

Association Between Low Triglyceride-Glucose Index and Mortality in Acute Decompensated Heart Failure Patients Without Diabetes

Qingqing Zhang^{1,2,*}, Yanling Xu^{3,*}, Si Sun^{1,*}, Xiangwei Ding⁴, Guoyu Wang^{1,4}, Suyun Jiang¹, Jing Zheng¹, Peng Gao¹, Jie Lin⁴, Yucheng Wu⁴

¹Department of Pan-Vascular Management Center, The Affiliated Taizhou People's Hospital of Nanjing Medical University, Taizhou School of Clinical Medicine, Nanjing Medical University, Taizhou, Jiangsu, People's Republic of China; ²Department of Endocrinology, The Affiliated Taizhou People's Hospital of Nanjing Medical University, Taizhou School of Clinical Medicine, Nanjing Medical University, Taizhou, Jiangsu, People's Republic of China; ³Department of General Practice, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, People's Republic of China; ⁴Department of Cardiology, The Affiliated Taizhou People's Hospital of Nanjing Medical University, Taizhou School of Clinical Medicine, Nanjing Medical University, Nanjing, Jiangsu, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jie Lin; Yucheng Wu, Department of Cardiology, The Affiliated Taizhou People's Hospital of Nanjing Medical University, Taizhou School of Clinical Medicine, Nanjing Medical University, 366 Taihu Road, Taizhou, Jiangsu, 225300, People's Republic of China, Email tzcg7909@163.com; 2567181759@qq.com

Background: The relationship between a low TyG index and mortality risk in Acute Decompensated Heart Failure (ADHF) also remains unclear. This study aimed to investigate the association between a low TyG index and 1-year mortality in ADHF patients without diabetes.

Methods: A total of 652 hospitalized patients with ADHF without diabetes from January, 2020 to May, 2023 were included in this retrospective study. The primary outcomes were all-cause mortality and cardiovascular mortality within one year. The association between the TyG index and both all-cause and cardiovascular mortality was investigated using restricted cubic splines and multivariate Cox proportional hazards models.

Results: The study enrolled a total of 652 patients with acute decompensated heart failure (ADHF) who were free from diabetes (70.6% male). Within one year, there were 72 deaths from all causes and 40 deaths from cardiovascular disease. In multivariate Cox proportional hazards models, a significant negative relationship was observed between the TyG index and both all-cause mortality (hazard ratio [HR] = 0.371, 95% confidence interval [CI] 0.201–0.685) and cardiovascular mortality (HR = 0.336, 95% CI 0.151–0.744). The restricted cubic spline analysis illustrated a decrease in the risk of all-cause and cardiovascular mortality as the TyG index increased. Hypertension, BMI, age, atrial fibrillation significantly interacted with the TyG index in relation to all-cause mortality, while hypertension specifically interacted with the TyG index regarding cardiovascular mortality.

Conclusion: In patients diagnosed with ADHF without diabetes, a lower TyG index is strongly related to a higher risk of 1-year all-cause and cardiovascular mortality. Therefore, it is important to pay close attention to low TyG index levels and implement appropriate measures in clinical practice.

Keywords: acute decompensated heart failure, all-cause death, cardiovascular death, retrospective study, triglyceride glucose product index

Introduction

Insulin resistance, serving as a marker of metabolic dysregulation and systemic inflammation, is an independent and significant risk factor for heart failure and cardiovascular mortality.^{1,2} Traditional methods of assessment such as the homeostasis model assessment (HOMA) have been utilized to evaluate insulin resistance, typically requiring fasting insulin and glucose levels.³ The triglyceride glucose (TyG) product index, first proposed by Unger et al in 2013, combines fasting plasma glucose (FPG) and triglyceride levels (TG), providing an alternative indicator of insulin resistance.⁴ Many studies have

demonstrated that the TyG index is superior to HOMA in assessing insulin resistance.⁵ Furthermore, there is increasing evidence supporting a positive correlation between TyG index and the incidence of carotid atherosclerosis, coronary artery disease, hypertension, myocardial infarction, and other cardiovascular diseases.^{6–8} Additionally, within specific patient cohort—such as those with chronic coronary artery syndrome, ischemic stroke, chronic heart failure, type 2 diabetes, acute myocardial infarction, coronary angiography patients, or critically ill individuals—there is evidence of a positive relationship between the TyG index and both all-cause and cardiovascular mortality.^{9–13}

While many studies have demonstrated a positive correlation between the TyG index and mortality, several studies have found a negative correlation. For example, a recent study by Dai L et al utilizing data from the MIMIC database demonstrated a negative correlation between the TyG index and mortality risk in critically ill patients.¹⁴ Similarly, data from the US National Health and Nutrition Examination Survey (2007–2018) revealed that TyG index values were negatively associated with all-cause and cardiovascular mortality risks among individuals with previous CVD.¹⁵ The underlying mechanisms for these divergent findings are not yet clear.

A recently study revealed a U-shaped association between the baseline TyG index and both all-cause and cardiovascular mortality in patients with cardiovascular disease and diabetes or pre-diabetes. Specifically, a baseline TyG index below the threshold values was negatively associated with mortality, while a TyG index above the threshold values was positively associated with mortality.¹⁶ Although extensive research has focused on the risks associated with high TyG index levels,¹⁷ comparatively less attention has been given to the potential hazards of low TyG index levels. The relationship between a low TyG index and mortality risk in acute decompensated heart failure (ADHF) also remains unclear. Therefore, we conducted a retrospective cohort study to investigate the association between a low TyG index and 1-year mortality in ADHF patients without diabetes.

Methods

Study Design and Population

This is a single-center retrospective analysis of 1274 ADHF patients admitted to our hospital from January 1st, 2020 to May 31st, 2023. ADHF was defined according to the definitions established in the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Of the 1274 patients, 622 patients were excluded due to the following exclusion criteria: (1) incomplete clinical data, (2) presence of diabetes mellitus, (3) the TyG index > 9.08 mmol/L (Rong Huang et al found that in the Chinese population, patients exhibited a rapidly increase in hazard ratios (HR) for all-cause mortality when the TyG index surpassed 9.08)¹⁸, (4) presence of malignant tumors, (5) acute coronary syndrome, (6) lost to follow up. Finally, 652 patients were included in this study (Figure 1). Diabetes was diagnosed according to the ADA criteria. The study was approved by the Ethics Research Committee of Taizhou People's Hospital.

Anthropometric and Biochemical Measurements

The data of all patients were collected through the electronic medical record system, including age, gender, weight, height, systolic blood pressure (SBP), diastolic blood pressure (DBP), medical history, laboratory test results, electrocardiogram data, and echocardiographic data at admission. Body mass index (BMI) was calculated by dividing weight (in kilograms) by the square of height (in meters). For laboratory-related examinations, all patients fasted and abstained from water for 8 to 12 hours before venous blood was drawn from the cubital vein on the next morning to determine serum levels of FPG, glycosylated hemoglobin (HbA1c), total cholesterol (TC), TG, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), sodium, creatinine, alanine aminotransferase (ALT), and aspartate aminotransferase (AST). The TyG index was calculated using the formula $\ln[\text{TG (mg/dL)} \times \text{FBG (mg/dL)} / 2]$.

Endpoints

The start date of follow-up was the date of hospital admission. The study examined two predefined primary endpoints: (1) 1-year all-cause mortality, which includes both cardiovascular and non-cardiovascular deaths; and (2) 1-year cardiovascular mortality, defined as death from fatal stroke, myocardial infarction, congestive heart failure, malignant arrhythmia, or other cardiac structural or functional issues.

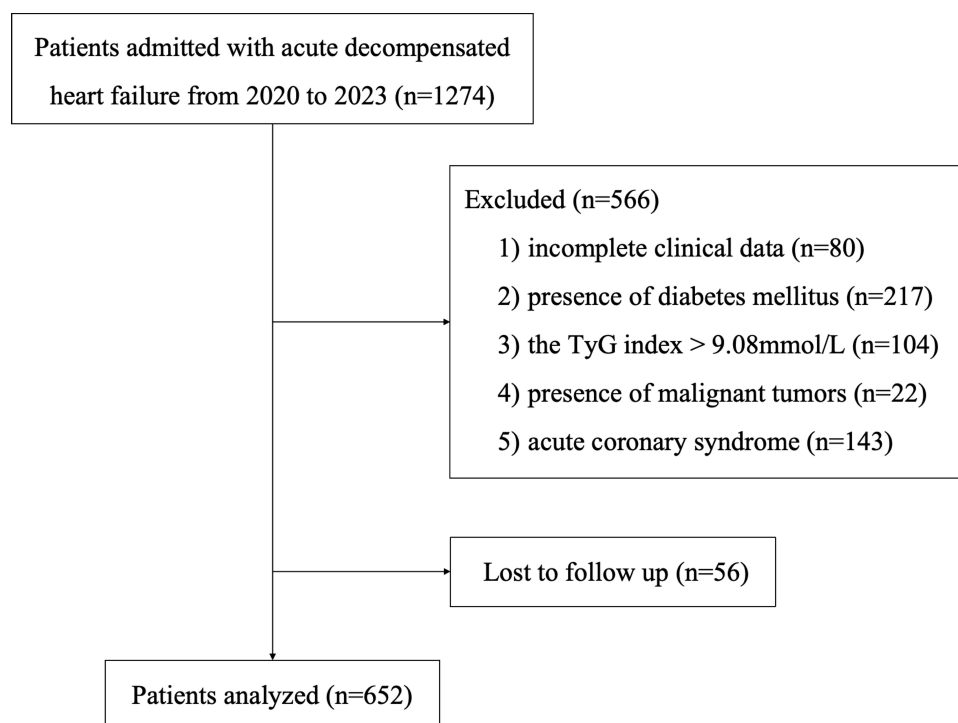


Figure 1 Flow diagram of patient selection.

Statistical Analysis

This study utilized SPSS 26.0 and R 4.1.0 statistical software for analysis. The Shapiro–Wilk test was employed to assess the normality of continuous variable distributions. Normally distributed continuous variables were expressed as mean \pm standard deviation. Non-normally distributed continuous variables were expressed as median (interquartile range). Categorical data were presented as frequency and percentage (%). Patients were stratified into three tertiles based on their TyG index levels: the lowest tertile with TyG index < 8.19; the middle tertile with TyG index between 8.19 and 8.55; and the highest tertile with TyG index \geq 8.55. Continuous variables were compared by analysis of variance (ANOVA) or the Kruskal–Wallis test among the three groups. Categorical variables were compared by the chi-square test among groups. Both all-cause and cardiovascular mortality in relation to the TyG index were evaluated using Cox proportional hazards models. Schoenfeld residuals were visualized to check the validity of the proportional hazards assumption before conducting the analyses. Variables with a *P*-value less than 0.1 or with clinically significant were selected and included in a multivariate model. There were three models to control for confounding factors. Model 1 was unadjusted, Model 2 was adjusted for age and gender, Model 3 included additional adjustments for BMI, SBP, DBP, heart rate, HbA1c, NT-proBNP, LDL-C, HDL-C, ejection fraction (EF), and history of hypertension, ischemic cardiomyopathy, and atrial fibrillation. Missing data were handled using multiple imputation. Restricted cubic splines (RCS) analysis was employed to further examine the dose–response relationship between the TyG index and both all-cause and cardiovascular mortality. For subgroup analysis of the association between the TyG index and both all-cause and cardiovascular mortality, the data were stratified by age (< 24/ \geq 24 years), gender (male/female), BMI (< 24/ \geq 24 kg/m²), hypertension (yes/no), smoking status (yes/no), atrial fibrillation (yes/no) and ischemic cardiomyopathy (yes/no). Statistical significance was defined as a *P*-value less than 0.05.

Results

Baseline Characteristics of Study Participants

Table 1 presented the baseline characteristics of the study participants, stratified by tertiles of the TyG index. Of the 652 patients, 70.6% were male, with a median age of 69 years. Statistically significant differences were in gender, BMI, heart rate, SBP, ALT, TC, TG, FPG, HDL-C, LDL-C, HbA1c, NT-proBNP, EF, left atrial diameter (LAD), left ventricular end-

Table 1 Baseline Clinical Characteristics by TyG Group

Characteristic	Total (n=652)	Tertile 1 (n = 216) TyG < 8.19	Tertile 2 (n = 219) 8.19 ≤ TyG < 8.55	Tertile 3 (n = 217) TyG ≥ 8.55	P value
Male sex, n(%)	460 (70.6)	168 (77.8)	147 (67.1)	145(66.8)	0.017
Age (years)	69 (55, 75)	67 (54, 75)	70 (52, 75)	68 (55, 76)	0.774
BMI (kg/m ²)	23.47 ± 4.69	22.63 ± 3.87	22.93 ± 4.37	24.82 ± 5.40	<0.001***&&&
Smoking, n(%)	260 (39.9)	72 (33.3)	95 (43.4)	93 (42.9)	0.056
Medical history, n (%)					
Ischemic cardiomyopathy	224 (34.3)	68 (31.5)	72 (32.9)	84(38.7)	0.243
Atrial fibrillation	176 (27.0)	72 (33.3)	59 (26.9)	45 (20.7)	0.013
Hypertension	232 (35.6)	68 (31.5)	72 (32.9)	92 (42.4)	0.035
Heart rate (bpm)	80 (72, 92)	80 (70, 92)	84 (76, 95)	78 (72, 90)	0.034 ^{&}
SBP (mmHg)	114.93 ± 19.93	112.19 ± 18.44	111.17 ± 18.50	121.45 ± 20.02	<0.001***&&&
DBP (mmHg)	70.0 (60.0, 80.0)	69.5 (59.0, 80.0)	70.0 (60.0, 80.0)	74.0 (60.0, 81.0)	0.654
ALT (mmol/L)	20.0 (14.0, 30.0)	19.5 (15.0, 29.0)	19.0 (11.0, 27.0)	24.0 (15.0, 35.0)	0.004 ^{&&}
AST (mmol/L)	25.0 (19.0, 36.0)	29.5 (21.0, 36.0)	23.0 (19.0, 33.0)	26.0 (19.0, 37.0)	0.800
TC (mmol/L)	3.66 ± 1.02	3.28 ± 0.80	3.42 ± 0.94	4.26 ± 1.02	<0.001***&&&
TG (mmol/L)	1.13 (0.88, 1.46)	0.79 (0.65, 0.92)	1.12 (1.01, 1.25)	1.77 (1.42, 2.07)	<0.001***&&&###
HDL-C (mmol/L)	0.95 (0.79, 1.13)	0.99 (0.76, 1.19)	0.97 (0.78, 1.09)	0.92 (0.81, 1.07)	0.036 [#]
LDL-C (mmol/L)	2.26 ± 0.75	1.98 ± 0.51	2.09 ± 0.71	2.71 ± 0.78	<0.001***&&&
FPG (mmol/L)	4.92 (4.35, 5.49)	4.40 (3.93, 5.06)	4.92 (4.41, 5.42)	5.39 (4.83, 6.00)	<0.001***&&&###
HbA1c (%)	5.80 (5.50, 6.10)	5.70 (5.40, 6.08)	5.80 (5.50, 6.10)	5.80 (5.50, 6.30)	0.001 [*]
NT-proBNP (pg/mL)	4587.76 (2374.80, 9111.80)	5199.00 (3009.40, 12233.25)	4006.20 (2264.63, 7593.13)	3839.70 (1897.40, 9075.30)	0.007 ^{###}
TyG	8.33 (8.06, 8.68)	7.92 (7.74, 8.06)	8.33 (8.25, 8.46)	8.83 (8.68, 9.03)	<0.001***&&&###
EF (%)	36.0 (30.0, 43.0)	34.5 (27.0, 42.0)	35.0 (31.0, 43.0)	37.0 (32.0, 43.0)	0.002 ^{**}
LAD	49.25 ± 8.88	50.61 ± 8.51	48.30 ± 8.01	48.84 ± 9.90	0.018 [#]
LVDd	63.37 ± 10.09	65.44 ± 9.60	61.05 ± 11.13	63.64 ± 8.94	<0.001 ^{####}
LVDs	52.06 ± 9.58	53.98 ± 10.30	51.06 ± 8.51	51.16 ± 9.59	0.001 ^{###*}
LVPW	8.87 ± 1.41	8.61 ± 1.70	9.00 ± 1.18	8.98 ± 1.29	0.005 ^{##}
IVS	9 (8, 10)	9 (8, 10)	9 (8, 10)	9 (8, 10)	0.042 [#]

Notes: [#]P < 0.05, ^{###}P < 0.01, ^{####}P < 0.001: T1 group vs T2 group. ^{*}P < 0.05, ^{**}P < 0.01, ^{***}P < 0.001: T1 group vs T3 group. [&]P < 0.05, ^{&&}P < 0.001: T2 group vs T3 group. The data is presented as mean ± standard deviation or median (interquartile range).

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; TyG, triglyceride glucose product Index; EF, ejection fraction; LAD, left atrial diameter; LVDd, left ventricular end-diastolic diameter; LVDs, Left Ventricular end-systolic Diameter; LVPW, Left ventricular posterior wall thickness; IVS, interventricular septal thickness.

diastolic diameter (LVDd), Left Ventricular end-systolic Diameter (LVDs), Left ventricular posterior wall thickness (LVPW), interventricular septal thickness (IVS), hypertension and atrial fibrillation across the TyG index tertiles (all *P* < 0.05). In the lowest TyG index tertile, the proportion of individuals with atrial fibrillation was significantly higher, along with elevated levels of HDL-C, NT-proBNP, LAD, LVDd, and LVDS (all *P* < 0.05). Conversely, the lowest TyG index tertile exhibited lower levels of TC, TG, FPG, LDL-C, HbA1c, BMI, and EF, and a reduced prevalence of hypertension (all *P* < 0.05).

Association of TyG Index With All-Cause Mortality and Cardiovascular Mortality

During the 1-year follow-up period, there were 72 cases of all-cause death (11.0%) and 40 cases of cardiovascular death (6.13%). Among the deceased, 40 patients (18.5%) were in the lowest tertile, 16 patients (7.3%) in the median tertile, and 16 patients (7.4%) in the highest tertile. For deaths attributed to cardiovascular, there were 28 patients (13.0%) in the lowest tertile, 8 patients (3.7%) in the median tertile, and 4 patients (1.8%) in the highest tertile.

Three Cox regression models were used to assess the independent effects of the TyG index on all-cause and cardiovascular mortality (Table 2). In Model 1, a significant negative relationship was found between the TyG index and all-cause mortality (HR 0.492, 95% CI 0.288–0.841). This association remained significant in the minimally adjusted model (HR 0.500, 95% CI 0.290–0.860) and persisted after full adjustment (HR 0.371, 95% CI 0.201–0.685). When participants were stratified into tertiles based on the TyG index, similar results were evident. Specifically, in Model 1, the HRs for all-cause mortality in the second and third tertiles of the TyG index were 0.347 (95% CI 0.188–0.641) and 0.350 (95% CI 0.190–0.647), respectively. In Model 2, these

Table 2 HRs (95% CI) for Mortality According to the TyG Index

	HR (95% CI), P value		
	Model 1	Model 2	Model 3
All-cause mortality			
TyG index (continuous)	0.492 (0.288, 0.841), 0.009	0.500 (0.290, 0.860), 0.012	0.371 (0.201, 0.685), 0.002
TyG index (Tertiles)			
Tertile 1	Reference	Reference	Reference
Tertile 2	0.347 (0.188, 0.641), <0.001	0.349 (0.188, 0.648), <0.001	0.233 (0.112, 0.586), <0.001
Tertile 3	0.350 (0.190, 0.647), <0.001	0.352 (0.190, 0.654), <0.001	0.277 (0.127, 0.605), 0.001
P for trend (median)	<0.001	<0.001	<0.001
CVD mortality			
TyG index (continuous)	0.315 (0.153, 0.648), 0.002	0.317 (0.154, 0.654), 0.002	0.336 (0.151, 0.744), 0.007
TyG index (Tertiles)			
Tertile 1	Reference	Reference	Reference
Tertile 2	0.248 (0.110, 0.558), <0.001	0.244 (0.108, 0.552), <0.001	0.216 (0.090, 0.518), <0.001
Tertile 3	0.125 (0.043, 0.364), <0.001	0.124 (0.042, 0.361), <0.001	0.078 (0.021, 0.296), <0.001
P for trend (median)	<0.001	<0.001	<0.001

Notes: Model 1: No covariates were adjusted; Model 2: Age and gender were adjusted; Model 3: Adjusted for age, gender, body mass index, systolic blood pressure, diastolic blood pressure, heart rate, HbA1c, NT-proBNP, LDL-C, HDL-C, LVEF, and history of hypertension, ischemic cardiomyopathy, and atrial fibrillation.

Abbreviations: HR, hazard ratio; CI, confidence interval; TyG, triglyceride glucose index; CVD, cardiovascular disease.

HRs were 0.349 (95% CI 0.188–0.648) for the second tertile and 0.352 (95% CI 0.190–0.654) for the third tertile. In the fully adjusted Model 3, the HRs were 0.233 (95% CI 0.112–0.586) for the second tertile and 0.277 (95% CI 0.127–0.605) for the third tertile.

We identified a negative association between lower TyG index values and increased risk of cardiovascular death. This inverse relationship was statistically significant in both Model 1 (HR 0.315, 95% CI 0.153–0.648) and Model 2 (HR 0.317, 95% CI 0.154–0.654). The association remained strong in Model 3 (HR 0.336, 95% CI 0.151–0.744). When participants were divided into tertiles based on the TyG index, the HRs for cardiovascular mortality across these tertiles were 1.00 (reference), 0.216 (95% CI 0.090–0.518), and 0.078 (95% CI 0.021–0.296), respectively.

RCS Analysis

To validate the association between the TyG index and the risk of all-cause and cardiovascular death, RCS analysis was used. The analysis confirmed a linear relationship between the TyG index and both all-cause and cardiovascular mortality with non-linearity *P*-values of 0.421 and 0.460, respectively (Figure 2). The RCS models indicated that the risk of all-cause and cardiovascular death initially decreased linearly and then leveled off.

Subgroup Analysis

The analyses were stratified by gender, age, BMI, hypertension, atrial fibrillation, and ischemic cardiomyopathy (Figure 3). Hypertension significantly modified the relationship between the TyG index and both all-cause and cardiovascular mortality (*P*_{for interaction} < 0.05). Specifically, the relationship between the TyG index and both all-cause and cardiovascular mortality was more pronounced in patients without hypertension. Significant interactions between stratification variables and the TyG index were also observed concerning all-cause mortality. The detrimental impact of a low TyG index on all-cause mortality appeared more pronounced in individuals who are younger (< 60 years), have a BMI ≥ 24 kg/m², and are free from atrial fibrillation.

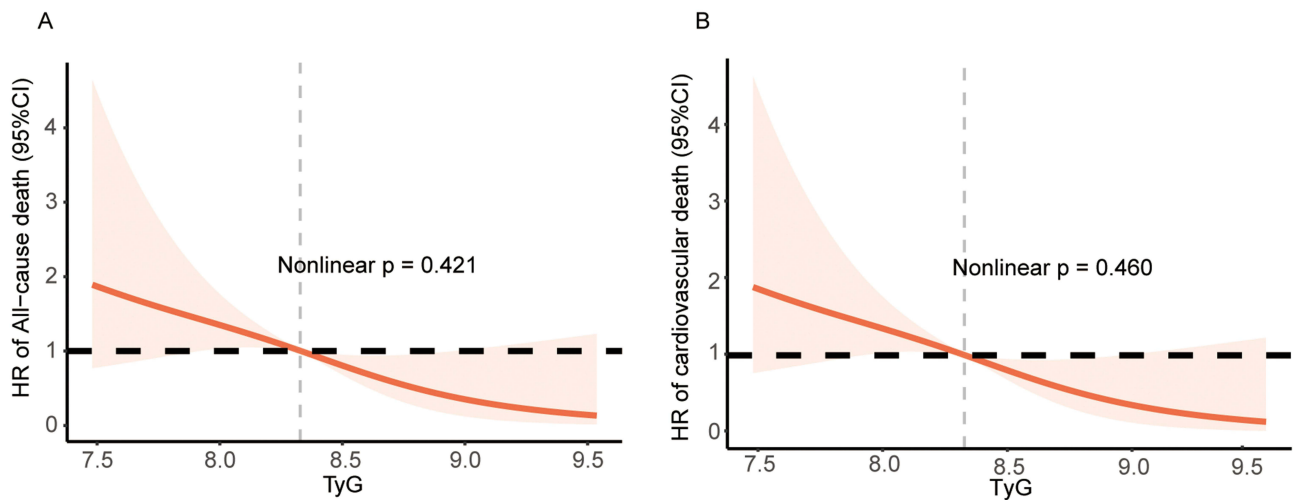


Figure 2 Restricted cubic spline (RCS) analysis of the TyG index with mortality in patients with ADHF without diabetes. **(A)** RCS analysis between the TyG index and the all-cause mortality; **(B)** RCS analysis between the TyG index and the CVD mortality.

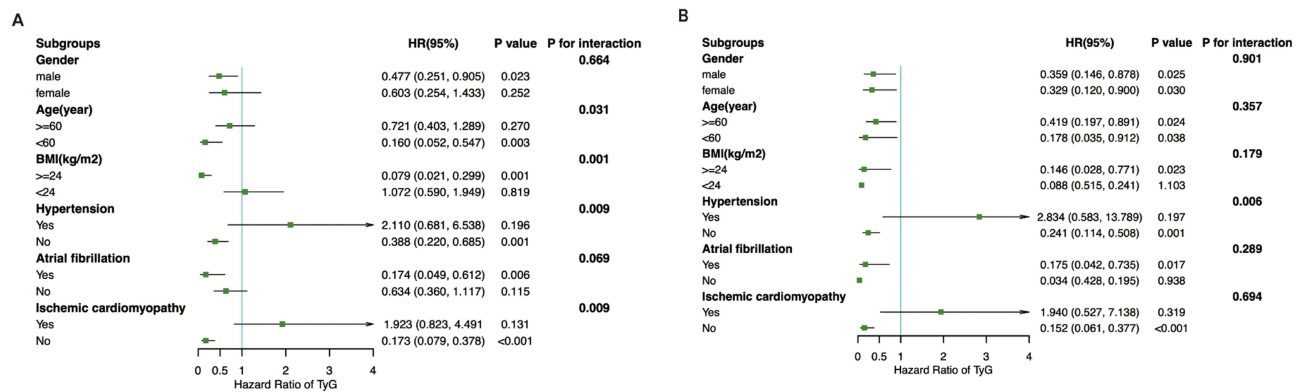


Figure 3 Forest plots of subgroup analyses for the association between the TyG index and mortality in patients with acute decompensated heart failure (ADHF) without diabetes. **(A)** Subgroup analysis for all-cause mortality; **(B)** Subgroup analysis for CVD mortality. Adjusted for Age, gender, body mass index, systolic blood pressure, diastolic blood pressure, heart rate, HbA1c, NT-proBNP, LDL-C, HDL-C, LVEF, and history of hypertension, ischemic cardiomyopathy, and atrial fibrillation.

Discussion

To our knowledge, this is the first study to identify the lower TyG index as a strong predictor of all-cause and cardiovascular mortality among ADHF patients without diabetes. Additionally, our study revealed a linear association between a low TyG index and both all-cause and cardiovascular mortality.

Recent research has increasingly focused on the association between the TyG index and risk of metabolic-related diseases and death.^{19–22} An increasing number of studies have shown that the relationship between the TyG index and diseases or mortality is not linear.²³ Furthermore, many studies have demonstrated a U-shaped or J-shaped association between the TyG index and diseases or mortality.^{24–26} Liu C. et al found that the TyG index exhibited a U-shaped association with both all-cause and cardiovascular mortality in young patients with diabetes, with threshold values of 9.18 and 9.16, respectively. Below these threshold values, the TyG index was not significantly associated with all-cause or cardiovascular mortality. However, above these thresholds, it demonstrated a significant positive association with both all-cause and cardiovascular mortality.²⁷ Zhang Q et al also revealed a U-shaped association between the baseline TyG index and both all-cause and cardiovascular mortality in patients with cardiovascular disease and diabetes or pre-diabetes. Specifically, a baseline TyG index below the threshold values was negatively associated with mortality, while a TyG index above the threshold values was positively associated

with mortality.¹⁶ Therefore, the potential hazards associated with a low TyG index warrant increased attention and further investigation.

Huang R et al recently highlighted that an elevated TyG index is independently associated with poor prognosis, suggesting its utility in risk stratification for patients with ADHF. Furthermore, they also found that when the TyG index was treated as a continuous variable, the hazard ratios for three primary endpoints increased significantly in the higher ranges of the TyG index: all-cause mortality (TyG > 9.08), cardiovascular mortality (TyG > 9.46), and major adverse cardiovascular and cerebrovascular events (TyG > 9.87).¹⁸ To enhance the precision of using the TyG index for risk stratification in patients with ADHF, this study primarily focused on non-diabetic patients with a TyG index below 9.08. This study found that a lower TyG index was negatively correlated with both all-cause and cardiovascular mortality. After adjusting for confounding factors, each unit increase in baseline TyG index decreases the risk of all-cause and cardiovascular mortality by almost 62.9% and 66.4%, respectively. Recently, a retrospective study utilizing the MIMIC-IV database found that a lower TyG-BMI index was strongly associated with a higher risk of 360-day mortality in patients diagnosed with heart failure.²⁸ We believe this finding is not solely attributable to the “obesity paradox”; the TyG index also plays a significant role.

The mechanism by which a low TyG index is associated with increased mortality may be explained by several factors. Hypoglycemia has been shown to elevate counter-regulatory hormones such as adrenaline, which can lead to vasoconstriction and enhanced platelet aggregation,²⁹ thereby increasing the risk of cardiovascular or cerebrovascular events. Additionally, the increased mortality may be associated with the severity of the underlying condition, as Tsujimoto et al found that blood glucose levels could serve as a novel marker of disease severity.³⁰ Furthermore, malnutrition has been identified as the primary cause of non-diabetic hypoglycemia,³⁰ and has been demonstrated to predict worse mortality in heart failure patients.³¹ It is also plausible that sarcopenia or cachexia, often associated with malnutrition and chronic disease, may contribute to the observed relationship between a low TyG index and increased mortality. Sarcopenia, characterized by the loss of muscle mass and strength, and cachexia, a complex metabolic syndrome associated with underlying illness, have both been linked to poor outcomes in heart failure patients.^{32–34} Future studies should explore the potential role of these factors in mediating the relationship between a low TyG index and mortality. Low TG levels have also been associated with adverse outcomes; a prospective cohort study revealed that low serum TG levels were linked to an elevated risk of hemorrhagic stroke in women,³⁵ and similarly, low TG levels were identified as a predictor of cardiac death in patients with heart failure.³⁶

This study also has several limitations. Firstly, it is a single-center retrospective study, which carries a risk of information bias. Secondly, although various adjustments were made, there may still be unaccounted confounding factors, such as medication use. Due to the retrospective nature of the study, detailed information on medication use was not systematically collected, which could influence the study outcomes. Thirdly, selection bias may have been introduced due to the exclusion of individuals with incomplete data. To address missing data in other variables, we employed multiple imputation methods to ensure the robustness of our analysis. Fourthly, while focusing on a population without diabetes increased the sensitivity of the study and avoided the confounding effects of hyperglycemia associated with diabetes, it also limits the broader applicability of the findings. Lastly, as fasting triglyceride and fasting blood glucose levels were measured only at enrollment, they do not reflect changes in exposure over the duration of the follow-up.

Conclusion

In summary, this study demonstrated that a low TyG index was directly associated with both all-cause mortality and cardiovascular mortality in patients with ADHF without diabetes. Therefore, the low TyG index should be given significant attention, and appropriate interventions should be considered to address the poor prognosis associated with it.

Data Sharing Statement

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Clinical Research, Taizhou People's Hospital. All procedures were performed in accordance with the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants.

Acknowledgment

We thank all the participants in this study.

Author Contributions

Qingqing Zhang, Yanling Xu and Si Sun are equal contributors and co-first authors. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

Clinical Research Project of Nanjing Medical University Taizhou School of Clinical Medicine (TZKY20240202) and Clinical Research Project of Nanjing Medical University Taizhou School of Clinical Medicine (TZKY20240208).

Disclosure

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

- Zheng L, Li B, Lin S, Chen L, Li H. Role and mechanism of cardiac insulin resistance in occurrence of heart failure caused by myocardial hypertrophy. *Aging*. 2019;11(16):6584–6590. doi:10.18632/aging.102212
- Wenzl FA, Ambrosini S, Mohammed SA, et al. Inflammation in Metabolic Cardiomyopathy. *Front Cardiovasc Med*. 2021;8(742178). doi:10.3389/fcvm.2021.742178
- Bonora E, Targher G, Alberiche M, et al. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care*. 2000;23(1):57–63. doi:10.2337/diacare.23.1.57
- Unger G, Benozzi SF, Perruzza F, Pennacchiotti GL. Triglycerides and glucose index: a useful indicator of insulin resistance. *Endocrinol Nutr*. 2014;61(10):533–540. doi:10.1016/j.endonu.2014.06.009
- Irace C, Carallo C, Scavelli FB, et al. Markers of insulin resistance and carotid atherosclerosis. A comparison of the homeostasis model assessment and triglyceride glucose index. *Int J Clin Pract*. 2013;67(7):665–672. doi:10.1111/ijcp.12124
- Li S, Guo B, Chen H, et al. The role of the triglyceride (triacylglycerol) glucose index in the development of cardiovascular events: a retrospective cohort analysis. *Sci Rep*. 2019;9(1):7320. doi:10.1038/s41598-019-43776-5
- Thai PV, Tien HA, Van Minh H, Valensi P. Triglyceride glucose index for the detection of asymptomatic coronary artery stenosis in patients with type 2 diabetes. *Cardiovasc Diabetol*. 2020;19(1):137. doi:10.1186/s12933-020-01108-2
- Sanchez-Inigo L, Navarro-Gonzalez D, Fernandez-Montero A, Pastrana-Delgado J, Martinez JA. The TyG index may predict the development of cardiovascular events. *Eur J Clin Invest*. 2016;46(2):189–197. doi:10.1111/eci.12583
- Zhou Y, Pan Y, Yan H, et al. Triglyceride glucose index and prognosis of patients with ischemic stroke. *Front Neurol*. 2020;11:456. doi:10.3389/fneur.2020.00456
- Ma X, Han Y, Jiang L, Li M. Triglyceride-glucose index and the prognosis of patients with acute ischemic stroke: a meta-analysis. *Horm Metab Res*. 2022;54(6):361–370. doi:10.1055/a-1853-9889
- Guo W, Zhao L, Mo F, et al. The prognostic value of the triglyceride glucose index in patients with chronic heart failure and type 2 diabetes: a retrospective cohort study. *Diabet Res Clin Pract*. 2021;177:108786. doi:10.1016/j.diabres.2021.108786
- Zhang Y, Ding X, Hua B, et al. Predictive effect of triglyceride-glucose index on clinical events in patients with type 2 diabetes mellitus and acute myocardial infarction: results from an observational cohort study in China. *Cardiovasc Diabetol*. 2021;20(1):43. doi:10.1186/s12933-021-01236-3
- Liao Y, Zhang R, Shi S, et al. Triglyceride-glucose index linked to all-cause mortality in critically ill patients: a cohort of 3026 patients. *Cardiovasc Diabetol*. 2022;21(1):128. doi:10.1186/s12933-022-01563-z
- Dai L, Yu Y, Wang K, Hu C, Wu D, Shan S. Association between TyG index and long-term mortality of critically ill patients: a retrospective study based on the MIMIC database. *BMJ Open*. 2023;13(5):e065256. doi:10.1136/bmjopen-2022-065256
- Hu B, Wang Y, Wang Y, Feng J, Fan Y, Hou L. Association between triglyceride-glucose index and risk of all-cause and cardiovascular mortality in adults with prior cardiovascular disease: a cohort study using data from the US National Health and Nutrition Examination Survey, 2007–2018. *BMJ Open*. 2024;14(7):e084549. doi:10.1136/bmjopen-2024-084549
- Zhang Q, Xiao S, Jiao X, Shen Y. The triglyceride-glucose index is a predictor for cardiovascular and all-cause mortality in CVD patients with diabetes or pre-diabetes: evidence from NHANES 2001–2018. *Cardiovasc Diabetol*. 2023;22(1):279. doi:10.1186/s12933-023-02030-z
- Liu X, Tan Z, Huang Y, et al. Relationship between the triglyceride-glucose index and risk of cardiovascular diseases and mortality in the general population: a systematic review and meta-analysis. *Cardiovasc Diabetol*. 2022;21(1):124. doi:10.1186/s12933-022-01546-0
- Huang R, Wang Z, Chen J, et al. Prognostic value of triglyceride glucose (TyG) index in patients with acute decompensated heart failure. *Cardiovasc Diabetol*. 2022;21(1):88. doi:10.1186/s12933-022-01507-7
- Liu X, Abudukeremu A, Jiang Y, et al. U-shaped association between the triglyceride-glucose index and atrial fibrillation incidence in a general population without known cardiovascular disease. *Cardiovasc Diabetol*. 2023;22(1):118. doi:10.1186/s12933-023-01777-9

20. Li H, Chen W, Lin X, et al. Influence of renal function on the ability of TyG index to predict all-cause mortality. *Lipids Health Dis.* **2023**;22(1):193. doi:10.1186/s12944-023-01958-1
21. Jiang Y, Chen P, Zhao Y, et al. Association between triglyceride glucose index and all-cause mortality in patients with cerebrovascular disease: a retrospective study. *Diabetol Metab Syndr.* **2024**;16(1):1. doi:10.1186/s13098-023-01243-2
22. Qin Y, Xuan L, Deng Y, Wang F, Liu B, Wang S. Triglyceride-glucose index and mortality risk in individuals with or without chronic kidney disease: insights from a national survey of United States adults, 1999–2018. *Nutr Metab Cardiovasc Dis.* **2024**;34(8):1994–2001. doi:10.1016/j.numecd.2024.04.003
23. Zhou Z, Liu Q, Zheng M, et al. Comparative study on the predictive value of TG/HDL-C, TyG and TyG-BMI indices for 5-year mortality in critically ill patients with chronic heart failure: a retrospective study. *Cardiovasc Diabetol.* **2024**;23(1):213. doi:10.1186/s12933-024-02308-w
24. Zhao M, Xiao M, Tan Q, Lu F. Triglyceride glucose index as a predictor of mortality in middle-aged and elderly patients with type 2 diabetes in the US. *Sci Rep.* **2023**;13(1):16478. doi:10.1038/s41598-023-43512-0
25. Ke J, Ruan X, Liu W, et al. Prospective cohort studies underscore the association of abnormal glycemic measures with all-cause and cause-specific mortalities. *iScience.* **2024**;27(7):110233. doi:10.1016/j.isci.2024.110233
26. Shen R, Lin L, Bin Z, Qiao X. The U-shape relationship between insulin resistance-related indexes and chronic kidney disease: a retrospective cohort study from National Health and Nutrition Examination Survey 2007–2016. *Diabetol Metab Syndr.* **2024**;16(1):168. doi:10.1186/s13098-024-01408-7
27. Liu C, Liang D, Xiao K, Xie L. Association between the triglyceride-glucose index and all-cause and CVD mortality in the young population with diabetes. *Cardiovasc Diabetol.* **2024**;23(1):171. doi:10.1186/s12933-024-02269-0
28. Dou J, Guo C, Wang Y, et al. Association between triglyceride glucose-body mass and one-year all-cause mortality of patients with heart failure: a retrospective study utilizing the MIMIC-IV database. *Cardiovasc Diabetol.* **2023**;22(1):309. doi:10.1186/s12933-023-02047-4
29. Galassetti P, Davis SN. Effects of insulin per se on neuroendocrine and metabolic counter-regulatory responses to hypoglycaemia. *Clin Sci.* **2000**;99(5):351–362. doi:10.1042/cs0990351
30. Tsujimoto T, Yamamoto-Honda R, Kajio H, et al. Prediction of 90-day mortality in patients without diabetes by severe hypoglycemia: blood glucose level as a novel marker of severity of underlying disease. *Acta Diabetol.* **2015**;52(2):307–314. doi:10.1007/s00592-014-0640-9
31. Yoshihisa A, Kanno Y, Watanabe S, et al. Impact of nutritional indices on mortality in patients with heart failure. *Open Heart.* **2018**;5(1):e000730. doi:10.1136/openhrt-2017-000730
32. Maeda D, Fujimoto Y, Nakade T, et al. Frailty, sarcopenia, cachexia, and malnutrition in heart failure. *Korean Circ J.* **2024**;54(7):363–381. doi:10.4070/kcj.2024.0089
33. von Haehling S, Anker SD. Cachexia as major underestimated unmet medical need: facts and numbers. *Int J Cardiol.* **2012**;161(3):121–123. doi:10.1016/j.ijcard.2012.09.213
34. von Haehling S, Ebner N, Dos Santos MR, Springer J, Anker SD. Muscle wasting and cachexia in heart failure: mechanisms and therapies. *Nat Rev Cardiol.* **2017**;14(6):323–341. doi:10.1038/nrcardio.2017.51
35. Rist PM, Buring JE, Ridker PM, Kase CS, Kurth T, Rexrode KM. Lipid levels and the risk of hemorrhagic stroke among women. *Neurology.* **2019**;92(19):e2286–e2294. doi:10.1212/WNL.0000000000007454
36. Kozdag G, Ertas G, Emre E, et al. Low serum triglyceride levels as predictors of cardiac death in heart failure patients. *Tex Heart Inst J.* **2013**;40(5):521–528.