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Measurement of the Combined Levels of Serum Uric Acid and Alanine Aminotransferase and the Risk of Metabolic Syndrome in a Population Aged 60 Years or More in Northeastern China

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Data Interpretation D
Manuscript Preparation E
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Background:

Serum uric acid (SUA) and alanine aminotransferase (ALT) levels are increased in patients with metabolic syndrome. This study aimed to investigate the association between the combined levels of SUA and ALT and the risk of metabolic syndrome in residents ≥ 60 years of age in Northeastern China.

Material/Methods:

A population study included nine communities in Shenyang, Northeast China, and 3,998 participants (1,434 men and 2,564 women) who were ≥ 60 years old. SUA and ALT measurements (levels 1–3) and clinical parameters were recorded. Metabolic syndrome was diagnosed according to the criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III). The association between the combined SUA and ALT levels and metabolic syndrome was determined by multivariate logistic regression analysis in tertiles that included Groups 1–9.

Results:

The prevalence of metabolic syndrome was 43.2% (men), and 61.9% (women), and the prevalence and odds ratio (OR) values increased with increasing SUA and ALT levels. The OR values of metabolic syndrome in the ALT Groups 2–3 were 1.329 (95% CI, 1.137–1.554) and 2.362 (95% CI, 2.006–2.781), and in the SUA Groups 2–3 the OR values were 1.718 (95% CI, 1.466–2.015) and 2.743 (95% CI, 2.310–3.256). The OR of the combined increase in SUA and ALT and metabolic syndrome in Groups 1–9 ranged from 1.494–5.889 (all, $p < 0.05$).

Conclusions:

Increased combined SUA and ALT was more significantly associated with metabolic syndrome than an increase in SUA or ALT alone.

MeSH Keywords:

Alanine Transaminase • Metabolic Syndrome X • Uric Acid

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Background

Metabolic syndrome includes abdominal obesity, increased serum triglyceride, reduced serum high-density lipoprotein cholesterol (HDL-C), hyperglycemia, and hypertension [1]. Metabolic syndrome is considered a risk factor for type 2 diabetes mellitus (T2DM) and cardiovascular disease [2]. Previous studies have shown that the prevalence of cardiovascular disease in populations with metabolic syndrome is increased by three-fold, the risk of cardiovascular disease-related death is doubled, the risk of diabetes is increased by five-fold, and mortality increases by 50% [3]. The increasing prevalence of metabolic syndrome is an important public health issue [4]. However, early diagnosis and intervention in individuals with metabolic syndrome may prevent the occurrence and development of T2DM and cardiovascular disease [5].

Although measurement of levels of serum uric acid (SUA) and alanine aminotransferase (ALT) are not diagnostic criteria for metabolic syndrome, studies have shown associations between SUA and ALT and metabolic syndrome [6–9]. Metabolic syndrome is associated with a variably increased risk of cardiovascular disease in different ethnic groups [10,11]. SUA and ALT are easily measured during routine laboratory testing and could be valuable diagnostic markers in high-risk populations. However, the combined effect of SUA and ALT on metabolic syndrome remains unknown.

The prevalence of metabolic syndrome increases with age, and it would be helpful to identify serum markers of metabolic syndrome to prevent T2DM and cardiovascular disease in the elderly population. Therefore, this population-based study aimed to investigate the association between the combined levels of SUA and ALT and the risk of metabolic syndrome in residents ≥ 60 years of age in nine communities in Shenyang, Northeast China.

Material and Methods

Study population and study design

A retrospective randomized cross-sectional population study was conducted between May to October 2017 that included nine communities in Shenyang, Liaoning Province, Northeast China. The study was known as the Promoting the Transformation Model of the Elderly Residents Community and Hospital Chronic Disease Management System. Ethical approval for the study was obtained from the Ethics Committee of the First Affiliated Hospital of China Medical University (No. AF-SOP-07-1.0-01). Written informed consent was obtained from all study participants. If the participants were illiterate, their authorized agents provided signed informed consent on their behalf. The original

study data were registered with the China Clinical Trial Center (ChiCTR-ERC-17011100).

The study population included residents ≥ 60 years of age in nine communities in Shenyang, Northeast China, who had complete and available clinical data. The study exclusion criteria included a diagnosis of hepatitis, liver cirrhosis, malignant tumor, myocardial infarction, and fatty liver in the previous six months. Individuals were also excluded who were treated with drugs that affected liver function and uric acid metabolism, including atorvastatin, rifampicin, sodium bicarbonate, febuxostat, allopurinol, benzbromarone, and furosemide. The study sample size was 3,998 participants, including 1,434 men and 2,564 women.

Data collection

Data were collected by geriatricians at the China Medical University who conducted face-to-face interviews with the subjects using standardized questionnaires. Before conducting the survey, investigators received standardized training. The training included the explanation of study objectives, how to use and store the questionnaires, the use of standardized methods of measurement, and the study protocol. After the training sessions, the investigators were selected following a test to assess their ability to participate in the study. During the surveys, research staff instructed and supported the research. Demographic data included gender, age, ethnicity, education level, smoking history, drinking history, disease history, and drug use were obtained with standardized questionnaires. Epidemiologists, statisticians, and clinical experts designed the questionnaire, and a quality control subcommittee randomly assessed 5% of the questionnaires. If the questionnaire was incomplete, it was removed from the study.

Anthropometric measurements

Anthropometric data included blood pressure, height, weight, body mass index (BMI), and waist circumference (WC). The study participants wore lightweight clothes and removed their shoes for height and weight assessment. Measurements were taken twice, and an average was taken that was accurate to within 0.1 cm and 0.1 kg. The BMI was calculated as the average weight (in kilograms) divided by average height (in meters²). The WC was measured with an inelastic cord at the levels of the navel and in a standing position, and were accurate to within 0.1 cm. A standard mercury manometer was used to measure systolic blood pressure (SBP) and diastolic blood pressure (DBP). Subjects sat quietly for five minutes before blood pressure measurement, and the mean value of two measurements taken within two minutes was recorded.

Table 1. Sociodemographic and biochemical characteristics in study participants ≥ 60 years of age, with and without metabolic syndrome (n=3,998).

Variables	With metabolic syndrome	Without metabolic syndrome	p-Value
	n=2,207	n=1,791	
Age (years)	68.79 $\pm$ 6.53	68.34 $\pm$ 6.58	0.033 [#]
Gender (M/F)	620/1587	814/977	<0.001*
SBP, mmHg	143.37 $\pm$ 19.10	133.72 $\pm$ 20.09	<0.001*
DBP, mmHg	81.43 $\pm$ 11.39	78.32 $\pm$ 11.26	<0.001*
WC, cm	90.80 $\pm$ 8.32	82.95 $\pm$ 8.76	<0.001*
BMI, kg/m ²	26.12 $\pm$ 3.41	23.58 $\pm$ 3.31	<0.001*
TC, mmol/L	5.16 $\pm$ 1.05	5.03 $\pm$ 0.98	<0.001*
TG, mmol/L	2.06 $\pm$ 1.23	1.18 $\pm$ 0.56	<0.001*
HDL-C, mmol/L	1.25 $\pm$ 0.44	1.62 $\pm$ 3.93	<0.001*
LDL-C, mmol/L	3.25 $\pm$ 1.01	3.16 $\pm$ 0.94	0.002 [#]
FBG, mmol/L	6.56 $\pm$ 1.92	5.48 $\pm$ 1.25	<0.001*
ALT, U/L	22.32 $\pm$ 18.39	18.27 $\pm$ 13.52	<0.001*
AST, U/L	23.18 $\pm$ 14.31	22.08 $\pm$ 10.98	0.006 [#]
UA, mmol/L	324.82 $\pm$ 87.10	302.80 $\pm$ 84.45	<0.001*

SBP – systolic blood pressure; DBP – diastolic blood pressure; WC – waist circumference; TC – total cholesterol; TG – triglyceride; HDL – high-density lipoprotein; LDL – low-density lipoprotein; FBG – fasting blood glucose; ALT – alanine aminotransferase; AST – aspartate aminotransferase; SUA – serum uric acid; [#] Significant at $p < 0.05$; * Significant at $p < 0.001$.

Measurement of serum uric acid (SUA), alanine aminotransferase (ALT), and serum lipids

Blood samples were collected into vacuum test tubes after eight hours of fasting. Biochemical data included the fasting blood glucose (FBG), serum uric acid (SUA) (ULN, 420 μ mol/L), serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) (ULN, 40 U/L), total plasma cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). All biochemical indicators were measured on a Roche Modular Analytics System (Roche Diagnostics, Basel, Switzerland) and tested in a clinical laboratory using standard operating procedures.

Criteria for the diagnosis of metabolic syndrome

Metabolic syndrome was defined according to the criteria of the National Cholesterol Education Program, Adult Treatment Panel III (NCEP-ATP III) [12]. Study participants were identified as having metabolic syndrome when they had at least three of the following risk factors: a WC ≥ 90 cm (men) or ≥ 80 cm (women); a serum TG ≥ 150 mg/dL (1.7 mmol/L); HDL-C < 40 mg/dL or 1.04 mmol/L (men) or < 50 mg/dL or 1.3 mmol/L (women); hypertension, defined as a SBP ≥ 130 mmHg, DBP ≥ 85 mmHg, or treated hypertension; hyperglycemia defined as a fasting blood glucose (FBG) ≥ 5.6 mmol/L, or who were prescribed antidiabetic agents.

Study groups

Study participants included three groups based on the SUA and ALT levels in the tertiles, or nine groups, based on a combination of SUA and ALT levels in the tertiles. The nine groups included: Group 1 (the first tertiles of both ALT and SUA levels); Group 2 (the first tertile of ALT and the second tertile of SUA); Group 3 (the first tertile of ALT and the third tertile of SUA); Group 4 (the second tertile of ALT and the first tertile of SUA); Group 5 (the second tertile of ALT and the second tertile of SUA); Group 6 (the second tertile of ALT and the third tertile of SUA); Group 7 (the third tertile of ALT and the first tertile of SUA); Group 8 (the third tertile of ALT and the second tertile of SUA); Group 9 (the third tertiles of both ALT and SUA); and Group 1 as the control group.

Statistical analysis

Data were analyzed using SPSS version 20.0 (IBM, Chicago, IL, USA). Continuous variables were presented as the mean $\pm$ standard deviation (SD), and categorical variables were presented as frequencies and percentages. Independent sample t-tests were used to compare normal distribution parameters. The chi-squared (χ^2) test used for correlations between classification variables and for inter-group analysis. Logistic regression analysis was used to determine the effects of SUA

Table 2. Multiple logistic regression analysis of the risk factors associated with metabolic syndrome.

Metabolic syndrome	b	Wals	P-value	Exp (B)
Constant	-2.722	47.906	<0.001	0.066
ALT	0.023	51.825	<0.001	1.024 (1.017,1.030)
SUA	0.005	110.484	<0.001	1.005 (1.004,1.006)
Age	0.017	10.646	0.001	1.018 (1.007,1.028)
Gender	-1.037	132.558	<0.001	0.355 (0.297,0.423)
Smoking	0.224	4.040	0.044	1.251 (1.006,1.557)
Drinking alcohol	-0.004	0.001	0.972	0.996 (0.818,1.214)

SUA – serum uric acid; ALT – alanine aminotransferase.

Table 3. Correlation analysis of the relationship between serum uric acid (SUA) and alanine aminotransferase (ALT) and metabolic syndrome in the two models.

Variable	Model 1		Model 2	
	r	P-value	r	P-value
ALT	0.163	<0.001	0.118	<0.001
UA	0.132	<0.001	0.182	<0.001

Model 1, unadjusted; Model 2, adjusted for age, gender, history of smoking, and history of drinking.

Table 4. Multivariate-adjusted stratified analysis of serum levels of alanine aminotransferase (ALT) and metabolic syndrome and its components.

	Alanine aminotransferase (ALT) (U/L)					
	≤14.00	P-value	14.01–20.30	P-value	≥20.31	P-value
Abdominal obesity						
OR _U (95% CI)	1	<0.001*	1.292 (1.103–1.515)	0.002 [#]	1.853 (1.570–2.186)	<0.001*
OR _A (95% CI)	1	<0.001*	1.440 (1.216–1.705)	<0.001*	2.337 (1.953–2.797)	<0.001*
Hypertriglyceridemia						
OR _U (95% CI)	1	<0.001*	1.244 (1.053–1.471)	0.01 [#]	2.299 (1.955–2.703)	<0.001*
OR _A (95% CI)	1	<0.001*	1.271 (1.074–1.504)	0.005 [#]	2.417 (2.052–2.848)	<0.001*
Low HDL						
OR _U (95% CI)	1	0.006 [#]	1.041 (0.89–1.220)	0.615	1.268 (1.084–1.484)	0.003 [#]
OR _A (95% CI)	1	<0.001*	1.094 (0.929–1.288)	0.282	1.399 (1.189–1.646)	<0.001*
High blood pressure						
OR _U (95% CI)	1	0.013 [#]	1.062 (0.891–1.267)	0.5	1.302 (1.086–1.562)	0.004 [#]
OR _A (95% CI)	1	<0.001*	1.143 (0.955–1.368)	0.146	1.506 (1.250–1.815)	<0.001*
Hyperglycemia						
OR _U (95% CI)	1	<0.001*	1.104 (0.948–1.285)	0.202	1.518 (1.303–1.770)	<0.001*
OR _A (95% CI)	1	<0.001*	1.142 (0.979–1.330)	0.09	1.607 (1.375–1.879)	<0.001*
Metabolic syndrome						
OR _U (95% CI)	1	<0.001*	1.234 (1.060–1.436)	0.007 [#]	2.033 (1.740–2.376)	<0.001*
OR _A (95% CI)	1	<0.001*	1.329 (1.137–1.554)	<0.001*	2.362 (2.006–2.781)	<0.001*

OR_U – univariate odds ratio; OR_A – adjusted odds ratio with adjustment for age, gender, physical strength, smoking status, drinking status; CI – confidence interval; [#] Significant at p<0.05; * Significant at p<0.001.

Table 5. Multivariate-adjusted stratified analysis of serum levels of serum uric acid (SUA) and metabolic syndrome and its components.

	Serum uric acid (SUA) (mg/dl)					
	≤274	P-value	175–344	P-value	≥345	P-value
Abdominal obesity						
OR _U (95% CI)	1	<0.001*	1.334 (1.137–1.566)	<0.001*	1.542 (1.310–1.815)	<0.001*
OR _A (95% CI)	1	<0.001*	1.851 (1.552–2.207)	<0.001*	3.105 (2.562–3.763)	<0.001*
Hypertriglyceridemia						
OR _U (95% CI)	1	<0.001*	1.597 (1.354–1.883)	<0.001*	2.007 (1.704–2.363)	<0.001*
OR _A (95% CI)	1	<0.001*	1.810 (1.529–2.143)	<0.001*	2.708 (2.271–3.228)	<0.001*
Low HDL						
OR _U (95% CI)	1	0.361	1.120 (0.957–1.310)	0.157	1.074 (0.917–1.257)	0.375
OR _A (95% CI)	1	<0.001*	1.328 (1.129–1.563)	0.001#	1.606 (1.353–1.906)	<0.001*
High blood pressure						
OR _U (95% CI)	1	<0.001*	1.309 (1.100–1.558)	0.002#	1.759 (1.465–2.113)	<0.001*
OR _A (95% CI)	1	<0.001*	1.258 (1.054–1.502)	0.11	1.615 (1.336–1.953)	<0.001*
Hyperglycemia						
OR _U (95% CI)	1	<0.001*	1.327 (1.140–1.545)	<0.001*	1.483 (1.273–1.727)	<0.001*
OR _A (95% CI)	1	<0.001*	1.312 (1.127–1.529)	<0.001*	1.449 (1.243–1.690)	<0.001*
Metabolic syndrome						
OR _U (95% CI)	1	<0.001*	1.454 (1.248–1.693)	<0.001*	1.859 (1.593–2.170)	<0.001*
OR _A (95% CI)	1	<0.001*	1.718 (1.466–2.015)	<0.001*	2.743 (2.310–3.256)	<0.001*

OR_U – univariate odds ratio; OR_A – adjusted odds ratio with adjustment for age, gender, physical strength, smoking status, drinking status; CI – confidence interval; # Significant at p<0.05; * Significant at p<0.001.

and ALT and their combination on metabolic syndrome after adjustment for age, gender, smoking, drinking, and physical activity. The prevalence of metabolic syndrome in the nine study groups for the combination of SUA and ALT following multiple comparisons used Bonferroni's correction (0.05/9=0.006). A P-value <0.05 was considered to be statistically significant.

Results

Sociodemographic and biochemical characteristics of the study group with metabolic syndrome and the control group

Table 1 shows the clinical features of the 3,998 study participants with and without metabolic syndrome, which included 1434 men and 2564 women (age, ≥60 years). The prevalence of metabolic syndrome was 55.2% (43.2% for men and 61.9% for women). Compared with individuals without metabolic syndrome in the control group, study participants with metabolic syndrome showed significantly higher values for systolic blood pressure (SBP), diastolic blood pressure (DBP), waist circumference (WC), total cholesterol (TC), triglyceride

(TG), low-density lipoprotein cholesterol (LDL-C), fasting blood glucose (FBG), serum uric acid (SUA) and alanine aminotransferase (ALT), but lower values for high-density lipoprotein cholesterol (HDL-C) (all, p<0.05).

Identification of risk factors associated with metabolic syndrome

Multiple logistic regression analysis was used to analyze the risk factors associated with metabolic syndrome. As shown in Table 2, ALT, UA, gender, age, and smoking were identified as the risk factors for metabolic syndrome. The correlation analysis results are presented in Table 3, which shows that the correlation values of ALT and UA with metabolic syndrome risk were 0.163 and 0.132, respectively. After adjusting for age, gender, smoking, drinking alcohol, and using the partial correlation analysis method, the correlation values of ALT and UA with the risk of metabolic syndrome were 0.118 and 0.182, respectively, indicating that ALT and UA were associated with metabolic syndrome.

Figure 1. Increased levels of serum uric acid (SUA) combined with alanine aminotransferase (ALT) was associated with metabolic syndrome and its components.

The association between SUA and ALT and metabolic syndrome and its components

Tables 4 and 5 show the SUA and ALT tertiles associated with metabolic syndrome and cardiovascular risk factors. The study subjects were grouped into tertiles based on the serum concentrations of ALT and SUA. For serum ALT levels <14.00 U/L, 14.01–20.30 U/L, and ≥20.31 U/L, the number of study participants was 1,337, 1,333, and 1,328 in the tertiles, respectively. For SUA levels ≤274 μmol/L, 275–344 μmol/L, and ≥345 μmol/L, the number of study participants were 1,343, 1,334, and 1,321 in the tertiles, respectively. The prevalence rates of metabolic syndrome at the three serum ALT levels were 47.7%, 53.0%, and 65.0%. The prevalence rates of metabolic syndrome at the three SUA levels were 47.1%, 56.4%, and 62.3%, respectively. After adjusting for the confounding factors of gender, age, physical strength, smoking, drinking, and

a history of coronary heart disease, the high levels of ALT and SUA were significantly correlated with metabolic syndrome and cardiovascular risk factors.

The combined level of SUA and ALT was associated with metabolic syndrome and its components

To further investigate the association between SUA and ALT in metabolic syndrome and its components, all participants were classified into nine groups based on a combination of ALT and SUA levels in the tertiles. Figure 1 shows the effects of ALT combined with SUA on metabolic syndrome and its components. Compared with the control group, the incidence of metabolic syndrome and cardiovascular risk factors increased with increasing levels of ALT and UA. The prevalence, odds ratio (OR), and 95% confidence intervals (CIs) of metabolic syndrome in the nine groups were 38.8% (OR=1), 51.2% (OR=1.957;

Table 6. The prevalence of metabolic syndrome in the nine study groups for the combination of serum uric acid (SUA) and alanine aminotransferase (ALT) following multiple comparisons using Bonferroni's correction (0.05/9=0.006).

Variable	Study groups for ALT combined with SUA (n=9)									χ^2	P-value
	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	Group 8	Group 9		
Waist circumference										77.401	<0.001
0	228	160	130	166 ^c	147 ^a	125 ^a	112 ^a	109 ^{abd}	117 ^{abcde}		
1	285	285	249	301 ^c	295 ^a	299 ^a	251 ^a	338 ^{abd}	401 ^{abcde}		
Triglyceridemia										170.958	<0.001
0	415	312 ^a	250 ^a	345 ^b	299 ^a	270 ^{ad}	230 ^{ad}	239 ^{abcd}	250 ^{abcd}		
1	98	133 ^a	129 ^a	122 ^b	143 ^a	154 ^{ad}	133 ^{ad}	208 ^{abcd}	268 ^{abcd}		
Low HDL										13.250	0.104
0	333	286	250	303	281	270	227	255	307		
1	180	159	129	164	161	154	136	192	211		
Blood pressure										52.289	<0.001
0	167	99 ^a	71 ^a	129	117	75 ^{ad}	84	93 ^a	96 ^{ad}		
1	346	346 ^a	308 ^a	338	325	349 ^{ad}	279	354 ^a	422 ^{ad}		
Glycemia										54.690	<0.001
0	291	215	181	249	218	185 ^a	168	176 ^{ad}	201 ^{ade}		
1	222	230	198	218	224	239 ^a	195	271 ^{ad}	317 ^{ade}		
Metabolic syndrome										136.878	<0.001
0	314	217 ^a	168 ^a	246	210 ^a	171 ^{ad}	151 ^a	155 ^{abde}	159 ^{abcdeg}		
1	199	228 ^a	211 ^a	221	232 ^a	253 ^{ad}	212 ^a	292 ^{abde}	359 ^{abcdeg}		

0 – within the normal range; 1 – abnormal; ^a compared with Group 1, the difference was statistically significant; ^b compared with Group 2, the difference was statistically significant; ^c compared with Group 3, the difference was statistically significant; ^d compared with Group 4, the difference was statistically significant; ^e compared with Group 5, the difference was statistically significant; ^f compared with Group 6, the difference was statistically significant; ^g compared with Group 7, the difference was statistically significant.

CI, 1.500–2.554), 55.7% (OR=2.809; CI, 2.111–3.739), 47.3% (OR=1.494; CI, 1.152–1.937), 52.5% (OR=2.157; CI, 1.652–2.815), 59.7% (OR=3.652; CI, 2.761–4.832), 58.4% (OR=2.480; CI, 1.871–3.287), 65.3% (OR=3.926; CI, 2.981–5.170), 69.3% (OR=5.889; CI, 4.467–7.764) (all $p<0.05$). Compared with the first tertiles of both ALT and SUA, the OR values of the groups with higher ALT and SUA were increased, and the OR value of Group 9 was six-times that of Group 1. ALT combined with SUA was significantly correlated with central obesity, hypertriglyceridemia, hyperglycemia, and hypertension ($P<0.05$). ALT combined with SUA was poorly correlated with levels LDL-C. Logistic regression analysis showed that the combination of SUA and ALT was significantly associated with the risk of metabolic syndrome and cardiovascular disease when compared with a single factor (Figure 1).

Table 6 shows the prevalence of metabolic syndrome in the nine study groups for the combination of SUA and ALT following multiple comparisons using Bonferroni's correction (0.05/9=0.006). Except for LDL-C, there were significant differences between the groups, regardless of whether metabolic syndrome was present, or whether the components of metabolic syndrome were within the normal range. For example, regardless of whether the patient had metabolic syndrome, Group 2 was significantly different from Group 1; Group 3 was significantly different from Group 1; Group 5 was significantly different from Group 1; Group 6 was significantly different from Group 1 and Group 2; Group 7 was significantly different from Group 1; Group 8 was significantly different from Group 1, Group 2, Group 4, and Group 5; Group 9 was significantly different from Group 1, Group 2, Group 3, Group 4, Group 5, and Group 7.

Discussion

The findings from the present study that included a community of individuals ≥ 60 years of age in Northeast China, the combined increase in serum uric acid (SUA) and alanine aminotransferase (ALT) were significantly correlated with metabolic syndrome and its components. To the best of our knowledge, this study is the first to report the combined effects of ALT and SUA on metabolic syndrome and cardiovascular risk factors in the elderly. ALT and SUA were both increased and were more strongly correlated with metabolic syndrome than either index alone.

Previous epidemiological studies have reported significant associations between ALT, SUA, and metabolic syndrome. ALT has been identified as a predictor of metabolic syndrome, diabetes, obesity, and dyslipidemia in people of varied races and ages [13,14]. Also, ALT has been proposed as a predictor of metabolic syndrome even when it is within the normal range [15,16]. In 2015, Janičko et al. showed that redefining the upper limit of normal (ULN) for ALT, defined as 72% of the original ULN, improved the risk prediction of metabolic syndrome [17]. ALT is also a specific indicator of fatty liver [18], and meta-analysis data showed that the incidence of T2DM and metabolic syndrome increase exponentially with the development of fatty liver [19]. The mechanism involved may be associated with hepatic lipid deposition, insulin resistance, and oxidative stress [20]. ALT is released as a consequence of liver cell injury, which is associated with hepatic fat accumulation and is a surrogate indicator of nonalcoholic fatty liver disease (NAFLD). NAFLD has been identified as the hepatic presentation of metabolic syndrome and should be considered as one of the diseases constituting metabolic syndrome [21].

Free fatty acids are released from adipose tissue into the portal vein, which inhibits the physiological processes that mediate insulin resistance, increase the absorption of free fatty acids in the liver, and resynthesizing them into triglycerides, ultimately leading to the increase in ALT in NAFLD [22]. Previous studies have shown that NAFLD induces insulin resistance in the liver, which may interfere with tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1) and IRS-2 by activating protein kinase C-epsilon (PKC-epsilon) and JNK1, resulting in the impaired ability of insulin to activate glycogen synthesis and inhibit glycogenesis [23]. Recent studies have shown that hepatic diacylglycerol activates ectopic protease C in NAFLD [24–26], and that in NAFLD, circulating mediators are released that include alpha-fetoprotein A, selenoprotein P, fibroblast growth factor-21, and other factors involved in glucose metabolism and insulin sensitivity, which play key roles in hepatic insulin resistance [27]. Also, oxidative stress is an important mechanism in the development of NAFLD [28,29]. In a study of 207 patients with NAFLD, NADPH in the liver was

shown to lead to the production of reactive oxygen species (ROS), and the levels of ALT increased with increasing NADPH oxidase 4 (NOX4) levels [30].

Previous studies have shown that metabolic syndrome is associated with increased SUA levels in women, regardless of their menopausal status [31,32]. Similar findings have been reported in patients with diabetes [33], the elderly [9,32], and even in adolescents [35]. However, Petrikova et al. found that there was a high prevalence of metabolic syndrome in Romania, but this population had a significant decrease in the levels of SUA levels, which may have been due to genetic factors [36]. From the findings of the present study, and several previous studies, the mechanism for the association between metabolic syndrome and an increase in SUA may be explained by liver metabolism. Fructose enters liver cells and is rapidly phosphorylated, and as intracellular levels of phosphate decrease, AMP activity increases, and ATP consumption increases the levels of SUA. However, the consumption of ATP and the increase in SUA levels in the liver may lead to inflammation and generation of ROS, which can promote fat storage and insulin resistance and lead to abnormal glucose metabolism [37,38]. SUA also blocks the release of insulin-mediated nitric oxide (NO) from endothelial cells, which is essential for the effects of insulin [39]. In adipocytes, SUA induces redox-dependent signal transduction and oxidative stress, leading to the reduced adiponectin synthesis and altered lipid metabolism [40].

Although both ALT and SUA are closely associated with metabolic syndrome through lipid deposition, insulin resistance, and oxidative stress, there are currently no diagnostic markers for metabolic syndrome and cardiovascular events [41]. The results of the present population-based study support the use of these simple and routinely available biochemical markers to assess metabolic syndrome and cardiovascular risk in the elderly. Although the subjects in this study were all older than 60 years, age was a risk factor for metabolic syndrome and cardiovascular disease. Following adjustment for age, the study data showed a six-fold increase in the odds ratio (OR) values in the third tertile of ALT and SUA compared with the control group. However, the OR value in the third level group of ALT and SUA alone only increased by 2.4-times and 2.7-times compared with the control group, and the single factor correlation was far weaker than the combined effect. Also, analysis of the significance of ALT combined with SUA included nine groups, and the differences between each level were found to be significant. With increasing ALT and SUA levels, the OR values of metabolic syndrome and each clinical component increased. ALT and SUA were used as biochemical markers for routine clinical diagnosis, and their combined evaluation may be valuable in predicting the risk of metabolic syndrome and planning preventive interventions and treatments. Also, the combined use of ALT and AUA may be used

to identify and treat metabolic syndrome and prevent cardiovascular disease by controlling blood pressure, blood glucose, serum lipids, and weight.

This study had several limitations. This large population study relied on the available recorded clinical data for the study participants, and there were limited data on adverse cardiovascular, cerebrovascular, or metabolic outcomes. ALT and SUA were only measured once, and the potential individual variations may have impacted the results. Although the subjects diagnosed with hepatitis in their medical records were excluded, the absence of serological test results did not exclude viral hepatitis as a cause of increased ALT in study participants. Although several potential confounding factors were controlled in the statistical models, it is possible that there were residual confounding factors that were not analyzed. Finally, this population study included individuals in nine communities in Northeast China, and the findings should be investigated further in other ethnic groups.

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Conclusions

This study aimed to investigate the association between the combined levels of serum uric acid (SUA) and alanine aminotransferase (ALT) and the risk of metabolic syndrome in residents ≥ 60 years of age in nine communities in Shenyang, Northeast China. The combined increase in SUA and ALT was more significantly associated with metabolic syndrome than an increase in SUA or ALT alone. Further studies are needed to investigate whether interventions aimed at reducing ALT and SUA levels can reduce the risk of metabolic syndrome and cardiovascular disease.

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Conflict of interest

None.

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