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Association between triglyceride-glucose-body mass index and risk of aortic stenosis progression in patients with non-severe aortic stenosis: a retrospective cohort study

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Abstract

Background Triglyceride-glucose-BMI (TyG-BMI) index is a surrogate marker of insulin resistance and an important predictor of cardiovascular disease. However, the predictive value of TyG-BMI index in the progression of non-severe aortic stenosis (AS) is still unclear.

Methods The present retrospective observational study was conducted using patient data from Aortic valve diseases RISk facTOr assessmenT andprognosis modeL construction (ARISTOTLE). A total of 190 patients were recruited from one-center. Patients were divided into two groups according to the cut-off value of TyG-BMI index (Ln[triglycerides (mg/dL)* glucose (mg/dL)/2]*BMI). Cox regression and restricted subgroup analysis were used to evaluate the association of TyG-BMI index and progression of non-severe AS.

Results A total of 190 patients (mean age 72.52 ± 11.97 years, 51.58% male) were included in the study. During a median follow-up period of 27.48 months, 44 participants experienced disease progression. The cut-off of the TyG-BMI index is 239. After fully adjusting for confounding factors, high TyG-BMI index group was associated with a 2.219-fold higher risk of aortic stenosis progression (HR 2.219, 95%CI 1.086–4.537, $p = 0.029$).

Conclusion TyG-BMI index was significantly associated with a higher risk of progression to non-severe AS. TyG-BMI index, as an effective alternative indicator of IR, can identify people at high risk of AS progression at an early stage of the disease, thereby improving the prognosis and reducing the socio-economic burden.

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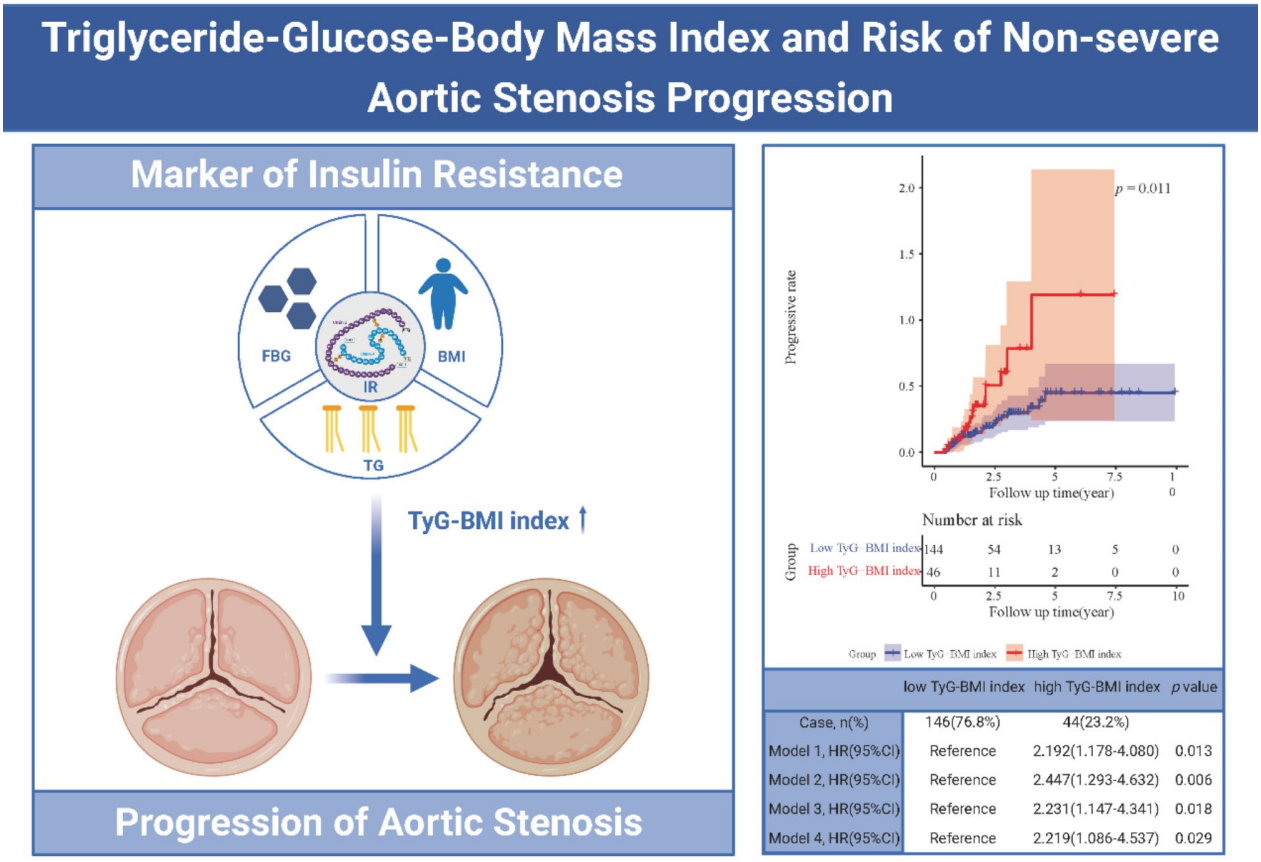
Graphical abstract



	low TyG-BMI index	high TyG-BMI index	*p* value
Case, n(%)	146(76.8%)	44(23.2%)	
Model 1, HR(95%CI)	Reference	2.192(1.178-4.080)	0.013
Model 2, HR(95%CI)	Reference	2.447(1.293-4.632)	0.006
Model 3, HR(95%CI)	Reference	2.231(1.147-4.341)	0.018
Model 4, HR(95%CI)	Reference	2.219(1.086-4.537)	0.029

Keywords Triglyceride-glucose-body mass index, Aortic stenosis, Risk of progression

Introduction

Aortic stenosis(AS) is the most common type of heart valve disease, especially in the elderly. In the aging era, the disease burden of AS is increasing [1]. Typically lacks distinct symptoms and signs, making early detection challenging. This is due to the subtle decrease in valve orifice area and the preservation of normal cardiac output through various compensatory mechanisms [2]. In the mild to moderate progressive stage, the patient's condition is relatively stable, and once it develops to severe stage, the prognosis is significantly worse. Without timely treatment, the 2-year survival rate is less than 50% and the 5-year survival rate is less than 20% [3]. Although there are significant individual differences in the rate of progression in patients with non-severe AS, historical progression of AS is common, and once mild stenosis occurs, most of them eventually progress to severe [4]. At present, there is no medication that can delay the progression of AS, and aortic valve replacement (AVR) is the only treatment [5]. However, the proportion of patients who have indications for AVR but do not receive AVR is still large [6, 7]. At the same time, it should be noted that even with active intervention, the prognosis of patients after the onset of symptoms is still poor [8]. Related complications after AVR, such as paravalvular leak, valve embolism, and annular rupture, are significantly associated with increased mortality and rehospitalization rates [9, 10]. Therefore, it is essential to identify patients at high risk of AS progression and control the progression at the early stage of the disease.

Insulin resistance (IR), defined as decreased sensitivity of tissues to normal plasma insulin levels, is a prominent feature of metabolic syndrome [11]. As the gold standard for measuring IR, the hyperinsulinemic euglycemic clamp test is complex and invasive and is not suitable for clinical research [12].TyG index is a simple, effective and reliable surrogate marker of IR in epidemiological studies [13, 14]. A large number of large-scale clinical studies have proved that TyG index is an important factor in predicting cardiovascular events [15–20]. Recent

studies have found that the composite index formed by the combination of TyG index and BMI can significantly improve the effectiveness of evaluating IR. The area under the receiver operating characteristic curve for TyG in predicting IR was 0.690, and the AUC for TyG-BMI prediction was 0.748, with this difference remaining in the analysis of different genders [21]. In the studies on the correlation between TyG-BMI index and cardiovascular disease, stroke, diabetes, etc. TyG-BMI index shows a better role than TyG index alone in replacing IR [22–26]. In the population with Type 2 Diabetes Mellitus (T2DM) and Coronary Heart Disease (CHD), the TyG-BMI index is positively correlated with the risk of Major Adverse Cardiovascular Events (MACE) after multivariable adjustment (HR 1.012, 95% CI 1.005 to 1.019, $P = 0.001$) [27]. Among Chinese middle-aged and elderly populations, TyG-BMI index and the cumulative change in TyG-BMI index are associated with an increased risk of hypertension and cumulative elevation of systolic blood pressure (SBP) and diastolic blood pressure (DBP), with baseline TyG-BMI index having higher accuracy in predicting hypertension compared to TyG [28]. In the population with Cardiovascular-Renal-Metabolic (CKM) syndrome stages 0–3, the TyG-BMI index is positively linearly associated with the incidence of cardiovascular disease (CVD) [29]. In the NHANES study, higher TyG-BMI index values were significantly associated with an increased prevalence of CVD ($p < 0.001$), with individuals in the highest tertile of TyG-BMI index having a 38% higher prevalence of CVD compared to those in the lowest quartile (OR = 1.380; 95% CI = 1.080, 1.763) [30]. Previous studies have shown that TyG-BMI index has significant advantages in predicting cardiovascular and cerebrovascular diseases, but there is a gap in this research concerning the progression of aortic stenosis (AS). Therefore, our study aims to explore the correlation between the two and assess the significance of TyG-BMI index in predicting the progression of aortic stenosis.

The determinants of progression of aortic stenosis are not well defined. Previous studies have found that metabolic syndrome and diabetes mellitus play an active role in progression [31]. Among them, IR is a prominent feature of metabolic syndrome, and type 2 diabetes mellitus has been shown to be associated with the pathogenesis of AS. However, supporting studies are few and conflicting. At the same time, there are conflicting findings on the correlation of TyG with AS progression. BMI is a risk factor for AS, but it does not affect the progression of AS [32]. There is still a lack of research on the correlation between TyG-BMI index and the risk of AS progression, and the predictive value of TyG-BMI index for AS progression is still unclear. Therefore, the aim of this study was to evaluate the association between TyG-BMI index and progression of non-severe AS (Graphical abstract).

Methods

Study design and subjects

The present retrospective study was conducted using patient data from Aortic valve diseases RISk facTOr assessmenT andprognosis modeL construction (ARISTOTLE). The ARISTOTLE study was a real-world study of hospitalized patients with aortic valve diseases at the multicenter in South China, intending to measure aortic valve disease and analyze the risk factors affecting its prognosis and was registered in the Chinese Clinical Trials Registry (registration number: NCT06069232).

This retrospective observational cohort study included 284 patients who were diagnosed with calcific non-severe aortic stenosis from October 2013 to August 2023 at the First Affiliated Hospital of Sun Yat-sen University. The relevant data of the participants were obtained from their previous hospital medical records. The participants included have been contacted by phone to obtain their informed consent. The inclusion criteria were as follows: (1) over 18 years old; (2) non-severe AS (including mild and moderate AS) diagnosed by echocardiography according to the guidelines [33]. Mild AS was defined as peak aortic jet velocity (Vmax) 2.6–2.9 m/s, mean aortic pressure gradient (MG) < 20 mmHg, or aortic valve area (AVA) > 1.5 cm2. Moderate AS was defined as peak aortic jet velocity (Vmax) 3–4 m/s, mean aortic pressure gradient (MG) 20–40 mmHg, or aortic valve area (AVA) 1.0-1.5 cm2. (3) Two or more echocardiograms; (4) The interval between two echocardiograms was more than 6 months. Exclusion criteria were as follows: (1) diagnosis of rheumatic heart disease; (2) missing baseline TyG-BMI index data; (3) Other covariates were missing. Finally, 190 patients with non-severe AS were included in the study for subsequent analysis (Fig. 1). The study was conducted after the Declaration of Helsinki and was approved by the ethical Review Board of the First Affiliated Hospital of Sun Yat-sen University. All clinical data were collected through the electronic medical record. All participants were informed by telephone contact and informed consent was obtained from all participants.

TyG-BMI index

Triglycerides and fasting plasma glucose were obtained from the electronic medical record. Height and weight were obtained from patient measurements on admission. Fasting plasma glucose and triglyceride levels were obtained using venous blood samples obtained after overnight fasting and analyzed by standard techniques. They were measured using an automated biochemical analyzer (Model: AU5800, Manufacturer: Beckman Coulter, Inc., USA). The TyG index was calculated as: Ln[triglycerides (mg/dL)* glucose (mg/dL)/2]. BMI was calculated as weight (kg)/ height (m2). The TyG-BMI index was calculated as: TyG*BMI. According to ROC

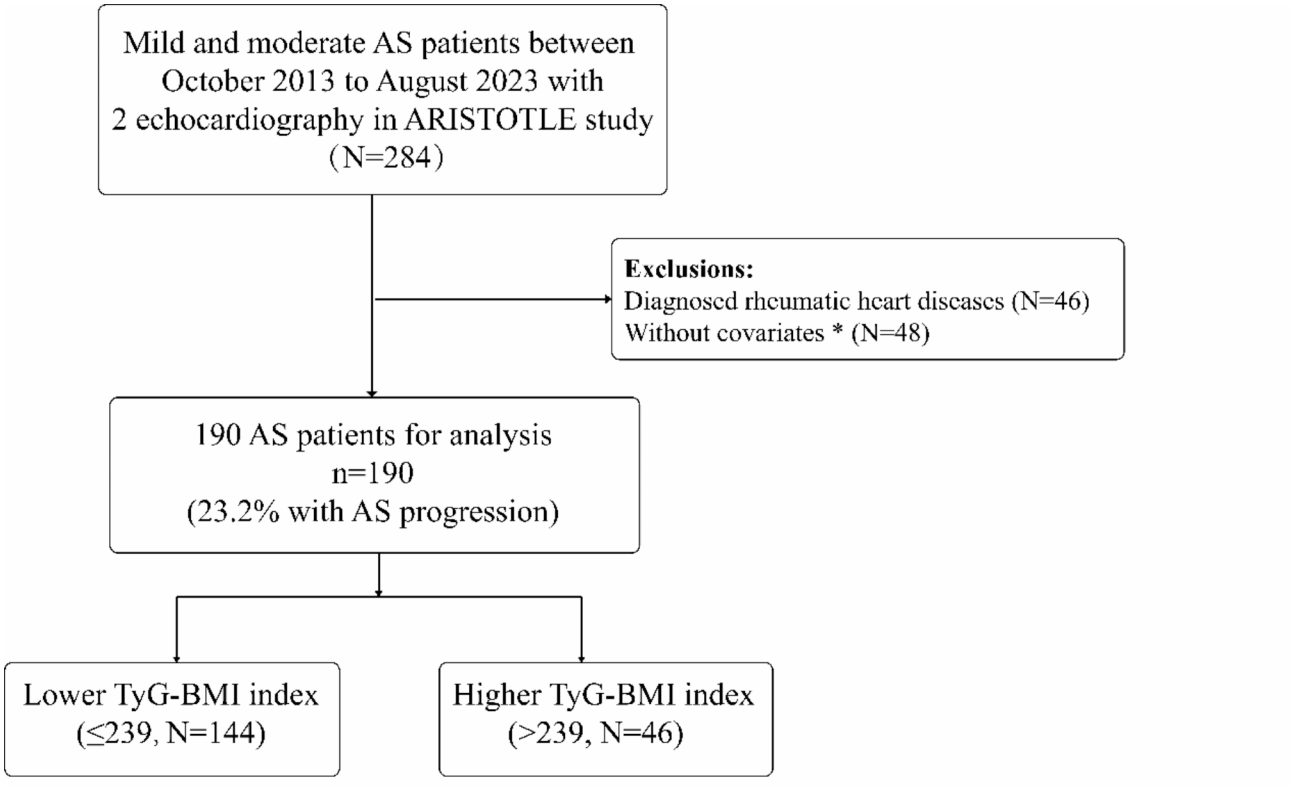


Fig. 1 Flow chart for selecting patients with non-severe aortic stenosis from ARISTOTLE study for analysis

curve analysis(supplementary Fig. 1), the best cut-off value of TyG-BMI index was 239.

Definitions of outcome

The endpoint of this study was progression of non-severe AS. Non-severe AS was defined AS mild or moderate AS diagnosed by echocardiography as required by the guideline at baseline. Progression was defined as ΔVmax(m/s)/Δtime(year) > 0.3 m/(s*year). When the ratio of the difference in peak aortic jet velocity to time between two echocardiograms more than 6 months apart exceeded 0.3 m/(s*year) [34–36]. In August 2023 to complete the follow-up of all patients included in this study.

Covariates

Baseline clinical data, including age, sex, smoking history, alcohol use history, medication use, hypertension history, diabetes history, and stroke history, were obtained by self-report and were further verified by health care professionals with the use of auxiliary testing during hospitalization. The number of diabetic patients is less than the number of patients taking hyperglycemic medications. Our cohort includes patients with heart failure and coronary artery disease, and according to the guidelines, these groups have used SGLT2 inhibitors, even though some participants do not have diabetes. In such cases, non-diabetic patients using SGLT2 inhibitors are still classified as being in the category of those taking hyperglycemic medications.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with an electronic sphygmomanometer after a 5-minute morning break. Hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg, or use of antihypertensive medication and a self-reported history of hypertension. Diabetes was defined as fasting plasma glucose (FPG) ≥ 7.0 mmol/L, or HbA1c ≥ 6.5%, with a self-reported history of type 2 diabetes mellitus (T2DM). Stroke was defined as self-reported history of stroke or is being treated for a stroke. Laboratory data were obtained from venous blood after overnight fasting and were analyzed by standard techniques for total cholesterol (CHOL), high-density lipoprotein and cholesterol (HDL-C). Left ventricular ejection fraction (LVEF), bicuspid aortic valve (BAV), peak aortic jet velocity (Vmax), aortic valve area (AVA) and mean aortic pressure gradient (MG) were recorded by transthoracic echocardiography. The severity of AS was graded according to the American Society of Echocardiography guidelines [33].

Statistical analysis

Continuous variables are presented as means ± standard deviation (SD) and categorical variables as numbers (percentages). At present, there is no clear clinical cut-off

point of TyG-BMI index, so the receiver operating characteristic (ROC) curve analysis was used to determine the best cut-off point value of TyG-BMI index for predicting the primary endpoint. Patients with higher than the optimal cut-off value were divided into the high TyG-BMI index group, and those with lower TyG-BMI index were divided into the low TyG-BMI index group. The Kaplan–Meier method was used to calculate the cumulative incidence of AS progression according to the best cut-off point of TyG-BMI index, and the log-rank test was used to evaluate the differences between groups.

To determine the association of TyG-BMI index with progression to non-severe AS, adjusting for potential confounders, this study calculated hazard ratios (HR) and 95% confidence (95%CI) intervals using a multivariable adjusted cox proportional hazards model. By using the cox.zph function to test the proportional hazards consumption for the fitted model, the p-value for TyG-BMI index was 0.061, which satisfied the proportional hazards assumption. Model 1 was an unadjusted model. Age and gender were adjusted in model 2. Model 3 was further adjusted for LVEF, BAV, smoking, alcohol consumption, CHOL and HDL-C. Model 4 was further adjusted for hypertension, diabetes, stroke, antihypertension medication, hypoglycemic medication and lipid-lowering medication on the basis of model 3. Additionally, subgroup and interaction analysis were used to investigate whether the relationships between the change in TyG-BMI index and progression of AS varied according to the status of the covariates (age, gender, BAV, smoking, drinking, hypertension, diabetes, stroke, antihypertension medication, hyperglycemic medication, and lipid-lowering medication). All analyses were performed with the use of R, version 4.3.3 (the Statistical Foundation for R), and stata17.0 (Stata Corp LLC). A two-sided p value of less than 0.05 was considered to indicate statistical significance.

Result

Baseline characteristics

The TyG-BMI index did not fit the normal distribution. According to the ROC curve analysis, the best cut-off value of TyG-BMI index for predicting the progression of non-severe AS was 239. TyG-BMI index was grouped according to the best cutoff point, and Table 1 presents the baseline characteristics of 190 patients, including anthropometric data, biochemical characteristics, and echocardiographic data. The average age of the patients was 72.52 ± 11.97 years, and males accounted for 51.58%. Compared to the low TyG-BMI index group, the high TyG-BMI index group has a higher proportion of females, higher CHOL levels, and a higher proportion of individuals using hypoglycemic medications ($p < 0.05$).

Figure 2 shows the correlation between TyG-BMI index and traditional risk factors for CVD. In patients with non-severe AS, TyG-BMI index was positively correlated with BMI, CHOL, TG, LDL-C, FBG and diabetes, but negatively correlated with gender, lipoprotein[a](Lp[a]) and HDL-C ($p < 0.05$). There was no significant correlation between TyG-BMI index and age, SBP, DBP, smoking, drinking and hypertension. However, the correlation coefficients between the TyG-BMI index and traditional cardiovascular risk factors ranged from − 0.15 to 0.2, with BMI and fasting blood glucose showing larger correlation coefficients with the TyG-BMI index. This result suggests that although the correlation between the TyG-BMI index and traditional cardiovascular risk factors is not strong, there is some overlap with traditional factors in predicting cardiovascular events, which may capture some risk dimensions that traditional factors do not fully cover. This emphasizes the potential value of including the TyG-BMI in cardiovascular risk assessment, especially when combined with other obesity indicators, which may improve the accuracy of predicting cardiovascular disease risk.

The size of the circles indicates the correlation, with blue representing positive correlations and red representing negative correlations. The values in the lower left section report the correlation coefficients, while the asterisks in the upper right section indicate the p-values, where "*" represents $p < 0.05$ and "**" represents $p < 0.01$.

Association between TyG-BMI index and progress in aortic stenosis

During a median follow-up of 27.48 months(interquartile range: 12.41 months to 36.04 months), a total of 44 patients had progression of aortic stenosis. The mean time between two echo exams in the progression group(19.92 ± 12.11months) is significantly less than that in the non-progression group(27.48 ± 20.08months) ($p = 0.007$).The incidence of AS progression was 34.78% in the high TyG-BMI index group and 19.44% in the low TyG-BMI index group. There were significant differences in progression rates between the two groups ($p = 0.011$) (Fig. 3). Table 2 presents the penalized maximum likelihood analysis of the association between TyG-BMI index and progression of aortic stenosis by cox proportional-hazards model. Our results were significant. TyG-BMI index was significantly associated with progression of aortic stenosis in unadjusted model (model 1), and this significant association persisted in models 2,3 and 4. In the fully adjusted model, higher TyG-BMI index was associated with a 2.219-fold higher risk of aortic stenosis progression compared with low TyG-BMI index (HR 2.219, 95%CI 1.086–4.537, $p = 0.029$).

Subgroup analyses were performed according to bicuspid valve (yes or no), sex (male or female), age (> 65 years

Table 1 Baseline clinical characteristics of patients stratified by the optimal cutoff point of the TyG-BMI index

		Overall (*N* = 190)	low TyG-BMI index (*N* = 144)	high TyG-BMI index (*N* = 46)	*p* value
TyG-BMI index		216.000 ± 35.721	200.621 ± 23.490	264.142 ± 21.904	< 0.001
Age		72.521 ± 11.965	72.854 ± 12.144	71.478 ± 11.452	0.499
Gender (%)	Female	92 (48.42)	63 (43.75)	29 (63.04)	0.035
	Male	98 (51.58)	81 (56.25)	17 (36.96)	
LVEF, %		63.416 ± 14.076	63.236 ± 14.371	63.978 ± 13.247	0.757
BAV (%)	No	176 (92.63)	135 (93.75)	41 (89.13)	0.472
	Yes	14 (7.37)	9 (6.25)	5 (10.87)	
CHOL, mmol/L		4.370 ± 1.311	4.242 ± 1.222	4.770 ± 1.504	0.017
HDL-C, mmol/L		1.181 ± 0.718	1.225 ± 0.800	1.043 ± 0.327	0.135
Lp(a), mmol/L		370.255 ± 398.202	387.402 ± 412.838	313.357 ± 343.383	0.281
Smoking (%)	No	132 (69.47)	98 (68.06)	34 (73.91)	0.571
	Yes	58 (30.53)	46 (31.94)	12 (26.09)	
Drinking (%)	No	168 (88.42)	127 (88.19)	41 (89.13)	1.000
	Yes	22 (11.58)	17 (11.81)	5 (10.87)	
Hypertension (%)	No	48 (25.26)	38 (26.39)	10 (21.74)	0.662
	Yes	142 (74.74)	106 (73.61)	36 (78.26)	
Diabetes (%)	No	121 (63.68)	95 (65.97)	26 (56.52)	0.325
	Yes	69 (36.32)	49 (34.03)	20 (43.48)	
Stroke (%)	No	153 (80.53)	114 (79.17)	39 (84.78)	0.533
	Yes	37 (19.47)	30 (20.83)	7 (15.22)	
Antihypertension medication (%)	No	23 (12.11)	18 (12.50)	5 (10.87)	0.972
	Yes	167 (87.89)	126 (87.50)	41 (89.13)	
Hyperglycemic medication (%)	No	128 (67.37)	104 (72.22)	24 (52.17)	0.019
	Yes	62 (32.63)	40 (27.78)	22 (47.83)	
Lipid-lowering medication (%)	No	60 (31.58)	47 (32.64)	13 (28.26)	0.708
	Yes	130 (68.42)	97 (67.36)	33 (71.74)	

Data are shown as mean ± SD or n (%). Baseline characteristics of the 190 eligible patients from the ARISTOTLE study, stratified by the optimal cutoff point of triglyceride-glucose-body mass index index. TyG-BMI index, triglyceride-glucose-body mass index; LVEF, left ventricular ejection fraction; BAV, bicuspid aortic valve; CHOL, total cholesterol; HDL-C, high-density lipoprotein cholesterol. Antihypertensive medication include: angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), beta-blockers, calcium channel blockers (CCB), diuretics, alpha-blockers, and currently available combination formulations of the aforementioned medication. Hyperglycemic medication include: biguanides, sulfonylurea secretagogues, non-sulfonylurea secretagogues, alpha-glucosidase inhibitors, Thiazolidinediones, DPP-4 inhibitors, sodium-dependent glucose transporters 2 (SGLT-2) inhibitors, and insulin and its analogues. Lipid-lowering medication include: statins, fibrates, cholesterol absorption inhibitors, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, niacin, cholestyramine (bile acid sequestrants), omega-3 polyunsaturated fatty acids, and traditional Chinese medicine for lipid-lowering

Association between TyG-BMI index and traditional risk factors for cardiovascular events

and ≤ 65 years), smoking (yes or no), drinking (yes or no), hypertension (yes or no), diabetes (yes or no), stroke (yes or no), use of antihypertension medication (yes or no), use of hyperglycemic medication (yes or no) and use of lipid-lowering medication (yes or no) (Fig. 4). After adjusting for confounders in all subgroups, the influence of TyG-BMI index on the progression of aortic stenosis was consistent except for the lipid-lowering medication group, and there was no significant interaction between subgroups (all interactions $p > 0.05$). There was a significant interaction between the use of lipid-lowering medication ($p = 0.032$), and TyG-BMI index and the risk of progression were significantly higher in the untreated group (HR 5.48, 95%CI 1.8–16.74, $p = 0.003$), while the association between TyG-BMI index and the risk of progression of AS was not significant in the lipid-lowering drug group. These results suggest that TyG-BMI index is an important predictor of AS progression. This result highlights the importance of individualized treatment, namely, the need to give special consideration to the use of lipid-lowering medication in patients with high TyG-BMI index to reduce the risk of AS progression.

Discussion

Our study is the first to examine the association between TyG-BMI index and progression of non-severe AS. The main findings were that higher TyG-BMI index was significantly associated with non-severe AS progression. The risk of AS progression in the non-severe AS population with TyG-BMI index higher than 239 was 2.116 times that of the population with TyG-BMI index lower than 239.

TyG index is a reliable and readily available surrogate of IR [37]. A large number of studies have shown that TyG index is related to atherosclerotic heart disease. But in a Chinese valve cohort study, it was shown that after adjusting for potential confounding factors in patients with moderate and severe AS, for every 1 SD increase in

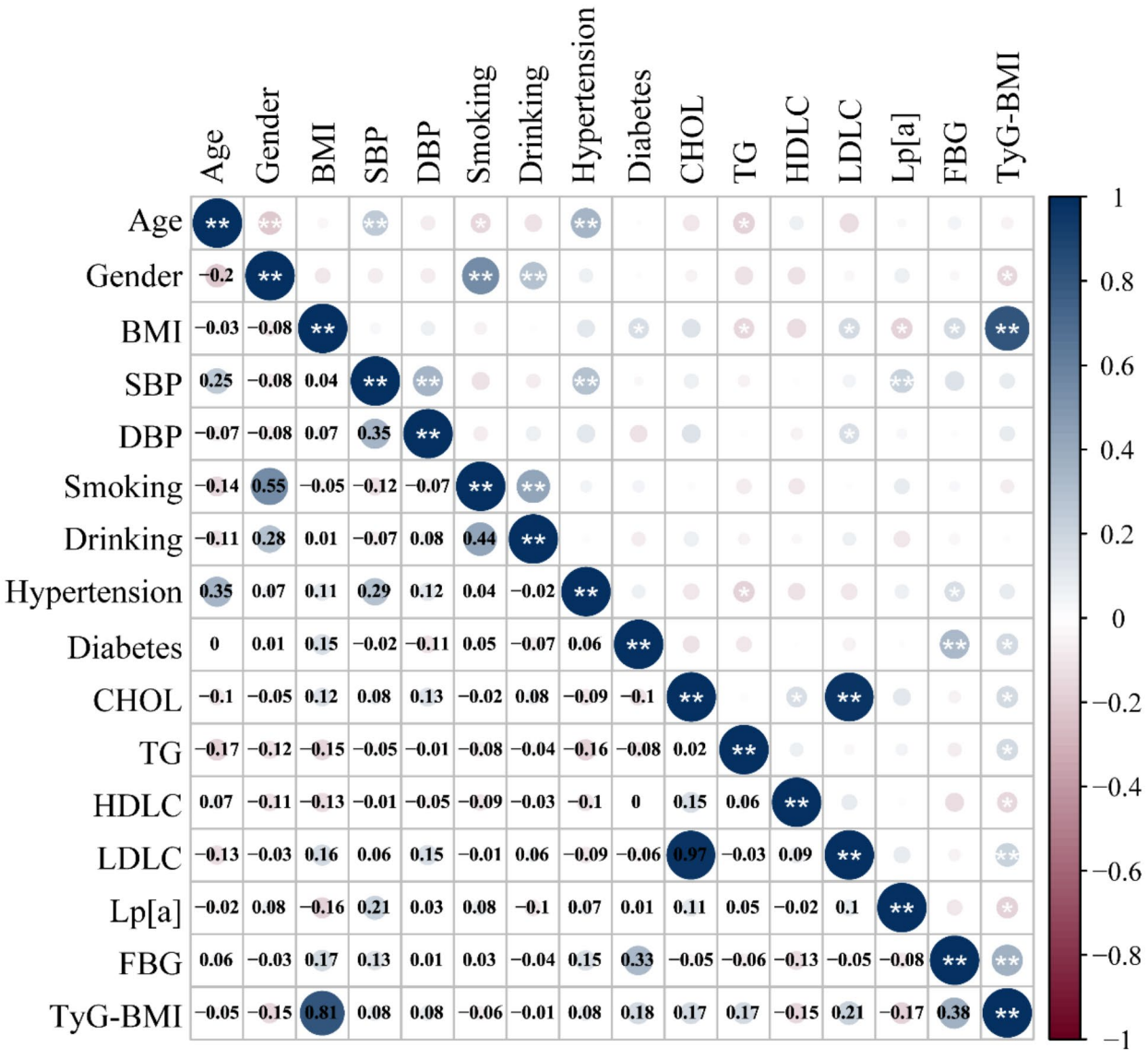


Fig. 2 Correlations between the TyG-BMI index and traditional cardiovascular risk factors. TyG-BMI index, triglyceride-glucose-body mass index; BMI, body mass index; FPG, fasting plasma glucose; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure

the TyG index, the risk of all-cause mortality increased by 62.2%, with an adjusted HR of 1.622 (95% CI = 1.086, 2.416) [38]. In addition, the association between obesity and valvular heart disease has been confirmed by many studies. BMI is a key indicator of obesity, and a large number of studies have shown that BMI is significantly positively correlated with the incidence of aortic stenosis, mortality, and prognosis after aortic valve replacement [39–41]. TyG-BMI index is the product of TyG and BMI, which is an emerging and more accurate surrogate indicator of IR in recent years and has been shown to be associated with a variety of diseases. TyG-BMI index was positively associated with the risk of stroke in middle-aged and elderly Chinese, with a nonlinear association (inflection point 174.63). When TyG-BMI index falls below 174.63, the risk of stroke can be significantly reduced [42]. TyG-BMI index is an independent predictor of new-onset diabetes, which is more obvious in young and middle-aged people and non-obese people [23]. In addition, compared with other traditional indicators, TyG-BMI index can better predict the risk of non-alcoholic fatty liver disease (AUC = 0.886, 95%CI:

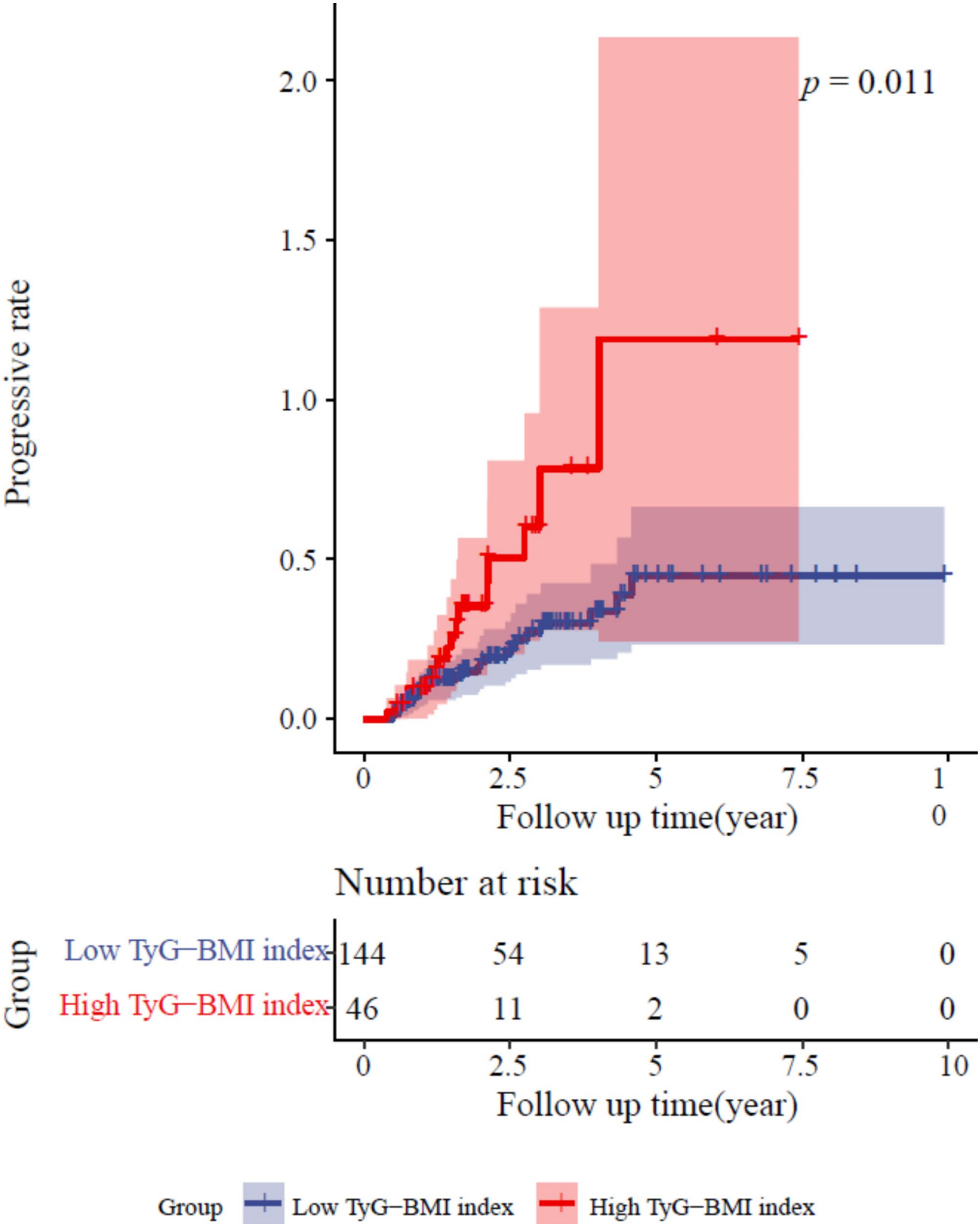


Fig. 3 Cumulative incidence of progression according to the optimal cutoff point of the TyG-BMI index

Table 2 Association between the TyG-BMI index and progression in the non-severe AS patients*

	low TyG-BMI index	high TyG-BMI index	*p* value
Case, n(%)	146(76.8%)	44(23.2%)	
Model 1, HR(95%CI)	Reference	2.192(1.178–4.080)	0.013
Model 2, HR(95%CI)	Reference	2.447(1.293–4.632)	0.006
Model 3, HR(95%CI)	Reference	2.231(1.147–4.341)	0.018
Model 4, HR(95%CI)	Reference	2.219(1.086–4.537)	0.029

*Cox regressions with Firth's penalized maximum likelihood method were used

Model 1 Unadjusted model

Model 2 Adjusted for age and gender

Model 3 Adjusted for model 1 + LV ejection fraction, bicuspid aortic valve, smoking, drinking, total cholesterol and high-density lipoprotein cholesterol

Model 4 Adjusted for model 2 + diabetes, hypertension, stroke, antihypertension medication, hyperglycemic medication and lipid-lowering medication

TyG-BMI index, triglyceride-glucose-body mass index; HR, hazard ratio; CI, confidence interval

0.8797–0.8927), and this correlation is nonlinear and positive [24]. TyG-BMI index was an independent risk factor for the prevalence of hypertension with a significance of 34% [43]. At the same time, TyG-BMI index is an important indicator to predict all-cause death in patients with heart failure, and people with low TyG-BMI index have a higher risk of death [44].

In this study, we demonstrated that higher TyG-BMI index was significantly associated with higher risk of AS progression after fully adjusting for potential confounders in patients with non-severe AS. In subgroup analyses, results were consistent except for the use of lipid-lowering medication. In previous studies, it has been found that lipid-lowering medication have not shown good efficacy in combating calcific aortic valve stenosis. Given the key role of lipid peroxidation and infiltration, HMG-CoA reductase inhibitors are the most promising targets. Early animal studies found that atorvastatin inhibits osteogenesis in the aortic valve by increasing the expression and activity of endothelial nitric oxide synthase [45, 46]. However, in numerous large randomized controlled trials, statins have not slowed the progression of AS [47, 48]. The AHA/ACC guidelines do not recommend the use of statin therapy to prevent the hemodynamic progression of AS. In a secondary analysis of the FOURIER trial, PCSK9 inhibitors may reduce the risk of development or progression of AS, but this was a post-hoc analysis involving a small number of events and requires further validation by dedicated large randomized controlled trials [49]. The use of other lipid-lowering treatments, including cholesteryl ester transfer protein (CETP) inhibitors and antisense oligonucleotides targeting apolipoprotein A and apolipoprotein B, in slowing or reversing AS has not yet been studied. In this result, it may be due to the short follow-up period, small sample size, and limited number of AS progression events. Further research with a larger sample size and longer follow-up time is needed to prove the reliability of our study results. In conclusion, TyG-BMI index was significantly associated with AS progression in patients with non-severe AS.

At present, the exact biological mechanism of IR and AS progression is not clear. Existing studies have found that IR not only affects the occurrence of aortic stenosis, but also participates in the progression of the disease [50]. Aortic valve stromal cells differentiate into myofibroblasts and osteoblasts, promoting valve calcification and osteogenic changes, and further aggravating valve stenosis [51]. Osteoblasts are one of the target cells of insulin, and the survival, proliferation and differentiation of osteoblasts are regulated by the insulin signaling receptor pathway [52]. Lack of insulin receptors increases the incidence of obesity and IR. IR is a disorganized biological response to insulin stimulation, which increases the level of oxidative stress by disrupting different molecular pathways in target tissues and affecting the body's glucose metabolism and lipid metabolism [53]. However, there is no research on the correlation mechanism between IR and progression of AS, and such correlation research is needed in the future.

At present, the exact mechanisms underlying the association between insulin resistance and lipoprotein(a) [Lp(a)] have not been fully elucidated. The concentration of Lp(a) is primarily influenced by genetic factors, accounting for more than 90% of its variation, but non-genetic factors may also play a role in regulating Lp(a) levels [1]. Analytical studies have shown that Lp(a) is negatively correlated with insulin resistance [2], a relationship that may be related to the structural characteristics of Lp(a). In individuals with higher levels of insulin or glucose, the molecular size of apolipoprotein(a) is significantly larger, and the size of apolipoprotein(a) is negatively correlated with plasma Lp(a) concentration [3, 4]. Furthermore, a large-scale cross-sectional study in China has indicated that low levels of Lp(a) are associated with an increased risk of prediabetes, insulin resistance, and hyperinsulinemia [5]. Therefore, it is logical that the TyG-BMI index, as an alternative indicator of insulin resistance, would be negatively correlated with Lp(a). Although Lp(a) has a significant correlation with the occurrence of aortic valve stenosis and calcification, and is considered a key risk factor in the development of calcific aortic valve disease, there is some contradiction in the research conclusions regarding its association with disease progression [6, 7]. It is noteworthy that in our study, although the TyG-BMI index is negatively correlated with Lp(a), the correlation coefficient is relatively

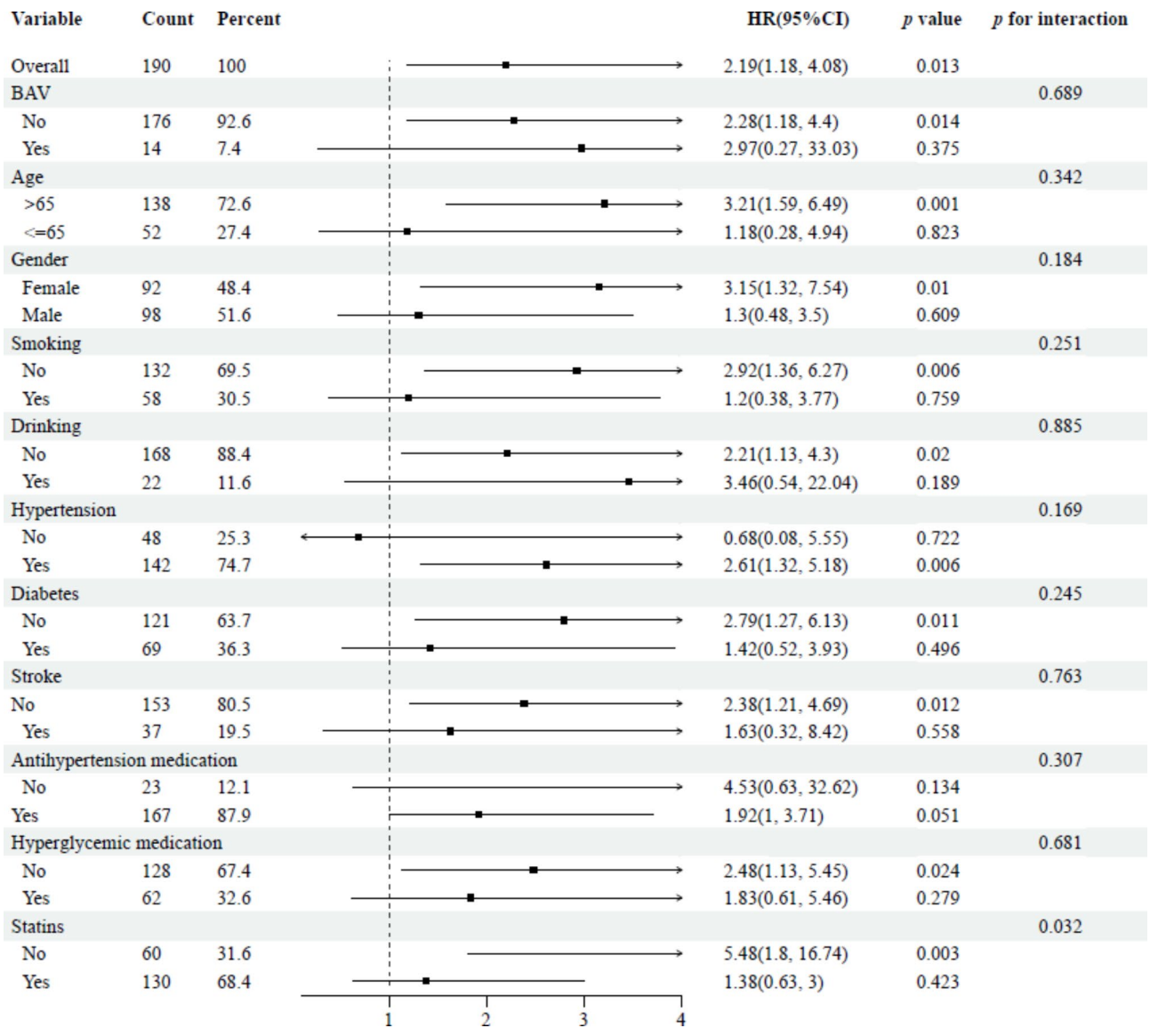


Fig. 4 Subgroup analysis of the association between baseline TyG-BMI index and progression of AS. HR, hazard ratios; CI, confidence interval; TyG-BMI index, triglyceride-glucose-body mass index; BAV, bicuspid aortic valve

small ($r = -0.17$), so caution should be exercised when interpreting the correlation between the two, especially in terms of their interaction with cardiovascular diseases. This also suggests that in clinical practice, the direct link between these two variables may not be very strong, or there may be more complex mechanisms of mutual influence.

The results of this study have important clinical significance. Progression of aortic stenosis is common, and once advanced to severity, aortic valve replacement is essential, mortality is greatly increased, and the economic burden on individuals and society is enormous. Early identification and control of progression is therefore key to reducing the rate of aortic valve replacement and mortality. We found that there was a significant relationship between TyG-BMI index and AS progression in the non-severe AS population. These results suggest that TyG-BMI index can be used as an effective tool for stratification and management of populations at high risk of progression. In addition, the comprehensive subgroup analysis in this study enhances confidence in the assessment of the association between TyG-BMI index and AS progression. This has certain guiding significance for the management of patients with non-severe AS in clinical practice. Based on the level of the TyG-BMI index, it can be determined whether patients need stricter monitoring and adjustment of treatment plans. At the same time, for patients with high TyG-BMI index, regular re-examination of the TyG-BMI index should be conducted to

promptly detect changes in health status and make corresponding interventions.

Our study has some limitations. First of all, although we performed multivariate adjustment in the cox regression models, the potential for residual or measured confounding bias remains. Second, our sample size is relatively small and the level of evidence is not high, which may lead to insufficient analysis capacity. In the future, we will continue to increase the sample size and add multicenter, ethnically diverse participants to improve the credibility of the analysis. Third, blood test data only on admission test data, there may be a measurement error caused by the deviation. Fourth, our study included only Chinese patients, and further validation is needed in other ethnic groups. Fifth, observational studies cannot assess the progression of the causal relationship between the TyG-BMI index and non-severe AS, and further basic and clinical research is needed to verify the reliability of our current results, and future longitudinal studies or potential interventional research could further strengthen the discussion on future directions. Sixth, the average age of the participants is 72 years old, and our conclusions may not be applicable to younger populations.

Conclusion

Our study is the first to report an association between higher TyG-BMI index and a higher risk of progression to non-severe AS. Our findings suggest that TyG-BMI index can be used as a predictor of the progression of aortic stenosis in patients with non-severe AS, providing more references for promoting clinical consultation and optimizing decisions on aortic stenosis prevention.

Abbreviations

TyG-BMI index	Triglyceride-glucose-body mass index
AS	Aortic stenosis
ARISTOTLE	Aortic valve diseases RISk facTOr assessmenT andprognosis modeL construction
IR	Insulin resistance
AVR	Aortic valve replacement
Vmax	Peak aortic jet velocity
MG	Mean aortic pressure gradient
AVA	Aortic valve area
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
FPG	Fasting plasma glucose
T2DM	Type 2 diabetes mellitus
CHOL	Total cholesterol
HDL-C	High-density lipoprotein and cholesterol
LVEF	Left ventricular ejection fraction
BAV	Bicuspid aortic valve
SD	Standard deviation
ROC	receiver operating characteristic
HR	Hazard ratio
95%CI	95% confidence
Lp[a]	Lipoprotein[a]

Supplementary Information

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Supplementary Material 1

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Author contributions
Xinxue Liao, Xiaodong Zhuang and Zhen Guo contributed to the conception or design of the work. All authors were responsible for the acquisition, analysis and interpretation of data. Xinxue Liao, Xiaodong Zhuang and Zhenyu Xiong drafted the manuscript. Critical revision of the manuscript for important intellectual content were performed by all authors. All authors agreed with the content of the article to be submitted.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Review Committee of the First Affiliated Hospital of Sun Yat-Sen University. Patient follow-up was conducted via telephone contact, with verbal informed consent approved by the institutional ethics committee.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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