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The association between new insulin resistance indices and all-cause mortality in elderly patients with diabetes: a prospective cohort study

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Abstract

Background The association between newly developed insulin resistance (IR) indices and all-cause mortality in elderly patients with diabetes has not been investigated.

Methods Baseline data and all-cause mortality for 1,248 elderly diabetes patients from the National Health and Nutrition Examination Survey (NHANES) conducted between 2001 and 2018 were collected. The traditional IR index homeostasis model assessment of insulin resistance (HOMA-IR) and several newly developed indices, including metabolic score for insulin resistance (METS-IR), triglyceride to high-density lipoprotein cholesterol ratio (TG/HDL-C), triglyceride glucose index (TyG), triglyceride glucose combined with body mass index (TyG-BMI), estimated glucose disposal rate (eGDR), and visceral adiposity index (VAI), were calculated for the patients. Cox proportional hazards regression and restricted cubic spline (RCS) regression models assessed the relationship between IR indices and all-cause mortality.

Results In a median follow-up period of 73.3 months, there were 381 recorded deaths. In the total cohort, METS-IR ($p < 0.001$), TyG-BMI ($p < 0.001$), and eGDR ($p = 0.011$) demonstrated a significant association with all-cause mortality as continuous variables. HOMA-IR, METS-IR, TyG-BMI, and eGDR exhibited significant correlations with all-cause mortality in the Cox regression models ($p < 0.05$) when analyzed as categorical variables. A U-shaped relationship exists between METS-IR, TyG-BMI, eGDR, and all-cause mortality (p-overall < 0.0001, p-nonlinear < 0.05). No significant associations were found between TyG, TG/HDL-C, VAI, and all-cause mortality. Among male patients, TyG-BMI and HOMA-IR exhibited superior prognostic value, whereas in female patients, METS-IR, TyG-BMI, and eGDR showed better performance.

Conclusion HOMA-IR, TyG-BMI, METS-IR, and eGDR were associated with mortality in elderly diabetic patients, with gender differences in their prognostic values.

Keywords Insulin resistance, Diabetes mellitus, All-cause mortality, Gender interaction, Elderly patients

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Background

Diabetes is increasingly acknowledged as a significant public health concern, especially in the elderly population. The annual increase in global diabetes prevalence within this demographic is influenced by factors including aging, urbanization, dietary changes, and lifestyle modifications. Elderly people with diabetes exhibit significantly elevated mortality rates relative to their non-diabetic counterparts [1–3]. Improving health management for elderly individuals with diabetes and examining the factors affecting mortality in this demographic are critically significant from both social and economic perspectives.

Insulin resistance (IR) is a hallmark of metabolic syndrome, characterized by a reduced effectiveness of insulin in facilitating glucose utilization. A significant correlation exists between IR and mortality, particularly concerning cardiovascular disease-related mortality and all-cause mortality. Research indicates that an increase in IR is associated with an elevated risk of mortality, especially among the elderly and individuals with underlying conditions such as diabetes, stroke, and myocardial infarction [4–7].

The hyperinsulinemic-euglycemic clamp (HEC) is considered the gold standard for assessing insulin resistance status. This test is infrequently employed in clinical practice due to its complexity and invasiveness. The homeostasis model assessment of insulin resistance (HOMA-IR) is more commonly utilized for evaluating insulin resistance. HOMA-IR is calculated from fasting blood glucose (FBG) and fasting insulin levels, and it shows a strong correlation with HEC [8, 9]. However, due to the infrequent measurement of fasting insulin in primary care, more straightforward and practical alternatives for assessing insulin resistance have been created. The newly developed indices comprise the triglyceride glucose index (TyG), triglyceride glucose combined with body mass index (TyG-BMI), metabolic score for insulin resistance (METS-IR), triglyceride to high-density lipoprotein cholesterol ratio (TG/HDL-C), estimated glucose disposal rate (eGDR), and visceral adiposity index (VAI). These indices can be calculated using FBG, fasting triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), waist circumference (WC), body mass index (BMI), blood pressure, or glycosylated hemoglobin (HbA1c) [10–13].

However, the association between newly developed IR indices and all-cause mortality in elderly patients with diabetes has not been investigated. This study used data from the National Health and Nutrition Examination Survey (NHANES) to examine the association between new IR indices and mortality within this population, to identify which new IR indices are more relevant to the survival status of elderly patients with diabetes, thereby facilitating their application in clinical practice.

Methods

Study population

NHANES consists of a series of cross-sectional studies focusing on both adults and children, aimed at evaluating the health and nutritional status of the U.S. population through interviews and physical examinations [14, 15]. This study utilized data from NHANES, covering the years 2001 to 2018. Patients with diabetes aged 65 years or older at enrollment were selected. Diabetes is characterized by a self-reported physician diagnosis, the use of insulin or hypoglycemic medications, plasma fasting glucose levels of 7.0 mmol/L or greater (126 mg/dL), or HbA1c levels of 6.5% or greater [16]. Participants were excluded if they: (1) had incomplete follow-up data or unknown survival status; or (2) lacked essential baseline clinical measurements, such as FBG, fasting insulin, lipid profiles, WC, BMI, blood pressure, or HbA1c. The study included 1248 elderly patients with diabetes (Fig. 1). All participants were informed and provided written consent.

IR indices

This study calculated seven IR indices derived from prior research: HOMA-IR, TyG, METS-IR, TyG-BMI, TG/HDL-C, eGDR, and VAI. The equations used for these calculations are as follows: (1) HOMA-IR = [FBG (mmol/L) ×fasting insulin (μU/mL)]/22.5 [17]; (2) TyG = ln[fasting TG (mg/dL) × FBG (mg/dL)/2] [18]; (3) METS-IR = ln[2 × FBG (mg/dL) + fasting TG (mg/dL)] × BMI/ln HDL-C (mg/dL) [19]; (4) TyG-BMI = TyG × BMI; (5) TG/HDL-C = fasting TG (mg/dL)/HDL-C (mg/dL) [20]; (6) eGDR = 21.158 - [0.09 × WC (cm)] - [3.407 × hypertension (yes = 1 or no = 0)] - [0.551 × HbA1c (%)] [21]; (7) VAI = [WC (cm)/(39.68 + 1.88 × BMI)] × [fasting TG (mmol/L)/1.03] × [1.31/fasting HDL-C (mmol/L)] for males; [WC (cm)/(36.58 + 1.89 × BMI)] × [fasting TG (mmol/L)/0.81] × [1.52/fasting HDL-C (mmol/L)] for females [22].

Assessment of covariates

Baseline demographic data and medical history, including gender, age, weight, height, smoking status, WC, ethnicity, educational levels, medication status (encompassing hypoglycemic medications, antihypertensive drugs, and lipid-lowering drugs), and the presence of hypertension, hyperlipidemia, coronary artery disease (CAD), and stroke, were collected using standardized questionnaires. Educational levels were classified as below high school, high school or equivalent, and college

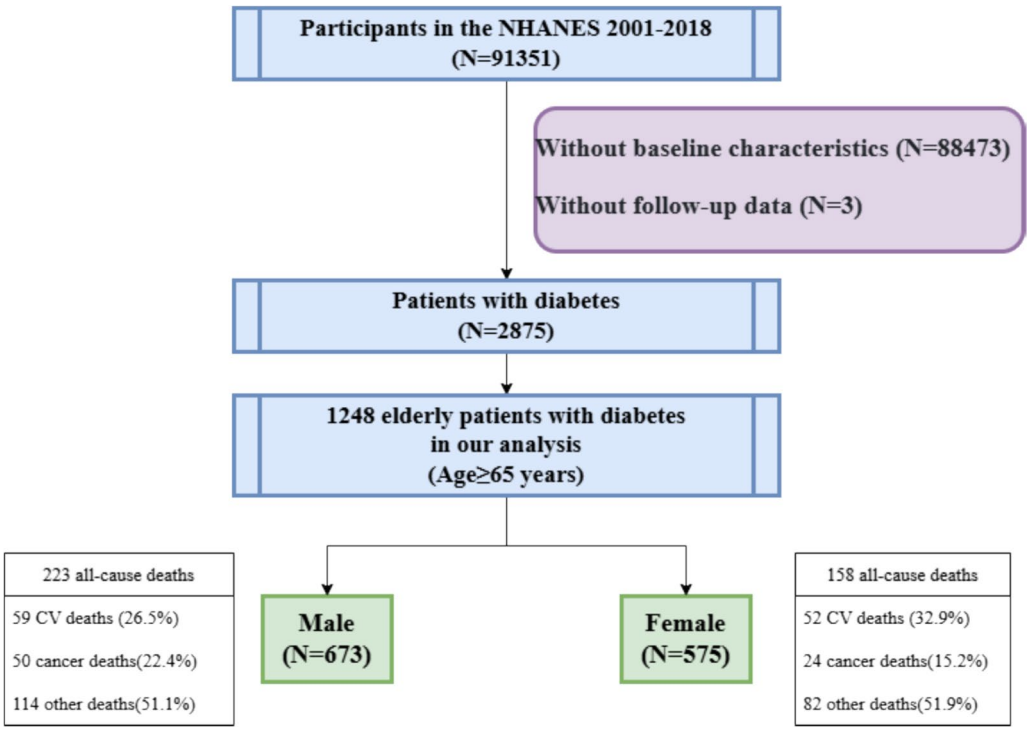

Fig. 1 The screening flowchart of the study population. NHANES, National Health and Nutrition Examination Survey; N, number; CV, cardiovascular

or higher. Smoking status was classified as either current or never/former smoking. BMI was calculated by dividing weight in kilograms by the square of height in meters. Hypertension was defined as a self-reported history of diagnosis, the use of antihypertensive medications, a systolic blood pressure (SBP) of 140 mmHg or greater, or diastolic blood pressure (DBP) of 90 mmHg or greater. CAD was characterized by self-reported coronary heart disease, myocardial infarction, or heart attack [16]. Hyperlipidemia is defined by self-reported high cholesterol levels, the use of cholesterol-lowering medications, or laboratory results indicating total cholesterol (TC) of 200 mg/dL or higher, TG of 150 mg/dL or higher, low-density lipoprotein cholesterol (LDL-C) of 130 mg/dL or higher, and HDL-C less than 40 mg/dL for males or less than 50 mg/dL for females [23].

Baseline laboratory data were extracted, comprising FBG, fasting insulin, HbA1c, TC, TG, LDL-C, HDL-C, serum albumin, serum creatinine, urinary albumin, urinary creatinine, and uric acid (UA). The estimated glomerular filtration rate (eGFR) was calculated from serum creatinine concentrations utilizing the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation. The random urine albumin-creatinine ratio (UACR) was calculated as the ratio of urinary albumin concentration (mg/dL) to urinary creatinine concentration (mg/L). Additional information concerning these measurements is provided in the NHANES Laboratory Medical Technologists Procedures Manual [24].

Ascertainment of mortality

We determined the mortality status of patients during follow-up by utilizing the NHANES Public-Use Linked Mortality Files, which were linked to the National Death Index records using a probabilistic matching algorithm until 31 December 2019 [25]. All-cause mortality refers to death resulting from any cause. Causes of death were determined using the International Statistical Classification of Diseases, 10th Revision (ICD-10). Cardiovascular mortality includes rheumatic heart diseases, hypertensive heart and renal disease, ischemic heart disease, and heart failure, as classified by ICD-10 codes I00-I09, I11, I13, and I20-I51. Cancer-related mortality is defined as death resulting from malignant neoplasms, as classified by ICD-10 codes C00-C97. In addition to deaths from cardiovascular diseases and cancer, individuals not categorized under these causes were classified as having died from other causes. Supplemental Table 1 provides comprehensive information on the causes of death.

Statistical analysis

Patients were categorized into male and female groups. Baseline characteristics were reported as median (25th-75th percentile) for continuous variables and as number

(percentage) for categorical variables, followed by comparisons among the different groups. Group differences were assessed using the Wilcoxon rank-sum test and the Kruskal-Wallis test. The association between IR indices and all-cause mortality was assessed by analyzing the indices as both continuous and categorical variables. Cox proportional hazards analysis was performed to determine hazard ratios (HRs) and 95% confidence intervals (CIs). The verification of the proportional hazards assumption was conducted through the analysis of Schoenfeld residuals. Covariates were selected based on clinical relevance and prior literature. The variance inflation factor (VIF) was calculated to assess multicollinearity, with variables showing VIFs greater than 5 being excluded from the analysis (Supplementary Table 2). Univariate and multivariate models were constructed, and interactions by gender were assessed. Model 1 was unadjusted. Model 2 accounted for age, ethnicity, and educational levels. Model 3 incorporated covariates identified through the least absolute shrinkage and selection operator (LASSO) method (Supplemental Fig. 1). Model 4 included a comprehensive adjustment for covariates such as age, ethnicity, educational levels, BMI, albumin, UACR, UA, creatinine, current smoking status, insulin treatment, hypoglycemic drugs, antihypertensive drugs, lipid-lowering drugs, hypertension, hyperlipidemia, stroke, CAD, FBG, fasting insulin, HbA1c, and eGFR. A restricted cubic spline (RCS) regression model with four knots (5%, 35%, 65%, and 95%) was utilized to examine potential nonlinear relationships between IR indices and mortality. Subgroup analyses were conducted among patients with varying levels of eGFR, UACR, stroke, CAD, smoking status, hypertension, and hyperlipidemia. All analyses were performed utilizing R software, version 4.4.1. Adjustments for multiple comparisons were not applied due to the exploratory nature of these analyses. A p-value below 0.05 indicates statistical significance.

Results

Baseline characteristics

This study enrolled 1248 participants, with a median age of 72 years and a male proportion of 53.9%. The median values for HOMA-IR, TyG, METS-IR, TyG-BMI, TG/HDL-C, eGDR, and VAI among participants were 4.6, 9.06, 47, 272, 2.52, 4.74, and 1.90, respectively. The baseline characteristics of the participants are presented in Table 1, categorized by gender. Female participants exhibited lower levels of WC, HbA1c, albumin, UA, serum creatinine, FBG, and TG/HDL-C compared to male participants, while demonstrating higher levels of HDL-C, LDL-C, TC, eGDR, and VAI. A higher prevalence of CAD and cancer mortality was observed in male participants. No significant difference in all-cause mortality was observed between male and female participants.

Associations between IR indices and mortality in the total cohort

Four Cox regression models were fitted to examine the independent associations between IR indices and the risk of all-cause mortality (Table 2). Model 1 was unadjusted. Model 2 was adjusted for age, ethnicity, and educational attainment. The LASSO method was employed for factor selection, with detailed information provided in Supplemental Fig. 1. Model 3 for all-cause mortality, in conjunction with the feature selection outcomes of the LASSO method, included adjustments for age, educational levels, BMI, creatinine, smoking, lipid-lowering drug use, and CAD. Model 4 was adjusted for various factors including age, ethnicity, educational levels, BMI, albumin, UACR, UA, creatinine, smoking status, insulin treatment, other hypoglycemic medications, antihypertensive medications, lipid-lowering medications, hypertension, hyperlipidemia, stroke, CAD, FBG, fasting insulin, HbA1c, and eGFR. The analysis revealed that in Model 1 and Model 2, when treated as continuous variables, METS-IR and TyG-BMI exhibited a significant correlation with all-cause mortality [METS-IR: Model 1, HR (95% CI) 0.97 (0.96-0.99), $p < 0.001$; Model 2, HR (95% CI) 0.99 (0.97-1.00), $p = 0.029$; TyG-BMI: Model 1, HR (95% CI) 1.00 (0.99-1.00), $p < 0.001$; Model 2, HR (95% CI) 1.00 (1.00-1.00), $p = 0.021$]. A significant association was observed between eGDR and all-cause mortality as a continuous variable in Model 1 [HR (95% CI) 1.07 (1.01-1.12), $p = 0.011$]. When analyzed as categorical variables, HOMA-IR, METS-IR, TyG-BMI, and eGDR demonstrated a significant association with all-cause mortality in the Cox regression models ($p < 0.05$); however, not all models indicated elevated HRs for patients with moderate and high IR indices. Nonetheless, no notable associations were found between TyG, TG/HDL-C, VAI, and all-cause mortality in both continuous and categorical analyses.

Associations between IR indices and mortality in different gender

In the male cohort, HOMA-IR and TyG-BMI, when treated as categorical variables, exhibited an association with all-cause mortality (Table 3). In the female group, METS-IR, TyG-BMI, and eGDR, assessed as both continuous and categorical variables, showed associations with all-cause mortality in Model 1. Comparable associations were observed in Model 2 (Table 4). After thorough adjustments for potential confounders in Models 3 and 4, the gender interaction remained statistically significant.

Table 1 Baseline Characteristics of Elderly Patients with Diabetes by Gender

Variables	Total (N = 1248)	Male (N = 673)	Female (N = 575)	p-value
Age (years)	72.0 (67.0, 78.0)	71.0 (67.0, 77.0)	73.0 (67.0, 79.0)	0.071
BMI (kg/m^2)	30.2 (26.6, 34.0)	29.4 (26.3, 33.7)	30.6 (26.7, 34.6)	0.13
Smoking	84 (5.4%)	60 (6.8%)	24 (4.0%)	0.10
WC (cm)	108 (98, 117)	110 (102, 119)	106 (96, 115)	**< 0.001**
Ethnicity				**0.006**
Mexican American	167 (5.7%)	84 (5.2%)	83 (6.2%)	
Other Hispanic	115 (4.1%)	56 (3.6%)	59 (4.6%)	
Non-Hispanic White	578 (72%)	337 (75%)	241 (69%)	
Non-Hispanic Black	266 (11%)	126 (7.8%)	140 (13%)	
Other Race	122 (7.3%)	70 (8.0%)	52 (6.5%)	
Educational levels				**0.026**
Less than high school	478 (27%)	251 (24%)	227 (29%)	
High school or equivalent	307 (25%)	154 (22%)	153 (28%)	
College or above	463 (48%)	268 (53%)	195 (43%)	
Medications				
Insulin treatment	250 (19%)	137 (20%)	113 (18%)	0.6
Other hypoglycemic drugs	751 (61%)	402 (62%)	349 (61%)	0.8
Antihypertensive drugs	850 (66%)	433 (64%)	417 (69%)	0.15
Lipid-lowering drugs	650 (55%)	349 (57%)	301 (52%)	0.2
Comorbidities				
Hypertension	997 (78%)	522 (77%)	475 (78%)	0.7
Hyperlipidemia	1077 (87%)	567 (85%)	510 (90%)	0.088
Coronary artery disease	308 (25%)	199 (31%)	109 (20%)	**< 0.001**
Stroke	141 (12%)	79 (11%)	62 (13%)	0.4
Laboratory measurements				
FBG (mg/dL)	133 (122, 158)	135 (126, 161)	131 (119, 154)	**0.004**
Fasting insulin (pmol/L)	77 (50, 130)	77 (48, 124)	77 (51, 140)	0.4
HbA1c (%)	6.60 (6.10, 7.30)	6.60 (6.10, 7.40)	6.50 (6.00, 7.20)	**0.039**
Triglyceride (mg/dL)	123 (90, 173)	125 (89, 172)	121 (90, 174)	0.7
Cholesterol (mg/dL)	166 (144, 196)	158 (138, 181)	177 (156, 211)	**< 0.001**
HDL-C mg/dL)	49 (41, 60)	44 (38, 52)	54 (46, 64)	**< 0.001**
LDL-C (mg/dL)	88 (70, 114)	84 (67, 108)	91 (73, 121)	**< 0.001**
Serum albumin (g/dL)	4.10 (3.90, 4.40)	4.20 (4.00, 4.40)	4.10 (3.90, 4.30)	**0.015**
Uric acid (umol/L)	351 (292, 416)	363 (303, 428)	333 (280, 399)	**< 0.001**
Serum creatinine (umol/L)	86 (71, 105)	93 (82, 112)	75 (63, 94)	**< 0.001**
UACR (mg/g)	13 (7, 41)	12 (7, 47)	15 (8, 37)	0.4
eGFR (mL/min/1.73 m^2)	69 (52, 84)	68 (52, 83)	69 (53, 84)	0.4
IR indices				
TyG	9.06 (8.68, 9.45)	9.05 (8.66, 9.48)	9.07 (8.69, 9.40)	> 0.9
METS-IR	47 (41, 55)	48 (41, 55)	46 (40, 54)	0.067
TyG-BMI	272 (236, 314)	269 (234, 314)	275 nnnn	0.3
TG/HDL-C	2.52 (1.62, 3.94)	2.79 (1.79, 4.32)	2.30 (1.48, 3.62)	**< 0.001**
HOMA-IR	4.6 (2.7, 7.7)	4.6 (2.7, 7.8)	4.6 (2.7, 7.7)	> 0.9
eGDR	4.74 (3.57, 6.30)	4.59 (3.27, 6.02)	4.94 (3.79, 6.52)	**0.006**
VAI	1.90 (1.25, 3.03)	1.81 (1.13, 2.77)	2.10 (1.35, 3.30)	**0.001**
All-cause mortality	381(29%)	223(28%)	158(30%)	0.6
CV mortality	111 (8.1%)	59 (7.8%)	52 (8.4%)	0.8
Cancer mortality	74 (5.5%)	50 (6.8%)	24 (4.2%)	**0.043**
Other mortality	196 (15%)	114 (13%)	82 (17%)	0.083

Table 1 (continued)

BMI, body mass index; WC, waist circumference; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; UACR, urine albumin-creatinine ratio; eGFR, estimated glomerular filtration rate; TyG, triglyceride glucose index; TyG-BMI, triglyceride glucose combined with body mass index; METS-IR, metabolic score for insulin resistance; TG/HDL-C, triglyceride to high-density lipoprotein cholesterol ratio; HOMA-IR, homeostasis model assessment of insulin resistance; eGDR, estimated glucose disposal rate; VAI, visceral adiposity index; CV, cardiovascular.

HOMA-IR demonstrated a significant association with all-cause mortality solely in males, whereas METS-IR and eGDR were significantly linked to all-cause mortality in females. No significant associations were found between TyG, TG/HDL-C, VAI, and all-cause mortality in the overall cohort or within the male and female subgroups after adjustments.

RSC regression analysis

Figure 2 displayed the association between HOMA-IR, METS-IR, TyG-BMI, eGDR, and all-cause mortality using RCS analysis in the overall cohort. However, after adjusting for all covariates in Model 4, no significant nonlinear association was observed between HOMA-IR and all-cause mortality (p-overall < 0.0001, p-nonlinear > 0.05, Fig. 2D). In contrast, METS-IR, TyG-BMI, and eGDR exhibited nonlinear associations with all-cause mortality (p-overall < 0.0001, p-nonlinear < 0.05). There was a U-shaped association between METS-IR, TyG-BMI, eGDR, and all-cause mortality. Therefore, it showed that both excessively high and low levels of METS-IR, TyG-BMI, and eGDR were associated with a higher risk of all-cause mortality.

Stratified analyses

Subgroup analysis was employed to assess the robustness of the aforementioned results. eGFR, UACR, stroke, CAD, smoking status, hypertension, and hyperlipidemia are significant factors in evaluating physiological states and disease risks, potentially influencing the relationships between insulin resistance indices and all-cause mortality. The analysis revealed that eGFR, UACR, stroke, CAD, smoking status, hypertension, and hyperlipidemia did not affect the relationships between HOMA-IR, TyG-BMI, METS-IR, and all-cause mortality in elderly participants with diabetes, as determined by model 4. eGDR demonstrated differential effects among various eGFR populations (Figs. 3 and 4).

Discussion

Our study examined the relationships between the traditional IR index HOMA-IR, newly developed IR indices, and all-cause mortality in elderly patients with diabetes from the NHANES cohort, while also comparing the prognostic values of seven IR indices. HOMA-IR, METS-IR, TyG-BMI, and eGDR demonstrated significant associations with all-cause mortality. Conversely, TyG, TG/HDL-C, and VAI exhibited no significant associations with all-cause mortality. Furthermore, we confirmed that the associations between IR indices and all-cause mortality in this specific population were influenced by gender. In the male population, HOMA-IR and TyG-BMI exhibited superior prognostic value, whereas in the female population, METS-IR, TyG-BMI, and eGDR displayed enhanced performance following adjustments for traditional risk factors. The subgroup analysis results indicated that our findings demonstrate a certain level of robustness.

IR denotes a condition characterized by reduced sensitivity and responsiveness to insulin action [26]. IR induces adverse metabolic alterations and disrupts glucose metabolism, potentially leading to oxidative stress and inflammatory responses that cause cellular damage [27]. IR was linked to various chronic conditions [28] and, in certain cases, mortality [29, 30]. On the other hand, due to the complexity and invasiveness of the gold standard for assessing IR, alternative measures have been widely used to explore the relationship between IR and various clinical conditions. HOMA-IR, a widely utilized measure for evaluating insulin resistance, demonstrated a correlation with mortality [7]. Recently, several new insulin resistance alternative indices have emerged, including TyG, METS-IR, TyG-BMI, TG/HDL-C, HOMA-IR, eGDR, and VAI. Recent meta-analyses strongly suggested that the TyG is a promising biomarker for screening and predicting numerous medical conditions. Specifically, it has remarkable value for insulin-resistance-related and metabolic disorders, such as type 2 diabetes mellitus, ischemic stroke, dementia, atrial fibrillation, heart failure, obstructive sleep apnea, post-percutaneous coronary intervention events, and multiple others, highlighting its potential in clinical decision-making [31–36]. Previous research has shown that elevated TyG levels correlate with a heightened risk of all-cause mortality in patients with diabetes under the age of 65 [16]. Ryu HE et al. found a positive correlation between METS-IR and both all-cause and cancer-related mortality in individuals aged over 60 years [37]. TyG-BMI has been demonstrated as an effective predictor of all-cause and cardiovascular mortality risks in patients with diabetes [38], whereas higher eGDR has been associated with reduced risks of stroke and mortality in individuals with type 2 diabetes [39]. Wang L et al. identified a J-shaped relationship between VAI levels and all-cause mortality [40].

Table 2 Association between IR indices and all-cause mortality in the total cohort

	Hazard ratio (95% confidence interval)			
	Model 1	**Model 2**	**Model 3**	**Model 4**
TyG				
TyG (continuous)	0.86 (0.68–1.09)	0.90 (0.71–1.14)	0.96 (0.76–1.22)	0.91 (0.67–1.23)
	p = 0.207	p = 0.370	p = 0.733	p = 0.533
TyG (categorical)				
TyG tertile 1	Reference	Reference	Reference	Reference
TyG tertile 2	0.78 (0.59–1.04)	0.97 (0.72–1.32)	1.03 (0.76–1.41)	0.98 (0.69–1.39)
	p = 0.093	p = 0.856	p = 0.831	p = 0.898
TyG tertile 3	0.76 (0.56–1.03)	0.81 (0.60–1.11)	0.87 (0.64–1.18)	0.80 (0.57–1.12)
	p = 0.078	p = 0.188	p = 0.364	p = 0.185
p for trend	p = 0.138	p = 0.327	p = 0.489	p = 0.323
METS-IR				
METS-IR (continuous)	**0.97 (0.96–0.99)***	**0.99 (0.97–1.00)***	0.99 (0.96–1.03)	0.98 (0.94–1.02)
	p < 0.001	**p = 0.029**	p = 0.576	p = 0.325
METS-IR (categorical)				
METS-Rtertile 1	Reference	Reference	Reference	Reference
METS-IR tertile 2	**0.66 (0.49–0.89)***	**0.70 (0.52–0.93)***	0.82 (0.61–1.10)	0.85 (0.62–1.18)
	p = 0.007	**p = 0.015**	p = 0.183	p = 0.333
METS-IRtertile 3	**0.62 (0.44–0.86)***	0.82 (0.59–1.14)	1.26 (0.80–1.99)	1.25 (0.73–2.16)
	p = 0.004	p = 0.247	p = 0.322	p = 0.412
p for trend	**p = 0.006**	p = 0.051	**p = 0.050**	p = 0.095
TyG-BMI				
TyG-BMI (continuous)	**1.00 (0.99–1.00)***	**1.00 (1.00–1.00)***	1.00 (0.99–1.01)	1.00 (0.99–1.01)
	p < 0.001	**p = 0.021**	p = 0.857	p = 0.601
TyG-BMI (categorical)				
TyG-BMI tertile 1	Reference	Reference	Reference	Reference
TyG-BMI tertile 2	**0.59 (0.44–0.78)***	**0.67 (0.51–0.86)***	**0.68 (0.50–0.92)***	**0.71 (0.50–0.99)***
	p < 0.001	**p = 0.002**	**p = 0.013**	**p = 0.043**
TyG-BMI tertile 3	**0.52 (0.39–0.69)***	**0.71 (0.52–0.96)***	0.90 (0.53–1.55)	0.94 (0.51–1.72)
	p < 0.001	**p = 0.024**	p = 0.712	p = 0.840
p for trend	**p < 0.001**	**p = 0.007**	**p = 0.015**	**p = 0.025**
TG/HDL-C				
TG/HDL-C (continuous)	0.97 (0.91–1.03)	0.97 (0.91–1.04)	0.97 (0.91–1.04)	0.98 (0.91–1.05)
	p = 0.259	p = 0.376	p = 0.390	p = 0.555
TG/HDL-C (categorical)				
TG/HDL–C Itertile 1	Reference	Reference	Reference	Reference
TG/HDL-C tertile 2	1.02 (0.77–1.36)	1.02 (0.78–1.35)	1.05 (0.79–1.39)	1.09 (0.80–1.47)
	p = 0.866	p = 0.860	p = 0.759	p = 0.584
TG/HDL-C tertile 3	0.85 (0.63–1.15)	0.84 (0.62–1.12)	0.83 (0.63–1.10)	0.85 (0.62–1.17)
	p = 0.284	p = 0.230	p = 0.195	p = 0.313
p for trend	p = 0.403	p = 0.311	p = 0.258	p = 0.255
HOMA-IR				
HOMA-IR (continuous)	1.00 (0.98–1.01)	1.00 (0.99–1.01)	1.00 (0.99–1.01)	0.98 (0.95–1.01)
	p = 0.563	p = 0.936	p = 0.633	p = 0.141
HOMA-IR (categorical)				
HOMA-IR tertile 1	Reference	Reference	Reference	Reference
HOMA-IR tertile 2	**0.66 (0.48–0.92)***	**0.69 (0.50–0.94)***	0.77 (0.55–1.08)	0.75 (0.52–1.07)
	p = 0.015	**p = 0.019**	p = 0.132	p = 0.108

Table 2 (continued)

	Hazard ratio (95% confidence interval)			
	Model 1	**Model 2**	**Model 3**	**Model 4**
HOMA-IR tertile 3	**0.70 (0.51–0.96)***	0.80 (0.59–1.07)	0.93 (0.68–1.27)	0.82 (0.55–1.24)
	p = 0.025	p = 0.134	p = 0.645	p = 0.356
p for trend	**p = 0.021**	p = 0.056	p = 0.302	p = 0.274
eGDR				
eGDR (continuous)	**1.07 (1.01–1.12)***	1.03 (0.97–1.08)	0.98 (0.91–1.05)	0.87 (0.73–1.05)
	p = 0.011	p = 0.346	p = 0.567	p = 0.157
eGDR (categorical)				
eGDR tertile 1	Reference	Reference	Reference	Reference
eGDR tertile 2	1.01 (0.72–1.40)	0.82 (0.60–1.11)	**0.66 (0.48–0.92)***	0.70 (0.47–1.05)
	p = 0.976	p = 0.192	**0.014**	p = 0.085
eGDR tertile 3	**1.39 (1.02–1.89)***	1.16 (0.88–1.55)	0.83 (0.57–1.20)	0.93 (0.53–1.65)
	p = 0.035	p = 0.296	0.316	p = 0.815
p for trend	**p = 0.014**	**p = 0.019**	**p = 0.023**	p = 0.059
VAI				
VAI (continuous)	0.95 (0.87–1.03)	0.94 (0.87–1.03)	0.96 (0.88–1.05)	0.97 (0.88–1.06)
	p = 0.197	p = 0.172	p = 0.338	p = 0.470
VAI (categorical)				
VAI tertile 1	Reference	Reference	Reference	Reference
VAI tertile 2	0.96 (0.73–1.27)	0.93 (0.71–1.22)	0.97 (0.75–1.26)	0.98 (0.74–1.30)
	p = 0.792	**p = 0.609**	p = 0.827	p = 0.893
VAI tertile 3	**0.75 (0.57–1.00)***	0.71 (0.53–0.96)	0.75 (0.55–1.01)	0.74 (0.53–1.02)
	p = 0.047	p = 0.027	p = 0.061	p = 0.068
p for trend	p = 0.116	p = 0.078	p = 0.149	p = 0.143

Model 1 was unadjusted; Model 2 was adjusted for age, ethnicity, and educational levels; Model 3 was adjusted for age, educational levels, BMI, creatinine, smoking, lipid-lowering drugs, and CAD; Model 4 was adjusted for age, ethnicity, educational levels, BMI, albumin, UACR, UA, creatinine, smoking, insulin treatment, hypoglycemic drugs, antihypertensive drugs, lipid-lowering drugs, hypertension, hyperlipidemia, stroke, CAD, FBG, fasting insulin, HbA1c, and eGFR

TyG, triglyceride glucose index; TyG-BMI, triglyceride glucose combined with body mass index; METS-IR, metabolic score for insulin resistance; TG/HDL-C, triglyceride to high-density lipoprotein cholesterol ratio; HOMA-IR, homeostasis model assessment of insulin resistance; eGDR, estimated glucose disposal rate; VAI, visceral adiposity index; BMI, body mass index; UACR, urine albumin-creatinine ratio; UA, uric acid; CAD, coronary artery disease; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; eGFR, estimated glomerular filtration rate; CI, confidence interval

*Indicated that the p-value was less than 0.05

Nonetheless, it was unclear which new IR indices were most pertinent to the survival status of elderly patients with diabetes.

Our study involved 1248 elderly diabetes patients drawn from a nationally representative sample of the U.S. population, focusing on identifying which new IR indices are most closely linked to the survival status of elderly patients with diabetes. HOMA-IR, METS-IR, TyG-BMI, and eGDR were found to be associated with all-cause mortality, while TyG, TG/HDL-C, and VAI did not demonstrate similar associations in this population. This discrepancy may be due to the differing physiological and metabolic pathways evaluated by these indices in the assessment of insulin resistance [41]. TyG and TG/HDL-C primarily focused on lipid and blood glucose levels, whereas METS-IR, TyG-BMI, and eGDR incorporated additional factors such as blood pressure, WC, and BMI [18, 39, 42]. The accuracy of TyG can be enhanced by integrating it with adiposity indicators such as BMI. This integration gives rise to the TyG-BMI [43]. METS-IR effectively incorporates multiple defining components of metabolic syndrome, including WC, blood pressure, FBG, and lipid parameters, which can accurately quantify IR [19]. eGDR can provide a more comprehensive model of metabolic health assessment by taking into account WC, hypertension, and HbA1c [21]. VAI is another index that probably predicts insulin resistance. It is calculated using BMI, WC, TG levels, and HDL-C levels [44]. Excess visceral fat, typically mirrored by elevated TyG-BMI, METS-IR, eGDR, and VAI values, contributes to chronic low-grade inflammation. This inflammatory state further impairs insulin signaling pathways [45]. In the elderly, indices of insulin resistance associated with blood pressure, WC, and

Table 3 Association between IR indices and all-cause mortality in male group

	Hazard ratio (95% confidence interval)			
	Model 1	**Model 2**	**Model 3**	**Model 4**
TyG				
TyG (continuous)	0.77 (0.55–1.08)	0.86 (0.61–1.21)	0.86 (0.61–1.20)	1.00 (0.70–1.42)
	p = 0.134	p = 0.381	p = 0.372	p = 0.996
TyG (categorical)				
TyG tertile 1	Reference	Reference	Reference	Reference
TyG tertile 2	0.70 (0.44–1.11)	0.84 (0.55–1.28)	0.87 (0.58–1.30)	0.89 (0.59–1.36)
	p = 0.126	p = 0.417	p = 0.495	p = 0.601
TyG tertile 3	**0.64 (0.41–1.00)***	0.69(0.44–1.07)	0.68 (0.44–1.07)	0.74 (0.48–1.15)
	p = 0.048	p = 0.100	p = 0.099	p = 0.180
p for trend	p = 0.123	p = 0.257	p = 0.252	p = 0.402
METS-IR				
METS-IR (continuous)	**0.98 (0.97–1.00)***	0.99 (0.98–1.01)	0.97 (0.92–1.02)	0.97 (0.92–1.03)
	p = 0.026	p = 0.355	p = 0.260	p = 0.315
METS–IR (categorical)				
METS-Rtertile 1	Reference	Reference	Reference	Reference
METS-IR tertile 2	0.88 (0.61–1.25)	0.81 (0.57–1.15)	0.84 (0.61–1.16)	0.97 (0.67–1.40)
	p = 0.467	p = 0.244	p = 0.296	p = 0.877
METS-IRtertile 3	0.74 (0.50–1.12)	0.97 (0.64–1.46)	1.08 (0.55–2.11)	1.37 (0.68–2.73)
	p = 0.153	p = 0.871	p = 0.823	p = 0.378
p for trend	p = 0.360	p = 0.404	p = 0.281	p = 0.351
TyG-BMI				
TyG-BMI (continuous)	1.00 (0.99–1.00)	1.00 (1.00–1.00)	1.00 (0.98–1.01)	1.00 (0.99–1.01)
	p = 0.054	p = 0.571	p = 0.494	p = 0.919
TyG-BMI (categorical)				
TyG-BMI tertile 1	Reference	Reference	Reference	Reference
TyG-BMI tertile 2	0.67 (0.47–0.96)	**0.63 (0.45–0.88)***	0.74 (0.47–1.14)	0.92 (0.60–1.41)
	p = 0.030	**p = 0.006**	p = 0.173	p = 0.689
TyG-BMI tertile 3	0.72 (0.47–1.10)	0.99 (0.63–1.55)	1.29 (0.56–2.97)	1.92 (0.83–4.44)
	p = 0.129	p = 0.953	p = 0.552	p = 0.129
p for trend	p = 0.072	**p = 0.012**	**p = 0.024**	**p = 0.036**
TG/HDL-C				
TG/HDL–C (continuous)	0.96 (0.89–1.04)	0.98 (0.90–1.06)	0.97 (0.89–1.05)	1.00 (0.92–1.08)
	p = 0.297	p = 0.639	p = 0.439	p = 0.944
TG/HDL-C (categorical)				
TG/HDL-C Itertile 1	Reference	Reference	Reference	Reference
TG/HDL-C tertile 2	0.92 (0.60–1.41)	0.96 (0.67–1.38)	0.95 (0.68–1.34)	1.06 (0.75–1.51)
	p = 0.714	p = 0.822	p = 0.783	p = 0.729
TG/HDL-C tertile 3	0.72 (0.47–1.08)	0.73 (0.50–1.06)	0.67 (0.47–0.96)	0.76 (0.51–1.12)
	p = 0.111	p = 0.099	p = 0.031	p = 0.168
p for trend	p = 0.269	p = 0.226	p = 0.095	p = 0.262
HOMA-IR				
HOMA-IR (continuous)	0.99 (0.97–1.01)	0.99 (0.97–1.01)	0.99 (0.98–1.01)	0.97 (0.91–1.03)
	p = 0.178	p = 0.279	p = 0.425	p = 0.291
HOMA-IR (categorical)				
HOMA–IR tertile 1	Reference	Reference	Reference	Reference
HOMA–IR tertile 2	**0.54 (0.36–0.81)***	**0.54 (0.37–0.77)***	**0.62 (0.42–0.91)***	0.72 (0.47–1.10)
	p = 0.003	**p < 0.001**	**p = 0.014**	p = 0.125

Table 3 (continued)

	Hazard ratio (95% confidence interval)			
	Model 1	**Model 2**	**Model 3**	**Model 4**
HOMA-IR tertile 3	0.70 (0.45–1.08)	0.76 (0.51–1.13)	0.83 (0.51–1.35)	1.02 (0.57–1.83)
	p = 0.104	p = 0.180	p = 0.457	p = 0.942
p for trend	**p = 0.011**	**p = 0.003**	**p = 0.038**	p = 0.149
eGDR				
eGDR (continuous)	1.03 (0.96–1.11)	1.01 (0.93–1.09)	0.99 (0.90–1.08)	0.92 (0.61–1.37)
	p = 0.343	p = 0.894	p = 0.775	p = 0.670
eGDR (categorical)				
eGDR tertile 1	Reference	Reference	Reference	Reference
eGDR tertile 2	0.97 (0.62–1.53)	0.73 (0.48–1.13)	0.69 (0.46–1.04)	0.66 (0.42–1.04)
	p = 0.897	p = 0.157	p = 0.074	p = 0.071
eGDR tertile 3	1.19 (0.77–1.85)	1.00 (0.65–1.54)	0.79 (0.47–1.32)	0.64 (0.29–1.43)
	p = 0.433	p = 0.999	p = 0.372	p = 0.278
p for trend	p = 0.514	p = 0.080	p = 0.162	p = 0.195
VAI				
VAI (continuous)	0.94 (0.84–1.06)	0.97 (0.86–1.10)	0.96 (0.84–1.09)	1.00 (0.89–1.13)
	p = 0.320	p = 0.676	p = 0.500	p = 0.996
VAI (categorical)				
VAI tertile 1	Reference	Reference	Reference	Reference
VAI tertile 2	0.95 (0.63–1.42)	0.96 (0.67–1.37)	0.95 (0.68–1.33)	1.06 (0.75–1.49)
	p = 0.788	p = 0.820	p = 0.785	p = 0.742
VAI tertile 3	0.73 (0.49–1.09)	0.74 (0.51–1.09)	**0.68 (0.47–0.99)***	0.79 (0.53–1.18)
	p = 0.119	p = 0.126	**p = 0.044**	p = 0.246
p for trend	p = 0.270	p = 0.281	p = 0.125	p = 0.376

Model 1 was unadjusted; Model 2 was adjusted for age, ethnicity, and educational levels; Model 3 was adjusted for age, educational levels, BMI, creatinine, smoking, lipid–lowering drugs, and CAD; Model 4 was adjusted for age, ethnicity, educational levels, BMI, albumin, UACR, UA, creatinine, smoking, insulin treatment, hypoglycemic drugs, antihypertensive drugs, lipid-lowering drugs, hypertension, hyperlipidemia, stroke, CAD, FBG, fasting insulin, HbA1c, and eGFR

TyG, triglyceride glucose index; TyG-BMI, triglyceride glucose combined with body mass index; METS-IR, metabolic score for insulin resistance; TG/HDL-C, triglyceride to high-density lipoprotein cholesterol ratio; HOMA-IR, homeostasis model assessment of insulin resistance; eGDR, estimated glucose disposal rate; VAI, visceral adiposity index; BMI, body mass index; UACR, urine albumin-creatinine ratio; UA, uric acid; CAD, coronary artery disease; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; eGFR, estimated glomerular filtration rate; CI, confidence interval

*Indicated that the p-value was less than 0.05

BMI are more significant than in the young. Research indicates that hypertension in the elderly frequently coexists with insulin resistance, and there is a notable correlation between insulin resistance and blood pressure in this demographic [46]. Additionally, WC and BMI demonstrate superior predictive value for insulin resistance in the elderly [47]. Beyond the direct metabolic pathways captured by these indices, emerging evidence highlights the role of gut-liver interactions in modulating insulin sensitivity. Gut microbiota dysbiosis, prevalent in elderly populations, has been linked to systemic inflammation and impaired glucose homeostasis. Recent research demonstrated that microbiome-targeted therapies improve lipid profiles and glycemic control in patients with type 2 diabetes [48], suggesting that dysbiosis-driven metabolic disturbances may exacerbate IR severity. These could explain why lipid-integrated indices strongly predict mortality in our cohort. A compromised gut barrier may further contribute to hepatic inflammation and steatosis. In patients with non-alcoholic fatty liver disease (NAFLD), gut microbiome manipulation has been shown to improve liver enzyme levels and glycemic indices [28]. This implies that gut-derived metabolites regulate hepatic lipid metabolism, and their deficiency in aging populations may worsen IR. NAFLD, a common comorbidity in elderly diabetics, underscores the liver's central role in IR. Hepatic lipid accumulation disrupts insulin's suppression of gluconeogenesis, as evidenced by the association between microbiome-targeted therapies and reduced liver fat content [49]. The METS-IR, which incorporates HDL-C levels, may capture hepatic IR progression, given that HDL-C inversely correlates with liver fat in NAFLD patients [48]. The

Table 4 Association between IR indices and all-cause mortality in female group

	Hazard ratio (95% confidence interval)			
	Model 1	**Model 2**	**Model 3**	**Model 4**
TyG				
TyG (continuous)	0.96 (0.67–1.37)	0.97 (0.70–1.34)	1.15 (0.81–1.62)	0.78 (0.45–1.36)
	p = 0.816	p = 0.840	p = 0.437	p = 0.384
TyG (categorical)				
TyG tertile 1	Reference	Reference	Reference	Reference
TyG tertile 2	0.97 (0.66–1.42)	1.23 (0.81–1.88)	1.54 (0.98–2.40)	1.10 (0.63–1.92)
	p = 0.870	p = 0.330	p = 0.060	p = 0.746
TyG tertile 3	0.94 (0.63–1.39)	1.02 (0.69–1.50)	1.28 (0.87–1.88)	0.85 (0.46–1.56)
	p = 0.748	p = 0.923	p = 0.212	p = 0.590
p for trend	p = 0.949	p = 0.561	p = 0.160	p = 0.585
METS–IR				
METS-IR (continuous)	**0.96 (0.95–0.98)***	**0.98 (0.96–1.00)***	1.00 (0.95–1.06)	0.96 (0.89–1.03)
	p < 0.001	**p = 0.025**	p = 0.991	p = 0.254
METS-IR (categorical)				
METS-Rtertile 1	Reference	Reference	Reference	Reference
METS-IR tertile 2	**0.58 (0.36–0.94)***	0.69 (0.45–1.08)	0.82 (0.47–1.44)	0.82 (0.48–1.40)
	p = 0.026	p = 0.104	p = 0.487	p = 0.456
METS-IRtertile 3	**0.47 (0.31–0.71)***	**0.62 (0.42–0.93)***	0.94 (0.48–1.85)	0.82 (0.36-1.84)
	p < 0.001	**p = 0.020**	p = 0.856	p = 0.627
p for trend	**p < 0.001**	**p = 0.048**	p = 0.745	p = 0.757
TyG-BMI				
TyG-BMI (continuous)	**0.99 (0.99–1.00)***	**1.00 (0.99–1.00)***	1.00 (0.99–1.02)	0.99 (0.97–1.01)
	p < 0.001	**p = 0.022**	p = 0.417	p = 0.343
TyG-BMI (categorical)				
TyG-BMI tertile 1	Reference	Reference	Reference	Reference
TyG-BMI tertile 2	**0.48 (0.31–0.73)***	**0.62 (0.41–0.94)***	0.61 (0.35–1.10)	0.60 (0.32–1.11)
	p < 0.001	**p = 0.025**	p = 0.099	p = 0.103
TyG-BMI tertile 3	**0.42 (0.28–0.63)***	**0.56 (0.36–0.87)***	0.74 (0.35–1.57)	0.61 (0.24-1.57)
	p < 0.001	**p = 0.009**	p = 0.429	p = 0.306
p for trend	**p < 0.001**	**p = 0.017**	p = 0.232	p = 0.259
TG/HDL-C				
TG/HDL-C (continuous)	0.96 (0.87–1.06)	0.95 (0.86–1.03)	0.97 (0.88–1.07)	0.95 (0.84–1.07)
	p = 0.453	p = 0.222	p = 0.524	p = 0.415
TG/HDL-C (categorical)				
TG/HDL-C Itertile 1	Reference	Reference	Reference	Reference
TG/HDL-C tertile 2	1.13 (0.77–1.66)	1.10 (0.77–1.59)	1.24 (0.87–1.78)	1.19 (0.78–1.81)
	p = 0.535	p = 0.594	p = 0.230	p = 0.425
TG/HDL-C tertile 3	0.85 (0.57–1.27)	0.79 (0.52–1.21)	0.89 (0.57–1.38)	0.80 (0.48–1.34)
	p = 0.429	p = 0.286	p = 0.601	p = 0.400
p for trend	p = 0.439	p = 0.319	p = 0.297	p = 0.318
HOMA-IR				
HOMA-IR (continuous)	1.01 (0.99–1.03)	1.01 (1.00–1.02)	**1.01 (1.00–1.02)***	0.99 (0.96–1.02)
	p = 0.321	p = 0.101	**p = 0.020**	p = 0.574
HOMA-IR (categorical)				
HOMA-IR tertile 1	Reference	Reference	Reference	Reference
HOMA-IR tertile 2	0.75 (0.46–1.22)	0.87 (0.53–1.42)	1.10 (0.65–1.88)	0.85 (0.48–1.52)
	p = 0.242	p = 0.581	p = 0.713	p = 0.584

Table 4 (continued)

	Hazard ratio (95% confidence interval)			
	Model 1	**Model 2**	**Model 3**	**Model 4**
HOMA-IR tertile 3	0.69 (0.46–1.04)	0.85 (0.56–1.31)	1.14 (0.71–1.84)	0.69 (0.39–1.22)
	p = 0.074	p = 0.472	p = 0.577	p = 0.203
p for trend	p = 0.184	p = 0.746	p = 0.853	p = 0.425
eGDR				
eGDR (continuous)	**1.11 (1.03–1.19)***	1.06 (0.98–1.15)	0.97 (0.86–1.09)	0.90 (0.65–1.24)
	p = 0.006	p = 0.118	p = 0.618	p = 0.512
eGDR (categorical)				
eGDR tertile 1	Reference	Reference	Reference	Reference
eGDR tertile 2	1.42 (0.90–2.24)	1.17 (0.79–1.73)	1.01 (0.61–1.66)	1.19 (0.67–2.11)
	p = 0.137	p = 0.425	p = 0.983	p = 0.560
eGDR tertile 3	**2.12 (1.41–3.20)***	**1.70 (1.14–2.55)***	1.23 (0.67–2.27)	1.96 (0.90–4.26)
	p < 0.001	**p = 0.010**	p = 0.498	p = 0.092
p for trend	**p = 0.001**	**p = 0.030**	p = 0.666	p = 0.152
VAI				
VAI (continuous)	0.96 (0.86–1.07)	0.94 (0.85–1.04)	0.97 (0.87–1.08)	0.95 (0.83–1.09)
	p = 0.459	p = 0.245	p = 0.553	p = 0.437
VAI (categorical)				
VAI tertile 1	Reference	Reference	Reference	Reference
VAI tertile 2	1.17 (0.79–1.72)	1.11 (0.78–1.58)	1.19 (0.83–1.71)	1.20 (0.78–1.83)
	p = 0.428	p = 0.566	p = 0.983	p = 0.402
VAI tertile 3	0.91 (0.60–1.36)	0.85 (0.57–1.28)	0.98 (0.65–1.47)	0.85 (0.51–1.40)
	p = 0.635	p = 0.439	p = 0.498	p = 0.526
p for trend	p = 0.471	p = 0.389	p = 0.525	p = 0.320

Model 1 was unadjusted; Model 2 was adjusted for age, ethnicity, and educational levels; Model 3 was adjusted for age, educational levels, BMI, creatinine, smoking, lipid-lowering drugs, and CAD; Model 4 was adjusted for age, ethnicity, educational levels, BMI, albumin, UACR, UA, creatinine, smoking, insulin treatment, hypoglycemic drugs, antihypertensive drugs, lipid-lowering drugs, hypertension, hyperlipidemia, stroke, CAD, FBG, fasting insulin, HbA1c, and eGFR

TyG, triglyceride glucose index; TyG-BMI, triglyceride glucose combined with body mass index; METS-IR, metabolic score for insulin resistance; TG/HDL-C, triglyceride to high-density lipoprotein cholesterol ratio; HOMA-IR, homeostasis model assessment of insulin resistance; eGDR, estimated glucose disposal rate; VAI, visceral adiposity index; BMI, body mass index; UACR, urine albumin-creatinine ratio; UA, uric acid; CAD, coronary artery disease; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; eGFR, estimated glomerular filtration rate; CI, confidence interval

*Indicated that the p-value was less than 0.05

newly developed indices, including METS-IR, TyG-BMI, and eGDR, may exhibit improved sensitivity and comprehensiveness in assessing mortality risk in elderly patients with diabetes.

We examined the nonlinear relationships between IR indices and all-cause mortality, identifying a statistically significant U-shaped association between METS-IR, TyG-BMI, eGDR, and all-cause mortality in elderly people with diabetes. Evidence indicates that very low levels of TG or FBG and elevated levels of HDL-C are linked to negative health outcomes and may play a role in disease development. Research conducted at the University of Leicester indicated that hypoglycemia is associated with an elevated risk of cardiovascular events and a markedly increased risk of all-cause mortality in patients with diabetes compared to those without hypoglycemia [50]. A study found that low serum triglyceride levels were positively correlated with cardiac death in patients with heart failure [51]. Ma Feng's study indicates that elevated HDL-C levels correlate with increased cardiovascular risk and mortality in patients exhibiting extremely high HDL-C levels when compared to healthy normolipidemic controls, thereby questioning the assumption that higher HDL-C is invariably advantageous for heart health. This indicates an optimal range for HDL-C, as both low and high levels may negatively impact health [52]. METS-IR, TyG-BMI, and eGDR were derived from FBG, HDL-C, and TG, which may elucidate the nonlinear relationships observed between these indices and all-cause mortality. Furthermore, numerous studies indicate nonlinear associations between METS-IR, TyG-BMI, and eGDR with all-cause mortality, suggesting that both extremely low and high levels of these indices correlate with a heightened incidence of all-cause mortality in different

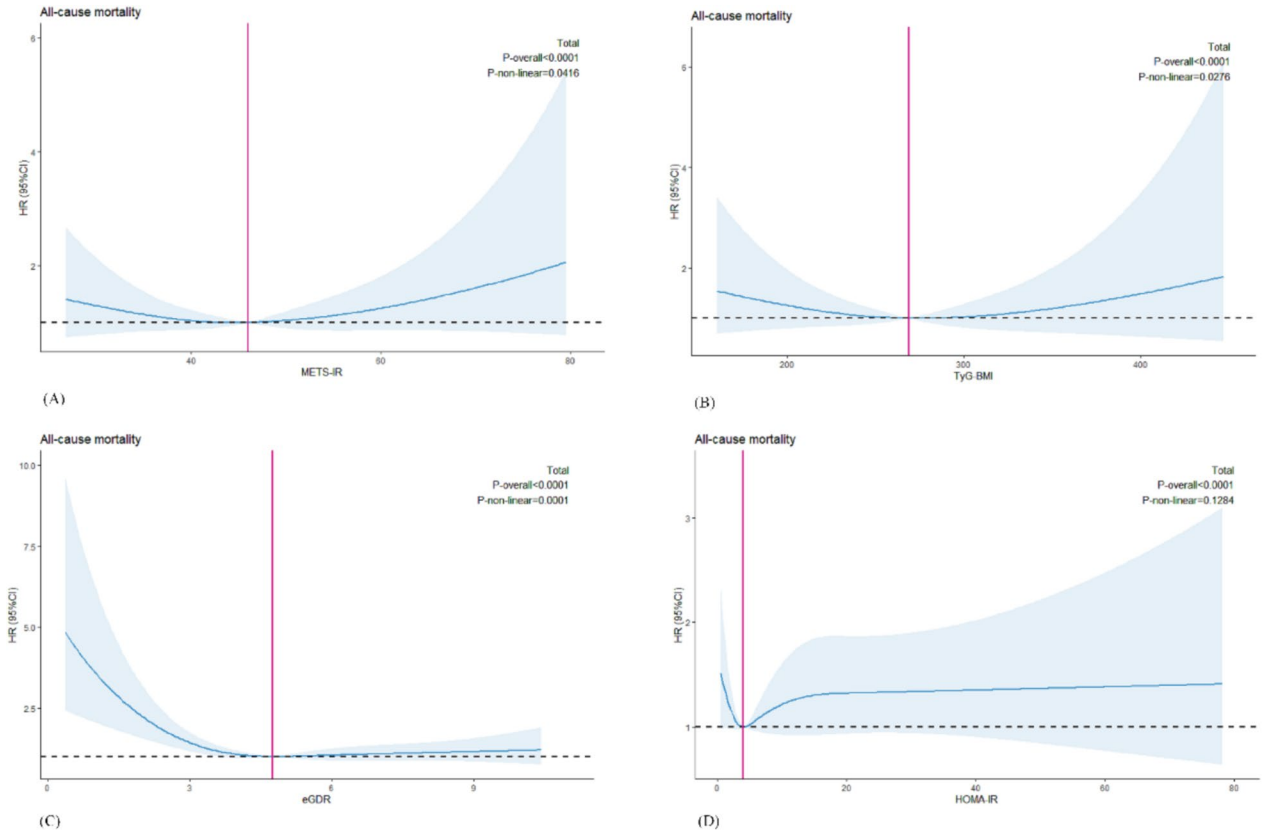

Fig. 2 Association between METS-IR (**A**), TyG-BMI (**B**), eGDR (**C**), HOMA-IR (**D**) and all-cause mortality in elderly patients with diabetes. Adjusted for age, ethnicity, educational levels, BMI, albumin, UACR, UA, creatinine, smoking, insulin treatment, hypoglycemic drugs, antihypertensive drugs, lipid-lowering drugs, hypertension, hyperlipidemia, stroke, CAD, FBG, fasting insulin, HbA1c, and eGFR. The solid line and blue area represented the estimated values and their corresponding 95% CIs, respectively. TyG-BMI, triglyceride glucose combined with body mass index; METS-IR, metabolic score for insulin resistance; TG/HDL-C, triglyceride to high-density lipoprotein cholesterol ratio; HOMA-IR, homeostasis model assessment of insulin resistance; eGDR, estimated glucose disposal rate; BMI, body mass index; UACR, urine albumin-creatinine ratio; UA, uric acid; CAD, coronary artery disease; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; eGFR, estimated glomerular filtration rate; CI, confidence interval

populations [12, 38, 53], aligning with our findings. It is essential to sustain adequate levels of METS-IR, TyG-BMI, and eGDR in elderly people with diabetes.

It was surprising that in our study HOMA-IR and TyG-BMI demonstrated better prognostic value in males, while in the females, METS-IR, TyG-BMI, and eGDR demonstrated enhanced performance. Gender differences may be attributed to variations in physiological mechanisms, metabolic pathways, and disease manifestations of insulin resistance between males and females, as well as differences in the calculation of various indicators. Glycemic control, lipid control, and fat distribution were considered in the calculations of METS-IR, TyG-BMI, and eGDR. In the calculation of HOMA-IR, blood glucose and insulin are the primary factors considered. In males, specific factors may enhance the prognostic value of TyG-BMI and HOMA-IR. Differences in hormonal profiles may influence outcomes. Previous studies have shown an inverse relationship between testosterone and fasting insulin levels in men [54]. Low testosterone levels are associated with increased insulin resistance [55]. Lower testosterone levels correlate with higher HOMA-IR, reflecting reduced insulin sensitivity. Additionally, men may exhibit distinct patterns of fat distribution and metabolic processes. Males possess a greater muscle mass, whereas females exhibit a higher proportion of body fat [56]. In women, a negative correlation was observed between thigh muscle fat content and muscle insulin sensitivity, a relationship that was not present in men. Furthermore, adipose tissue, particularly visceral fat, is significantly associated with insulin resistance [57]. The improved performance of METS-IR, TyG-BMI, and eGDR in females may be attributed to various factors. Estrogen, an essential hormone in females, may significantly influence metabolism and insulin sensitivity [58, 59]. Estrogen deficiency and/or resistance may result in insulin resistance [60]. Estrogen levels fluctuate across various life stages, including pre-menopause and

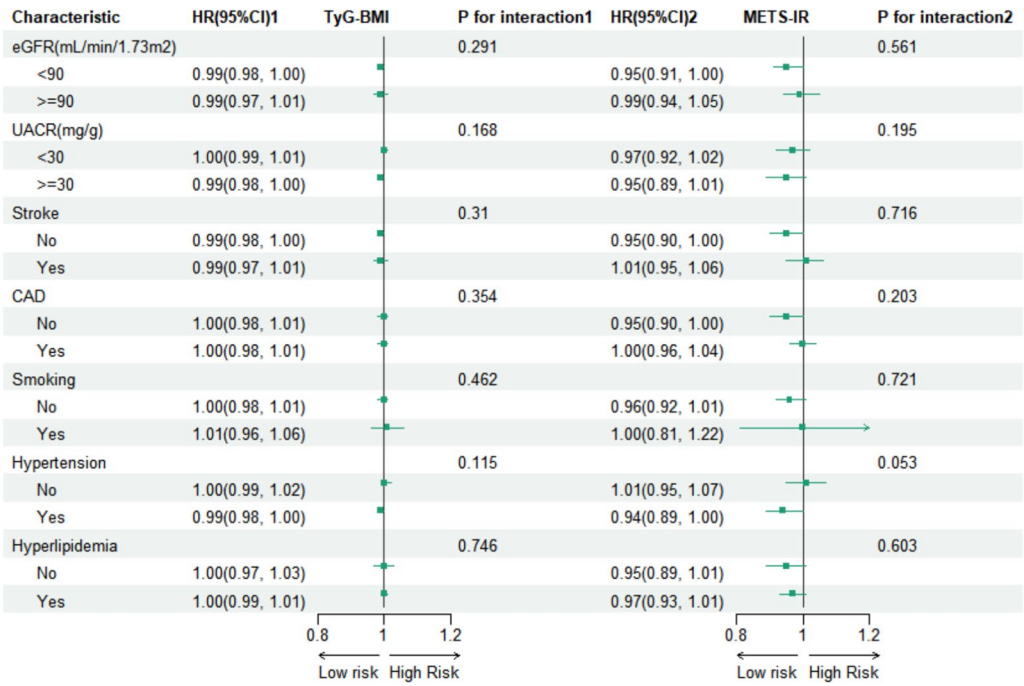

Fig. 3 Subgroup analysis of the association between TyG-BMI, METS-IR and all-cause mortality. Adjusted for age, ethnicity, educational levels, BMI, albumin, UACR, UA, creatinine, smoking, insulin treatment, hypoglycemic drugs, antihypertensive drugs, lipid-lowering drugs, hypertension, hyperlipidemia, stroke, CAD, FBG, fasting insulin, HbA1c, and eGFR. TyG-BMI, triglyceride glucose combined with body mass index; METS-IR, metabolic score for insulin resistance; BMI, body mass index; UACR, urine albumin-creatinine ratio; UA, uric acid; CAD, coronary artery disease; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval.

post-menopause, influencing the body's insulin response and the metabolism of glucose and lipids. The decline in estrogen levels in postmenopausal women hastens the onset of insulin resistance and type 2 diabetes [60]. Estrogen also promotes the accumulation of subcutaneous fat in contrast to visceral fat [61]. In postmenopausal women, a significant decline in estrogen levels occurs. Concomitantly, there is a marked increase in the percentage of visceral fat. This physiological change results in elevated WC and a higher visceral adiposity index. The increase in visceral fat may potentially enhance the prognostic value of both the METS-IR and eGFR. Lifestyle factors and genetic variations between genders may also influence the observed differences in insulin resistance indices. The baseline characteristics of our cohort demonstrated notable differences in lipid control, waist circumference, and blood glucose control between genders, which may affect the relationship between insulin resistance indices and the risk of all-cause mortality. Men and women may exhibit varying levels of cholesterol, triglycerides, and other lipid markers in relation to lipid control. WC is another variable that may differ between genders. Women may exhibit distinct patterns of abdominal fat distribution relative to men (visceral vs. subcutaneous), potentially influencing metabolic health [62]. Blood glucose control may vary by gender, with women possibly exhibiting greater susceptibility to fluctuations in blood glucose levels [63].

Subgroup analysis revealed that eGDR demonstrated differential effects across various eGFR populations. This may pertain to the renal function status evaluated by eGDR in the assessment of IR. Giuseppe Penno's research demonstrated that albuminuria and eGFR or diabetic kidney disease phenotypes influence the relationship between eGDR and mortality [5]. The impact of eGDR on mortality across various eGFR groups may vary according to differences in kidney function, necessitating additional research.

These IR indices offer practical tools for risk stratification. Notably, new indices such as METS-IR, TyG-BMI, and eGDR, which can be calculated using routine lipid and anthropometric data, could identify high-risk elderly diabetics who need intensified management. Gender-specific cutoffs might further refine prognostication. The U-shaped associations suggest that both excessively high and low levels of METS-IR, TyG-BMI, and eGDR indicate metabolic dysregulation. Clinically, this underscores the need to avoid extreme values. Regular monitoring of these indices and setting personalized targets could optimize the treatment outcomes for elderly

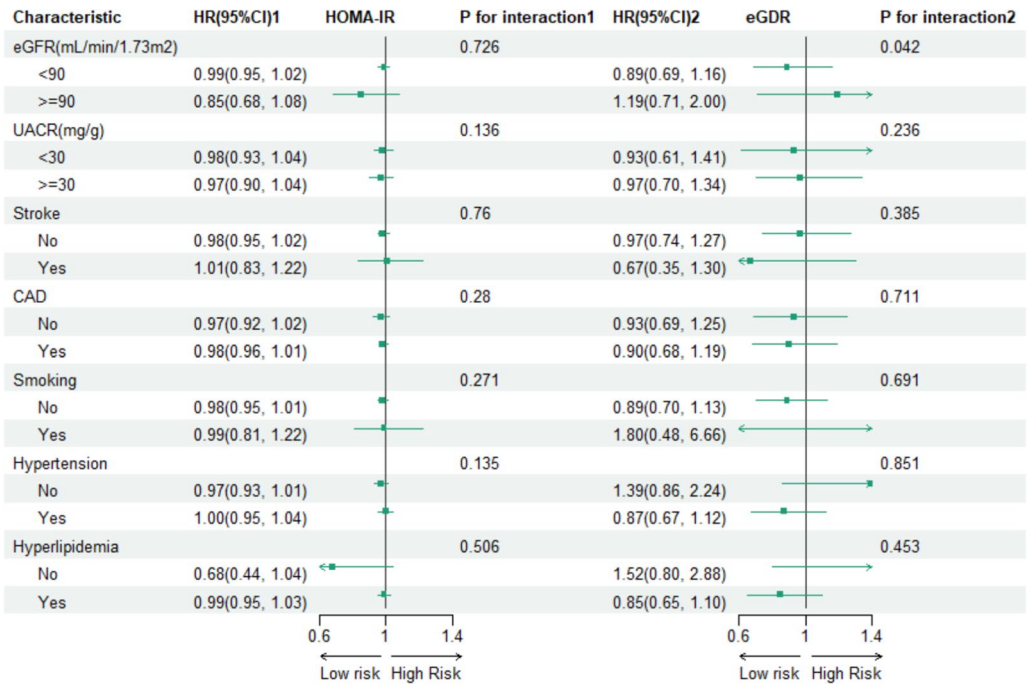

Fig. 4 Subgroup analysis of the association between HOMA-IR, eGDR and all-cause mortality. Adjusted for age, ethnicity, educational level, BMI, albumin, UACR, UA, creatinine, smoking, insulin treatment, hypoglycemic drugs, antihypertensive drugs, lipid-lowering drugs, hypertension, hyperlipidemia, stroke, CAD, FBG, fasting insulin, HbA1c, and eGFR. HOMA-IR, homeostasis model assessment of insulin resistance; eGDR, estimated glucose disposal rate; BMI, body mass index; UACR, urine albumin-creatinine ratio; UA, uric acid; CAD, coronary artery disease; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval.

diabetics. Integrating these indices into electronic health records could automate risk alerts, enhancing clinical decision-making.

Strengths and limitations

To our knowledge, this is the first study to explore the prognostic significance of various new IR indices related to mortality in elderly patients with diabetes. The study utilized a large cohort of 1248 elderly patients with diabetes from the NHANES database. The study's large sample size and nationally representative cohort, combined with a prolonged follow-up period, allowed for a thorough analysis of the relationship between IR indices and all-cause mortality risk. We identified significant associations between several IR indices and mortality, emphasizing the importance of gender differences in their prognostic value. The utility and simplicity of these indices offer clinicians effective tools for managing mortality risk in this population.

However, our study has several limitations. First, we used only baseline IR indices and could not assess the impact of temporal variations in these biomarkers on cause-specific mortality. Second, as an observational study, we could not entirely rule out the influence of unmeasured confounding factors. Additionally, our findings are based solely on survey data from elderly diabetic patients in the United States, limiting the generalizability of our results. While the overall sample size provided sufficient statistical power for primary analyses (highly significant p-values < 0.001), gender-specific subgroup analyses (male: $N = 673$; female: $N = 575$) may have limited power to detect smaller effect sizes or subtle gender differences. Future research should account for these limitations to improve our comprehension of this field.

Our study provides new insights into the role of new IR indices in the prognosis of elderly patients with diabetes, emphasizing the non-linear relationship between these indices and mortality, as well as gender-specific differences in their prognostic implications. These findings could provide valuable insights for future research and clinical practice.

Conclusions

In elderly patients with diabetes, HOMA-IR and new IR indices including TyG-BMI, METS-IR, and eGDR were associated with mortality, exhibiting gender differences in their prognostic significance. No significant associations were found between TyG, TG/HDL-C, VAI, and all-cause mortality. A U-shaped relationship exists between METS-IR, TyG-BMI, eGDR, and all-cause mortality.

It is essential to maintain appropriate levels of METS-IR, TyG-BMI, and eGDR in the elderly population with diabetes.

Abbreviations

BMI	Body mass index
CAD	Coronary artery disease
CIs	Confidence intervals
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CV	Cardiovascular
DBP	Diastolic blood pressure
eGDR	Estimated glucose disposal rate
eGFR	Estimated glomerular filtration rate
FBG	Fasting blood glucose
HbA1c	Glycosylated hemoglobin
HDL-C	High-density lipoprotein cholesterol
HEC	Hyperinsulinemic-euglycemic clamp
HOMA-IR	Homeostasis model assessment of insulin resistance
HRs	Hazard ratios
IR	Insulin resistance
LASSO	Least absolute shrinkage and selection operator
LDL-C	Low-density lipoprotein cholesterol
METS-IR	Metabolic score for insulin resistance
NHANES	National Health and Nutrition Examination Survey
NAFLD	Non-alcoholic fatty liver disease
RCS	Restricted cubic spline
SBP	Systolic blood pressure
TC	Total cholesterol
TG	Fasting triglyceride
TG/HDL-C	Triglyceride to high-density lipoprotein cholesterol ratio
TyG	Triglyceride glucose index
TyG-BMI	Triglyceride glucose combined with body mass index
UA	Uric acid
UACR	Random urine albumin-creatinine ratio
VAI	Visceral adiposity index
VIF	Variance inflation factor
WC	Waist circumference

Supplementary Information

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Additional file 1.

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Not applicable.

Author contributions
Y.Y. and Z.L. contributed to the conception and design of the study; Y.Y. and X.Y. contributed to manuscript drafting; Y.Y. and H.D. contributed to the statistics analysis; B.L. and Y.H. contributed to the acquisition of data; J.Y. and W.X. contributed to the funding support; L.Z., J.Y., and W.X. contributed to critical revisions of the manuscript. All authors read and approved the final manuscript.

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Data availability
The datasets generated and analyzed during the current study are available in the NHANES repository (https://www.cdc.gov/nchs/nhanes/index.htm).

Declarations

Ethics approval and consent to participate
The study was performed according to the guidelines of the Helsinki Declaration. Consent to participate was obtained and the National Center for Health Statistics ethics committee approved the protocol of the NHANES study. The data is publicly available, therefore, the ethical approval statement and the requirement for informed consent were waived for this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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