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Association between triglyceride-glucose index and all cause mortality in critically ill patients with heart failure

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The triglyceride-glucose (TyG) index is regarded as a surrogate marker of systemic insulin resistance (IR). Studies have substantiated the impact of IR on cardiovascular diseases. Nonetheless, the prognostic value of the TyG index in critical patients with heart failure (HF) with intensive care unit (ICU) admission remains unclear. This study aims to assess the association between the TyG index and all-cause mortality in critically ill patients with HF. Patients with HF requiring ICU admission were identified from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database and subsequently stratified into quartiles based on their TyG index. The primary outcome was 30-day all-cause mortality, and the secondary outcome was 1-year all-cause mortality. The relationship between the TyG index and all-cause mortality in HF patients was analyzed using multivariable Cox proportional hazards models and restricted cubic splines. A total of 1220 patients (62.4% men) were enrolled, with a mean age of 70.6 years. The 30-day and one-year all-cause mortality rate were 15.7% and 34.6%, respectively. Multivariable Cox regression revealed that TyG index was significantly associated with an elevated risk of 30-day all-cause mortality (adjusted HR, 1.360; 95% CI, 1.093–1.694; $P = 0.006$), but not with one-year mortality (adjusted HR 1.046; 95% CI 0.895–1.222, $P = 0.574$). Restricted cubic splines showed a progressively increasing risk of 30-day mortality was linearly related to an elevated TyG index. Subgroup analyses indicated a more prominent association between TyG index and 30-day mortality in patients with age ≤ 65, female or BMI > 30 kg/m². In critically ill patients with HF, the TyG index is significantly associated with short-term all-cause mortality. Our results highlight that the TyG index can be useful in identifying HF patients at high risk of all-cause mortality and require close follow-up after discharge.

Heart failure (HF) is a serious, life-threatening clinical syndrome characterized by high morbidity, mortality, readmission rates, and significant healthcare costs. HF has been regarded as a global pandemic, with a prevalence of 1.0–2.0% among adults in developed countries[1]. According to the China Hypertension Survey conducted from 2012 to 2015, the prevalence of HF in adults 35 years and older is 1.3%, corresponding to approximately 13.7 million patients[2]. Consequently, it has become a critical global public health priority to reduce the heavy socio-economic burden of HF. Accurate diagnosis and timely screening of patients undergoing deteriorated situations are essential prerequisites for the effective treatment of HF.

Insulin resistance (IR) refers to the diminished physiological effect of insulin in the body and is a common pathological mechanism underlying various metabolic disorders[3]. One of the earliest metabolic disturbances observed in failing hearts is cardiac IR, which is generally defined as a significant reduction in insulin-stimulated glucose oxidation rates. IR only serves as a marker for HF severity, but also contributes to contractile dysfunction[4]. IR is a predominated metabolic dysfunction in HF, especially among patients with preserved ejection fraction (HFpEF), and the relationship seem to be bidirectional[5]. Existing evidence indicates that IR is associated with

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left ventricular (LV) remodeling and adverse outcomes in patients with HF[6,7]. Therefore, improving IR in HF patients is believed to alleviate the severity of their disease. The triglyceride-glucose (TyG) index, a great surrogate measurement of IR, has been widely utilized in clinical research. Several cross-sectional studies have shown that the TyG index is associated with hypertension[8], arterial stiffness[9], and stroke[10]. However, the situation becomes more sophisticated for HF patients admitted to the intensive care unit (ICU). Recently, a study utilizing the MIMIC-IV database, indicated an inverse association between TyG-BMI and all-cause mortality among critically ill patients with HF, while included only 423 participants[11]. However, other studies have reported the positive relationship between the TyG index and mortality in HF patients[12–14]. The predicative value of the TyG index in critical ill patients with HF remains a topic of ongoing debate. Our study is to evaluate the association between the TyG index and all-cause mortality in critically ill patients with HF utilizing the MIMIC-IV database. The aim of this evaluation is to inform the development of new clinical treatment strategies and to improve the prognosis for HF patients.

Methods

Study population

This is a retrospective observational study utilizing data from the MIMIC-IV database (version 2.2), which includes records of patients admitted to the ICU of Beth Israel Deaconess Medical Center from 2008 to 2019. This publicly available, de-identified database contains detailed patient information such as physiological signals, medication use, laboratory results, and nursing notes. Created by MIT's Computational Physiology Laboratory, it supports clinical research and medical informatics education. One author (JX) completed NIH training on human research participant protection and passed CITI assessments to access the data. The MIT and Beth Israel Deaconess Medical Center review boards approved the database's use in research. Informed consent was waived due to the database's de-identified and anonymous nature.

This study included 9383 HF patients from the MIMIC-IV database who were admitted to the ICU for the first time, aged ≥ 18 years, and had an ICU stay exceeding 24 h. ICD-9 and ICD-10 codes were used to identify HF patients. Follow-up began at admission and ended at death. The final study included 1220 patients, excluding patients with incomplete triglyceride (TG) or glucose measurements and patients without other essential information. These patients were divided into four groups based on the quartiles of the TyG index (Fig. 1).

Data collection

A structured query language (SQL) with PostgreSQL (version 13.13) and Navicate Premium 15 was used to extract baseline characteristics, including age, sex, body mass index (BMI) and multiple vital signs. These vital signs encompassed heart rate (HR), systolic and diastolic blood pressure (SBP and DBP), mean blood pressure (MBP), respiratory rate (RR), body temperature (T), and oxygen saturation (SpO2). Various scoring systems were used to assess the severity of each case at the time of admission. These included the systemic inflammatory response syndrome (SIRS), the simplified acute physiological score II (SAPSII), the logistic organ dysfunction system (LODS), the Glasgow coma scale (GCS), the acute physiology scores III (APSIII), and the sequential organ failure assessment (SOFA) score. Patients' medical histories were also considered, including heart attacks, peripheral vascular disease, strokes, dementia, chronic lung disease, rheumatic disease, peptic ulcers, mild liver disease, paraplegia, kidney disease, cancer, severe liver disease, metastatic solid tumors, AIDS, and diabetes.
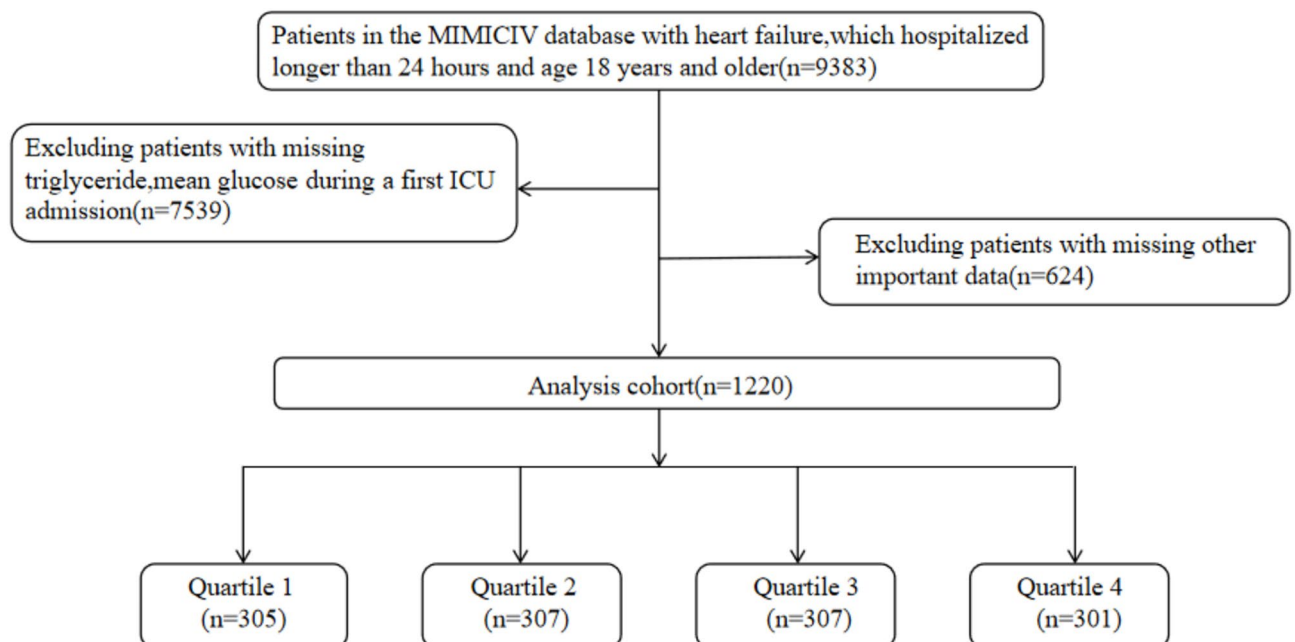

Fig. 1. Flowchart illustrating selection of patients from the MIMIC-IV database.

The laboratory parameters measured included red blood cells (RBC), white blood cells (WBC), hemoglobin, platelet counts, albumin, bilirubin, liver enzymes (ALT and AST), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), glucose, HbA1c, anion gap, blood urea nitrogen (BUN), calcium, bicarbonate, chloride, creatinine, sodium, potassium, troponin T, CK-MB, NT-pro-BNP and coagulation function indicators (INR, PT, and PTT). The initial recorded value was taken into account when a variable was recorded more than once within the preceding 24 h. In addition, we also included the patients' left ventricular ejection fraction (LVEF) manually case by case. Outcomes including 30-day and one-year all-cause mortality, as well as hospital and ICU length of stay (LOS), were also collected.

Calculation of TyG index

The TyG index was usually calculated as ln [fasting TG (mg/dl) × fasting glucose (mg/dl)]/2[15]. However, given the difficulty in obtaining accurate fasting blood glucose data from the MIMIC-IV database and considering that initial ICU glucose levels could be affected by acute stressors like pain, infection, or trauma and interventions like epinephrine administration, leading to transient hyperglycemia, we used the average glucose level during the ICU stay as a surrogate measurement of fasting glucose. And to expand the sample size, also to account for the fact that the triglyceride levels cannot fluctuate significantly in the short term, we extracted the patient's initial triglyceride levels during admission.

Outcomes

The primary outcome was 30-day all-cause mortality, and the secondary outcome was one-year all-cause mortality.

Statistical analysis

Variables with over 20% missing data were excluded from the study. In instances where less than 20% of the data was missing, the gaps were filled using random forest interpolation. Continuous variables are presented as either mean (standard deviation) or median with interquartile range and were analyzed using the Mann–Whitney U test or the student t-test. On the other hand, categorical variables are expressed as frequencies and percentages, and the differences between groups were assessed using the Pearson chi-square test or Fisher's exact test. We applied Kaplan-Meier survival analysis to evaluate the incidence rate of primary outcome events across groups with different TyG index levels. Differences among these groups were examined using log-rank tests. The association between the TyG index and primary outcomes was determined using Cox proportional hazards models, which provided the hazard ratio (HR) and 95% confidence interval (CI). This was done while adjusting for various models that incorporated clinically relevant variables associated with prognosis. For instance, model 1 adjusted for age, sex, BMI, and race; model 2 further included RR, MBP, hemoglobin, creatinine, potassium, INR, and LVEF; model 3 additionally adjusted for SAPSII, LODS, APSIII, and SOFA scores. The restricted cubic spline method was used to investigate the potential nonlinear relationships between the TyG index and outcomes. The TyG index was included in the models as either a continuous variable or an ordinal variable, with the lowest quartile used as the reference. Further stratified analyses were conducted based on sex, age (≤ 65 and > 65 years), BMI (< 30 and ≥ 30 kg/m²), LVEF (< 40 and ≥ 40%), diabetes, and myocardial infarction to assess the consistency of the prognostic significance of the TyG index for primary outcomes. The interactions between the TyG index and stratification variables were evaluated using likelihood ratio tests.

All data analyses were conducted using R version 4.4.0 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided P-value < 0.05 was deemed statistically significant for all analyses.

Results

Baseline characteristics

The study included 1220 critical patients with HF, with an average age of 70.6 ± 13.7 years, and 62.4% were male. During follow-up, 191 (15.7%) patients died within 30 days, and 422 (34.6%) patients died within one year (Table 1).

Patients were categorized into quartiles based on their admission TyG index (Q1: 7.252–8.544; Q2: 8.544–8.937; Q3: 8.937–9.376; Q4: 9.376–12.634). Patients with a higher TyG index (Q4 quartile) were generally younger, had higher BMI, more severe illness scores at admission, and a higher incidence of diabetes and myocardial infarction. These patients also had severer liver dysfunction and elevated levels of WBC, platelets, creatinine, serum potassium, troponin-T, HbA1c, and LVEF, but lower levels of HDL than those in the lower quartiles. Besides, there were no significant differences in RBC, hemoglobin, albumin, bicarbonate, calcium, sodium, BUN, LDL, or coagulation function ($P > 0.05$). As the TyG index increased, so did the length of stay in the ICU (5.40 days vs. 6.13 days vs. 7.14 days vs. 8.83 days, $P < 0.001$), while no differences were observed in the morality within 30-day (12.5% vs. 17.6% vs. 15.3% vs. 17.3%, $P = 0.426$) and one-year (33.4% vs. 40.1% vs. 32.2% vs. 32.6%, $P = 0.236$).

Comparisons between survivors and non-survivors on 30-day after discharge are detailed in Supplementary Table 1. The non-survivors were older, with elevated levels of BMI, HR, DBP, and temperature at admission, and higher prevalence of cerebrovascular disease, liver disease, renal disease, and malignant cancer ($P < 0.05$). Regarding the laboratory examinations, patients in the non-survival group exhibited higher levels of WBC, anion gap, creatinine, and BUN, as well as INR and PT, while lower levels of RBC, hemoglobin, albumin, total cholesterol, HDL, and bicarbonate ($P < 0.05$). Furthermore, non-survivors had higher scores of SOFA, SIRS, APSIII, LODS, and SAPSII compared to survivors, indicating more severe illness ($P < 0.05$). As for the duration of hospitalization, it was found that the non-survivors experienced a shorter in-hospital stay (16.6 days vs. 12.6 days, $P = 0.027$) and a longer ICU stay (6.69 days vs. 7.79 days, $P < 0.001$) in comparison to the survivors.

Categories	Overall (N = 1220)	Q1 (N = 305)	Q2 (N = 307)	Q3 (N = 307)	Q4 (N = 301)	P-value
Age, years	70.6 (13.7)	73.1 (13.9)	73.0 (13.2)	69.1 (12.6)	67.1 (14.2)	< 0.001
Gender, n (%)						
Female	459 (37.6%)	108 (35.4%)	119 (38.8%)	117 (38.1%)	115 (38.2%)	0.927
Male	761 (62.4%)	197 (64.6%)	188 (61.2%)	190 (61.9%)	186 (61.8%)	
Race, n (%)						
White	1007 (82.5%)	245 (80.3%)	260 (84.7%)	254 (82.7%)	248 (82.4%)	
Asian	31 (2.5%)	8 (2.6%)	7 (2.3%)	9 (2.9%)	7 (2.3%)	0.708
Black	86 (7.0%)	31 (10.2%)	18 (5.9%)	21 (6.8%)	16 (5.3%)	
Hispanic-Latino	31 (2.5%)	10 (3.3%)	7 (2.3%)	7 (2.3%)	7 (2.3%)	
Other	65 (5.3%)	11 (3.6%)	15 (4.9%)	16 (5.2%)	23 (7.6%)	
Weight, kg	85.4 (24.2)	78.1 (20.5)	82.3 (21.3)	87.5 (25.5)	93.8 (26.1)	< 0.001
BMI, kg/m^2	29.7 (7.36)	27.3 (6.40)	28.9 (6.29)	30.4 (8.16)	32.2 (7.54)	< 0.001
Vital signs						
HR, bpm	86.2 (16.3)	85.2 (16.6)	85.8 (16.3)	86.6 (16.1)	87.4 (16.2)	0.553
SBP, mmHg	116 (16.9)	114 (16.7)	117 (16.8)	116 (17.0)	118 (17.1)	0.0395
DBP, mmHg	63.3 (11.7)	62.8 (11.7)	63.3 (12.5)	63.8 (11.1)	63.2 (11.6)	0.722
MBP, mmHg	78.2 (11.1)	77.1 (11.5)	78.4 (11.4)	78.7 (10.7)	78.7 (10.9)	0.184
RR, times/min	20.4 (3.96)	19.7 (3.70)	20.4 (3.90)	20.6 (3.90)	20.9 (4.23)	0.00599
T, °C	36.8 (0.577)	36.7 (0.517)	36.7 (0.495)	36.9 (0.549)	36.9 (0.690)	< 0.001
SpO$_2$, %	96.6 (2.16)	96.7 (2.35)	96.7 (1.98)	96.5 (2.26)	96.5 (2.03)	0.595
Laboratory parameters						
RBC, m/uL	3.69 (0.826)	3.61 (0.823)	3.65 (0.785)	3.78 (0.869)	3.74 (0.819)	0.0734
WBC, m/uL	12.6 (7.61)	11.2 (5.20)	12.6 (10.1)	12.9 (6.83)	13.6 (7.30)	< 0.001
Hematocrit, %	33.5 (7.23)	32.8 (7.19)	33.3 (6.87)	34.2 (7.69)	33.8 (7.08)	0.166
Hemoglobin, g/dL	11.0 (2.43)	10.8 (2.39)	10.9 (2.32)	11.2 (2.59)	11.1 (2.41)	0.244
Platelet, K/uL	209 (93.9)	196 (82.0)	210 (98.1)	217 (94.5)	215 (98.9)	0.0131
Albumin, g/dL	3.34 (0.619)	3.36 (0.657)	3.36 (0.632)	3.37 (0.549)	3.28 (0.635)	0.455
Bilirubin, g/dL	1.35 (2.70)	1.47 (2.70)	1.26 (1.48)	1.08 (1.82)	1.59 (4.02)	0.0328
ALT, IU/L	169 (680)	161 (524)	137 (637)	201 (892)	170 (585)	0.0282
AST, IU/L	268 (1110)	208 (615)	238 (1110)	351 (1580)	267 (839)	0.0478
TC, mg/dL	145 (51.7)	132 (41.9)	146 (57.5)	148 (49.7)	159 (54.6)	0.00376
HDL, mg/dL	42.5 (16.8)	47.8 (18.2)	44.2 (15.5)	39.2 (14.6)	36.9 (16.8)	< 0.001
LDL, mg/dL	79.8 (42.8)	72.8 (32.5)	82.0 (51.1)	82.7 (42.4)	83.0 (43.2)	0.482
TG, mg/dL	141 (147)	67.7 (17.4)	97.5 (20.9)	135 (32.8)	267 (250)	< 0.001
Glucose, mg/dL	145 (45.5)	117 (22.8)	135 (27.7)	146 (35.8)	181 (59.9)	< 0.001
HbA1c, %	6.48 (1.82)	5.80 (0.932)	6.07 (1.55)	6.60 (1.75)	7.60 (2.36)	< 0.001
Anion gap, mmol/L	15.3 (4.42)	14.5 (4.49)	15.0 (4.04)	15.7 (4.27)	16.3 (4.68)	< 0.001
BUN, mg/dL	32.0 (23.4)	29.1 (18.8)	31.4 (22.3)	32.8 (24.5)	34.8 (27.1)	0.158
Calcium, mg/dL	8.34 (0.765)	8.28 (0.720)	8.35 (0.699)	8.39 (0.821)	8.34 (0.813)	0.565
Bicarbonate, mmol/L	23.1 (4.93)	23.3 (4.97)	23.3 (4.67)	23.1 (4.79)	22.8 (5.27)	0.743
Chloride, mEq/L	103 (6.67)	103 (7.02)	103 (6.66)	103 (6.87)	102 (6.02)	0.0142
Creatinine, mg/dL	1.65 (1.52)	1.41 (1.03)	1.60 (1.49)	1.76 (1.84)	1.84 (1.57)	< 0.001
Sodium, mEq/L	138 (5.33)	138 (5.91)	138 (4.99)	139 (5.56)	138 (4.78)	0.0774
Potassium, mEq/L	4.25 (0.687)	4.17 (0.640)	4.23 (0.695)	4.26 (0.697)	4.35 (0.706)	0.0138
INR, s	1.52 (0.808)	1.53 (0.656)	1.54 (0.767)	1.56 (1.08)	1.47 (0.644)	0.156
PT, s	16.6 (7.66)	16.7 (6.93)	16.8 (7.93)	16.7 (8.90)	16.0 (6.65)	0.125
PTT, s	45.0 (30.7)	47.9 (33.1)	43.1 (28.2)	44.0 (29.0)	44.9 (32.2)	0.0863
Troponin-t, ng/mL	1.50 (3.34)	1.11 (2.80)	1.32 (3.02)	1.96 (4.02)	1.51 (3.24)	0.00429
Ck-mb, ng/mL	38.0 (85.2)	30.7 (75.6)	31.4 (71.3)	42.7 (92.0)	46.0 (97.2)	0.364
NT-pro-BNP, pg/mL	9500 (11700)	7420 (9550)	7700 (7600)	11,400 (12600)	10,400 (14900)	0.605
LVEF (%)	41.5 (15.8)	39.3 (15.1)	41.6 (15.9)	41.2 (15.7)	43.8 (16.1)	0.0259
Clinical severity						
SIRS	2.61 (0.917)	2.44 (0.944)	2.56 (0.874)	2.66 (0.905)	2.79 (0.911)	< 0.001
SAPSII	40.1 (14.0)	39.0 (12.9)	40.6 (14.2)	39.5 (13.8)	41.3 (14.9)	0.416
LODS	5.49 (3.08)	5.02 (2.86)	5.32 (3.00)	5.56 (3.19)	6.08 (3.17)	< 0.001
Continued						

Categories	Overall (N = 1220)	Q1 (N = 305)	Q2 (N = 307)	Q3 (N = 307)	Q4 (N = 301)	P-value
GCS	14.4 (1.98)	14.3 (2.06)	14.5 (1.75)	14.3 (2.11)	14.5 (2.00)	0.283
APSIII	49.2 (20.7)	46.6 (19.8)	48.4 (19.8)	48.7 (21.2)	53.2 (21.6)	< 0.001
SOFA	5.64 (3.73)	5.10 (3.46)	5.34 (3.56)	5.83 (3.77)	6.30 (4.02)	0.00286
Comorbidities, n (%)						
Myocardial infarct	561 (46.0%)	120 (39.3%)	141 (45.9%)	147 (47.9%)	153 (50.8%)	0.0689
Peripheral vascular disease	194 (15.9%)	45 (14.8%)	55 (17.9%)	48 (15.6%)	46 (15.3%)	0.856
Cerebrovascular disease	308 (25.2%)	74 (24.3%)	94 (30.6%)	70 (22.8%)	70 (23.3%)	0.168
Dementia	41 (3.4%)	16 (5.2%)	10 (3.3%)	6 (2.0%)	9 (3.0%)	0.254
Chronic pulmonary disease	426 (34.9%)	110 (36.1%)	96 (31.3%)	116 (37.8%)	104 (34.6%)	0.541
Rheumatic disease	57 (4.7%)	13 (4.3%)	15 (4.9%)	12 (3.9%)	17 (5.6%)	0.879
Peptic ulcer disease	29 (2.4%)	9 (3.0%)	3 (1.0%)	10 (3.3%)	7 (2.3%)	0.399
Mild liver disease	133 (10.9%)	38 (12.5%)	28 (9.1%)	37 (12.1%)	30 (10.0%)	0.653
Severe liver disease	50 (4.1%)	16 (5.2%)	10 (3.3%)	14 (4.6%)	10 (3.3%)	0.699
Paraplegia	118 (9.7%)	30 (9.8%)	40 (13.0%)	27 (8.8%)	21 (7.0%)	0.15
Renal disease	410 (33.6%)	90 (29.5%)	93 (30.3%)	109 (35.5%)	118 (39.2%)	0.0741
Malignant cancer	105 (8.6%)	21 (6.9%)	38 (12.4%)	27 (8.8%)	19 (6.3%)	0.0683
Metastatic solid tumor	32 (2.6%)	6 (2.0%)	10 (3.3%)	8 (2.6%)	8 (2.7%)	0.91
AIDS	5 (0.4%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.7%)	0.959
Diabetes	476 (39.0%)	61 (20.0%)	88 (28.7%)	138 (45.0%)	189 (62.8%)	< 0.001
Outcomes, n (%)						
30-Day mortality	191 (15.7%)	38 (12.5%)	54 (17.6%)	47 (15.3%)	52 (17.3%)	0.426
One-year mortality	422 (34.6%)	102 (33.4%)	123 (40.1%)	99 (32.2%)	98 (32.6%)	0.236
LOS of hospital, days	16.0 (13.5)	15.2 (11.5)	15.2 (14.1)	16.3 (13.9)	17.3 (14.4)	0.417
LOS of ICU, days	6.87 (7.95)	5.40 (6.06)	6.13 (6.78)	7.14 (8.31)	8.83 (9.78)	< 0.001

Table 1. Baseline characteristics of critical patients with heart failure grouped according to TyG quartiles. *BMI* body mass index, *HR* Heart rate, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MBP* mean blood pressure, *RR* respiratory rate, *T* temperature, *WBC* white blood cell, *RBC* red blood cell, *AST* aspartate transaminase, *ALT* alanine aminotransferase, *TC* total cholesterol, *TG* triglyceride, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *HbA1c* hemoglobin A1c, *BUN* blood urea nitrogen, *INR* international normalized ratio, *PT* prothrombin time, *PTT* partial thromboplastin time, *SIRS* systemic inflammatory response syndrome, *SAPSII* simplified acute physiological score II, *LODS* logistic organ dysfunction system, *GCS* glasgow coma scale, *APSIII* acute physiology score III, *SOFA* sequential organ failure assessment, *TyG index* triglyceride glucose index, *LOS* length of stay. [a]TyG index: Q1 (7.252–8.544), Q2 (8.544–8.937), Q3 (8.937–9.376), Q4 (9.376–12.634).

Relationship between TyG index and prognosis of critical patients with HF

Figure 2 illustrates the Kaplan-Meier survival curves of the incidence of 30-day all-cause mortality stratified by TyG quartiles. It was showed that patients with the higher TyG index were more vulnerable to suffer from mortality within 30 days after discharge, compared to those in the lowest quartile of TyG index (log-rank $P < 0.001$).

To further investigate the association between the TyG index and all-cause mortality in critical HF patients, multivariable Cox proportional hazards models were constructed (Table 2). It was showed that the TyG index was significantly associated with 30-day mortality in the crude Model (HR 1.585 [95% CI 1.274–1.972], $P < 0.001$) and the fully adjusted model (HR 1.360 [95% CI 1.093–1.694], $P = 0.006$) when the TyG index was treated as a continuous variable. Furthermore, the TyG quartiles were also included in rank order, with the lowest quartile (Q1) as the reference group. After adjusting for age, gender, BMI, and race (Model 1), the TyG index was dose-responsibly associated with 30-day mortality (Q1 vs. Q2: HR 1.599 [95% CI 1.054–2.427], $P = 0.027$; Q3: HR 1.600 [95% CI 1.037–2.468], $P = 0.034$; Q4: HR 2.25 [95% CI 1.34–3.77], $P < 0.001$), indicating an increasing trend with rising TyG index levels. After full-adjustment for clinical characteristics and severity scores in Model 3, the TyG index still maintained a strong association with 30-day mortality (Q1 vs. Q2: HR, 1.545 [95% CI 1.012–2.359], $P = 0.044$; Q3: HR, 1.466 [95% CI 0.943–2.278], $P = 0.089$; Q4: HR, 1.782 [95% CI 1.145–2.772], $P = 0.010$), while non-significant association were found between TyG index and one-year mortality (adjusted HR, 1.046; 95% CI, 0.895–1.222; $P = 0.574$,Tab. S2).

The restricted cubic spline regression indicated that the risk of 30-day all-cause mortality increased linearly with rising TyG index levels (P for nonlinear = 0.351, Fig. 3), as did the risk of one-year all-cause mortality (P for nonlinear = 0.534, Fig. S2).
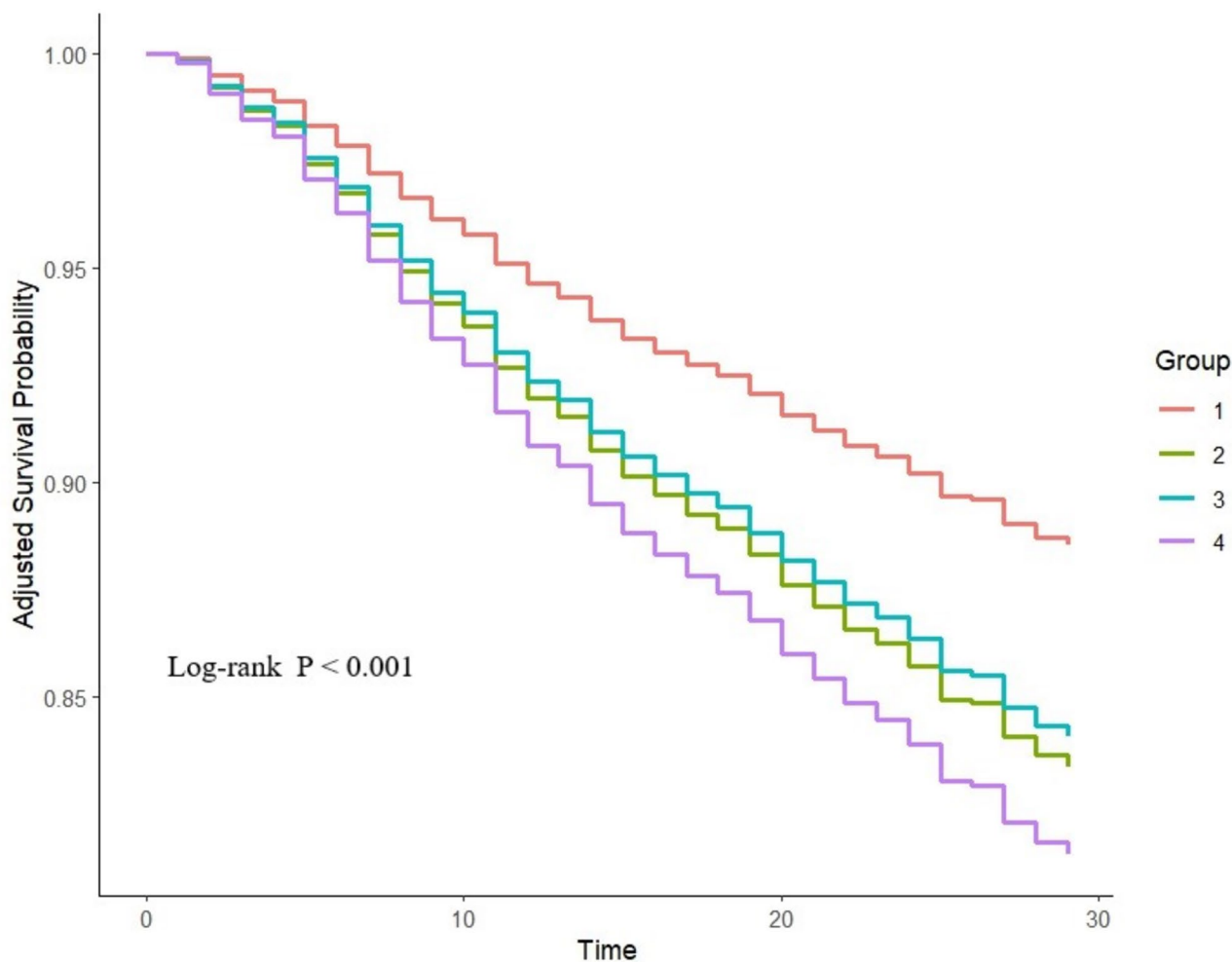
Fig. 2. Kaplan–Meier survival analysis curve for 30-day all-cause mortality. TyG index quartiles: Q1 (7.252–8.544), Q2 (8.544–8.937), Q3 (8.937–9.376), Q4 (9.376–12.634). Kaplan–Meier survival curve shows cumulative probability of all-cause mortality according to TyG quartiles at 30 days adjusted for age, gender, BMI, race, RR, MBP, hemoglobin, creatinine, potassium, INR, LVEF, SAPSII, LODS, APSIII, SOFA.

Categories	Model 1		Model 2		Model 3	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
TyG	1.585 (1.274,1.972)	< 0.001	1.535 (1.228,1.913)	< 0.001	1.360 (1.093,1.694)	0.006
Quartiles						
Q1 (*n* = 305)	Ref.		Ref.		Ref.	
Q2 (*n* = 307)	1.599 (1.054,2.427)	0.027	1.581 (1.039,2.407)	0.032	1.545 (1.012,2.359)	0.044
Q3 (*n* = 307)	1.600 (1.037,2.468)	0.034	1.519 (0.978,2.361)	0.063	1.466 (0.943,2.278)	0.089
Q4 (*n* = 301)	2.166 (1.402,3.348)	< 0.001	2.039 (1.312,3.269)	0.002	1.782 (1.145,2.772)	0.010

Table 2. Cox proportional hazard ratios (HR) for all-cause mortality at 30 days. Model 1: adjusted for age, gender, BMI, race. Model 2: adjusted for age, gender, BMI, race, RR, MBP, hemoglobin, creatinine, potassium, INR, LVEF. Model 3: adjusted for age, gender, BMI, race, RR, MBP, hemoglobin, creatinine, potassium, INR, LVEF, SAPSII, LODS, APSIII, SOFA. [a]TyG index: Q1 (7.252–8.544), Q2 (8.544–8.937), Q3 (8.937–9.376), Q4 (9.376–12.634).

Subgroups analyses

To further explore whether the association between the TyG index and 30-day all-cause mortality persisted under different conditions, subgroup analyses were conducted stratified by age, gender, BMI, LVEF, diabetes, and myocardial infarction (Fig. 4). The results indicated a more prominent association between TyG index and 30-day mortality in patients with age ≤ 65 (HR, 1.94; 95% CI, 1.00–3.77) and female (HR, 2.27; 95% CI, 1.25–4.10), with P for interaction of 0.142, 0.011, respectively.

Discussion

In this study, we explored the association between the TyG index and mortality in critical patients with HF within 30 days and one year. Through a detailed retrospective analysis of the MIMIC database, we found a significant positive association between the TyG index and 30-day all-cause mortality in HF patients requiring ICU admission. Specifically, increasing of the TyG index was corresponded with proportional rising of the mortality risk within 30 days after discharge. This relationship remains robust after careful adjustment for possible confounding factors. However, there was no significant association found between the TyG index and long-term mortality at one year.
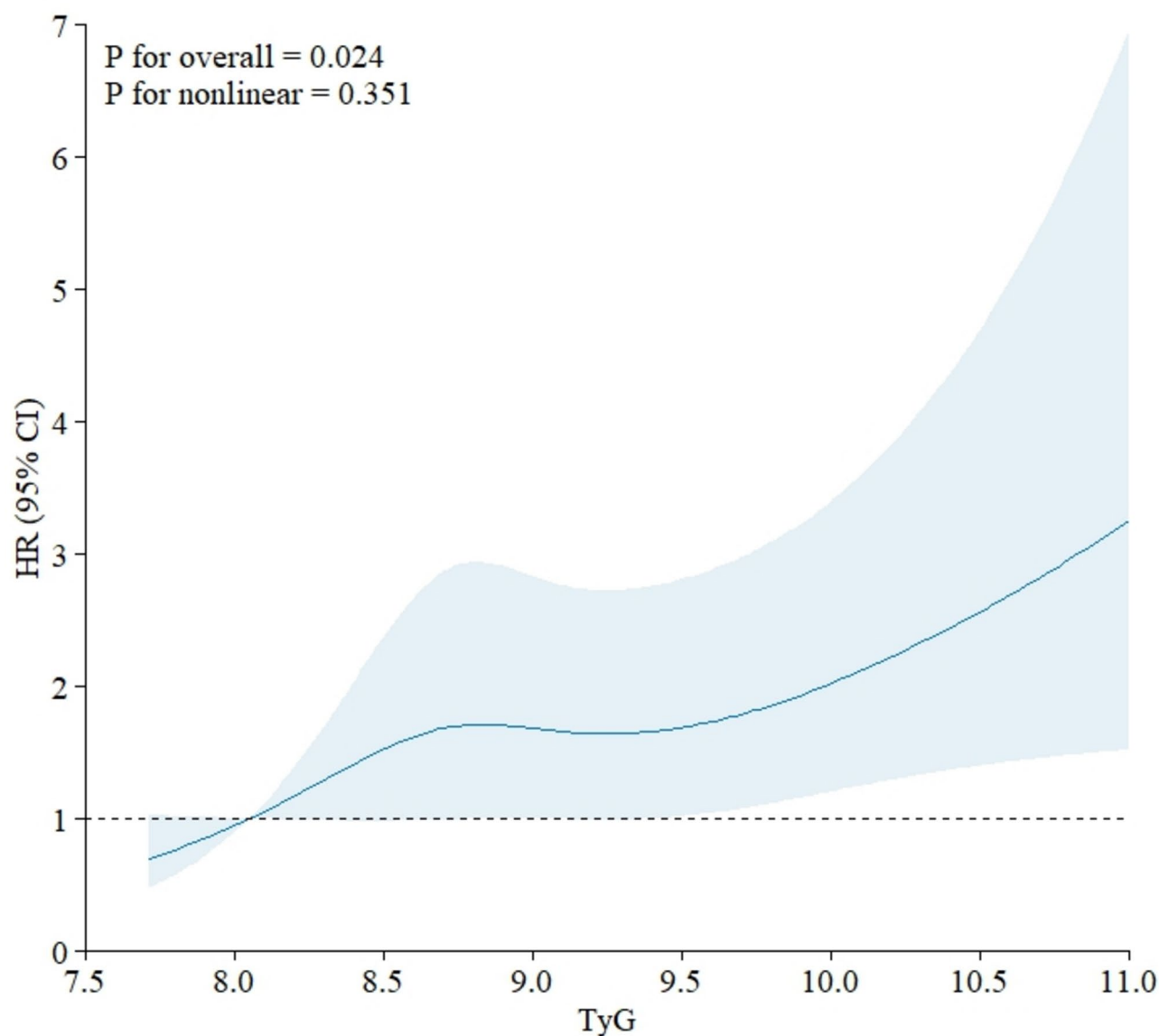

Fig. 3. The relationship between TyG index and the risk of 30-day mortality in critical ill patients with HF by restricted cubic spline regression. Graphs show HR for 30-day mortality according to TyG index adjusted for age, gender, BMI, race, RR, MBP, hemoglobin, creatinine, potassium, INR, LVEF, SAPSII, LODS, APSIII, SOFA. Data were fitted by a Cox regression model, and the model was conducted with 4 knots at the 5th, 35th, 65th, 95th percentiles of TyG index (reference is the 5th percentile). Solid lines indicate ORs, and shadow shape indicate 95% CIs. *HR* hazard ratio, *CI* confidence interval, *TyG* triglyceride-glucose index.
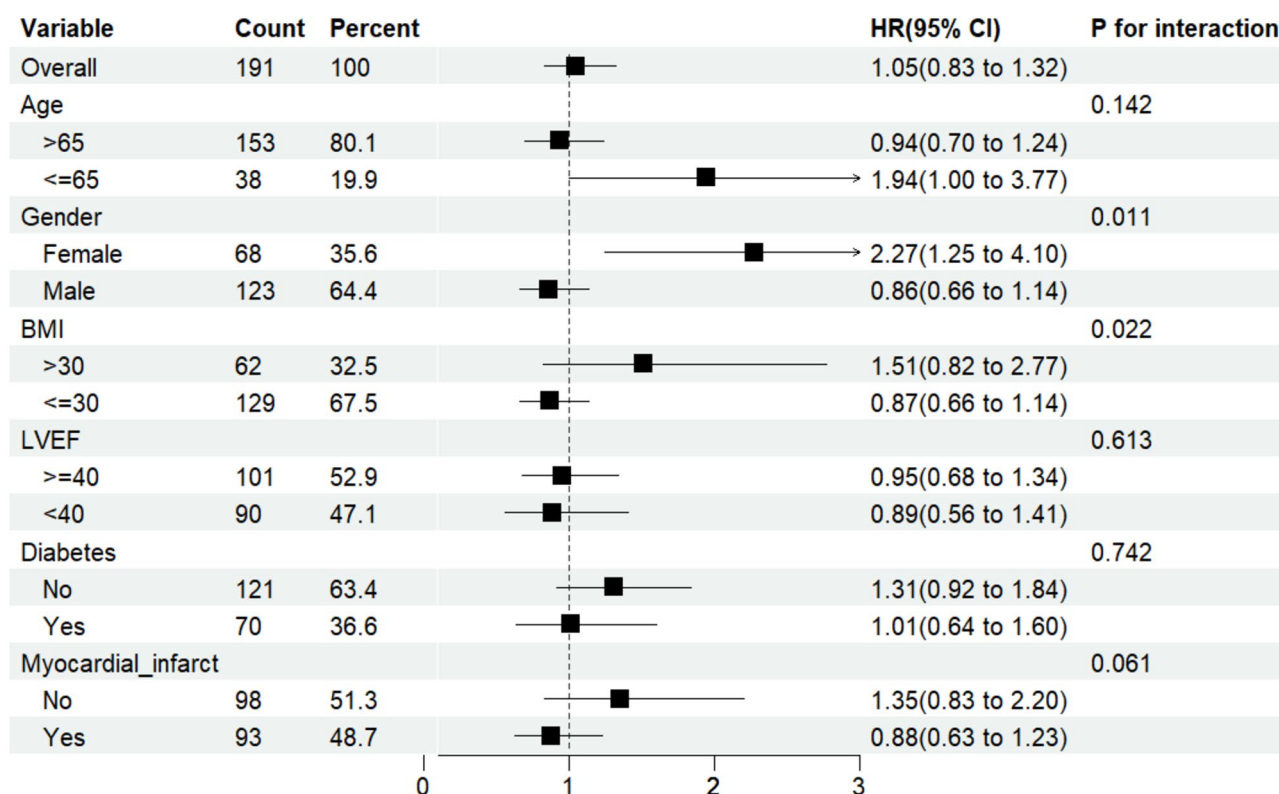
Variable	Count	Percent		HR(95% CI)	P for interaction
Overall	191	100		1.05(0.83 to 1.32)	
Age					0.142
>65	153	80.1		0.94(0.70 to 1.24)	
<=65	38	19.9		1.94(1.00 to 3.77)	
Gender					0.011
Female	68	35.6		2.27(1.25 to 4.10)	
Male	123	64.4		0.86(0.66 to 1.14)	
BMI					0.022
>30	62	32.5		1.51(0.82 to 2.77)	
<=30	129	67.5		0.87(0.66 to 1.14)	
LVEF					0.613
>=40	101	52.9		0.95(0.68 to 1.34)	
<40	90	47.1		0.89(0.56 to 1.41)	
Diabetes					0.742
No	121	63.4		1.31(0.92 to 1.84)	
Yes	70	36.6		1.01(0.64 to 1.60)	
Myocardial_infarct					0.061
No	98	51.3		1.35(0.83 to 2.20)	
Yes	93	48.7		0.88(0.63 to 1.23)	

Fig. 4. Forest plots of hazard ratios for the primary endpoint in different subgroups. *HR* hazard ratio, *CI* confidence interval, *BMI* body mass index, *LVEF* left ventricular ejection fraction.

While the precise mechanism undermine the TyG index and HF has yet to be clarified, the close relationship between TyG index and insulin resistance (IR) indicates that systemic IR could play a crucial role. It has been reported that IR is closely associated with the increased risk of HF mobility and mortality, no matter complicated with or without diabetes[15]. Epidemically, patients with HFpEF often combined with a higher prevalence of diabetes, obesity, and metabolic syndrom[16]. IR is regarded to deeply participate in the pathogenesis of the above metabolic disorders, thus fueling up the onset of cardiac remolding and LV dysfunction[17]. Studies had shown that IR could impair the nitric oxide biogenesis in vessels wall, leading to endothelia dysfunction and vasodilation disorder, ultimately resulting in cardiac myocyte apoptosis. Additionally, endothelial IR further contributes to the release of endothelin-1, which acts as a strong vasocontractile factor inducing cardiac hypertrophy and fibrosis[18]. Elevated levels of insulin and aldosterone can reduce the bioavailability of nitric oxide and promote pathological vascular sclerosis[19]. Although the euglycemia-hyperinsulinemic clamp test is regarded as the benchmark for assessing systemic IR, its complexity and high-expense have disturbed its application under sophisticated clinical conditions. The TyG index is widely used in clinical research as a simpler and more affordable alternative to gauge IR. Previous studies have demonstrated that the TyG index is an effective tool for assessing IR, with a sensitivity of 96.5% and a specificity of 85.0%, compared to the gold standard[20].

Recently, numerous studies have investigated the relationship between the TyG index and the occurrence and progression of HF. However, the results remain debated. A large prospective cohort study involving 138,620 participants demonstrated that the TyG index was positively associated with the risk of HF in a J-shaped dose–response relationship, and persisted in both genders and patients with or without abdominal obesity[21]. Additionally, a high TyG index observed in two large, geographically diverse Chinese cohorts was identified as an independent risk factor for the development of HF among the general population[22]. Similar findings have been reported in studies involving patients with acute decompensated heart failure (ADHF), where the TyG index was directly linked to poor prognosis in ADHF patients, irrespective of diabetes mellitus status[14]. In a study of critically ill patients with chronic HF, Zhou et al. found a positive correlation between the TyG index and patients' mortality. Notably, compared to TyG-BMI and TG/HDL-C ratio, the TyG index is the most promising indicator for prevention and risk stratification. The study showed that each unit increase in TyG index is associated with an increased 5-year mortality risk with a HR of 1.56 (95% CI, 1.29–1.9). In contrast, TyG-BMI and TG/HDL-C have weaker associations with 5-year mortality, with HRs of 1.002 (95% CI, 1.000-1.003) and 1.01 (95% CI, 1.00-1.03), respectively[13]. However, another study of critically ill patients with HF reported an inverse association between the TyG-BMI index and mortality[11]. Correspondingly, a cross-sectional study utilizing the UK Biobank database had yielded no significant association between the TyG index and HF outcomes[23]. In our study, we identified a linearly positive association between the TyG index and short-term mortality in critically ill patients with HF, but no significant association with one-year mortality in long-term. This discrepancy may be attributed to both the IR status and the acute stress. In the early acute stages, IR is

associated with hyperinsulinemia, and elevated insulin levels can stimulate sympathetic nerve excitation and induce vasoconstriction[24]. This could lead to a poorer prognosis in HF patients in the short-term. However, the situation may be more complex and sophisticated in terms of long-term prospects. Those who have successfully survived the acute period should have greater resilience and gained more advantages for long-term survival. In addition, complications, medication and control of risk factor also exert important effects on the prognosis of HF patients. Novack and colleagues had retrospectively assessed the association between routine blood glucose levels and 30-day or 1-year mortality in patients admitted for decompensated HF. Similarly, no association was found between glucose levels and 1-year mortality in non-diabetic patients[25]. It should be noted that in our study patients were suffered from more severe illness and required ICU admission, complicated multiple underlying diseases and complex conditions which may affect their long-term mortality.

Subgroup analyses indicated a more prominent association between the TyG index and 30-day mortality in patients ≤ 65 years and in women. In patients > 65 years, the predictive value of the TyG index for short-term outcomes might be partly masked by a higher burden of chronic comorbidities and disease severity scores (Table S3). In women of postmenopausal, the loss of estrogen-dependent cardiometabolic protection may worsen IR and dyslipidemia[26,27], and their typically higher fat-to-lean mass ratio may amplify metabolic risks via proinflammatory and oxidative stress pathways[28,29]. Moreover, HFpEF which is more common in women and closely related to IR and metabolic dysfunction[30–32], also enhances the prognostic value of the TyG index in this population. In addition, our findings indicate that higher TyG indices are associated with longer stays in ICU, which undoubtedly puts a heavy economic burden on patients. Greater attention should be paid to the prognosis of critical patients with HF, together with the identification of possible risk factors contributing to this residual mortality.

Strengths and limitations

Our study have some strengths. Prior studies utilizing the MIMIC-IV database typically used the non-fasting or first-recorded glucose values upon ICU admission to calculate the TyG index, rather than fasting blood glucose[11,33]. It's because timely obtaining fasting blood from patients admitted into ICU is usually impractical. Our study here used the average glucose level during the ICU stay for calculation of TyG index. it is better to reduce extreme fluctuations from single measurements, such as stress—induced hyperglycemia or iatrogenic hypoglycemia, and provide a more stable reflection of the overall IR status. And it has been demonstrated that glycemic variability, rather than single glucose values, is an independent predictor of mortality risk in ICU patients[34], suggesting that averaged glucose measurements may be a better surrogate measurement rather than the first record glucose level. Moreover, LVEF is a crucial predictor of prognosis in HF patients, and is typically neglected in similar studies. We manually extracted the LVEF measurements from the MIMIC-IV database and incorporated them into a fully adjusted regression model. LVEF levels were found to be higher in the highest quintiles of TyG values compared to the lowest quintiles, suggesting that IR is more prevalent in HF patients with preserved EF.

Our study also has some limitations. Firstly, it is a single-center retrospective analysis, which limits the ability to establish causation. Although we had integrated multiple variables and sensitivity analysis, it is important to note that the impact of confounding factors cannot be completely ruled out. Second, our study was limited to the evaluation of the prognostic significance of baseline TyG index in HF patients, without monitoring the dynamic alterations of TyG index during hospitalization and follow-up. Third, it's difficult to verify whether the triglyceride and glucose measurements have been performed in fasting patients, which could potentially bias our findings. In addition, we did not incorporate medication in the regression analysis, and future studies are warranted to further investigate the association between the TyG index and mortality in patients with HF.

Conclusion

The TyG index is a highly reliable independent predictor of short-term mortality in patients with severe heart failure. In addition, there is a significant and linear correlation between the TyG index and the short-term risk of all-cause mortality in critically ill patients with heart failure. Therefore, measuring the TyG index is useful for stratifying risk and predicting future outcomes in this population.

Data availability

The datasets generated and analyzed during this study are available from the corresponding author upon reasonable request.

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Author contributions

TH, CYZ, JD, and YZ were responsible for study conception and data collection. YZ, CYZ, FYC, and JD designed the study. Data extraction was performed by HG and FYC. Data analysis and intellectual guidance were provided by TH, YL, JX, and FXD. The initial manuscript draft was written by TH, YL, and JX. WJ, CXW, CYZ, JD, and YZ revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

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