885 = 1
Hypertension	No = 0; Yes = 1
NAFLD	No = 0; Yes = 1
TG (mmol/L)	≤ 2.335 = 0; > 2.335 = 1
TC (mmol/L)	< 6.22 = 0; ≥ 6.22 = 1
LDL-C (mmol/L)	≤ 3.195 = 0; > 3.195 = 1
HDL-C (mmol/L)	< 1.04 = 0; ≥ 1.04 = 1
FPG (mmol/L)	≤ 6.015 = 0; > 6.015 = 1

Abbreviations: BMI, body mass index; NAFLD, non-alcoholic fatty liver disease; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose.

the determinants of hyperuricaemia and analysed with the CRT model. The minimum sample size of the root nodes and the child nodes was restricted. After tree growth and trimming, the CRT model included 5 layers, 29 nodes, and 15 terminal nodes and selected 7 variables with a significant effect on hyperuricaemia, including age, gender, BMI, TG, LDL-C, FPG, and NAFLD, wherein three variables, TG, BMI, and NAFLD, were most closely related to hyperuricaemia, with interactions between TG and NAFLD and between TG and BMI, as shown in **Figure 1**.

Evaluation of the CRT model

An ROC curve was plotted based on the CRT-predicted probability, and the area under the ROC curve was 76.2% (CI: 75.1%-77.2%), indicating that the CRT model well predicted the risk factors for hyperuricaemia (**Figure 2**; **Table 2**).

Interactions among the risk factors for hyperuricaemia

Hyperuricaemia was used as the dependent variable, and TG (most closely related to hyperuricaemia in adults) was split into dichotomous variables with the cut-off point in the CRT model, which was 2.335 mmol/L, as the prevalence of hyperuricaemia was higher in individuals with TG > 2.335 mmol/L. Moreover, the CRT results indicated that BMI > 24.885 kg/m^2, age > 39.5, LDL-C > 3.195 mmol/L, and FPG > 6.015 mmol/L were associated with a higher prevalence of hyperuricaemia. Thus, the respective values of BMI, age, LDL-C, and FPG were used as the cut-off point. The value of the other determinants was assigned on the basis of professional experience (**Table 3**).

The CRT model indicated interactions between TG and NAFLD and between TG and BMI. We used non-conditional logistic regression to quantitatively analyse the potential interactions among the determinants. Univariate logistic regression suggested that gender (male), high BMI, hypertension, NAFLD, high TC, high TG, high LDL-C, high FPG, low HDL-C, and the interaction between high TG and high BMI were the risk factors for hyperuricaemia ($P < 0.01$). The prevalence of hyperuricaemia was 8.675-fold higher in individuals with high TG and high BMI than in those with low TG and low BMI, with a positive interaction between these two factors [OR (AB) > OR (A) + OR (B) - 1]. Further multivariate non-conditional logistic regression analysis, after controlling for the risk factors for hyperuricaemia (α_{input} = 0.10, α_{output} = 0.15), showed that gender (male), high BMI, hypertension, NAFLD, high TG, high LDL-C, and the interaction between high TG and high BMI were risk factors for hyperuricaemia ($P < 0.01$), wherein the prevalence of hyperuricaemia was 3.957-fold higher in individuals with high TG and high BMI than in those with low TG and low BMI, with a positive interaction between these two factors [OR (AB) > OR (A) + OR (B) - 1] (**Tables 4**, **5**), and no interaction between TG and NAFLD.

We quantitatively analysed interactions among the risk factors. OR (A^0B^0) indicated the odds ratio in the absence of both high TG and high BMI, OR (AB^0) indicated the odds ratio in the presence of high TG but not high BMI, OR (A^0B) indicated the odds ratio in the presence of high BMI but not high TG, and OR (AB) indicated the odds ratio in the presence of both high BMI and high TG. We used the additive model in which the OR values were incorporated into the formula to quantitatively analyse the interaction effects. Attributed interaction [I (AB)] = OR (AB) - OR (AB^0) - OR (A^0B) + OR (A^0B^0), the attributable percent (AP) = I (AB)/OR (AB), the percentage of attributed interaction between pure factors [AP*(AB)] = I (AB)/[OR (AB) - OR (A^0B^0)], and

Table 4. Univariate non-conditional logistic regression analysis of the risk factors for hyperuricaemia

Variables		B	SE	Wald	*P*-value	OR	95% *CI*
BMI	TG						
-	-			493.592	0.000		
-	+	1.509	0.130	135.237	0.000	4.522	3.506~5.831
+	-	0.959	0.085	127.808	0.000	2.609	2.209~3.081
+	+	2.160	0.101	456.972	0.000	8.675	7.116~10.576
Gender (male)		1.059	0.075	197.887	0.000	2.883	2.488~3.341
Hypertension		0.672	0.075	80.771	0.000	1.958	1.691~2.267
NAFLD		1.324	0.075	314.765	0.000	3.760	3.248~4.353
High TC		0.639	0.110	33.597	0.000	1.894	1.526~2.351
High LDL-C		0.871	0.071	152.395	0.000	2.389	2.081~2.743
Low HDL-C		1.023	0.084	147.970	0.000	2.782	2.359~3.280
High FPG		0.583	0.091	41.459	0.000	1.792	1.501~2.141

Abbreviations: BMI, body mass index; NAFLD, non-alcoholic fatty liver disease; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose.

Table 5. Multivariate non-conditional logistic regression analysis of the risk factors for hyperuricaemia

Variables		B	SE	Wald	*P*-value	OR	95% CI
BMI	TG						
-	-			147.953	0.000		
-	+	1.056	0.138	58.722	0.000	2.875	2.194~3.766
+	-	0.542	0.093	33.870	0.000	1.719	1.432~2.064
+	+	1.375	0.120	131.879	0.000	3.957	3.129~5.004
Gender (male)		0.684	0.080	72.991	0.000	1.982	1.694~2.319
NAFLD		0.610	0.087	49.306	0.000	1.841	1.553~2.183
Hypertension		0.258	0.082	10.017	0.002	1.295	1.103~1.520
High LDL-C		0.338	0.078	18.653	0.000	1.403	1.203~1.635

Abbreviations: BMI, body mass index; NAFLD, non-alcoholic fatty liver disease; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol.

Table 6. Quantitative analysis of the interaction effect between high TG and high BMI on hyperuricaemia

	Univariate logistic regression	Multivariate logistic regression
S	1.50	1.14
I (AB)	2.544	0.363
AP	29.33%	9.17%
AP*(AB)	33.15%	12.28%

Abbreviations: I (AB), attributed interaction; AP, percentage of attributed interaction; AP*(AB), percentage of attributed interaction between pure factors; S, synergy index.

synergy index (S) = [OR (AB) - 1]/[OR (AB^0) - 1 + OR (A^0B) - 1]. The results showed that the S was > 1, indicating a positive interaction between high TG and high BMI. After controlling for confounding factors, the multivariate logistic regression analysis showed that AP was 9.17%, indicating that the interaction between these two factors was responsible for 9.17% of hyperuricaemia prevalence (**Table 6**).

Discussion

In this study, we analysed the metabolic parameters of hyperuricaemia and showed that the levels of SBP, DBP, BMI, UA, FPG, TG, TC, LDL-C, and NAFLD prevalence were significantly higher in the HUA group than in the control group, whereas the HDL-C level was significantly lower in the HUA group than in the control group, suggesting that these metabolic parameters were closely related to hyperuricaemia [18]. These metabolic abnormalities suggested that cardiovascular risk factors clustered in individuals with hyperuricaemia, who were thus at high risk for cardiovascular and cerebrovascular diseases [19].

In this study, we used the CRT model to analyse the risk factors for hyperuricaemia. A total of 7 risk factors were selected (age, gender, BMI, TG, LDL-C, FPG, and NAFLD), which was consistent with literature reports [14, 20, 21]. In addition to the selection of risk factors, the CRT model provides additional useful information. In the CRT method, the target variables are split according to the chi-square value; therefore, the independent variable in the main branch has a bigger impact on the target variables, and the impact gradually diminishes as the branches branch further out. Therefore, the CRT method shows how important each variable is in the model [15, 22].

This study showed that TG was most closely related to hyperuricaemia, indicating that TG

had biggest impact on the risk of hyperuricaemia. The prevalence of hyperuricaemia was significantly higher in individuals with TG > 2.335 mmol/L (39.4%) than in individuals with TG < 2.335 mmol/L (12.4%); thus, individuals with TG > 2.335 mmol/L are at a high risk for hyperuricaemia. A multivariate non-conditional logistic regression analysis showed that the prevalence of hyperuricaemia was 2.875-fold higher in individuals with high TG than in individuals with low TG, suggesting that dyslipidemia was closely related to hyperuricaemia, which was consistent with the results of other researches [23]. Therefore, it is important to screen individuals with high TG to reduce the prevalence of hyperuricaemia. Dyslipidemia may cause hyperuricaemia, as high TG promotes the generation and utilisation of free fatty acids, which in turn accelerates ATP utilisation, thus leading to high uric acid [24]. Moreover, abnormal lipid metabolism affects afferent and efferent arterioles, causing vessel stenosis or even occlusion, lower renal clearance of uric acid, and high serum uric acid level.

After TG, BMI and NAFLD were also closely related to hyperuricaemia. The cut-off point for BMI was 24.885 kg/m^2, which was determined on the basis of statistical significance, rather than clinical practice or personal experience. This determination enabled a more rational setting of the cut-off point, and the cut-off value was consistent with the criterion for overweight/obese individuals in China [25] indicating that the prevalence of hyperuricaemia was significantly higher in overweight or obese individuals (BMI > 24.885 kg/m^2), which was consistent with the results of other Chinese and foreign studies [26]. A multivariate non-conditional logistic regression analysis showed that the prevalence of hyperuricaemia was 1.719-fold higher in individuals with high BMI than in individuals with low BMI. Obesity and being overweight are part of the metabolic syndrome. Serum uric acid levels increased linearly with BMI. For obese and overweight individuals, endocrine disorders, such as low levels of androgen and adrenocorticotropic hormone, inhibit the clearance of uric acid [27]; in addition, a high calorie intake, including high consumption of purine-containing food, accelerates the production of uric acid, while a high keto acid level resulting from fatty acid metabolism inhibits the clearance of uric acid. Moreover, this study showed that NAFLD was an independent risk factor for hyperuricaemia. Recent studies have shown that hyperuricaemia is associated with the development and progression of NAFLD [28]. Both hyperuricaemia and NAFLD are part of the metabolic syndrome, and insulin resistance plays a key role as the condition activates the renin-angiotensin system, wherein angiotensin II reduces renal blood flow and the clearance of uric acid and aggravates oxidative stress and promotes the production of uric acid. As an inflammatory cytokine, uric acid promotes oxidative stress and causes endothelial dysfunction and is thus involved in the development and progression of NAFLD [29]. Therefore, overweight or obese and NAFLD individuals must watch for hyperuricaemia, change their lifestyle and diet, manage their weight, address insulin resistance, and treat NAFLD [30] to prevent hyperuricaemia.

The CRT model can be used to quickly and effectively identify the main determinants of disease and display the interactions among the different levels of the variables on the tree graph. In this study, the CRT analysis showed that TG interacted with NAFLD and with BMI. In individuals with TG > 2.335 mmol/L, the prevalence of hyperuricaemia was significantly higher in individuals with BMI > 24.885 kg/m^2 (45.0%) than in individuals with BMI < 24.885 kg/m^2 (29.9%). Moreover, TG and BMI were two primary variables on all levels of tree branches, suggesting that these two variables were closely related to hyperuricaemia.

The CRT model can be used to screen variables with potential interactions but cannot be used to analyse the effect of linear superposition of independent variables. Thus, we used a logistic regression model to quantitatively analyse the effect of interactions to confirm any interactions. Univariate and multivariate logistic regression models both showed that TG and BMI were independent risk factors for hyperuricaemia. The prevalence of hyperuricaemia was 3.957-fold higher in individuals with high TG than in individuals with low TG and in individuals with high BMI than in individuals with low BMI, with a positive interaction between TG and BMI [OR (AB) > OR (A) + OR (B) - 1]]. Furthermore, we used the additive model [31] to investigate the effect of the interaction between TG and BMI on hyperuricaemia. After controlling for confounding factors, the multivariate logistic regression model showed that the attributable

percent of the interaction was 9.17%, demonstrating that 9.17% of hyperuricaemia onset could be attributed to the interaction between TG and BMI. The prevalence of hyperuricaemia was significantly higher in individuals with both high TG and high BMI than in individuals with high TG or high BMI alone, suggesting that these two factors had significant synergistic effects on the prevalence of hyperuricaemia. Therefore, in addition to weight control, obese individuals must heed their lipid levels to reduce the prevalence of hyperuricaemia.

Tree classification models are becoming powerful tools for analysing complex multi-factorial diseases [32, 33], especially in large aetiology studies. Given the large sample size in this study, the tree classification model was indicated for this study. However, the CRT model used in this study had certain limitations. First, given the numerous explanatory variables and many classifications, the tree became quite large, requiring tree trimming. Second, all subjects in this study were from Guilin, China, thus representing a selection bias. Moreover, many other factors, such as race, diet, lifestyle [10], genetic factors, and gene polymorphisms [34, 35], may affect hyperuricaemia, and further studies are needed to investigate the relationship between more factors and hyperuricaemia.

In summary, this study showed that the interaction between TG and BMI was an important risk factor for hyperuricaemia. This finding deepens our understanding of the cause of hyperuricaemia and enables us to establish active and effective preventive measures to reduce the prevalence of hyperuricaemia, with important implications for reducing the prevalence of cardiovascular and cerebrovascular diseases in individuals with hyperuricaemia.

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Disclosure of conflict of interest

None.

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