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ORIGINAL ARTICLE

Gamma-Glutamyltransferase Levels and Hypertension Risk: A U-Shaped Relationship in a Large Chinese Health Checkup Population

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Abstract

OBJECTIVE: The association of Gamma-glutamyltransferase (GGT) with hypertension remains unclear due to previous studies. This study aims to investigate the relationship between GGT and hypertension in a large health checkup population from Wuhu, China.

METHODS: A cross-sectional study was conducted at the First Affiliated Hospital of Wannan Medical College from 2011 to 2016. A total of 303,431 individuals who underwent physical examination and biochemical testing were enrolled in this study. Multivariable logistic regression model and restricted cubic spline models were employed to examine the relationship between GGT levels and hypertension.

RESULTS: Compared to individuals with normal blood pressure, GGT levels were higher in the hypertensive group (23.15 [14.00-34.98] vs. 37.00 [21.00-51.00] U/L, $p < 0.001$), and the prevalence of elevated GGT was also higher (9.59% vs. 25.12%, $p < 0.001$). After adjusting for age, sex, smoking, drinking, BMI, triglycerides, total cholesterol, total protein, and albumin (Model 4), GGT quartiles were significantly associated with hypertension ($p < 0.001$). Compared with Q1, the odds ratios (ORs) for hypertension were 0.958 (95% CI: 0.926-0.991), 0.717 (95% CI: 0.691-0.743), and 2.421 (95% CI: 2.340-2.504), respectively. The restricted cubic spline model demonstrated a nonlinear association between GGT and hypertension ($p < 0.001$). The odds ratio (OR) for hypertension initially decreased and then increased as GGT levels rose. When GGT levels ranged from 15.03 U/L to 24.61 U/L, the OR for hypertension was less than 1.0. Similar trends were observed after grouping by gender.

CONCLUSIONS: This study found a positive association between GGT and hypertension at both low and high GGT levels, while a negative association was observed at moderate GGT levels.

INTRODUCTION

Hypertension is one of the most prevalent chronic diseases worldwide and a major risk factor for cardiovascular diseases and related complications (GBD 2019 Risk Factors Collaborators 2020). Approximately 1.39 billion people worldwide are affected by hypertension and its prevalence is higher in low- and middle-income countries (Mahmood *et al.* 2014; Zibara *et al.* 2021). In China, the prevalence of hypertension is estimated to be as high as 24.7%, making it one of the major public health challenges (Yin *et al.* 2022a; China PEACE Collaborative Group *et al.* 2023; Zhang *et al.* 2023). Furthermore, with changes in lifestyle, dietary habits, and an aging population, the burden of hypertension is expected to continue rising (Basu & Millett 2013; Mills *et al.* 2016; Yin *et al.* 2022a).

Gamma-glutamyl transferase (GGT) is a well-known liver enzyme commonly used in the diagnosis of liver and biliary disorders, as well as an indicator of biliary obstruction and hepatic inflammation (Kunutsor 2016; Brennan *et al.* 2022). In recent years, GGT has been increasingly recognized for its close association with the development of various chronic diseases, including metabolic syndrome, diabetes, cardiovascular diseases, and hypertension (Sluik *et al.* 2012; Neuman *et al.* 2020; Rhee 2023). Elevated GGT levels have been associated with markers of oxidative stress and endothelial dysfunction (Liu *et al.* 2012; Kunutsor *et al.* 2015). A study conducted among adults in Bangladesh found that elevated GGT levels were associated with hypertension (Rahman *et al.* 2020). Similarly, a cohort study in Korea observed that patients with severe hypertension had significantly higher mean GGT levels compared to those with moderate or mild hypertension (Jo *et al.* 2009). However, these studies were direct estimates of the linear relationship between GGT and hypertension, which may have led to some details being overlooked. A cohort study conducted in New York, USA, found that the risk of hypertension was significantly lower in the second quintile (Q2) of GGT levels compared to the first quintile (Q1). Furthermore, the risk was higher in the third (Q3), fourth (Q4), and fifth quintiles (Q5) than in Q2 (Stranges *et al.* 2005). Based on these results, it can be speculated that there is a nonlinear relationship between GGT and hypertension, which requires further study.

In conclusion, the association of GGT with hypertension remains unclear in previous studies (Stranges *et al.* 2005; Ndrepepa & Kastrati 2016). Investigating the association between GGT and hypertension not only aids in understanding the mechanisms underlying hypertension, but also offers potential biomarkers for prevention and intervention strategies. Therefore, further investigation of this relationship is of great importance. In this study, we performed a cross-sectional analysis of individuals undergoing health check-ups in Wuhu, China, to examine the relationship between GGT levels and hypertension. However, the temporal sequence cannot be established from this cross-sectional analysis.

METHOD

Subjects

This cross-sectional study involved participants who underwent physical examinations at the First Affiliated Hospital of Wannan Medical College from 2011 to 2016. The inclusion criteria were as follows: (1) subjects aged between 18 and 80 years; and (2) availability of data on biochemical indicators such as sex, age, height, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), among others. Subjects were excluded if they met any of the following criteria: (1) diagnosed chronic liver disease (e.g., viral hepatitis, cirrhosis, primary biliary cholangitis); (2) severe elevation of liver enzymes (≥3 times the upper limit of normal); or (3) missing clinical data. After application of the exclusion criteria, a total of 303,431 participants, consisting of 176,890 males and 126,541 females, were enrolled. The study was conducted in compliance with the Helsinki guidelines of the Hel-sinki Declaration of the World Medical Association and approved by the Ethics Committee of Wannan Medical College (Approval No. (2024) 7), with a formal waiver of informed consent granted for the use of pre-existing anonymized health records.

Questionnaire survey

The questionnaire, designed by several specialists and clinicians, included items on general information, biochemical indicators, medical history, and behavioral characteristics. The general information comprised age, gender, occupation, and education. Biochemical indicators encompassed blood counts, liver function, and kidney function. Medical history covered hypertension, diabetes mellitus, dyslipidemia, renal disease, major surgeries, cancer, and usage of antihypertensive and hypoglycemic drugs. Behavioral characteristics inquired about smoking habits (never smoked: didn't smoke in the last year; occasional smoker: smoked more than 1 day but less than 3 days per week; regular smoker: smoked for more than 3 days every week) and drinking habits (never drank: didn't drink in the last year; occasional drinker: drank more than 1 time but less than 3 times per week; regular drinker: drank for more than 3 times per week).

Physical examination

All height, weight, and blood pressure measurements were performed by trained professionals adhering to the guidelines set by the World Health Organization and the International Society of Hypertension. Blood pressure was measured in the right arm using a mercury sphygmomanometer after the subject had sat quietly for five minutes. Three consecutive measurements were

Tab. 1. Baseline characteristics of populations grouped by blood pressure categories

Variables	Overall (n = 303,431)	Normotensive (n = 246,399)	Hypertensive (n = 57,032)	t/z/χ^2	*p*
Male/Female	176,890/126,541	135511/110,888	41,379/15,653		
Age (year)	47.59±13.56	45.69±13.01	55.78±18.87	-167.17	<0.001
BMI (kg/m^2)	23.80±3.24	23.38±3.10	25.61±3.17	-154.15	<0.001
SBP (mmHg)	119.27±16.68	113.66±11.79	143.49±13.77	-526.86	<0.001
DBP (mmHg)	77.41±9.96	74.40±7.45	90.39±8.96	-443.70	<0.001
TP (g/L)	76.22±4.58	76.10±4.53	76.74±4.73	-30.04	<0.001
ALB (g/L)	47.80±3.30	47.75±3.28	47.93±3.32	-18.10	<0.001
TG (mmol/L)	1.24 (0.87-1.86)	1.18 (0.83-1.74)	1.59 (1.11-2.33)	109.43	<0.001
TC (mmol/L)	4.63±0.90	4.56±0.88	4.89±0.94	-79.00	<0.001
AST (U/L)	21.00 (17.00-26.00)	20.00 (17.00-26.00)	23.00 (19.00-29.00)	74.56	<0.001
ALT (U/L)	21.00 (14.00-32.00)	20.00 (14.00-31.00)	25.00 (17.00-38.00)	78.84	<0.001
GGT (U/L)	25.08 (15.00-36.00)	23.15 (14.00-34.98)	37.00 (21.00-51.00)	134.85	<0.001
Elevated GGT (%)	12.51	9.59	25.12	10207.33	<0.001
Drinking (%)				4837.56	<0.001
Never	66.59	69.81	55.40		
Occasionally	9.51	8.09	15.63		
Frequently	23.90	22.73	28.78		
Smoking (%)				893.46	<0.001
Never	72.90	73.98	68.24		
Occasionally	21.57	20.51	26.15		
Frequently	5.52	5.50	5.61		

* BMI: body massive index; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglyceride; TC: total cholesterol; HDL-C: high density liptein cholesterol; AST: aspartate aminotransferase; ALT: glutamic-oxaloacetic aminotransferase; GGT: gamma-glutamyl transferase; TP: total protein; ALB: albumin.

taken at 1-minute intervals, and the average of the last two readings was used for analysis. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or current use of antihypertensive medication. Height was measured with the subjects in an upright position, permitting their upper limbs to hang down naturally at their sides with their heels united together on the stadiometer. Each subject's height was measured twice consecutively with half-minute intervals between measurements. In terms of weight measurement, the subject stood centrally on the scale, and readings were taken once the scale numbers had stabilized. The Body Mass Index (BMI) was subsequently calculated as weight (in kg) divided by the square of height (in m^2). The obtained BMI data were accurate to the nearest 0.1 kg/m^2.

Biochemical assays

Fasting venous blood samples were collected in the morning for relevant marker analysis. Tests were performed to detect various indicators, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), triglycerides (TG), total cholesterol (TC), albumin (ALB), and total protein (TP). Fasting venous blood samples were analyzed for gamma-glutamyl transferase (GGT) using an enzymatic assay on a Roche Cobas c501 analyzer, with an inter-assay coefficient of variation of 3.5%. All calibration and quality control procedures were performed regularly by the hospital's professional staff to guarantee measurement reliability.

Definitions

Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg. Prehypertension was defined as systolic blood pressure (SBP) between 120 and 139 mmHg and/or diastolic blood pressure (DBP) between 80 and 89 mmHg (Yin *et al.* 2022b). Hyperglycemia was defined as a fasting blood glucose ≥ 7.0 mmol/L or current usage of glucose-lowering medication (Ceriello *et al.* 2022). Obesity was defined as a body mass index (BMI) greater than 28 (Kaplan 2003). Elevated gamma-glutamyl transferase (GGT) was defined as serum GGT > 55 U/L for men and > 38 U/L for women. Elevated alanine aminotransferase (ALT) was defined as serum ALT > 40 U/L,

Tab. 2. Pearson's correlation coefficients between GGT and the baseline variables

	Overall		Normotensive		Hypertensive	
	r	*p*	*r*	*p*	*r*	*p*
Age	0.075	<0.001	0.079	<0.001	0.058	<0.001
BMI	0.222	<0.001	0.224	<0.001	0.110	<0.001
SBP	0.178	<0.001	0.143	<0.001	0.275	<0.001
DBP	0.244	<0.001	0.202	<0.001	0.305	<0.001
TG	0.274	<0.001	0.272	<0.001	0.226	<0.001
TC	0.168	<0.001	0.166	<0.001	0.116	<0.001
TP	0.083	<0.001	0.074	<0.001	0.084	<0.001
ALB	0.056	<0.001	0.055	<0.001	0.065	<0.001
AST	0.364	<0.001	0.338	<0.001	0.445	<0.001
ALT	0.359	<0.001	0.367	<0.001	0.343	<0.001

and elevated aspartate aminotransferase (AST) was defined as serum AST > 35 U/L (Tapper *et al.* 2017).

Statistical analysis

Data were analyzed using SPSS 22.0 and R-Project version 4.4.2. Continuous variables are presented as either mean ± standard deviation or median [interquartile range (IQR)], depending on the distribution of the data. Categorical variables are expressed as frequencies and proportions. Baseline characteristics were compared between the normotensive and hypertensive groups using the chi-square test, t-test, and Wilcoxon rank-sum test. The associations between GGT and hypertension were assessed using multinomial logistic regression models and restricted cubic spline models, adjusting for age, sex, smoking, drinking, BMI, triglycerides (TG), total cholesterol (TC), total protein (TP), and albumin (ALB). All *p*-values are two-tailed, and statistical significance was set at 0.05.

RESULTS

Baseline characteristics of participants

Table 1 shows that among 303,431 participants, 57,032 (41,379 males and 15,653 females) were diagnosed with hypertension. The mean ages of the normotensive and hypertensive groups were 45.69±13.01 and 55.78±18.87, respectively. Compared to the normotensive group, the hypertensive group had significantly higher GGT levels (23.15 (14.00–34.98) vs. 37.00 (21.00–51.00) U/L, $p < 0.001$) and a greater prevalence of elevated GGT (9.59% vs. 25.12%, $p < 0.001$). BMI, TP, ALB, TG, TC, AST, and ALT levels were also significantly higher in the hypertensive group than in the normotensive group ($p < 0.001$). Behaviorally, smoking and alcohol consumption rates were higher in the hypertensive group than in the normotensive group ($p < 0.001$).

The correlation between GGT and risk factors for hypertension

Table 2 shows the correlations between GGT and baseline clinical indicators, which are common risk factors for hypertension. GGT showed significant positive correlations with age, BMI, SBP, DBP, TG, TC, TP, ALB, AST, and ALT ($p < 0.001$), with stronger associations observed for BMI, DBP, TG, AST, and ALT. After stratifying by hypertension status, the correlations between GGT and SBP, DBP, TP, ALB, and AST became stronger in the hypertensive group.

Tab. 3. Association of hypertension with GGT quartiles

	Q1 (≤15.00 U/L) n=75,627	Q2 (15.00-25.10U/L) n=75,308	Q3 (25.11-36.00 U/L) n=76,708	Q4 (>36.00 U/L) n=75,788	*p* value for trend
Model 1	1 (Reference)	1.447 (1.403-1.492)	1.383 (1.340-1.427)	5.477 (5.329-5.629)	<0.001
Model 2	1 (Reference)	1.146 (1.108-1.084)	1.000 (0.967-1.036)	4.084 (3.959-4.213)	<0.001
Model 3	1 (Reference)	1.009 (0.976-1.044)	0.782 (0.754-0.810)	2.762 (2.673-2.854)	<0.001
Model 4	1 (Reference)	0.958 (0.926-0.991)	0.717 (0.691-0.743)	2.421 (2.340-2.504)	<0.001

Model 1: Unadjusted
Model 2: Adjusted for age and sex
Model 3: Adjusted for age, sex, smoking, drinking and BMI
Model 4: Adjusted for age, sex, smoking, drinking, BMI, TG, TC, TP, and ALB

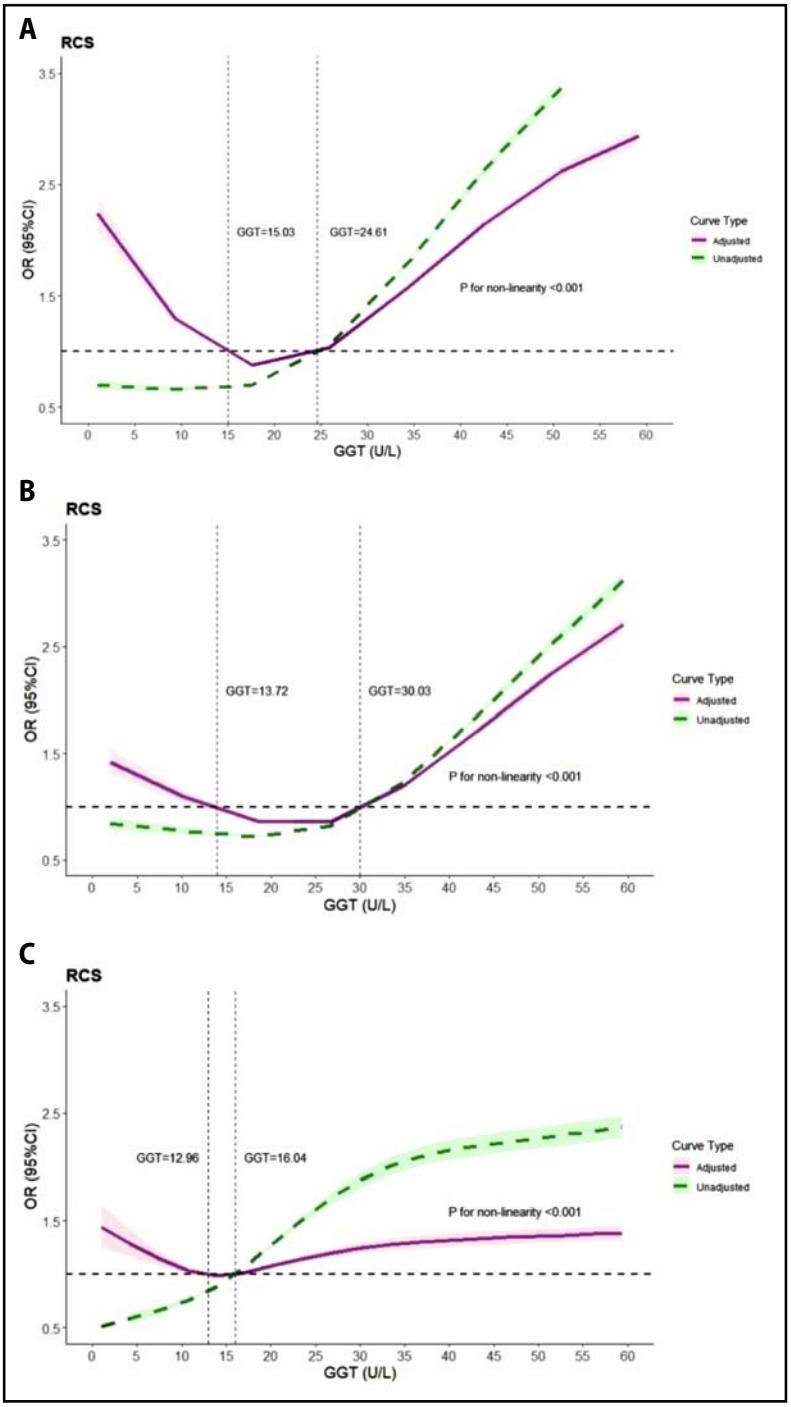

Fig. 1. Associations of GGT with hypertension (The horizontal axis represents various levels of GGT and the vertical axis is the odds ratio risk of hypertension). Green line: without adjustment; purple line: adjustment for age, sex, smoking, drinking, BMI, TG, TC, TP, and ALB. The shaded area shows the 95% confidence interval. **A** in all populations. **B** in males. **C** in females.

Association between GGT and hypertension

Table 3 presents the findings of the multivariable logistic regression analysis. In Model 1, compared with Q1, the odds ratios (ORs) for hypertension were 1.447 (95% CI: 1.403–1.492), 1.383 (95% CI: 1.340–1.427), and 5.477 (95% CI: 5.329–5.629) ($p < 0.001$). In Model 2, after adjustment for age and sex, the ORs were 1.146 (95% CI: 1.108–1.084), 1.000 (95% CI: 0.967–1.036), and 4.084 (95% CI: 3.959–4.213) ($p < 0.001$). In Model 3, with further adjustments for smoking, drinking, and BMI, the ORs were 1.009 (95% CI: 0.976–1.044), 0.782 (95% CI: 0.754–0.810), and 2.762 (95% CI: 2.673–2.854) ($p < 0.001$). In Model 4, after additional adjustments for triglycerides (TG), total cholesterol (TC), total protein (TP), and albumin (ALB), the ORs were 0.958 (95% CI: 0.926–0.991), 0.717 (95% CI: 0.691–0.743), and 2.421 (95% CI: 2.340–2.504) ($p < 0.001$). These results suggest that as GGT levels increased, the ORs for hypertension initially decreased and subsequently increased.

After adjusting for potential confounders, the relationship between GGT levels and hypertension was further examined using a restricted cubic spline model. The results revealed a U-shaped association in the overall population. The odds ratio (OR) for

Tab. 4. Comparison of hypertension prevalence based on critical threshold grouping and recognized GGT reference range in male and female populations

Group	Critical threshold grouping	Prehypertension	Hypertension	Recognized reference range	Prehypertension	Hypertension
Male	GGT≤13.72	51.13%	13.07%	GGT≤55	54.78%	20.58%
	GGT>13.72 and ≤30.02	49.94%	15.35%	GGT>55	61.18%	38.56%
	GGT>30.03	69.04%	31.06%			
Female	GGT≤12.96	36.29%	7.83%	GGT≤38	40.04%	10.19%
	GGT>12.96 and ≤16.04	36.22%	10.37%	GGT>38	58.34%	35.32%
	GGT>16.04	47.65%	16.37%			

hypertension initially decreased and subsequently increased with rising GGT levels. Specifically, when GGT levels ranged between 15.03 U/L and 24.61 U/L, the OR for hypertension was significantly below 1.0 (Figure 1A). Similar U-shaped trends were observed when stratified by sex. In males, the OR for hypertension was less than 1.0 when GGT levels ranged from 13.72 U/L to 30.03 U/L, while in females, this range was between 12.96 U/L and 16.04 U/L (Figure 1B and 1C).

Comparison of hypertension prevalence based on critical threshold grouping and recognized GGT reference range

Table 4 showed that in the male group, when GGT exceeded 30.03 U/L, the prevalence of prehypertension and hypertension was 69.04% and 31.06%, respectively. In comparison, using the conventional reference range with GGT >55 U/L, the prevalence of prehypertension and hypertension was 61.18% and 38.56%, respectively. In the female group, when GGT exceeded 16.04 U/L, the prevalence of prehypertension and hypertension was 47.65% and 16.37%, respectively. At the conventional cutoff of GGT >38 U/L, the prevalence of prehypertension and hypertension was 58.34% and 35.32%, respectively. These findings indicate that in the male group, the derived cutoff value exhibits greater sensitivity for identifying prehypertension.

Subgroup analysis of the association between GGT and hypertension

Table 5 shows the findings of the subgroup analysis. The association was stronger among females, non-obese individuals, participants younger than 65 years, non-drinkers, and frequent smokers ($p < 0.001$). However, the association did not reach statistical significance between the diabetic and non-diabetic groups ($p = 0.057$).

DISCUSSION

This large-scale cross-sectional analysis investigated the association between serum GGT levels and hypertension. The findings demonstrated that serum GGT levels were significantly higher in the hypertensive group compared with the normotensive group. The prevalence of elevated GGT in the hypertensive group was approximately 2.5 times that of the normotensive group. Furthermore, significant associations were observed between systolic blood pressure (SBP), diastolic blood pressure (DBP), and GGT levels, with these associations being stronger in the hypertensive group. These results are consistent with previous studies, further supporting the role of GGT in the development and progression of hypertension (Rahman *et al.* 2020; Liu *et al.* 2023).

To further investigate the association between GGT levels and hypertension, we performed regression analysis. Interestingly, the results revealed a U-shaped relationship: as GGT levels increased, the odds ratios (ORs) for hypertension initially decreased and subsequently increased. Specifically, GGT was positively associated with hypertension at both low and high levels, whereas a negative association was observed at moderate levels. This finding contrasts with previous studies, such as that by Liu *et al.* which reported exclusively a positive association between GGT and hypertension (Liu *et al.* 2023). The observed discrepancy may be attributed to our treatment of GGT as a continuous variable, allowing us to explore the dynamic changes in ORs with increasing GGT levels. Furthermore, prior studies predominantly focused on smaller sample sizes in European and North American populations (Kunutsor *et al.* 2015). But our study analyzed the association between GGT and hypertension in a large-scale population, providing more robust and generalizable evidence.

Moderate GGT levels are negatively correlated with hypertension, potentially because they reflect a balanced or compensatory oxidative stress state (Lee *et al.* 2004; Ndrepepa *et al.* 2018). This compensatory mechanism is associated with less vascular damage and a lower likelihood of hypertension. In contrast, low GGT levels may indicate inadequate glutathione levels. GGT plays a crucial role in the glutathione cycle, and a deficiency in GGT may point to impaired glutathione cycling (Kunutsor 2016; Mitrić & Castellano 2023). As a major antioxidant, insufficient glutathione levels are

Tab. 5. Subgroup analysis of the association between GGT and hypertension

Subgroup	Hypertension prevalence rate	OR (95%CI)	*p* for interaction
Total	16.15%	1.012 (1.011-10.14)	
Sex			<0.001
Male	23.45%	1.009 (1.009-1.010)	
Female	12.38%	1.015 (1.015-1.016)	
Age			<0.001
<65	16.16%	1.014 (1.014-1.014)	
≥65	39.62%	1.004 (1.003-1.004)	
Obesity			<0.001
No	16.82%	1.011(1.011-1.012)	
Yes	39.33%	1.007 (1.006-1.007)	
Diabetes			0.057
No	16.46%	1.007 (1.006–1.009)	
Yes	17.61%	1.009 (1.006–1.012)	
Elevated ALT			<0.001
No	17.37%	1.020 (1.020-1.021)	
Yes	26.28%	1.004 (1.003-1.004)	
Elevated AST			<0.001
No	17.78%	1.017 (1.017-1.017)	
Yes	29.73%	1.003 (1.002-1.003)	
Drinking			0.009
Never	14.47%	1.017 (1.016-1.017)	
Occasionally	20.04%	1.006 (1.006-1.007)	
Frequently	20.68%	1.010 (1.010-1.011)	
Smoking			<0.001
Never	16.27%	1.010 (1.009-1.011)	
Occasionally	21.17%	1.009 (1.008-1.009)	
Frequently	16.71%	1.013 (1.012-1.014)	

Adjustments were made for age, sex, smoking, drinking, BMI, TG, TC, TP, ALB, except when used as a stratification variable.

associated with the accumulation of oxidative stress, which is linked to endothelial dysfunction and hypertension (Diaz-Vivancos *et al.* 2015; Averill-Bates 2023; Mitrić & Castellano 2023). Conversely, elevated GGT levels are associated with higher levels of inflammatory mediators, such as C-reactive protein and IL-6, which in turn are linked to higher blood pressure through pathways potentially involving vasoconstriction (Mikolajczyk *et al.* 2021; Kuppa *et al.* 2023; Guzik *et al.* 2024).

To explore the differences in hypertension detection between this study's derived GGT cutoff and conventional reference ranges, we compared the prevalence rates of hypertension and prehypertension across groups. The results revealed that in the male group, the cutoff value identified in this study demonstrated statistically significant higher sensitivity for detecting prehypertension. This finding underscores the potential utility of GGT monitoring in the early detection and prevention of hypertension. However, to determine a more precise cutoff value, large-scale prospective cohort studies are still required.

The primary novelty of this study lies in our approach to analyzing GGT as a continuous variable. While previous studies were direct estimates of the linear relationship between GGT and hypertension, which may have led to some details being overlooked. However, several limitations should be noted. First, this is a cross-sectional study, and the analysis was based on data from a single time point, limiting the ability to establish causal relationships. Second, the sample data were obtained exclusively from a single hospital, potentially introducing selection bias. In the future, we aim to broaden the scope of our research by incorporating multicenter data and longitudinal analyses, which will allow for more comprehensive and robust results.

CONCLUSION

This cross-sectional analysis identified a U-shaped association between serum GGT levels and hypertension prevalence in a health checkup population from Wuhu, China, with lower hypertension prevalence observed at moderate GGT levels (15.03-24.61 U/L) compared to both lower and higher levels. This pattern persists after adjustment for age, sex, lifestyle factors, and metabolic markers. The mechanisms underlying this association and its clinical significance require investigation in prospective cohort studies and mechanistic research.

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ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted in compliance with the Helsinki guidelines of the Hel-sinki Declaration of the World Medical Association and approved by the Ethics Committee of Wannan Medical College (Approval No. (2024) 7), with a formal waiver of informed consent granted for the use of pre-existing anonymized health records. All personally identifiable information (including names, ID numbers, and contact details) was permanently removed by the Medical Examination Center prior to data analysis, ensuring complete anonymization in compliance. Strict data protec-tion protocols were maintained throughout the research.

AUTHORS' CONTRIBUTIONS

Xinyu Ma and Wang Tong wrote the main text of the manuscript; Yue Wu and Yicheng Fang prepared figures; Chengxu Wang and Wendan Mei conducted the experiments; Huan Wu analyzed the data; Fan Su provided additional input and support; W.Y. supervised the entire project. All authors reviewed the manuscript.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AVAILABILITY OF DATA AND MATERIALS

The authors collected participant data and uploaded it to a database. This system conveniently shields irrelevant data and effectively protects participant privacy. The data supporting this study's findings are available from the Health Management Center at the First Affiliated Hospital of Wannan Medical College, Wuhu, China. However, access to these data is restricted as they were used under license for this study and are not publicly available. Data can be provided upon reasonable request and with the Health Management Center's permission. For data requests, please contact Yufeng Wen, the corresponding author.

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