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Association Between Triglyceride Glucose Index and All-Cause Mortality in the Psoriasis Patients

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Triglyceride glucose (TyG) index has been discovered to be significantly associated with a higher risk of mortality. However, the specific association between the TyG index and all-cause mortality in psoriasis patients remains unclear. Data of this study came from the National Health and Nutrition Examination Survey (NHANES). The weighted multivariable Cox regression models and restricted cubic spline (RCS) models were applied to assess the association between the TyG index as continuous variables and tertiles and the risk of mortality. Kaplan-Meier (KM) methods were used to plot survival curves to describe the survival of participants. Additionally, sensitivity and subgroup analyses were conducted to test the robustness of the results. Psoriasis participants who died had substantially higher TyG index than those survived (9.00 ± 0.68 vs. 8.64 ± 0.60, $P = 0.008$). Multivariable Cox regression showed that TyG index was positively associated to the risk of all-cause mortality (hazard ratios (HR) 1.78, 95% confidence intervals (CI): 1.13-2.81; $P = 0.012$) after fully adjustment. After converting TyG index from a continuous variable to a categorical variable by tertiles, the unadjusted, partly-adjusted and fully adjusted HR for risk of all-cause mortality were 3.96 (95% CI: 1.47-10.7; $P = 0.007$), 3.10 (95% CI: 1.20-7.99; $P = 0.019$) and 3.05 (95% CI: 1.14-8.16; $P = 0.027$) in participants in tertile 3 of TyG index, compared with tertile 1. The significance of the association persisted across sensitivity and subgroup analysis. The TyG index was positively correlated with the risk of all-cause mortality among psoriasis. These findings suggest that TyG index may be a promising predictor of all-cause mortality for the psoriasis patients during the long-term follow-up.

Keywords: all-cause mortality; psoriasis; triglyceride glucose index; US national survey
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Introduction

Psoriasis is a chronic inflammatory skin disease associated with immune system disorders and affects approximately 3.0% of the American adult population (Armstrong et al. 2021). Studies have shown that psoriasis patients have an increased risk of death, and this risk is related to an increased risk of cardiovascular disease and metabolic syndrome in psoriasis patients (Semenov et al. 2021; Palmer et al. 2023). Therefore, the early detection and prompt intervention of cardiovascular and metabolic abnormalities assume paramount importance in improving the prognosis of individuals grappling with psoriasis.

Triglyceride Glucose (TyG) index has emerged as an effective surrogate marker for insulin resistance (Fritz et al. 2020), showing associations with inflammation, endothelial dysfunction, and disorders in glucose and lipid metabolism, as well as thrombosis, etc (Xie et al. 2023b). Researches have underscore the positive association between the TyG index and the risk, adverse prognosis, and mortality associated with cardiovascular disease (Ding et al. 2021; Tian et al. 2021; Tao et al. 2023; Xie et al. 2023a), positioning it as a potentially valuable tool for timely detection of individuals with an elevated risk of cardiovascular events (Hong et al. 2020). Moreover, the TyG index has been also linked to various conditions, including diabetes and hypertension and

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sepsis and suicidal ideation (Pang et al. 2023; Zhao et al. 2023; Zheng et al. 2023; Lee et al. 2024). This diverse range of associations underscores the multifaceted utility of the TyG index as a comprehensive indicator reflecting not only cardiovascular risks but also its potential relevance in diverse health contexts.

Psoriasis patients was more likely to develop cardiovascular diseases; TyG index was positively associated with the risk of cardiovascular disease and mortality. Therefore, whether the TyG index is associated to the mortality of patients with psoriasis has not been reported in previous studies. Consequently, this study aimed to filling this void by exploring the correlation between the TyG index and all-cause mortality among patients with psoriasis. This investigation aims to establish a foundation for identifying and enhancing prognostic outcomes in patients grappling with psoriasis.

Materials and Methods

Study participants

The National Health and Nutrition Examination Survey (NHANES) is an extensive nationwide survey conducted biennially, employing a stratified, clustered, and multistage probability sampling approach. Its main purpose is to assess the health and nutritional status of the non-institutionalized civilian population in the United States. All NHANES initiatives received approval from the Ethics Review Committee of the National Center for Health Statistics (NCHS), and participants gave written consent upon enrollment. The NCHS has linked data collected from several NCHS population surveys with death certificate records from the National Death Index (NDI). All participants with sufficient identifying data were eligible for mortality follow-up. Any survey participant record that did not meet the minimum data requirements was ineligible for record linkage. For this study, data were extracted from four NHANES cycles spanning the years 2005-2006, 2009-2010, 2011-2012, and 2013-2014. Psoriasis was defined based on self-reported information. Exclusion criteria involved individuals under 20 years old or those with missing data on fasting glucose, fasting triglycerides, mortality status, or weight. The study ultimately included a total of 232 participants with psoriasis showed in Fig. 1.

Variables and outcomes

The TyG index was computed using the formula in [fasting triglycerides (mg/dL) * fasting glucose (mg/dL)/2]. Enzymatic measurements of fasting serum triglycerides and glucose were conducted using the Roche Modular P chemistry analyzer. Covariates, chosen with reference to rele-

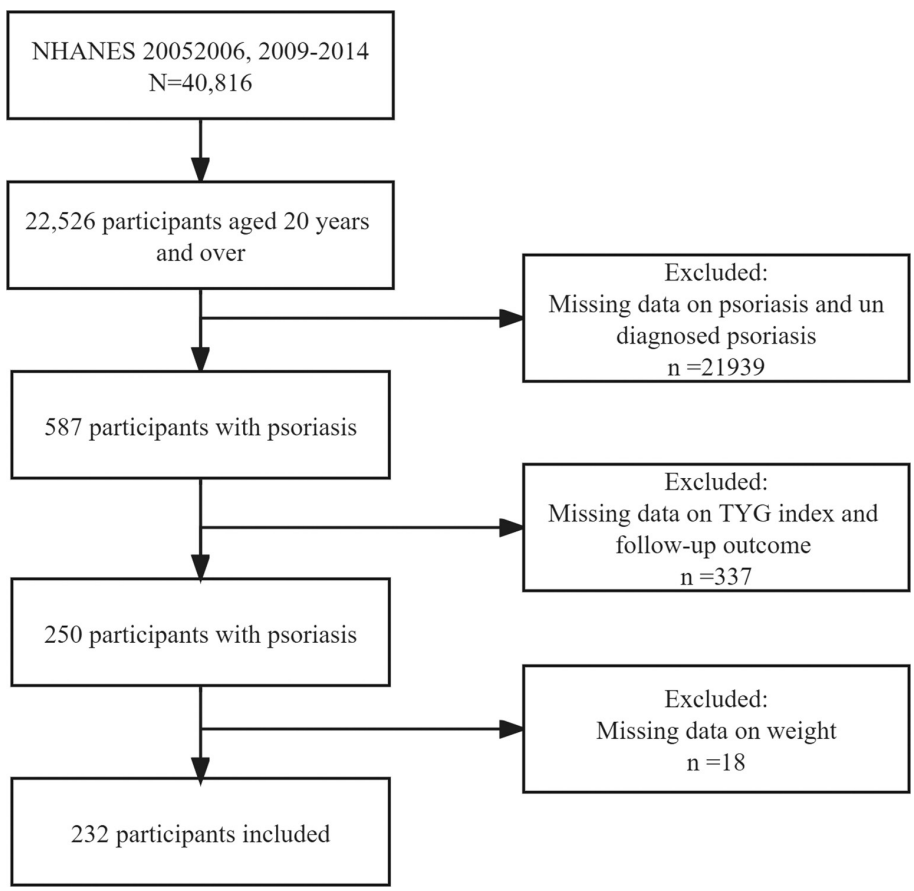

Fig. 1. Flowchart of the subjects included in this study.
TyG, triglyceride-glucose; NHANES, National Health and Nutrition Examination Survey.

vant literature, encompassed details regarding age, sex, race, education level, marital status, smoking, physical activity, diabetes, hypertension, cardiovascular disease, arthritis, hypoglycemic therapy and anti-hypertensive therapy, collected via standardized questionnaires, examination and laboratory data. The race was classified as two groups: non-Hispanic white and others. Education level was classified into two groups: high school and below and or college and above. Marital status featured two classifications: widowed or divorced or separated or never married and married or living with partner. Smoking, physical activity, diabetes, hypertension, cardiovascular disease, arthritis, hypoglycemic therapy and anti-hypertensive therapy were dichotomized as yes or no. A history of physician-diagnosed hypertension, a measured average systolic blood pressure of at least 140 mmHg, a measured average diastolic blood pressure of at least 90 mmHg, or a history of antihypertensive medication use were all considered indicators of hypertension. A self-reported diagnosis of diabetes, a fasting plasma glucose level ≥ 126 mg/dL, glycosylated hemoglobin (HbA1c) ≥ 6.5%, and/or the usage of insulin were all considered indicators of diabetes. A self-reported diagnosis of congestive heart failure, coronary heart disease, angina, or heart attack were considered an indicator of cardiovascular disease. A self-reported history of arthritis was considered an indicator of arthritis. A self-reported history of use of hypoglycemic or anti-hypertensive medicine was considered hypoglycemic or anti-hypertensive therapy. Mortality status was determined by linking to the NDI by December 31, 2019. The comprehensive inclusion of these variables ensures an exploration of potential confounding factors in the investigation of the TyG index and its association with all-cause mortality.

Statistical analysis

The data was presented either as mean ± standard deviation or as numerical values and corresponding proportions. To investigate variations in mortality status, the t-test and chi-square test were employed. The TyG index was categorized into tertiles for analysis. Kaplan-Meier (KM) methods were utilized to establish event rates during follow-up and to construct time-to-event curves. Differences among KM estimates between groups were evaluated through the log-rank test. To examine the nonlinear relationship between the TyG index and all-cause mortality, restricted cubic splines (RCS) with four knots were applied in both unadjusted and adjusted Cox regression models. Multivariable Cox regression models were utilized to assess the associations between the TyG index and the risk of all-cause mortality, presenting results as hazard ratios (HR) with corresponding 95% confidence intervals (CI). Model 1 remained unadjusted, while model 2 adjusted for age, sex, race, education, marital status, physical activity and smoking. Model 3 extended adjustments to include age, sex, race, education, marital status, physical activity, smoking, diabetes, hypertension, cardiovascular disease, arthritis, hypoglycemic therapy and anti-hypertensive therapy. Subgroup and interaction analyses were conducted based on age group, sex, race, education level, marital status, smoking, physical activity, diabetes, hypertension, cardiovascular disease and arthritis in the Cox regression models. Sensitivity analysis was executed to evaluate the robustness of the results. All psoriasis participants were divided into three groups based on tertile or quintile of TyG index respectively. The 1-2 and 3-4 quantiles were considered as a group, defined as Q1 and Q2 respectively, and the fifth quintile was defined as Q3. Sample weights, clustering, and stratification were integrated into all analysis. All analysis were carried out using R version 4.3.1. The threshold for statistical significance was set at a level of < 0.05 for all *P*-values.

Results

Baseline characteristics

Participant characteristics, stratified by mortality status, were delineated in Table 1. Over an average follow-up period of 111.9 ± 38.9 months, 12.9% of psoriasis participants experienced all-cause death. In weighted analysis, the mean age was 48.8 ± 15.8 years, and 44.54% of psoriasis participants were male. Dead psoriasis participants exhibited a notably higher TyG index than the surviving participants (9.00 ± 0.68 vs. 8.64 ± 0.60, $P = 0.003$).

KM and RCS results

The KM curve analysis displayed that the psoriasis patients with different TyG index levels had different survival rates (log-rank $P = 0.01$), elucidated in Fig. 2. In both unadjusted and adjusted models, RCS indicated an overall increasing trend in the hazard of all-cause mortality with higher TyG index, but no discernible nonlinear association was observed, as depicted in Fig. 3. These suggested that a linear dose-response relationship existed between TyG index and all-cause mortality (all P non-linearity > 0.05 and P overall < 0.05). Consequently, this study established tertile 1 as the reference group for subsequent analysis.

Multivariable Cox regressions results

The results of multivariable Cox regressions were presented in Table 2. These findings showed that a higher chance of all-cause mortality was connected with a higher TyG index. TyG index and all-cause mortality were found to be positively correlated in models 1, 2, and 3. Subjects with a higher TyG index had a 78% higher risk of all-cause mortality after full adjustment in model 3 (HR 1.78, 95% CI: 1.13-2.81; $P = 0.012$). After converting TyG index from a continuous variable to a categorical variable, the correlation remained statistically significant. The all-cause mortality in tertile 3 was 3.96 times (HR 3.96, 95% CI: 1.47-10.7; $P = 0.007$) higher than that in reference tertile 1 in model 1, and 3.10 times (HR 3.10, 95% CI: 1.20-7.99; $P = 0.019$) in model 2, and 3.05 times (HR 3.05, 95% CI: 1.14-8.16.1; $P = 0.027$) in model 3. Compared to Q1, the

Table1. The characteristics of participants by mortality status.

Characteristics	Overall, N = 232[1]	Mortality status		*P value*[2]
		Survival, N = 202[1]	Death, N = 30[1]	
Age (years), mean±sd	48.8 ± 15.8	47.1 ± 15.1	63.5 ± 14.0	< 0.001
Sex, n (%)				0.454
Male	108 (44.54%)	93 (43.71%)	15 (51.55%)	
Female	124 (55.46%)	109(56.29%)	15 (48.45%)	
Race, n (%)				0.762
Non-Hispanic White	137(78.83%)	115 (79.13%)	22 (76.32%)	
Others	95 (21.17%)	87 (20.87%)	8 (23.68%)	
Education level, n (%)				0.1
High school and below	101 (35.80%)	85 (33.65%)	16 (53.91%)	
College and above	131 (64.20%)	117 (66.35%)	14 (46.09%)	
Marital status, n (%)				0.169
Widowed/Divorced/Separated/Never married	143 (63.97%)	127 (65.54%)	16 (50.76%)	
Married/Living with partner	89 (36.03%)	75 (34.46%)	14 (49.24%)	
Physical activity, n (%)				0.511
No	107 (44.25%)	89 (43.47%)	18 (50.88%)	
Yes	125 (55.75%)	113 (56.53%)	12 (49.12%)	
Smoking, n (%)				0.354
No	106 (44.81%)	101 (47.25%)	5 (24.25%)	
Yes	126 (55.19%)	101 (52.75%)	25 (75.75%)	
Diabetes, n (%)				0.009
No	189 (87.63%)	169 (89.92%)	20 (68.31%)	
Yes	43 (12.37%)	33 (10.08%)	10 (31.69%)	
Hypertension, n (%)				0.015
No	111 (52.27%)	106 (55.70%)	5 (23.27%)	
Yes	121 (47.73%)	96 (44.30%)	25 (76.73%)	
Cardiovascular disease, n (%)				< 0.001
No	202 (88.68%)	185 (92.42%)	17 (57.11%)	
Yes	30 (11.32%)	17 (7.58%)	13 (42.89%)	
Arthritis, n (%)				0.042
No	124 (55.78%)	116 (58.54%)	8 (32.48%)	
Yes	108 (44.22%)	86 (41.46%)	22 (67.52%)	
Hypoglycemic therapy, n (%)				0.002
No	200 (91.01%)	179 (93.45%)	21 (70.43%)	
Yes	31 (8.99%)	22 (6.55%)	9 (29.57%)	
Anti-hypertensive therapy, n (%)				0.002
No	132 (60.67%)	126 (64.85%)	6 (25.47%)	
Yes	100 (39.33%)	76 (35.15%)	24 (74.53%)	
Follow-up time (months), mean ± sd	111.9 ± 38.9	116.5 ± 36.3	72.9 ± 39.4	< 0.001
Fasting blood glucose (mg/dL), mean ± sd	107.05 ± 33.86	103.81 ± 28.28	134.38 ± 57.70	0.018
Triglyceride (mg/dL), mean ± sd	137.43 ± 147.26	136.56 ± 153.74	144.73 ± 73.93	0.67
TyG index, mean ± sd	8.68 ± 0.62	8.64 ± 0.60	9.00 ± 0.68	0.008

TyG index, triglyceride-glucose index. Data are presented as mean ± standard deviation or number (percentage). [1]N not Missing (unweighted); [2]Sample weight correction recommended by NHANES was used for data analysis.

Q3 of TyG index continued to exhibit a significant association with an increased risk of all-cause mortality in model 1 (HR 4.58, 95% CI 1.77-11.80, P = 0.002), model 2 (HR 3.44, 95% CI 1.42-8.32, P = 0.006), and model 3 (HR 3.34, 95% CI 1.30-8.63, P = 0.013). This robust consistency across various models further underscored the reliability of the association between a higher TyG index and a greater likelihood of experiencing all-cause mortality.

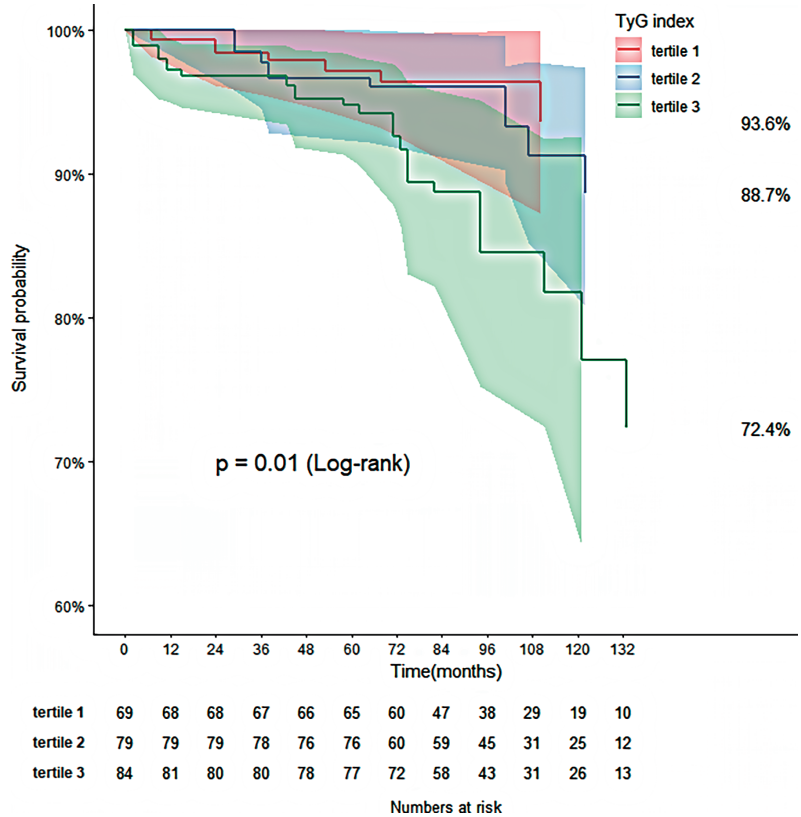

Fig. 2. The Kaplan-Meier analysis of the prognostic effect of TyG index on all-cause mortality.
The TyG index was categorized into tertiles for analysis. the psoriasis patients with diferent TyG index levels had diferent survival rates. TyG, triglyceride-glucose.

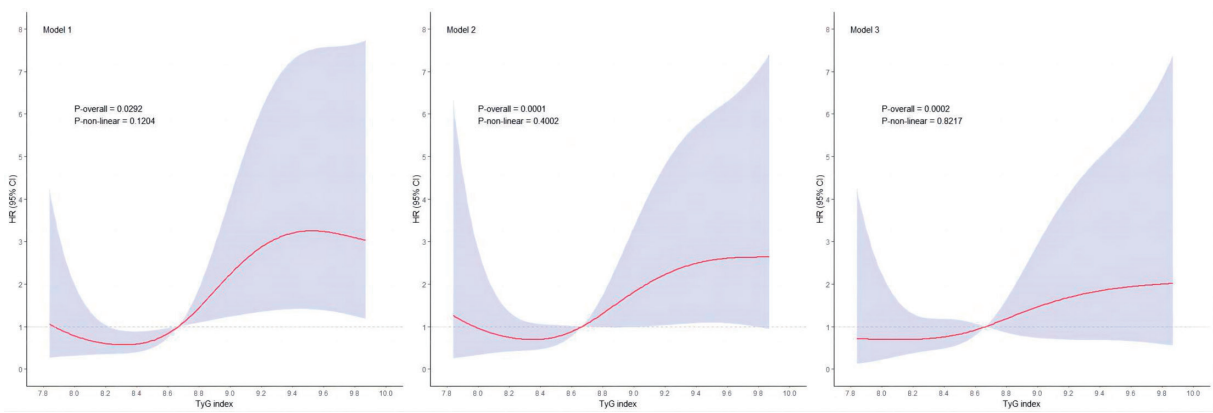

Fig. 3. The restricted cubic splines between TyG index with all-cause mortality.
TyG, triglyceride-glucose; HR, hazard ratio. Model 1: not adjusted; Model 2 adjusted for age, sex, race, education, marital status, physical activity and smoking; Model 3 adjusted for age, sex, race, education, marital status, physical activity, smoking, diabetes, hypertension, cardiovascular disease, arthritis, hypoglycemic therapy and anti-hypertensive therapy. The solid red line indicates the HR of all-cause mortality relative to TyG index, with purple indicating the 95% confidence interval (95% CI).

Subgroup analyses results

The findings from the subgroup analyses were presented through a forest plot in Fig. 4. The association did not garner support from subgroup analysis stratified by age group, marital status, physical activity, diabetes and hypertension. Additionally, there were no significant interactions observed between the TyG index and age group, sex, race, education level, marital status, smoking, physical activity, diabetes, hypertension, cardiovascular disease and arthritis (all P for interaction > 0.05), emphasizing the consistency of the association across diverse demographic and lifestyle subgroups.

Table 2. Association of TyG index with all-cause mortality.

TyG index	Model 1		Model 2		Model 3	
	HR (95%CI)	*P value*	HR (95%CI)	*P value*	HR (95%CI)	*P value*
Continuous	1.84 (1.09, 3.12)	0.023	1.87 (1.03, 3.39)	0.040	1.78 (1.13, 2.81)	0.012
Categorical						
Tertile1	Reference		Reference		Reference	
Tertile2	1.54 (0.42, 5.62)	0.516	1.66 (0.42, 6.57)	0.802	2.48 (0.59, 10.5)	0.218
Tertile3	3.96 (1.47, 10.7)	0.007	3.10 (1.20, 7.99)	0.019	3.05 (1.14, 8.16)	0.027
P for trend		0.007		0.019		0.027
Q1	Reference		Reference		Reference	
Q2	1.80 (0.53, 6.09)	0.341	2.22 (0.72, 6.88)	0.166	2.38 (0.60, 9.42)	0.217
Q3	4.58 (1.77, 11.80)	0.002	3.44 (1.42, 8.32)	0.006	3.34 (1.30, 8.62)	0.013
P for trend		0.002		0.006		0.013

TyG, triglyceride-glucose; HR, hazard ratio; CI, confidence interval. In sensitivity analysis, TyG index was converted from a continuous variable to a categorical variable. All psoriasis participants were divided into three groups based on tertile and quintile of TyG index respectively. The 1-2 and 3-4 quantiles were considered as a group, defined as Q1 and Q2 respectively, and the fifth quintile was defined as Q3. Model 1: not adjusted; Model 2 adjusted for age, sex, race, education, marital status, physical activity and smoking; Model 3 adjusted for age, sex, race, education, marital status, physical activity, smoking, diabetes, hypertension, cardiovascular disease, arthritis, hypoglycemic therapy and anti-hypertensive therapy.

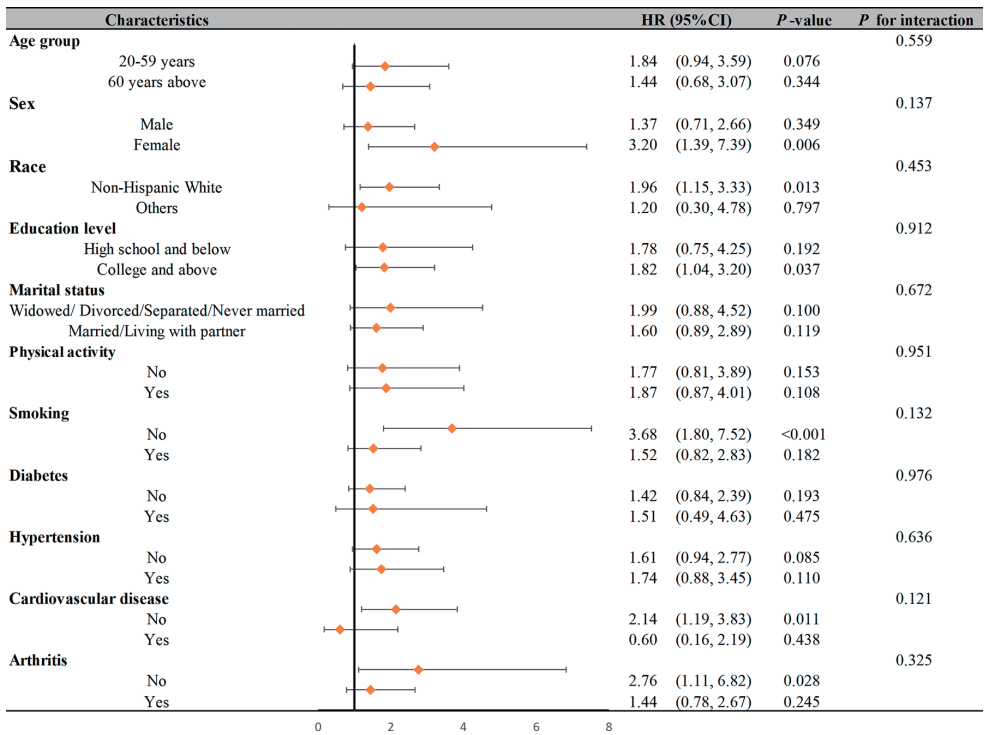

Fig. 4. Subgroup analysis for the association of TyG index with all-cause mortality.
The model adjusted for age, sex, race, education, marital status, physical activity, smoking, diabetes, hypertension, cardiovascular disease, arthritis, hypoglycemic therapy and antihypertensive therapy in all subgroups, with the exception of the stratification variable. TyG, triglyceride-glucose; HR, hazard ratio; CI, confidence interval.

Discussion

This study has unveiled the positively association between the TyG index and all-cause mortality among participants with psoriasis. This positive association was consistently evident in both subgroup and sensitivity analysis, underscoring the robustness of this finding. Furthermore, these findings reveal that the psoriasis participants along with those who faced mortality outcomes, collectively display heightened levels of fasting glucose and uncontrollable cardiovascular risk factors, particularly advanced age. Collectively, these results strongly indicate that the TyG

index holds promise as a predictor and a reference value for all-cause mortality in patients with psoriasis during long-term follow-up. The potential implications of this insight are substantial, as it could has the potential to substantially enhance the prognosis for patients with psoriasis.

The TyG index is computed using fasting triglycerides and fasting glucose. Prolonged hyperglycemia is predisposed to trigger microvascular alterations, impede normal immune system function, escalate inflammatory responses, and contribute to the development of atherosclerosis and arteriosclerosis (Genito et al. 2023; Liontos et al. 2023; Sheng et al. 2023; Li et al. 2024). Hypertriglyceridemia, in addition to influencing the aforementioned outcomes, is intricately associated with acute pancreatitis, metabolic syndrome, nonalcoholic fatty liver disease and other conditions (Egea et al. 2023; Malick et al. 2023; Zakaria et al. 2023). These factors are implicated in the initiation of diverse chronic diseases and all-cause mortality. This index goes beyond merely reflecting insulin resistance. It functions as a comprehensive biomarker with the capacity to encompass information related to various physiological procedure, including insulin susceptibility, inflammation, and glucose and lipid metabolism (Li et al. 2023). Functioning as a convenient yet thorough measuring tool, it provides a more holistic perspective for comprehending the body's internal metabolic status. Analyzing the dynamic changes in the TyG index enables us to obtain a more comprehensive understanding of the progression of insulin resistance and associated metabolic abnormalities, offering profound insights for early disease prediction and intervention. Numerous studies have consistently highlighted the TyG index's positive correlation with predicting the susceptibility to morbidity and mortality in chronic conditions such as cardiovascular disease and hypertension and Alzheimer's disease (Sun et al. 2023; Tian et al. 2023; Xiao et al. 2023). Hence, in this investigation, the TyG index was deliberately chosen as a predictive tool to assess the risk of all-cause mortality among individuals with psoriasis.

As anticipated, these findings reveal a positive association between the TyG index and all-cause mortality in psoriasis participants, even after the adjustment for covariates. The association was robust, but the mechanisms behind this association are not fully understood. Psoriasis, characterized by immune-mediated origins and systemic inflammation, primarily presents itself through skin and joint lesions. Intriguingly, its intricacies extend beyond dermatological concerns, intertwining with an elevated risk of cardiovascular disease and metabolic syndrome (Hu and Lan 2017; Rodriguez-Zuniga and Garcia-Perdomo 2017; Piaserico et al. 2022; Liu et al. 2023; Svedbom and Stahle 2023). Research indicates that the elevated risk of mortality in patients with psoriasis is, in part, attributable to the heightened prevalence of cardiovascular disease among this patient population (Terui and Asano 2023). Central to this inter connectedness is inflammation, serving as the linchpin in forging these associations. The mechanism of psoriasis is intricately associated with the dysregulation of diverse immune cells, including macrophages and lymphocytes, coupled with the release of pro-inflammatory factors such as tumor necrosis factor (TNF)-α, interleukin (IL)-17, IL-23 and IL-1β (Schon et al. 2021; Reali and Ferrari 2023). Analogous processes unfold in cardiovascular disease and metabolic syndrome. Sustained vascular inflammation profoundly influences the intricate phases of atherosclerotic plaque development. The impairment of vascular endothelial cells initiates monocyte migration into the vascular wall, setting off a series of events that involve the release of various pro-inflammatory mediators, including cytokines and chemokines. This, in turn, instigates a bidirectional activation of endothelial cells and inflammatory cells, fostering the formation of atherosclerotic plaques and, consequently, plays a role in the initiation of cardiovascular disease (Kang 2023; Wieland et al. 2024). The parallels in these inflammatory processes underscore the intricate nexus between psoriasis, cardiovascular health, and metabolic syndrome. Therefore, this association is likely attributable to the systemic inflammatory response induced by psoriasis, resulting in insulin resistance and thereby elevating the risk of all-cause mortality. This novel insight underscores the significance of the TyG index as a valuable prognostic indicator in the context of psoriasis-related mortality, shedding light on the intricate interplay between inflammation, insulin resistance, and overall health outcomes in individuals grappling with psoriasis. Nonetheless, there was no difference of the association among subgroups. This phenomenon could be attributed to the multifaceted impact of mortality-related factors on psoriasis participants, suggesting that the risk of all-cause mortality is influenced by various factors beyond just an elevated TyG index.

This study boasts several notable strengths. Firstly, it specified the positive correlation between the TyG index and all-cause mortality among psoriasis patients. This study furnishes compelling evidence, substantiating the prognostic value of the TyG index in predicting adverse outcomes in individuals with psoriasis. Secondly, the data utilized in this research derives entirely from four cycles in the NHANES. NHANES systematically collects health, nutritional, and sociological data from a broad spectrum of the United States population, endowing the study with extensive information coverage, a formidable sample size, and representative demographics. Thirdly, efforts were undertaken to fortify the robustness of the study's findings. Covariate effects were adjusted, and the incorporation of subgroup analysis and sensitivity analysis further fortify the reliability and validity of the results.

However, certain limitations exist that could impact the interpretation of these findings. Firstly, data on participants' fasting triglyceride and glucose levels were obtained only once during the survey, lacking continuous information throughout the extended follow-up. Secondly, the diagnosis of psoriasis relied on self-reported information from the questionnaire, introducing the potential for recall

bias. Thirdly, this study was observational in nature and unable to draw causal inferences from the findings.

Conclusions

Even after accounting for covariates, the TyG index continued to exhibit a positive association with the risk of all-cause mortality in psoriasis participants. From a clinical perspective, the TyG index stands out as a straight forward, easily obtainable, and reliable metric. Its simplicity positions it as a valuable tool for early vigilance against the risk of all-cause mortality and improvement outcomes in psoriasis patients. Incorporating the TyG index into clinical assessments has the potential to optimize blood glucose and lipid levels among patients with psoriasis aiming to mitigate the risk of mortality within this patient cohort.

Author Contributions

Yanqian Su and Huijuan Shi proposed the conceptualization and designed the study. YS was a major contributor in writing the manuscript. Yanqian Su, Huijuan Shi, Xuan Li, Jue Tang, Siqi Zhao and Jing Wang collected, analyzed and interpreted the data. Yanling He critically reviewed, edited and approved the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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