

Association Between Triglyceride-Glucose Index and Prognosis of Patients with Hypertrophic Cardiomyopathy and Heart Failure with Preserved Ejection Fraction

ABSTRACT

Background: The value of the triglyceride-glucose (TyG) index for predicting the prognosis in patients with hypertrophic cardiomyopathy (HCM) and heart failure with preserved ejection fraction (HFpEF) remains unexplored.

Methods: Patients from 15 centers were included. The primary outcome was all-cause mortality. The secondary outcomes were cardiovascular mortality and sudden cardiac death (SCD). Restricted cubic spline analyses, multivariate Cox regression analyses, competing risk models, subgroup and mediation analyses were used to assess the relationship between the TyG index and outcomes.

Results: A total of 1095 patients with HCM and HFpEF were included. During a median follow-up period of 69 months, 224 all-cause deaths, 142 cardiovascular deaths, and 56 SCDs occurred. Multivariable Cox regression showed that the highest TyG index quartile was associated with a lower incidence of all-cause (hazard ratio (HR) 0.74, 95% CI 0.56-0.99, $P = .046$) and cardiovascular mortality (HR 0.65, 95% CI 0.44-0.94, $P = .024$) compared to the lowest quartile. However, no significant association was found between the TyG index and SCD (HR 0.74, 95% CI 0.41-1.31, $P = .300$). The competing risk model confirmed a significant association between the TyG index and reduced cardiovascular mortality (HR, 0.56; 95%CI, 0.40-0.78, $P = .001$) but no significant association with SCD (HR, 0.69; 95% CI, 0.37-1.27, $P = .230$). Mediation analyses indicated N-terminal pro-B-type natriuretic peptide mediated the association between TyG index and cardiovascular survival, while serum creatinine had a suppression effect.

Conclusion: A higher TyG index was associated with lower risks of all-cause and cardiovascular mortality but with no significant influence on SCD risk in patients with HCM and HFpEF.












Keywords: All-cause mortality, cardiovascular mortality, heart failure with preserved ejection fraction, hypertrophic cardiomyopathy, sudden cardiac death, triglyceride-glucose index

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a common genetic cardiac disorder characterized by left ventricular hypertrophy, with its estimated prevalence being 1/500-1/200 in the general population.¹ The HCM is a cause of heart failure (HF).² Conversely, around 50% of HCM patients with mid-adulthood develop HF.³ The HF typically presents as a heart failure with preserved ejection fraction (HFpEF) phenotype, exhibiting specific characteristics in patients with left ventricular obstruction.^{4,5}

Metabolic disturbances have been shown to be associated with the pathogenesis and progression of HFpEF.⁶ The triglyceride-glucose (TyG) index, calculated as the product of triglyceride (TG) and glucose levels, has gained attention as a surrogate marker for metabolic syndrome and cardiovascular risk.^{7,8} An elevated TyG index has been demonstrated to be associated with increased risks of cardiovascular diseases, adverse cardiometabolic outcomes, and mortality.^{9,10} Despite

ORIGINAL INVESTIGATION

Lei Liu^{1,*} 
Yi Zheng^{2,*} 
Huihui Ma³ 
Qian Liao³ 
Ming Jiang Liu³ 
Hongqiang Ren¹ 
Gary Tse^{2,4} 
Ligang Ding⁵ 
Wei Hua⁵ 
Tong Liu^{2,*} 
Xiaoping Li^{3,5,*} 

¹Department of Cardiology, Suining Central Hospital, Suining, China

²Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin, China

³Institute of Cardiovascular Diseases & Department of Cardiology, Ultrasound in Cardiac Electrophysiology and Biomechanics Key Laboratory of Sichuan Province, Sichuan Provincial People's Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China

⁴School of Nursing and Health Sciences, Hong Kong Metropolitan University, Hong Kong, China

⁵Cardiac Arrhythmia Center, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Corresponding author:

Tong Liu
✉ liutongdoc@126.com

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*These authors contributed equally.

* Joint senior authors.

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limited data, recent studies have shown that a high TyG index is associated with a higher risk of mortality and rehospitalization in HFpEF patients.^{11,12}

However, in patients with HCM, large changes in myocardial metabolism may occur in the presence of elevated left ventricular pressure load. The ATP produced through fatty acid oxidation is insufficient to meet the high energy demands of the heart. Thus, glucose oxidation, which provides higher productivity, will dominate. This transformation of energy substrates represents an adaptive metabolic remodeling that facilitates the protection of damaged myocardium, mitigates further injury, and provides energy with enhanced efficiency.¹³ Evidence from a 2-center study found that the TyG index might function as a potential protective factor for patients with hypertrophic obstructive cardiomyopathy without diabetes.¹⁴

To the best of knowledge, to date, no studies have explored the role of the TyG index in patients with HCM and HFpEF. This study aimed to explore the association between the TyG index and the risk of all-cause mortality, cardiovascular mortality, and sudden cardiac death (SCD) in patients with HCM and HFpEF.

METHODS

Study Design and Participants

The study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all participants. The participants in this study were from 15 medical institutions. The inclusion criteria were patients with both HCM and HFpEF. The exclusion criteria were N-terminal pro-B-type natriuretic peptide (NT-proBNP) < 300 pg/mL, left ventricular ejection fraction (LVEF) < 50% and New York Heart Association (NYHA) < II, or missing TG or fasting plasma glucose (FPG) data.

Echocardiographic Parameters for Diagnosis

The HCM was confirmed by demonstrating unexplained left ventricular hypertrophy, characterized by a maximum ventricular wall thickness of ≥ 15 mm in the general population, or ≥ 13 mm in patients with a family history of HCM in the absence of any other causes of hypertrophy. Left ventricular maximal wall thickness was measured by transthoracic echocardiography in the long and short-axis view at end

diastole. Echocardiographic parameters for the diagnosis of HFpEF include septal early diastolic mitral annular velocity (e') < 7 cm/s, lateral e' < 10 cm/s, tricuspid regurgitation velocity > 2.8 m/s, left atrial volume index > 34 ml/m², LVEF $\geq 50\%$, $E/e' > 8$, and $E/A \leq 0.8$, or defined according to reported diastolic dysfunction.

Data Collection and Outcomes

Baseline demographic data and clinical data were retrieved from the electronic medical recording system, including age, sex, NYHA class, smoking and drinking history, vital signs, laboratory tests, comorbidities, medication history, and electrocardiogram and echocardiographic data. Laboratory tests included measurements of TyG index, free triiodothyronine (FT3), free thyroxine (FT4), thyroid stimulating hormone, aspartate aminotransferase, alanine aminotransferase, total bilirubin, total protein, albumin, TG, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, FPG, NT-proBNP, cardiac troponin I, creatine kinase-MB, lactate dehydrogenase, uric acid, serum creatinine (SCR), blood urea nitrogen (BUN), and C-reactive protein (CRP). The TyG index was calculated using the following formula: $\text{TyG index} = \ln(\text{fasting TG [mg/dL]} \times \text{FPG [mg/dL]}/2)$.

Medication use included diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, cordarone, digoxin, aspirin, and anticoagulants. Comorbidities were also recorded, including diabetes mellitus (DM), hypertension, stroke, thromboembolism, ventricular arrhythmias (VA), atrial fibrillation (AF), atrioventricular block, syncope, familial HCM, SCD family history, coronary artery disease (CAD), pulmonary hypertension (PH) and apical HCM. The primary endpoint of the present study was all-cause mortality, and the secondary outcomes were cardiovascular mortality and SCD, which were further analyzed separately.

Statistical Analysis

Participants were stratified into 4 groups according to the quartiles of their TyG index. To evaluate the robustness of the findings to alternative classification methods, supplementary analyses were performed that treated the TyG index as a continuous variable. The Kolmogorov–Smirnov test was employed to assess whether the quantitative data followed a normal distribution. Quantitative data exhibiting non-normal distributions were presented as median and interquartile range, and the Kruskal–Wallis test was utilized to evaluate differences among the 4 groups. Quantitative data conforming to a normal distribution were described using mean \pm standard deviation, and 1-way analyses of variance were employed to compare differences among the 4 groups. Qualitative data were expressed as numbers and percentages (%) and compared via the chi-square test or Fisher's exact test.

Kaplan–Meier survival analyses were conducted to investigate differences in event-free survival across the 4 TyG index groups. Restricted cubic splines (RCS) were employed to explore the relationship between the TyG index and endpoints. Hazard ratios (HRs) and 95% CIs for outcomes across TyG index quartiles were calculated using Cox proportional

HIGHLIGHTS

- To the best of knowledge, this is the first study to suggest a potential protective role of the triglyceride-glucose (TyG) index in patients with hypertrophic cardiomyopathy (HCM) and heart failure with preserved ejection fraction (HFpEF).
- A higher TyG index was associated with a lower risk of all-cause and cardiovascular mortality, but no significant association was observed with the risk of sudden cardiac death in patients with HCM and HFpEF.
- These findings may inform risk assessment in this population.

hazards regression models. Multivariable-adjusted models were shown as follows: model 1 adjusted for sex, age, smoking, and drinking; model 2 adjusted for sex, age, smoking, drinking, NYHA, DM, hypertension, VA, AF, systolic blood pressure, CAD, PH, FT3, FT4, SCR, BUN, CRP; model 3 adjusted for sex, age, smoking, drinking, NYHA, DM, hypertension, VA, AF, systolic blood pressure, CAD, PH, FT3, FT4, SCR, BUN, CRP, syncope, SCD family history, left ventricular diameter (LVD), left atrial diameter (LAD), right atrial diameter, LVEF, maximum wall thickness, apical HCM, left ventricular outflow tract gradient (LVOTG), logNT-proBNP.

Subgroup analyses were conducted for age (<60 vs. ≥60), sex (male vs. female), smoking (yes vs. no), drinking (yes vs. no), hypertension (yes vs. no), DM (yes vs. no), VA (yes vs. no), AF (yes vs. no), PH (yes vs. no), LVOTG ≥ 30 mm Hg (yes vs. no), LAD (<45 vs. ≥45), and LVD (<55 vs. ≥55). Competing risk analyses for cardiovascular mortality and SCD were conducted, with all-cause death considered as the competing event. A mediation analysis was conducted to figure out the mediating role of mediators between the TyG index and cardiovascular survival. The proportion of the effect was calculated using the formula (mediated effect/total effect) × 100%. R software (version 4.3.0) was used for statistical analyses. No artificial intelligence tools or technologies were used in the preparation of this article. A 2-tailed *P*-value of <.05 indicated statistical significance.

RESULTS

Baseline Characteristics

Initially, 2738 patients with HCM were identified. After excluding 494 patients missing TyG index data, 464 patients lacking N-terminal pro-B-type natriuretic peptide (NT-proBNP) measurements and NYHA class assessments, and 230 patients with unavailable LVEF values, a total of 1550 HCM patients were identified. Subsequently, after excluding 126 patients with reduced LVEF (LVEF < 50%) and 329 patients who had preserved LVEF (LVEF ≥ 50%) and no clinical symptoms of HF, a total of 1095 patients diagnosed with HCM and HFpEF were included in the study, among whom 71 patients were restrictive pattern with biatrial dilatation. The mean age of these participants was 55.9 ± 14.4 years, comprising 643 (58.7%) male patients.

The patients were subsequently categorized into quartiles according to their admission TyG index levels: the first quartile consisted of 274 patients with a TyG index between 7.03 and 8.34, the second quartile included 274 patients with a TyG index ranging 8.34-8.71, the third quartile comprised 274 individuals with a TyG index ranging 8.71-9.08, and the fourth quartile contained 273 patients with a TyG index of 9.08-11.23. The baseline characteristics of the included patients stratified by TyG index quartiles are presented in Table 1. Participants in the higher TyG index quartiles had higher levels of FT3, total protein, albumin, TG, low-density lipoprotein cholesterol, fasting blood glucose, uric acid, and SCR, and were more likely to be smokers. A higher TyG index was associated with a higher prevalence of DM, and hypertension. In addition, patients with higher TyG index had lower levels

of total bilirubin, high-density lipoprotein cholesterol, and NT-proBNP.

Triglyceride-Glucose Index and All-Cause Mortality

During a median follow-up of 69 months, a total of 224 patients died (20.5%). The Kaplan–Meier curve demonstrated that patients in the fourth quartile had the highest survival rate (*P* = .023; Figure 1A). The RCS curve initially almost remained constant, and then rapidly decreased (Figure 2A). In all 3 models, the highest TyG index quartile was associated with a lower incidence of all-cause death compared with those in the lowest TyG index quartile (model 1: HR 0.70, 95% CI 0.55-0.91, *P* = .007; model 2: HR 0.66, 95% CI 0.50-0.87, *P* = .003; model 3: HR 0.74, 95% CI 0.56-0.99, *P* = .046) (Figure 3). When analyzed the TyG index as a continuous variable, consistent relationships were observed (model 1: HR 0.72, 95% CI 0.57-0.92, *P* = .007; model 2: HR 0.66, 95% CI 0.51-0.84, *P* = .001; model 3: HR 0.76, 95% CI 0.59-0.98, *P* = .037; Figure 3). In the subgroup analyses, an interaction between sex and the TyG index was observed (*P* for interaction = .041). The TyG index was shown to decrease all-cause mortality in males (HR 0.57, 95% CI 0.42-0.79, *P* = .001) but not in females (HR 0.95, 95% CI 0.65-1.37, *P* = .764). No significant differences were observed in other subgroups (Figure 4A).

Triglyceride-Glucose Index and Cardiovascular Mortality

A total of 142 (13.0%) patients suffered from cardiovascular death during the follow-up duration. The Kaplan–Meier curve showed that compared to the first quartile TyG index, the fourth quartile TyG index had a significantly higher event-free survival rate (*P* = .006; Figure 1B). The RCS curve showed a decreasing trend in the risk of cardiovascular mortality as the TyG index increased (Figure 2B). In all 3 models, the highest TyG index quartile was associated with lower cardiovascular mortality compared with those in the lowest TyG index quartile (model 1: HR 0.59, 95% CI 0.42-0.82, *P* = .002; model 2: HR 0.57, 95% CI 0.39-0.83, *P* = .003; model 3: HR 0.65, 95% CI 0.44-0.94, *P* = .024) (Figure 3). When analyzed the TyG index as a continuous variable, the TyG index was also associated with lower cardiovascular mortality (model 1: HR 0.59, 95% CI 0.43-0.80, *P* = .001; model 2: HR 0.51, 95% CI 0.37-0.72, *P* < .001; model 3: HR 0.61, 95% CI 0.44-0.85, *P* = .003; Figure 3). In the subgroup analyses, an interaction between sex and the TyG index was observed (*P* for interaction = .020). Additionally, smoking (*P* for interaction = .024), and LAD (*P* for interaction = .043) also showed significant interactions with the TyG index. The association between the TyG index and cardiovascular mortality was more prominent in males, smokers, and patients with LAD <45 mm (Figure 4B). A multivariable competing risk model for sensitivity analysis revealed a significant association between the TyG index and a lower risk of cardiovascular mortality (HR, 0.56; 95% CI, 0.40-0.78, *P* = .001; Figure 5A).

Triglyceride-Glucose Index and Sudden Cardiac Death

Regarding SCD, 56 (5.1%) cases were recorded. Kaplan–Meier curve showed that no significant difference was observed for SCD between quartiles of the TyG index (Figure 1C). The RCS curve showed a decreasing trend in the risk of SCD as the TyG index increased (Figure 2C). In all 3 models, the

Table 1. Baseline Characteristics of Participants

Characteristics	Total (n=1095)	TyG Index				P
		7.03 ≤ TyG < 8.34 (n=274)	8.34 ≤ TyG < 8.71 (n=274)	8.71 ≤ TyG < 9.08 (n=274)	9.08 ≤ TyG < 11.23 (n=273)	
Age, years	55.9 ± 14.4	56.1 ± 15.7	54.9 ± 15.3	55.5 ± 13.2	57.0 ± 13.2	.365
Male, n (%)	643 (58.7)	157 (57.3)	155 (56.6)	163 (59.5)	168 (61.5)	.634
NYHA class, n (%)						.054
II	523 (47.8)	142 (51.8)	126 (46.0)	112 (40.9)	143 (52.4)	
III	415 (37.9)	99 (36.1)	112 (40.9)	111 (40.5)	93 (34.1)	
IV	157 (14.3)	33 (12.0)	36 (13.1)	51 (18.6)	37 (13.6)	
Smoking, n (%)	404 (36.9)	80 (29.2)	100 (36.5)	112 (40.9)	112 (41.0)	.013
Drinking, n (%)	242 (22.1)	57 (20.8)	57 (20.8)	64 (23.4)	64 (23.4)	.784
Vital signs						
Heart rate, beats/min	73.6 ± 16.6	74.0 ± 18.5	73.0 ± 17.6	73.6 ± 14.5	73.8 ± 15.7	.894
SBP, mm Hg	125.1 ± 21.9	123.4 ± 22.1	124.2 ± 20.9	125.0 ± 22.0	127.6 ± 22.4	.118
DBP, mm Hg	75.9 ± 12.7	74.6 ± 12.3	76.1 ± 11.6	76.1 ± 11.9	76.6 ± 14.6	.280
Laboratory test						
TyG index	8.8 ± 0.6	8.1 ± 0.2	8.5 ± 0.1	8.9 ± 0.1	9.5 ± 0.4	<.001
FT3, pg/mL	3.2 ± 1.0	3.3 ± 1.3	3.1 ± 0.7	3.1 ± 0.9	3.4 ± 1.2	.014
FT4, pg/mL	4.6 ± 6.9	4.8 ± 6.0	4.5 ± 8.9	3.9 ± 5.8	5.2 ± 6.6	.297
TSH, mIU/L	2.9 ± 5.4	2.8 ± 3.3	2.5 ± 2.4	3.1 ± 6.2	3.1 ± 7.9	.648
AST/ALT	1.2 ± 0.8	1.3 ± 1.0	1.2 ± 0.8	1.2 ± 0.7	1.1 ± 0.7	.156
Total bilirubin, μmol/L	15.6 (11.7-20)	16.3 (12.05-20.7)	16.5 (12.4-21.1)	15.8 (11.7-19.5)	14.4 (10.9-19.0)	.001
Total protein, g/L	66.9 ± 6.6	65.4 ± 5.8	66.2 ± 6.6	67.7 ± 6.6	68.3 ± 7.0	<.001
Albumin, g/L	41.1 ± 4.7	40.0 ± 4.4	41.1 ± 5.1	41.7 ± 4.6	41.6 ± 4.5	<.001
Triglycerides, mmol/L	122.3 (91.3-173.7)	75.3 (61.1-87.7)	108.1 (95.9-122.3)	149.7 (126.0-169.0)	216.2 (181.6-295.0)	<.001
HDL-C, mmol/L	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	<.001
LDL-C, mmol/L	2.6 ± 0.9	2.3 ± 0.8	2.5 ± 0.8	2.8 ± 1.0	2.7 ± 1.0	<.001
FBG, mmol/L	5.2 (4.7-6.1)	4.7 (4.4-5.2)	5.2 (4.8-5.7)	5.3 (4.8-6.3)	6.1 (5.3-7.7)	<.001
logNT-proBNP, pg/mL	3.2 ± 0.4	3.3 ± 0.4	3.2 ± 0.4	3.2 ± 0.4	3.1 ± 0.4	<.001
cTnl, ng/mL	0.05 (0.02-0.83)	0.05 (0.02-0.73)	0.05 (0.03-0.37)	0.05 (0.03-0.44)	0.05 (0.02-3.01)	.199
CK-MB, U/L	12 (10-16)	12 (9.3-16)	13 (10-17)	12.6 (10-16)	12 (9.3-16)	.453
LDH, IU/L	199 (166-255)	195 (164-236.5)	202 (168-263.5)	202.5 (167-263)	201.5 (165.5-259.8)	.324
Uric acid, μmol/L	352.1 (290-429.7)	332.7 (275.6-395.4)	339.8 (274.8-437.7)	359.4 (298.5-424.7)	382.1 (321.0-455.0)	.009
SCR, μmol/L	78.0 (65.9-92.6)	75.2 (64.1-88.7)	78.0 (66.8-94.1)	79.6 (66.9-92.0)	79.6 (68.2-98.4)	.003
BUN, mmol/L	6.2 (5.0-7.9)	5.9 (4.9-7.5)	6.2 (5.0-7.7)	6.4 (5.1-8.1)	6.3 (4.9-8.3)	.132
CRP, mg/L	1.7 (0.7-5.0)	1.3 (0.5-3.9)	1.6 (0.6-4.4)	1.9 (1.0-5.8)	1.9 (1.0-5.7)	.501
Comorbidity						
Diabetes, n (%)	137 (12.5)	20 (7.3)	24 (8.8)	35 (12.8)	58 (21.3)	<.001
Hypertension, n (%)	463 (42.3)	104 (38.0)	94 (34.3)	133 (48.5)	132 (48.4)	<.001
Stroke, n (%)	98 (9.0)	29 (10.6)	19 (6.9)	26 (9.5)	24 (8.8)	.499
Thromboembolism, n (%)	18 (1.6)	7 (2.6)	7 (2.6)	2 (0.7)	2 (0.7)	.131
VA, n (%)	187 (17.1)	40 (14.6)	59 (21.5)	48 (17.5)	40 (14.7)	.102
Atrial fibrillation, n (%)	238 (21.7)	71 (25.9)	65 (23.7)	50 (18.3)	52 (19.1)	.087
AVB, n (%)	46 (4.2)	16 (5.8)	12 (4.4)	9 (3.3)	9 (3.3)	.395
Syncope, n (%)	151 (13.8)	38 (13.9)	34 (12.4)	43 (15.7)	36 (13.2)	.715
FHCM, n (%)	93 (8.5)	32 (11.7)	23 (8.4)	23 (8.4)	15 (5.5)	.081
SCD family history, n (%)	16 (1.5)	8 (2.9)	1 (0.4)	4 (1.5)	3 (1.1)	.086
CAD, n (%)	270 (24.7)	67 (24.5)	63 (23.0)	60 (21.9)	80 (29.3)	.194
PH, n (%)	101 (9.8)	30 (11.7)	28 (10.7)	20 (7.8)	23 (9.0)	.459
AHCM, n (%)	123 (11.2)	26 (9.5)	32 (11.7)	28 (10.2)	37 (13.6)	.449

(Continued)

Table 1. Baseline Characteristics of Participants (Continued)

Characteristics	Total (n = 1095)	TyG Index				P
		7.03 ≤ TyG < 8.34 (n = 274)	8.34 ≤ TyG < 8.71 (n = 274)	8.71 ≤ TyG < 9.08 (n = 274)	9.08 ≤ TyG < 11.23 (n = 273)	
Medication use						
Diuretic, n (%)	397 (36.3)	100 (36.5)	103 (37.6)	102 (37.2)	92 (33.7)	.777
AECI/ARB, n (%)	407 (37.2)	100 (36.5)	81 (29.6)	120 (43.8)	106 (38.8)	.006
Beta blocker, n (%)	928 (84.8)	233 (85.0)	240 (87.6)	230 (83.9)	225 (82.4)	.389
CCB, n (%)	289 (26.4)	62 (22.6)	78 (28.5)	79 (28.8)	70 (25.6)	.318
Cordarone, n (%)	80 (7.3)	17 (6.2)	20 (7.3)	27 (9.9)	16 (5.9)	.266
Digoxin, n (%)	52 (4.8)	18 (6.6)	13 (4.7)	16 (5.8)	5 (1.8)	.049
Aspirin, n (%)	482 (44.0)	116 (42.3)	111 (40.5)	120 (43.8)	135 (49.5)	.175
Anticoagulant, n (%)	145 (13.3)	36 (13.1)	36 (13.1)	42 (15.3)	31 (11.4)	.605
ECG						
PR, ms	173.1 ± 39.1	179.1 ± 45.8	169.7 ± 36.1	171.3 ± 35.9	172.9 ± 38.1	.062
QRS, ms	107.2 ± 26.7	105.3 ± 25.3	110.0 ± 29.4	107.8 ± 27.0	105.4 ± 24.6	.152
QT, ms	423.1 ± 50.3	421.7 ± 52.1	423.1 ± 51.1	421.1 ± 48.1	422.3 ± 50.1	.516
QTc, ms	457.9 ± 48.0	456.5 ± 44.2	462.4 ± 50.4	456.0 ± 48.2	456.6 ± 48.7	.374
Echocardiography						
IVS, mm	18.4 ± 5.3	18.6 ± 5.1	18.2 ± 5.7	18.5 ± 5.3	18.3 ± 5.0	.865
LVD, mm	44.4 ± 6.9	44.3 ± 6.9	44.3 ± 7.0	44.4 ± 7.1	44.4 ± 6.5	.996
RVD, mm	20.2 ± 3.2	20.1 ± 3.1	20.2 ± 3.2	20.3 ± 3.6	20.2 ± 3.1	.918
LAD, mm	41.2 ± 7.0	41.3 ± 7.4	41.3 ± 7.2	41.4 ± 6.7	40.9 ± 6.9	.834
LVEF (%)	66.4 ± 10.3	65.9 ± 10.7	65.7 ± 10.3	67.0 ± 9.8	67.1 ± 10.1	.232
LVPW, mm	11.9 ± 3.0	11.7 ± 3.2	11.9 ± 3.2	11.9 ± 2.9	11.9 ± 2.8	.850
LVOTG, mm Hg	52.1 ± 41.0	54.8 ± 43.8	51.2 ± 41.5	56.1 ± 40.4	45.5 ± 37.2	.125
PAP, mm Hg	35 (28-43)	36 (30-44.2)	34 (29-41.9)	36 (28-43)	34 (26-44)	.890
Maximum wall thickness, mm	20.2 ± 4.7	20.2 ± 4.6	20.2 ± 4.7	20.3 ± 5.3	20.5 ± 4.5	.354

ACEI, angiotensin-converting enzyme inhibitors; AHCM, apical hypertrophic cardiomyopathy; ALT, alanine aminotransferase; ARB, angiotensin receptor blockers; AST, aspartate aminotransferase; AVB, atrioventricular block; BUN, blood urea nitrogen; CAD, coronary artery disease; CCB, calcium channel blockers; CK-MB, creatine kinase-MB; CRP, C-reactive protein; cTnI, cardiac troponin I; DBP, diastolic blood pressure; ECG, electrocardiogram; FBG, fasting blood glucose; FHCM, familial hypertrophic cardiomyopathy; FT3, free triiodothyronine; FT4, free thyroxine; HDL-C, high-density lipoprotein cholesterol; IVS, interventricular septum; LAD, left atrial diameter; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; LVD, left ventricular diameter; LVEF, left ventricular ejection fraction; LVOTG, left ventricular outflow tract gradient; LVPW, left ventricular posterior wall; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PAP, pulmonary artery pressure; PH, pulmonary hypertension; RVD, right ventricular diameter; SBP, systolic blood pressure; SCD, sudden cardiac death; SCR, serum creatinine; TSH, thyroid stimulating hormone; TyG, triglyceride-glucose; VA, ventricular arrhythmias.

highest TyG index quartile was not associated with lower incidence of SCD compared with those in the lowest TyG index quartile (model 1: HR 0.65, 95% CI 0.38-1.10, $P = .105$; model 2: HR 0.71, 95% CI 0.40-1.23, $P = .221$; model 3: HR 0.74,

95% CI 0.41-1.31, $P = .300$) (Figure 3). When treating the TyG index as a continuous variable, there was also no significant association between the TyG index and SCD (model 1: HR 0.65, 95% CI 0.40-1.06, $P = .084$; model 2: HR 0.62, 95% CI

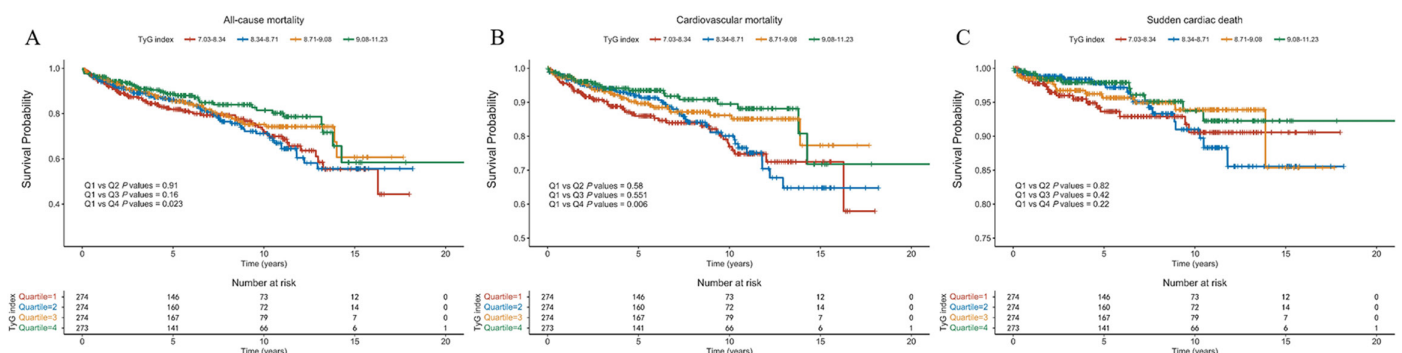


Figure 1. Kaplan–Meier analyses for different endpoints among the TyG index quartiles. TyG index quartile 1 was used as the reference group. A, all-cause mortality. B, cardiovascular mortality. C, sudden cardiac death. TyG, triglyceride-glucose.

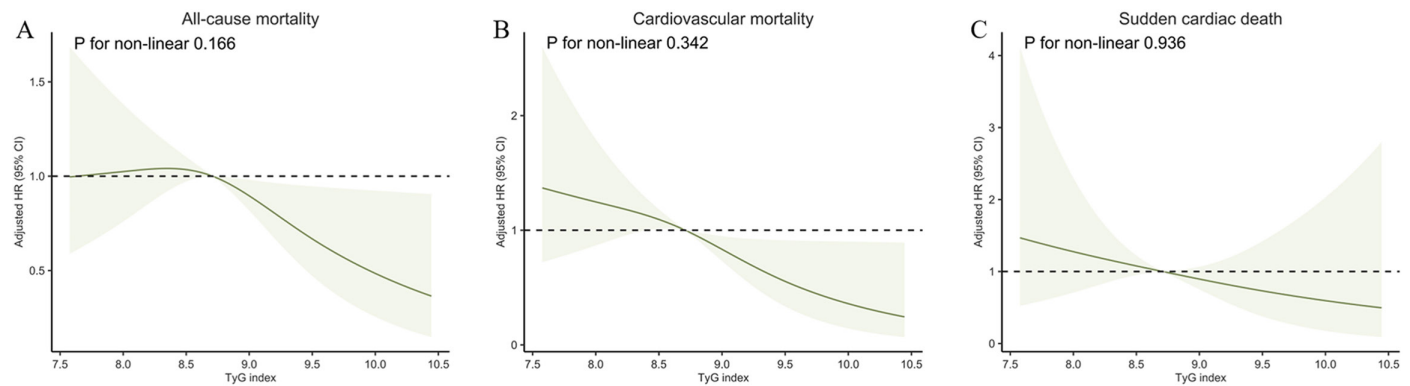


Figure 2. Restricted cubic spline curves representing the association between the TyG index and the risk of outcomes. **A**, all-cause mortality. **B**, cardiovascular mortality. **C**, sudden cardiac death. HR, hazard ratio; TyG, triglyceride-glucose.

0.37-1.06, $P = .080$; model 3: HR 0.69, 95% CI 0.41-1.17, $P = .170$; Figure 3). Subgroup analyses indicated that sex (P for interaction = .035), smoking (P for interaction = .018), and LAD (P for interaction = .005) influenced this association. The association remained significant in males, smokers, and patients with LAD < 45 mm (Figure 4C). In the multivariable competing risk model, no significant association between the TyG index and SCD was observed (HR, 0.69; 95% CI, 0.37-1.27, $P = .230$) (Figure 5B).

Mediation Analysis

Mediation analyses were conducted to explore the mediating effect of indicators. Figure 6 shows the mediating role of indicators in the relationship between the TyG index and cardiovascular survival. The NT-proBNP significantly mediated the association between TyG index and cardiovascular survival ($P < .001$), explaining 23.3% of the association (Figure 6A), while SCR had a significant suppression effect ($P < .001$, Figure 6B). For LVEF, PH, LVOTG, and LVD, although the direct effects were all significant in these 4 indicators, the mediating role tended to be non-significant (Figure 6C-F).

DISCUSSION

To the best of knowledge, this study is the first to examine the relationship between the TyG index and the prognosis in patients with HCM and HFpEF. The main findings are that the TyG index was associated with the prognosis of patients with HCM and HFpEF. The TyG index was found to be a potential protective factor for all-cause mortality and cardiovascular mortality. No significance between the TyG index and SCD was observed. Mediation analysis suggested that NT-proBNP significantly mediated the association between the TyG index and cardiovascular survival, while SCR had a significant suppression effect.

Few studies have reported the prevalence and characteristics of HFpEF in patients with HCM.^{15,16} A prospective cohort study enrolled a total of 1178 HCM patients, of whom 513 (43.5%) were diagnosed with HFpEF.¹⁵ Chen et al¹⁶ found that patients with HFpEF and HCM had a higher prevalence of AF, chronic kidney disease, and larger left atrial size compared to those HCM patients without HFpEF, and patients with HCM-HFpEF had a 2.13-fold elevated risk of major adverse

cardiovascular events compared to patients without HF. Compared with patients without HF, HFpEF patients have a higher risk of end-stage HF, which is associated with poor prognosis.^{17,18} Thus, it is important to explore the factors affecting the prognosis of patients with HCM and HFpEF.

In the past decade, the TyG index has gradually become an alternative index of insulin resistance (IR). Although the hyperinsulinemic-euglycemic clamp technique remains the most accurate method to assess insulin sensitivity, the TyG index provides a more practical, cost-effective, and reliable alternative for routine use. Previous studies have explored the potential clinical utility of the TyG index in assessing prognosis in HFpEF patients. Liao et al¹⁹ found that the TyG index was higher in patients with HFpEF compared to those without HFpEF, and was associated with cardiac diastolic dysfunction, which was significantly associated with the incidence of HFpEF in patients with hypertension. A recent cross-sectional study identified a significant positive association between the TyG index and the risk of subclinical HFpEF in individuals with type 2 DM. Specifically, patients with a TyG index ≥ 9.47 exhibited an elevated risk of developing metabolic syndrome and diastolic dysfunction.¹² Zhou et al¹¹ have shown that a higher TyG index is associated with a worse prognosis in HFpEF patients, including an increased risk of mortality and rehospitalization.

The pathophysiological mechanisms underlying the association between the TyG index and HFpEF are complex. The TyG index can impact prognosis through several mechanisms: First, a higher TyG index indicates greater IR, which is associated with metabolic syndrome. The IR can lead to increased adipose tissue, oxidative stress, and inflammation, all of which can worsen cardiac function.²⁰ Second, elevated TG levels and glucose metabolism issues can lead to endothelial dysfunction, which impairs vasodilation and increases vascular resistance, leading to further stress on the heart.^{21,22} Third, IR and metabolic dysfunction are associated with systemic inflammation, leading to the activation of inflammatory pathways and increased levels of pro-inflammatory cytokines. Chronic inflammation can aggravate HF symptoms and promote cardiac remodeling.²³ Fourth, IR can affect myocardial energy metabolism, potentially leading to a mismatch between energy supply and demand in the heart,

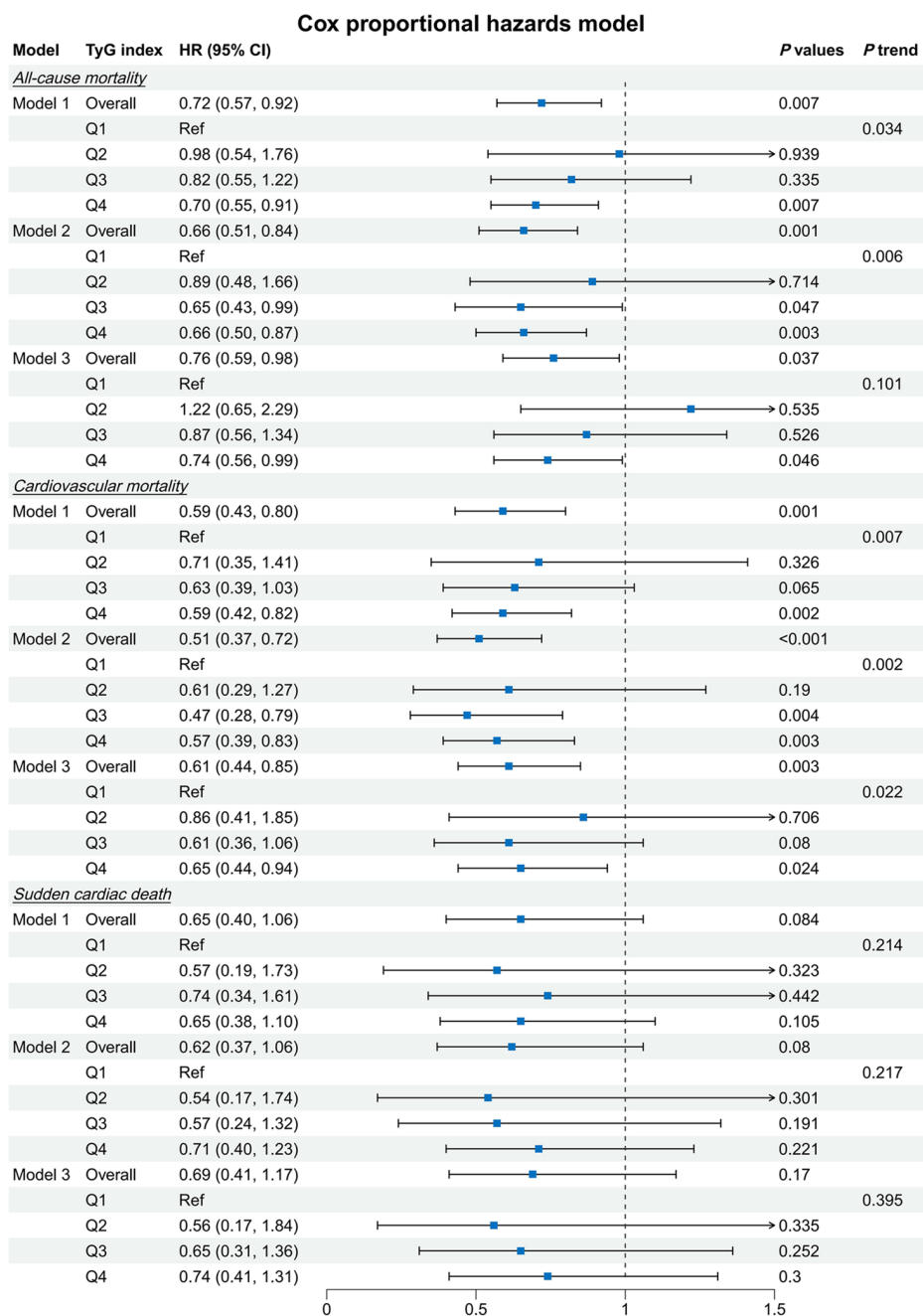


Figure 3. Multivariable Cox regression analysis for outcomes. HR, hazard ratio; TyG, triglyceride-glucose.

which is critical for maintaining function in HFpEF patients.²⁴ Last but not least, a higher TyG index is often associated with obesity, diabetes, and hypertension, which can affect the prognosis of HF patients.^{20,25}

However, the relationship between the TyG index and cardiac function in HCM patients may indicate a more complex interaction between metabolic health and cardiac outcomes. A study included 713 hypertrophic obstructive cardiomyopathy patients found that glucose metabolism in the ventricular septum of hypertrophic obstructive cardiomyopathy was enhanced, and patients who had higher TyG index levels had better outcomes.¹⁴ The findings of this study indicate that the TyG index may function as a potential

protective factor for HCM patients. The increased inter-ventricular septal glucose metabolism in HCM patients may help to clarify the relationship between the TyG index and the prognosis of HCM.

Several previous studies have shown that patients with HCM exhibit altered myocardial energy metabolism characterized by a shift toward enhanced glucose utilization.^{26,27} Myocardial perfusion and metabolism imaging studies utilizing positron emission tomography have revealed increased glucose uptake in the hypertrophied myocardium of HCM patients, further supporting the notion of a metabolic transition towards glucose metabolism.²⁸ In HCM, the elevated left ventricular pressure load can induce modifications in

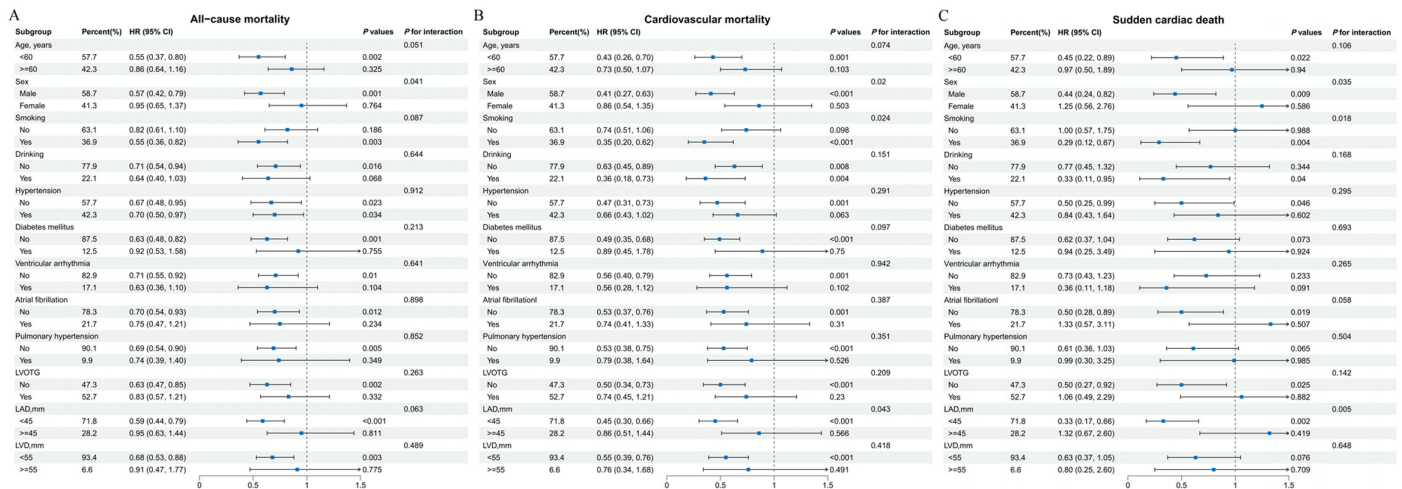


Figure 4. Subgroup analyses of the association between the TyG index and the risk of outcomes. A, all-cause mortality. B, cardiovascular mortality. C, sudden cardiac death. HR, hazard ratio; LAD, left atrial diameter; LVD, left ventricular diameter; LVOTG, left ventricular outflow tract gradient.

myocardial energy metabolism. This may result in a shift in the energy substrate preference of the myocardium from fatty acid oxidation to glucose oxidation, with such metabolic remodeling potentially exerting a protective effect on the compromised myocardial tissue.²⁹ This enhanced glucose utilization is facilitated by multiple factors, including the

upregulation of glucose transporters, the activation of the insulin signaling pathway, and the increased expression of glycolytic enzymes.³⁰

The study found that a higher TyG index was associated with a lower risk of all-cause mortality and cardiovascular

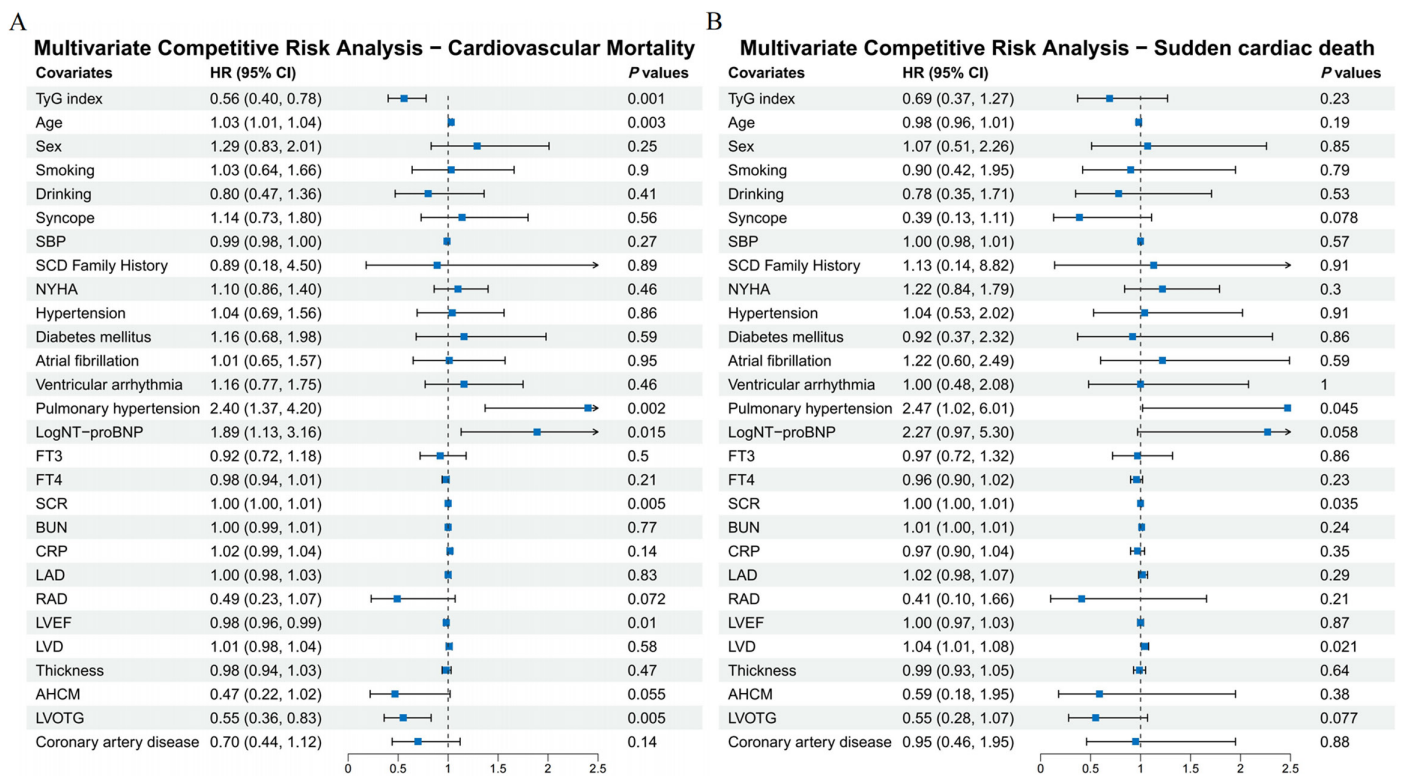


Figure 5. Competing risk models for outcomes. A, cardiovascular mortality; B, sudden cardiac death; AHCM, apical hypertrophic cardiomyopathy; BUN, blood urea nitrogen; CRP, C-reactive protein; FT3, free triiodothyronine; FT4, free thyroxine; HR, hazard ratio; LAD, left atrial diameter; LVD, left ventricular diameter; LVEF, left ventricular ejection fraction; LVOTG, left ventricular outflow tract gradient; NYHA, New York Heart Association; RAD, right atrial diameter; SBP, systolic blood pressure; SCD, sudden cardiac death; SCR, serum creatinine; TyG, triglyceride-glucose.

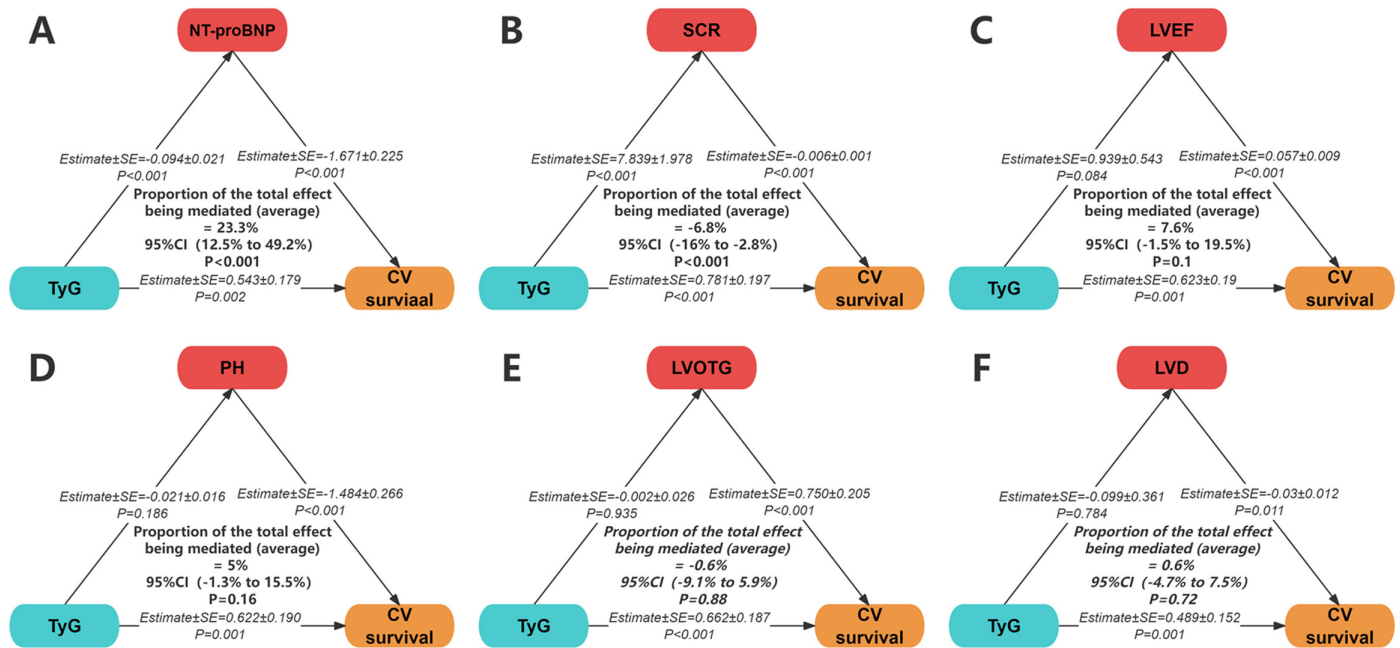


Figure 6. Path diagram of the mediation analysis of indicators on the relationship between TyG and CV survival. CV, cardiovascular; LVD, left ventricular diameter; LVEF, left ventricular ejection fraction; LVOTG, left ventricular outflow tract gradient; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PH, pulmonary hypertension; SCR, serum creatinine; TyG, triglyceride-glucose.

mortality in patients with HCM and HFpEF. A higher TyG index may serve as a protective factor in patients with HCM and HFpEF, as both HCM and HFpEF are characterized by diastolic dysfunction and metabolic disturbances. In patients with HCM who already exhibit cardiometabolic alterations, a higher TyG index may indicate a specific metabolic state that paradoxically provides some protective mechanism against HF progression.³¹ A proposed mechanism points out that IR can lead to increased fatty acid oxidation and preferential use of glucose by the myocardium.³² Such a shift in substrate utilization may improve cardiac efficiency and thereby preserve diastolic function in HCM patients with HFpEF. Adaptive changes in metabolism help the heart better cope with the increased load and pressure overload associated with HCM.³³ In addition, a higher TyG index may be associated with better overall metabolic health, which is essential for the management of HFpEF. Patients with a higher TyG index tend to have lifestyle habits that promote cardiovascular health, such as regular physical activity and healthier diet choices.^{34,35} These factors not only contribute to improved metabolic status, but may also enhance cardiac function by reducing systemic inflammation and oxidative stress, both of which are associated with worsening HF.³⁶ The combination of a higher TyG index and lower eGFR level was associated with the highest risk of cardiovascular diseases.

The mediation analysis revealed that the relationship between the TyG index and cardiovascular survival is partly mediated by NT-proBNP. This finding is consistent with previous literature. A recent study found that IR showed an inverse relationship with NT-proBNP, even after adjusting for various measures of fat mass and lean mass.³⁷ The IR can lead to hyperinsulinemia, which may improve cardiovascular outcomes by reducing NT-proBNP levels through upregulating

the expression of natriuretic peptide-clearance receptors in subcutaneous fat.³⁸ Interestingly, the mediation analysis also showed that SCR suppressed the association between the TyG index and cardiovascular survival. SCR is a recognized indicator of renal function. The TyG index has been confirmed to be significantly associated with decreased renal function.³⁹ Cui et al⁴⁰ found that renal function could mediate the association between the TyG index and cardiovascular risk. A higher TyG index combined with a lower estimated glomerular filtration rate level was associated with a higher risk of cardiovascular diseases. Considering the established role of renal function as a significant risk factor for cardiovascular events and its strong association with the TyG index, it was proposed that renal function might mediate the relationship between the TyG index and cardiovascular mortality. It was found that SCR suppressed approximately 6.8% of the relationship between the TyG index and cardiovascular survival. Further studies are needed to explore the underlying mechanisms.

The TyG index has important clinical application value. Clinicians can use the TyG index to assess metabolic health and guide lifestyle modifications to improve insulin sensitivity and cardiac function. In addition, the incorporation of the TyG index into routine clinical practice may facilitate the early detection of metabolic disorders that may exacerbate HF, and help clinicians implement preventive measures and therapeutic interventions that have the potential to improve the overall management of HCM and reduce the burden of HFpEF. With the development of research, the TyG index is expected to become a standard part of the risk assessment scheme for this population, and provide a basis for the development of more individualized and effective treatment strategies. Notably, the TyG index cut-offs between

studies may arise from variations in study populations (e.g., ethnicity, comorbidities, sample size) or methodological factors (e.g., assay techniques, timing of blood sampling). Future multicenter studies or meta-analyses are needed to establish standardized TyG index thresholds for clinical or research use.

Study Limitations

The study has some limitations. Firstly, the retrospective and observational nature of the study design limits its ability to establish a causal relationship between the TyG index and the prognosis of patients with HCM and HFpEF. Secondly, although the study adjusted for a range of covariates, unmeasured confounding factors, such as lifestyle behaviors, genetic predispositions, and the specific medical treatment regimens of the patients, may still influence the results. Thirdly, while the study did not find a significant association between the TyG index and SCD, the small number of SCD events ($n=56$) may have limited statistical power to detect meaningful associations. Further studies with more events are necessary to confirm this relationship. Fourthly, since only a minimal proportion of patients in this cohort had available genetic testing and late gadolinium enhancement data, HCM might be overlooked during the diagnostic evaluation. In addition, this limitation precludes reliable differentiation between sarcomeric gene mutation-driven subtypes and non-sarcomeric genomic variants of HCM. Last but not least, the cut-off values for elevated NT-proBNP in diagnosing HFpEF remain inconsistent between the guidelines (European Society of Cardiology vs. American Heart Association), particularly in populations with comorbid conditions such as HCM. The diagnostic criteria relied on NT-proBNP ≥ 300 pg/mL, which may not fully generalize to populations where guideline cut-offs differ. Importantly, the validity of these thresholds in HCM-related HFpEF has not been rigorously validated, potentially affecting the generalizability of the findings to this population. Future studies should investigate specific NT-proBNP thresholds in HCM populations through multicenter cohorts to clarify their diagnostic and prognostic roles. Despite inherent limitations, the primary strength of this study lies in its focus on a clinically significant yet under-researched population of patients with HCM and HFpEF. The large sample size, comprising 1095 patients with HCM and HFpEF, significantly enhances its statistical power and the reliability of its findings. Notably, this study is the first to demonstrate the protective role of the TyG index in this population.

CONCLUSION

A higher TyG index was associated with lower risks of all-cause mortality and cardiovascular mortality, but not with SCD, in patients with HCM and HFpEF. Further research is necessary to refine its application and establish standardized cut-off values specific to different populations.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Committee Approval: Ethical approvals were obtained from the Sichuan Provincial People's Hospital Research Ethics Committees (No. 2022424; Date: November 5, 2022).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Conception – L.L., Y.Z., T.L., X.P.L.; Design – L.L., Y.Z.; Supervision – T.L., X.P.L.; Resource – H.H.M., Q.L., M.J.L., H.Q.R., G.T., L.G.D., W.H., T.L., X.P.L.; Materials – H.H.M., Q.L., M.J.L., H.Q.R., G.T., L.G.D., W.H., T.L., X.P.L.; Data Collection and/or Processing – H.H.M., Q.L., M.J.L., H.Q.R., G.T., L.G.D., W.H.; Analysis and/or Interpretation – L.L., Y.Z.; Literature Search – L.L., Y.Z.; Writing – L.L., Y.Z.; Critical Reviews: H.H.M., Q.L., M.J.L., H.Q.R., G.T., L.G.D., W.H., T.L., X.P.L.

Declaration of Interests: The authors declare that there are no conflicts of interest.

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