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Association between triglyceride-glucose index and all-cause mortality in patients underwent transcatheter aortic valve replacement

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Abstract

Backgrounds The prognosis of the triglyceride-glucose (TyG) index, a validated surrogate marker for insulin resistance, in patients with severe aortic stenosis (AS) undergoing transcatheter aortic valve replacement (TAVR) remains unknown.

Methods This study consecutively enrolled patients diagnosed with severe AS who underwent TAVR in a Chinese tertiary hospital from March 2013 to September 2023. Participants were stratified based on the TyG index cut-off value. Cox proportional hazards regression models were utilized to explore the association between the TyG index and all-cause mortality, including an assessment of interactions between the TyG index and various covariates on mortality outcomes.

Results Among 1045 patients (mean age 74.7 years, 58.2% male), there was 134 all-cause mortality, resulting in a crude mortality rate of 64.3 per 1000 person-years. Adjusting for age, sex, body mass index, smoking, hypertension, diabetes mellitus, bicuspid aortic valve, atrial fibrillation, Society of Thoracic Surgeons (STS) score, and left ventricular ejection fraction, a per-unit increase in the TyG index was associated with a 41% higher all-cause mortality risk (HR 1.41, 95% CI 1.03–1.93, $p = 0.030$). Notably, the relationship between the TyG index and all-cause mortality was significantly modified by age ($p_{interaction} = 0.027$), sex ($p_{interaction} = 0.007$), hypertension ($p_{interaction} = 0.030$), and STS score ($p_{interaction} = 0.002$).

Conclusions A higher TyG index is significantly associated with an increased risk of all-cause mortality in AS patients after TAVR. These results underscore the importance of considering the TyG index in the prognostic evaluation of AS patients following TAVR.

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Keywords Insulin resistance, Severe aortic stenosis, Transcatheter aortic valve replacement, Mortality

Introduction

Transcatheter aortic valve replacement (TAVR) has become a standard treatment for severe aortic stenosis (AS) [1–6]. While patients undergoing TAVR for severe AS often experience favorable short- and long-term outcomes, the presence of comorbidities such as hypertension, diabetes mellitus, metabolic syndrome, or chronic lung disease in this elderly population can hinder long-term prognosis [7–10]. Therefore, with increasing life expectancy, early identification of poor prognostic factors and the discovery of potential therapeutic targets are of critical importance.

Insulin resistance (IR) denotes reduced sensitivity and responsiveness to insulin's action, often preceding the onset of type 2 diabetes mellitus by several years [11]. Mounting evidence indicates that IR and its associated conditions contribute to cardiovascular disease (CVD) development in both diabetic and nondiabetic individuals [12–14]. Individuals with IR are prone to various metabolic disorders, including hyperglycemia, dyslipidemia, and hypertension, all of which strongly correlate with adverse cardiovascular outcomes [14, 15]. IR is not only recognized as a causal factor but also as a predictor of CVD in both general populations and those with diabetes [16].

The triglyceride-glucose (TyG) index has been proposed as a reliable surrogate for IR, not requiring insulin quantification and making it applicable to individuals regardless of their insulin treatment status [17, 18]. A previous study reported that higher IR, as assessed by the TyG index, was associated with an increased risk of all-cause mortality in patients with moderate and severe AS [19]. However, there is currently a lack of data regarding the associations between the TyG index and all-cause mortality in AS patients undergoing TAVR.

Hence, this study aims to assess the relationship between insulin resistance, as evaluated by the TyG index, and all-cause mortality among severe AS patients undergoing TAVR.

Methods

Study design and population

The present study utilized patient data from the TORCH registry (Transcatheter Aortic Valve Replacement Single Center Registry in the Chinese Population, NCT02803294). The design and methods of the TORCH study have been previously described [20]. TORCH registry is a single-center prospective cohort study in Chinese population who underwent TAVR procedures for severe AS.

In the present study, a total of 1474 patients diagnosed with severe AS who underwent TAVR procedure at the Second Affiliated Hospital of Zhejiang University between March 2013 and September 2023 were consecutively enrolled. The inclusion criteria were as follows: (1) over 18 years old; (2) diagnosis of severe symptomatic aortic stenosis or regurgitation by echocardiography; (3) subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent; (4) the subject agrees to comply with specified follow-up evaluations and to return to the investigational site where the procedure was performed; (5) patients are technical and anatomical eligible for interventions. The exclusion criteria were as follows: (1) the first 100 TAVR cases in learning curve ($N=100$); (2) underwent TAVR procedure for severe aortic regurgitation ($N=246$); (3) periprocedural severe complications, like coronary rupture, coronary obstruction, aorta dissection, or unplanned conversion to surgical procedure ($N=37$); (4) without data for baseline TyG index ($N=46$). Finally, 1045 patients with severe AS underwent TAVR procedure were included for analysis (Fig. 1). This study was conducted following the Declaration of Helsinki and was approved by the Ethics Review Committee of the Second Affiliated Hospital of Zhejiang University.

Data collection and definitions

Clinical data, including age, sex, height, weight, history of smoking, hypertension, diabetes mellitus, atrial fibrillation, chronic obstructive pulmonary disease, New York Heart Association functional classification, creatinine, fasting plasma glucose (FPG), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were extracted from electronic medical records. The body mass index (BMI) was calculated by dividing the weight in kilograms by the square of height in meters. The TyG index was computed using $\ln(\text{TG [mg/dl]} \times \text{FPG [mg/dl]}/2)$. Indicators in the TyG index were calculated based on the fasting blood glucose and triglyceride indices of the patients at the time of admission. The classification of bicuspid AS was performed in multi-slice computed tomography imaging before TAVR [20]. The left ventricular ejection fraction was measured in echocardiography before TAVR. The TORCH registry database comprehensively archived all clinical, imaging, and follow-up data pertinent to this study, providing complete traceability of the data sources.

Outcome

Follow-up assessments were conducted at 30 days post-procedure and subsequently on an annual basis by our

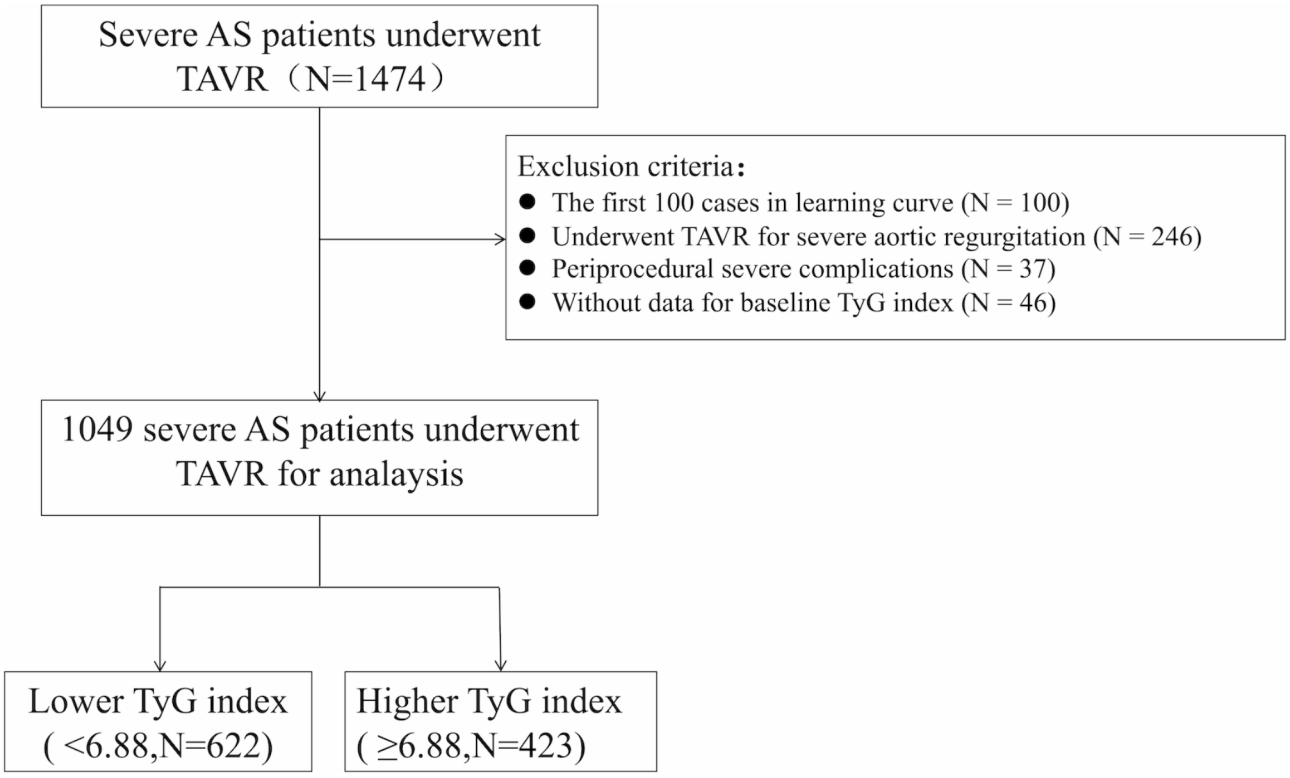

Fig. 1 Flow chart for selecting patients with severe aortic stenosis from TORCH study for analysis

professional follow-up team. The majority of patients received follow-up care at our center, whereas others were monitored via telephone interviews. All follow-up data were collected into our database. The primary outcome of this study was all-cause mortality. We also evaluated the cardiovascular mortality as the secondary outcome. The duration of follow-up was defined as the time from the index TAVR procedure to the date of death or the last recorded follow-up. The follow-up of all patients who were included in this study was completed in September 2023.

Statistical analysis

Continuous variables were reported as means±standard deviations (SD) for normally distributed data, or medians with interquartile ranges (IQR) for non-normally distributed data. Categorical data were expressed as counts and percentages. Based on the optimal cutoff value of the TyG index, patients were stratified into lower and higher TyG index groups. The optimal cutoff value for the TyG index was established for the prediction of the primary outcome via receiver operating characteristic (ROC) curve analysis. Group comparisons for continuous variables were conducted using the Student's t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. Categorical variables were analyzed using the Pearson chi-square test or Fisher's exact test, depending on the expected frequencies.

Crude incidence rates for all-cause and cardiovascular mortality were reported as events per 1000 patient-years. The stratified incidence rates for all-cause and cardiovascular mortality were estimated within each TyG index category (lower or higher), with 95% confidence intervals (CIs) derived using the jackknife method. Cumulative survival rates for all-cause mortality, stratified by TyG index group (lower or higher), were computed using the Kaplan-Meier method and adjusted for age, sex, and BMI. Cox proportional hazards regression with a backward stepwise approach was employed to estimate hazard ratios (HRs) and 95% CIs for the relationship between the TyG index and mortality outcomes, both all-cause and cardiovascular. The proportional hazards assumption was tested using Schoenfeld residuals. Two multivariable models were constructed for adjustment: Model 1 included baseline age, sex, and BMI, whereas Model 2 further adjusted for smoking, hypertension, diabetes mellitus, BAV, atrial fibrillation, STS, and LVEF. Moreover, a landmark analysis excluding patients who experienced the outcome within the first 30 days was performed as sensitivity analysis.

Subgroup analyses were conducted to assess the consistency of the TyG index's prognostic value for all-cause mortality across various baseline characteristics,

including baseline age (<75 and ≥75 years), sex, BMI (<24 and ≥24 kg/m^2), smoking status, hypertension, diabetes mellitus, BAV, atrial fibrillation, STS score (low risk for STS<4% and intermediate/high risk for STS≥4%), and LVEF (<50% and ≥50%). Interaction terms for these subgroups were integrated into the Cox proportional hazards regression model to test for statistical interactions (p for interaction).

Statistical analyses were performed using STATA software, version 19.0 (StataCorp LP, College Station, TX), and R, version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided P value<0.05 was considered statistically significant.

Results

The ROC curve analysis showed that the optimal TyG index threshold for predicting the primary outcome was 6.88. Table 1 shows the baseline characteristics of the 1045 patients with severe AS who underwent TAVR, grouped according to the optimal cut-off point of the TyG index. The mean age of all patients was 74.7±7.2 years, of whom 608 (58.2%) were male. Patients with TyG index≥6.88 had higher levels of TC, LDL-C, TG, FPG, DBP and BMI, lower levels of HDL-C, lower median age, lower proportions of COPD and higher proportions of males, hypertension and diabetes mellitus compared with patients with TyG index<6.88.

During a median follow-up of 17.59 months, a total of 134 (12.8%) all-cause mortality were recorded for analysis. Of these, 42 (4.0%) were cardiovascular mortality. Cox regression analysis of the association between the TyG index and mortality is shown in Table 2. In the model that measured the baseline TyG index as a continuous variable, although the relationship between the TyG index and all-cause mortality was not significant in model 1, the value of the relationship was highly significant after further adjustment for potential confounders in model 2. The association between TyG index and cardiovascular mortality was not significant despite further adjustment for potential confounders in model 2. In fully adjusted model 2, each 1-unit increase in the TyG index was associated with a 41% increase in the risk of all-cause mortality (HR 1.41, 95% CI 1.03–1.93, p=0.03). Furthermore, in model 1, the risk of all-cause mortality was 1.62 times higher in the higher TyG index group compared with the lower TyG index group (HR 1.62, 95% CI 1.14–2.32, p=0.008). In model 2, the relationship remains robust to the fact that the higher TyG index group increases the risk of all-cause mortality relative to the lower TyG index group after further adjustment for other potential confounders (HR 1.53, 95% CI 1.08–2.17,

Table 1 Baseline characteristics of participants

	Total Population (*n*=1045)	**Lower TyG index (<6.88, *n*=622)**	**Higher TyG index (≥6.88, *n*=423)**	***P* value**
TyG index	6.76 (6.41–7.14)	6.49 (6.28–6.68)	7.25 (7.02–7.52)	<0.001
Age	74.7±7.2	75.1±7.4	74.0±6.9	0.010
Sex				0.015
Female	437 (41.8%)	241 (38.7%)	196 (46.3%)	
Male	608 (58.2%)	381 (61.3%)	227 (53.7%)	
BMI, kg/m^2	22.80 (20.30–25.00)	22.00 (19.60–24.30)	23.70 (21.50–25.80)	<0.001
Smoking	216 (20.7%)	133 (21.4%)	83 (19.6%)	0.490
Hypertension	582 (55.7%)	304 (48.9%)	278 (65.7%)	<0.001
Diabetes mellitus	215 (20.6%)	82 (13.2%)	133 (31.4%)	<0.001
Atrial fibrillation	185 (17.7%)	116 (18.7%)	69 (16.3%)	0.331
COPD	198 (18.9%)	132 (21.2%)	66 (15.6%)	0.023
NYHA III/IV	787 (75.3%)	477 (76.7%)	310 (73.3%)	0.211
STS	4.10 (2.29–7.52)	4.15 (2.33–7.65)	4.03 (2.25–7.35)	0.453
Creatinine, mmol/L	73.0 (60.0–90.0)	73.0 (60.0–90.0)	72.0 (60.0-90.3)	0.860
FPG, mmol/L	5.07 (4.61–5.76)	4.83 (4.45–5.23)	5.72 (5.07–6.85)	<0.001
Total Cholesterol, mmol/L	3.95 (3.35–4.75)	3.79 (3.24–4.51)	4.23 (3.51–5.04)	<0.001
TG, mmol/L	0.99 (0.77–1.36)	0.82 (0.67–0.98)	1.51 (1.23–1.87)	<0.001
LDL-C, mmol/L	2.04 (1.57–2.64)	1.89 (1.47–2.42)	2.30 (1.80–2.98)	<0.001
HDL-C, mmol/L	1.18 (1.01–1.41)	1.26 (1.08–1.47)	1.09 (0.93–1.27)	<0.001
BAV	573 (56.3%)	347 (57.5%)	226 (54.6%)	0.366
LVEF	59.7 (49.2–65.5)	59.4 (48.1–65.8)	60.0 (50.4–65.1)	0.980

Data are shown as mean±SD or n (%). Baseline characteristics of the 1045 patients who underwent transcatheter aortic valve replacement, stratified by the optimal cutoff point of triglyceride glucose index

BAV, bicuspid aortic valve; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons; TG, triglyceride; TyG, triglyceride-glucose

Table 2 Association between the TyG index and mortality*

	Event/Total	IR (95% CI), per 1000 person-years	Model 1		Model 2	
			HR (95% CI)	*P* value	HR (95% CI)	*P* value
All-cause Mortality						
Continuous (per unit)	134/1045 (12.8%)	64.3 (54.3–76.2)	1.32 (0.96–1.81)	0.085	1.41 (1.03–1.93)	0.030
Lower TyG index	72/622 (11.6%)	57.6 (45.7–72.6)	Reference	-	Reference	-
Higher TyG index	62/423 (14.7%)	74.3 (58.0-95.3)	1.62 (1.14–2.32)	0.008	1.53 (1.08–2.17)	0.017
Cardiovascular Mortality						
Continuous (per unit)	42/1043 (4.0%)	20.2 (14.9–27.3)	1.56 (0.92–2.65)	0.098	1.63 (0.94–2.84)	0.085
Lower TyG index	20/620 (3.2%)	16.0 (10.3–24.8)	Reference	-	Reference	-
Higher TyG index	22/423 (5.2%)	26.4 (17.4–40.1)	1.78 (0.97–3.28)	0.063	1.60 (0.85-3.00)	0.144

*Cox regressions with backward stepwise method were used

Model 1 Adjusted by age, sex, BMI

Model 2 Adjusted by age, sex, BMI, smoking, hypertension, diabetes mellitus, BAV, atrial fibrillation, STS, and LVEF

BAV, bicuspid aortic valve; BMI, body mass index; CI, confidence interval; HR, hazard ratio; IR, incidence rate; STS, Society of Thoracic Surgeons; LVEF, left ventricular ejection fraction; TyG, triglyceride-glucose

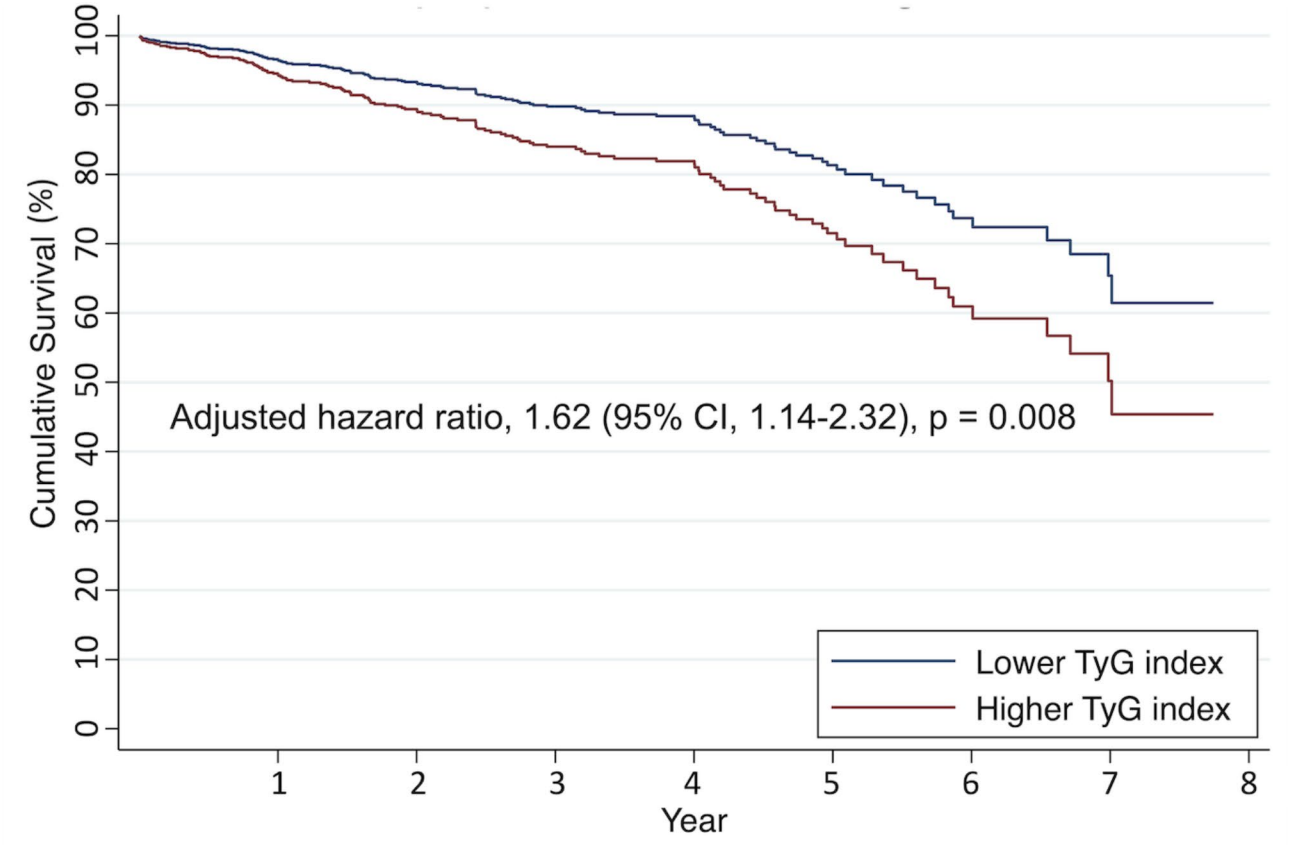

Fig. 2 Kaplan-Meier cumulative survival analysis curves for all-cause mortality adjusted for age, sex and BMI for the higher TyG index and lower TyG index groups

$p=0.017$). A landmark analysis excluding patients who experienced the outcome within the first 30 days showed a similar results and were presented in Supplementary Table 1. Figure 2 shows Kaplan-Meier cumulative survival analysis curves for all-cause mortality adjusted for age, sex and BMI for the higher TyG index and lower TyG index groups. During a follow-up period of up to 8 years, a statistically significant difference in all-cause mortality was observed between the two groups.

The relationship between the TyG index and all-cause mortality was significantly modified by age (pinteraction=0.027), sex (pinteraction=0.007), hypertension (pinteraction=0.030), and STS score (pinteraction=0.002). The TyG index had higher hazard ratio for all-cause mortality in patients with severe AS underwent

TAVR in the subgroup of those aged ≥ 75 years (HR 1.42, 95% CI 1.00-2.01, $p=0.047$) compared with aged < 75 yeas (HR 0.77, 95% CI 0.37–1.63, $p=0.495$), in the subgroup of male (HR 1.71, 95% CI 1.16–2.52, $p=0.007$) compared with female (HR 0.92, 95% CI 0.50–1.71, $p=0.801$), in the subgroup of hypertension (HR 1.52, 95% CI 1.03–2.26, $p=0.036$) compared with no hypertension (HR 1.00, 95% CI 0.56–1.78, $p=0.030$), in the subgroup of intermediate- or high-risk (HR 1.32, 95% CI 0.94–1.86, $p=0.110$) compared with low-risk (HR 0.82, 95% CI 0.28–2.42, $p=0.714$). Interaction and subgroup analysis was shown in Fig. 3.

Discussion

To the best of our knowledge, this study is the first study to examine the association between the TyG index and prognostic outcomes in patients with severe AS who have underwent TAVR. The main finding indicates that an elevated TyG index was significantly associated with an increased risk of all-cause mortality in these patients. Furthermore, the prognostic implication of a higher TyG index appears to be more pronounced in older patients, males, individuals with hypertension, and those with a higher STS risk score.

IR is a fundamental pathogenic factor in metabolic syndrome, encompassing conditions such as impaired glucose metabolism, dyslipidemia, obesity, and hypertension, all of which escalate the risk of CVD and mortality [21, 22]. The TyG index, derived from fasting blood glucose and triglyceride levels, has emerged as a straightforward and effective indicator of IR [17]. There is mounting evidence suggesting the TyG index's association with both all-cause and cardiovascular mortality across the general populace and among individuals with various cardiometabolic disorders [16, 23–27]. Nonetheless, the literature remains sparse regarding the TyG index's link to calcification or mortality in patients with AS [19, 28]. While the impact of metabolic syndrome on heart valve interventions has been acknowledged, investigations directly exploring the relationship between IR, as quantified by the TyG index, and mortality in AS patients undergoing TAVR are limited [29]. This study is the first to demonstrate a significant association between elevated IR, as quantified by the TyG index, and an enhanced risk of all-cause mortality among patients with severe AS undergoing TAVR, even after adjustments for potential confounders. Our findings highlight that the relationship between the TyG index and all-cause mortality is

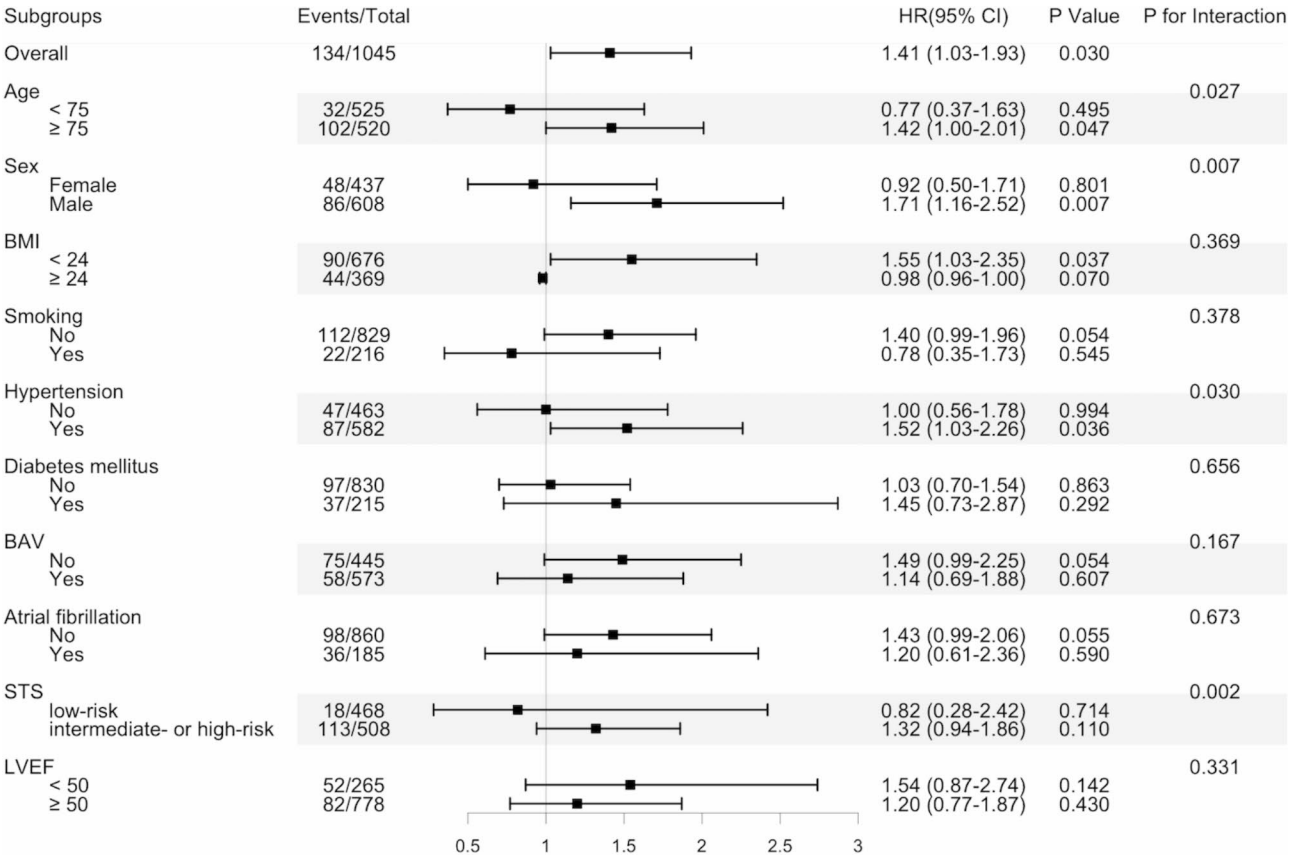

Fig. 3 Subgroup analysis of the association between baseline TyG index and all-cause mortality. HR, hazard ratios; CI, confidence interval; BMI, body mass index; BAV, bicuspid aortic valve; STS, Society of Thoracic Surgeons; LVEF, left ventricular ejection fraction

modified by age, sex, hypertension, and the STS score. This observation aligns with prior research, which has similarly reported that the association between the TyG index and mortality is modified by age and sex [30, 31].

The underlying mechanism connecting the TyG index with CVD remains elusive. However, it is evident that the TyG index encompasses two pivotal CVD risk factors, the lipid and glucose metabolism, indicative of IR in the body. IR itself is a recognized risk factor for CVD, implicated in the disease's onset across both the general and diabetic populations, and is a predictor of cardiovascular outcomes [15]. A prior study involving 1574 patients, who presented with acute coronary syndrome and underwent successful percutaneous coronary intervention using drug-eluting stents, identified a positive, independent association between elevated TyG levels and the incidence of in-stent restenosis [32]. This relationship might be attributed to several mechanisms, including the excessive proliferation of vascular smooth muscle cells mediated by various signaling pathways, endothelial dysfunction through inflammation, oxidative stress, and metabolic changes [33–37]. Furthermore, as a surrogate marker for IR, the TyG index has been closely linked to both the prevalence and progression of coronary artery calcification, suggesting another potential mechanism [38, 39]. The initial phase of calcified AS mirrors atherosclerotic processes, where valve endothelial dysfunction arises from mechanical stress, inflammation, and lipid accumulation. Subsequent oxidative stress prompts the differentiation of valvular interstitial cells into myofibroblasts and osteoblast-like cells, fostering calcification and osteogenic alterations in the valve, thus exacerbating valve narrowing. The progression of calcified AS may, in certain contexts, be associated with IR or the TyG index [19, 28]. Nevertheless, additional research is required to fully decipher the mechanisms underlying the TyG index's association with calcification and mortality.

A principal strength of our investigation is its novelty; to the best of our knowledge, this is the first study to assess the relationship between the TyG index and future mortality among patients with severe AS undergoing TAVR. An additional merit is our ability to track and analyze long-term outcomes spanning up to 8 years post-TAVR, offering valuable insights into patient prognoses over an extended period. Furthermore, the comprehensive dataset allows for detailed subgroup analyses and identification of potential effect modification. Critically, our findings carry significant clinical implications by suggesting the TyG index as a potential marker for risk stratification and management in AS patients post-TAVR. This underscores the necessity for future research to explore whether interventions targeting IR could yield benefits in this patient population. For instance, the use of Glucagon-like peptide-1 (GLP-1) analogs, known to mitigate major adverse cardiac events partly through their effects on vascular redox status and IR, points towards the therapeutic potential of addressing IR to enhance clinical outcomes [40].

Nonetheless, the present study has several potential limitations. Firstly, as a single-center, observational study, it cannot establish causality between the TyG index and all-cause mortality in patients with AS after TAVR. Although efforts were made to mitigate confounding through multivariate adjustments, the potential for residual confounding remains, which might affect the prognostic implications. Secondly, due to the absence of insulin level measurements and hyperinsulinemic-euglycemic clamp tests, this study could not evaluate the comparative prognostic relevance of the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and the TyG index in the post-TAVR mortality context. Thirdly, given that laboratory parameters were assessed only at the point of admission, the impact of changes in the TyG index over time on mortality outcomes is still uncertain, highlighting the need for future longitudinal studies to explore this aspect further. Fourthly, we were unable to record patients' baseline medication data, which limits our ability to assess how current medications might affect triglyceride and glucose levels. Future research would benefit from including such data to provide a more comprehensive understanding of the factors influencing triglyceride and glucose levels.

Conclusions

In conclusion, our study is pioneering in demonstrating that an elevated TyG index is correlated with an increased risk of all-cause mortality in patients with severe AS who have undergone TAVR. These findings propose that the TyG index may serve as a viable prognostic marker for all-cause mortality in this patient population. Consequently, therapeutic interventions targeting insulin resistance could potentially enhance clinical outcomes for patients post-TAVR.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-024-04177-3.

Supplementary Material 1

Author contributions

J.F., X.L., and J.W. contributed to the conception and design of the work; J.F., A.A., and A.Y. contributed to the acquisition, analysis, and interpretation of data; J.F. and A.A. drafted the manuscript; J.F., A.A., A.Y., X.L., and J.W. critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Data availability
The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Ethical approval and consent to participate
All methods were carried out in accordance with the Declaration of Helsinki. The Ethics Review Committee of the Second Affiliated Hospital of Zhejiang University approved the study and written informed consents were obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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