Postprint: Restricted Cubic Spline Analysis of the Relationship Between Serum Liver Transaminases and Metabolic Syndrome

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Abstract

Background: Metabolic syndrome (MS) has become a global health issue. While most current research focuses on the correlation between MS and its components with alanine aminotransferase (ALT) and aspartate aminotransferase (AST), the dose-response relationship between ALT, AST and MS requires further exploration. Objective: To investigate the association between ALT, AST and the risk of MS among the elderly population, providing a reference basis for MS prevention and control. Methods: In 2022, a multi-stage sampling method was employed to select residents aged $ $60 years from 162 townships (subdistricts) across 18 prefecture-level cities in Henan Province for health examinations. Physical examinations and laboratory tests were conducted. Logistic regression models and restricted cubic spline models were utilized to analyze the relationship between ALT, AST and MS risk. Results: A total of 112,605 participants were included, with an MS prevalence of 18.6% (20,935/112,605), ALT abnormality rate of 5.4% (6,132/112,605), and AST abnormality rate of 6.8% (7,661/112,605). ALT levels were higher in MS patients compared to non-MS patients, while AST levels were lower (P<0.05). Logistic regression analysis and trend tests revealed that after adjusting for confounding factors, the risk of MS increased with elevated ALT levels in both the total population and gender-stratified groups, while showing a "U"-shaped trend with AST level changes (P<0.05). Restricted cubic spline analysis demonstrated that ALT and MS risk exhibited a positive linear dose-response relationship in the total population and gender-stratified groups (P for overall trend <0.001, P for nonlinearity >0.05); AST and MS risk showed a nonlinear dose-response relationship (P for overall trend <0.001, P for nonlinearity <0.001), with an approximately "U"-shaped curve. Conclusion: ALT and AST can serve as important predictive factors for MS development, particularly elevated ALT levels.

Full Text

Relationship between Serum Liver Transaminase and Metabolic Syndrome based on Restrictive Cubic Spline Analysis

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Abstract

Background: Metabolic syndrome (MS) has become a global health problem. While most studies have focused on the correlation between MS and its components with alanine aminotransferase (ALT) and aspartate aminotransferase (AST), whether a dose-response relationship exists between ALT, AST and MS requires further exploration.

Objective: To investigate the relationship between ALT, AST and the risk of MS among elderly individuals, providing a reference basis for MS prevention and control.

Methods: In 2022, a multi-stage sampling method was used to select residents aged $ $60 years from 162 townships (streets) across 18 prefecture-level cities in Henan Province for health examinations. Physical examinations and laboratory tests were conducted. Logistic regression analysis combined with restricted cubic spline models was employed to analyze the relationship between ALT, AST and MS risk.

Results: A total of 112,605 participants were enrolled, with an MS prevalence of 18.6% (20,935/112,605), ALT abnormality rate of 5.4% (6,132/112,605), and AST abnormality rate of 6.8% (7,661/112,605). The MS group had higher ALT levels but lower AST levels compared to the non-MS group ($P<0.05$). Logistic regression and trend tests showed that after adjusting for confounders, the risk of MS increased with elevated ALT levels in both the total population and gender-stratified groups, while showing a U-shaped trend with AST levels ($P<0.05$). Restricted cubic spline results demonstrated a positive linear dose-response relationship between ALT and MS risk in both the total population and gender-stratified groups (P for overall trend <0.001, P for nonlinearity >0.05). AST showed a nonlinear dose-response relationship with MS risk (P for overall trend <0.001, P for nonlinearity <0.001), with an approximately U-shaped curve.

Conclusion: ALT and AST can serve as important predictive factors for MS

development, particularly elevated ALT levels.

Keywords: Metabolic syndrome; Transaminases; Alanine transaminase; Aspartate aminotransferases; Restricted cubic spline; Aged; Henan

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Introduction

Metabolic syndrome (MS) is a chronic non-communicable syndrome characterized primarily by abdominal obesity, hypertension, hyperglycemia, and dyslipidemia [1-2]. MS has become a global health concern, with patients being susceptible to various diseases including cardiovascular disease, type 2 diabetes, stroke, and non-alcoholic fatty liver disease, posing a serious threat to human health [3-4]. Serum liver transaminases mainly include alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which are important markers of liver injury [5]. Non-alcoholic fatty liver disease is considered one of the hepatic manifestations of MS and is significantly associated with elevated ALT and AST levels [6-7]. Multiple studies have shown that ALT and AST are closely related to MS occurrence, though conclusions remain inconsistent [8-10]. Currently, most research has only examined the correlation between serum liver transaminases and MS and its components, with limited domestic studies on the relationship between AST and MS. This study utilizes large-sample health examination data from Henan Province residents to explore the dose-response relationship between ALT, AST and MS risk through restricted cubic spline models, providing a reference basis for MS prevention and control.

1.1 Data Source

In 2022, a multi-stage sampling method was used to select residents aged $ $60 years from 18 prefecture-level cities in Henan Province for health examinations. The sampling was conducted in three stages: first, 18 prefecture-level cities served as primary sampling units; second, three counties (districts) were randomly selected from each city using simple random sampling; third, three townships (streets) were randomly selected from each county (district). A total of 162 townships (streets) were selected, with a 1% sampling ratio of elderly residents from each township (street), yielding 123,741 elderly individuals. Inclusion criteria were: (1) age $ $60 years; (2) voluntary participation in health examinations; (3) registered or non-registered residents living in Henan Province for more than six months; and (4) complete examination records. Exclusion criteria were: (1) incomplete examination data or illogical outliers; (2) severe mental disorders; and (3) liver diseases including chronic viral hepatitis, cirrhosis, liver cancer, or autoimmune liver disease. Ultimately, 112,605 participants were included in this study, all of whom provided informed consent.

1.2.1 Basic Information Collection

Basic personal information was collected through the health record system, including gender, age, education level, marital status, disability status, and other indicators.

1.2.2 Physical Examination

Standard instruments and standardized methods were used to measure height, weight, waist circumference, systolic blood pressure (SBP), and diastolic blood pressure (DBP).

1.2.3 Laboratory Testing

Professional medical staff conducted various laboratory tests, including AST, ALT, total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting plasma glucose (FPG), and other indicators.

1.3 Related Indicators and Definitions

MS diagnosis criteria followed the "Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes Mellitus (2020 Edition)" [2]. MS was diagnosed when three or more of the following criteria were met: (1) Hypertension: blood pressure >130/85 mmHg and/or diagnosed hypertension under treatment; (2) Hyperglycemia: FPG $ $6.1 mmol/L and/or diagnosed diabetes under treatment; (3) Abdominal obesity: waist circumference $ $90 cm for men and $ $85 cm for women; (4) TG $ $1.70 mmol/L; (5) HDL-C <1.04 mmol/L.

Waist-to-height ratio (WHtR) was used as an alternative measure of visceral fat, calculated as waist circumference (cm)/height (m). WHtR $ $0.5 indicated high obesity [11]. Overweight was defined as BMI $ $24.0 kg/m^{2}$. ALT abnormality was defined as ALT >40 U/L, and AST abnormality as AST >40 U/L [5].

1.4 Statistical Methods

SPSS 21.0 and R 4.3.1 were used for statistical analysis. Measurement data were expressed as ($\bar{x}\pm s$) and compared between groups using independent samples t-tests. Count data were analyzed using ^{2} tests. ALT and AST were divided into four groups according to quartiles, with the first group (Q1) as the reference for logistic regression analysis, and trend tests were performed using group medians. Restricted cubic spline models were used to analyze the dose-response relationship between ALT, AST and MS. The significance level was set at α=0.05.

2.1 General Characteristics

This study included 112,605 participants, including 50,732 males (45.1%) and 61,873 females (54.9%). The prevalence of MS among elderly residents in Henan Province was 18.6% (20,935/112,605), the ALT abnormality rate was 5.4% (6,132/112,605), and the AST abnormality rate was 6.8% (7,661/112,605). Significant differences were observed between MS and non-MS groups in gender, age, education level, marital status, disability status, WHtR, overweight status, abdominal obesity, SBP, DBP, FPG, TC, TG, HDL-C, LDL-C, ALT, and AST ($P<0.05$) (Table 1).

2.2 Logistic Regression Analysis of ALT, AST and MS

Based on quartiles, ALT and AST were each divided into four groups (Q1, Q2, Q3, Q4). The median values for ALT groups were 10.14, 16.00, 21.06, and 32.00 U/L, respectively. The median values for AST groups were 17.00, 22.00, 27.00, and 36.00 U/L, respectively (Table 2).

Before adjusting for confounders, results showed that compared with the ALT Q1 group, the risk of MS increased in Q2-Q4 groups ($P<0.05$); compared with the AST Q1 group, the risk of MS decreased in Q2-Q4 groups ($P<0.05$). After adjusting for confounders (Model 2), results remained consistent: compared with ALT Q1, Q2-Q4 groups showed increased MS risk ($P<0.05$); compared with AST Q1, Q2-Q4 groups showed decreased MS risk ($P<0.05$). Trend tests showed MS risk increased with ALT levels ($Ptrend<0.001$) and exhibited a U-shaped trend with AST levels ($Ptrend<0.001$) (Table 3).

2.3 Gender-Stratified Logistic Regression Analysis

When stratified by gender, both males and females showed similar patterns. Before adjustment, ALT Q2-Q4 groups had higher MS risk compared to Q1 ($P<0.05$), while AST Q2-Q4 groups had lower risk ($P<0.05$). After adjustment (Model 2), these relationships remained significant ($P<0.05$) with $Ptrend<0.001$ for both ALT and AST, indicating statistically significant trends in MS risk across ALT and AST levels (Tables 4 and 5).

2.4 Dose-Response Relationship Between ALT, AST and MS Risk

After adjusting for confounders, a linear dose-response relationship was observed between ALT and MS risk in the total population (P for overall trend <0.001, P for nonlinearity $=0.550$), while AST showed a nonlinear dose-response relationship (P for overall trend <0.001, P for nonlinearity <0.001) (Figure 1 [Figure 1: see original paper]). When ALT >18.33 U/L, the OR exceeded 1. For AST, when 23.90 U/L $<$ AST <30.68 U/L, the OR was <1, indicating a protective effect, with the lowest point at AST $=26.40$ U/L.

Gender-stratified analysis revealed similar patterns. In males, ALT showed a linear dose-response relationship (P for overall trend <0.001, P for nonlinearity

=0.480), while AST showed a nonlinear relationship (P for overall trend <0.001, P for nonlinearity <0.001). ALT >19.13 U/L was associated with OR>1, while 23.74 U/L < AST <40.74 U/L showed protective effects, with the nadir at AST =30.11 U/L (Figure 2 [Figure 2: see original paper]).

In females, ALT also showed a linear dose-response relationship (P for overall trend <0.001, P for nonlinearity =0.890), while AST showed a nonlinear relationship (P for overall trend <0.001, P for nonlinearity <0.001). ALT >17.91 U/L was associated with OR>1, while 23.82 U/L < AST <32.35 U/L showed protective effects, with the nadir at AST =27.33 U/L (Figure 3 [Figure 3: see original paper]).

Discussion

As a new type of chronic non-communicable disease, MS has become increasingly common among Chinese residents with economic development and the spread of Western lifestyles [3,12]. Studies indicate that the rising prevalence of MS is closely related to high-calorie, low-fiber diets and reduced physical activity [3]. Our survey found that the prevalence of MS among elderly residents in Henan Province was 18.6%, lower than the 35.61% reported in a community of the Pearl River Delta [10] but higher than the 17.5% reported in rural elderly populations in Guizhou Province [13], possibly due to differences in geography, economic conditions, and lifestyle.

Multivariate logistic regression analysis showed that ALT levels were positively associated with MS risk in both the total population and gender-stratified groups, consistent with findings from Zhou et al. [14] regarding elderly populations. Our results align with ZHANG et al. [8] regarding gender-stratified ALT and MS associations, and with LIU et al. [9] who reported significant associations between ALT and MS and its components in elderly populations. Multiple studies demonstrate that MS risk increases with elevated ALT levels. However, findings regarding AST and MS have been inconsistent. Our results showed an inverse association between AST levels and MS risk in both the total population and gender-stratified groups, with MS risk decreasing as AST levels increased. This contrasts with ZHANG et al. [8], who found MS risk increased with AST levels in both total and gender-stratified populations, and with LIU et al. [9], who found no association between AST and MS (P>0.05). Chen [10] reported an inverse association between AST and MS risk within the reference range, similar to our findings. These discrepancies may be attributable to regional differences and varying numbers of confounding factors, warranting further investigation.

Restricted cubic spline plots provide a more intuitive and accurate description of the relationship between ALT, AST and MS, revealing how MS risk changes with varying transaminase levels. Our results showed a positive linear dose-response relationship between ALT and MS in both the total population and gender-stratified groups, while AST showed a nonlinear dose-response relation-

ship with an approximate U-shaped curve. Yang et al. [15] found a linear dose-response relationship between ALT within the normal range and MS in adults over 65, consistent with our findings. However, WU et al. [16] reported that among Chinese adults over 18, males showed a linear dose-response relationship while females showed a nonlinear relationship between normal-range ALT and MS, contrary to our results. This gender difference in WU et al. [16] may be attributed to menopausal status differences, while the discrepancy between studies may stem from differences in population age and ALT ranges. Our findings suggest that both ALT and AST can serve as early indicators of MS. Within the reference ranges, MS risk generally increases with ALT levels, while AST shows more complex patterns. This may be because ALT is primarily found in liver cells, whereas AST is also present in cardiac cells, bone marrow cells, and other tissues, making ALT a more specific indicator [5,10,17].

This study has several limitations. First, as a cross-sectional study, it cannot establish causal relationships between ALT, AST and MS development. Second, the elderly population generally had low education levels and included many advanced-age individuals, posing challenges during data collection. However, all investigators received rigorous training, and the large sample size maximized data reliability.

In conclusion, ALT and AST are closely associated with MS and can serve as important predictive factors, particularly elevated ALT levels. Monitoring serum liver transaminase levels in elderly populations may help identify individuals at risk for MS early, enabling preventive interventions to improve health and quality of life.

Author Contributions

WANG Wenjuan conceptualized the study, performed statistical analysis, analyzed results, and drafted the manuscript. WANG Rui, ZENG Hongji, LIU Yahui, and WEI Shufan were responsible for quality control and manuscript review. TIAN Qingfeng analyzed implementation feasibility. WANG Wenjuan and TIAN Qingfeng revised the manuscript.

Conflicts of Interest: None declared.

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Note: Figure translations are in progress. See original paper for figures.