Cardiovascular Diabetology

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Association between insulin resistance indices and outcomes in patients with heart failure with preserved ejection fraction

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Abstract

Background Insulin resistance (IR) plays a pivotal role in the interplay between metabolic disorders and heart failure with preserved ejection fraction (HFpEF). Various non-insulin-based indices emerge as reliable surrogate markers for assessing IR, including the triglyceride-glucose (TyG) index, the TyG index with body mass index (TyG-BMI), atherogenic index of plasma (AIP), and the metabolic score for insulin resistance (METS-IR). However, the ability of different IR indices to predict outcome in HFpEF patients has not been extensively explored.

Methods Patients having HFpEF were recruited from January 2012 and December 2023. The outcome was defined as major adverse cardiovascular event (MACE), encompassing all-cause mortality and rehospitalization for heart failure. The potential linear relationship was visualized by the restricted cubic spline (RCS) curve. Both univariable and multivariable Cox proportional hazards models were employed to examine the association between the IR indexes and MACE. Furthermore, to assess the incremental prognostic value of the TyG index, we conducted comprehensive analyses using area under the curve (AUC), the continuous net reclassification index (cNRI), and the integrated discrimination index (IDI).

Results A total of 8693 patients met the inclusion criteria and were included in the final analysis. The mean age of the patients was 70.59 ± 10.6 years, with 5045 (58.04%) being male. The Kaplan-Meier survival analysis revealed that higher degree of the four IR indexes was associated with higher risk of MACE (all log-rank $P < 0.05$). When treated as a continuous variable, the TyG index showed a significant association with MACE (HR 2.1, 95% CI 1.98–2.23, $P < 0.001$ in model 1; HR 1.81, 95% CI 1.73–1.9, $P < 0.001$ in model 2; HR 1.68, 95% CI 1.6–1.76, $P < 0.001$ in model 3). When categorized into quartiles, the highest quartile of the TyG index (Q4) was significantly associated with MACE (HR 2.48, 95% CI 2.24–2.76, $P < 0.001$ in model 3). Similar significant associations were found between TyG-BMI, AIP, METS-IR, and MACE. The TyG index was found to enhance the risk stratification capability of the MAGGIC score (AUC from 0.601 to 0.666). When compared to other IR indicators, the TyG index exhibited superior discrimination and reclassification abilities in predicting MACE. Additionally, the TyG-BMI index revealed a U-shaped correlation with MACE, indicating that both an elevated and a lower TyG-BMI index were associated with an increased risk.

Conclusion All four IR indices are independently associated with MACE in patients with HFpEF. Notably, these IR indices significantly enhance the predictive accuracy of the MAGGIC score, a widely used risk assessment tool in

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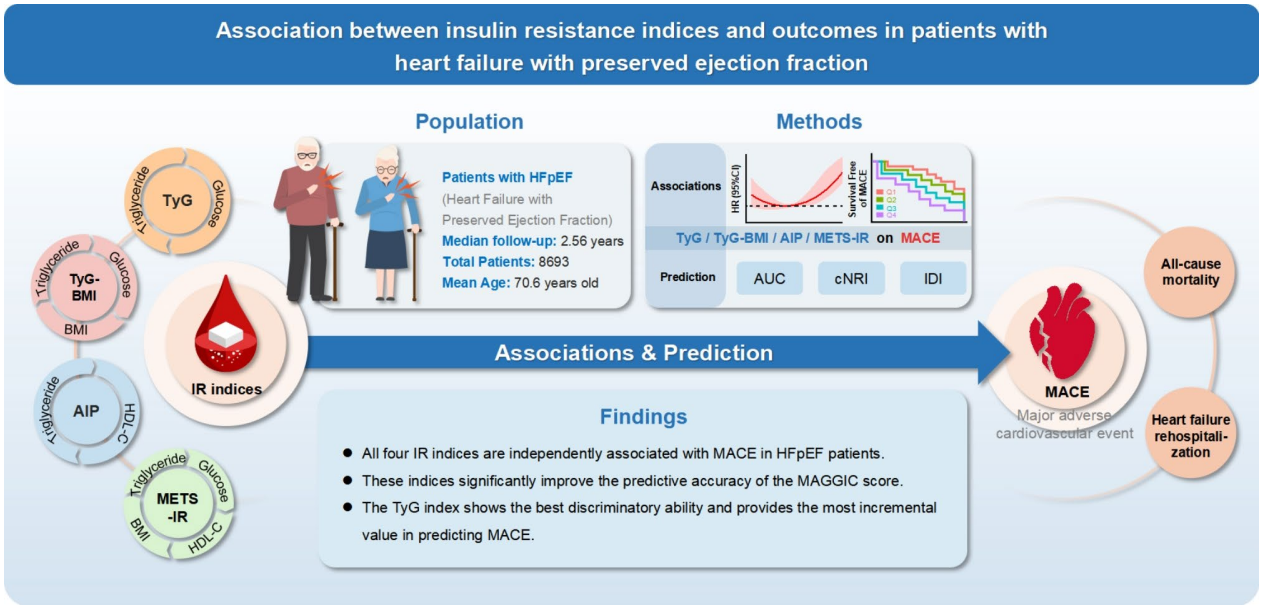
HFpEF. Among these indices, the TyG index demonstrated the highest discriminatory and reclassification abilities, providing the greatest incremental value in predicting MACE and exhibiting significant superiority compared to the other indices. These findings highlight the importance of assessing IR indices, particularly the TyG index, in the risk assessment and management strategies for HFpEF patients. However, it should be noted that our findings need to be validated in diverse populations to ensure their applicability and generalizability.

Graphical Abstract



Keywords Triglyceride-glucose index, Triglyceride-glucose with body mass index, Atherogenic index of plasma, The metabolic score for insulin resistance, Heart failure with preserved ejection fraction, Insulin resistance

Introduction

Heart failure with preserved ejection fraction (HFpEF) represents a highly prevalent, complex, and heterogeneous condition characterized by symptoms and signs of heart failure (HF) without overt left ventricular systolic dysfunction [1–2]. Despite a declining trend in the incidence of HF overall, the prevalence of HFpEF continues to rise, accounting for over half of newly diagnosed HF cases, with an incidence rate of approximately 27 cases per 10,000 person-years [3–5]. Given the limited therapeutic options for HFpEF and the substantial burden imposed by its high mortality and readmission rates on healthcare expenditures [6], it is paramount to identify high-risk patients based on modifiable clinical characteristics and intervene on these variables to mitigate their risks.

HFpEF frequently coexists with metabolic comorbidities, with over 80% of patients being overweight or obese [7], approximately 20-40% having diabetes, and more than 40% suffering from hyperlipidemia [8]. Evidence suggests that insulin resistance (IR) plays a pivotal role in the interplay between metabolic disorders and HFpEF [9, 10], significantly impacting cardiomyocyte function [10, 11]. IR refers to a decreased sensitivity and responsiveness to insulin [12]. Currently, several non-insulin-based indices are commonly used as surrogate markers for assessing IR. These include the triglyceride-glucose (TyG) index, the TyG index with body mass index (TyG-BMI), the atherogenic index of plasma (AIP), and the metabolic score for insulin resistance (METS-IR). The TyG index is derived from the calculation of fasting plasma glucose (FBG) and triglyceride (TG) levels. Optimal cut-off values for the TyG index have been reported as 8.72 for males and 8.92 for females [13, 14]. TyG-BMI is a comprehensive index that multiplies the TyG index by the BMI. This index aims to provide a more comprehensive assessment of an individual's insulin resistance status and obesity-related risks. Corresponding values for TyG-BMI have been reported as 224.59 for males and 234.02 for females [14]. The AIP is calculated as the logarithm base 10 of the ratio of TG to high-density lipoprotein cholesterol (HDL-C). The AIP is used to evaluate the relationship between lipid profiles and the risk of atherosclerosis. Although it does not directly measure IR, high levels of AIP are often associated with IR states. Values ranging from − 0.3 to 0.1 are associated with low cardiovascular

(CV) risk, 0.1 to 0.24 with medium CV risk, and above 0.24 with high CV risk [15]. METS-IR is a scoring system that integrates multiple metabolic parameters to quantify an individual's degree of insulin resistance. It includes indicators such as FBG, BMI, TG, and HDL-C. A score above 40.16 on the METS-IR has been reported to be linked to a significantly increased risk of diabetes [16]. It is important to note that there is currently no definitive range for normal values for these IR indices. The normal ranges can vary depending on the study population and outcomes of interest. Therefore, the thresholds mentioned above should be considered as reference values rather than absolute boundaries. Studies have demonstrated that elevations in these indices are closely associated with increased risks of all-cause mortality and adverse cardiovascular events in various cardiovascular disease [17, 18]. However, the ability of different IR indices to predict all-cause mortality and HF hospitalization in HFpEF patients has not been extensively explored, and a head-to-head comparison of their predictive value for clinical outcomes in HFpEF is lacking.

Therefore, this longitudinal cohort study aims to investigate and compare the predictive performance of four IR indices—TyG, TyG-BMI, AIP, and METS-IR—for long-term outcome in the HFpEF population. Additionally, we examine the incremental effect of these indices on the existing risk prediction tool, the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score [19].

Methods

Study design

This retrospective cohort study encompassed patients diagnosed with HFpEF who were hospitalized in the Department of Cardiology, The First Affiliated Hospital of Wenzhou Medical University, between January 2012 and December 2023. Exclusion criteria were as follows: (1) lack of crucial data essential for the calculation of IR indices, such as FBG, TG, BMI, and HDL-C; (2) age below 18 years or above 90 years; (3) loss of follow-up.

Baseline data for all participants were retrospectively collected through the electronic medical record system, encompassing medical history, demographic characteristics, laboratory findings, echocardiographic data, and medication profiles. This study adhered to the principles outlined in the Declaration of Helsinki and obtained approval from the Ethics Committee of The First Affiliated Hospital of Wenzhou Medical University (Number: ky-20240483). Given the retrospective nature of the study, informed consent was waived.

Echocardiographic data were obtained from comprehensive echocardiographic reports generated using two-dimensional and targeted M-mode echocardiography, augmented by Doppler color flow mapping. Our institution employed the Phillip EPIQ7C system (Philips Ultrasound, Bothell, WA, USA), the Hitachi Aloka Prosound F75 system, and the UST-52,105 probe operating within a frequency range of 1.0–5.0 MHz. These echocardiographic assessments were conducted as part of routine clinical practice by skilled sonographers and subsequently reviewed by expert echocardiologists, adhering to established professional guidelines. The left ventricular ejection fraction (LVEF) is calculated via biplane modified Simpson's method in the apical four- and two-chamber view. The left ventricular end-diastolic diameter (LVEDD), interventricular septal end-diastolic thickness (IVSTd), and left ventricular posterior wall end-diastolic thickness (LVPWTd) was measured using parasternal long-axis views. The left atrial diameter (LAD) was measured via apical 4-chamber views at the end of systole. Measure the left atrial volume (LAV) using the biplane Simpson's method at end-systole. Doppler echocardiographyis plays the spectral pattern of mitral annular motion on both the lateral wall and septal side of the LV, allowing for the measurement of e' on both the septal and lateral sides. The average of these two measurements is taken as AS-L e'. Pulsed-wave Doppler is then used to display the blood flow spectrum at the mitral valve orifice, from which the E wave peak is measured. This results in the mean E/e' ratio. The echocardiographic indices were derived using the following formulas: Left ventricular mass index (LVMI, g/m^2) $=[0.80 \times 1.04 \times [(IVSTd + LVEDD + LVPWTd)^3 - LVEDD^3] + 0.6]$/body surface area (BSA); Left atrial volume index (LAVI) (mL/m^2) = LAV/BSA; Relative wall thickness (RWT) = 2×[LVPWTd/LVEDD].

Definitions and follow-up

The diagnostic criteria for HFpEF, as per the 2021 ESC guideline, entailed a LVEF of 50% or greater, accompanied by symptoms and signs of HF, along with the presence of at least one of the following conditions: cardiac structural abnormalities, left ventricular diastolic dysfunction (LVDD), or evidence of filling pressure (including elevated natriuretic peptide level and pulmonary arterial systolic pressure > 35mmHg [tricuspid regurgitation velocity > 2.8 m/s]) without competing diagnoses [20]. The cardiac structural abnormalities including LAVI > 34 mL/m^2 (> 40 ml/m^2 in the presence of atrial fibrillation), a LVMI ≥ 115 g/m^2 for males and ≥ 95 g/m^2 for females, and a RWT > 0.42 [20]. LVDD is defined as three of the four or all the four criterion (mean E/e' >14, septal e'<7 cm/s or lateral e'<10 cm/s, tricuspid regurgitant velocity > 2.8 m/s, LAVI > 34 mL/m^2).

The TyG index was calculated using the formula: Ln[TG (mg/dL) × FBG (mg/dL) / 2] [13]. The TyG-BMI was derived by multiplying the TyG index by the BMI [14]. The AIP was computed as log10 [TG (mg/dL) /

HDL-C (mg/dL)] [15]. The METS-IR score was calculated as Ln[2 × FBG (mg/dL) + TG (mg/dL)] × BMI / Ln HDL-C (mg/dL) [16].

The outcome was defined as major adverse cardiovascular event (MACE), compassing all-cause mortality and re-hospitalization due to HF. Follow-up data were obtained through the electronic medical record system and via telephone interviews. Follow-up commenced from the date of admission and concluded upon the patient's death. For patients without any event, the last recorded medical encounter or telephone interview date served as the censoring value.

Statistical analysis

For continuous variables, data are presented as mean ± standard deviation (SD) or median and interquartile range (IQR). Categorical variables are expressed as number (%). For comparisons between groups, Student's t-test is employed for normally distributed continuous variables, Mann-Whitney U test for non-normally distributed continuous variables, and Chi-square test for categorical variables.

Kaplan-Meier (K-M) survival analysis is utilized to compare the differences in event-free survival between different groups. Multivariable Cox proportional hazards model is constructed to evaluate the impact of different levels of IR indices on MACE. Covariates included in the model are determined based on clinical relevance or a p-value < 0.05 in univariate Cox analysis. Restricted cubic spline (RCS) analysis is performed to explore potential nonlinear relationships between IR indices and outcome events, with 5 knots placed at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles.

Area under the curve (AUC), continuous net reclassification improvement (cNRI), and integrated discrimination improvement (IDI) are calculated to assess and compare the predictive abilities of the four IR indices, in combination with the MAGGIC risk score, for MACE.

All reported p-values are two-sided, with $p < 0.05$ considered statistically significant. All statistical analyses and computations are performed using SPSS version 25.0 (IBM Corporation, Armonk, NY, USA) and R version 4.2.2.

Results

Baseline characteristics

Figure 1 presents a flowchart illustrating the patient selection and exclusion process, ultimately including 8693 patients in the study analysis. At baseline, the mean age was 70.59 ± 10.6 years, with 5045 patients (58.04%)

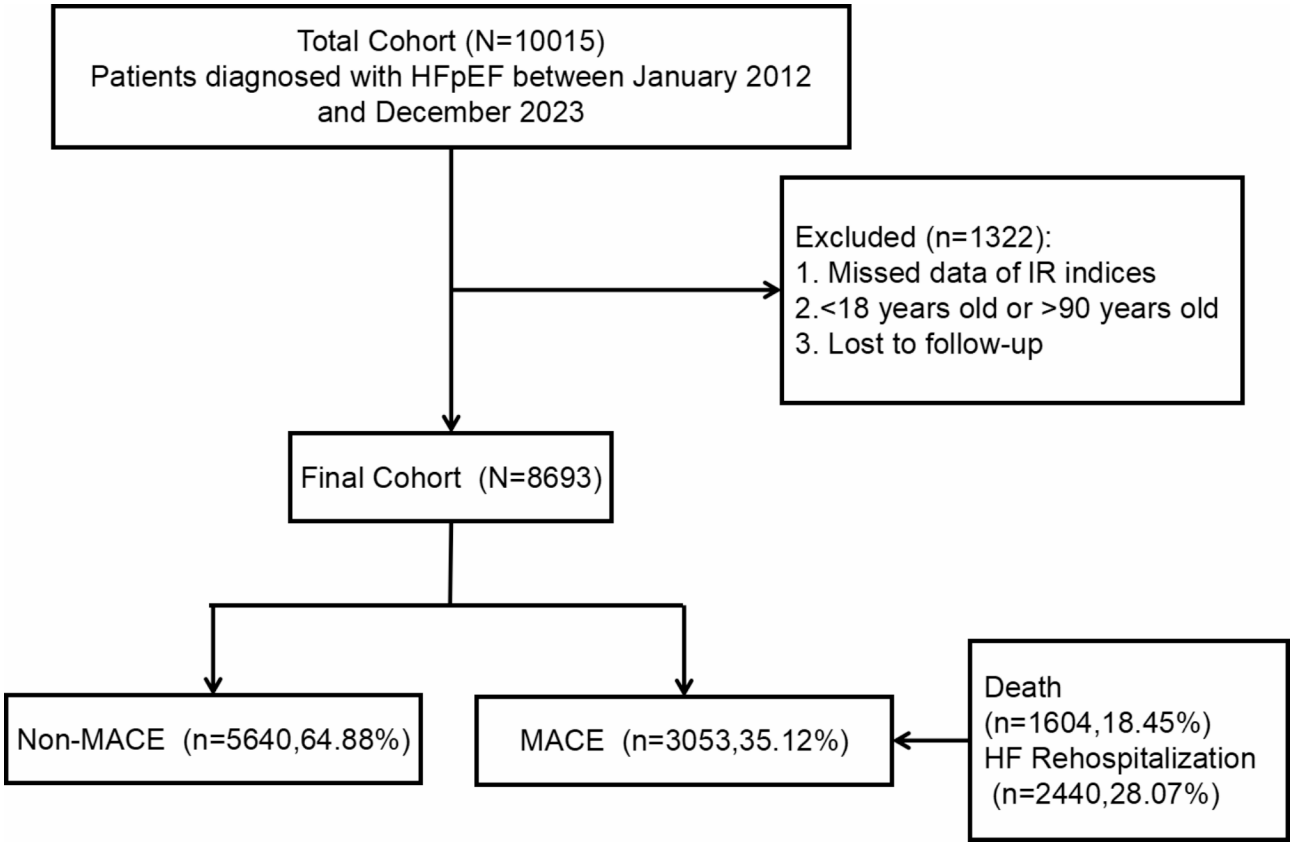


Fig. 1 Flowchart of the study design. HFpEF, heart failure with preserved ejection fraction. IR, insulin resistance

being male. Based on outcomes, patients were classified into the MACE group (3053, 35.12%) and the non-MACE group (5640, 64.88%). Comparisons between the two groups revealed that the MACE group was older, more likely to be male, had more comorbidities, and significantly lower proportions of patients receiving pharmacological therapy. Additionally, compared to the non-MACE group, the MACE group had higher levels of N-terminal pro-Brain Natriuretic Peptide (NT-proBNP), HDL-C, Left Ventricular End-Systolic Diameter (LVESD), Left Ventricular End-Diastolic Diameter (LVEDD), Left Atrium (LA), pulmonary arterial pressure, and MAGGIC scores. The MACE group also exhibited significantly lower Systolic Blood Pressure (SBP), TG, and LVEF. Table 1 provides a detailed comparison between the MACE and non-MACE groups.

TyG index and risk of MACE

During a median follow-up period of 2.56 years (IQR: 0.81–5.46), 3053 (35.12%) MACE events were recorded. As shown in Fig. 2A, K-M survival analysis revealed that patients with a high TyG index had a significantly higher incidence of MACE compared to those with a low TyG index (log-rank $P < 0.0001$). RCS analysis (Fig. 3A) demonstrated a J-shaped association between the TyG index and the risk of MACE (P for nonlinear = 0.042).

As presented in Table 2, when the TyG index was treated as a continuous variable, Cox proportional hazards analysis showed a significant association between the TyG index and MACE events (model 1: HR 2.1, 95% CI 1.98–2.23, $P < 0.001$; model 2: HR 1.81, 95% CI 1.73–1.9, $P < 0.001$; model 3: HR 1.68, 95% CI 1.6–1.76, $P < 0.001$). When the TyG index was categorized into quartiles, Cox proportional hazards analysis found that even after full adjustment, the highest quartile of the TyG index (Q4) was significantly associated with MACE (HR 2.48, 95% CI 2.24–2.76, $P < 0.001$). In subgroup analysis (Fig. 4A), the association between the TyG index and MACE was present across subgroups defined by age (65 years), sex, BMI (25 kg/m²), hyperlipidemia, diabetes, chronic kidney disease (CKD), and LVEF (65%). Significant interactions were observed for age (p for interaction < 0.001) and BMI (P for interaction = 0.003) subgroups.

TyG-BMI and risk of MACE

The KM survival curve showed that patients in the fourth quartile of the TyG-BMI had the highest rate of MACE (log-rank $P < 0.0001$, Fig. 2B). Figure 3B revealed a U-shaped association between TyG-BMI and MACE through RCS analysis (P for nonlinear < 0.001).

The fully adjusted Cox analysis revealed that for every one-point increment in the TyG-BMI index, there was a 0.3% elevation in the risk of MACE (HR 1.003, 95% CI 1.002–1.004). Simultaneously, patients exhibiting the highest level of TyG-BMI, in contrast to those with the lowest level, confront an elevated risk of MACE by 30% (HR 1.3, 95% CI 1.18–1.43) (Table 2). The subgroup analysis (Fig. 4B) showed that as a continuous variable, TyG-BMI had significant interactions with the subgroups of age, BMI, diabetes, CKD, and pulmonary hypertension (all p for interaction < 0.05). Consistent association between TyG-BMI and MACE was observed in the subgroups of gender, hyperlipidemia, LVEF, and increased LA size.

AIP and risk of MACE

The survival curves stratified by quartiles of AIP, as shown in Fig. 2C, indicate that the incidence of MACE events increases with higher levels of AIP (log-rank $P < 0.0001$). Further RCS analysis suggests a linear relationship between AIP and MACE (p for nonlinear = 0.358, Fig. 3C).

Furthermore, Cox analysis revealed that when compared to the fully adjusted HR (model 3) of MACE in the first quarter, individuals in the second, third, and forth quarters of the AIP exhibited significantly higher HRs of 1.2 (95% CI: 1.07–1.34), 1.4 (95% CI: 1.26–1.56), and 1.78 (95% CI: 1.61–1.97) respectively. Similarly, when considered as a continuous variable, every one-point increase in the AIP was associated with a 133% heightened risk of MACE (95CI%: 2.05–2.64, Table 2). The subsequent subgroup analysis revealed that the association between AIP and MACE was consistent across the subgroups of gender, BMI, hyperlipidemia, CKD, and LVEF, but there were interactions in the subgroups of age and diabetes (Fig. 4C).

METS-IR and risk of MACE

METS-IR demonstrates a significant association with the incidence of MACE. As illustrated in Fig. 2D, the K-M survival curves show a clear trend of increasing MACE event rates with elevated METSIR levels (log-rank $P < 0.0001$). Further analysis using the RCS curve (Fig. 3D) reveals a J-shaped relationship between METS-IR and MACE, with statistical significance for nonlinearity (p for nonlinear < 0.001).

When considered as a continuous variable, each incremental unit in METS-IR is associated with a 3% heightened risk of MACE (HR: 1.03; 95% CI: 1.02–1.03) in model 3. Additionally, when METSIR is categorized into quartiles, individuals in the third quartile (Q3) and fourth quartile (Q4) exhibit significantly higher hazards ratios for MACE compared to those in the lowest quartile. Specifically, the HRs (model 3) for MACE are 1.15 (95% CI: 1.03–1.28) for Q3 and 1.60 (95% CI: 1.45–1.77) for Q4. Subsequent subgroup analyses reveal that the association between METS-IR and MACE is consistent across various subgroups, including gender, BMI, hyperlipidemia,

Table 1 Baseline characteristics of the study cohort according to MACE

Variables	Overall (*N* = 8693)	Non-MACE (*n* = 5640)	MACE (*n* = 3053)	*P* value
Baseline characteristics				
Age(years)	70.59 ± 10.6	69.6 ± 10.93	72.41 ± 9.68	< 0.001
Male, n (%)	5045 (58.04%)	3190 (56.56%)	1855 (60.76%)	< 0.001
BMI(kg/m2)	24.38 ± 3.6	24.42 ± 3.56	24.31 ± 3.66	0.153
SBP(mmHg)	137.83 ± 23.45	137.68 ± 22.98	138.13 ± 24.29	0.4
DBP(mmHg)	75.3 ± 13.28	75.78 ± 13.26	74.4 ± 13.27	< 0.001
Current smoker, n (%)	2735 (31.55%)	1778 (31.59%)	957 (31.48%)	0.915
MAGGIC score	18 (13,22)	17 (13,21)	20 (15,24)	< 0.001
Comorbidities, n (%)				
Hyperlipidemia	3911 (44.99%)	2642 (46.84%)	1269 (41.57%)	< 0.001
Diabetes	4040 (46.47%)	2549 (45.2%)	1491 (48.84%)	0.001
Hypertension	6060 (69.71%)	3850 (68.26%)	2210 (72.39%)	< 0.001
Coronary artery disease	4609 (53.02%)	2857 (50.66%)	1752 (57.39%)	< 0.001
Atrial fibrillation	2580 (29.68%)	1473 (26.12%)	1107 (36.26%)	< 0.001
CKD	2299 (26.45%)	1252 (22.2%)	1047 (34.29%)	< 0.001
Medications, n (%)				
ACEI/ARB/ARNI	5842(67.2%)	3963(70.27%)	1879(61.54%)	< 0.001
Beta-blocker	5742 (68.1%)	3977(70.52%)	1943 (63.63%)	< 0.001
MRA	3999(46%)	2946 (52.23%)	1053(34.49%)	< 0.001
SGLT2i	606 (6.97%)	379 (6.72%)	227 (7.44%)	0.211
Loop diuretics	4000 (46.01%)	2215 (39.27%)	1785 (58.47%)	< 0.001
Laboratory data				
Total cholesterol, mmol/L	4.52 ± 1.27	4.52 ± 1.29	4.52 ± 1.25	0.892
Low-density lipoprotein cholesterol, mmol/L	2.61 ± 0.96	2.62 ± 0.97	2.6 ± 0.95	0.555
High-density lipoprotein cholesterol, mmol/L	1.09 ± 0.29	1.09 ± 0.29	1.1 ± 0.29	0.015
Triglycerides, mmol/L	1.56 ± 1.05	1.48 ± 1	1.61 ± 1.08	< 0.001
N-terminal pro-B-type natriuretic peptide, pg/mL	850 (313,2050.5)	721 (286,1617.5)	1245 (428.25,3361.75)	< 0.001
Fasting plasma glucose, mmol/L	7.61 ± 4.04	7.58 ± 4.02	7.66 ± 4.08	0.393
High-sensitivity cardiac troponin,μg/L	0.03 (0.01,0.62)	0.02 (0.01,0.52)	0.04 (0.01,0.77)	0.884
Glycated haemoglobin,%	5.80 (5.30, 6.80)	5.70 (5.30, 6.60)	5.90 (5.40, 7.00)	< 0.001
Echocardiography				
LVEF,%	64.03 ± 7.91	64.7 ± 7.35	62.79 ± 8.72	< 0.001
LVESD, mm	31.66 ± 5.52	31.28 ± 5.11	32.36 ± 6.15	< 0.001
LVEDD, mm	49.18 ± 6.2	48.96 ± 5.91	49.58 ± 6.68	< 0.001
Pulmonary arterial systolic pressure, mmHg	33.55 ± 10.58	32.69 ± 9.92	35.17 ± 11.52	< 0.001
Left atrial diameter, mm	44.55 ± 6.87	43.89 ± 6.55	45.79 ± 7.28	< 0.001
IVSTd, mm	11.03 ± 2.33	10.92 ± 2.26	11.25 ± 2.45	< 0.001
LVPWTd, mm	10.53 ± 1.37	10.47 ± 1.37	10.64 ± 1.38	< 0.001
LVMI, g/m^2	121.44 ± 33.31	118.99 ± 31.67	126.02 ± 35.74	< 0.001
RWT	0.43 ± 0.08	0.43 ± 0.07	0.43 ± 0.08	0.140
LAVI, ml/m^2	35.97 ± 9.79	35.01 ± 9.15	37.75 ± 10.66	< 0.001
Mean E/e'	13.82 ± 4.97	13.69 ± 4.82	14.16 ± 5.34	< 0.001
IR indexes				
TyG index	8.72 (8.31, 9.21)	8.61 (8.23, 9.06)	8.94 (8.46, 9.48)	< 0.001
TyG-BMI	212.93 (187.95, 239.61)	211.06 (186.44, 235.58)	217.08 (191.09, 246.23)	< 0.001
AIP	0.48 (0.30, 0.67)	0.45 (0.28, 0.63)	0.54 (0.35, 0.74)	< 0.001
METS-IR	38.78 (33.83, 44.08)	38.07 (33.38, 43.08)	40.28 (34.94, 46.06)	< 0.001

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CKD, chronic kidney disease; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor II blocker—neprilysin inhibitor; MRA, aldosterone receptor antagonist; SGLT2i, sodium-glucose cotransporter-2 inhibitors; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVEDD, left ventricular end-diastolic dimension; IVSTd, interventricular septal end-diastolic thickness; LVPWTd, left ventricular posterior wall end-diastolic thickness; LVMI, left ventricular mass index; RWT, relative wall thickness; LAVI, left atrial volume index; IR, insulin resistance; TyG, triglyceride-glucose; TyG-BMI, triglyceride-glucose index with body mass index; AIP, atherogenic index of plasma; METS-IR, metabolic score for insulin resistance

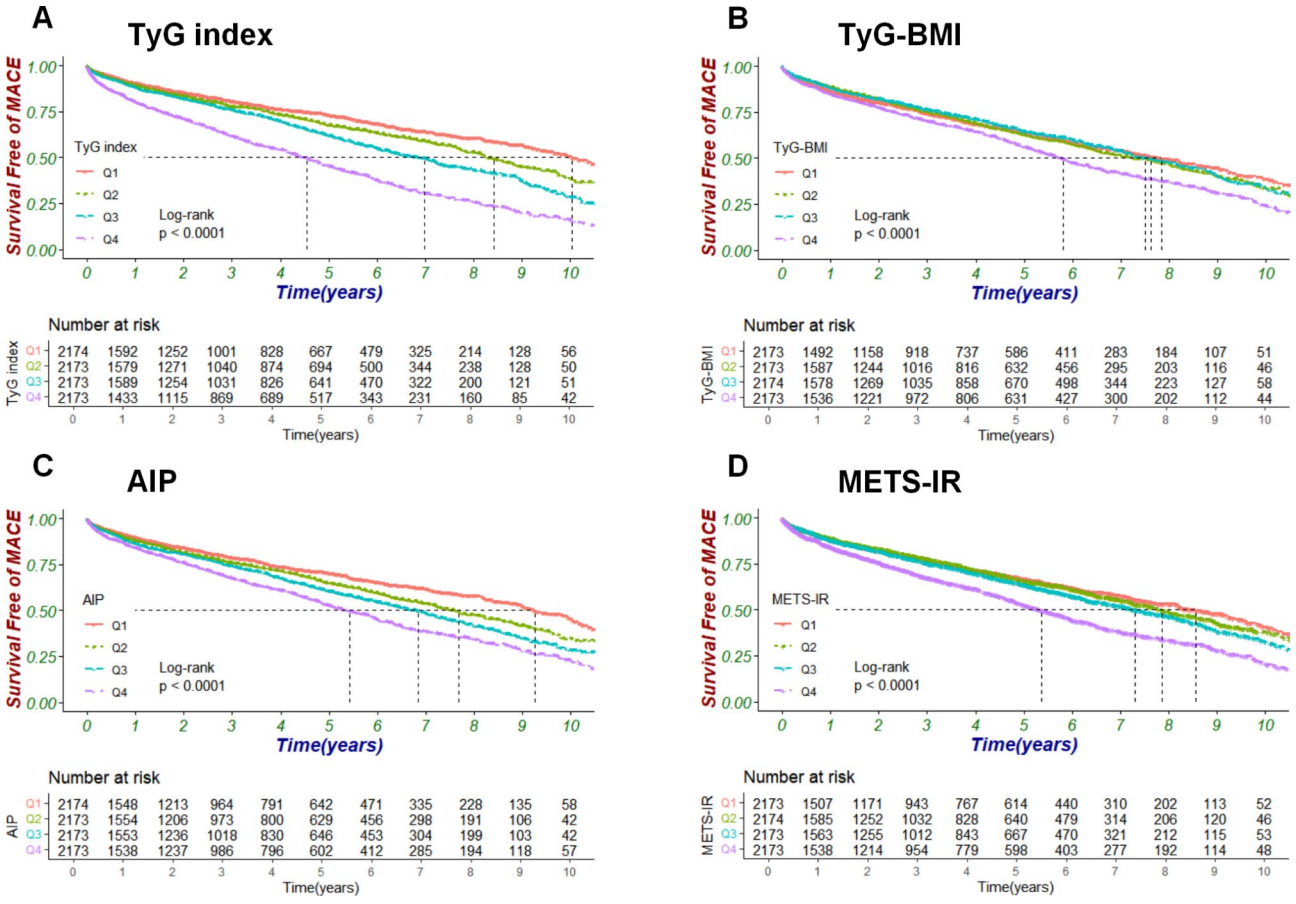


Fig. 2 Kaplan-Meier curves by the category of the IR indexes. TyG index (**A**), TyG-BMI (**B**), AIP (**C**), METS-IR (**D**). IR, insulin resistance; TyG, triglyceride-glucose; TyG-BMI, triglyceride-glucose index with body mass index; AIP, atherogenic index of plasma; METS-IR, metabolic score for insulin resistance

CKD, and LVEF (Fig. 4D). However, interactions are observed in the subgroups of age and diabetes, suggesting that the relationship between METS-IR and MACE may differ in these specific populations.

Comparative analysis of the IR indexes for predicting MACE

Table 3 compares four IR indexes: TyG, TyG-BMI, AIP, and METS-IR, in terms of their discrimination ability for MACE. The AUC (95%CI) values for TyG, TyG-BMI, AIP, and METS-IR are 0.631 (0.619–0.643), 0.549 (0.537–0.562), 0.594 (0.581–0.607), and 0.581 (0.568–0.593) respectively. All IR indexes, although significant, still had weak discrimination ability for MACE (AUCs 0.549 to 0.631). When comparing TyG with the other three indices, TyG shows statistically significant differences in AUC with p-values less than 0.001 for all comparisons. This suggests that TyG performs better than TyG-BMI, AIP, and METS-IR in discriminating the outcome. Additionally, based on the comparison of the AUC values, it appears that TyG-BMI, when compared to AIP and METS-IR, exhibits inferior performance (all $p < 0.001$).

In terms of both categorical Net Reclassification Improvement (cNRI) and Integrated Discrimination Improvement (IDI), TyG demonstrates notable superiority over other indices, with all p-values < 0.001. This underscores its enhanced capacity to reassign individuals into more precise risk categories and to clearly differentiate between those with and without MACE. When TyG-BMI is compared to AIP and METS-IR, a decrease of 1.3% in IDI and a cNRI value of -0.151 are observed, respectively, both with p-values < 0.001. These findings imply that TyG-BMI may be a less effective predictor compared to the aforementioned indices.

Supplementary Fig. 1 illustrates the correlations between the IR index and Age, NYHA class, and Statin treatment. Age exhibits a significant positive correlation with TyG and AIP ($r = 0.11$ and 0.04, respectively, both $p < 0.01$), a significant negative correlation with TyG-BMI (r = -0.03, $p < 0.05$), and no correlation with METS-IR ($p > 0.05$). The NYHA class demonstrates a significant positive correlation with all four IR indices (TyG: $r = 0.1$; TyG-BMI: $r = 0.06$; AIP: $r = 0.06$; METS-IR: $r = 0.06$, all $p < 0.01$). Statin treatment is not significantly correlated with any of the four IR indices (all $p > 0.05$).

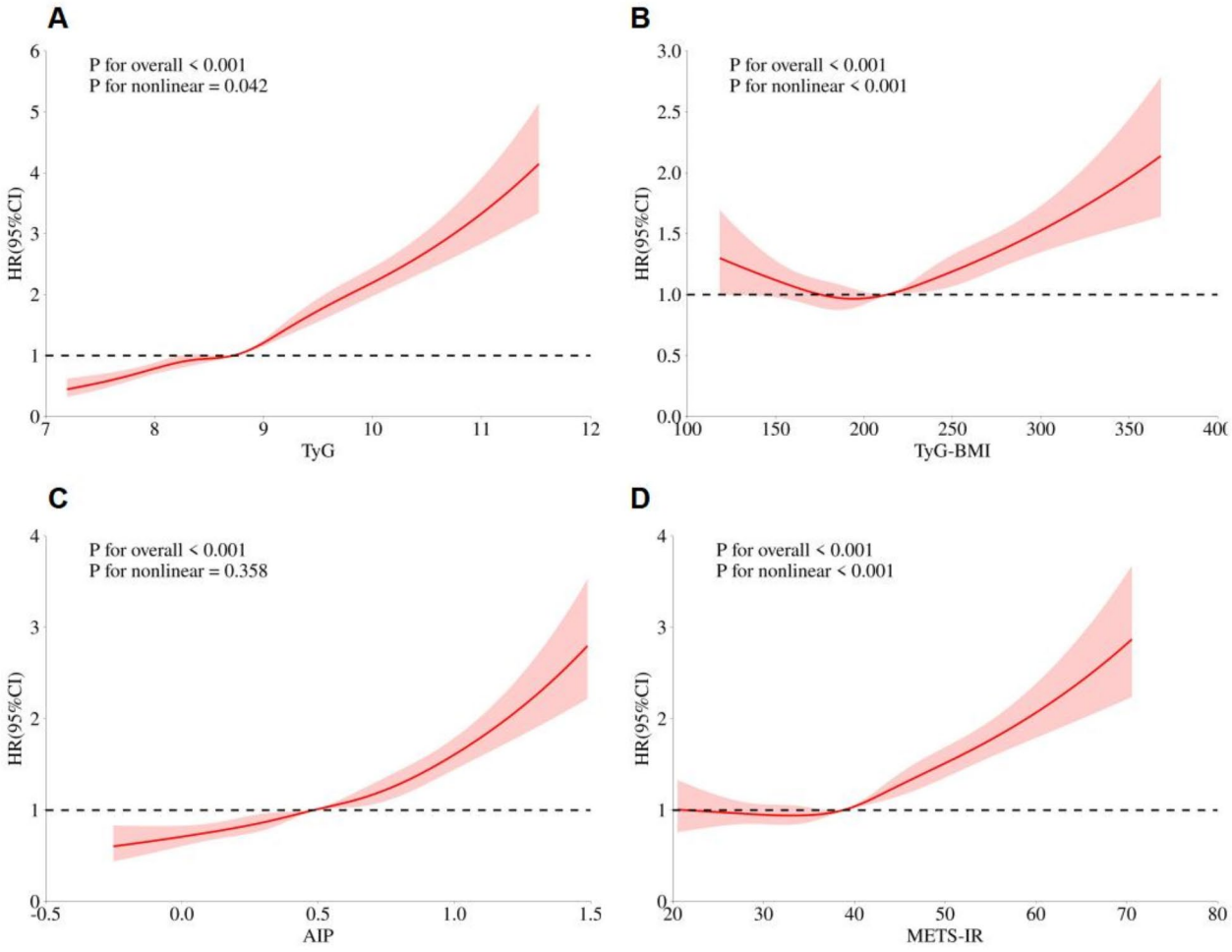


Fig. 3 RCS for the associations between the IR indexes and MACE. Red shadows and lines represent the 95% CI. TyG index (**A**), TyG-BMI (**B**), AIP (**C**), METS-IR (**D**). HR (95%CI) was adjusted according to the model 3. RCS, restricted cubic spline; IR, insulin resistance; MACE, major adverse cardiovascular event; HR, hazard ratio; CI, confidence interval; TyG, triglyceride-glucose; TyG-BMI, triglyceride-glucose index with body mass index; AIP, atherogenic index of plasma; METS-IR, metabolic score for insulin resistance

Incremental value of IR indexes for predicting MACE

Table 4 demonstrates that all four IR indices provide significant incremental prognostic value to the MAGGIC score for predicting future MACE risk. Among them, the TyG index offers the highest incremental value, with an increase in the AUC from 0.601 to 0.666, an IDI of 0.046, and a cNRI of 0.167, all of which are statistically significant at $P < 0.001$. In contrast, the TyG-BMI provides a lower incremental value, with an AUC increase from 0.601 to 0.621, an IDI of 0.02, and a cNRI of 0.099, all of which are also statistically significant at $P < 0.001$.

Sensitivity analysis

After excluding patients with NT-proBNP levels exceeding the upper limit of the reference range, this study compared the ability of different IR indices to predict MACE and their additional effects on the MAGGIC score among patients with near normal/normal NT-proBNP levels ($n = 1682$). Supplementary Table 1 shows that the AUC (95%CI) values for TyG, TyG-BMI, AIP, and METS-IR are 0.601 (0.57–0.632), 0.522 (0.490–0.555), 0.582 (0.550–0.614), and 0.544 (0.512–0.575), respectively. When compared with other IR indices, TyG demonstrated superior discriminatory and reclassification capabilities. Supplementary Table 2 reveals that the TyG index offers the highest incremental value, with an increase in the AUC from 0.599 to 0.653, an IDI of 0.036, and a cNRI of 0.133, all of which are statistically significant at $P < 0.001$.

After excluding patients with elevated HDL levels, the study compared the ability of different IR indices to predict MACE among the remaining patients ($n = 7621$). Supplementary Table 3 shows that the AUC (95%CI) values for TyG, TyG-BMI, AIP, and METS-IR are 0.629 (0.616–0.642), 0.550 (0.536–0.563), 0.595 (0.581–0.608), and 0.584 (0.571–0.598), respectively. In terms of discriminatory power and reclassification ability, the TyG

Table 2 Association between IR index and MACE (Cox regression)

	Model 1		Model 2		Model 3	
	HR [95% CI]	***P***	**HR [95% CI]**	***P***	**HR [95% CI]**	***P***
TyG (continuous)	2.1[1.98,2.23]	< 0.001	1.81[1.73,1.90]	< 0.001	1.68[1.60,1.76]	< 0.001
Q1	Ref		Ref		Ref	
Q2	1.42[1.26,1.6]	< 0.001	1.29[1.15,1.45]	< 0.001	1.2[1.07,1.35]	0.002
Q3	2.03[1.81,2.28]	< 0.001	1.68[1.5,1.87]	< 0.001	1.51[1.35,1.69]	< 0.001
Q4	3.77[3.34,4.26]	< 0.001	2.86[2.58,3.18]	< 0.001	2.48[2.24,2.76]	< 0.001
TyG-BMI (continuous)	1.003[1.002,1.004]	< 0.001	1.004[1.003,1.005]	< 0.001	1.003[1.002,1.004]	< 0.001
Q1	Ref		Ref		Ref	
Q2	1.05[0.94,1.16]	0.417	1.06[0.96,1.18]	0.257	1.01[0.91,1.12]	0.888
Q3	1.09[0.98,1.21]	0.131	1.06[0.96,1.18]	0.268	0.98[0.88,1.09]	0.688
Q4	1.37[1.23,1.53]	< 0.001	1.46[1.32,1.61]	< 0.001	1.3[1.18,1.43]	< 0.001
AIP (continuous)	3.704[3.194,4.295]	< 0.001	2.78[2.45,3.16]	< 0.001	2.33[2.05,2.64]	< 0.001
Q1	Ref		Ref		Ref	
Q2	1.29[1.15,1.44]	< 0.001	1.24[1.11,1.39]	< 0.001	1.2[1.07,1.34]	0.001
Q3	1.66[1.49,1.85]	< 0.001	1.53[1.37,1.7]	< 0.001	1.4[1.26,1.56]	< 0.001
Q4	2.48[2.21,2.79]	< 0.001	2.02[1.82,2.24]	< 0.001	1.78[1.61,1.97]	< 0.001
METS-IR (continuous)	1.03[1.02,1.03]	< 0.001	1.03[1.03,1.04]	< 0.001	1.03[1.02,1.03]	< 0.001
Q1	Ref		Ref		Ref	
Q2	1.05[0.94,1.17]	0.393	1.07[0.96,1.2]	0.209	1.03[0.93,1.15]	0.557
Q3	1.21[1.08,1.35]	0.001	1.23[1.1,1.37]	< 0.001	1.15[1.03,1.28]	0.01
Q4	1.62[1.46,1.81]	< 0.001	1.73[1.57,1.92]	< 0.001	1.6[1.45,1.77]	< 0.001

Model 1: unadjusted

Model 2: adjusted for age and gender

Model 3: further adjusted for DBP, hyperlipidemia, diabetes, coronary artery disease, atrial fibrillation, CKD, ACEI/ARB/ARNI, beta-blocker, MRA, loop diuretics, N-terminal pro-B-type natriuretic peptide, LVESD, pulmonary arterial pressure, left atrial diameter, and MAGGIC score

Other abbreviations as in Table 1

index also performed better. Supplementary Table 4 explores the additional effects of different IR indices on the MAGGIC score, and the results show that all IR indices can improve the predictive performance of the MAGGIC score, with the TyG index performing the best. The TyG index increased the AUC from 0.602 to 0.666, with an IDI of 0.047, a cNRI of 0.167, and all p-values less than 0.001.

Discussion

Currently, there is a lack of studies that compare the prognostic significance of different IR indices (such as TyG, TyG-BMI, AIP, and METS-IR) in patients with HFpEF. Furthermore, this is the first study to investigate the long-term prognostic value of TyG-BMI and AIP in the HFpEF population. In this large cohort study of HFpEF patients, we have made the following novel findings: (1) All four IR indices are independently associated with MACE in HFpEF patients; (2) These four IR indices significantly improve the statistical accuracy of the MAGGIC score; and (3) TyG is the most promising indicator for risk stratification in HFpEF patients.

Previous studies have established the association between IR and HF. A prospective cohort study published in 2005 found that IR, assessed using the hyperinsulinemic-euglycemic clamp technique, was associated with future risk of HF independently of diabetes [21]. Although the hyperinsulinemic-euglycemic clamp technique is considered the gold standard for quantifying IR, its high cost and invasiveness pose challenges for its application in clinical practice and research. In recent years, several non-insulin-based indices (including TyG, TyG-BMI, AIP, and METS-IR) have been proven to be simple and reliable surrogate markers of IR, and have been widely used in clinical events and scientific research [13–16].

The current data regarding the association between the TyG index and long-term prognosis in patients with HFpEF are primarily derived from small observational studies, which support our findings [22, 23]. Data from HFpEF patients hospitalized for acute heart failure indicate that the TyG index can predict long-term all-cause mortality and HF rehospitalization, and it enhances the risk stratification capability of the MAGGIC score [22]. Furthermore, a retrospective cohort study including patients with chronic heart failure (CHF) and conducting subgroup analyses based on LVEF found that the TyG index is associated with long-term mortality in HFpEF but not in heart failure with reduced ejection fraction [23]. Our research results demonstrate that an elevated TyG index is correlated with an increased risk of MACE in HFpEF patients, and the TyG index improves the

A TyG index

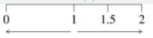
Subgroup	n (%)	HR (95%CI)	P	P for interaction
All patients	8693 (100.00)	1.44 (1.39 ~ 1.49)	<.001	
Age				<.001
>65 yr	6510 (74.89)	1.41 (1.36 ~ 1.46)	<.001	
≤ 65 yr	2183 (25.11)	1.72 (1.59 ~ 1.85)	<.001	
Gender				0.145
Female	3648 (41.96)	1.49 (1.41 ~ 1.56)	<.001	
Male	5045 (58.04)	1.42 (1.36 ~ 1.48)	<.001	
BMI				0.003
<25 kg/m2	5135 (59.07)	1.40 (1.34 ~ 1.46)	<.001	
≥25 kg/m2	3558 (40.93)	1.56 (1.48 ~ 1.65)	<.001	
Hyperlipidemia				0.108
No	4782 (55.01)	1.75 (1.65 ~ 1.84)	<.001	
Yes	3911 (44.99)	1.64 (1.56 ~ 1.73)	<.001	
Diabetes				0.082
No	4653 (53.53)	1.39 (1.31 ~ 1.48)	<.001	
Yes	4040 (46.47)	1.49 (1.42 ~ 1.55)	<.001	
CKD				0.598
No	6394 (73.55)	1.39 (1.33 ~ 1.45)	<.001	
Yes	2299 (26.45)	1.36 (1.30 ~ 1.43)	<.001	
LVEF				0.672
<65%	4474 (51.47)	1.44 (1.38 ~ 1.51)	<.001	
≥65%	4219 (48.53)	1.43 (1.36 ~ 1.50)	<.001	
Increased LA Size				0.290
No	2409 (27.71)	1.49 (1.39 ~ 1.59)	<.001	
Yes	6284 (72.29)	1.42 (1.37 ~ 1.48)	<.001	
Pulmonary Hypertension				0.008
No	5186 (59.66)	1.53 (1.46 ~ 1.59)	<.001	
Yes	3507 (40.34)	1.38 (1.31 ~ 1.45)	<.001	

B TyG-BMI

Subgroup	n (%)	HR (95%CI)	P	P for interaction
All patients	8693 (100.00)	1.11 (1.07 ~ 1.15)	<.001	
Age				0.005
>65 yr	6510 (74.89)	1.10 (1.06 ~ 1.14)	<.001	
≤ 65 yr	2183 (25.11)	1.25 (1.16 ~ 1.36)	<.001	
Gender				0.155
Female	3648 (41.96)	1.15 (1.09 ~ 1.21)	<.001	
Male	5045 (58.04)	1.09 (1.04 ~ 1.14)	<.001	
BMI				0.020
<25 kg/m2	5135 (59.07)	1.24 (1.15 ~ 1.33)	<.001	
≥25 kg/m2	3558 (40.93)	1.39 (1.31 ~ 1.49)	<.001	
Hyperlipidemia				0.101
No	4782 (55.01)	1.12 (1.07 ~ 1.18)	<.001	
Yes	3911 (44.99)	1.20 (1.13 ~ 1.26)	<.001	
Diabetes				<.001
No	4653 (53.53)	1.01 (0.96 ~ 1.07)	0.677	
Yes	4040 (46.47)	1.16 (1.10 ~ 1.22)	<.001	
CKD				0.010
No	6394 (73.55)	1.06 (1.01 ~ 1.10)	0.017	
Yes	2299 (26.45)	1.16 (1.10 ~ 1.23)	<.001	
LVEF				0.928
<65%	4474 (51.47)	1.11 (1.06 ~ 1.16)	<.001	
≥65%	4219 (48.53)	1.11 (1.05 ~ 1.17)	<.001	
Increased LA Size				0.430
No	2409 (27.71)	1.11 (1.03 ~ 1.19)	0.008	
Yes	6284 (72.29)	1.07 (1.03 ~ 1.12)	<.001	
Pulmonary Hypertension				0.014
No	5186 (59.66)	1.17 (1.12 ~ 1.23)	<.001	
Yes	3507 (40.34)	1.08 (1.02 ~ 1.13)	0.004	

C AIP

Subgroup	n (%)	HR (95%CI)	P	P for interaction
All patients	8693 (100.00)	1.26 (1.22 ~ 1.31)	<.001	
Age				<.001
>65 yr	6510 (74.89)	1.26 (1.21 ~ 1.31)	<.001	
≤ 65 yr	2183 (25.11)	1.50 (1.39 ~ 1.63)	<.001	
Gender				0.079
Female	3648 (41.96)	1.31 (1.24 ~ 1.39)	<.001	
Male	5045 (58.04)	1.23 (1.18 ~ 1.29)	<.001	
BMI				0.152
<25 kg/m2	5135 (59.07)	1.25 (1.20 ~ 1.31)	<.001	
≥25 kg/m2	3558 (40.93)	1.33 (1.25 ~ 1.40)	<.001	
Hyperlipidemia				0.811
No	4782 (55.01)	1.47 (1.38 ~ 1.56)	<.001	
Yes	3911 (44.99)	1.45 (1.37 ~ 1.54)	<.001	
Diabetes				<.001
No	4653 (53.53)	1.16 (1.10 ~ 1.22)	<.001	
Yes	4040 (46.47)	1.34 (1.28 ~ 1.40)	<.001	
CKD				0.139
No	6394 (73.55)	1.20 (1.14 ~ 1.25)	<.001	
Yes	2299 (26.45)	1.26 (1.19 ~ 1.33)	<.001	
LVEF				0.529
<65%	4474 (51.47)	1.27 (1.22 ~ 1.34)	<.001	
≥65%	4219 (48.53)	1.25 (1.19 ~ 1.32)	<.001	
Increased LA Size				0.356
No	2409 (27.71)	1.30 (1.21 ~ 1.40)	<.001	
Yes	6284 (72.29)	1.25 (1.20 ~ 1.30)	<.001	
Pulmonary Hypertension				0.006
No	5186 (59.66)	1.35 (1.29 ~ 1.41)	<.001	
Yes	3507 (40.34)	1.22 (1.16 ~ 1.29)	<.001	



D METS-IR

Subgroup	n (%)	HR (95%CI)	P	P for interaction
All patients	8693 (100.00)	1.22 (1.18 ~ 1.26)	<.001	
Age				0.004
>65 yr	6510 (74.89)	1.21 (1.16 ~ 1.25)	<.001	
≤ 65 yr	2183 (25.11)	1.38 (1.27 ~ 1.49)	<.001	
Gender				0.114
Female	3648 (41.96)	1.26 (1.19 ~ 1.33)	<.001	
Male	5045 (58.04)	1.19 (1.14 ~ 1.25)	<.001	
BMI				0.307
<25 kg/m2	5135 (59.07)	1.43 (1.34 ~ 1.52)	<.001	
≥25 kg/m2	3558 (40.93)	1.50 (1.42 ~ 1.59)	<.001	
Hyperlipidemia				0.152
No	4782 (55.01)	1.23 (1.18 ~ 1.29)	<.001	
Yes	3911 (44.99)	1.30 (1.23 ~ 1.37)	<.001	
Diabetes				<.001
No	4653 (53.53)	1.12 (1.06 ~ 1.18)	<.001	
Yes	4040 (46.47)	1.27 (1.21 ~ 1.33)	<.001	
CKD				0.058
No	6394 (73.55)	1.15 (1.10 ~ 1.21)	<.001	
Yes	2299 (26.45)	1.23 (1.17 ~ 1.30)	<.001	
LVEF				0.665
<65%	4474 (51.47)	1.22 (1.17 ~ 1.28)	<.001	
≥65%	4219 (48.53)	1.21 (1.14 ~ 1.27)	<.001	
Increased LA Size				0.805
No	2409 (27.71)	1.20 (1.11 ~ 1.29)	<.001	
Yes	6284 (72.29)	1.19 (1.14 ~ 1.24)	<.001	
Pulmonary Hypertension				0.009
No	5186 (59.66)	1.29 (1.22 ~ 1.35)	<.001	
Yes	3507 (40.34)	1.17 (1.12 ~ 1.23)	<.001	

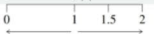


Fig. 4 Subgroup analysis of the IR indexes (per 1 SD) for MACE. TyG index (**A**), TyG-BMI (**B**), AIP (**C**), METS-IR (**D**). IR, insulin resistance; SD, standard deviation; MACE, major adverse cardiovascular event; TyG, triglyceride-glucose; TyG-BMI, triglyceride-glucose index with body mass index; AIP, atherogenic index of plasma; METS-IR, metabolic score for insulin resistance; HR, hazard ratio; CI, confidence interval; BMI, body mass index; CKD, chronic kidney disease; LVEF, left ventricular ejection fraction; LA, left atrial

predictive ability of the MAGGIC score, which aligns with previously published studies to some extent. In contrast, our study, with a larger sample size, is the first to compare the TyG index with other IR indicators, revealing that the TyG index exhibits superior discrimination and reclassification abilities in predicting MACE compared to other IR indicators. Additionally, subgroup analyses found interactions between the TyG index and age as well as BMI, suggesting that the cardiovascular risk posed by IR is more pronounced in younger and obese HFpEF patients.

The relationship between the TyG-BMI index and prognosis in patients with HFpEF has not been reported before. Lv et al. reported a reverse "J"-shaped association between the TyG-BMI index and all-cause mortality in patients with coronary heart disease complicated by HF, as well as a U-shaped nonlinear relationship with HF rehospitalization [24]. A study from The Medical Information Mart for Intensive Care (MIMIC-IV) database, which included 1,329 patients with chronic HF admitted to the ICU, found that the TyG-BMI index could predict 5-year mortality in CHF but did not improve the predictive performance of the basic risk model [25]. However, due to the lack of LVEF data, these studies did not delve into the specific phenotype of HFpEF. In our study, we reported for the first time the prognostic value of the

Table 3 Comparative analysis of IR indices for predicting MACE

Discrimination ability	AUC (95%CI)		Sensitivity (95%CI)		Specificity (95%CI)	
TyG	0.631(0.619–0.643)		0.651 (0.638–0.663)		0.545 (0.527–0.562)	
TyG-BMI	0.549(0.537–0.562)		0.724 (0.713–0.736)		0.359 (0.342–0.376)	
AIP	0.594(0.581–0.607)		0.600 (0.588–0.613)		0.539 (0.521–0.557)	
METS-IR	0.581(0.568–0.593)		0.700 (0.688–0.712)		0.423 (0.406–0.441)	
Comparison	**TyG vs. TyG-BMI**		**TyG vs. AIP**		**TyG vs. METS-IR**	
	Difference	**P value**	**Difference**	**P value**	**Difference**	**P value**
AUC	0.081	< 0.001	0.037	< 0.001	0.053	< 0.001
cNRI	0.161	< 0.001	0.163	< 0.001	0.143	< 0.001
IDI	0.038	< 0.001	0.036	< 0.001	0.026	< 0.001
Comparison	**TyG-BMI vs. AIP**		**TyG-BMI vs. METS-IR**		**AIP vs. METS-IR**	
	Difference	**P value**	**Difference**	**P value**	**Difference**	**P value**
AUC	-0.045	< 0.001	-0.031	< 0.001	0.013	0.019
cNRI	-0.037	0.909	-0.151	< 0.001	-0.039	0.364
IDI	-0.013	< 0.001	-0.011	0.182	0.001	0.909

MACE, major adverse cardiovascular event; cNRI, continuous net reclassification improvement; IDI, integrated discrimination improvement; other abbreviations as in Tables 1 and 2

Table 4 Model performance after the addition of IR indices to the MAGGIC score for predicting MACE

Model	AUC[95%CI]	*P*-value	IDI	*P*-value	cNRI	*P*-value
MAGGIC	0.601[0.588,0.613]	ref	ref		ref	
MAGGIC + TyG	0.666[0.654,0.678]	< 0.001	0.046	< 0.001	0.167	< 0.001
MAGGIC + TyG-BMI	0.621[0.609,0.633]	< 0.001	0.02	< 0.001	0.099	< 0.001
MAGGIC + AIP	0.641[0.629,0.653]	< 0.001	0.025	< 0.001	0.142	< 0.001
MAGGIC + METS-IR	0.635[0.623,0.647]	< 0.001	0.027	< 0.001	0.161	< 0.001

Abbreviations as in Tables 1 and 2, and 3

TyG-BMI index in HFpEF patients. RCS analysis revealed a U-shaped correlation with MACE, indicating that besides an elevated TyG-BMI index, a lower TyG-BMI index is also closely associated with an increased risk of MACE. This phenomenon may be explained by the obesity paradox, where a lower BMI level reflects a chronic catabolic state with insufficient physiological reserve to combat depletion, leading to a poorer prognosis [31, 32]. While both TyG and TyG-BMI were found to be significantly associated with MACE in our Cox regression analyses, the HRs for these markers differed substantially. This discrepancy can be attributed to the large numerical range of TyG-BMI compared to TyG, as well as the non-linear relationship between BMI and prognosis in HFpEF patients, which is often referred to as the obesity paradox. Therefore, when interpreting HR estimates for continuous variables with large numerical ranges, such as TyG-BMI, it is important to consider these factors. Despite the potential additional information provided by incorporating BMI into the TyG index, our findings suggest that TyG may have better predictive value for MACE in HFpEF patients. Future studies are needed to further explore the clinical utility of TyG-BMI and to validate our findings in larger and more diverse populations.

AIP was initially invented as a biomarker for plasma atherosclerosis but is now recognized as an effective surrogate for assessing IR [15, 26]. A study from the Kailuan cohort, using trajectory analysis, found that long-term elevation of AIP is significantly associated with an increased future risk of HF among hypertensive patients [27]. Yu et al. discovered a U-shaped correlation between AIP and 30-day mortality in patients with acute decompensated HF [28]. However, there have been limited reports on the relationship between AIP and the prognosis of patients with HFpEF. Our study is the first to establish a link between AIP and MACE in HFpEF patients, and has identified a linear correlation between them. Further subgroup analysis revealed that the cardiovascular risk associated with AIP is more pronounced in HFpEF patients who are ≤ 65 years old and have diabetes.

METS-IR, as a novel scoring system for screening insulin sensitivity, can identify IR by combining several simple and inexpensive indicators [16]. In a study from the National Health and Nutrition Examination Survey (NHANES), Su et al. found that METS-IR was independently positively correlated with the risk of HF in the general population, and also discovered a nonlinear "J"-shaped relationship between them [29]. Due to the lack of detailed information reflecting heart failure, such as brain natriuretic peptide levels and echocardiographic findings, the study did not further evaluate the relationship between METS-IR and different types of HF. Zhou

et al. included 4,702 patients with HFpEF and found that METS-IR was closely related to the risk of mortality, significantly improving the baseline risk model [30]. Our results also support the value of METS-IR in risk prediction for individuals with HFpEF. In comparison, while the predictive value of METS-IR was significant across different subgroups, we found that it posed an even greater risk in HFpEF patients with diabetes and those aged ≤ 65 years.

What mechanisms mediate the association between IR and poor prognosis in patients with HFpEF? Compared with HFrEF, HFpEF is more frequently associated with metabolic complications such as diabetes, obesity, and hyperlipidemia [31, 32]. As one of the key features of metabolic disturbances, IR can promote the transformation of fibroblasts into myofibroblasts through triggering inflammation, oxidative stress, and endothelial dysfunction, leading to myocardial hypertrophy and stiffness, which in turn reduces coronary blood flow reserve and ultimately results in increased cardiac chamber pressure/diastolic dysfunction [33–37].

Natriuretic peptide (NP) play a pivotal role in the diagnostic workup of patients with suspected HFpEF, as recommended by guidelines [20]. Current research and the new European guidelines acknowledge that 18-36% of HFpEF patients exhibit normal NP levels [20, 38–40]. A secondary analysis of a large prospective study by Verbrugge and colleagues found that patients with HFpEF and normal NP levels had an incidence of events (mortality or hospitalization for HF) almost three times higher compared to those without HFpEF [38]. Patients with HFpEF and normal NP levels constitute a distinct group exhibiting clear, unequivocal cardiac and vascular abnormalities that meet a priori definitions of cardiac failure, as demonstrated in previous studies [38–40]. Several causes of NP deficiency exist, including genetic factors, African ancestry, increased androgenicity in women, hypercortisolism, insulin resistance, and obesity [41]. Therefore, in our study, a sensitivity analysis was conducted among patients with near-normal/normal NT-proBNP levels. We found that even within this population, all IR indexes demonstrated significant discriminatory ability for MACE. Compared to other IR indexes, the TyG index exhibited superior discriminatory and reclassification capabilities.

Our study observed that approximately 60% of patients with HFpEF had a BMI < 25, which contrasts with the reported finding in the I-PRESERVE Trial that the over 80% of HFpEF patients are overweight or obese [7]. Firstly, the I-PRESERVE Trial specifically included elderly patients aged 60 and older with an LVEF threshold of 45%, whereas our HFpEF cohort did not impose an age restriction and used an LVEF threshold of 50%. Secondly, the I-PRESERVE Trial enrolled predominantly white participants (over 90%), whereas our study focused on a Chinese population. Existing research has demonstrated that, among patients with HFpEF, the prevalence of obesity and BMI levels are lower in Asian-Pacific populations compared to those in North America and Western Europe [42]. This ethnic variability in BMI distribution could account for the observed inconsistency. Furthermore, when defining overweight and obesity, different studies may adopt varying BMI thresholds or classification standards. Notably, for Asian populations, the BMI thresholds for overweight and obesity are generally lower compared to other populations [43].

This study has several notable strengths. Firstly, it is one of the first to comprehensively compare the prognostic significance of different insulin resistance indices, such as TyG, TyG-BMI, AIP, and METS-IR, in patients with HFpEF. By doing so, it provides valuable insights into which index may be most useful for risk stratification in this patient population. Secondly, the study utilizes a large cohort of HFpEF patients, allowing for more robust statistical analysis and increasing the generalizability of the findings. Additionally, the study employs rigorous methodological approaches, including K-M survival analysis, multivariable Cox proportional hazards models, and various measures of predictive performance, such as AUC, cNRI, and IDI, to ensure accurate and reliable results. These strengths collectively enhance the quality and impact of the study's contributions to the field.

Despite the novel findings and contributions of this study, several limitations merit consideration. Firstly, the study population was confined to patients with HFpEF hospitalized in a single tertiary care center, potentially limiting the generalizability of our results to other patient populations or healthcare settings. Additionally, although we utilized a comprehensive array of non-insulin-based indices to assess IR, direct measures of insulin sensitivity, such as the hyperinsulinemic-euglycemic clamp technique, were not employed. These direct measures are considered the gold standard for quantifying IR but are less feasible in large-scale observational studies due to their high cost and invasiveness. Furthermore, the retrospective nature of our study precluded the ability to obtain some detailed information including data on quality of life, which may have influenced the observed associations between IR indices and clinical outcomes. Besides, the findings have not yet undergone external validation in diverse patient populations, which is essential to improve the applicability and generalizability of our results. Lastly, although we performed extensive subgroup analyses, the possibility of residual confounding or unmeasured variables remains, which could affect the robustness of our findings. Therefore, future studies with larger, more diverse populations, and incorporating

longitudinal data on potential confounders, are needed to validate and extend our results.

Conclusions

Our findings demonstrate that all four IR indices—TyG, TyG-BMI, AIP, and METS-IR—are independently associated with MACE in patients with HFpEF. Importantly, these IR indices significantly augment the predictive accuracy of the MAGGIC score, which is a widely used tool for risk stratification in this HF population. Among these indices, the TyG index stands out with the highest discriminatory and reclassification abilities, offering incremental value in predicting MACE over other indices. This suggests that the TyG index may be particularly useful in risk assessment and guiding management strategies for HFpEF patients. However, it is crucial to acknowledge that our results need to be externally validated in diverse populations to ensure their accuracy and applicability.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02595-x.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

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Author contributions
WN was instrumental in the design and overall coordination of the research. RJ contributed to the data collection and initial analysis. JZ assisted in the statistical analysis and interpretation of the results. JC provided valuable insights into the clinical implications of the findings. YL helped in refining the research questions and methods. YZ was crucial in the literature review and theoretical framework. HZ, as the corresponding author, was responsible for integrating all contributions, drafting the manuscript, and ensuring the accuracy and completeness of the final version. All authors have reviewed and approved all versions of the final manuscript and have agreed to take responsibility and accountability for the content of the manuscript.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The First Affiliated Hospital of Wenzhou Medical University's Ethics Committee in Clinical Research reviewed and approved the studies that involved human participants (Number: ky-20240483). The informed consent requirement was waived by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University for this retrospective study. Furthermore, all data were anonymized to prevent any potential breach of patient privacy.

Consent for publication
All authors gave consent for the publication of the article.

Competing interests
The authors declare no competing interests.

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