Original Paper

The Glucose-to-leukocyte Ratio (GLR) is a Predictor for Malignant and All-cause Mortality in Malignancy Patients: Evidence from NHANES 1999-2018

Panguo Wang[1] & Yong Chen[1*]

[1] Hepatobiliary Surgery, The First Affiliated Hospital of Chongqing Medical University, Medical College Street, Yuzhong District, 404100, Chongqing, China

[*] Corresponding author, E-mail: Chenyong61@126.com

Abstract

Background: The glucose-to-leukocyte ratio (GLR), a marker of glucose metabolism and systemic inflammation, is linked to poor prognoses in various diseases. However, the association between GLR and mortality in cancer patients remains unclear. This study aim to investigate the relationship between GLR index and all-cause and malignant mortality in cancer patients.

Methods: A total of 2,186 cancer patients (except for hematological neoplasms) were enrolled from the National Health and Nutrition Examination Survey (1999-2018). Mortality outcomes were assessed by linking to National Death Index (NDI) records until December 31, 2019. Kaplan-Meier analysis, LogRank tests, and weighted multivariate logistic regression were conducted to examine the association between GLR and mortality in these patients. Additionally, restricted cubic splines (RCS) were used to explore non-linear relationships, and a two-piecewise Cox proportional hazards model was constructed around the inflection points.

Results: Restricted cubic splines revealed a U-shaped relationship between the GLR index and both all-cause and malignant mortality in cancer patients. Kaplan-Meier survival analysis indicated that patients with low GLR had significantly better overall survival than those with high GLR (P < 0.05). Specifically, a baseline GLR index below threshold values (GLR < 2.95 for all-cause and < 2.97 for malignant mortality) was associated with reduced mortality (HR: 0.72, 95% CI: 0.52–0.99 for all-cause; HR: 0.40, 95% CI: 0.24–0.67 for malignant). Conversely, a baseline GLR index above the thresholds (GLR ≥ 2.95 for all-cause and ≥ 2.97 for malignant) correlated with increased risk (HR: 1.06, 95% CI: 1.03–1.09 for all-cause; HR: 1.08, 95% CI: 1.02–1.14 for malignant).

Conclusion: *A U-shaped association was found between the baseline GLR index and both malignant and all-cause mortality in American cancer patients, with both excessively high and low levels potentially leading to negative health outcomes.*

1. Introduction

Despite advancements in detection and therapeutic interventions, malignancy persists as a major global public health crisis. In the United States alone, more than 2.0 million new cancer cases would be diagnosed in 2024, with over 600,000 estimated deaths [1]. It was predicted that between 2.2 and 3.0 million cases were diagnosed per year by 2050 [2]. Potentially modifiable risk factors contribute significantly to both the incidence of cancer and overall cancer mortality, including cigarette and second-hand smoking, excess body weight, alcohol consumption, dietary factors associated with cancer risk, physical inactivity, ultraviolet radiation, and infections [1]. Infections and chronic inflammatory conditions contribute to roughly one-quarter of etiological factors associated with carcinogenesis [3].

Furthermore, several evidence indicated that inflammation-related factors play a crucial role in prognosis of cancer. The systemic immune-inflammation index (SII) [4], the neutrophil-to-lymphocyte ratio (NLR) [5], and the nutrition risk index (NRI) [6] have been recognized as significant prognostic indicators in cancer patients. Metabolic derangements linked to hyperglycemia and diabetes contribute to oncogenesis. Furthermore, lymphocytes, which are pivotal components of the systemic inflammatory response, are integral to cell-mediated antitumor immunity. The glucose-to-leukocyte ratio (GLR) serves as an indicator of both systemic inflammation levels and serum glucose status in patients. GLR has been reported as an excellent prognostic marker in several cancer, including pancreatic cancer [7] and gallbladder cancer [8]. It was found that the risk of mortality significantly increased with rising GLR values in unresected pancreatic cancer. Additionally, higher GLR values were significantly associated with disease-free survival in resected gallbladder cancer.

Nevertheless, research on the relationship between GLR and all-cause mortality in cancer patients remains limited. As we know, both hyperglycemia and hypoglycemia are significantly linked to poor prognosis in these patients. We hypothesize that the relationship between the GLR index and prognosis is non-linear, making a simple division into high and low groups inadequate for accurate prediction. Therefore, this study aims to examine the association between the GLR index and both all-cause and cancer-specific mortality in cancer patients.

2. Methods

2.1 Population

Data were extracted from the National Health and Nutrition Examination Survey (NHANES) database covering the period from 1999 to 2018. NHANES is a nationally representative, ongoing survey

conducted by the U.S. Centers for Disease Control and Prevention (CDC) to assess the health and nutritional status of the American population. All NHANES protocols received approval from the National Center for Health Statistics (NCHS) ethics review board, and written informed consent was obtained from all participants. To ascertain the survival status of the participants, we linked the NHANES data with the National Death Index (NDI) managed by the NCHS. Using these linked data, we constructed a longitudinal follow-up cohort. The NCHS Ethics Review Board approved the study protocol. Eligible participants with diabetes aged 18 years and older were enrolled. Those without complete survival or laboratory test information, as well as pregnant individuals, were excluded from the study.

2.2 Definition of Glucose-to-leukocyte Ratio (GLR) and Malignancy

The GLR index was calculated by GLR index = Plasma Fasting Glucose (mmol/L) / Lymphocyte number (1000 cells/uL). Complete blood count measurements were conducted following the Beckman Coulter methodology. Fasting glucose concentrations were assessed using enzymatic assays on Roche Cobas 6000 analyzers. The presence of malignancy was determined using the questionnaire item, " Ever told you had cancer or malignancy?" A definitive "yes" response was used to indicate the presence of cancer or malignancy.

2.3 Definition of Mortality

Mortality information was obtained from the National Death Index (NDI) database (https://www.cdc.gov/nchs/data-linkage/mortality-public.htm), which is maintained by the Centers for Disease Control and Prevention (CDC). The follow-up period for each participant was determined from the time of enrollment until the date of death or until December 31, 2019, the most recent update date of the NDI database. Disease-specific deaths were classified using the International Statistical Classification of Diseases, 10th Revision (ICD-10). The National Center for Health Statistics (NCHS) categorized heart diseases (I00-I09, I20-I51), malignant neoplasms (C00-C97), and all other causes according to the relevant ICD-10 codes for the purposes of this study [9].

2.4 Covariates

The following covariates were included in the analysis: age, sex (Male/Female), race/ethnicity (Mexican American, Non-Hispanic Black, Non-Hispanic White, Other Hispanic, and other races), education level (Less than 9th grade, 9-11th grade, High school graduate, Some college, and College graduate or above), ratio of family income to poverty, cigarette smoking status, diabetes status (yes, no, borderline), and hypertension status. Cigarette smoking status was defined as having smoked at least 100 cigarettes in one's lifetime [10]. Diabetes and hypertension statuses were identified based on self-reported diagnoses from healthcare professionals.

2.5 Statistical Analyses

Statistical analyses were conducted using R software (version 4.4.1; https://www.r-project.org/). During the analysis, sample weights, clustering, and stratification were applied consistent with the NHANES analytic and reporting guidelines [11]. The sampling weight was adjusted as follows: The

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full sample 2-year interview weight was normalized by dividing by 10. Continuous variables were summarized as means and standard deviations (SD), whereas categorical variables were presented as frequencies and percentages. Comparisons of baseline characteristics among GLR groups were conducted using one-way ANOVA for continuous variables and the Pearson chi-square test for categorical variables. Incidence rates of all-cause mortality and cancer-specific mortality were computed for each GLR group throughout the entire follow-up period. Study participants were divided into four groups based on quartiles (Q1-Q4) of the GLR index. Subsequently, weighted multivariate Cox regression analysis was employed to assess the independent predictive value of the GLR index, adjusting for age, gender, race, educational level, ratio of family income to poverty threshold, cigarette smoking status, diabetes status, and hypertension status. Covariates with missing values were adjusted by multiple imputation. Kaplan-Meier analysis and Log-rank tests were performed to estimate the probabilities of survival outcomes. A restricted cubic spline (RCS) model with four knots was utilized to illustrate the potentially nonlinear relationship between the GLR and both all-cause mortality and cancer-specific mortality in patients with cancer. And we use two-piecewise Cox proportional risk model on both sides of the inflection point to investigate the association between GLR index and the risk of all-cause mortality and malignant mortality. Subgroups analysis were conducted by weighted multivariate Cox regression analysis based on age (≤ 60 years old and > 60 years old), gender (male and female), hypertension (yes and no), diabetes (yes, no), and smoke status (yes and no). $P < 0.05$ was considered to indicate statistical significance.

3. Results

3.1 Population Baseline

Between 1999 and 2017, a cohort of 2186 malignant patients were analyzed for demographic characteristics (Table 1). Participants were divided into four groups based on quartiles (Q1-Q4) of the GLR index. Participants with a higher GLR index were more likely to be older, male, non-Hispanic white, and have hypertension, and diabetes, compared with patients in Q1.

Table 1. Baseline Characteristics of the Patients in the Model

Characteristics	Q1 N=545	Q2 N=548	Q3 N=546	Q4 N=547	P value
Sex:					**<0.001**
Female	355 (65.1%)	340 (62.0%)	258 (47.3%)	224 (41.0%)	
Male	190 (34.9%)	208 (38.0%)	288 (52.7%)	323 (59.0%)	
Age					**<0.001**
<60	257 (47.2%)	192 (35.0%)	117 (21.4%)	83 (15.2%)	
≥60	288 (52.8%)	356 (65.0%)	429 (78.6%)	464 (84.8%)	

Race/ ethnicity				**0.033**
MA	44 (8.07%)	42 (7.66%)	41 (7.51%)	39 (7.13%)
NHB	35 (6.42%)	27 (4.93%)	33 (6.04%)	19 (3.47%)
NHW	349 (64.0%)	384 (70.1%)	394 (72.2%)	404 (73.9%)
Other Hispanic	87 (16.0%)	66 (12.0%)	63 (11.5%)	60 (11.0%)
Other races	30 (5.50%)	29 (5.29%)	15 (2.75%)	25 (4.57%)
Education level				**<0.001**
< 9th grade	43 (7.89%)	63 (11.5%)	54 (9.89%)	62 (11.3%)
9-11th grade	88 (16.1%)	56 (10.2%)	68 (12.5%)	63 (11.5%)
HSG	125 (22.9%)	127 (23.2%)	144 (26.4%)	132 (24.1%)
Some college	183 (33.6%)	157 (28.6%)	147 (26.9%)	128 (23.4%)
CG or above	106 (19.4%)	145 (26.5%)	133 (24.4%)	162 (29.6%)
PIR				0.068
0 < PIR ≤ 1.5	179 (32.8%)	162 (29.6%)	140 (25.6%)	144 (26.3%)
1.5 < PIR ≤ 3.0	151 (27.7%)	137 (25.0%)	169 (31.0%)	167 (30.5%)
3.0 < PIR ≤ 4.5	91 (16.7%)	100 (18.2%)	89 (16.3%)	106 (19.4%)
≥ 4.5	124 (22.8%)	149 (27.2%)	148 (27.1%)	130 (23.8%)
Hypertension				**<0.001**
Yes	272 (49.9%)	292 (53.3%)	311 (57.0%)	358 (65.4%)
No	273 (50.1%)	256 (46.7%)	235 (43.0%)	189 (34.6%)
Diabetes				**<0.001**
Yes	66 (12.1%)	59 (10.8%)	99 (18.1%)	195 (35.6%)
No	467 (85.7%)	468 (85.4%)	428 (78.4%)	330 (60.3%)
Borderline	12 (2.20%)	21 (3.83%)	19 (3.48%)	22 (4.02%)
Smoking				0.518
Yes	313 (57.4%)	290 (52.9%)	299 (54.8%)	301 (55.0%)
No	232 (42.6%)	258 (47.1%)	247 (45.2%)	246 (45.0%)

Date are presented as n (%); Abbreviations: MA, Mexican American; NHB, non-Hispanic black; NHW, non-Hispanic white, HSG: High school graduate, CG: College graduate

3.2 Association GLR with All-cause and Malignant Mortality

Over a median follow-up period of 91 months (interquartile range [IQR], 55.5–131.0 months), 782 deaths were observed among the 2,186 patients with malignancies (35.8%). Of these, 237 deaths (10.8%) were cancer-related, and 545 deaths (24.9%) were due to non-cancer causes. In the unadjusted model (Crude Model), we observed that the risk of both all-cause and malignant and non-malignant mortality significantly increased with rising GLR values (all-cause mortality: HR = 1.06, 95% CI: 1.03-1.09; malignant mortality: HR = 1.06, 95% CI: 1.02-1.11; non-malignant mortality: HR = 1.06,

95% CI: 1.03-1.10). In the crude model, the risk of all-cause mortality was 2.54 times higher in the Q4 group compared to the Q1 group (HR = 2.54, 95% CI: 1.91-3.38). Additionally, the risks of cancer-specific mortality and non-cancer-specific mortality were 2.31 times and 2.82 times higher, respectively, in the Q4 group compared to the Q1 group (cancer-specific mortality: HR = 2.31, 95% CI: 1.55-3.45; non-cancer-specific mortality: HR = 2.82, 95% CI: 1.97-4.05). In Model 1, after adjusting for covariates including age, sex, race/ethnicity, education level, ratio of family income to poverty, cigarette smoking status, diabetes status, and hypertension status, each one-unit increase in the GLR value was associated with a 6% increased risk of all-cause mortality (HR = 1.06, 95% CI: 1.03-1.09), a 7% increased risk of cancer-specific mortality (HR = 1.07, 95% CI: 1.03-1.13), and a 6% increased risk of non-cancer-specific mortality (HR = 1.06, 95% CI: 1.02-1.09), respectively. In Model 1, which was adjusted for all covariates, the HR were 1.43, 1.54, and 1.40 of all-cause, malignant-, and non-malignant mortality, respectively, (all cause: HR = 1.43, 95% CI: 1.10-1.87; malignant: HR = 1. 54, 95%CI: 0.98-2.43; non-malignant: HR = 1.40, 95%CI: 1.01-1.94), indicating a significant association with the risk of mortality (Q4 group compared to Q1 group) (Table 2). Kaplan-Meier survival analysis revealed that the survival rates were significantly lower in the Q4 group compared to the Q1 group within all-cause, malignant, and non-malignant cohorts, respectively (all p < 0.001) (Fig 1).

Table 2. The Relationships between GLR and Mortality in Cancer by Weighted Multivariate Cox Regression

Characteristics	Crude Model		Model 1	
	HR(95%CI)	*P*-value	HR(95%CI)	*P*-value
All-cause mortality				
GLR	1.06 (1.03-1.09)	**< 0.001**	1.06 (1.03-1.09)	**< 0.001**
GLR category				
Q1	Reference		Reference	
Q2	0.98 (0.73-1.32)	0.903	0.80 (0.61-1.04)	0.096
Q3	1.40 (1.05-1.86)	**0.021**	0.91 (0.69-1.19)	0.477
Q4	2.54 (1.91-3.38)	**< 0.001**	1.43 (1.10-1.87)	**0.008**
Malignant mortality				
GLR	1.06 (1.02-1.11)	**< 0.001**	1.07 (1.03-1.13)	**< 0.001**
GLR category				
Q1	Reference		Reference	
Q2	0.69 (0.42-1.13)	0.142	0.56 (0.35-0.87)	**0.010**
Q3	1.08 (0.69-1.68)	0.730	0.75 (0.49-1.16)	0.196
Q4	2.31 (1.55-3.45)	**< 0.001**	1.54 (0.98-2.43)	0.061
Non-malignant mortality				

GLR	1.06 (1.03-1.10)	**< 0.001**	1.06 (1.02-1.09)	**0.003**
GLR category				
Q1	Reference		Reference	
Q2	1.09 (0.74-1.59)	0.662	0.87 (0.61-1.23)	0.429
Q3	1.35 (0.94-1.93)	0.101	0.83 (0.60-1.14)	0.248
Q4	2.82 (1.97-4.05)	**< 0.001**	1.40 (1.01-1.94)	**0.04**

Crude model: Non-adjusted

Model 1: adjusted by age, sex, race/ethnicity, education level, ratio of family income to poverty, cigarette smoking status, diabetes status, and hypertension status.
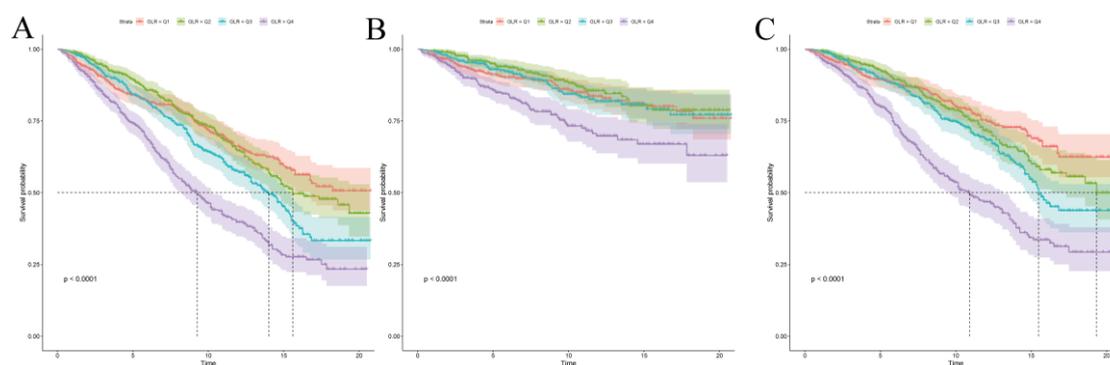

Figure 1. Kaplan–Meier Survival Analysis of At-risk Cancer Patients in Q1, Q2, Q3 and Q4. (A) All-cause Mortality. (B) Malignant Mortality. (C) Non-malignant Mortality.

3.3 The Detection of Nonlinear Relationships and Subgroup Analysis

Restricted cubic splines were used to model the relationship between GLR and the risk of all-cause, malignant, and non-malignant mortality. After adjusting for covariates such as age, sex, race/ethnicity, education, income-to-poverty ratio, smoking status, diabetes, and hypertension, a significant nonlinear association was observed (all P < 0.001) (Fig 2). Interestingly, the adjusted smoothed plots revealed U-shaped associations between the GLR index and all-cause (Fig 2A), malignant (Fig 2B), and non-malignant mortality (Fig 2C). We utilized both standard and two-piecewise Cox proportional hazards regression models to analyze the relationship between baseline GLR index and mortality. From the two-piecewise models, we identified the inflection points for all-cause, malignant, and non-malignant mortality as 2.95, 2.97, and 2.88, respectively, with both P values for the log-likelihood ratio being less than 0.05. After adjusting for factors such as age, sex, race/ethnicity, education, income-to-poverty ratio, smoking status, diabetes, and hypertension, the risk of all-cause mortality decreased by about 28% (HR: 0.72, 95% CI: 0.52–0.99), while malignant and non-malignant mortality risks decreased by 60% (HR: 0.40, 95% CI: 0.24–0.67) with each unit increase in the GLR index up to the inflection points (Table 3). In contrast, when the GLR index exceeded 2.95 (HR: 1.06, 95% CI: 1.03–1.09), 2.97 (HR: 1.08, 95% CI: 1.02–1.14), and 2.88 (HR: 1.08, 95% CI: 1.04–1.12) for all-cause,

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malignant, and non-malignant mortality, respectively, a significant positive association was observed (Table 3). These findings confirm a persistent U-shaped relationship between the GLR index and all-cause, malignant, and non-malignant mortality in cancer patients (both P for non-linearity < 0.01).

A subgroup analysis was performed to assess how the relationship between GLR and all-cause, malignant, and non-malignant mortality varied by age, gender, hypertension, and diabetes. After controlling for confounding factors, we found that the association between GLR and all-cause mortality was consistent across sex, diabetes, and hypertension. Notably, higher GLR levels were linked to an increased risk of all-cause mortality in individuals over 60 (Table 4). Additionally, elevated GLR levels were associated with a higher risk of malignant mortality in females, older adults, and patients without hypertension or diabetes (Table 5). In contrast, higher GLR levels also correlated with an increased risk of non-malignant mortality in males, older individuals, and patients with hypertension but without diabetes (Table 6).
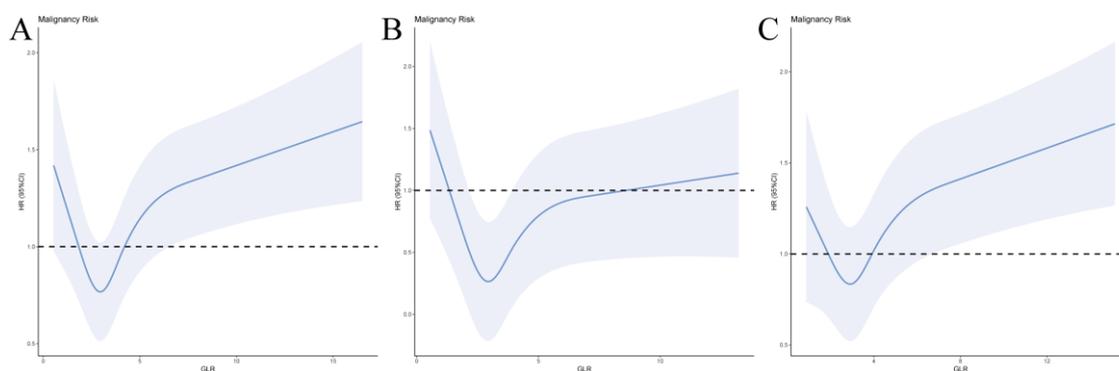

Figure 2. The U-shaped Association of GLR with All-cause (A) Malignant (B) and Non-malignant (C) by RCS Analysis

Table 3. Threshold Effect Analysis of GLR Index on All-cause, Malignant, and Non-malignant Mortality in Cancer Patients

Characteristics	OR(95%CI)	P-value
All-cause mortality		
Fitting by two-piecewise Cox risk model		
Inflection point 2.95		
GLR index < 2.95	0.72 (0.52,0.99)	**0.042**
GLR index ≥ 2.95	1.06 (1.03,1.09)	**0.0004**
P for Log-likelihood ratio		**<0.001**
Malignant mortality		
Fitting by two-piecewise Cox risk model		
Inflection point 2.97		

GLR index < 2.97	0.40 (0.24-0.67)	**0.0005**
GLR index ≥ 2.97	1.08 (1.02-1.14)	**0.005**
P for Log-likelihood ratio		**<0.001**
Non-malignant mortality		
Fitting by two-piecewise Cox risk model		
Inflection point 2.88		
GLR index < 2.88	1.01 (0.63-1.62)	0.962
GLR index ≥ 2.88	1.08 (1.04-1.12)	**<0.001**
P for Log-likelihood ratio		**<0.001**

Adjusted by age, sex, race/ethnicity, education level, ratio of family income to poverty, cigarette smoking status, diabetes status, and hypertension status

Table 4. Subgroup Analysis of the Associations between GLR and All-cause Mortality

Characteristics	OR(95%CI)	P-value
Sex		
Male	1.08 (1.03-1.13)	**0.001**
Female	1.05 (1.01-1.09)	**0.011**
Age		
<60	1.03 (0.96-1.10)	0.404
≥60	1.09 (1.05-1.13)	**<0.001**
Hypertension		
Yes	1.05 (1.01-1.08)	**0.008**
No	1.10 (1.03-1.18)	**0.008**
Diabetes		
Yes	1.04 (1.01-1.07)	**0.016**
No	1.14 (1.07-1.22)	**<0.001**

Confounding factors: age, sex, race/ethnicity, education level, ratio of family income to poverty, cigarette smoking status, diabetes status, and hypertension status

Table 5. Subgroup Analysis of the Associations between GLR and Malignant Mortality

Characteristics	OR(95%CI)	P-value
Sex		
Male	1.09 (0.98-1.21)	0.099
Female	1.07 (1.02-1.13)	**0.008**
Age		
<60	1.03 (0.96-1.10)	0.400

≥60	1.14 (1.06-1.22)	**0.0006**
Hypertension		
Yes	1.05 (0.99-1.12)	0.08
No	1.17 (1.05-1.31)	**0.006**
Diabetes		
Yes	1.03 (0.96-1.10)	0.396
No	1.04 (1.01-1.08)	**0.025**

Confounding factors: age, sex, race/ethnicity, education level, ratio of family income to poverty, cigarette smoking status, diabetes status, and hypertension status

Table 6. Subgroup Analysis of the Associations between GLR and Non-malignant Mortality

Characteristics	OR(95%CI)	P-value
Sex		
Male	1.09 (1.03-1.15)	**0.002**
Female	1.05 (0.99-1.10)	0.053
Age		
<60	1.03 (0.95-1.12)	0.484
≥60	1.09 (1.05-1.13)	**<0.001**
Hypertension		
Yes	1.05 (1.01-1.09)	**0.01**
No	1.07 (0.99-1.15)	0.09
Diabetes		
Yes	1.03 (0.96-1.10)	0.396
No	1.22 (1.08-1.38)	**0.001**

Confounding factors: age, sex, race/ethnicity, education level, ratio of family income to poverty, cigarette smoking status, diabetes status, and hypertension status

4. Discussion

In this study, to our knowledge, it is the first study to investigate the correlation between GLR and both all-cause and malignant mortality in patients with malignancies. Among the 2,186 cancer participants from ten NHANES cycles (1999–2018), we observed significant increases in the risk of all-cause, malignant, and non-malignant mortality of approximately 6%, 7%, and 6%, respectively, for each unit increase in the GLR index. Additionally, cancer patients in the Q4 group had a higher risk of all-cause, malignant, and non-malignant mortality compared to those in the Q1 group. Notably, it is identified that a U-shaped association between the baseline GLR index and all-cause and malignant mortality in cancer patients, with inflection points of 2.95, 2.97, and 2.88 for all-cause, malignant, and

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non-malignant mortality, respectively.

The advantages of the GLR index are significant and widespread, as it is simply calculated using the formula: GLR = Plasma Glucose / Lymphocyte Count. Hyperglycemia and lower lymphocyte count [12] are well-established indicators of poor survival. However, quantitatively assessing mortality risk can also be challenging by only plasma glucose and lymphocyte. The GLR serves as a marker of glucose metabolism and systemic inflammation, both of which correlate with poor prognoses in various diseases [13]. Therefore, using GLR to predict survival outcomes in cancer patients is a valuable option and more predictive than plasma glucose and lymphocyte count alone. Previous studies have shown that elevated preoperative GLR values are significantly associated with poor prognosis in cancer patients undergoing surgery, including those with NSCLC, CRC, and breast cancer [14]. It was also reported that GLR was a independent risk factor in CRC and gastric cancer patients [15, 16]. Interestingly, patients with papillary thyroid cancer and type 2 diabetes are more likely to have preoperative central lymph node metastasis if they have a high preoperative GLR value [17].

Researches using GLR to assess the mortality risk in cancer patients have yielded certain achievement. However, our finding firstly have revealed that a significant nonlinear association was observed between GLR and all-cause, malignant, and non-malignant mortality, resembling a U-shaped relationship based on RCS analysis. In patients with a GLR index below the inflection points, adjusting for factors such as age, sex, race/ethnicity, education, income-to-poverty ratio, smoking status, diabetes, and hypertension, resulted in a 28% decrease in the risk of all-cause mortality, while malignant mortality risks decreased by 60% for each unit increase in the GLR index, which indicated that hypoglycemia and lymphocytosis may lead to the development of diseases [18, 19]. It has been reported that morbidity and mortality rates are higher in inpatients with hypoglycemia [19]. Hypoglycemia is a risk factor for adverse vascular events and increased mortality [20]. Additionally, reversing hypoglycemia may help prevent Alzheimer's disease neuropathology [21]. In patients with a GLR index above the inflection points, each unit increase in the GLR index led to a 6% decrease in the risk of all-cause mortality and an 8% decrease in malignant mortality risk. Persistent hyperglycemia can have devastating effects on various cell types due to increased reactive oxygen species (ROS) production and DNA damage [22]. In addition, hyperglycemia is believed to play a critical role in the development, angiogenesis, and metastasis of cancer. Thus, both high and low levels of GLR can be harmful to cancer patients. Specifically, higher GLR levels were associated with an increased risk of all-cause mortality in individuals over 60, likely due to higher mortality rates in older patients.

In summary, a U-shaped association was found between the baseline GLR index and both malignant and all-cause mortality in American cancer patients, with both excessively high and low levels potentially leading to negative health outcomes. Although this is the first study to identify a U-shaped relationship between GLR and both all-cause and malignant mortality, there are several limitations. First, we used a cross-sectional design, necessitating a prospective study to validate our findings. Second, as an observational study conducted at a single center, it cannot definitively establish causality.

5. Conclusion

In summary, our study identified a U-shaped association between the baseline GLR index and both malignant and all-cause mortality in cancer patients from the American population. Therefore, measuring the GLR index could be useful for assessing risk and predicting prognosis in this population.

Declarations

Abbreviations

GLR: glucose-to-leukocyte ratio

NHANES: National Health and Nutrition Examination Survey

NDI: National Death Index

RCS: restricted cubic splines

SII: systemic immune-inflammation index

NLR: neutrophil-to-lymphocyte ratio

NRI: nutrition risk index

CDC: Centers for Disease Control

NCHS: National Center for Health Statistics

ICD-10: International Statistical Classification of Diseases, 10th Revision

SD: standard deviations

NSCLC: non-small cell lung cancer

CRC: colorectal cancer

ROS: reactive oxygen species

Ethics approval and consent to participate

We hereby state that the research presented in our manuscript has been conducted in full compliance with the ethical principles outlined in the Declaration of Helsinki.

Consent for publication

Not Applicable

Availability of data and materials

The datasets used for these analyses are publicly available in National Health and Nutrition Examination Survey (https://www.cdc.gov/nchs/nhanes/index.htm). The code will be provided as needed.

Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

Panguo Wang collected the data and conceptualized the article, conducted the literature search, and

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drafted the initial manuscript. Yong Chen made essential revisions to the manuscript's content. All authors have read and agreed to the published version of the manuscript.

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