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ORIGINAL RESEARCH

TYG Index as a Novel Predictor of Clinical Outcomes in Advanced Chronic Heart Failure with Renal Dysfunction Patients

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Background: The triglyceride-glucose (TYG) index is a novel and reliable marker reflecting insulin resistance. Its predictive ability for cardiovascular disease onset and prognosis has been confirmed. However, for advanced chronic heart failure (acHF) patients, the prognostic value of TYG is challenged due to the often accompanying renal dysfunction (RD). Therefore, this study focuses on patients with aHF accompanied by RD to investigate the predictive value of the TYG index for their prognosis.

Methods and Results: 717 acHF with RD patients were included. The acHF diagnosis was based on the 2021 ESC criteria for acHF. RD was defined as the eGFR < 90 mL/(min/1.73 m^2). Patients were divided into two groups based on their TYG index values. The primary endpoint was major adverse cardiovascular events (MACEs), and the secondary endpoints is all-cause mortality (ACM). The follow-up duration was 21.58 (17.98–25.39) months. The optimal cutoff values for predicting MACEs and ACM were determined using ROC curves. Hazard factors for MACEs and ACM were revealed through univariate and multivariate COX regression analyses. According to the univariate COX regression analysis, high TyG index was identified as a risk factor for MACEs (hazard ratio = 5.198; 95% confidence interval [CI], 3.702–7.298; P < 0.001) and ACM (hazard ratio = 4.461; 95% CI, 2.962–6.718; P < 0.001). The multivariate COX regression analysis showed that patients in the high TyG group experienced 440.2% MACEs risk increase (95% CI, 3.771–7.739; P < 0.001) and 406.2% ACM risk increase (95% CI, 3.268–7.839; P < 0.001). Kaplan-Meier survival analysis revealed that patients with high TyG index levels had an elevated risk of experiencing MACEs and ACM within 30 months.

Conclusion: This study found that patients with high TYG index had an increased risk of MACEs and ACM, and the TYG index can serve as an independent predictor for prognosis.

Keywords: TyG index, advanced chronic heart failure, renal dysfunction, prognosis factor

Introduction

Heart failure (HF) is the final stage of various heart diseases. In recent years, with improvements in the treatment of related diseases such as acute myocardial infarction, the mortality rate of patients has significantly decreased, while the incidence of HF has been steadily rising.[1] Due to the reduced circulatory capacity caused by advanced chronic heart failure (acHF), it often leads to secondary organ complications, with renal dysfunction (RD) being one of the most common complications of acHF. The conflicting treatment principles between these two organs, coupled with the propensity of both to cause systemic complications, often result in frequent readmissions for patients with both CHF and RF, greatly impacting their quality of life.[2,3]

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Metabolic syndrome can be regarded as the root cause of cardiovascular diseases. In the case of the most common cardiovascular disease, coronary heart disease, prolonged abnormalities in glucose and lipid metabolism lead to endothelial dysfunction and lipid accumulation, triggering the formation of atherosclerosis.[4] Compared to other patients with coronary heart disease, those with glucose and lipid metabolism abnormalities often exhibit more severe coronary artery lesions and a worse clinical prognosis.[5] Patients with glucose and lipid metabolism abnormalities are also more prone to postoperative complications such as cerebral infarction and in-stent restenosis.[6,7]

For patients with chronic RD, although there is currently no term like "metabolic syndrome renal disease", the association between the two has been widely recognized. Diabetic nephropathy is a condition secondary to diabetes, involving renal damage due to long-term poorly controlled blood sugar levels leading to microvascular changes. Additionally, research has found that patients with prolonged elevation of blood lipids often have accompanying glomerulosclerosis.[8]

To comprehensively reflect the level of glucose and lipid metabolism in the patient's body, the TyG index has emerged. With the advancement of related research, the TyG index is currently considered to primarily reflect the level of insulin resistance (IR) in the body and is regarded as an excellent alternative assessment indicator. IR is believed to be the result of the combined effects of chronic inflammation, lipid metabolism abnormalities, or glucose abnormalities in the body. Currently, the prognostic predictive ability of the TyG index has been validated in patients with HF or RD. Through this analysis of clinical data from patients admitted to the department of cardiology in first affiliated hospital of Zhengzhou university, we have found that the TyG index is a novel tool for predicting the occurrence of MACEs and ACM in patients with advanced chronic HF combined with RD.

Method

Study and Population

This study included acHF patients admitted to the Department of Cardiology at the First Affiliated Hospital of Zhengzhou University from September 2019 to December 2020.

Inclusion Criteria

(1) Diagnosis of acHF, based on the 2021 ESC criteria for advanced chronic heart failure,[9] which includes the following criteria even with optimal treatment: (A) Severe and persistent heart failure symptoms, at least NYHA class III or IV; (B) Severe cardiac dysfunction meeting any of the following criteria: (a) LVEF ≤ 30%, (b) isolated right heart failure, (c) severe valve deformities not amenable to surgical treatment, (d) severe congenital abnormalities not amenable to surgical treatment, (e) elevated NT-proBNP with concomitant HFpEF; (C) Patients requiring intravenous diuretics due to pulmonary or systemic congestion or needing positive inotropic or vasopressor agents due to low cardiac output or malignant arrhythmias leading to more than one unscheduled outpatient visit within 12 months; (D) Impaired exercise capacity due to cardiac disease, inability to exercise, 6MWT < 300m, or pVO2 < 12 mL/kg/min, or <50% of predicted value. (2) Diagnosis of renal dysfunction with eGFR < 90 mL/(min/1.73 m^2). (3) Patients with at least two hospitalizations due to heart failure.

Exclusion Criteria

(1) Age <18 years old; (2) first episode of acute heart failure; (3) hospitalization duration <2 days; (4) patients with infectious diseases, malignant tumors, primary renal diseases, congenital heart disease or autoimmune diseases; (5) incomplete clinical records.

Based on the aforementioned criteria, a total of 815 patients were included. Out of these, 98 patients were lost to follow-up, resulting in a loss rate of 12.0%. Data were gathered and documented from the Hospital Information System, encompassing information such as gender, age, relevant medical histories, blood test results, and records of medication treatments.

Definitions

According to ESC recommendations,[10] hypertension is defined as having a systolic blood pressure (SBP) of ≥140 mmHg and/or diastolic blood pressure (DBP) of ≥90 mmHg measured on at least three occasions in two separate places, or the use of any antihypertensive medication. Diabetes is defined as having a fasting blood glucose level of ≥7.0 mmol/L or

a post-load blood glucose level of ≥11.1 mmol/L, or the use of antidiabetic medications.[11] Smoking and alcohol status are defined as current or past tobacco use and any alcohol consumption within the past six months.

Endpoints

The primary endpoint for patients is major adverse cardiovascular events (MACEs), which includes cardiovascular death, non-cardiovascular death, rehospitalization due to worsening HF, heart transplantation, use of mechanical circulatory support, malignant arrhythmias, myocardial infarction, and rehospitalization for unstable angina. The secondary endpoints is all-cause mortality (ACM).

Follow-Up

Clinical data of eligible patients were extracted from inpatient medical records and outpatient records. Patients receive regular follow-up after discharge, which included telephone follow-up and office visits. The final follow-up for this study was in March 2022, with a median follow-up duration of 21.58 (17.98–25.39) months. All data collection and follow-up were carefully assessed and executed by trained clinical physicians (Figure 1).

Calculation of TyG Index

The TyG index was calculated by fasting blood glucose and fasting triglyceride at admission:

$$\text{TyG index} = \text{Ln}[\text{TG(mg/dL)} * \text{FBG(mg/dL)}/2].$$

Statistical Analysis

Data analysis was conducted using SPSS 26.0 (IBM Corp., Armonk, NY, USA). Receiver Operating Characteristic (ROC) curves were constructed for both endpoints as state variables, and the corresponding areas under the curve (AUC) and Youden's index were calculated to determine the optimal cutoff values for TyG index. Patients were then categorized into high-TyG and low-TyG groups, with the best cutoff value for the primary endpoint is 8.48 (AUC = 0.759, $P < 0.001$). The best cutoff value for the secondary endpoint is 8.50 (AUC = 0.700, $P < 0.001$).

Categorical variables were presented as case numbers (percentages) and analyzed using the χ^2 test. Continuous variables were expressed as means ± standard deviation (SD) or as medians (interquartile range). For continuous variables, the *t*-test was used if they satisfied both normal distribution and homogeneity of variances; otherwise, the Mann–Whitney *U*-test was employed. We employed Multivariate Cox regression analysis to identify independent variables influencing prognosis. Subsequently, we constructed sequential models to assess the added prognostic value of these variables. The inclusion of additional factors in each step was considered statistically significant when the change in log likelihood associated with each model reached a significance level of $P<0.05$. Kaplan-Meier survival analysis was employed to assess long-term survival rates. Two-sided p-values were used, and significance was defined as $P<0.05$.

Results

Baseline Characteristics

Among the 717 patients included, the TyG cutoff value for the primary endpoint (MACEs) was determined to be 8.48, with an area under the curve (AUC) of 0.759. Sensitivity was 0.836, specificity was 0.588, and the Youden's index was 0.424 (Figure 2). Patients were categorized into low-TyG (TyG<8.48, n=318) and high-TyG (TyG≥8.48, n=399) groups, and their baseline characteristics are presented in Table 1. Between the two groups, differences were observed in terms of gender, demographic characteristics (coronary heart disease, diabetes, hyperlipidemia and chronic renal disease), white blood cell, platelet, neutrophil, fibrinogen, blood urea nitrogen, creatinine, uric acid, eGFR, albumin, globulin, t total cholesterol, triglyceride, HDL-C, LDL-C, troponin, C-reactive protein, blood glucose, glycated hemoglobin, and medication history (clopidogrel, Beta-blocker, diuretics and statins) ($p<0.05$). However, certain common risk factors associated with cardiovascular disease, such as advanced age, smoking history, and hypertension, showed no significant differences.

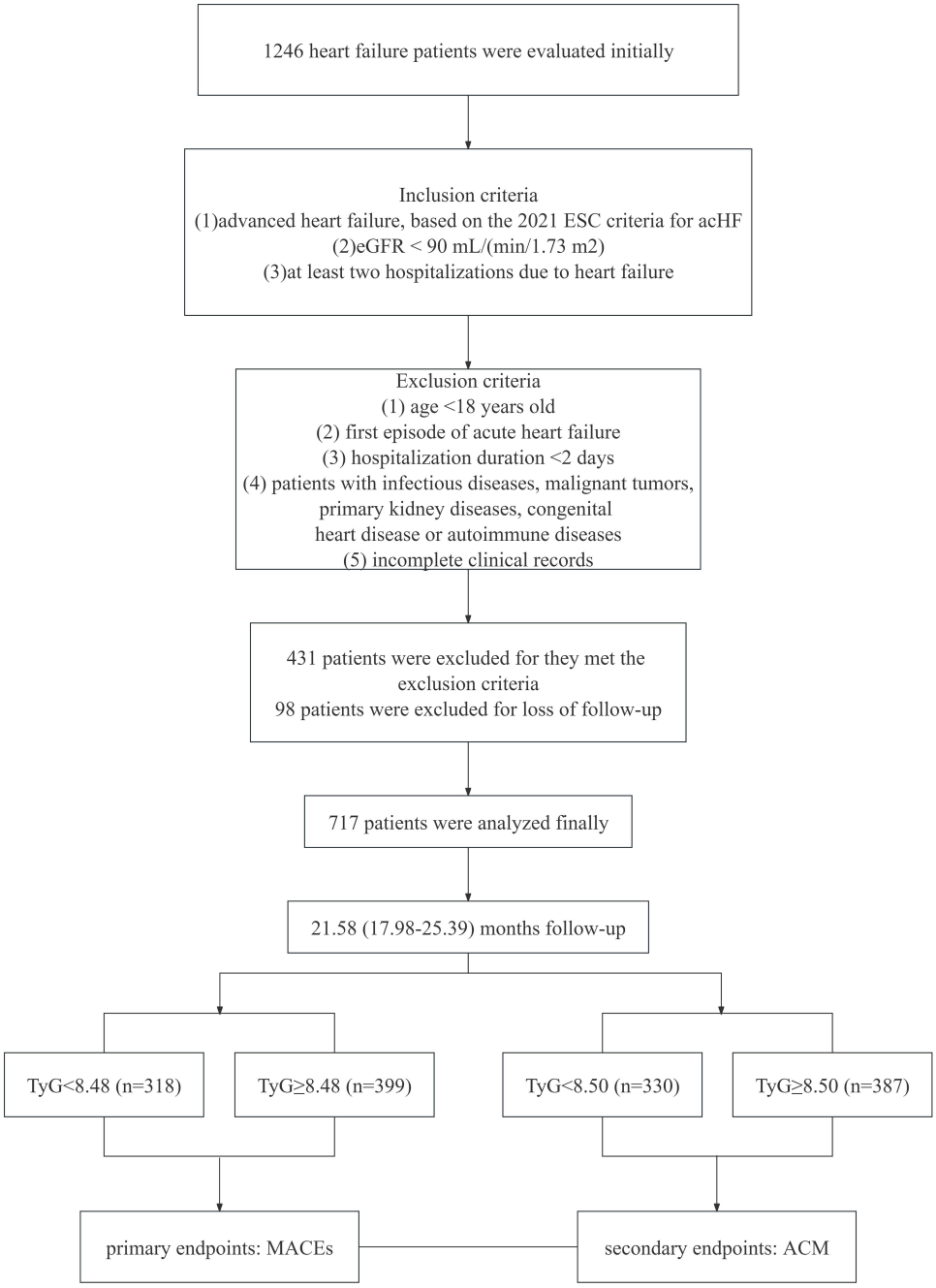

Figure 1 The flow chart of participants inclusion.

In the grouping based on ACM as the endpoint, the TyG cutoff value was determined to be 8.50, with an area under the curve (AUC) of 0.700. Sensitivity was 0.821, specificity was 0.538, and the Youden's index was 0.359 (Figure 3). Patients were divided into low-TyG (TyG<8.50, n=330) and high-TyG (TyG≥8.50, n=387) groups, and their baseline characteristics are presented in Table 2. Between the two groups, differences were observed in terms of gender, demographic characteristics (coronary heart disease, diabetes and hyperlipidemia), white blood cell, platelet, neutrophil, fibrinogen, creatinine, albumin, globulin, t total cholesterol, triglyceride, HDL-C, LDL-C, troponin, blood glucose, glycated hemoglobin, and medication history (clopidogrel, ARNI and statins) ($p<0.05$). However, certain common risk factors associated with cardiovascular disease, such as advanced age, smoking history, and hypertension, showed no significant differences. Failure with renal dysfunction.

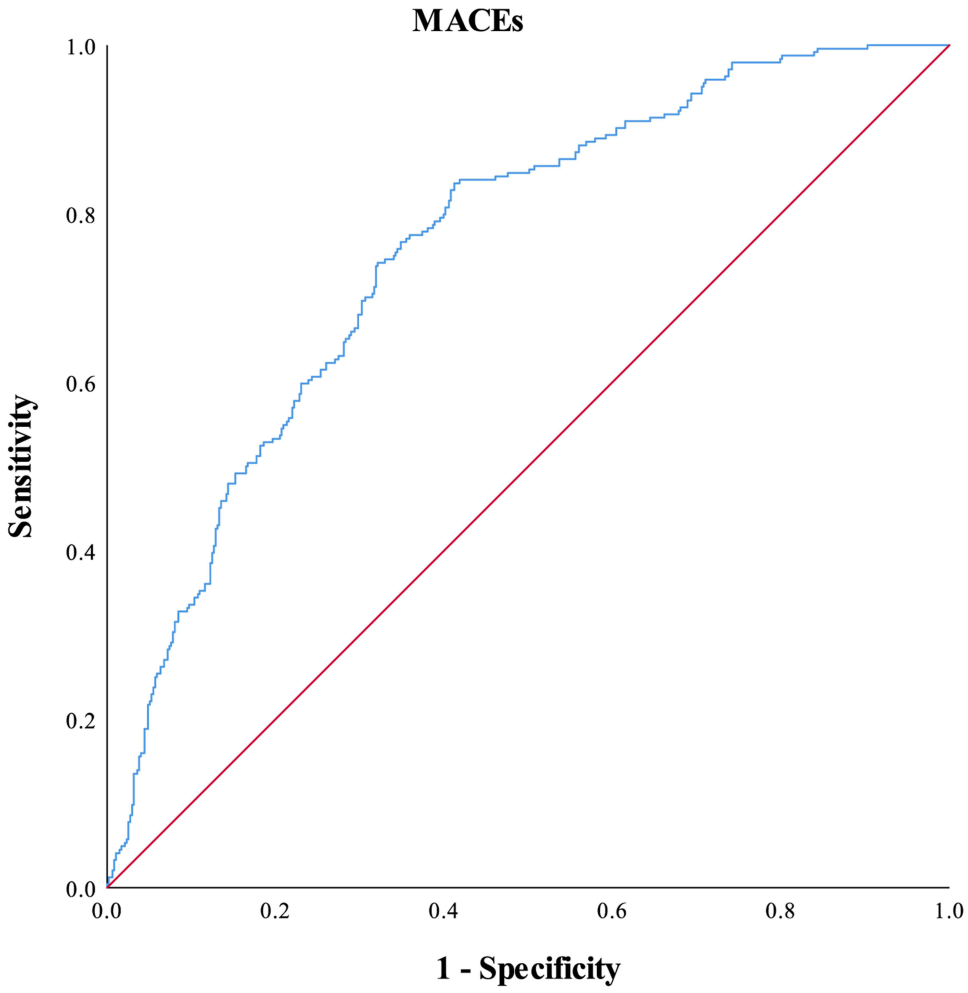

Figure 2 ROC curve of TyG predicting long-term MACEs in patients with advanced chronic heart.

Relationship Between TyG and MACEs

We constructed univariate Cox models for each predictive variable (Table 3) and created a multivariate Cox regression analysis based on the results of the univariate COX regression analysis and traditional clinical prognostic factors. The results showed that age>60, a history of arrhythmia, elevated CRP, and high TyG were risk factors for the occurrence of MACEs in patients with acHF and RD.

On the other hand, low-density lipoprotein cholesterol (LDL-C) was identified as a protective factor (Table 4). Patients with high TyG levels had a 440.2% increase in the risk of experiencing MACEs (hazard ratio [HR] = 5.402; 95% confidence interval [CI], 3.771–7.739; P < 0.001).

Relationship Between TyG and ACM

We constructed univariate Cox models for each predictive variable (Table 5) and created a multivariate Cox regression analysis based on the results of the univariate COX regression analysis and traditional clinical prognostic factors. The results showed that age>60, a history of arrhythmia, elevated CRP, and high TyG were risk factors for the occurrence of ACM in patients with acHF and RD.

Conversely, a history of hypertension and LDL-C were identified as protective factors (Table 6). Patients with high TyG levels had a 406.2% increase in the risk of experiencing ACM (hazard ratio [HR] = 5.062; 95% confidence interval [CI], 3.268–7.839; P < 0.001).

Table 1 Clinical and Laboratory Characteristics According to the TyG (MACEs)

Variables	Low TyG (n=318)	High TyG (n=399)	χ^2/t/z	P
Age>60, n (%)	154 (48.43)	206 (51.63)	χ^2=0.73	0.394
Male, n (%)	217 (68.24)	219 (54.89)	χ^2=13.24	<0.001
Coronary heart disease, n (%)	130 (40.88)	210 (52.63)	χ^2=9.80	0.002
Hypertension, n (%)	223 (70.13)	273 (68.42)	χ^2=0.24	0.623
Arrhythmia, n (%)	101 (31.76)	121 (30.33)	χ^2=0.17	0.680
Diabetes, n (%)	86 (27.04)	162 (40.60)	χ^2=14.38	<0.001
Hyperlipidemia, n (%)	1 (0.31)	15 (3.76)	χ^2=9.63	0.002
Cerebrovascular disease, n (%)	53 (16.67)	76 (19.05)	χ^2=0.68	0.410
Chronic kidney disease, n (%)	219 (68.87)	244 (61.15)	χ^2=4.60	0.032
Peripheral vascular disease, n (%)	42 (13.21)	65 (16.29)	χ^2=1.32	0.250
Thyroid disease, n (%)	71 (22.33)	74 (18.55)	χ^2=1.57	0.211
Chronic lung disease, n (%)	65 (20.44)	94 (23.56)	χ^2=1.00	0.318
Smoking history, n (%)	87 (27.36)	111 (27.82)	χ^2=0.02	0.891
Drinking history, n (%)	60 (18.87)	67 (16.79)	χ^2=0.52	0.469
White blood cell, 10^9/L	6.21 (5.10, 8.25)	7.01 (5.59, 9.47)	Z=−3.98	<0.001
Red blood cell, 10^9/L	3.42 (2.81, 4.11)	3.53 (2.95, 4.22)	Z=−1.88	0.060
Hemoglobin, g/L	104.60 (85.00, 126.00)	107.30 (86.25, 128.50)	Z=−1.33	0.184
Platelet, 10^9/L	176.00 (136.00, 225.00)	190.00 (140.00, 251.00)	Z=−2.57	0.010
Neutrophil, 10^9/L	4.42 (3.36, 6.03)	5.18 (3.87, 7.41)	Z=−4.38	<0.001
Lymphocyte, 10^9/L	1.04 (0.74, 1.45)	1.06 (0.76, 1.50)	Z=−0.66	0.510
Eosinophil, 10^9/L	0.10 (0.03, 0.19)	0.08 (0.03, 0.16)	Z=−1.53	0.125
Basophil, 10^9/L	0.03 (0.01, 0.04)	0.02 (0.01, 0.04)	Z=−1.05	0.295
Thrombin time, s	11.20 (10.40, 12.20)	11.00 (10.30, 12.45)	Z=−0.96	0.338
Fibrinogen, g/L	3.36 (2.83, 4.11)	3.69 (2.89, 4.52)	Z=−2.78	0.005
Blood urea nitrogen, mmol/L	17.72 (9.30, 26.15)	15.40 (8.50, 24.18)	Z=−1.83	0.068
Creatinine, μmol/L	392.35 (99.25, 789.08)	259.00 (100.00, 607.60)	Z=−2.48	0.013
Uric acid, mmol/L	385.00 (286.25, 476.25)	409.00 (305.50, 512.00)	Z=−1.97	0.049
eGFR, mL/(min/1.73 m^2)	11.76 (5.82, 60.52)	19.82 (6.61, 60.53)	Z=−2.17	0.030
Albumin, g/L	36.85 (33.12, 40.70)	35.90 (31.90, 40.30)	Z=−2.28	0.023
Globulin, g/L	27.70 (23.10, 32.98)	29.60 (25.20, 33.25)	Z=−2.84	0.004
Total bilirubin, μmol/L	8.20 (5.38, 14.18)	8.40 (5.55, 14.65)	Z=−0.65	0.516
Total cholesterol, mmol/L	3.46 (2.85, 4.15)	3.89 (3.21, 4.75)	Z=−5.89	<0.001
Triglyceride, mmol/L	0.76 (0.59, 1.00)	1.73 (1.25, 2.30)	Z=−19.23	<0.001
HDL-C, mmol/L	1.03 (0.84, 1.24)	0.90 (0.73, 1.17)	Z=−4.60	<0.001
LDL-C, mmol/L	1.98 (1.51, 2.55)	2.26 (1.64, 2.91)	Z=−3.54	<0.001
Troponin, ng/mL	0.03 (0.01, 0.09)	0.05 (0.03, 0.14)	Z=−4.12	<0.001
CK-MB ng/mL	13.00 (8.00, 18.00)	13.00 (7.00, 22.00)	Z=−1.13	0.260
C-reactive protein, mg/L	8.85 (2.78, 27.49)	11.08 (4.16, 33.30)	Z=−2.29	0.022
Blood glucose, mmol/L	4.60 (3.97, 5.64)	6.88 (5.30, 9.11)	Z=−13.31	<0.001
Glycosylated hemoglobin, %	5.70 (5.20, 6.10)	6.00 (5.50, 7.18)	Z=−6.89	<0.001
Aspirin, n (%)	99 (31.13)	138 (34.59)	χ^2=0.95	0.329
Ticagrelor, n (%)	21 (6.60)	40 (10.03)	χ^2=2.66	0.103
Clopidogrel, n (%)	43 (13.52)	80 (20.05)	χ^2=5.31	0.021
ARNI, n (%)	92 (28.93)	91 (22.81)	χ^2=3.49	0.062
ACEI, n (%)	147 (46.23)	168 (42.11)	χ^2=1.22	0.269
Beta-blocker, n (%)	163 (51.26)	237 (59.40)	χ^2=4.75	0.029
Diuretics, n (%)	121 (38.05)	181 (45.36)	χ^2=3.88	0.049
Statins, n (%)	130 (40.88)	195 (48.87)	χ^2=4.56	0.033
Digoxin, n (%)	37 (11.64)	45 (11.28)	χ^2=0.02	0.881
CCB, n (%)	142 (44.65)	150 (37.59)	χ^2=3.65	0.056

Notes: Continuous variables are expressed using the median and interquartile range (25%, 75%). Categorical variables are presented as case numbers (percentages).

Abbreviations: eGFR, estimated glomerular filtration rate; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; CK-MB, creatine kinase-myoglobin binding; ARNI, angiotensin receptor/neprilysin inhibitor; ACEI, Angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker.

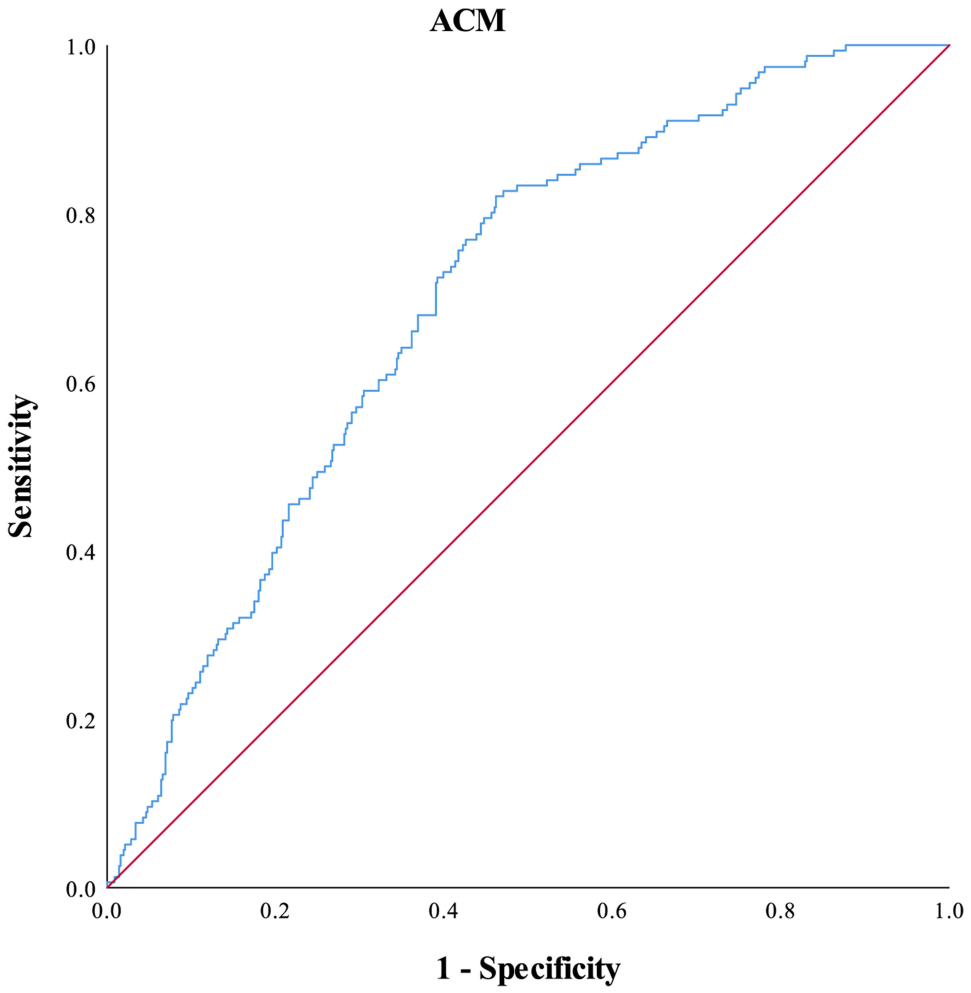

Figure 3 ROC curve of TyG predicting long-term ACM in patients with advanced chronic heart failure with renal dysfunction.

Kaplan-Meier Survival Analysis

Kaplan-Meier survival analysis was conducted to predict the occurrence rate of MACEs (Figure 4) and ACM (Figure 5) in patients.

Table 2 Clinical and Laboratory Characteristics According to the TyG (ACM)

Variables	Low TyG (n=330)	High TyG (n=387)	χ^2/t/z	P
Age>60, n (%)	159 (48.18)	201 (51.94)	χ^2=1.01	0.316
Male, n (%)	227 (68.79)	209 (54.01)	χ^2=16.33	<0.001
Coronary heart disease, n (%)	135 (40.91)	205 (52.97)	χ^2=10.39	0.001
Hypertension, n (%)	230 (69.70)	266 (68.73)	χ^2=0.08	0.781
Arrhythmia, n (%)	106 (32.12)	116 (29.97)	χ^2=0.38	0.535
Diabetes, n (%)	89 (26.97)	159 (41.09)	χ^2=15.69	<0.001
Hyperlipidemia, n (%)	2 (0.61)	14 (3.62)	χ^2=7.40	0.007
Cerebrovascular disease, n (%)	55 (16.67)	74 (19.12)	χ^2=0.73	0.394
Chronic kidney disease, n (%)	224 (67.88)	239 (61.76)	χ^2=2.92	0.088
Peripheral vascular disease, n (%)	45 (13.64)	62 (16.02)	χ^2=0.80	0.372
Thyroid disease, n (%)	74 (22.42)	71 (18.35)	χ^2=1.84	0.175

(*Continued*)

Table 2 (Continued).

Variables	Low TyG (n=330)	High TyG (n=387)	χ^2/t/z	P
Chronic lung disease, n (%)	69 (20.91)	90 (23.26)	χ^2=0.57	0.451
Smoking history, n (%)	90 (27.27)	108 (27.91)	χ^2=0.04	0.850
Drinking history, n (%)	64 (19.39)	63 (16.28)	χ^2=1.19	0.276
White blood cell, 10^9/L	6.22 (5.12, 8.30)	7.01 (5.60, 9.40)	Z=−3.73	<0.001
Red blood cell, 10^9/L	3.42 (2.83, 4.14)	3.53 (2.94, 4.22)	Z=−1.73	0.083
Hemoglobin, g/L	104.60 (85.05, 126.00)	107.30 (86.00, 128.00)	Z=−1.16	0.247
Platelet, 10^9/L	176.50 (136.25, 225.00)	190.00 (139.50, 252.00)	Z=−2.51	0.012
Neutrophil, 10^9/L	4.44 (3.39, 6.14)	5.19 (3.88, 7.37)	Z=−4.11	<0.001
Lymphocyte, 10^9/L	1.04 (0.74, 1.44)	1.07 (0.75, 1.52)	Z=−0.93	0.351
Eosinophil, 10^9/L	0.09 (0.03, 0.19)	0.08 (0.03, 0.16)	Z=−1.19	0.233
Basophil, 10^9/L	0.03 (0.01, 0.04)	0.02 (0.01, 0.04)	Z=−0.56	0.573
Thrombin time, s	11.20 (10.40, 12.38)	11.00 (10.30, 12.40)	Z=−1.43	0.152
Fibrinogen, g/L	3.37 (2.84, 4.11)	3.67 (2.89, 4.54)	Z=−2.73	0.006
Blood urea nitrogen, mmol/L	17.55 (9.26, 26.10)	15.54 (8.50, 24.29)	Z=−1.58	0.115
Creatinine, μmol/L	381.50 (99.25, 787.75)	259.40 (100.00, 607.60)	Z=−2.26	0.024
Uric acid, mmol/L	391.00 (287.25, 482.00)	408.00 (305.50, 508.50)	Z=−1.58	0.114
eGFR, mL/(min/1.73 m^2)	12.43 (5.84, 61.00)	19.68 (6.59, 59.43)	Z=−1.85	0.065
Albumin, g/L	36.80 (33.12, 40.68)	35.90 (31.90, 40.30)	Z=−2.05	0.041
Globulin, g/L	27.75 (23.13, 32.90)	29.60 (25.20, 33.30)	Z=−2.96	0.003
Total bilirubin, μmol/L	8.30 (5.40, 14.84)	8.34 (5.45, 14.35)	Z=−0.02	0.984
Total cholesterol, mmol/L	3.46 (2.86, 4.15)	3.90 (3.21, 4.79)	Z=−5.82	<0.001
Triglyceride, mmol/L	0.78 (0.60, 1.01)	1.78 (1.30, 2.34)	Z=−19.65	<0.001
HDL-C, mmol/L	1.03 (0.84, 1.24)	0.90 (0.72, 1.16)	Z=−4.69	<0.001
LDL-C, mmol/L	1.98 (1.51, 2.57)	2.27 (1.64, 2.92)	Z=−3.54	<0.001
Troponin, ng/mL	0.04 (0.02, 0.09)	0.05 (0.02, 0.14)	Z=−3.68	<0.001
CK-MB ng/mL	13.00 (8.00, 18.00)	13.00 (7.00, 22.00)	Z=−1.08	0.280
C-reactive protein, mg/L	9.23 (2.82, 28.66)	10.66 (4.16, 33.10)	Z=−1.91	0.057
Blood glucose, mmol/L	4.66 (3.97, 5.73)	6.92 (5.27, 9.39)	Z=−12.98	<0.001
Glycosylated hemoglobin, %	5.70 (5.20, 6.10)	6.00 (5.50, 7.20)	Z=−6.95	<0.001
Aspirin, n (%)	103 (31.21)	134 (34.63)	χ^2=0.94	0.333
Ticagrelor, n (%)	22 (6.67)	39 (10.08)	χ^2=2.66	0.103
Clopidogrel, n (%)	46 (13.94)	77 (19.90)	χ^2=4.45	0.035
ARNI, n (%)	98 (29.70)	85 (21.96)	χ^2=5.60	0.018
ACEI, n (%)	154 (46.67)	161 (41.60)	χ^2=1.85	0.173
Beta-blocker, n (%)	172 (52.12)	228 (58.91)	χ^2=3.33	0.068
Diuretics, n (%)	129 (39.09)	173 (44.70)	χ^2=2.30	0.129
Statins, n (%)	133 (40.30)	192 (49.61)	χ^2=6.23	0.013
Digoxin, n (%)	39 (11.82)	43 (11.11)	χ^2=0.09	0.767
CCB, n (%)	145 (43.94)	147 (37.98)	χ^2=2.62	0.106

Notes: Continuous variables are expressed using the median and interquartile range (25%, 75%). Categorical variables are presented as case numbers (percentages).

Abbreviations: eGFR, estimated glomerular filtration rate; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; CK-MB, creatine kinase-myoglobin binding; ARNI, angiotensin receptor/neprilysin inhibitor; ACEI, Angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker.

Discussion

In recent years, with the advancement of molecular biology technologies, new biomarkers have emerged, such as miRNA and genomic sequencing.[12,13] Although most of these biomarkers are still in the experimental research stage, they often offer advantages of high sensitivity and specificity. However, their adoption is limited by the lack of more in-depth clinical studies or their relatively higher costs. Some ratio-based biological markers, on the other hand, not only have the advantage of being cost-effective but also significantly improve diagnostic efficacy compared to traditional single

Table 3 Univariate COX Regression Analysis Results for MACEs

Variables	β	S.E	Wald χ^2	HR (95% CI)	P
Age>60	0.783	0.134	34.079	2.189 (1.683–2.847)	<0.001
Male	−0.386	0.128	9.066	0.68 (0.529–0.874)	0.003
Coronary heart disease	0.733	0.132	31.012	2.081 (1.608–2.694)	<0.001
Arrhythmia	0.727	0.13	31.482	2.069 (1.605–2.667)	<0.001
Diabetes	−0.013	0.135	0.01	0.987 (0.757–1.286)	0.922
Hyperlipidemia	0.514	0.36	2.039	1.671 (3.382–1.286)	0.153
Cerebrovascular disease	0.122	0.162	0.561	11.129 (0.821–1.553)	0.454
Chronic kidney disease	−0.838	0.128	42.619	0.433 (0.336–0.556)	<0.001
Hypertension	−0.181	0.047	15.117	0.834 (0.761–0.914)	<0.001
Chronic lung disease	0.667	0.137	23.7	1.948 (1.489–2.548)	<0.001
Smoking history	0.04	0.142	0.08	1.041 (0.788–1.376)	0.777
Drinking history	−0.001	0.17	0	0.999 (0.716–1.393)	0.995
White blood cell	0.045	0.014	9.568	1.046 (1.017–1.076)	0.002
Red blood cell	0.126	0.066	3.664	1.134 (0.997–1.29)	0.056
Hemoglobin	0.001	0.001	2.676	1.001 (1–1.002)	0.102
Platelet	0	0.001	0.013	1(0.999–1.002)	0.91
Neutrophil	0.018	0.009	4.417	1.018 (1.001–1.036)	0.036
Lymphocyte	−0.084	0.096	0.754	0.92 (0.761–1.111)	0.385
Eosinophil	−0.732	0.386	3.593	0.481 (0.225–1.025)	0.058
Basophil	0.146	0.275	0.283	1.158 (0.675–1.985)	0.595
Thrombin time	0.019	0.006	11.689	1.019 (1.008–1.03)	0.001
Fibrinogen	−0.015	0.044	0.121	0.985 (0.904–1.073)	0.728
Blood urea nitrogen	−0.026	0.006	15.936	0.975 (0.962–0.987)	<0.001
Creatinine	−0.002	0	52.686	0.998 (0.998–0.999)	<0.001
Uric acid	0.001	0	3.691	1.001 (1–1.001)	0.055
eGFR	0.009	0.002	26.208	1.009 (1.006–1.012)	<0.001
Albumin	−0.006	0.008	0.62	0.994 (0.979–1.009)	0.431
Globulin	0.004	0.002	4.321	1.004 (1–1.008)	0.038
Total bilirubin	0.009	0.002	21.975	1.009 (1.005–1.013)	<0.001
Total cholesterol	−0.006	0.034	0.028	0.994 (0.93–1.063)	0.866
Triglyceride	0.277	0.049	32.267	1.319 (1.199–1.451)	<0.001
HDL-C	0.054	0.089	0.367	1.055 (0.887–1.255)	0.544
LDL-C	−0.173	0.065	7	0.841 (0.74–0.956)	0.008
Troponin	0.048	0.016	8.953	1.049 (1.017–1.082)	0.003
CK-MB	0.007	0.002	14.859	1.007 (1.004–1.011)	<0.001
C-reactive protein	0.004	0.001	13.316	1.004 (1.002–1.006)	<0.001
Blood glucose	0.092	0.011	73.166	1.097 (1.074–1.12)	<0.001
Glycosylated hemoglobin	0.148	0.038	15.321	1.16 (1.077–1.249)	<0.001
Aspirin	0.373	0.131	8.11	1.452 (1.123–1.877)	0.004
Ticagrelor	0.235	0.208	1.281	1.265 (0.842–1.9)	0.258
Clopidogrel	0.734	0.147	25.054	2.084 (1.563–2.777)	<0.001
ARNI	−0.329	0.163	4.072	0.72 (0.523–0.991)	0.044
ACEI	−0.104	0.13	0.631	0.902 (0.698–1.164)	0.427
Beta-blocker	−0.039	0.129	0.09	0.962 (0.747–1.239)	0.764
Statins	0.481	0.129	13.933	1.617 (1.256–2.081)	<0.001
Diuretics	0.935	0.131	50.538	2.546 (1.968–3.295)	<0.001
Digoxin	0.514	0.173	8.81	1.672 (1.191–2.347)	0.003
CCB	−0.734	0.144	26.05	0.48 (0.362–0.636)	<0.001
TyG	1.648	0.173	90.598	5.198 (3.702–7.298)	<0.001

Abbreviations: eGFR, estimated glomerular filtration rate; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; CK-MB, creatine kinase-myoglobin binding; ARNI, angiotensin receptor/neprilysin inhibitor; ACEI, Angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker.

Table 4 Univariate COX Regression Analysis Results for ACM

Variables	β	S.E	Wald χ^2	HR (95% CI)	P
Age>60	1.123	0.181	38.596	3.075 (2.157–4.383)	<0.001
Male	−0.484	0.161	9.072	0.616 (0.45–0.844)	0.003
Coronary heart disease	0.638	0.165	15.039	1.893 (1.371–2.613)	<0.001
Arrhythmia	0.712	0.162	19.434	2.039 (1.485–2.799)	<0.001
Diabetes	−0.015	0.169	0.008	0.985 (0.707–1.373)	0.929
Hyperlipidemia	−0.184	0.583	0.1	0.832 (0.265–2.608)	0.752
Cerebrovascular disease	0.222	0.199	1.255	1.249 (0.846–1.843)	0.263
Chronic kidney disease	−0.634	0.161	15.554	0.531 (0.387–0.727)	<0.001
Hypertension	−0.863	0.161	28.796	0.422 (0.308–0.578)	<0.001
Chronic lung disease	0.687	0.169	16.442	1.987 (1.426–2.77)	<0.001
Smoking history	−0.087	0.182	0.229	0.916 (0.641–1.31)	0.632
Drinking history	−0.119	0.218	0.296	0.888 (0.579–1.362)	0.586
White blood cell	0.06	0.017	12.224	1.062 (1.027–1.099)	<0.001
Red blood cell	0.064	0.084	0.581	1.066 (0.904–1.258)	0.446
Hemoglobin	0.001	0.001	2.267	1.001 (1–1.003)	0.132
Platelet	−0.001	0.001	1.646	0.999 (0.997–1.001)	0.2
Neutrophil	0.025	0.009	7.429	1.025 (1.007–1.043)	0.006
Lymphocyte	−0.364	0.147	6.146	0.695 (0.521–0.927)	0.013
Eosinophil	−2.317	0.723	10.269	0.099 (0.024–0.407)	0.001
Basophil	0.221	0.313	0.5	1.247 (0.676–2.303)	0.48
Thrombin time	0.022	0.006	11.778	1.022 (1.009–1.035)	0.001
Fibrinogen	−0.138	0.072	3.627	0.871 (0.756–1.004)	0.057
Blood urea nitrogen	−0.007	0.007	0.88	0.993 (0.979–1.007)	0.348
Creatinine	−0.001	0	24.206	0.999 (0.998–0.999)	<0.001
Uric acid	0.001	0	9.892	1.001 (1.001–1.002)	0.002
eGFR	0.004	0.002	3.69	1.004 (1–1.009)	0.055
Albumin	−0.032	0.012	7.268	0.969 (0.946–0.991)	0.007
Globulin	0.002	0.003	0.289	1.002 (0.995–1.008)	0.591
Total bilirubin	0.011	0.002	28.069	1.011 (1.007–1.015)	<0.001
Total cholesterol	0.006	0.04	0.024	1.006 (0.931–1.087)	0.878
Triglyceride	0.236	0.066	12.661	1.266 (1.112–1.442)	<0.001
HDL-C	0.1	0.09	1.253	1.106 (0.927–1.318)	0.263
LDL-C	−0.223	0.085	6.867	0.8 (0.677–0.945)	0.009
Troponin	0.059	0.016	12.723	1.061 (1.027–1.095)	<0.001
CK-MB	0.008	0.002	17.687	1.008 (1.004–1.011)	<0.001
C-reactive protein	0.005	0.001	20.836	1.005 (1.003–1.007)	<0.001
Blood glucose	0.081	0.014	33.216	1.085 (1.055–1.115)	<0.001
Glycosylated hemoglobin	0.107	0.049	4.818	1.113 (1.012–1.225)	0.028
Aspirin	0.159	0.167	0.901	1.172 (0.844–1.627)	0.342
Ticagrelor	−0.066	0.29	0.051	0.936 (0.531–1.653)	0.821
Clopidogrel	0.628	0.184	11.667	1.873 (1.307–2.685)	0.001
ARNI	−0.393	0.206	3.632	0.675 (0.45–1.011)	0.057
ACEI	−0.311	0.167	3.486	0.733 (0.528–1.016)	0.062
Beta-blocker	−0.297	0.161	3.414	0.743 (0.542–1.018)	0.065
Statins	0.171	0.161	1.128	1.186 (0.866–1.625)	0.288
Diuretics	0.754	0.163	21.349	2.126 (1.544–2.927)	<0.001
Digoxin	0.539	0.212	6.479	1.715 (1.132–2.597)	0.011
CCB	−0.872	0.189	21.385	0.418 (0.289–0.605)	<0.001
TyG	1.495	0.209	51.243	4.461 (2.962–6.718)	<0.001

Abbreviations: eGFR, estimated glomerular filtration rate; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; CK-MB, creatine kinase-myoglobin binding; ARNI, angiotensin receptor/neprilysin inhibitor; ACEI, Angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker.

Table 5 Multivariate Cox Regression Analysis Results for MACEs

Variables	Beta	S.E	Wald χ^2	HR (95% CI)	P
Age>60	0.479	0.155	9.611	1.614 (1.193–2.185)	0.002
Male	−0.165	0.161	1.038	0.848 (0.618–1.164)	0.308
Coronary heart disease	0.129	0.162	0.638	1.138 (0.829–1.562)	0.424
Arrhythmia	0.436	0.146	8.919	1.547 (1.162–2.059)	0.003
Chronic kidney disease	−0.13	0.158	0.676	0.878 (0.645–1.197)	0.411
Chronic lung disease	0.217	0.147	2.179	1.243 (0.931–1.658)	0.14
Hypertension	−0.083	0.053	2.446	0.92 (0.829–1.021)	0.118
Glycosylated hemoglobin	−0.048	0.044	1.213	0.953 (0.874–1.039)	0.271
Aspirin	0.104	0.156	0.44	1.109 (0.817–1.506)	0.507
Clopidogrel	0.173	0.165	1.099	1.189 (0.86–1.644)	0.295
ARNI	−0.134	0.172	0.607	0.875 (0.625–1.225)	0.436
Statins	0.09	0.162	0.311	1.094 (0.797–1.502)	0.577
Diuretics	0.307	0.165	3.461	1.36 (0.984–1.879)	0.063
Digoxin	0.153	0.193	0.627	1.165 (0.798–1.701)	0.428
CCB	−0.223	0.165	1.821	0.8 (0.579–1.106)	0.177
TyG	1.687	0.183	84.567	5.402 (3.771–7.739)	0
Smoking history	−0.063	0.181	0.119	0.939 (0.658–1.34)	0.73
LDL-C	−0.158	0.07	5.06	0.854 (0.744–0.98)	0.024
HDL-C	0.081	0.072	1.247	1.084 (0.941–1.249)	0.264
Total cholesterol	0.009	0.027	0.103	1.009 (0.957–1.062)	0.749
C-reactive protein	0.002	0.001	4.657	1.002 (1–1.005)	0.031

Abbreviations: HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; ARNI, angiotensin receptor/neprilysin inhibitor; CCB, calcium channel blocker.

Table 6 Multivariate Cox Regression Analysis Results for ACM

Variables	Beta	S.E	Wald χ^2	HR (95% CI)	P
Age>60	0.936	0.203	21.215	2.549 (1.712–3.797)	0
Male	−0.259	0.202	1.642	0.772 (0.519–1.147)	0.2
Coronary heart disease	0.073	0.198	0.137	1.076 (0.73–1.585)	0.711
Arrhythmia	0.407	0.183	4.946	1.502 (1.049–2.149)	0.026
Chronic kidney disease	0.121	0.196	0.377	1.128 (0.768–1.658)	0.539
Chronic lung disease	0.259	0.183	2.017	1.296 (0.906–1.854)	0.156
Hypertension	−0.209	0.066	10.157	0.811 (0.714–0.923)	0.001
Glycosylated hemoglobin	−0.109	0.057	3.659	0.897 (0.802–1.003)	0.056
Aspirin	0.064	0.203	0.099	1.066 (0.716–1.586)	0.753
Clopidogrel	0.256	0.212	1.46	1.292 (0.853–1.959)	0.227
ARNI	−0.06	0.219	0.076	0.942 (0.613–1.445)	0.783
Statins	−0.276	0.204	1.84	0.759 (0.509–1.131)	0.175
Diuretics	0.089	0.206	0.186	1.093 (0.73–1.635)	0.666
Digoxin	0.227	0.237	0.918	1.255 (0.788–1.999)	0.338
CCB	−0.331	0.213	2.42	0.718 (0.473–1.09)	0.12
Smoking history	−0.073	0.23	0.101	0.929 (0.592–1.459)	0.751
LDL-C	−0.222	0.089	6.225	0.801 (0.673–0.953)	0.013
HDL-C	0.13	0.084	2.389	1.139 (0.966–1.342)	0.122
Total cholesterol	0.024	0.029	0.682	1.025 (0.967–1.085)	0.409
C-reactive protein	0.004	0.001	9.689	1.004 (1.001–1.006)	0.002
TyG	1.622	0.223	52.795	5.062 (3.268–7.839)	0

Abbreviations: HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; ARNI, angiotensin receptor/neprilysin inhibitor; CCB, calcium channel blocker.

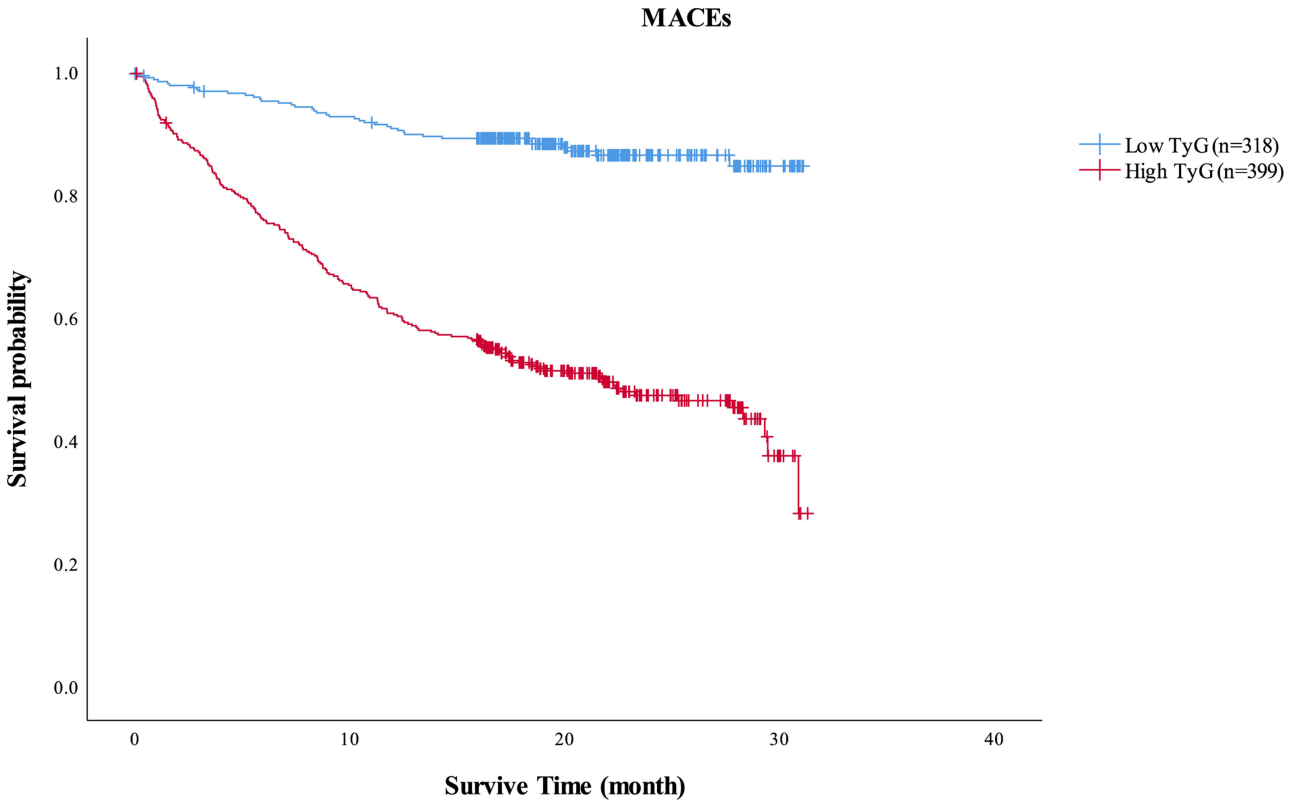

Figure 4 Kaplan–Meier curves for survival analysis of MACEs-free survival (Log rang p<0.001).

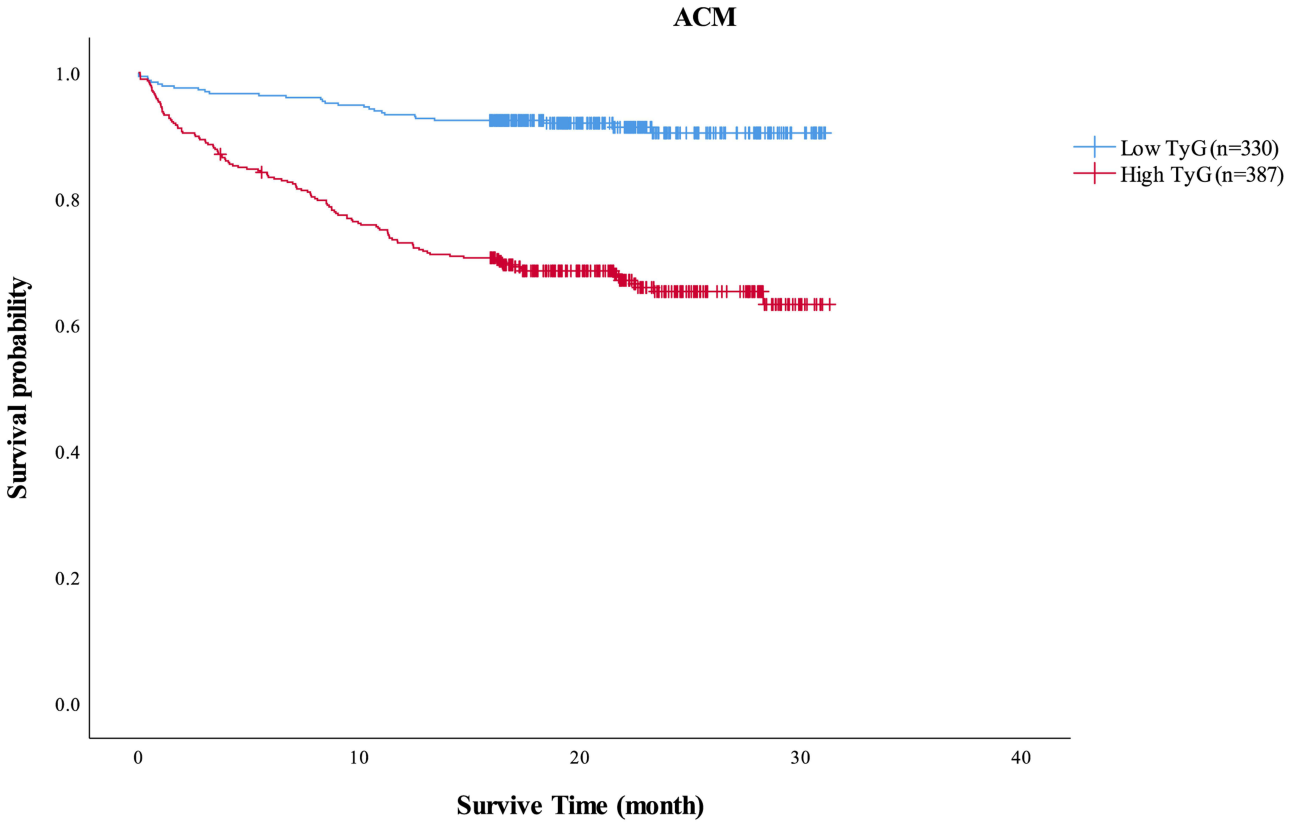

Figure 5 Kaplan–Meier curves for survival analysis of ACM-free survival (Log rang p<0.001).

biomarkers. The use of ratio-based biological markers in clinical practice has a long history, such as BMI. In recent years, some newly discovered biological ratios have also been validated for their clinical utility through multiple clinical studies.[14] These indicators can systematically reflect certain clinically significant conditions that impact disease. For instance, the SII can systematically indicate the overall level of inflammation in the body, and was found to be useful for predicting outcomes in patients with coronary heart disease.[15] Additionally, the Atherogenic Index of Plasma (AIP) can predict plaque burden in coronary artery disease patients undergoing IVUS examination.[16]

TyG index, discovered in recent years, is a novel biomarker believed to have the ability to reflect the level of insulin resistance (IR) in the body.[17] IR refers to a pathological condition characterized by a reduced response to insulin and often occurs in patients with type 2 diabetes mellitus (T2DM).[18] Besides diabetic patients, IR is also widely prevalent in conditions such as hyperlipidemia or hypertension and is considered a risk factor and predictor for a variety of cardiovascular diseases and renal diseases.[19,20] Existing research suggests that IR is a significant pathophysiological basis for metabolic syndrome and serves as a hallmark of systemic metabolic dysregulation or inflammatory response. When insulin-responsive cells are exposed to hormones secreted under conditions of hypoxia, excessive glucose, lipids, or obesity, various cellular stress responses coordinate to induce the occurrence of IR.[21] IR is a critical early pathophysiological process in atherosclerosis, which can promote plaque formation through various mechanisms, such as facilitating migration of vascular smooth muscle cells to the endothelium, exacerbating local inflammatory responses, damaging endothelial function, and subsequently promoting plaque formation.[22] In addition to its involvement in cardiovascular disease occurrence, IR is also associated with renal function impairment. Studies have found that insulin receptors are widely present on the surface of cells throughout the kidney. When IR occurs, insulin receptors in the kidney are simultaneously downregulated, affecting blood pressure and local vascular function through multiple pathways such as promoting sodium retention, downregulating eNOS production, and reducing NO bioavailability, thereby adversely affecting renal function.[21]

Currently, the commonly used method for assessing IR in clinical practice is the glucose tolerance test, but its complexity often results in poor patient compliance. HOMA-IR is a relatively convenient and accurate method for evaluating IR.[23] However, its accuracy is significantly reduced in patients receiving insulin treatment or those with complete loss of pancreatic beta-cell function, limiting its clinical applicability. In comparison to the previous two assessment methods, the TyG index is highly accurate, simple, and unaffected by insulin treatment, making it the focus of widespread attention in recent years.[24]

The association between the TyG index and cardiovascular diseases has been widely recognized. As mentioned earlier, since the TyG index primarily reflects the level of IR in the body, and IR is closely associated not only with the onset of type 2 diabetes mellitus but also with cardiovascular disease risk factors such as hyperlipidemia, hypertension, or coagulation abnormalities.[25,26] Currently, the TyG index has been confirmed to be closely associated with the prognosis of healthy individuals or patients with coronary heart disease. Yang et al studied 592,616 individuals and found an association between the TyG index and ischemic stroke.[27] Erdogan et al suggested that the TyG index could serve as a predictor of adverse cardiovascular outcomes in patients with chronic coronary heart disease.[28] A meta-analysis involving 10,164 patients found a strong correlation between high TyG index and post-PCI major adverse cardiovascular events (MACEs), non-fatal myocardial infarction, and all-cause mortality.[29]

Clinically, there are many factors that can influence the TyG index. Theoretically, any disease or medication that affects triglyceride levels and fasting blood glucose may affect the predictive ability of the TyG index. However, Sun et al found that regardless of whether patients have diabetes, the predictive ability of the TyG index for post-PCI MACEs risk remained consistent.[29] About 80% of obese patients have hypertriglyceridemia, and almost all cardiovascular diseases are associated with obesity, which adversely affects patient prognosis.[30] However, in patients with acHF accompanied by RD, weight gain due to water and sodium retention and worsening nutritional status may lead to a decrease in fat content, making BMI not a true reflection of obesity status. Therefore, for these patients, the potential application of the TyG index is higher because it can more accurately reflect the patient's glucose and lipid metabolism and insulin resistance capabilities.

The Tehran Lipid and Glucose Study indicated that the TyG index can serve as an alternative marker to HOMA-IR and is associated with an increased risk of chronic renal disease and decreased renal function.[31] Additionally, researchers have found a close association between elevated TyG index and decreased renal function in patients with diabetes and acute coronary

syndrome.[32,33] Since deteriorating renal function is a significant risk factor for poor prognosis in HF patients, with approximately 40% of HF patients experiencing renal impairment,[34] we hypothesize that there is also an association between the TyG index and patient prognosis in patients with acHF accompanied by RD. This study, by revealing the association between the TyG index and patient outcomes, found that patients with a high TyG index had significantly worse clinical outcomes. The TyG index can be used as a predictive factor for patient prognosis. We believe that the reasons for the poorer prognosis in patients with high TyG levels may include: (1) Dyslipidemia is a crucial risk factor for atherosclerosis and one of the initiating factors for HF. The increased blood viscosity due to elevated lipid levels imposes an additional burden on the cardiac of HF patients.[35] (2) Prolonged hyperlipidemia can induce oxidative stress in renal tubular epithelial cells and lead to glomerulosclerosis, adversely affecting renal function.[8] (3) Abnormal glucose metabolism resulting in a hyperglycemic state induces oxidative stress, impairs vascular relaxation and contraction, thereby contributing to the occurrence of cardiovascular diseases and renal failure.[36,37]

Conclusions

We identified the TyG index as an independent risk factor for MACEs and ACM in patients with acHF and RD, demonstrating significant predictive potential. Given that this study is retrospective and conducted at a single center, further multicenter studies are still needed to validate the conclusions.

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author, upon reasonable request.

Ethics Approval

This study has been approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University, and the ethics batch number is 2021-KY-0720-002. The data are anonymous, and the requirement for informed consent was therefore waived. Our research conformed to the Declaration of Helsinki. Personal information and data remained confidential and anonymous.

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Disclosure

The authors declare that there are no competing interests associated with the manuscript.

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