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The association between triglyceride-glucose index and its combination with systemic inflammation indicators and all-cause and cardiovascular mortality in the general US population: NHANES 1999–2018

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Abstract

Background The correlation between the triglyceride-glucose (TyG) index and mortality in the general population remains controversial, with inconsistent conclusions emerging from different studies.

Objective This study aims to investigate whether there is an association between the TyG index and mortality in the general population in the United States, and to explore whether a new index combining the TyG index with systemic inflammation indicators can better predict all-cause and cardiovascular mortality risks in the general population than using the TyG index alone.

Methods Calculate the systemic inflammation indicators and TyG index for each participant based on their complete blood count, as well as their triglyceride and glucose levels in a fasting state. TyG-inflammation indices were obtained by multiplying the TyG index with systemic inflammation indicators (TyG-NLR, TyG-MLR, TyG-lgPLR, TyG-lgSII, and TyG-SIRI). Based on the weighted Cox proportional hazards model, assess whether the TyG and TyG-Inflammation indices are associated with mortality risk in the general population. Restricted cubic splines (RCS) are used to clarify the dose-response relationship between the TyG and TyG-Inflammation indices and mortality, and to visualize the results. Time-dependent receiver operating characteristic (ROC) curves are used to evaluate the accuracy of the TyG and TyG-Inflammation indices in predicting adverse outcomes.

Results This study included 17,118 participants. Over a median follow-up period of 125 months, 2595 patients died. The TyG index was not found to be related to mortality after adjusting for potentially confounding factors. However, the TyG-inflammation indices in the highest quartile (Q4), except for TyG-lgPLR, were significantly associated with both all-cause and cardiovascular mortality, compared to those in the lowest quartile (Q1). Among them, TyG-MLR

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and TyG-lgSII showed the strongest correlations with all-cause mortality and cardiovascular mortality. Specifically, compared to their respective lowest quartiles (Q1), participants in the highest quartile (Q4) of TyG-MLR had a 48% increased risk of all-cause mortality (95% CI: 1.23–1.77, *P* for trend < 0.0001), while participants in the highest quartile (Q4) of TyG-lgSII had a 92% increased risk of cardiovascular mortality (95% CI: 1.31–2.81, *P* for trend < 0.001). Time-dependent ROC curve analysis showed that the TyG-MLR had the highest accuracy in predicting long-term mortality outcomes.

Conclusions The TyG-Inflammation indices constructed based on TyG and systemic inflammation indicators are closely related to mortality in the general population and can better predict the risk of adverse outcomes. However, no association between TyG and mortality in the general population was found.

Keywords TyG, Inflammation, Insulin resistance, Mortality, NHANES

Introduction

Insulin resistance (IR) plays a significant role in the occurrence and development of metabolic diseases such as obesity, hyperlipidemia, hypertension, and diabetes, and has been proven to significantly increase the risk of mortality for patients [1–3]. Currently, the hyperinsulinemic-euglycemic clamp (HIEC) is widely regarded as the most reliable method for evaluating insulin resistance (IR). However, its invasive nature and high cost make implementation in daily clinical practice challenging. In 1985, Turner et al. introduced the use of the homeostasis model assessment-insulin resistance (HOMA-IR) as a means to assess IR, thereby streamlining the IR evaluation process to some extent [4]. However, this method requires obtaining the fasting insulin levels of the patients. Further, it cannot be applied to patients receiving exogenous insulin therapy and those with impaired islet β-cell function, which limits its comprehensive implementation in clinical practice. The triglyceride-glucose (TyG) index, calculated based on triglyceride and glucose levels under fasting conditions, has been proven to be another valuable indicator of IR [5–7]. Due to its simplicity, ease of access, and low cost, it has been widely used in clinical settings [8, 9]. Multiple studies have investigated the association between the TyG index and mortality in individuals with metabolic disorders [10–15], demonstrating its effectiveness and advantages in predicting adverse outcomes in such patients. However, various factors such as gender, age, race, comorbidities, income level, etc. appear to influence the association between TyG and all-cause and cardiovascular mortality in the general population, and different studies have shown inconsistent conclusions [16–22]. Previous research based on American and Iranian populations indicated that a high TyG index significantly increases the risk of mortality in the general population [17, 21]. However, Liu et al. found through a meta-analysis of 12 related studies that the correlation between the TyG index and mortality is not significant [18]. Therefore, the association between the TyG index and mortality in the general population remains unclear.

Given the simplicity, ease of access, and low cost of the TyG index [23], it would be optimal to use the TyG index in primary care and health screening to assess the mortality risk in the general population. Therefore, we aimed to optimize and improve the TyG index. Considering that both IR and inflammation play crucial roles in exacerbating the progression of metabolic diseases and leading to adverse events, they exhibit synergistic effects in this process [24–26]. Accordingly, we attempted to combine the TyG index with inflammatory markers to construct a variety of novel indices (i.e., TyG-inflammation indices), and assess their associations with the risk of all-cause and cardiovascular mortality in the general population. Systemic inflammation indicators are novel indicators that are calculated based on the complete blood count, such as NLR (neutrophil-to-lymphocyte ratio), PLR (platelet-lymphocyte ratio), MLR (monocyte-lymphocyte ratio), SII (systemic immune inflammation index), and SIRI (system inflammation response index). Compared to single inflammatory markers, systemic inflammation indicators presented in the form of ratios are not only more stable, but the cumulative effects of interaction between multiple blood cells increase the predictability of adverse outcomes [27–29]. Similar to the TyG index, these markers are stable, easily accessible, inexpensive, and strongly associated with the risk of death in the general population [30–35]. Therefore, in this study, we chose to combine systemic inflammation indicators with the TyG index.

Overall, the aim of this longitudinal cohort study was to determine if the TyG-inflammation indices are more effective in predicting the risk of all-cause and cardiovascular mortality in the general US population compared to the TyG index alone.

Methods

Data source and outcome definition

The National Health and Nutrition Examination Survey (NHANES) is a research program led by the Centers for Disease Control and Prevention (CDC) in the United States, aimed at assessing the health of adults and children in the country. It was initially launched in 1960 and has been a continuous program since 1999, conducting annual nationwide surveys on approximately 5,000 individuals. These surveys cover a wide range of data, including demographics, socioeconomics, diet, and health [36]. This study utilized data from 10 cycles of NHANES from 1999 to 2018. Additionally, we linked the NHANES data with the National Death Index (NDI) data to obtain participants' follow-up information, including follow-up time, survival status, and cause of death. Figure 1 shows the participant screening flowchart.

Calculation of the TyG index, systemic inflammation indicators, and TyG-inflammation indices

The TyG index is obtained by calculating the product of triglyceride and glucose levels in the fasting state of each participant, taking its natural logarithm. Systemic inflammation indicators were calculated based on the complete blood cell counts. Owing to the excessively large base value of platelets, we applied a logarithmic transformation to the PLR and SII. TyG-inflammation indices were obtained by multiplying the TyG index by different systemic inflammation indicators, including the TyG-NLR, TyG-monocyte-MLR, TyG-lgPLR, TyG-lgSII, and TyG-SIRI. The calculation formulas for the above indicators are as follows:

$$\mathbf{TyG} = \ln[triglyceride\,(\mathrm{mg/dL}) \times fasting\,blood\,glucose\,(\mathrm{mg/dL})/2]$$

$$\mathbf{NLR} = \mathrm{Neutrophil\ Count/Lymphocyte\ Count}$$

$$\mathbf{MLR} = \mathrm{Monocyte\ Count/Lymphocyte\ Count}$$

$$\mathbf{lgPLR} = \lg(\mathrm{Platelet\ Count/Lymphocyte\ Count})$$

$$\mathbf{lgSII} = \lg(\mathrm{Neutrophil\ Count} \times \mathrm{Platelet\ Count/Lymphocyte\ Count})$$

$$\mathbf{SIRI} = \mathrm{Neutrophil\ Count} \times \mathrm{Monocyte\ Count/Lymphocyte\ Count}$$

$$\mathbf{TyG-NLR} = \mathrm{TyG} \times \mathrm{NLR}$$

$$\mathbf{TyG-MLR} = \mathrm{TyG} \times \mathrm{MLR}$$

$$\mathbf{TyG-lgPLR} = \mathrm{TyG} \times \mathrm{lgPLR}$$

$$\mathbf{TyG-lgSII} = \mathrm{TyG} \times \mathrm{lgSII}$$

$$\mathbf{TyG-SIRI} = \mathrm{TyG} \times \mathrm{SIRI}$$

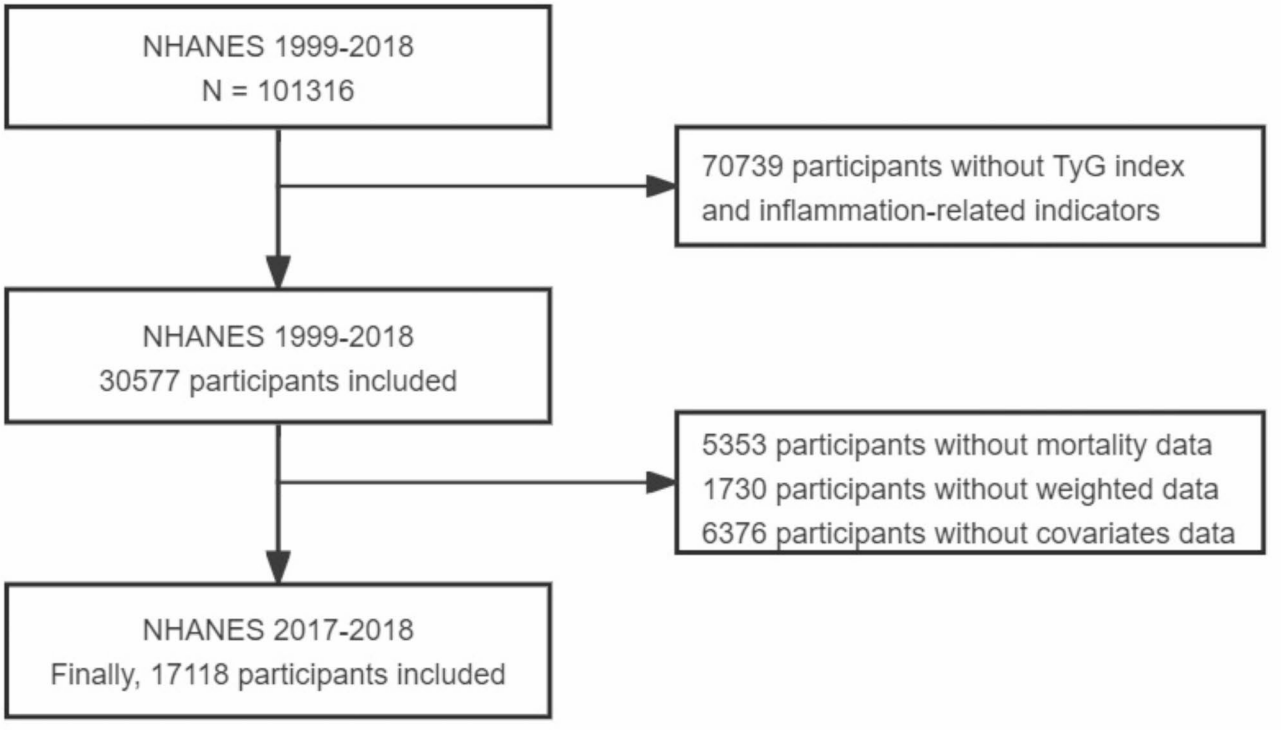

Fig. 1 Flow chart of the sample selection from NHANES 1999–2018

Covariates

The NHANES provided all the variables used in this study. The variables included sex, age, race, educational level, family socioeconomic status (assessed by the poverty income ratio [PIR]), smoking status, alcohol consumption, medical history (including hypertension, diabetes, hyperlipidemia, and cancer), medication use, body mass index (BMI), complete blood count, and blood biochemistry tests. Hyperlipidaemia is diagnosed by evaluating several parameters, including low-density lipoprotein cholesterol (LDL-C) levels of 130 mg/dL or higher (equivalent to 3.37 mmol/L or above), total cholesterol (TC) levels of 200 mg/dL or higher (5.18 mmol/L or above), triglycerides (TG) levels of 150 mg/dL or higher (1.7 mmol/L or above), and high-density lipoprotein cholesterol (HDL-C) levels below 40 mg/dL for men (less than 1.04 mmol/L) or below 50 mg/dL for women (less than 1.30 mmol/L). Furthermore, the consideration of lipid-lowering drugs is also taken into account when determining hyperlipidaemia [37]. Hypertension is diagnosed by considering various factors, such as self-reported medical history of the illness, current use of blood pressure-lowering medication, and having an average systolic blood pressure of 140 mmHg or higher, and/or an average diastolic blood pressure of 90 mmHg or higher [38]. The diagnostic criteria for diabetes mellitus (DM) include a confirmed diagnosis by a clinician, fasting glucose levels of 7.0 mmol/L or higher, HbA1c levels of 6.5% or above, and/or the current usage of anti-DM drugs. The use of medications and the presence of cancer are determined based on data from questionnaire surveys. The classification of smoking status is as follows: never smokers (individuals who have smoked less than 100 cigarettes in their lifetime), former smokers (individuals who have smoked in the past but have quit smoking now), and current smokers (individuals who have smoked at least 100 cigarettes in their lifetime and are still smoking now) [39]. Alcohol consumption is determined based on specific criteria: heavy drinking is defined as consuming ≥ 3 drinks per day for women, ≥ 4 drinks per day for men, or engaging in binge drinking on ≥ 5 days per month; moderate drinking is characterized by consuming two drinks per day for females, three drinks per day for males, or binge drinking on ≥ 2 days per month; mild drinking is designated for those who do not meet the criteria for heavy or moderate drinking, while never drinking refers to individuals who have consumed < 12 drinks in their lifetime [40].

Statistical analysis

All statistical analyses were conducted following the recommendations of the official NHANES guidelines [41]. Because we used fasting data, we chose fasting subsample weights. The data are presented as the unweighted frequency (weighted percentage) for categorical variables and median (interquartile range) for continuous variables.

We used the Kaplan–Meier method to calculate the survival probability of each subgroup at different quartiles of the TyG index and TyG-inflammation indices and compared the survival differences between groups using the log-rank test. Further, we assessed the association of the TyG index and TyG-inflammation indices with mortality using a weighted Cox proportional hazards model. Three different models were constructed to evaluate the impact of potential confounding factors on this association. Specifically, Model 1 was not adjusted for confounding factors. Model 2 was adjusted for sex and age. Model 3 was further adjusted for race, PIR, educational level, BMI, smoking status, alcohol consumption, hypertension, diabetes mellitus, hyperlipidemia, cancer, lipid-lowering drugs, ALT, and AST, based on Model 2.

We used a restricted cubic spline (RCS) with four knots to assess the dose-response relationship pattern between the TyG index and TyG-inflammation indices and mortality. Additionally, we evaluated the accuracy of the TyG index and TyG-inflammation indices in predicting survival outcomes at different time points by using time-dependent ROC curves. All statistical analyses were performed using R (4.2.2) software, and statistical significance was set at $P < 0.05$.

Results

Participants characteristics

This study ultimately included 17,118 participants, with 50.94% being male. During a median follow-up period of 125 months, a total of 2,595 participants experienced outcome events. Table 1 shows baseline data for survival group and non-survival group participants. Compared to survivors, non-survivors were characterized by being older; male; non-Hispanic whites; smokers; non-drinkers; having a history of comorbidities and cancer; using lipid-lowering drugs; higher fasting blood glucose, triglyceride, aspartate aminotransferase, white blood cell, neutrophil, and monocyte levels; and lower levels of lymphocytes. Most importantly, all non-survivors had higher TyG and TyG-inflammation indices values than survivors. Supplementary Table 1 summarize the detailed baseline information for each group of participants categorized based on different quartile levels of TyG and TyG-inflammation indices.

Table 1 Characteristics of participants

Variables	Total (*n* = 17118)	Survivors (*n* = 14523)	Non-survivors (*n* = 2595)	*P*-value
Age (years)	46.00(33.00,60.00)	45.00(32.00,57.00)	70.00(58.00,80.00)	< 0.0001
Age group, n(%)				< 0.0001
< 60	11,247(74.95)	10,755(79.70)	492(26.66)	
≥ 60	5871(25.05)	3768(20.30)	2103(73.34)	
Sex, n(%)				< 0.0001
Female	8558(50.94)	7457(51.41)	1101(46.19)	
Male	8560(49.06)	7066(48.59)	1494(53.81)	
BMI (kg/m^2)	27.74(24.06,32.30)	27.74(24.04,32.35)	27.64(24.10,32.17)	0.65
PIR, n(%)				< 0.0001
< 1	3212(13.06)	2717(12.88)	495(14.94)	
1–3	7197(36.21)	5877(34.98)	1320(48.61)	
> 3	6709(50.73)	5929(52.14)	780(36.45)	
Race, n(%)				< 0.0001
Non-Hispanic Black	3259(10.61)	2815(10.60)	444(10.70)	
Mexican American	2953(7.91)	2626(8.33)	327(3.64)	
Non-Hispanic White	8121(70.06)	6476(69.08)	1645(80.06)	
Other Race	2785(11.43)	2606(12.00)	179(5.60)	
Education levels, n(%)				< 0.0001
< high school	1841(5.02)	1337(4.37)	504(11.64)	
= high school	6361(33.97)	5256(32.96)	1105(44.23)	
> high school	8916(61.01)	7930(62.67)	986(44.13)	
Smoking status, n(%)				< 0.0001
Never	9196(54.19)	8179(55.80)	1017(37.75)	
Former	4420(25.42)	3378(24.09)	1042(38.88)	
Current	3502(20.40)	2966(20.11)	536(23.37)	
Alcohol consumption, n(%)				< 0.0001
Never	2314(10.60)	1914(10.28)	400(13.89)	
Former	2968(13.90)	2103(12.09)	865(32.26)	
Mild	5931(37.17)	5098(37.61)	833(32.73)	
Moderate	2536(17.31)	2307(18.06)	229(9.70)	
Heavy	3369(21.02)	3101(21.97)	268(11.41)	
Diabetes, n(%)				< 0.0001
No	11,306(69.49)	10,046(72.02)	1260(43.84)	
IFG	1606(9.36)	1284(9.08)	322(12.23)	
IGT	1109(6.72)	922(6.39)	187(10.07)	
Yes	3097(14.42)	2271(12.51)	826(33.86)	
Hyperlipidemia, n(%)				< 0.0001
No	4643(29.41)	4173(30.55)	470(17.74)	
Yes	12,475(70.59)	10,350(69.45)	2125(82.26)	
Hypertension, n(%)				< 0.0001
No	9890(62.83)	9134(66.01)	756(30.58)	
Yes	7228(37.17)	5389(33.99)	1839(69.42)	
Cancers, n(%)				< 0.0001
No	15,546(90.82)	13,512(92.24)	2034(76.43)	
Yes	1572(9.18)	1011(7.76)	561(23.57)	
Lipid-lowering drugs, n(%)				< 0.0001
No	13,976(82.30)	12,209(84.24)	1767(62.61)	
Yes	3142(17.70)	2314(15.76)	828(37.39)	
Laboratory data				
FBG (mmol/L)	5.50(5.11,5.99)	5.50(5.11,5.94)	5.83(5.27,6.66)	< 0.0001
TG (mmol/L)	1.15(0.80,1.68)	1.14(0.78,1.65)	1.33(0.97,1.91)	< 0.0001
LDL-C (mmol/L)	2.90(2.33,3.54)	2.90(2.35,3.54)	2.79(2.17,3.52)	< 0.0001

Table 1 (continued)

Variables	Total (*n* = 17118)	Survivors (*n* = 14523)	Non-survivors (*n* = 2595)	*P*-value
ALT (U/L)	21.00(16.00,28.00)	21.00(16.00,29.00)	19.00(16.00,26.00)	< 0.0001
AST (U/L)	22.00(19.00,27.00)	22.00(19.00,27.00)	23.00(20.00,28.00)	< 0.0001
WBC (10^9/L)	6.40(5.40,7.80)	6.40(5.40,7.80)	6.80(5.60,8.20)	< 0.0001
PLT (10^9/L)	241.00(205.00,284.00)	241.00(206.00,284.00)	233.00(191.00,280.00)	< 0.0001
Neutrophils (10^9/L)	3.70(2.90,4.70)	3.70(2.90,4.70)	4.10(3.20,5.30)	< 0.0001
Monocytes (10^9/L)	0.50(0.40,0.60)	0.50(0.40,0.60)	0.60(0.40,0.70)	< 0.0001
Lymphocytes (10^9/L)	1.90(1.60,2.30)	1.90(1.60,2.30)	1.70(1.30,2.20)	< 0.0001
TyG-Inflammation indicators				
TyG	8.55(8.14,8.97)	8.53(8.12,8.95)	8.77(8.39,9.17)	< 0.0001
TyG-NLR	16.57(12.48,22.19)	16.31(12.35,21.63)	20.77(14.90,29.26)	< 0.0001
TyG-MLR	2.27(1.80,2.89)	2.23(1.78,2.82)	2.86(2.13,3.72)	< 0.0001
TyG-SIRI	8.42(5.80,12.30)	8.18(5.69,11.82)	11.39(7.69,17.59)	< 0.0001
TyG-lgPLR	3.03(2.94,3.13)	3.03(2.94,3.13)	3.07(2.95,3.20)	< 0.0001
TyG-lgSII	3.60(3.45,3.75)	3.59(3.45,3.74)	3.68(3.51,3.86)	< 0.0001

Abbreviations: BMI: body mass index; PIR: poverty income ratio; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; FBG: fasting blood glucose; TG: triglyceride; LDL-C: low-density lipoprotein cholesterol; ALT: alanine aminotransferase; AST: aspartate aminotransferase; WBC: white blood cell; PLT: platelet; TyG: triglyceride-glucose; NLR: neutrophil-lymphocyte ratio; MLR: monocyte-lymphocyte ratio; SIRI: system inflammation response index; PLR: platelet-lymphocyte ratio; SII: systemic immune inflammation index

Kaplan–Meier survival curves of TyG and TyG-inflammation indices

Without correcting for any potential confounding factors, the groups with different TyG indices had significantly different long-term survival outcomes (all-cause mortality: Supplementary Fig. 1A, $P < 0.0001$; cardiovascular mortality: Supplementary Fig. 2A, $P < 0.0001$). Similar results were found in TyG-inflammation indices (all-cause mortality: Supplementary Fig. 1B–F, both $P < 0.0001$; cardiovascular mortality: Supplementary Fig. 2B–F, both $P < 0.001$).

Association of TyG and TyG-inflammation indices with all-cause mortality

We used three distinct models to assess the association between TyG and TyG-inflammation indices and the risk of all-cause mortality (Table 2). In the fully adjusted model (Model 3), we found no significant association between TyG (hazard ratio [HR] = 0.93, 95% confidence interval [CI]: 0.76–1.14, *P* for trend = 0.765) and TyG-lgPLR (HR = 1.11, 95%CI: 0.97–1.27, *P* for trend = 0.162) and the risk of all-cause mortality. However, the other TyG-inflammation indices showed significant positive associations with the risk of all-cause mortality. Specifically, compared to participants in the lowest quartile (Q1), those in the highest quartile (Q4) had significantly increased risks of all-cause mortality for TyG-NLR (HR = 1.31, 95%CI: 1.13–1.53, *P* for trend < 0.0001), TyG-MLR (HR = 1.48, 95%CI: 1.23–1.77, *P* for trend < 0.0001), TyG-SIRI (HR = 1.34, 95%CI: 1.11–1.63, *P* for trend < 0.0001), and TyG-lgSII (HR = 1.20, 95%CI: 1.02–1.41, *P* for trend = 0.004). We also analyzed the association between TyG-BMI, single systemic inflammation indicators, and all-cause mortality, as shown in Supplementary Table 2. However, both TyG-BMI and single systemic inflammation indicators have lower HR for all-cause mortality compared to TyG-MLR.

Association of TyG and TyG-inflammation indices with cardiovascular mortality

We analyzed the association of TyG and TyG-inflammation indices with cardiovascular mortality. All the TyG-inflammation indices were positively associated with cardiovascular mortality (Table 3). Specifically, compared to participants in the first quartile (Q1) based on their TyG-inflammation indices, the risk of cardiovascular mortality for participants in the highest quartile (Q4) increased by 79% (TyG-NLR: HR = 1.79, 95% CI: 1.17–2.72, *P* for trend < 0.0001), 73% (TyG-MLR: HR = 1.73, 95% CI: 1.16–2.56, *P* for trend < 0.0001), 65% (TyG-SIRI: HR = 1.65, 95% CI: 1.03–2.64, *P* for trend = 0.003), 92% (TyG-lgSII: HR = 1.92, 95% CI: 1.31–2.81, *P* for trend < 0.001), and 87% (TyG-lgPLR: HR = 1.87, 95% CI: 1.40–2.49, *P* for trend < 0.001), respectively. However, no association between the TyG index and cardiovascular death was observed in Model 3. Detailed information on the associations among TyG-BMI, single systemic inflammatory indicators, and cardiovascular mortality is presented in Supplementary Table 3. Interestingly, both TyG-BMI and single systemic inflammation indicators have lower HR for cardiovascular mortality compared to TyG-lgSII.

Table 2 Association of TyG and TyG-Inflammation indicators with all-cause mortality

All-cause mortality					
	Q1	Q2	Q3	Q4	*P* for trend
TyG					
Model 1 h (95%CI) *P*-value	REF	1.53(1.27–1.83) < 0.0001	1.96(1.66–2.33) < 0.0001	2.59(2.15–3.10) < 0.0001	< 0.0001
Model 2 h (95%CI) *P*-value	REF	0.91(0.76–1.09)0.31	0.96(0.82–1.13)0.62	1.15(0.97–1.36)0.10	0.013
Model 3 h (95%CI) *P*-value	REF	0.88(0.73–1.06)0.18	0.88(0.74–1.06)0.18	0.93(0.76–1.14)0.48	0.765
TyG-NLR					
Model 1 h (95%CI) *P*-value	REF	0.99(0.81–1.22)0.95	1.35(1.12–1.63)0.002	2.79(2.39–3.27) < 0.0001	< 0.0001
Model 2 h (95%CI) *P*-value	REF	0.93(0.76–1.14)0.50	1.00(0.83–1.19)0.98	1.50(1.29–1.74) < 0.0001	< 0.0001
Model 3 h (95%CI) *P*-value	REF	0.92(0.76–1.13)0.43	0.94(0.78–1.12)0.47	1.31(1.13–1.53) < 0.001	< 0.0001
TyG-MLR					
Model 1 h (95%CI) *P*-value	REF	1.29(1.07–1.54)0.01	1.66(1.36–2.02) < 0.0001	4.11(3.46–4.88) < 0.0001	< 0.0001
Model 2 h (95%CI) *P*-value	REF	0.99(0.82–1.19)0.92	0.96(0.79–1.17)0.68	1.46(1.23–1.72) < 0.0001	< 0.0001
Model 3 h (95%CI) *P*-value	REF	1.02(0.83–1.26)0.82	1.01(0.83–1.24)0.89	1.48(1.23–1.77) < 0.0001	< 0.0001
TyG-SIRI					
Model 1 h (95%CI) *P*-value	REF	1.05(0.86–1.29)0.64	1.74(1.43–2.11) < 0.0001	3.44(2.84–4.17) < 0.0001	< 0.0001
Model 2 h (95%CI) *P*-value	REF	0.88(0.71–1.09)0.23	1.19(0.98–1.45)0.08	1.64(1.37–1.98) < 0.0001	< 0.0001
Model 3 h (95%CI) *P*-value	REF	0.83(0.67–1.03)0.09	1.12(0.91–1.37)0.30	1.34(1.11–1.63)0.003	< 0.0001
TyG-lgSII					
Model 1 h (95%CI) *P*-value	REF	0.90(0.75–1.07)0.24	1.00(0.85–1.19)0.98	1.78(1.52–2.09) < 0.0001	< 0.0001
Model 2 h (95%CI) *P*-value	REF	0.91(0.76–1.09)0.31	0.89(0.75–1.06)0.19	1.38(1.18–1.61) < 0.0001	< 0.0001
Model 3 h (95%CI) *P*-value	REF	0.91(0.75–1.10)0.32	0.86(0.73–1.02)0.08	1.20(1.02–1.41)0.02	0.004
TyG-lgPLR					
Model 1 h (95%CI) *P*-value	REF	0.85(0.73-1.00)0.05	0.84(0.69–1.01)0.07	1.25(1.07–1.47)0.01	0.003
Model 2 h (95%CI) *P*-value	REF	0.83(0.72–0.97)0.02	0.77(0.64–0.91)0.003	0.97(0.85–1.12)0.69	0.963
Model 3 h (95%CI) *P*-value	REF	0.94(0.80–1.10)0.43	0.87(0.72–1.05)0.15	1.11(0.97–1.27)0.14	0.162

Model 1: crude model;

Model 2: Adjusted for sex and age;

Model 3: Adjusted for sex, age, race, PIR, educational levels, BMI, smoking status, alcohol consumption, hypertension, DM, hyperlipidemia, cancers, lipid-lowering drugs, ALT, and AST

Abbreviations: TyG: triglyceride-glucose; NLR: neutrophil-lymphocyte ratio; MLR: monocyte-lymphocyte ratio; SIRI: system inflammation response index; SII: systemic immune inflammation index; PLR: platelet-lymphocyte ratio; CI: confidence interval; REF: reference; PIR: poverty income ratio; BMI: body mass index; DM: diabetes mellitus; ALT: alanine aminotransferase; AST: aspartate aminotransferase

The dose-response relationship between TyG and TyG-inflammation indices and mortality

We analyzed the dose-response relationship patterns between TyG and TyG-inflammation indices and mortality based on the RCS after adjusting for potential confounding factors (the same as in Model 3). The dose-response relationships between TyG and TyG-inflammation indices and all-cause mortality were nonlinear (all *P* values for nonlinearity < 0.05), as shown in Fig. 2. However, when evaluating the dose-response relationship between TyG and TyG-inflammation indices and cardiovascular mortality (Fig. 3), we found a linear dose-response relationship between TyG-SIRI (*P* for nonlinearity = 0.2398) and TyG-lgPLR (*P* for nonlinearity = 0.1557) and cardiovascular mortality. At the same time, there was a nonlinear dose-response relationship between the TyG index, other TyG-inflammation indices, and cardiovascular death (*P* for non-linearity < 0.05). Notably, regardless of the specific pattern of the dose-response relationship between the TyG index, TyG-inflammation indices, and mortality, when the respective threshold points were surpassed, there was an elevated risk of mortality as the TyG and TyG-inflammation indices increased.

The ability of the TyG and TyG-inflammation indices to predict mortality

Time-dependent ROC curve analysis showed that TyG-SIRI best predicted all-cause mortality at one year, followed by TyG-NLR, by TyG-MLR, by TyG-lgSII, by TyG, and by TyG-lgPLR. However, TyG-MLR demonstrated superior performance in predicting all-cause mortality at 3, 5, and 10 years (Fig. 4). Similarly, TyG-MLR also demonstrated superior performance in predicting cardiovascular mortality at 3, 5, and 10 years (Fig. 5).

The time-dependent AUC further indicated that TyG-MLR exhibited the highest accuracy in predicting long-term all-cause (Fig. 6A) and cardiovascular mortality risk (Fig. 6B). Additionally, TyG-MLR, TyG-SIRI, and TyG-NLR, and TyG-SII significantly outperformed

Table 3 Association of TyG and TyG-Inflammation indicators with cardiovascular mortality

Cardiovascular mortality					
	Q1	**Q2**	**Q3**	**Q4**	***P* for trend**
TyG					
Model 1 h (95%CI) *P*-value	REF	2.24(1.56–3.21) < 0.0001	2.15(1.50–3.08) < 0.0001	3.88(2.69–5.60) < 0.0001	< 0.0001
Model 2 h (95%CI) *P*-value	REF	1.17(0.82–1.69)0.38	1.01(0.71–1.43)0.97	1.61(1.11–2.33)0.01	0.011
Model 3 h (95%CI) *P*-value	REF	1.13(0.75–1.71)0.56	0.86(0.56–1.34)0.52	1.17(0.72–1.89)0.52	0.694
TyG-NLR					
Model 1 h (95%CI) *P*-value	REF	0.77(0.49–1.23)0.28	1.80(1.18–2.74)0.01	3.88(2.58–5.82) < 0.0001	< 0.0001
Model 2 h (95%CI) *P*-value	REF	0.74(0.48–1.15)0.19	1.33(0.88–2.01)0.18	1.99(1.37–2.89) < 0.001	< 0.0001
Model 3 h (95%CI) *P*-value	REF	0.72(0.47–1.13)0.15	1.25(0.82–1.92)0.31	1.79(1.17–2.72)0.01	< 0.0001
TyG-MLR					
Model 1 h (95%CI) *P*-value	REF	0.87(0.56–1.35)0.52	1.85(1.19–2.86)0.01	5.10(3.43–7.57) < 0.0001	< 0.0001
Model 2 h (95%CI) *P*-value	REF	0.69(0.45–1.07)0.10	0.99(0.65–1.53)0.98	1.62(1.15–2.28)0.01	< 0.0001
Model 3 h (95%CI) *P*-value	REF	0.73(0.46–1.16)0.19	1.06(0.68–1.66)0.80	1.73(1.16–2.56)0.01	< 0.0001
TyG-SIRI					
Model 1 h (95%CI) *P*-value	REF	0.93(0.60–1.44)0.75	1.63(1.12–2.37)0.01	4.33(2.78–6.75) < 0.0001	< 0.0001
Model 2 h (95%CI) *P*-value	REF	0.78(0.51–1.21)0.27	1.10(0.75–1.60)0.64	1.92(1.28–2.88)0.002	< 0.0001
Model 3 h (95%CI) *P*-value	REF	0.78(0.50–1.20)0.26	1.05(0.69–1.58)0.82	1.65(1.03–2.64)0.04	0.003
TyG-lgSII					
Model 1 h (95%CI) *P*-value	REF	1.04(0.74–1.46)0.84	1.18(0.87–1.61)0.30	2.55(1.83–3.57) < 0.0001	< 0.0001
Model 2 h (95%CI) *P*-value	REF	1.08(0.75–1.55)0.69	1.06(0.77–1.47)0.71	2.09(1.50–2.93) < 0.0001	< 0.0001
Model 3 h (95%CI) *P*-value	REF	1.11(0.75–1.63)0.61	1.07(0.77–1.48)0.69	1.92(1.31–2.81) < 0.001	< 0.001
TyG-lgPLR					
Model 1 h (95%CI) *P*-value	REF	1.24(0.92–1.68)0.16	1.19(0.85–1.67)0.31	1.90(1.43–2.53) < 0.0001	< 0.0001
Model 2 h (95%CI) *P*-value	REF	1.26(0.93–1.70)0.13	1.15(0.80–1.65)0.45	1.57(1.19–2.08)0.002	< 0.007
Model 3 h (95%CI) *P*-value	REF	1.46(1.06-2.00)0.02	1.35(0.94–1.94)0.11	1.87(1.40–2.49) < 0.0001	< 0.001

Model 1: crude model;

Model 2: Adjusted for sex and age;

Model 3: Adjusted for sex, age, race, PIR, educational levels, BMI, smoking status, alcohol consumption, hypertension, DM, hyperlipidemia, cancers, lipid-lowering drugs, ALT, and AST

TyG: triglyceride-glucose; NLR: neutrophil-lymphocyte ratio; MLR: monocyte-lymphocyte ratio; SIRI: system inflammation response index; SII: systemic immune inflammation index; PLR: platelet-lymphocyte ratio; CI: confidence interval; REF: reference; PIR: poverty income ratio; BMI: body mass index; DM: diabetes mellitus; ALT: alanine aminotransferase; AST: aspartate aminotransferase

the TyG index in predicting mortality, whereas TyG-lgPLR did not show such an improvement.

Discussion

In this cohort study based on the general U.S. population, we found no association between the TyG index and mortality rates, either all-cause or cardiovascular mortality. Interestingly, we built a new indicator based on TyG and systemic inflammation indicators, TyG-inflammation indices, which shows a marked positive correlation with mortality. Furthermore, time-dependent ROC curve results showed that TyG-MLR had the highest accuracy in predicting long-term mortality outcomes in the general population.

IR and inflammation are closely related to various metabolic diseases and adverse outcomes [1–3] and have a synergistic effect in promoting the progression of metabolic diseases and the occurrence of adverse events [24–26]. Therefore, we combined the TyG index with inflammation-related indicators to construct new indices that may better assess the risk of death in the general population. Systemic inflammation indicators can reflect the systemic inflammatory status of the body [28, 42, 43] and have been shown to be closely associated with the risk of death in the general population [30–35]. They are also closely related to adverse outcomes in patients with metabolic diseases and cardiovascular diseases [44–49]. Most importantly, systemic inflammation indicators, like TyG index, can be obtained through simple peripheral blood tests, which is one of the important reasons why they can be widely used in clinical practice.

Several studies have explored the association between the TyG index and mortality in the general population; however, they have shown varying results [16–22]. Chen et al. analyzed data from NHANES 2009–2018 and found that for every one-unit increase in the TyG index, the participants' risk of all-cause mortality and cardiovascular mortality increased by 16% and 21.3%, respectively, and the association between the TyG index and mortality was influenced by gender. However, when the TyG index was analyzed

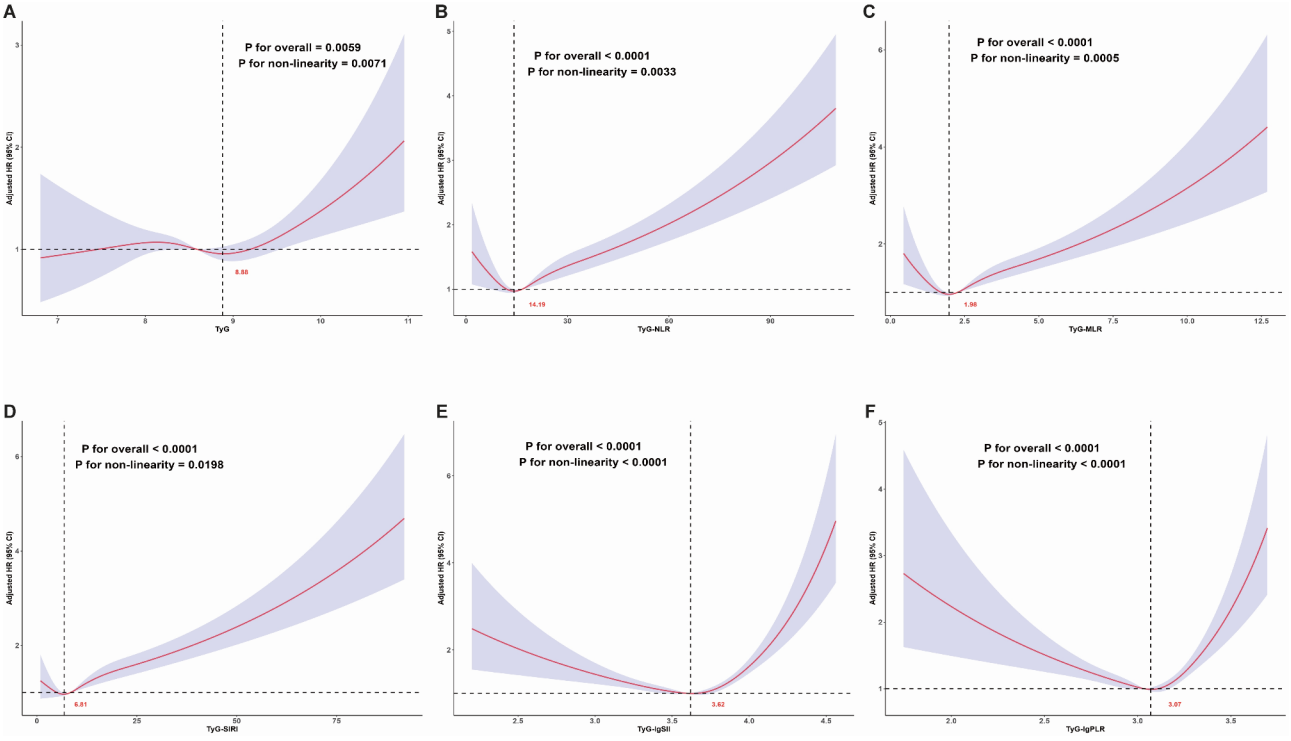

Fig. 2 Dose-response relationship between TyG, TyG-Inflammation indices, and all-cause mortality
Note: The red numbers in the figure represent the TyG and TyG-Inflammation indices corresponding to the threshold points. The solid and shaded areas represent estimates and their corresponding 95% confidence intervals(CIs), respectively. The adjusted potential confounding factors are the same as Model 3

as a categorical variable, no association with mortality was found [17]. Yu et al. [22] identified the inflection point between TyG and mortality using generalized additive models and penalized spline methods. They found that compared to participants with low TyG (< 8.5 or 8.7), those with high TyG (≥ 8.5 or 8.7) had a 1.39-fold and 1.82-fold increase in all-cause mortality risk and cardiovascular mortality risk, respectively. However, when TyG was grouped into tertiles, the association between TyG and mortality risk was no longer significant. Additionally, a cohort study based on the general population in Iran also found a close association between TyG and mortality, but after adjusting for the potential factor of diabetes, the association between TyG and mortality was no longer significant [21]. A prospective cohort study conducted by Professor Lopez-Jaramillo [19] found that the association between TyG and the general population was influenced by income levels; for example, TyG was not associated with mortality risk in high-income countries. It is worth mentioning that Liu et al., through a meta-analysis of 12 related studies, found that TyG was only associated with the risk of coronary artery disease in the general population but not with mortality [18]. Although some of the above studies found an association between TyG and mortality in the general population, these results may be influenced by various factors such as statistical analysis methods, potential confounding factors, study population, sample size, economic factors, etc. In conclusion, the association between the single indicator of TyG and mortality risk in the general population is not stable.

In our study, after adjustment confounders (e.g., presence of diabetes, income status, etc.), the association between TyG and all-cause and cardiovascular death was no longer significant. This finding is consistent with previous research results [19, 21]. Although several previous studies based on the NHANES database found that TyG is associated with mortality risk in the general population, these studies did not use all available NHANES data, which may introduce selection bias and subsequently affect the final results. In our study, to ensure reliability, we utilized all recorded data from NHANES 1999–2018. Our research findings indicate that, in the final model (Model3), compared to the lowest quartile (Q1), high levels of TyG-Inflammation indices (Q4) are closely associated with all-cause mortality (except for TyG-lgPLR) and cardiovascular mortality. However, it is noteworthy that the association between TyG-Inflammation indices and mortality is not significant when they are in the second and third quartiles. This may be because the association

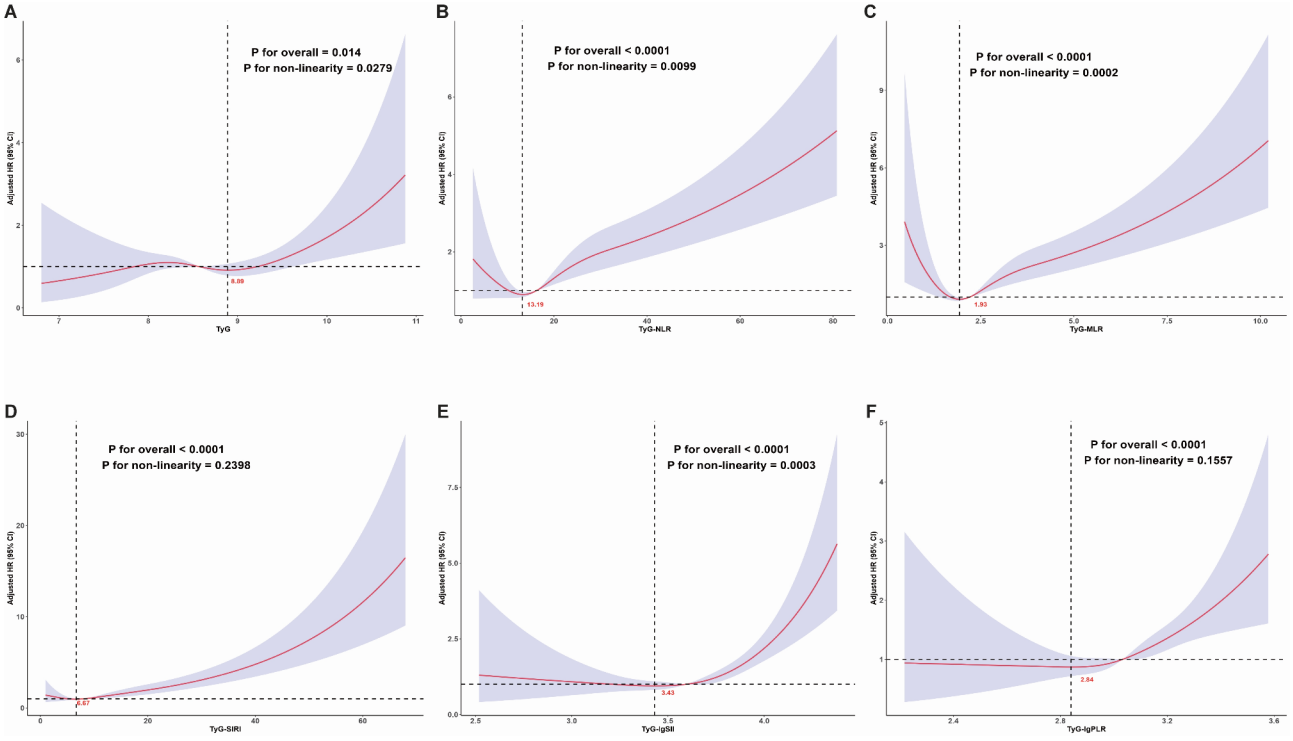

Fig. 3 Dose-response relationship between TyG, TyG-Inflammation indices, and cardiovascular mortality
Note: The red numbers in the figure represent the TyG and TyG-Inflammation indices corresponding to the threshold points. The solid and shaded areas represent estimates and their corresponding 95% confidence intervals(CIs), respectively. The adjusted potential confounding factors are the same as Model 3

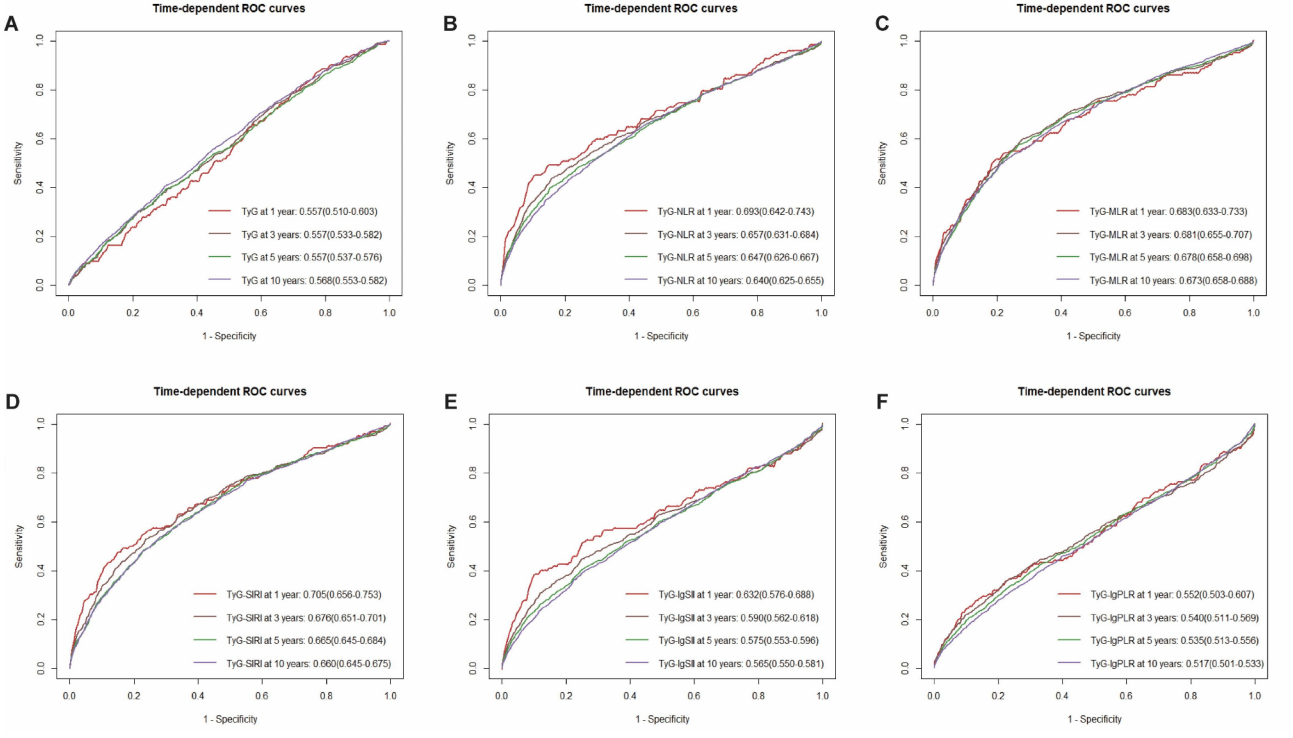

Fig. 4 Time-dependent ROC curves of the TyG and TyG-Inflammation indices for predicting all-cause mortality

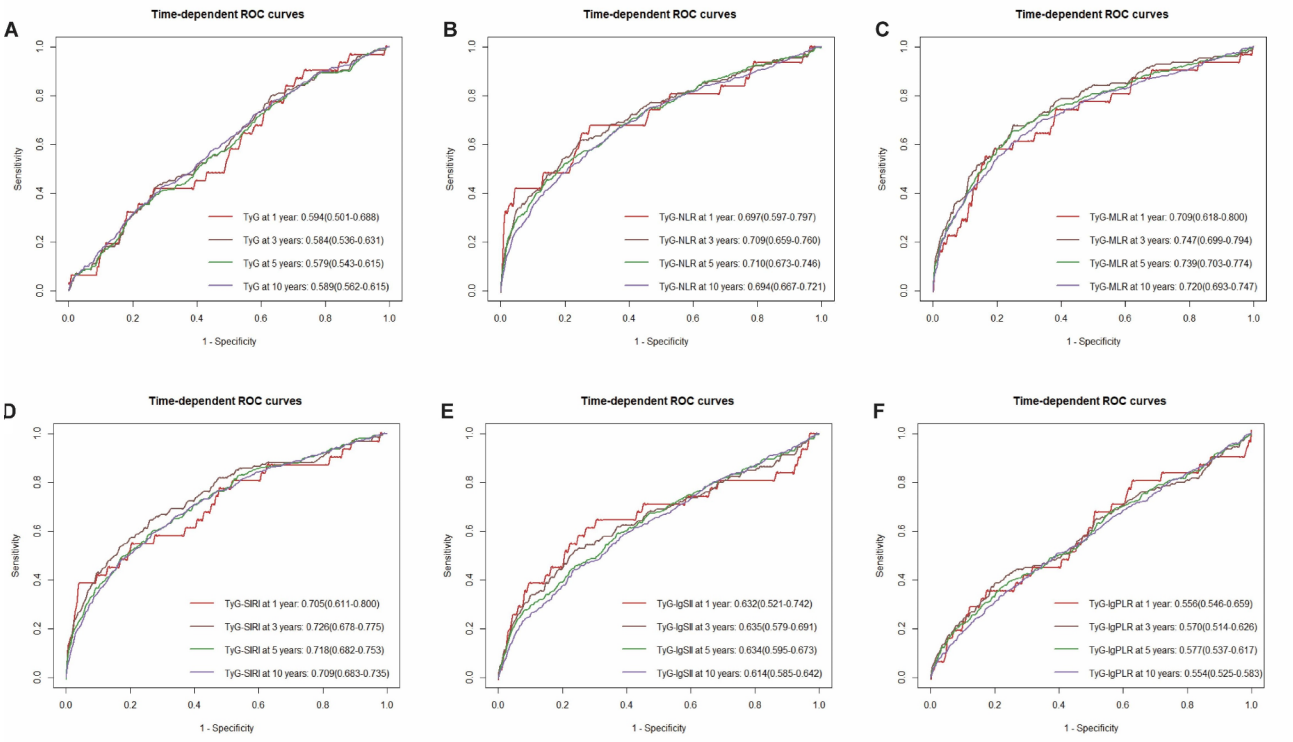

Fig. 5 Time-dependent ROC curves of the TyG and TyG-Inflammation indices for predicting cardiovascular mortality

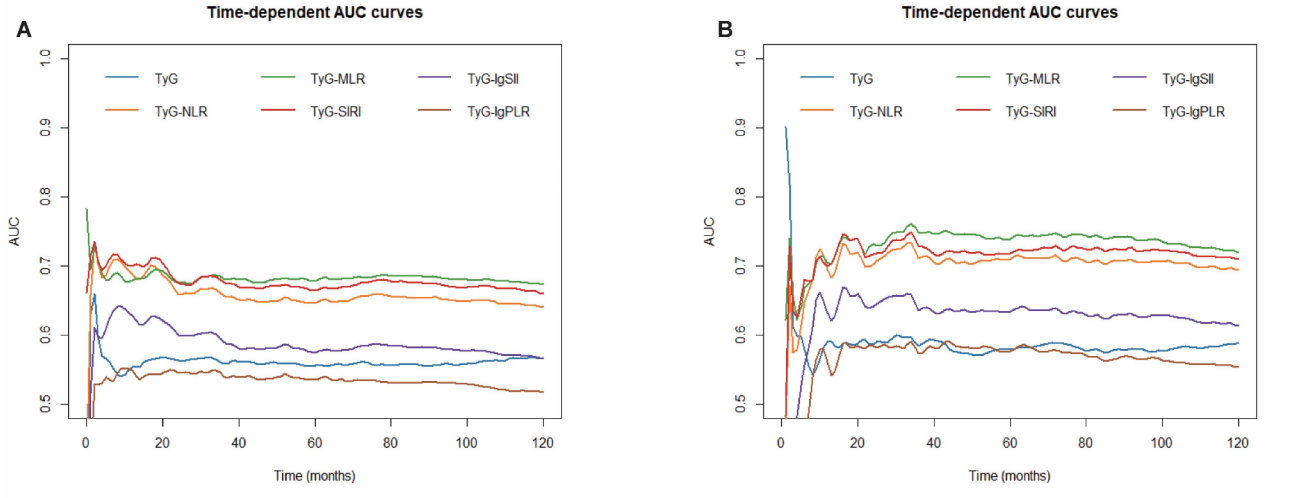

Fig. 6 Time-dependent AUC values of the TyG and TyG-Inflammation indices for predicting all-cause mortality (**A**) and cardiovascular mortality (**B**)

between TyG-Inflammation indices and mortality becomes significant only when they exceed a certain threshold. We believe that the strong association between the TyG-inflammation indices and mortality may be attributed to the following factors. First, insulin has anti-inflammatory effects, and when the body experiences IR, it is often accompanied by systemic low-grade inflammation [50]. Compared to the TyG index alone, the TyG-inflammation indices also consider the potential impact of the body's inflammatory status. IR is often accompanied by vascular endothelial dysfunction, and inflammation can further exacerbate damage to vascular endothelial function in individuals with IR, leading to target organ damage and an increased risk of mortality [24]. Second, previous studies have shown that individuals with both IR and inflammatory responses have an eight-fold increased risk of developing type 2 diabetes compared

to those without IR and inflammation [26]. The subsequent vascular, cardiac, and renal complications of type 2 diabetes also increase the risk of adverse outcomes [51]. Additionally, Anuurad et al. found that IR and inflammation could synergistically increase the risk of coronary heart disease in African-Americans and Caucasians [25].

It is worth mentioning that Dang et al. found that although TyG is not associated with mortality risk in the general population, when TyG is combined with BMI, TyG-BMI shows a positive correlation with mortality in the general population [20]. Based on this conclusion, we also analyzed the association between TyG-BMI and outcomes in our study, but the results were similar to those of TyG alone. This may be related to the inherent limitations of BMI. BMI is commonly used to assess overall obesity, but is ineffective in reflecting the distribution of visceral fat in the body [52]. Additionally, individuals with a normal BMI may still exhibit metabolic disorders; such individuals are referred to as metabolically unhealthy non-obese individuals [53, 54]. In other words, BMI can mask the actual metabolic abnormalities in individuals. However, the systemic inflammatory indices we used are different from BMI; they originate from the results of direct examination of individual blood and more accurately and truly reflect the level of inflammation, which may be one of the reasons why TyG-inflammation indices are closely related to mortality in the general population compared with TyG-BMI.

Notably, our findings and conclusions require further validation in larger cohorts and different populations to determine whether they are influenced by the economic environment of the participants, similar to the TyG index. In addition, the biological mechanisms underlying the association between TyG-inflammation indices and mortality need to be explored. In summary, both the TyG index and systemic inflammatory indicators can be measured through routine blood biochemical tests that are not expensive and do not require complex equipment. Once the effectiveness and stability of the TyG-inflammation indices are further validated in subsequent studies to assess mortality risk in the general population, they can be considered for use in primary care and health screening in the general population. Using the TyG-inflammation indices to stratify risk in these patients may provide specific treatment strategies to improve their prognosis.

Strengths and limitations

The strengths of this study are that it is the first to propose TyG-inflammation indices and to confirm the association between TyG-inflammation indices and mortality in the general population. Furthermore, unlike previous studies that primarily focused on metabolically abnormal populations, our study demonstrated that the TyG-inflammation indices can serve as a predictor of mortality risk in the general population. However, this study has several limitations. Firstly, because this was an observational cohort study, we could not determine a direct cause-and-effect association between TyG-inflammation indices and mortality. Furthermore, the potential mechanisms underlying the significant association between TyG-inflammation indices and mortality remain unclear. Finally, because the subjects of this study were from the US, the conclusions need to be validated in different populations and regions.

Conclusions

Our results showed that the TyG index was not associated with mortality in the general population. However, when the TyG index was combined with systemic inflammation indicators to form TyG-inflammation indices, we discovered a significant positive association between the TyG-inflammation indices and all-cause (except for TyG-lgPLR) and cardiovascular mortality. These simple, easily accessible, and inexpensive TyG-inflammation indices may serve as potential markers for identifying mortality risk in the general population at clinical practice.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-024-02277-9.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

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Author contributions

Conceptualization: YC; Methodology: YC, KX, and XZ; Validation: YC and HJ; Data Curation: YC, YH, HJ, and JS; Writing – Original Draft Preparation: YC; Visualization: YC, KX, and HJ; Supervision and Funding Acquisition: XZ.

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Data availability

All data related to this study can be accessed free of charge on the NHANES website (https://www.cdc.gov/nchs/nhanes/).

Declarations

Ethics approval and consent to participate

This study was approved by the Research Ethics Review Board of the National Center for Health Statistics. Informed consent was obtained from all the participants. This study complied with the ethical requirements of the Declaration of Helsinki and its subsequent revisions.

Consent for publication

All authors have reviewed and approved the final version of the manuscript.

Competing interests

The authors declare no competing interests.

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