

Association Between Triglyceride-Glucose Index and Mortality Risk in Cancer Survivors – An Analysis Based on NHANES 1999–2018 Data

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Article

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Abstract

Background

The triglyceride-glucose (TyG) index reflects insulin resistance, yet its dose-response relationship, threshold effect and cancer-specific heterogeneity linked to mortality remain unclear in cancer survivors. This study investigated TyG's associations with all-cause, cancer-specific and cardiometabolic mortality, along with non-linear trends, threshold effects and stratified results.

Methods

Data of 2139 cancer survivors from NHANES 1999–2018 were analyzed. Multiple imputation, Kaplan–Meier curves, Cox models, restricted cubic splines and piecewise linear models were adopted. Sensitivity analysis further verified result robustness.

Results

TyG exerted obvious threshold effects on all-cause (8.39) and cancer-specific mortality (8.24). Below the thresholds, mortality risks declined, while the protective effect vanished above them. Higher TyG increased cardiovascular and diabetes-related mortality risks, with discrepant effects across cancer types.

Conclusion

TyG is a practical prognostic marker for cancer survivors. Keeping TyG within 8.24–8.39 is advised to reduce mortality; targeted interventions are needed for patients with elevated TyG.

1. Introduction

Against the backdrop of global population aging and continuous advances in cancer diagnosis and treatment, cancer survivors have emerged as a rapidly growing group of vulnerable individuals(1). According to the latest global burden of disease and cancer statistics(2), the long-term health outcomes of cancer survivors differ significantly from those of the general population, who carry substantially elevated risks of all-cause mortality, cardiovascular diseases(3), metabolic disorders, second primary malignancies, and complications related to chronic inflammation(4). Although specialized cancer treatments have considerably prolonged survival, metabolic dysfunction, insulin resistance, chronic low-grade inflammation, and cardiovascular comorbidities have become core determinants of long-term prognosis among cancer survivors, representing key priorities and challenges in cancer rehabilitation and long-term management(5, 6).

As a critical pathophysiological hub linking obesity, glucolipid metabolic disorders, inflammation, and adverse prognosis, insulin resistance has been proven to participate in the entire process of tumorigenesis, cancer progression, treatment resistance, and long-term mortality(7). Insulin resistance can accelerate tumor progression and exacerbate cardiometabolic complications by activating inflammatory pathways, promoting oxidative stress and angiogenesis, and disturbing cellular energy metabolism, ultimately increasing the risk of death(8). However, classic indicators of insulin resistance, such as HOMA-IR, require simultaneous measurements of insulin and fasting glucose, which are costly and cumbersome, limiting their widespread use in large-scale population screening and long-term primary care follow-up(9). Simple, stable, and non-invasive surrogate indicators are urgently needed for clinical risk stratification.

The triglyceride-glucose index (TyG), calculated from fasting triglyceride and fasting glucose levels(10), offers the advantages of convenient detection, high stability, non-invasiveness, low cost, and easy popularization. It has been validated as a reliable surrogate marker for insulin resistance in the general population(11). Numerous cohort studies and meta-analyses have demonstrated that the TyG index is closely associated with the incidence and mortality of type 2 diabetes mellitus(12), atherosclerotic cardiovascular disease(13), non-alcoholic fatty liver disease(14), and multiple types of cancer(15), and can serve as an independent tool for metabolic and prognostic risk stratification(16).

Although existing studies have suggested a link between the TyG index and cardiovascular outcomes in cancer survivors(17), the dose–response relationship, non-linear threshold effect, and cancer-type heterogeneity of the TyG index with all-cause mortality, cancer-specific mortality, and cardiometabolic-related mortality remain unclear within the framework of insulin resistance(13). Large-sample, long-term follow-up, nationally representative prospective population evidence is still insufficient(9, 16, 17).

To address these research gaps, the present study used large-scale population data from the NHANES 1999–2018 to systematically investigate the associations of the TyG index with various mortality outcomes among cancer survivors and to identify the risk intervals through threshold analysis and non-linear fitting. This study aims to provide high-quality evidence for rapid clinical risk screening, precise metabolic stratification, and individualized interventions, helping to optimize long-term health management strategies and reduce the burden of late mortality among cancer survivors.

2. Materials and Methods

2.1. Population of the study

This cross-sectional study was conducted in accordance with the updated STROCSS 2025 guideline(18). Data were obtained from the NHANES 1999–2018 database. NHANES uses a stratified, multistage, probability sampling design to select a nationally representative sample of the US population, and collects information on sociodemographic characteristics, lifestyle, health status, and biomarkers via questionnaire interviews, physical examinations, and laboratory tests(19).

Inclusion and exclusion criteria for study participants: Individuals were excluded if they were younger than 20 years, lacked data on fasting triglycerides, fasting blood glucose, cancer diagnosis or survival outcomes, or were pregnant or breastfeeding. A total of 2139 participants were finally included for statistical analysis. The detailed participant screening process is presented in Supplementary Figure S1.

2.2. Main study variables

2.2.1. Definition of cancer

In this analysis, information on cancer history was collected via questionnaires related to medical conditions(20). Participants with a history of cancer or malignant tumors were identified based on their responses to the question: "Has a doctor or other health professional ever told you that you have cancer or any type of malignant tumor?"

2.2.2. Definition of the TyG index

TyG index: Calculated based on fasting triglyceride and fasting blood glucose levels. The formula is as follows(10):

$$\text{TyG} = \ln \frac{\text{fasting triglycerides (mg/dL)} \times \text{fasting blood glucose (mg/dL)}}{2}$$

2.2.3. Mortality assessment

The primary outcome was cancer-related mortality. The secondary outcomes included all-cause mortality, cardiovascular disease-related mortality, diabetes-related mortality and hypertension-related mortality. Mortality data from NHANES (1999–2018) were obtained by the National Center for Health Statistics (NCHS) via probabilistic record linkage with death certificate data from the National Death Index (NCHS Linked Mortality Files) up to December 31, 2019. Data integration and annotation were performed using the provided Sample R code(21). Additionally, cancer-related, cardiovascular disease-related, diabetes-related and hypertension-related mortality were defined according to the codes of the International Classification of Diseases, 10th Revision (ICD-10)(22).

2.2.4. Assessment of covariates

Covariates for adjustment were selected based on previous literature and clinical experience(23–25), including sex, age, race/ethnicity, educational attainment, marital status, poverty income ratio (PIR), alcohol consumption, smoking status, body mass index (BMI), diabetes mellitus (DM), hypertension, hyperlipidemia, cardiovascular disease (CVD) and cancer sites.

Sociodemographic factors: sex, age (< 60 years / ≥60 years), race/ethnicity (non-Hispanic White, non-Hispanic Black, Mexican American, other Hispanic, other races), educational attainment (less than high school, high school, college and above), marital status (married/living with partner, others), and PIR (< 1, 1–3, ≥ 3).

Lifestyle factors: smoking status (< 100 cigarettes per year, ≥ 100 cigarettes per year) and alcohol consumption (< 12 times per year, ≥ 12 times per year).

Clinical indicators: BMI; diabetes mellitus (defined as self-reported history of diabetes, insulin use, oral hypoglycemic agent use, glycated hemoglobin [HbA1c] ≥ 6.5%, or fasting blood glucose ≥ 126 mg/dL); hypertension (defined as self-reported history of hypertension, systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg); hyperlipidemia (defined as total cholesterol ≥ 240 mg/dL, triglycerides ≥ 160 mg/dL, high-density lipoprotein cholesterol < 40 mg/dL for males / <50 mg/dL for females, or low-density lipoprotein cholesterol ≥ 150 mg/dL); CVD (defined as a physician or other health professional diagnosis of coronary heart disease, congestive heart failure, heart attack, stroke or angina).

Cancer site was ascertained via the survey question "What type of cancer was diagnosed?". All cancer cases were classified into eight groups according to primary tumor site: Urogenital cancers: bladder cancer, renal cancer, prostate cancer and testicular cancer. Digestive system cancers: colon cancer, esophageal cancer, gallbladder cancer, pancreatic cancer, liver cancer, gastric cancer and rectal cancer. Female reproductive system cancers: breast cancer, cervical cancer, ovarian cancer and uterine cancer. Respiratory system cancers: laryngeal/tracheal cancer and lung cancer. Hematologic and lymphatic cancers: hematologic malignancy, leukemia, lymphoma and Hodgkin disease. Skin cancers: melanoma, non-melanoma skin cancer, and skin cancer of unknown subtype. Other site cancers: oral/tongue/lip cancer, soft tissue (muscle or adipose tissue) cancer, thyroid cancer, bone cancer, brain and nervous system cancer. Unknown or multiple cancer types: other cancers, more than two cancer types, and unspecified cancer.

2.3. Statistical analysis

All statistical analyses incorporated the sampling weights of the NHANES dataset to ensure the national representativeness of the results(20). Complex sampling weight correction was applied in this study to reflect the representativeness of the target population.

Multiple imputation was performed to handle missing values in covariates(26). The missing data proportions of covariates are presented in Supplementary Table S1, among which alcohol consumption, PIR and BMI had the highest missing rates and were considered critical variables. Multiple imputation approaches were adopted to impute missing data, and the distribution of imputed data was consistent with the original distribution, as illustrated in Supplementary Figures S2-S4. Multiple imputation by chained equations (MICE) package (version 4.5.1) with default settings was used for data imputation(27). The predictive mean matching (pmm) method was employed for continuous variables, logistic regression (logreg) for binary variables, and polytomous regression (polyreg) for multinomial categorical variables. A total of five imputed datasets were generated, and pooled analysis was conducted to synthesize the results across all datasets. Differences between the original and imputed datasets were examined(28). The Kolmogorov-Smirnov test was used for BMI, and the chi-square test was applied to PIR and alcohol consumption. All P values were greater than 0.05, indicating no significant difference in distribution between the original and imputed data and satisfactory performance of imputation, as shown in Supplementary Tables S2-S4.

Participants were categorized into four groups according to the quartiles of the TyG index: Q1 (< 8.31), Q2 (8.31–8.73), Q3 (8.73–9.15), and Q4 (≥ 9.15). Baseline characteristics were presented as mean (standard error, SE) for normally distributed continuous variables, median (interquartile range, IQR) for non-normally distributed continuous variables, and number (percentage) for categorical variables.

Kaplan-Meier survival curves were plotted to depict the all-cause mortality risk across different subgroups. Cumulative incidence function curves were generated to visualize mortality related to cancer, cardiovascular disease (CVD), diabetes mellitus and hypertension. Multiple models were established, and Cox proportional hazards models were applied to adjust for confounders for investigating the relationships between TyG levels and diverse mortality outcomes. Restricted cubic spline regression with three knots (5th, 50th and 75th percentiles) was used to assess the dose-response relationship between TyG index and mortality after adjusting for the aforementioned covariates. If a non-linear association was identified, a two-piece linear regression model was applied to characterize the relationship across the threshold. The optimal threshold was determined by screening all potential cut-

off values and selecting the one with the maximum likelihood. The log-likelihood ratio test was used to compare the association patterns between the two-piece linear model and the single linear model.

Furthermore, consistent survival analyses were conducted among survivors of skin cancer, female reproductive system cancers and urogenital cancers, with each subgroup having a sample size greater than 400. For sensitivity analysis, participants who died within the first two years of follow-up were excluded to mitigate reverse causation bias. Subsequently, to further clarify the stability of the associations between the TyG index and mortality outcomes and potential effect modifications across different subgroups, stratification analyses were performed according to age (< 60 years / ≥ 60 years), sex, BMI (< 30.0 kg/m² / ≥ 30.0 kg/m²), smoking status, and alcohol consumption. Interaction tests were conducted by introducing multiplicative interaction terms. A two-sided $P < 0.05$ was considered statistically significant. All statistical analyses were carried out using R software (version 4.5.1)(29).

3. Results

3.1. Baseline characteristics across TyG index quartiles

A total of 2139 cancer survivors were included in this study, with a weighted population of 19,552,778. The baseline characteristics stratified by TyG index quartiles are presented in Table 1. The results showed that no significant intergroup differences were observed in gender and smoking status ($P > 0.05$). By contrast, age, race, educational level, PIR, alcohol consumption, BMI and the prevalence of various chronic diseases differed significantly across TyG subgroups (all $P < 0.05$). With the increase in TyG index, participants had older age and higher BMI, while their educational attainment and household income decreased correspondingly. The prevalence of DM, hypertension, hyperlipidemia and CVD rose markedly. The distribution of cancer types also varied significantly among groups. For study outcomes, higher proportions of all-cause mortality, DM-related mortality, hypertension-related mortality and cancer-related mortality were found in groups with elevated TyG index, whereas no significant difference was detected in CVD-related mortality across all subgroups.

Table 1
Baseline Characteristics of Participants by TyG Subgroups in the NHANES 1999–2018

Total	Total	Q1(< 8.31)	Q2(8.31–8.73)	Q3(8.73–9.15)	Q4(> 9.15)	P
	2139	535	534	536	534	
TyG	8.73 ± 0.65	7.99 ± 0.27	8.53 ± 0.12	8.93 ± 0.13	9.60 ± 0.45	< 0.001
Age	62.53 ± 14.72	59.44 ± 16.50	63.25 ± 14.38	64.09 ± 13.79	63.68 ± 13.28	< 0.001
< 60	572(37.41)	182(45.24)	142(35.71)	128(33.81)	120(33.93)	< 0.001
≥ 60	1567(62.59)	353(54.76)	392(64.29)	408(66.19)	414(66.07)	
Gender						
Male	1000(41.45)	251(39.01)	250(40.59)	249(42.33)	250(44.32)	0.999
Female	1139(58.55)	284(60.99)	284(59.41)	287(57.67)	284(55.68)	
Race						< 0.001
Mexican American	163(2.56)	22(1.53)	37(2.80)	44(3.20)	60(2.82)	
Other Hispanic	111(2.91)	25(2.90)	28(2.41)	28(3.88)	30(2.46)	
Non-Hispanic White	1508(85.91)	361(84.01)	380(86.58)	384(83.60)	383(89.81)	
Non-Hispanic Black	266(5.42)	100(7.92)	69(5.17)	57(5.29)	40(2.92)	
Other Race	91(3.20)	27(3.64)	20(3.05)	23(4.02)	21(1.99)	
Education						< 0.001
< 9	217(5.38)	38(3.51)	46(4.45)	48(4.59)	85(9.41)	
9–11	273(85.04)	60(7.42)	65(8.75)	74(11.60)	74(10.91)	
≥ 12	1646(85.04)	437(89.06)	422(86.80)	413(83.82)	374(79.69)	
PIR						< 0.001
=<1	283(9.16)	58(7.72)	65(8.38)	72(10.48)	88(10.33)	
1–3	937(35.40)	214(29.76)	205(27.57)	255(40.26)	263(45.53)	
>=3	919(55.44)	263(62.52)	264(64.05)	209(49.26)	183(44.14)	
Smoke						0.067
≥ 100	1182(53.66)	272(49.34)	306(54.12)	294(55.26)	310(56.50)	
< 100	954(46.34)	263(50.66)	225(45.88)	242(44.74)	224(43.50)	
Drink						0.003
≥ 12	1366(68.69)	371(74.20)	350(69.13)	328(66.02)	317(64.59)	
< 12	773(31.31)	164(25.80)	184(30.87)	208(33.98)	217(35.41)	
BMI	28.72 ± 6.51	26.60 ± 6.01	27.53 ± 6.14	29.50 ± 6.45	31.67 ± 6.32	< 0.001
DM						< 0.001

Total	Total	Q1(< 8.31)	Q2(8.31–8.73)	Q3(8.73–9.15)	Q4(> 9.15)	P
	2139	535	534	536	534	
Yes	583(21.66)	43(4.21)	91(15.63)	158(23.46)	291(46.73)	
No	1556(78.34)	492(95.79)	443(84.37)	378(76.54)	243(53.27)	
Hypertension						< 0.001
Yes	1373(58.50)	294(45.48)	326(56.90)	367(64.19)	386(69.44)	
No	766(41.50)	241(54.52)	208(43.10)	169(35.81)	148(30.56)	
Hyperlipidemia						< 0.001
Yes	1514(71.05)	257(46.47)	323(64.42)	423(80.59)	511(96.96)	
No	625(28.95)	278(53.53)	211(35.58)	113(19.41)	23(3.04)	
CVD						< 0.001
Yes	529(19.73)	105(14.56)	119(18.64)	128(19.96)	177(26.69)	
No	1610(80.27)	430(85.44)	415(81.36)	408(80.04)	357(73.31)	
Cancer sites						0.038
Urinary and Reproductive System Cancers	458(15.62)	123(15.58)	113(16.46)	113(17.15)	109(13.12)	
Digestive System Cancers	192(7.28)	41(5.13)	42(6.10)	43(7.60)	66(10.74)	
Female Reproductive System Cancers	587(29.81)	142(10.74)	152(29.64)	151(30.55)	142(27.63)	
Respiratory System Cancers	49(1.83)	8(1.19)	11(1.35)	19(2.99)	11(1.91)	
Blood and Lymphatic System Cancers	67(3.28)	18(3.04)	27(4.48)	14(3.22)	8(2.28)	
Skin Cancers	613(34.15)	153(34.59)	147(32.98)	155(31.32)	158(37.88)	
Other Site Cancers	68(3.03)	20(3.62)	22(3.68)	14(2.53)	12(2.14)	
Unknown or Multiple Types of Cancers	104(5.01)	29(5.66)	20(5.30)	27(4.65)	28(4.31)	
Outcome cause of death						
All-cause mortality						< 0.001
Yes	769(26.63)	150(18.65)	196(27.45)	214(30.31)	209(31.15)	
No	1370(73.37)	385(81.35)	338(72.55)	322(69.69)	325(68.85)	
CVD-related mortality						0.134
Yes	157(5.19)	30(3.47)	35(4.07)	44(5.33)	48(8.31)	
No	1982(94.81)	505(96.53)	499(95.93)	492(94.67)	486(91.69)	
Hypertension-related mortality						0.029
Yes	107(3.42)	20(2.50)	19(2.18)	31(4.19)	39(5.05)	
No	2032(96.58)	515(97.50)	515(97.82)	505(95.81)	497(94.95)	

Total	Total	Q1(< 8.31)	Q2(8.31–8.73)	Q3(8.73–9.15)	Q4(> 9.15)	P
	2139	535	534	536	534	
DM-related mortality						< 0.001
Yes	72(2.20)	4(0.35)	11(1.79)	17(2.17)	40(4.85)	
No	2067(97.80)	531(99.65)	523(98.21)	519(97.83)	494(95.15)	
Cancer-related mortality						0.025
Yes	235(8.2)	45(6.21)	64(8.87)	74(10.79)	52(7.06)	
No	1904(91.8)	490(93.79)	470(91.13)	462(89.21)	484(92.94)	

3.2. Association between TyG index and cancer-related mortality risk

The cumulative incidence curves stratified by TyG index quartiles showed no significant difference in cancer-related mortality risk across subgroups (log-rank test, $P = 0.085$), as presented in Fig. 1-A. Restricted cubic spline regression revealed a significant non-linear association between TyG index and cancer-related mortality (P for non-linearity = 0.02), as shown in Fig. 1-B. Threshold effect analysis identified a clear inflection point at a TyG index of 8.24: below this threshold, an increase in TyG index was significantly associated with reduced cancer-related mortality risk (HR = 0.249, 95% CI: 0.072–0.860, $P = 0.0279$); above the threshold, this protective effect disappeared (HR = 0.883, 95% CI: 0.688–1.134, $P = 0.3296$). The likelihood ratio test ($P = 0.0165$) further confirmed the presence of this non-linear relationship, as detailed in Table 2.

Multivariable Cox regression analysis indicated that in the fully adjusted model, TyG index as a continuous variable was not significantly associated with cancer-related mortality risk (HR = 0.87, 95% CI: 0.66–1.15, $P = 0.313$). However, when stratified by quartiles with Q2 (8.31–8.73) as the reference group, the highest TyG quartile (Q4, > 9.15) showed a significantly reduced mortality risk (HR = 0.68, 95% CI: 0.66–0.69, $P < 0.001$), suggesting that higher TyG levels were associated with a lower risk of cancer-related mortality. The P for trend was marginally significant ($P = 0.064$), as shown in Table 3.

A B

Table 2
Threshold effect analysis of TyG on Cancer-related mortality

Outcome	Threshold value	<threshold value (per 1 increment)	≥threshold value (per 1 increment)	P for log likelihood ratio test
Cancer-related mortality	8.24	0.249(0.072,0.860)0.0279	0.883(0.688,1.134)0.3296	0.0165

Table 3
Hazard Ratios (95% CI) for Cancer-Related Mortality by TyG Index Quartiles

Model 1 ^a	TyG	Q1(< 8.31)	Q2(8.31– 8.73)	Q3(8.73–9.15)	Q4(> 9.15)	P trend
	0.84(0.54,1.31)0.441	0.89(0.58,1.35)0.572	1	1.06(0.78,1.45)0.698	0.64(0.57,0.72) < 0.001	0.356
Model 2	0.88(0.55,1.43)0.612	0.92(0.68,1.25)0.602	1	1.04(0.68,1.59)0.847	0.71(0.56,0.90)0.004	0.504
Model 3 ^c	0.87(0.66,1.15)0.313	0.91(0.78,1.06)0.221	1	0.98(0.73,1.31)0.896	0.68(0.66,0.69) < 0.001	0.064
^a Model 1: adjusted for age						
^b Model 2: further adjusted for sex, race, BMI, education, income-poverty ratio, alcohol use, smoking status, marital status						
^c Model 3: further adjusted for hypertension, dyslipidemia, CVD, DM						

3.3. Association between TyG index and all-cause mortality risk

The Kaplan-Meier survival curves for all-cause mortality stratified by TyG index quartiles showed no significant difference in cumulative mortality risk across subgroups (log-rank test, $P = 0.119$), as presented in Fig. 2-A. Restricted cubic spline regression indicated a marginally significant non-linear association between TyG index and all-cause mortality (P for non-linearity = 0.058), as shown in Fig. 2-B. Threshold effect analysis identified a clear inflection point at a TyG index of 8.39: below this threshold, an increase in TyG index was significantly associated with reduced all-cause mortality risk (HR = 0.534, 95% CI: 0.335–0.852, $P = 0.0085$); above the threshold, this protective effect disappeared (HR = 1.000, 95% CI: 0.868–1.152, $P = 0.9994$). The likelihood ratio test ($P = 0.0185$) confirmed the presence of a significant threshold effect between TyG index and all-cause mortality, as detailed in Table 4.

Multivariable Cox regression analysis showed that in the fully adjusted model, TyG index as a continuous variable was significantly associated with all-cause mortality risk (HR = 0.93, 95% CI: 0.88–0.98, $P < 0.001$). When stratified by quartiles with Q2 (8.31–8.73) as the reference group, the highest TyG quartile (Q4, > 9.15) showed a significantly reduced mortality risk (HR = 0.83, 95% CI: 0.80–0.87, $P < 0.001$), indicating that higher TyG levels were associated with a lower risk of all-cause mortality, with a significant P for trend ($P < 0.001$), as presented in Table 5.

A B

Table 4
Threshold effect analysis of TyG on all-cause mortality

Outcome	Threshold value	<threshold value (per 1 increment)	≥threshold value (per 1 increment)	P for log likelihood ratio test
All-cause mortality	8.39	0.534(0.335,0.852)0.0085	1.000(0.868,1.152)0.9994	0.0185

Table 5
Hazard Ratios (95% CI) for All-cause Mortality by TyG Index Quartiles

Model 1 ^a	TyG	Q1(< 8.31)	Q2(8.31– 8.73)	Q3(8.73–9.15)	Q4(> 9.15)	P trend
	0.98(0.88,1.09)0.669	0.96(0.85,1.09)0.518	1	0.99(0.94,1.05)0.739	0.89(0.88,0.91) < 0.001	0.242
Model 2	0.95(0.85,1.07)0.390	0.98(0.87,1.11)0.771	1	0.97(0.87,1.08)0.596	0.85(0.82,0.89) < 0.001	0.120
Model 3 ^c	0.93(0.88,0.98) < 0.001	1.02(0.96,1.09)0.520	1	0.96(0.85,1.08)0.045	0.83(0.80,0.87) < 0.001	< 0.001
^a Model 1: adjusted for age						
^b Model 2: further adjusted for sex, race, BMI, education, income-poverty ratio, alcohol use, smoking status, marital status						
^c Model 3: further adjusted for hypertension, dyslipidemia, CVD, DM						

3.4. Association between TyG index with Cardiometabolic Mortality (CVD, Diabetes, Hypertension)

The cumulative incidence curves for CVD-related mortality stratified by TyG index quartiles showed no significant difference in cumulative mortality risk across subgroups (log-rank test, $P = 0.414$), as presented in Fig. 3-A. Restricted cubic spline regression revealed no significant non-linear association between TyG index and CVD-related mortality (P for non-linearity = 0.846), as shown in Fig. 3-B. Threshold effect analysis indicated that the likelihood ratio test $P = 0.8664$, suggesting no significant association between TyG index elevation and CVD-related mortality risk on either side of the threshold, with no obvious threshold effect, as detailed in Table 6.

Multivariable Cox regression analysis showed that in the fully adjusted model, TyG index as a continuous variable was significantly associated with increased CVD-related mortality risk (HR = 1.15, 95% CI: 1.04–1.27, $P = 0.006$). When stratified by quartiles with Q2 (8.31–8.73) as the reference group, the highest TyG quartile (Q4, > 9.15) showed a significantly elevated mortality risk (HR = 1.45, 95% CI: 1.31–1.61, $P < 0.001$), indicating that higher TyG levels were associated with an increased risk of CVD-related mortality, with a significant P for trend ($P < 0.001$), as presented in Table 7.

A B

Table 6
Threshold effect analysis of TyG on CVD-related mortality

Outcome	Threshold value	<threshold value (per 1 increment)	≥threshold value (per 1 increment)	P for log likelihood ratio test
CVD-related mortality	8.77	0.784(0.443,1.387))0.4023	1.191(0.832,1.704)0.3395	0.864

Table 7
Hazard Ratios (95% CI) for CVD-related Mortality by TyG Index Quartiles

Model 1a	TyG	Q1(< 8.31)	Q2(8.31– 8.73)	Q3(8.73–9.15)	Q4(> 9.15)	P trend
	1.37(1.22,1.53) < 0.001	1.69(1.11,2.58)0.014	1	1.28(0.74,2.23)0.384	1.86(1.48,2.33) < 0.001	< 0.001
Model 2	1.29(1.16,1.43) < 0.001	1.46(0.93,2.27)0.097	1	1.11(0.70,1.74)0.659	1.54(1.19,2.00)0.001	< 0.001
Model 3c	1.15(1.04,1.27)0.006	1.77(1.26,2.48)0.001	1	1.15(0.81,1.63)0.440	1.45(1.31,1.61) < 0.001	< 0.001
^a Model 1: adjusted for age						
^b Model 2: further adjusted for sex, race, BMI, education, income-poverty ratio, alcohol use, smoking status, marital status						
^c Model 3: further adjusted for hypertension, dyslipidemia, CVD, DM						

For DM-related mortality, the cumulative incidence curves stratified by TyG index quartiles showed significant differences in cumulative mortality risk across subgroups (log-rank test, $P < 0.001$), as shown in Figure S5-A. Restricted cubic spline regression revealed a significant non-linear association between TyG index and DM-related mortality (P for non-linearity = 0.017), as presented in Figure S5-B. Threshold effect analysis identified a clear inflection point at a TyG index of 8.75: below this threshold, an increase in TyG index was significantly associated with reduced mortality risk (HR = 0.145, 95% CI: 0.034–0.619, $P = 0.0091$); above the threshold, an increase in TyG index was significantly associated with elevated mortality risk (HR = 2.142, 95% CI: 1.541–2.977, $P < 0.0001$). The likelihood ratio test yielded $P = 0.121$, indicating no statistically significant difference between the piecewise model and the linear model for the association between TyG index and DM-related mortality, as detailed in Table S5. Multivariable Cox regression analysis showed that in the fully adjusted model, TyG index as a continuous variable was significantly associated with DM-related mortality risk (HR = 1.42, 95% CI: 1.18–1.72, $P < 0.001$). However, quartile-based analysis revealed that compared with Q2 (8.31–8.73), the intermediate TyG level (Q3) was associated with significantly lower mortality risk (HR = 0.77, 95% CI: 0.64–0.92, $P = 0.003$), suggesting that the association is not simply linear but exhibits a threshold effect, as presented in Table S6.

For hypertension-related mortality, cumulative incidence curves stratified by TyG index quartiles showed no statistically significant differences in cumulative mortality risk among subgroups (log-rank test, $P = 0.122$), as shown in Figure S6-A. Restricted cubic spline regression suggested that there was no significant nonlinear association between the two (nonlinear $P = 0.555$), as shown in Figure S6-B. Threshold effect analysis showed that the P -value of the likelihood ratio test was 0.9002, indicating that elevated TyG index on both sides of the threshold was not significantly associated with the risk of hypertension-related mortality, and the threshold effect was not obvious, as shown in Table S7. Multivariate Cox regression analysis showed that in the fully adjusted model, TyG index as a continuous variable had no significant linear association with the risk of hypertension-related mortality (HR = 1.27, 95% CI: 0.76–2.12, $P = 0.365$); however, after grouping by quartiles, with Q2 (8.31–8.73) as the reference, the mortality risk of the highest TyG group (Q4, > 9.15) was significantly increased (HR = 2.03, 95% CI: 1.46–2.84, $P < 0.001$), suggesting that high TyG levels were associated with an increased risk of hypertension-related mortality, as shown in Table S8.

3.5. Subgroup Analysis Results Stratified by Cancer Type

This study further performed subgroup analyses among survivors of skin cancer, female reproductive system cancer, and urinary and reproductive system cancer, all with a sample size ≥ 400 . Due to the extremely low number of diabetes-related and hypertension-related mortality events in these subgroups, leading to unstable effect estimates, only the associations between the TyG index and all-cause mortality, cancer-related mortality, and CVD-related mortality are reported. The results showed that the association patterns of the TyG index with each mortality outcome in these subgroups were generally consistent with those observed in the overall population.

3.5.1. Skin cancer survivors (n = 613)

The cumulative incidence curves for cancer-related mortality stratified by TyG index quartiles showed significant differences across subgroups (log-rank test, $P = 0.043$), whereas the cumulative incidence curves for all-cause mortality and CVD-related mortality were not statistically significant (all $P > 0.05$). Restricted cubic spline analyses revealed no significant nonlinear associations (all P for nonlinearity > 0.05), as shown in Figure S7–S9. Threshold effect analyses were also not statistically significant (all likelihood ratio test $P > 0.05$), as presented in Table S9. In the fully adjusted Cox model, elevated TyG index was associated with reduced risks of all-cause mortality (HR = 0.92, 95% CI: 0.88–0.98, $P = 0.005$) and cancer-related mortality (Q4 vs Q2, HR = 0.12, 95% CI: 0.10–0.14, $P < 0.001$). In contrast, increased TyG index was positively associated with elevated CVD-related mortality (HR = 1.97, 95% CI: 1.90–2.04, $P < 0.001$), as detailed in Table S10.

3.5.2. Female reproductive system cancer survivors (n = 587)

The cumulative incidence curves for mortality stratified by TyG index quartiles showed no significant differences in all-cause, cancer-related, or CVD-related mortality across TyG subgroups (all log-rank test $P > 0.05$). No significant nonlinear associations were observed (all $P > 0.05$), as shown in Figure S10–S12. Threshold effect analyses were not statistically significant (all likelihood ratio test $P > 0.05$), as presented in Table S11. In the fully adjusted Cox model, elevated TyG was associated with decreased all-cause mortality (HR = 0.80, 95% CI: 0.74–0.87, $P = 0.025$). For cancer-related mortality, the highest TyG quartile had a higher mortality risk (Q4 vs Q2, HR = 1.72, 95% CI: 1.07–2.78, $P = 0.025$). Estimates for CVD-related mortality were unstable due to extremely sparse events and were not reported, as shown in Table S12.

3.5.3. Urinary and reproductive system cancer survivors (n = 458)

All cumulative incidence curves stratified by TyG index quartiles were not statistically significant (all log-rank test $P > 0.05$). No significant nonlinear associations or threshold effects were detected (all $P > 0.05$), as shown in Figure S13–S15. Threshold effect analyses were also not statistically significant (all likelihood ratio test $P > 0.05$), as presented in Table S13. In the fully adjusted Cox model, TyG index was not independently associated with all-cause mortality or cancer-related mortality (all $P > 0.05$). However, elevated TyG was strongly associated with an increased risk of CVD-related mortality (HR = 4.22, 95% CI: 3.85–4.62, $P < 0.001$), as detailed in Table S14.

3.6. Stratified Analyses by Participant Characteristics

After excluding participants who died within the first 2 years of follow-up, a sensitivity analysis was performed. Survival curves for all-cause mortality, cancer-related mortality, and CVD-related mortality stratified by TyG quartiles showed no significant between-group differences (all log-rank $P > 0.05$). Restricted cubic spline regression revealed no significant nonlinear associations (all nonlinearity $P > 0.05$), as shown in Figures S16–S18. Threshold effect analysis indicated that the effect estimates above and below the threshold were not statistically significant for all outcomes (all likelihood-ratio test $P > 0.05$), with no significant threshold effects observed, as presented in Table S15. In the fully adjusted multivariable Cox model, elevated TyG index remained significantly associated with a reduced risk of all-cause mortality (HR = 0.91, 95% CI: 0.87–0.95, $P < 0.001$). Compared with Q2, the highest TyG group (Q4) had a significantly lower risk of all-cause mortality (HR = 0.90, 95% CI: 0.88–0.92, $P < 0.001$), with a significant trend test ($P < 0.001$), consistent with the results before exclusion, confirming the robustness of the findings. The TyG index was not independently associated with cancer-related mortality (all $P > 0.05$), but was significantly positively associated with CVD-related mortality (HR = 0.89, 95% CI: 0.85–0.92, $P < 0.001$), which was opposite to the results before exclusion, as shown in Table S16.

Stratified analyses were performed according to age, sex, BMI, smoking status and alcohol consumption level. The results revealed that age (P for interaction = 0.013) and smoking status (P for interaction = 0.034) significantly modified the association between the TyG index and all-cause mortality. No statistically significant interactions were observed for sex, BMI and alcohol consumption (all $P > 0.05$). The protective effect of elevated TyG index was more pronounced in the subgroup aged ≥ 60 years, while the protective association between the TyG index and all-cause mortality was attenuated in the heavy smoking subgroup. The association between the TyG index and cancer-related mortality was significantly modified by multiple factors. Interaction analyses indicated significant interactions for age (P for interaction = 0.011), sex (P for interaction = 0.007) and BMI (P for interaction < 0.001). Specifically, the protective effect of the TyG index was stronger among individuals aged ≥ 60 years, females and those with BMI ≥ 30.0 kg/m², whereas this protective effect diminished in participants aged < 60 years, males and individuals with normal BMI. These findings suggest obvious population heterogeneity in the metabolic regulation of cancer-related mortality. The positive association between the TyG index and CVD-related mortality varied substantially across subgroups. Significant interactions were detected for sex (P for interaction < 0.001) and alcohol consumption status (P for interaction < 0.001). The elevated risk of CVD mortality

associated with high TyG levels was more prominent in females and alcohol drinkers, and the corresponding risk association was relatively weak in males and non-drinkers. Detailed results are presented in Table S17-S19.

4. Discussion

This large-sample cohort study of cancer survivors based on the NHANES 1999–2018 dataset demonstrates that the triglyceride-glucose index exhibits outcome-specific, threshold-dependent, and cancer-type-heterogeneous bidirectional prognostic value, and the results are robustly validated by multiple imputation, sensitivity analyses, and subgroup analyses. As a comprehensive non-invasive marker of insulin resistance, metabolic reserve, and chronic inflammation, the core mechanism of the TyG index lies in its simultaneous reflection of systemic energy storage status and metabolic inflammatory levels, thereby forming a unique bidirectional prognostic pattern in cancer survivors(11, 15). In the present cohort, a clear threshold of 8.39 was identified for the association between the TyG index and all-cause mortality. Below this threshold, an elevated TyG index indicates sufficient energy and nutritional reserves, which can mitigate frailty and muscle wasting and improve treatment tolerance(30). At or above this threshold, glucolipotoxicity, oxidative stress, and chronic inflammation become dominant, and the protective effect disappears(15, 31). This threshold represents the balance point between the benefits of metabolic reserve and the risks of metabolic damage. The TyG index also shows a threshold-dependent nonlinear association with cancer-specific mortality, with an inflection point at 8.24. Below this threshold, the TyG index improves host nutritional and immune function, alleviates cancer cachexia, and reduces mortality risk(32). Above this threshold, hyperinsulinemia activates the PI3K/Akt/mTOR pathway, enhances the tumor Warburg effect, and suppresses antitumor immunity, resulting in the loss of the protective effect(33, 34). This inflection point serves as a critical cutoff between host benefits and tumor progression risks. Regarding cardiometabolic mortality, the TyG index is stably and linearly positively associated with CVD-related mortality, as severe insulin resistance drives vascular inflammation, atherosclerosis, and myocardial injury with no protective interval(35). It presents a bidirectional threshold effect at 8.75 for diabetes-related mortality: below the threshold, it reflects reserve protection; above the threshold, it sharply exacerbates glucolipotoxicity and pancreatic β -cell failure, significantly increasing mortality risk(36). No independent association is observed between the TyG index and hypertension-related mortality, suggesting that its prognostic value is masked by strong confounding factors such as blood pressure control and target organ damage(37).

The prognostic value of the TyG index displays substantial heterogeneity across cancer types, determined by the degree of tumor metabolic dependence: skin cancer, a metabolism-insensitive and host-dominant tumor(38), shows bidirectional protective effects of the TyG index along with elevated cardiovascular risk; female reproductive system cancers, which are highly dependent on insulin/IGF-1 signaling(39), exhibit a bidirectional pattern of moderate protection at mild elevations and pro-tumor effects at excessive elevations; urinary and reproductive system cancers, driven mainly by gene mutations and non-metabolic pathways(40), show that the TyG index only predicts CVD risk without independent prognostic value for tumor outcomes.

Sensitivity analyses excluding participants who died within the first 2 years of follow-up confirm that the protective association between the TyG index and all-cause mortality remains robust, ruling out reverse causality bias. The association with cancer-specific mortality is attenuated, indicating a stronger impact of early events on this endpoint. The direction of the association with CVD-related mortality becomes stable, consistent with long-term metabolic risk patterns. Stratified analyses reveal that age, sex, BMI, smoking, and alcohol consumption significantly modify the associations of the TyG index with various mortality endpoints. The metabolic stratification value of the TyG index is more pronounced in vulnerable populations including the elderly, females, and individuals with high BMI, further supporting its application in precision management.

The strengths of this study include a large sample size, long follow-up duration, nationally representative data, rigorous missing value handling, and multi-model adjustment, ensuring reliable results. This study is also the first to systematically reveal the threshold effects and cancer-type heterogeneity of the TyG index in cancer survivors, with clear clinical translational value. The main limitations are its observational design, which precludes causal inference; lack of data on tumor stage, treatment regimens, and recurrence; and a predominantly American adult study population, warranting caution in extrapolation to other populations. Overall, the TyG index serves as a non-invasive, simple, and low-cost marker for metabolic risk stratification. Clinically, maintaining the TyG index within the optimal range of 8.24–8.39 is recommended for cancer survivors to reduce all-cause and cancer-specific mortality, while early interventions can lower cardiovascular and diabetes-related mortality, providing important evidence-based support for long-term clinical management.

5. Conclusions

In this study, the TyG index can be used as a simple, non-invasive, and low-cost marker for long-term prognostic evaluation and metabolic risk stratification in cancer survivors. Clinically, it is recommended to maintain the TyG index within the range of 8.24 to 8.39 to reduce the risks of all-cause and cancer-specific mortality. For individuals with elevated TyG index, early interventions including glucose-lowering, lipid-regulating, and insulin resistance-improving strategies should be implemented to reduce cardiometabolic-related mortality. This study provides reliable evidence-based support for precision metabolic management in cancer survivors.

Abbreviations

TyG	Triglyceride-Glucose Index
NHANES	National Health and Nutrition Examination Survey
CVD	Cardiovascular Disease
BMI	Body Mass Index
PIR	Poverty Income Ratio
DM	Diabetes Mellitus
MICE	Multivariate Imputation by Chained Equations
HR	Hazard Ratio
CI	Confidence Interval
ICD-10	International Classification of Diseases 10th Revision
STROCSS	Strengthening the Reporting of Cohort, Cross-Sectional and Case-Control Studies in Surgery
NCHS	National Center for Health Statistics
NDI	National Death Index
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
SE	Standard Error
KS	Kolmogorov-Smirnov
χ²	Chi-square

Declarations

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Author contributions

Baoyi Zou and Yanling Lin: Data curation, Formal analysis, Methodology, Validation. Haobo Huang: Conceptualization, Project administration. Yiqun Huang: Conceptualization, Validation, Resources. All authors contributed to manuscript drafting, approved the final manuscript, made substantial contributions to the study, and agreed to the submitted version of the manuscript.

Data availability statement

The datasets analyzed for this study can be found in the NHANES database (<https://wwwn.cdc.gov/nchs/nhanes/>).

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Figures

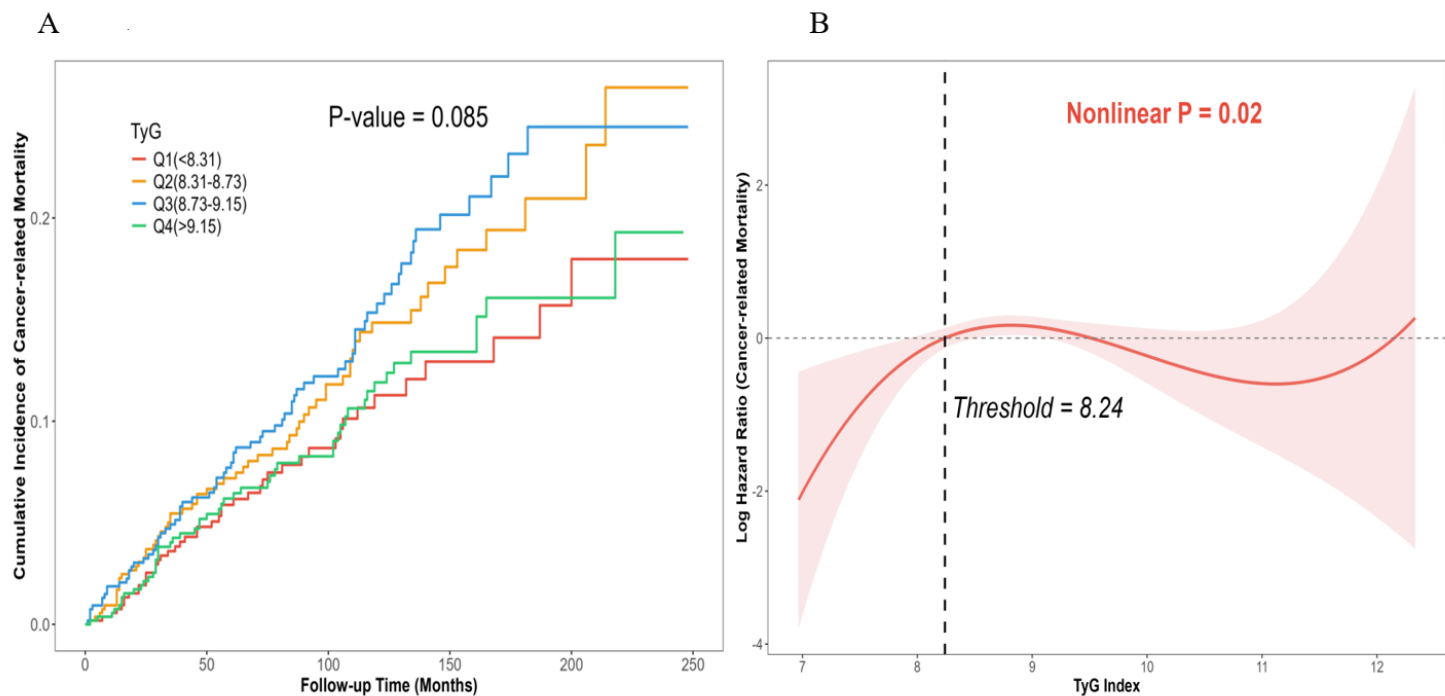


Figure 1

Cumulative incidence function of Cancer-related mortality categorized by different subgroups of TyG (A) and association between TyG and cancer-related mortality (B).

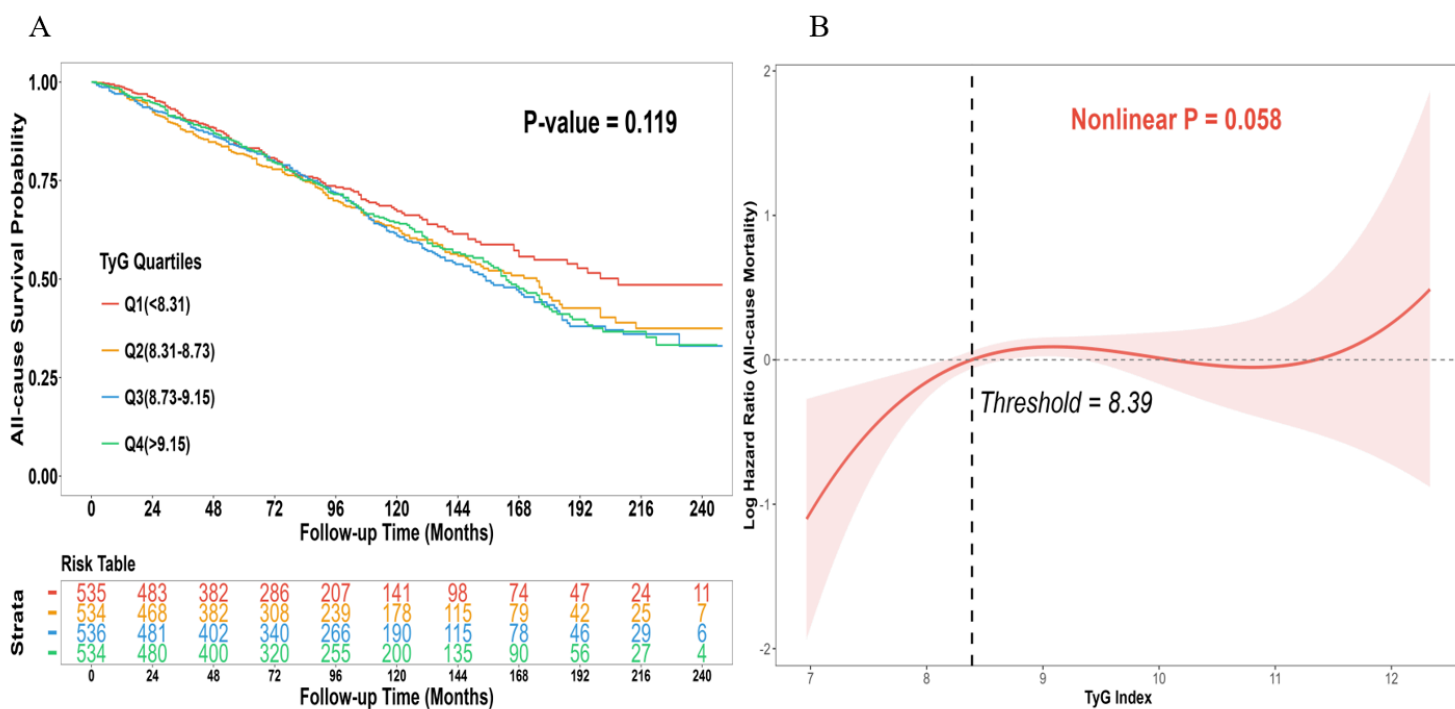


Figure 2

Kaplan-Meier curves of all-cause mortality stratified by TyG subgroups (A), and the nonlinear association and threshold effect of TyG on all-cause mortality (B).

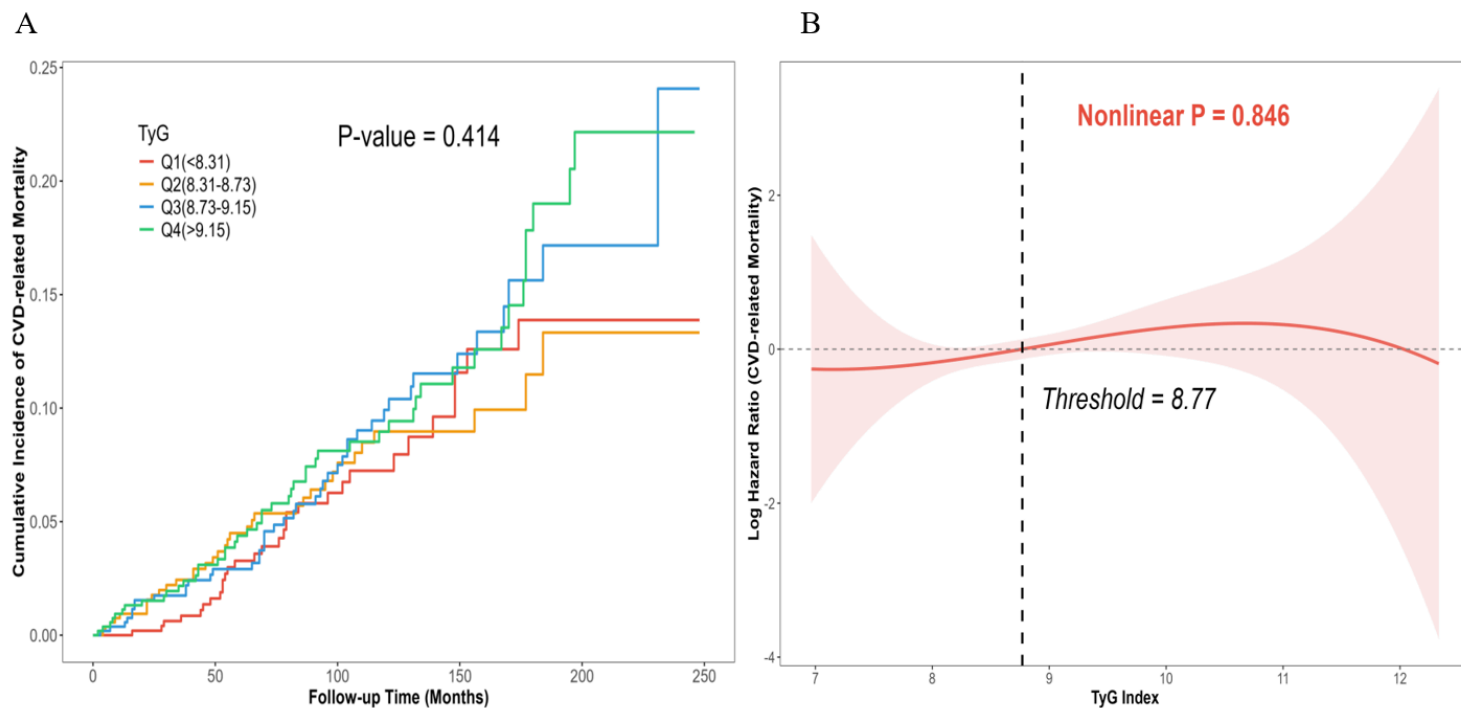


Figure 3

Cumulative incidence function of CVD-related mortality categorized by different subgroups of TyG (A) and association between TyG and CVD-related mortality (B).

Supplementary Files

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