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Insulin Resistance–Nutritional Index: A Simple Index and Potential Predictor of Mortality Risk in Patients with Chronic Heart Failure and Type 2 Diabetes

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Background: Patients with chronic heart failure (CHF) and type 2 diabetes mellitus (DM) are prone to insulin resistance and malnutrition, both of which are significant prognostic factors for CHF. However, the combined effect of the triglyceride–glucose index (TyG index) and prognostic nutritional index (PNI) on the mortality risk in patients with CHF and type 2 DM has not yet been studied.
Methods: We enrolled 3,315 patients with CHF and type 2 DM. We used a multivariate Cox regression model to assess hazard ratios (HRs) with 95% confidence intervals (CIs) for mortality risk based on TyG index and PNI levels. Furthermore, we constructed a novel index, the insulin resistance–nutritional index (IRNI), defined as TyG index/Ln (PNI), and evaluated its prognostic significance.
Results: During follow-up, 1,214 deaths occurred. Participants with a high TyG index and non-high PNI had a significantly higher mortality risk compared to those with a non-high TyG index and high PNI, with an adjusted HR of 1.91 (95% CI, 1.57–2.32). The multivariate Cox regression analysis revealed HRs for all-cause and cardiovascular deaths of 1.93 (95% CI, 1.66–2.26; $P < 0.001$) and 2.50 (95% CI, 2.05–3.06; $P < 0.001$), respectively, when comparing the highest and lowest IRNI tertiles. IRNI's predictive power was stronger in groups with higher adapted Diabetes Complications Severity Index scores (P for interaction < 0.05). Additionally, adding IRNI to the baseline risk model significantly improved predictive performance, showing a greater effect compared to the TyG index or PNI.
Conclusion: IRNI, a novel and composite index reflecting insulin resistance and nutritional status, emerges as a potentially valuable prognostic marker for patients with CHF and type 2 DM.

Keywords: combined effect, prognostic nutritional index, triglyceride–glucose index, insulin resistance–nutritional index, chronic heart failure and type 2 diabetes

Introduction

Chronic heart failure (CHF) is a multifactorial clinical syndrome characterized by high incidence and mortality rates. It is recognized globally as an epidemic affecting approximately 64.3 million people.[1] Diabetes mellitus (DM), a common and frequently occurring disease, is more prevalent among patients with heart failure (HF). The Framingham study indicated a 2.4- to 5-fold increase in HF incidence among patients with DM, while other studies have shown that the prevalence of DM among HF patients is 2–2.5 times higher than in the general population.[2,3] The prognosis of HF concomitant with DM is worse than that of either HF or DM alone.[4] Therefore, effective risk stratification of patients with HF and DM is essential for optimal management and enhancement of prognosis in this population.

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Insulin resistance (IR) has a significant effect on patients with either HF or DM and is closely associated with the development and progression of both diseases.[5,6] IR can affect cardiac function through various mechanisms, such as metabolic disruption and nerve damage.[7–9] Therefore, IR is an important factor that should be considered in the prognosis of patients with HF and DM. Additionally, HF and DM are both wasting disorders, which commonly lead to complications such as malnutrition. Poor nutritional status may cause muscle wasting, resulting in reduced mobility and worsening clinical outcomes,[10] while further aggravating the prognosis of related wasting conditions.[11,12] Importantly, IR and malnutrition can also interact with each other,[13–15] so it is essential to consider the combined effect of IR and nutritional status on the prognosis of patients with HF and DM.

The triglyceride–glucose index (TyG index) is a simple and reliable surrogate marker for IR, exhibiting a strong correlation with IR as confirmed by hyperinsulinemic–euglycemic clamping experiments.[16] Previous studies have confirmed that the TyG index is closely associated with various cardiovascular diseases (CVDs).[17–19] The prognostic nutritional index (PNI) is an easily obtainable and noninvasive biomarker that reflects nutritional and immune status. Higher PNI values are commonly associated with better disease prognoses, and PNI has been widely used in various research areas, including prognostic studies in cancer, chronic kidney disease, perioperative outcomes in surgery, and CVDs.[20–25]

Both IR and nutritional status have significant impacts on the prognosis of chronic cardiovascular diseases. However, existing studies predominantly focus on individual risk factors, such as the TyG index or PNI, with limited research exploring their combined effect. The combined use of the TyG index and PNI has the potential to provide more comprehensive prognostic information, which could lead to more accurate risk stratification.

To the best of our knowledge, this study is the first to investigate the combined effect of the TyG index and PNI on the prognosis of patients with CHF and type 2 DM. Based on these two indicators, we developed a novel and composite index, namely the insulin resistance–nutritional index (IRNI), which may comprehensively reflect both metabolic and nutritional status. In addition to investigating the prognostic prediction potential of this index, we compared its incremental predictive value with those of its constituent factors.

Methods

Study Design and Population

This was a retrospective, multicenter cohort study of patients with CHF and type 2 DM who were hospitalized at The First Affiliated Hospital of Henan University of Science and Technology from July 1, 2016, to June 30, 2021, and at The Third Affiliated Hospital from July 1, 2016, to June 30, 2020. CHF was defined in accordance with the 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure.[26] A clinical diagnosis of diabetes was confirmed based on one or more of the following criteria: a prior diagnosis of diabetes, fasting blood glucose (FBG) $\geq$ 7.0 mmol/L, random blood glucose $\geq$ 11.1 mmol/L, or the use of hypoglycemic agents. From the initial cohort of 4,313 patients with CHF and DM, 998 were excluded based on the following exclusion criteria: (1) age < 18 years; (2) pregnancy or a diagnosis of type 1 DM or other specific types of diabetes; (3) severe hepatic or renal dysfunction, defined as cirrhosis with ascites or chronic renal failure with dialysis treatment; (4) advanced cancer or connective tissue diseases; (5) missing data on lymphocyte count, albumin, FBG, or triglycerides (TG); and (6) in-hospital mortality or loss to follow-up. After applying these exclusion criteria, particularly criterion (2), the remaining cohort was considered to have CHF and type 2 DM, with 3,315 patients included in the final analysis. The patients were categorized into the following four groups based on their TyG index and PNI levels: (a) Group 1: non-high TyG index and high PNI (n = 660); (b) Group 2: non-high TyG index and non-high PNI (n = 1,549); (c) Group 3: high TyG index and high PNI (n = 445); and (d) Group 4: high TyG index and non-high PNI (n = 661) (Figure 1). The cutoff points for high levels of the TyG index and PNI were based on the 66 percentile values.

Ethics Statement

This study adhered to the principles outlined in the Declaration of Helsinki and received approval from the ethics committee of the First Affiliated Hospital of Henan University of Science and Technology (2023–03-K0026). Given its

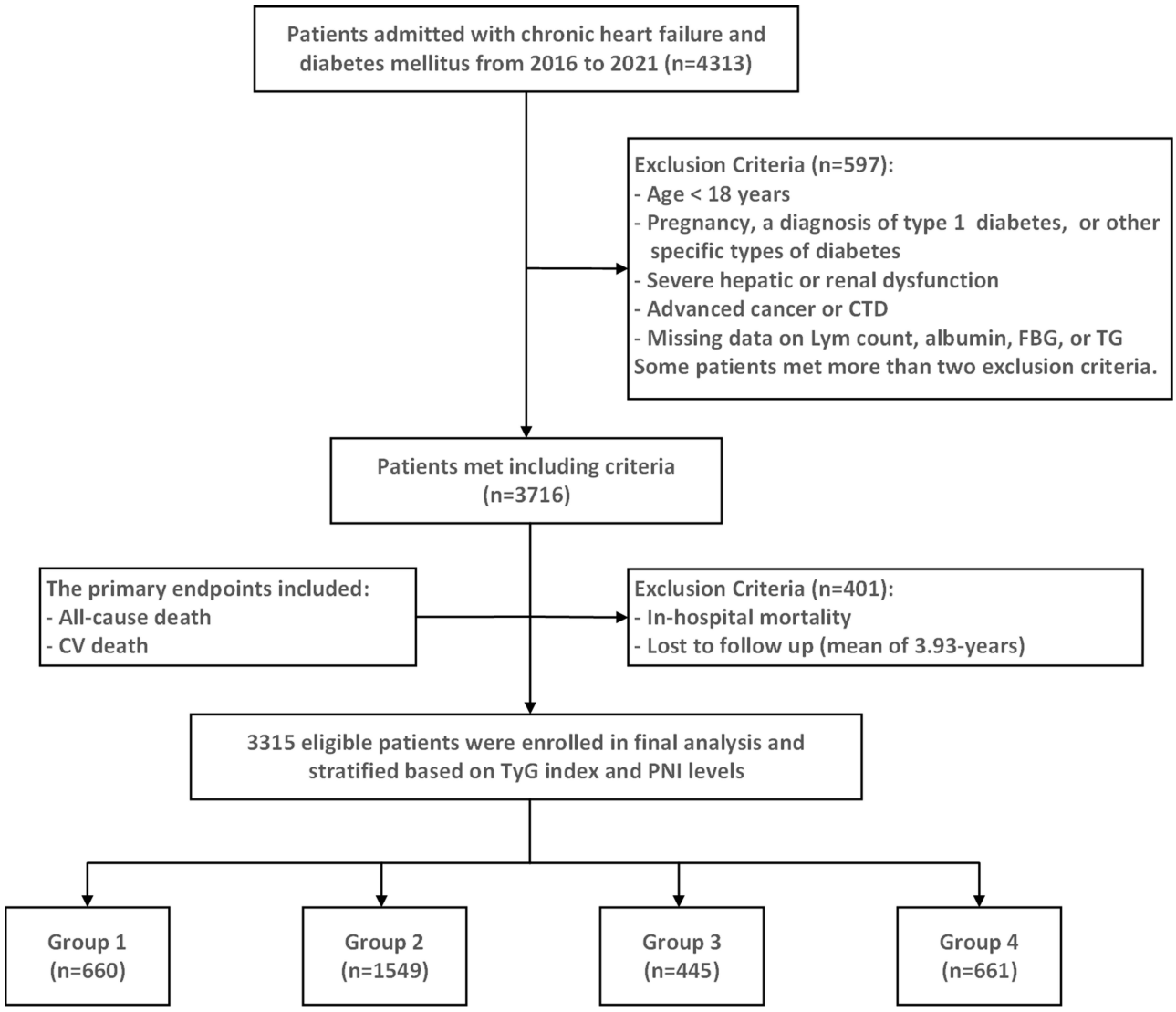

Figure 1 Flow diagram of patients selection. *CTD* connective tissue diseases, *FBG* fasting blood glucose, *TG* triglycerides, *CV death* cardiovascular death, *TyG index* triglyceride–glucose index, *PNI* prognostic nutritional index.

retrospective nature, the institutional review board exempted this study from the requirement for informed consent and guaranteed that all patient-related information was anonymized.

Data Collection and Definitions

Data on age, sex, comorbidities, laboratory values (eg, albumin, lymphocyte count, and FBG), and medications were extracted from an electronic medical records system. Body mass index (BMI) was calculated as body weight (kg) divided by the square of body height (m^2). Blood pressure was primarily measured using the cuff inflation technique with either electronic sphygmomanometers or mercury sphygmomanometers.[27] The mean arterial pressure (MAP) was calculated using the following formula: (systolic blood pressure + 2 × diastolic blood pressure)/3. The TyG index was calculated as ln (fasting TG [mg/dL] × FBG [mg/dL]/2).[16] The PNI was calculated as follows: albumin (g/L) + 5 × total lymphocyte counts (10^9/L).[20] Additionally, we constructed a novel indicator, IRNI, defined as TyG index/Ln (PNI).

Follow-Up and Outcomes

The primary end points assessed in this study included all-cause mortality and cardiovascular death. Prognostic information was gathered via telephone interviews or through a review of pertinent electronic medical records over a median follow-up duration of 4.1 years, with an interquartile range (IQR) of 2.6–5.5 years.

Statistical Analysis

The characteristics of the participants were compared across the four groups based on the TyG index and PNI levels. Continuous variables were expressed as mean ± standard deviation (SD), or median with IQR, depending on their normality of distribution. For continuous data, one-way ANOVA was used if data were normally distributed, while the Kruskal–Wallis test was used if data did not conform to normal distribution. Categorical variables were displayed as frequencies and percentages, and differences among groups were assessed using the chi-square test or Fisher's exact test, as appropriate.

The Kaplan–Meier analysis was used to estimate the cumulative incidence of the primary end points, and the Log rank test was applied to assess differences between the groups. Univariate and multivariate Cox proportional-hazards models were used to investigate the relationship between IRNI and the incidence of primary outcomes. IRNI was examined both as a categorical variable, using the lowest tertile as the reference, and as a continuous variable, per SD increase. The proportional-hazards assumption was evaluated using Schoenfeld residuals, which indicated no violations. To address missing covariates, multiple imputations with chained equations were used. Propensity score matching (PSM) was used to adjust for covariates, ensuring comparability among the groups when analyzing the baseline characteristics. A restricted cubic spline (RCS) regression model with three knots was applied to explore the relationship between IRNI and the hazard ratio (HR). We conducted exploratory analyses across various subgroups, including different comorbidities and diabetes severity levels (assessed by the adapted Diabetes Complications Severity Index, aDCSI),[28] using the likelihood ratio test to evaluate interactions among the subgroups. Finally, the predictive additive value of IRNI for risk stratification was evaluated using the C-statistic, net reclassification index (NRI), integrated discrimination improvement (IDI), and decision curve analysis (DCA) and was compared with those of the TyG index and PNI alone.

Statistical analyses were conducted using R software (version 4.4.0, R Foundation for Statistical Computing, Vienna, Austria). A two-tailed *P* value lower than 0.05 was considered statistically significant.

Results

Characteristics of the Participants

A total of 3,315 participants were included in the analysis. Their average age was 66.8 years, and 60.6% were male. General characteristics of the study population across different groups are presented in Table 1. Among the individuals with both risk factors (Group 4), the proportion of men was significantly reduced, whereas the proportion of insulin use was substantially elevated in comparison to the other groups (both $P < 0.05$). The patients in the high-nutritional-score groups (Groups 1 and 3) were younger and exhibited higher BMI, albumin, alanine aminotransferase, platelets, lymphocyte counts, estimated glomerular filtration rate, and sodium levels than those in the groups with lower nutritional scores (Groups 2 and 4). Conversely, they exhibited lower levels of creatinine and NT-proBNP, along with a reduced incidence of chronic kidney disease (CKD) (all $P < 0.05$).

The patients in the high-IR-score groups (Groups 3 and 4) exhibited higher MAP, FBG, total cholesterol, TG, and low-density lipoprotein cholesterol levels, along with lower high-density lipoprotein cholesterol values, than those in the groups with lower IR scores (Groups 1 and 2). Moreover, these groups had a higher incidence of myocardial infarction and an increased usage of antiplatelet agents, beta-blockers, and statins (all $P < 0.05$). Additionally, the proportions of elevated NYHA classification levels and diuretics usage were significantly lower in the group without any risk factors (Group 1) compared with other groups (both $P < 0.05$).

Combined Effect of the TyG Index and PNI Levels on Mortality

During the follow-up period, the incidence rate of all-cause mortality was 93.3 per 1000 person-years, and the cardiovascular death rate was 58.02 per 1000 person-years. The cumulative incidence rate of both all-cause and

Table 1 Baseline Characteristics of the Study Population Across Four Groups

Characteristics	Combined Effect of TyG Index and PNI				*P* value
	Group 1[a]	Group 2[b]	Group 3[c]	Group 4[d]	
No. of subjects	660	1549	445	661	–
Age (years)	64.0 (54.6–73.8)	71.0 (60.2–79.0)	61.0 (53.0–72.0)	68.7 (59.0–77.1)	<0.001
Male (%)	400 (60.61%)	985 (63.59%)	272 (61.12%)	353 (53.40%)	<0.001
MAP (mmHg)	96.7 (87.0–104.7)	95.3 (85.7–104.7)	98.3 (89.0–107.0)	97.7 (88.3–108.0)	<0.001
HR (bpm)	77.0 (68.0–86.0)	79.0 (68.0–89.0)	77.0 (68.0–86.0)	77.0 (68.0–88.0)	0.202
BMI (kg/m^2)	26.0 (23.7–28.6)	25.2 (22.5–28.3)	27.0 (24.8–30.1)	25.4 (23.3–28.3)	<0.001
Current/ex-Smoker (%)	201 (30.45%)	492 (31.76%)	134 (30.11%)	181 (27.38%)	0.239
Current/ex-Drinker (%)	126 (19.09%)	291 (18.79%)	90 (20.22%)	103 (15.58%)	0.184
NYHA classification (%)					0.006
I–II	316 (47.88%)	604 (38.99%)	176 (39.55%)	279 (42.21%)	
III	231 (35.00%)	630 (40.67%)	178 (40.00%)	239 (36.16%)	
IV	113 (17.12%)	315 (20.34%)	91 (20.45%)	143 (21.63%)	
AF	182 (27.58%)	434 (28.02%)	125 (28.09%)	178 (26.93%)	0.958
CKD	187 (28.33%)	634 (40.93%)	114 (25.62%)	264 (39.94%)	<0.001
COPD	77 (11.67%)	182 (11.75%)	63 (14.16%)	91 (13.77%)	0.347
Hypertension	481 (72.88%)	1164 (75.15%)	350 (78.65%)	491 (74.28%)	0.176
Previous MI	281 (42.58%)	578 (37.31%)	196 (44.04%)	306 (46.29%)	<0.001
Past PCI	267 (40.45%)	574 (37.06%)	178 (40.00%)	282 (42.66%)	0.076
Laboratory measurements					
Albumin (g/L)	43.2 (41.2–45.0)	38.1 (35.2–40.4)	43.5 (41.6–45.6)	38.3 (35.4–40.6)	<0.001
ALT (U/L)	24.0 (16.0–38.4)	22.0 (15.0–34.0)	26.0 (18.0–39.2)	22.0 (15.0–36.4)	<0.001
AST (U/L)	22.1 (17.0–31.0)	22.0 (17.0–33.0)	22.2 (17.0–31.4)	22.0 (16.0–33.0)	0.656
Platelets (10^9/L)	207.0 (168.8–244.0)	190.0 (148.0–233.0)	223.0 (186.0–264.0)	206.0 (164.0–256.0)	<0.001
Lymphocyte (10^9/L)	2.10 (1.73–2.60)	1.28 (0.94–1.65)	2.24 (1.81–2.80)	1.36 (0.96–1.72)	<0.001
Creatinine (umol/L)	75.0 (62.0–89.3)	80.0 (65.8–101.0)	71.4 (61.0–86.4)	78.6 (65.0–102.4)	<0.001
eGFR (mL/min/1.73m^2)	86.4 (69.5–99.9)	77.7 (55.9–92.5)	89.6 (73.8–101.0)	77.4 (54.4–93.8)	<0.001
FBG (mmol/L)	6.32 (5.25–7.74)	6.69 (5.27–8.06)	8.90 (7.20–11.3)	9.69 (7.61–12.9)	<0.001
TC (mmol/L)	3.99 (3.33–4.78)	3.77 (3.07–4.50)	4.72 (3.87–5.70)	4.30 (3.61–5.16)	<0.001
TG (mmol/L)	1.19 (0.88–1.53)	1.00 (0.77–1.30)	2.24 (1.78–2.93)	1.92 (1.56–2.49)	<0.001
LDL-C (mmol/L)	2.37 (1.82–2.97)	2.17 (1.65–2.81)	2.77 (2.14–3.46)	2.44 (1.91–3.17)	<0.001
HDL-C (mmol/L)	1.07 (0.88–1.31)	1.06 (0.86–1.27)	0.97 (0.81–1.14)	0.97 (0.78–1.14)	<0.001
Potassium (mmol/L)	3.98 (3.68–4.30)	3.97 (3.67–4.36)	3.93 (3.66–4.25)	3.95 (3.67–4.34)	0.147
Sodium (mmol/L)	141.2 (139.0–143.3)	140.3 (137.8–142.6)	141.0 (139.0–143.2)	140.6 (137.9–142.8)	<0.001
NT-proBNP (pg/mL)	1473.0 (721.9–4005.5)	2394.0 (981.0–6798.0)	1346.0 (657.0–3628.0)	2104.0 (908.9–6151.0)	<0.001
Echocardiography					
LVEF (%)	47.0 (38.0–56.0)	48.0 (37.0–57.0)	48.0 (38.0–57.0)	46.0 (38.0–56.0)	0.780
Medications (%)					
Antiplatelet agents	468 (70.91%)	1080 (69.72%)	329 (73.93%)	511 (77.31%)	0.002
ACEI/ARB/ARNI	368 (55.76%)	863 (55.71%)	266 (59.78%)	357 (54.01%)	0.296
Beta-blocker	475 (71.97%)	1107 (71.47%)	364 (81.80%)	505 (76.40%)	<0.001
Statins	472 (71.52%)	1071 (69.14%)	350 (78.65%)	496 (75.04%)	<0.001
Digoxin	136 (20.61%)	269 (17.37%)	74 (16.63%)	112 (16.94%)	0.213
Mineralocorticoid antagonists	448 (67.88%)	1057 (68.24%)	310 (69.66%)	448 (67.78%)	0.914
Diuretics	395 (59.85%)	1019 (65.78%)	304 (68.31%)	432 (65.36%)	0.017
SGLT2 inhibitors	142 (21.52%)	330 (21.30%)	117 (26.29%)	132 (19.97%)	0.078
Insulin	134 (20.30%)	352 (22.72%)	95 (21.35%)	198 (29.95%)	<0.001
Other oral antidiabetic agents	424 (64.24%)	961 (62.04%)	297 (66.74%)	412 (62.33%)	0.282

(*Continued*)

Table 1 (Continued).

Characteristics	Combined Effect of TyG Index and PNI				*P* value
	Group 1[a]	Group 2[b]	Group 3[c]	Group 4[d]	
Outcomes (1000 person-y)					
All-cause death	58.32	95.98	90.13	129.79	<0.001
CV death	33.43	59.08	52.48	88.19	<0.001

Notes: [a]Group 1 is non-high TyG index and high PNI. [b]Group 2 is non-high TyG index and non-high PNI. [c]Group 3 is high TyG index and high PNI. [d]Group 4 is high TyG index and non-high PNI.

Abbreviations: TyG index, triglyceride–glucose index; PNI, prognostic nutritional index; MAP, mean arterial pressure; HR, heart rate; BMI, body mass index; NYHA, New York Heart Association; AF, atrial fibrillation; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; TC, total cholesterol; TG, triglycerides, LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; NT-proBNP, N-terminal pro-brain natriuretic peptide; LVEF, left ventricular ejection fraction; SGLT2 inhibitors, sodium-glucose co-transporter-2 inhibitors; ACEI/ARB/ARNI, angiotensin converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor-neprilysin inhibitors; CV, death cardiovascular death.

Table 2 Associations Between the Combined Effect of TyG Index and PNI Levels with the Risk of Primary Outcomes in Patients with CHF and Type 2 DM

Categories	Incidence/1000 Person-y	Unadjusted		Model 1		Model 2	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
All-cause death							
Group 1 (n=660)	58.32	Ref.		Ref.		Ref.	
Group 2 (n=1549)	95.98	1.63 (1.37–1.94)	<0.001	1.55 (1.30–1.84)	<0.001	1.52 (1.27–1.81)	<0.001
Group 3 (n=445)	90.13	1.52 (1.23–1.90)	<0.001	1.54 (1.24–1.92)	<0.001	1.55 (1.24–1.95)	<0.001
Group 4 (n=661)	129.79	2.19 (1.81–2.64)	<0.001	2.10 (1.73–2.53)	<0.001	1.91 (1.57–2.32)	<0.001
CV death							
Group 1 (n=660)	33.43	Ref.		Ref.		Ref.	
Group 2 (n=1549)	59.08	1.75 (1.40–2.20)	<0.001	1.68 (1.34–2.12)	<0.001	1.65 (1.31–2.08)	<0.001
Group 3 (n=445)	52.48	1.55 (1.16–2.07)	0.003	1.56 (1.17–2.09)	0.002	1.66 (1.23–2.23)	<0.001
Group 4 (n=661)	88.19	2.60 (2.04–3.31)	<0.001	2.53 (1.98–3.24)	<0.001	2.39 (1.86–3.07)	<0.001

Notes: Group 1 is non-high TyG index and high PNI; Group 2 is non-high TyG index and non-high PNI; Group 3 is high TyG index and high PNI; Group 4 is high TyG index and non-high PNI. Model 1: adjusted for age, gender, BMI, MAP, and heart rate. Model 2: adjusted for Model 1 + NYHA classification, LVEF, NT-proBNP, creatinine, total cholesterol, LDL-C, HDL-C, atrial fibrillation, previous MI, COPD, ACEI/ARB/ARNI, β-blocker, mineralocorticoid antagonists, diuretics, SGLT2 inhibitors, and other hypoglycemic therapy.

Abbreviations: TyG index, triglyceride–glucose index; PNI, prognostic nutritional index; CHF, chronic heart failure; DM, diabetes mellitus; HR, hazard ratio; CI, confidence interval; CV death, cardiovascular death.

cardiovascular death increased with higher tertiles of the TyG index or lower tertiles of PNI (Figure S1, Log rank test, all $P < 0.001$). Table 2 presents the three Cox regression models used to assess the associations between the combined effect of the TyG index and PNI and the outcomes. In the multivariate model, compared with Group 1, the remaining three groups demonstrated significantly increased risks of all-cause mortality, particularly pronounced in Group 4 (HR, 1.52 [95% CI, 1.27–1.81] for Group 2; 1.55 [95% CI, 1.24–1.95] for Group 3; and 1.91 [95% CI, 1.57–2.32] for Group 4). When using cardiovascular death as the outcome, the results remained consistent (all $P < 0.001$) (Table 2).

Correlations Between IRNI and Adverse End Points

The incidence rates of primary events from the lowest to the highest IRNI tertiles were 63.99, 90.9, and 130.14 per 1000 person-years for all-cause death and 35.43, 55.87, and 86.76 per 1000 person-years for cardiovascular death. The Kaplan–Meier analysis demonstrated significant differences in the risk of primary end points across the three IRNI tertiles (Figure 2, Log rank test, both $P < 0.001$). The RCS regression model also revealed that higher levels of IRNI were associated with an increased risk of all-cause death (model 2: HR per SD increase, 1.31; 95% CI, 1.23–1.40) and

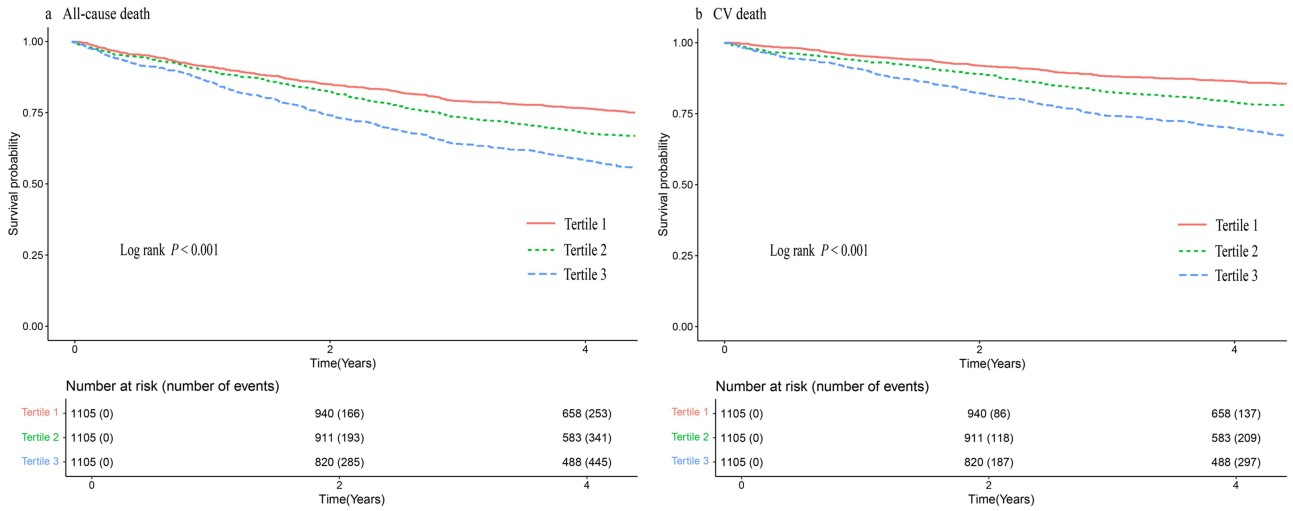

Figure 2 Kaplan-Meier estimation of (**a**) all-cause death and (**b**) CV death by tertiles of IRNI. *CV death* cardiovascular death, *IRNI* insulin resistance–nutritional index.

cardiovascular death (model 2: HR per SD increase, 1.43; 95% CI, 1.32–1.55) (both *P* for overall association < 0.001) (Figure S2).

The multivariate Cox regression analysis results demonstrated a significant association between IRNI and all-cause mortality (T1 vs T2: HR, 1.42 [95% CI, 1.22–1.66]; T3: HR, 1.93 [95% CI, 1.66–2.26]; all $P < 0.001$). When cardiovascular death was considered as the end point, the results remained consistent. Namely, the highest IRNI tertile was significantly associated with an increased incidence of CV mortality (model 2: HR, 2.50; 95% CI, 2.05–3.06; $P < 0.001$, comparing T1 vs T3) (Table 3). To evaluate the stability of the predictive efficacy of IRNI, PSM was used to adjust for primary confounding variables across the three groups (Table S1). The results indicated that even after PSM, IRNI continued to exhibit a strong association with adverse outcomes, with HRs of 1.89 (95% CI, 1.58–2.25, $P < 0.001$) for all-cause death and 2.58 (95% CI, 2.05–3.25, $P < 0.001$) for cardiovascular death, comparing T1 vs T3 (Table S2).

Implications of IRNI on Adverse Outcomes Across Different Subgroups

We further conducted exploratory analyses of the prognostic efficacy of IRNI across various subgroups. The Kaplan–Meier analysis demonstrated that the risk of primary end points (including all-cause death and cardiovascular death) varied significantly among the three IRNI tertiles across different subgroups, including the subgroups defined by age, sex,

Table 3 Univariable and Multivariable Cox Analyses of IRNI Predicting Primary Outcomes in Patients with CHF and Type 2 DM

Categories	Incidence/1000 Person-y	Unadjusted		Model 1		Model 2	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
All-cause death							
Continuous variable per SD		1.31 (1.24–1.38)	<0.001	1.30 (1.23–1.38)	<0.001	1.31 (1.23–1.40)	<0.001
T1 (<2.24)	63.99	Ref.		Ref.		Ref.	
T2 (2.24–2.39)	90.9	1.41 (1.21–1.64)	<0.001	1.40 (1.21–1.63)	<0.001	1.42 (1.22–1.66)	<0.001
T3 (≥2.39)	130.14	2.00 (1.73–2.31)	<0.001	1.99 (1.73–2.30)	<0.001	1.93 (1.66–2.26)	<0.001
CV death							
Continuous variable per SD		1.37 (1.28–1.46)	<0.001	1.37 (1.28–1.47)	<0.001	1.43 (1.32–1.55)	<0.001
T1 (<2.24)	35.43	Ref.		Ref.		Ref.	
T2 (2.24–2.39)	55.87	1.57 (1.29–1.91)	<0.001	1.56 (1.28–1.90)	<0.001	1.63 (1.33–2.00)	<0.001
T3 (≥2.39)	86.76	2.41 (2.00–2.90)	<0.001	2.41 (2.00–2.91)	<0.001	2.50 (2.05–3.06)	<0.001

Notes: Model 1: adjusted for age, gender, BMI, MAP, and heart rate. Model 2: adjusted for Model 1 + NYHA classification, LVEF, NT-proBNP, creatinine, total cholesterol, LDL-C, HDL-C, atrial fibrillation, previous MI, COPD, ACEI/ARB/ARNI, β-blocker, mineralocorticoid antagonists, diuretics, SGLT2 inhibitors, and other hypoglycemic therapy.

Abbreviations: IRNI, insulin resistance–nutritional index; CHF, chronic heart failure; DM, diabetes mellitus; HR, hazard ratio; CI, confidence interval; SD, standard deviation; CV, death cardiovascular death.

hypertension, myocardial infarction, CKD, and obesity (Figures S3 and S4, Log rank test, all $P < 0.001$). The results of the multivariate Cox proportional-hazards models, examining the relationships between IRNI and all-cause mortality across various subgroups, are presented in Figure 3. The findings consistently revealed that IRNI was significantly associated with all-cause mortality across diverse subgroups (all P for trend < 0.05). The associations between IRNI and cardiovascular mortality also displayed consistent results across the subgroups (Table S3, all P for trend < 0.05).

We further explored whether diabetes severity, measured by aDCSI, affects the predictive ability of IRNI for survival outcomes. A higher score on aDCSI indicates a greater number of diabetic complications and more severe disease.[28] The participants were categorized into three groups based on their aDCSI score levels, namely ≤ 3, 4–5, and ≥ 6. We found that IRNI consistently maintained a strong association with adverse outcomes across all levels of diabetes severity (Table S4, all P for trend < 0.05), but there was an increasingly pronounced correlation between IRNI and all-cause mortality in the groups with higher aDCSI scores. The HRs increased across the groups from low to high scoring 1.54 (95% CI, 1.20–1.99), 2.01 (95% CI, 1.56–2.58), and 2.45 (95% CI, 1.78–3.39) in T1 vs T3 comparisons, with a significant interaction ($P = 0.028$). The association between IRNI and cardiovascular death demonstrated a consistent trend across varying aDCSI levels, with

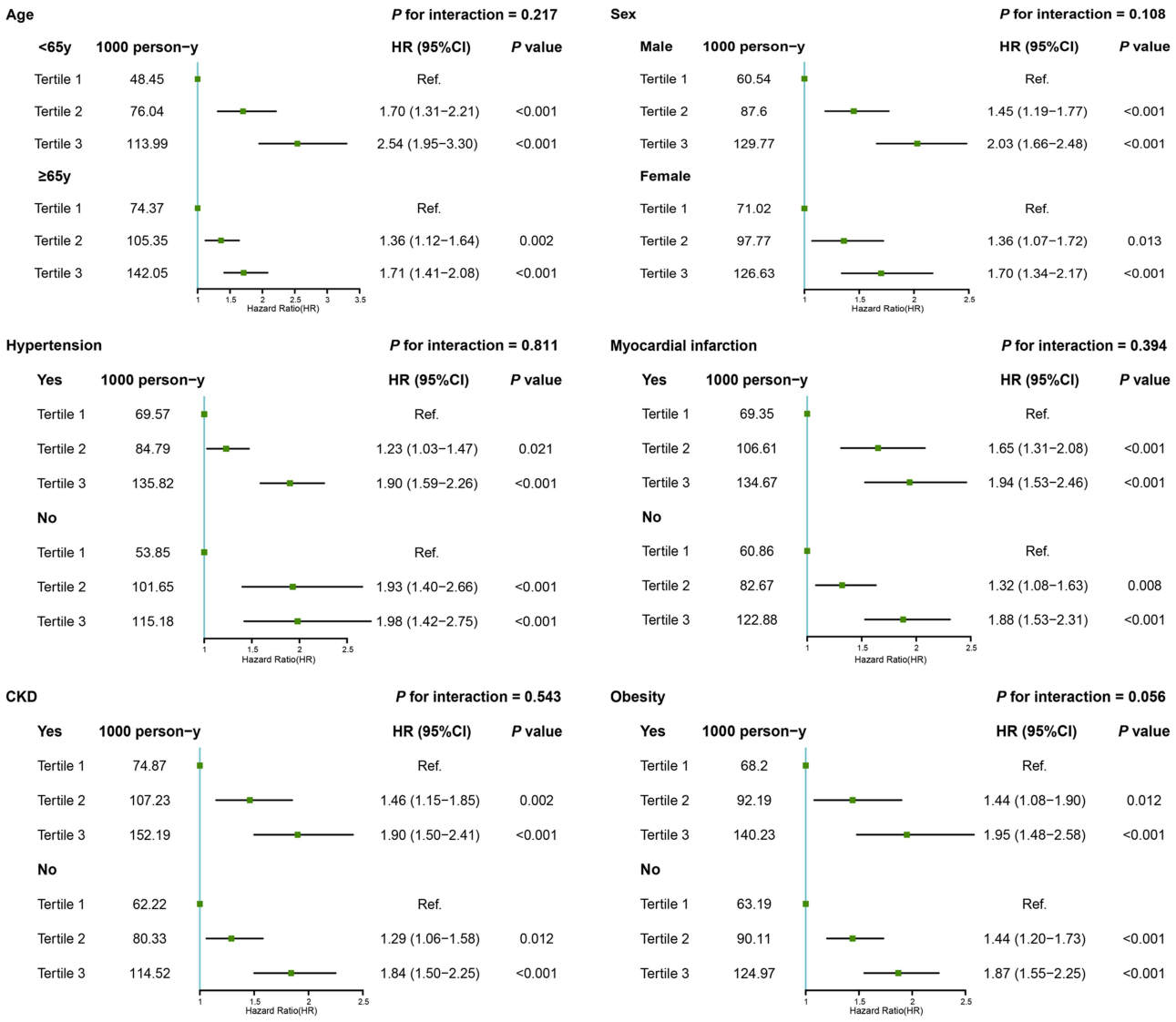

Figure 3 Forest plot of all-cause death according to tertiles of IRNI across different subgroups adjusted for model 2.
Abbreviations: HR, hazard ratio; CI, confidence interval; IRNI, insulin resistance–nutritional index; CKD, chronic kidney disease.

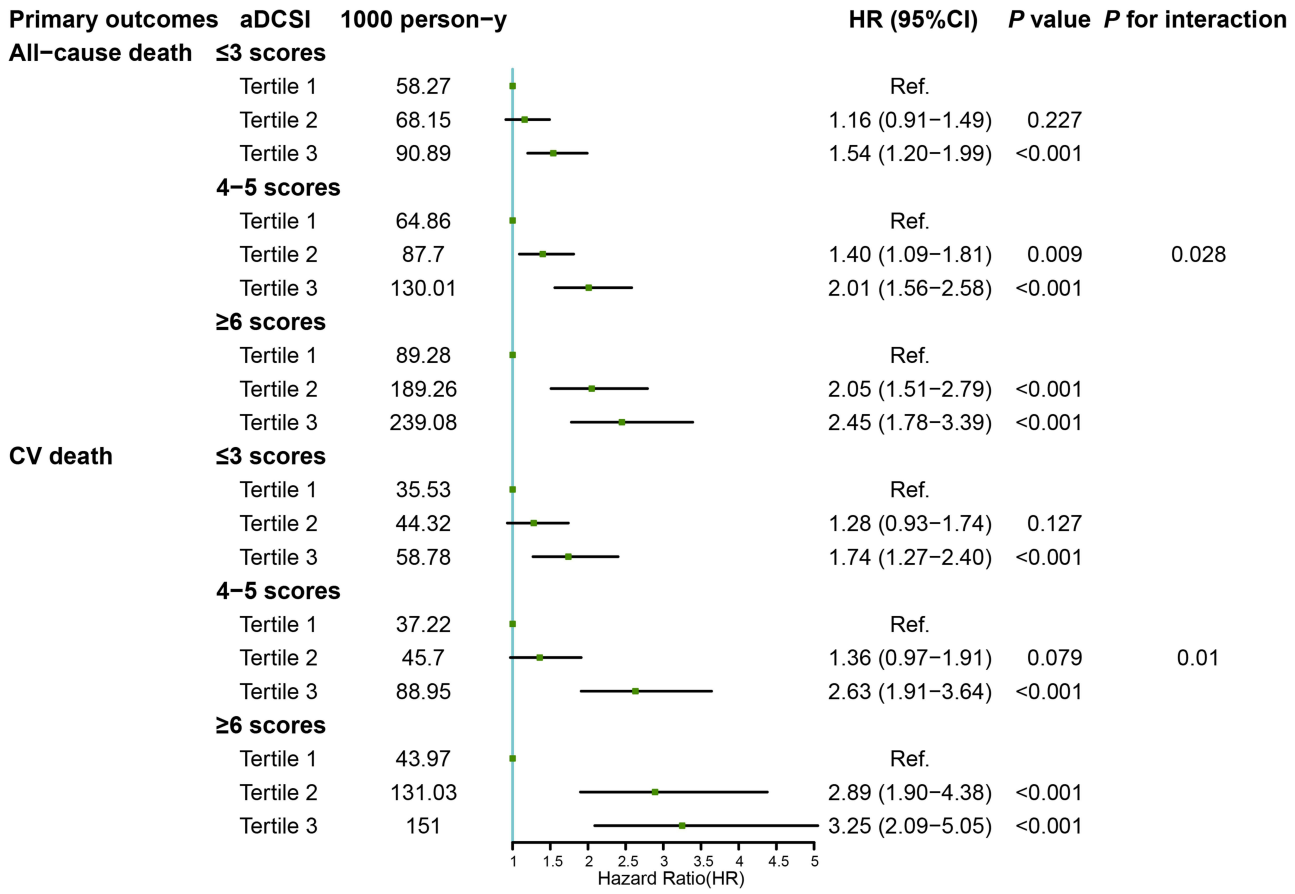

Figure 4 Forest plot of primary outcomes according to tertiles of IRNI stratified by different aDCSI scores adjusted for model 2.
Abbreviations: HR hazard ratio; CI, confidence interval; IRNI, insulin resistance–nutritional index; CV death, cardiovascular death; aDCSI, adapted Diabetes Complications Severity Index.

HRs of 1.74 (95% CI, 1.27–2.40), 2.63 (95% CI, 1.91–3.64), and 3.25 (95% CI, 2.09–5.05) with T1 vs T3 (Figure 4, *P* for interaction = 0.010).

Evaluation of the Incremental Predictive Value of IRNI on Risk Stratification

The incremental predictive value of IRNI for mortality is shown in Table 4. The addition of IRNI to the baseline risk model improved risk prediction, with the C-statistic increasing from 0.656 to 0.679 ($P < 0.01$). Analysis of NRI and IDI

Table 4 Evaluation of the Incremental Effect of Adding IRNI, TyG Index and PNI to the Baseline Risk Model for Predicting 3-Year Mortality

	AUC (95% CI)	*P* value	NRI (95% CI)	*P* value	IDI (95% CI)	*P* value
Baseline risk model[a]	0.656 (0.636–0.677)	Ref.	–	Ref.	–	Ref.
+ IRNI	0.679 (0.659–0.699)	<0.01	0.287 (0.211–0.362)	<0.01	0.016 (0.012–0.021)	<0.01
+ TyG index	0.668 (0.648–0.689)	<0.01	0.239 (0.163–0.315)	<0.01	0.010 (0.006–0.014)	<0.01
+ PNI	0.666 (0.645–0.686)	0.02	0.127 (0.051–0.203)	<0.01	0.005 (0.002–0.007)	<0.01
Pairwise comparison of AUC						
+ IRNI vs + TyG index	0.679 vs 0.668	<0.01	–	–	–	–
+ IRNI vs + PNI	0.679 vs 0.666	0.01	–	–	–	–
+ TyG index vs + PNI	0.668 vs 0.666	0.69	–	–	–	–

Notes: [a]The baseline risk model included age, gender, NYHA classification, LVEF, NT-proBNP, creatinine, hypertension, atrial fibrillation, previous MI, COPD, ACEI/ARB/ARNI, β-blocker and SGLT2 inhibitors.
Abbreviations: IRNI, insulin resistance–nutritional index; TyG index, triglyceride–glucose index; PNI, prognostic nutritional index; AUC, area under the receiver operating characteristic curve; CI, confidence interval; NRI, net reclassification improvement; IDI, integrated discrimination improvement.

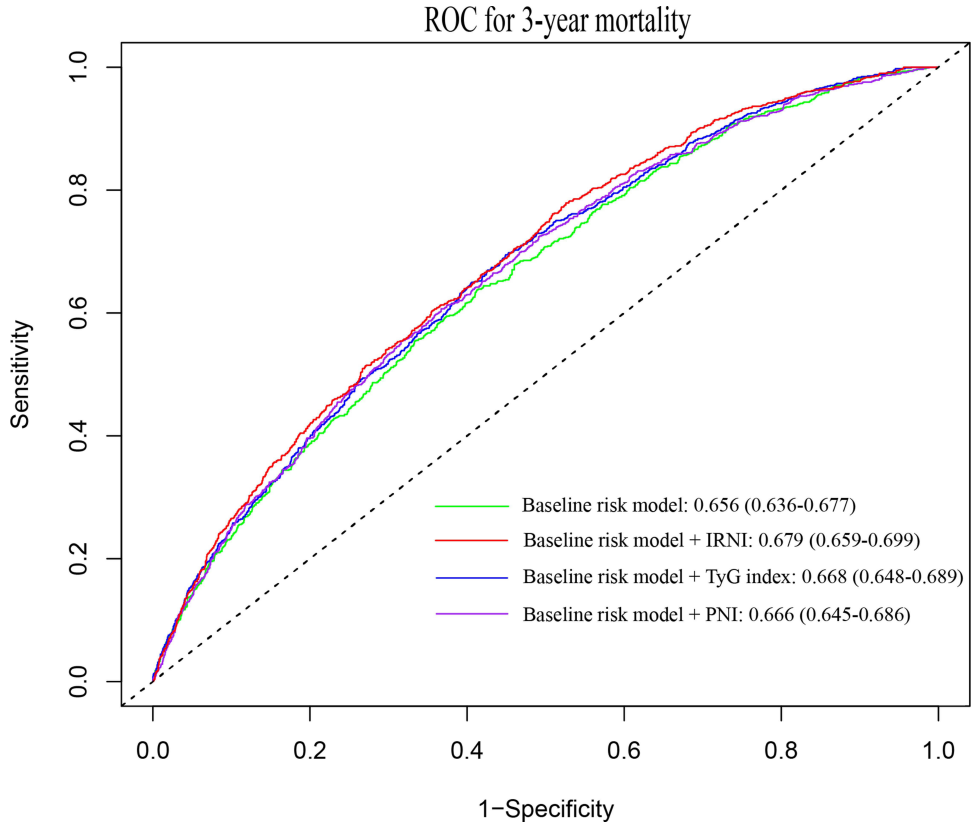

Figure 5 ROC curves evaluating the incremental effect of IRNI, TyG index and PNI beyond the baseline risk model. *ROC curve* receiver operator characteristic curve, *IRNI* insulin resistance–nutritional index, *TyG index* triglyceride–glucose index, *PNI* prognostic nutritional index. The baseline risk model included age, gender, NYHA classification, LVEF, NT-proBNP, creatinine, hypertension, atrial fibrillation, previous MI, COPD, ACEI/ARB/ARNI, β-blocker and SGLT2 inhibitors.

revealed statistically significant improvements in predictive accuracy; namely, NRI was 0.287 (95% CI, 0.211–0.362; $P < 0.01$), and IDI was 0.016 (95% CI, 0.012–0.021; $P < 0.01$). Next, we evaluated the predictive capabilities of IRNI in comparison with those of the TyG index and PNI alone. We found that IRNI consistently exhibited superior predictive performance, in terms of both numerical increase and statistical significance (Table 4, Figure 5, both P for difference < 0.05). DCA further demonstrated that adding IRNI to the baseline model markedly enhanced the net benefit, exceeding that provided by TyG or PNI alone (Figure S5).

Discussion

This study is the first to explore the combined effect of the TyG index and PNI on the prognosis of patients with CHF and type 2 DM. The key findings of our study are as follows: (1) The combined effect of the TyG index and PNI on prognosis was significantly greater than the effect of either factor alone, with the highest risk of adverse outcomes observed in the population exhibiting higher TyG levels in conjunction with lower PNI levels. (2) Based on the TyG index and PNI, we developed a novel composite indicator, IRNI, and validated its effective and robust prognostic value. (3) IRNI provided a significantly enhanced prognostic incremental value and was superior to its basic constituent indicators, including the TyG index and PNI. In summary, our study demonstrates that IRNI can serve as a novel and valuable prognostic factor for patients with CHF and type 2 DM.

IR and nutritional status are significant factors affecting the prognosis of patients with chronic diseases such as CHF and DM. Chronic wasting diseases such as CHF or DM are closely associated with IR and nutritional imbalances.[6,29–32] These issues are particularly pronounced in populations suffering from comorbidities of both conditions. The TyG index, based on FBG and TG, is a simple, easily obtainable, and reliable surrogate marker for IR. Previous studies have demonstrated that the TyG index has high sensitivity (96.5%) and specificity (85.0%) for identifying IR compared with

the hyperinsulinemic–euglycemic clamp technique, which is the gold standard for measuring IR.[16] Currently, the TyG index has been widely used in various research fields, such as cancer, cerebrovascular diseases, CKD, and CVDs. A large-scale study involving 155,167 cancer patients demonstrated a graded positive association between the TyG index and CVD hospitalization; namely, for each unit increase in the TyG index, the hospitalization rates for CVD and acute myocardial infarction increased by 16% and 45%, respectively.[33] Chen et al used the Medical Information Mart for Intensive Care IV (Version 2.2) repository to include 1,537 patients with HF and CKD. Kaplan–Meier survival analysis showed that the group with a higher TyG index had significantly lower survival rates than the group with a lower TyG index (Log rank test: $P < 0.001$). Additionally, there was a nonlinear association between the TyG index and all-cause mortality.[34]

The PNI, which quantifies serum albumin and lymphocyte counts through simple calculations to assess systemic nutritional status and immunocompetence, has garnered widespread attention.[35] This index was first introduced by Onodera in 1984 and was used as a comprehensive nutritional indicator for assessing the surgical risk in patients with gastrointestinal tumors.[36] It has attracted increasing attention. Initially applied extensively in cancer research, PNI has progressively been used in various non-oncological fields, including trauma, diabetes, and cardiomyopathy, demonstrating promising prospects for broader applications. In a previous study, researchers included 3,351 patients aged 45 years and older who underwent hip fracture surgery.[37] The patients were divided into low, medium, and high groups based on their PNI levels. The results showed that the patients in the high-PNI group had significantly fewer postoperative complications (odds ratio, 0.61; 95% CI, 0.40–0.93) and lower mortality rates (HR, 0.61; 95% CI, 0.42–0.88) compared to those in the low-PNI group. Ning et al included a total of 5,916 adult patients with DM, with an average follow-up period of 8 years. After grouping based on the quartile levels of PNI, it was found that with increasing PNI levels (ie, Q2, Q3, and Q4), all-cause mortality decreased by 24%, 38%, and 28%, respectively, and cardiovascular mortality decreased by 30%, 27%, and 26%, respectively.[38] Another study analyzed the effect of PNI in patients with hypertrophic cardiomyopathy, revealing that a higher PNI was significantly associated with improved survival outcomes. After adjusting for potential confounders, PNI was independently associated with both all-cause mortality and cardiovascular mortality, with HRs per SD of 0.46 (95% CI, 0.34–0.62) and 0.44 (95% CI, 0.30–0.63), respectively.[39]

Although numerous studies across diverse fields have shown a correlation between the TyG index and poor prognosis and an inverse correlation between PNI and adverse outcomes, research on the joint application of these two predictive markers for disease risk stratification is still limited. A previous study combined the TyG index and PNI, among other indicators, to develop a nomogram predicting contrast-induced nephropathy after percutaneous coronary intervention in patients with type 2 DM and acute coronary syndrome.[40] The results demonstrated high discriminative capability, with the area under the curve reaching 0.785 (95% CI, 0.729–0.841) in the training cohorts and 0.802 (95% CI, 0.699–0.905) in the validation cohorts. That study highlighted the potential of the combined use of the TyG index and PNI for stratifying disease risk. However, this combined approach has not yet been applied to other diseases.

Our study showed that in patients with CHF and type 2 DM, the combined effect of the TyG index and PNI on prognosis was significantly superior to that of either single indicator alone, suggesting that their combined use might produce a synergistic enhancement of the effect. Most importantly, to facilitate clinical use and encourage broader adoption, we developed a new composite indicator, IRNI, derived from these two indicators. This new indicator demonstrated a strong correlation with adverse outcomes and exhibited significant predictive value. We propose that the underlying mechanisms can be explained through the following aspects: First, IRNI positively correlates with IR. Numerous studies have confirmed that IR is not only associated with a high incidence of HF but also closely related to poor prognosis.[5,41] IR can influence cardiac function in multiple ways, including disruption of myocardial energy metabolism, damage to cardiac sympathetic nerves, endothelial dysfunction, oxidative stress, and inflammatory responses.[7–9] Second, IRNI positively correlates with poor nutritional status. The incidence of malnutrition in HF patients is notably high at approximately 46%, and compared with patients without malnutrition, those with nutritional deficiencies have an increased risk of all-cause mortality (HR, 2.15; 95% CI, 1.89–2.45).[29] Additionally, poor nutritional status may often be accompanied by significant muscle wasting, which mainly manifests as reduced mobility and weakened muscle strength, severely affecting clinical outcomes.[10] Third, IRNI may reflect both IR and nutritional status. According to previous studies, IR can trigger malnutrition by affecting protein-energy metabolism.[13] Moreover,

malnutrition may indirectly affect insulin sensitivity through various mechanisms,[15] including altering the function and number of immune cells, such as T cells. This can ultimately lead to or exacerbate IR. Thus, there is a mutual influence, even a vicious cycle, between IR and malnutrition. Therefore, considering these factors together can provide more comprehensive prognostic information.

In our subgroup analysis, IRNI consistently maintained robust predictive efficacy across different subgroups. However, its ability to identify high-risk individuals was particularly pronounced in populations with higher severity of diabetes. The enhanced predictive capability may be attributed to the fact that individuals with more severe diabetes complications may often exhibit higher degrees of IR and poorer nutritional status.[42] This finding reminds us that in clinical practice, the management of such high-risk populations should place greater emphasis on simultaneously addressing both IR and malnutrition. Finally, IRNI significantly enhances risk stratification to a greater extent than either of its components alone. Not only does this finding support the application of this novel index in our study population, but it also suggests its potential utility in other chronic diseases, pending further validation.

Strengths and Limitations

Our study has several advantages. First, the use of cohort data from two centers enhanced representativeness. Second, it was the first to explore the combined effect of the TyG index and PNI on the prognosis of patients with CHF and type 2 DM. Third, we innovatively constructed a new index, IRNI, and validated its effectiveness and robustness. Fourth, the analysis not only included a wide range of baseline characteristics to adjust for confounding factors but also used PSM analysis to enhance comparability between groups.

It is also important to acknowledge several limitations to the study. First, given the retrospective nature of the study, comprehensive baseline data for patients outside of the hospital setting could not be obtained. Second, the absence of insulin measurement data and other anthropometric indicators such as arm and hip circumference precluded the ability to perform a multidimensional comparison. Third, the follow-up results may be subject to varying degrees of recall or reporting bias. Fourth, this retrospective observational study may contain unmeasured confounding factors, and therefore, interpretations of the results should be approached with caution while also recognizing that causal relationships cannot be definitively established. Fifth, due to the limitations of the retrospective study design, the specific brands of the measurement instruments used were not available. Finally, although our study developed the new indicator IRNI, its effectiveness and universality, especially regarding the potential impact of population or ethnic differences, still need to be confirmed through other cohort studies and prospective research.

Conclusions

In patients with CHF and type 2 DM, the combination of the TyG index and PNI enhances the ability to predict adverse risks. Furthermore, our newly developed index, IRNI, demonstrates robust and effective predictive potential, surpassing the performance of its individual components. Not only does IRNI enhance the precision in assessing and managing disease risks, but it also warrants further investigation for its potential application in various other chronic or wasting disease populations.

Data Sharing Statement

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

Ethics

This study adhered to the principles outlined in the Declaration of Helsinki and received approval from the ethics committee of the First Affiliated Hospital of Henan University of Science and Technology. Due to its retrospective nature, the institutional review board exempted this study from the requirement for informed consent and guaranteed that all patient-related information was anonymized.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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