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The association between Glycated Hemoglobin to High Density Lipoprotein Cholesterol Ratio and risk of cardiovascular diseases caused death among adult cancer survivors: evidence from NHANES 1999–2018

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Abstract

Background The population of cancer survivors is growing markedly, facing an elevated risk of overall mortality as well as death from cardiovascular diseases (CVDs). Uncovering biomarkers that associated with CVDs among cancer survivors appears to be vital.

Methods We collected data from NHANES (1999–2018), focusing on cancer survivors with comprehensive Glycated Hemoglobin (GH), High Density Lipoprotein Cholesterol (HDL-C), CVDs history and survival follow-up information. We first executed test for Proportional Hazards assumptions among the variables, paving the way for constructing the COX proportional hazards model. By stratifying participants by age, we explored the association between GH/HDL-C levels and the CVDs-caused mortality risk across various age segments. Restricted cubic spline (RCS) curves were employed to detect any potential non-linear associations. When non-linear associations were identified, we proceeded with segmented analyses based on reference values to better understand the association between GH/HDL-C and the risk of CVDs-related mortality among cancer survivors. To further affirm the robustness of our findings, subgroup and sensitivity analyses were conducted.

Results A total of 3,244 eligible participants were included in this study. The GH/HDL-C levels in cancer survivors died from CVDs were markedly higher than those who survived the follow-up period. According to the results from the Proportional Hazards assumptions test, the endpoint for CVDs mortality was established at 168 months, and the subjects were classified into three age groups: <60 years, between 60 and 74 years, and ≥ 75 years. For the young cohort (< 60 years), there was no significant association between GH/HDL-C levels and CVDs mortality. However, in the 60 ~ 74 age group, a linear association was noted, with higher GH/HDL-C levels indicating a greater CVDs-related

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mortality risk. For cancer survivors aged 75 and older, the association appeared nonlinear, resembling a U-shaped curve, where high GH/HDL-C levels were associated with higher mortality risk above the certain reference point (4.25mmol/L^-1), while lower levels were associated with reduced risk or no significant impact.

Conclusion The study highlighted that in cancer survivors, the GH/HDL-C is significantly associated with the risk of CVDs mortality. Those between 60 and 74 years old showed a straightforward increase in CVD death risk with higher GH/HDL-C levels. In individuals aged 75 and older, the association was more complex, exhibiting a non-linear U-shaped trend.

Keywords Cancer survivor, Glycated hemoglobin, High density lipoprotein cholesterol, Cardiovascular diseases

Introduction

Cancer has increasingly become a significant global burden that deserves attention on a worldwide scale. Recent surveys indicate that around 20% of individuals will face a cancer diagnosis during their lifetimes, with about one in nine men and one in twelve women losing their lives to the disease [1]. The term "cancer survivor," first defined by Mullan in 1985, encompasses all individuals from the time of cancer diagnosis until death, and the number of people in this group continues to grow [2]. They typically experience dysfunctions in physiological, psychological, or social aspects compared to individuals without cancer, with an elevated risk of developing a second malignancy and a higher likelihood of experiencing cardiovascular diseases (CVDs) [3–7]. Therefore, focusing on the quality of life for cancer survivors following treatment and identifying specific survival predictive biomarkers or models is crucial for guiding their lifestyle and pharmaceutical interventions.

In fact, to better predict the prognosis of cancer survivors, researchers are striving to identify appropriate predictive indicators. For instance, multi-gene scoring has been used to identify the probability of recurrent tumors in children diagnosed with cancer [8]. A team from South Korea has found that the TyG index [Ln (fasting triglycerides (mg/dl) × fasting blood glucose (mg/dl)/2)], which serves as a non-invasive measure of insulin resistance, can predict the future risk of CVDs in cancer survivors [9]. The prognostic nutritional index (PNI), have been identified as potential biomarkers for evaluating future CVDs event risk in cancer survivors [10]. Additionally, there are numerous predictive models designed to forecast the survival duration of cancer survivors [11–13]. Despite advancements, there remains a deficiency in dependable predictive ability and consistency, leading to limited acceptance in clinical settings.

Abnormalities in carbohydrate and lipid metabolism are common characteristics in cancer patients [14], which also constitute a high-risk factor for CVDs. As a crucial diagnostic indicator of blood glucose levels, glycated hemoglobin (GH) has a strong association with the risk of CVDs [15]. High-density lipoprotein cholesterol (HDL-C) is typically viewed as an anti-atherogenic lipoprotein, which transports cholesterol from peripheral tissues back to the liver for metabolism; a decrease in HDL-C is indeed associated with an increased risk of CVDs [16]. As a result, the integration of these two critical indicators of glucose and lipid metabolism (GH to HDL-C Ratio, GH/HDL-C) is expected to be significantly associated with the CVDs mortality risk among cancer survivors. Studies have shown that the GH/HDL-C may be linked to the rate of stroke occurrence [17], and it can act as a useful marker for screening metabolic-related fatty liver disease [18]. Herein, we delved into the association between GH/HDL-C levels and the risk of CVDs-related deaths in cancer survivors.

According to statistics, there are over 16.9 million survivors in the United States [19]. To evaluate the association between GH/HDL-C levels and the risk of CVDs-related deaths in cancer survivors, we retrieved and collected relevant data on cancer survivors from the National Health and Nutrition Examination Survey (NHANES, a cross-sectional study that assesses the health and nutritional status of American adults and children) from 1999 to 2018, including general demographics, health-related issues, laboratory tests, and survival follow-up data. We initially performed proportionality assumption test for the variables, and then proceeded to construct the Cox proportional hazards model. Stratifying by age, we assessed the association between GH/HDL-C and CVDs mortality risk in various age groups. Restricted cubic spline (RCS) curves were used to identify potential nonlinear relationships. In the presence of any nonlinear associations, further segmented analyses were conducted based on reference values, aiming to explore the close association between GH/HDL-C and the risk of CVDs-caused mortality among cancer survivors. Furthermore, we carried out subgroup and sensitivity analyses to confirm the robustness of the observed associations.

Methods

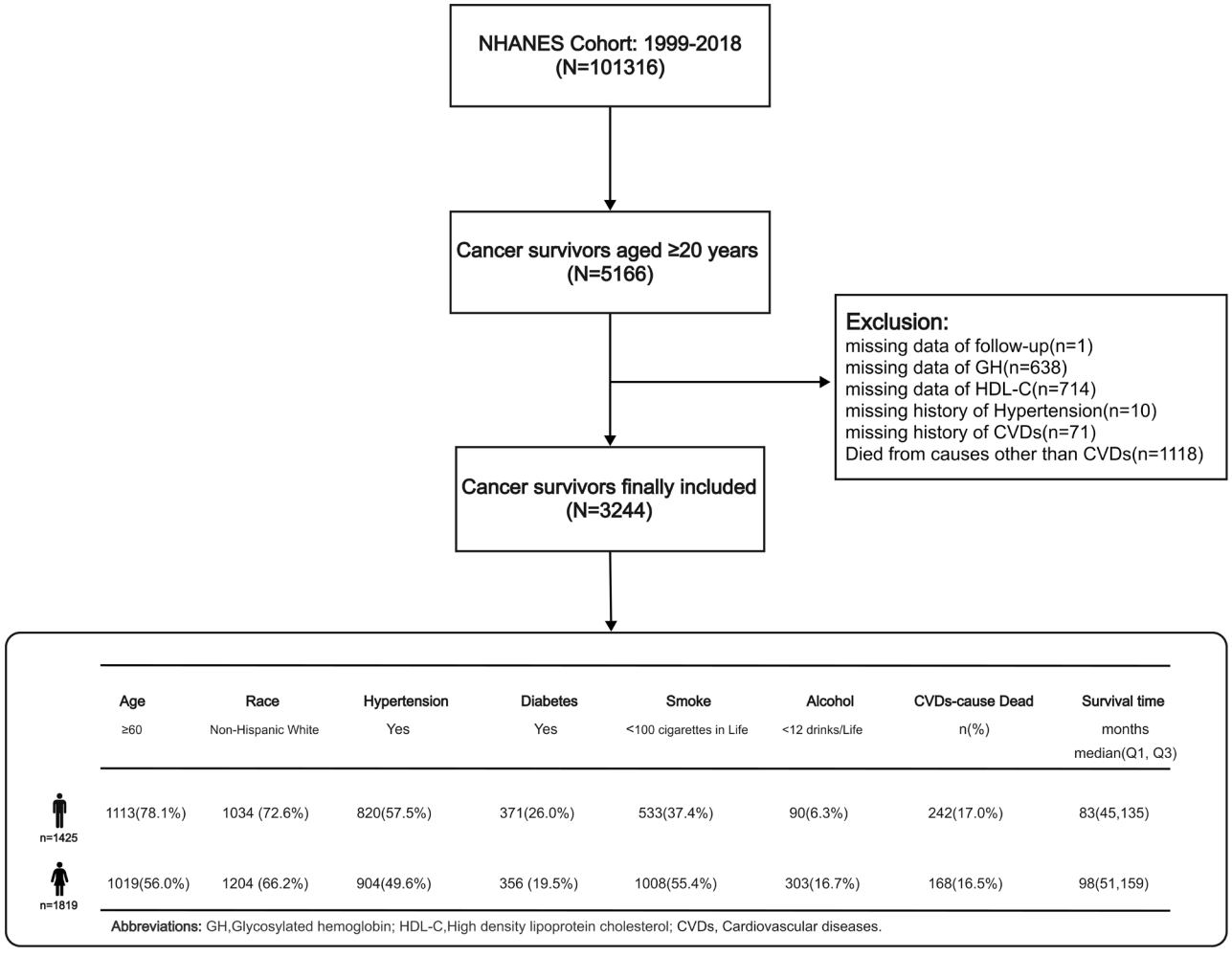
Study population

Based on the NHANES 1999–2018 survey data, we confirmed the cancer history of participants through the question 'Have you/Has SP ever been told by a doctor

or other health professional that you/s/he had cancer or a malignancy of any kind?'. Among them, 5,166 adult participants reported a history of cancer. We obtained the survival status of these subjects before 31 December 2019 ((the last update date of the platform) through linkage with the National Death Index (NDI) of the National Center for Health Statistics (NCHS). CVDs-caused mortality referred to death caused by CVDs (ICD-10 Codes I00-I99). A total of 3244 patients were enrolled in this study after excluding those with missing data on follow-up, HDL-C, GH, hypertension, and CVDs, as well as patients who died from non-CVD related causes (Fig. 1). Since the NHANES dataset is open and original, ethical approval has been obtained from the NCHS Ethical Review Board, and all study participants provided informed consent. Therefore, additional informed consent and ethical review were waived.

Definition of GH/HDL-C

The procedures for the collection and handling of laboratory specimens were meticulously followed according to the NHANES Laboratory/Medical Technicians Procedures Manual (LPM). Between 1999 and 2002, HDL-C levels were assessed through two methods: heparin manganese precipitation and direct HDL-C immunoassay, of which most participants in this period were evaluated using the precipitation method. From 2003, all HDL-C samples were analyzed solely using the direct HDL-C immunoassay method. It was noted that the heparin-manganese precipitation method and the direct immunoassay method for the years 1999–2000, 2001–2002, and 2005–2006 exhibited significant biases (greater than 4%) when compared to the laboratory's HDL-cholesterol quality controls. As a result, the HDL cholesterol values of 1999–2000, 2001–2002, and 2005–2006 were corrected using the following formula: Corrected HDL-C = (Solomon Park assigned HDL-C value) x (Participant HDL-C) / (Quality Control HDL-C value associated with Participant sample). The measurement of GH (HbA1c) for NHANES is conducted using the High-Performance Liquid Chromatography (HPLC) method. The GH/HDL-C refers to the ratio of GH to HDL-C.



	Age ≥60	Race Non-Hispanic White	Hypertension Yes	Diabetes Yes	Smoke <100 cigarettes in Life	Alcohol <12 drinks/Life	CVDs-cause Dead n(%)	Survival time months median(Q1, Q3)
n=1425	1113(78.1%)	1034 (72.6%)	820(57.5%)	371(26.0%)	533(37.4%)	90(6.3%)	242(17.0%)	83(45,135)
n=1819	1019(56.0%)	1204 (66.2%)	904(49.6%)	356 (19.5%)	1008(55.4%)	303(16.7%)	168(16.5%)	98(51,159)

Abbreviations: GH,Glycosylated hemoglobin; HDL-C,High density lipoprotein cholesterol; CVDs, Cardiovascular diseases.

Fig. 1 A diagram representing the process of participant recruitment in this study, including demographic information of the final cohort

Covariables

We collected basic information about the cohort, which included gender, age, body mass index (BMI), the Healthy Eating Index (HEI, a tool to evaluate how well a specific group of foods conforms to the Dietary Guidelines for Americans), smoking, and alcohol consumption. Smoking status was determined by survey, which classified individuals as non-smokers, former smokers, or current smokers. The evaluation of alcohol consumption was conducted through Alcohol Use questionnaire, which was classified into three categories: never or rarely (< 12 drinks in a lifetime), occasionally (< 12 drinks annually), and regularly (≥12 drinks annually). Additionally, we verified the presence of hypertension among subjects by inquiring if they had ever been informed by a doctor or health professional that they were suffering from it. Diabetes was defined as self-reported diagnosis, or employing diabetes medication, or fasting glucose levels (detected by hexokinase method) ≥ 7 mmol/L, or GH (HbA1c) levels ≥ 6.5% [20]. Prior history of CVDs, such as congestive heart failure (CHF), coronary heart disease (CHD), angina, and acute myocardial infarction (AMI) and stroke was confirmed based on information provided by a doctor or other health professional in the past. Furthermore, we gathered the test results of Total cholesterol (TC) of the included subjects from NHANES platform.

Missing data handling

Among the included subjects, 73 (2.25%) had no BMI information, 165 (5.09%) were missing details on alcohol consumption, 4 (0.12%) did not provide smoking information, and 164 (5.06%) lacked HEI data. We performed imputation for these four variables, using the mode for smoking and alcohol consumption, and the mean for BMI and HEI.

Statistical analysis

The NHANES survey employs a complex sampling design to ensure that the findings are representative of the civilian population in the United States. In our research, we included sample weights (mobile examination center [MEC] weight), along with stratification and clustering, for analytical purposes. To investigate the characteristics of different survival status, we conducted comparison between the CVDs-caused mortality group and the survival group. For continuous variables, data conforming to a normal distribution were presented as mean ± standard deviation (SD), while data with a skewed distribution were presented as median (interquartile range [IQR]). We selected either the t-test, Mann–Whitney U or Kruskal–Wallis tests to evaluate the differences between groups as appropriate. Categorical data were presented as frequency (%), and the chi-square test was used for hypothesis testing.

Next, we utilized the Cox proportional hazards model for univariable and multivariable analyses, calculating the hazard ratios (HR) and 95% confidence intervals (95%CI). Prior to this, we divided GH/HDL-C into three equal parts and plotted the corresponding Kaplan-Meier survival curves and log(-log(survival)) plots to assess whether this variable meets the Proportional Hazards assumptions. As illustrated in Fig. 2, we found that after 168 months of follow-up, the survival curves and log(-log(survival)) plots for tertile 1 and tertile 2 intersect. Thus, we defined the follow-up cutoff at 168 months. Furthermore, to confirm if the variables adhered to the Proportional Hazards assumption, we employed the Schoenfeld residual method for evaluation. The results revealed that GH/HDL-C and other 12 variables (Gender, Race, Alcohol consumption, HEI, BMI, Diabetes, Hypertension, AMI, Stroke, CHD, Angina and TC) satisfied the

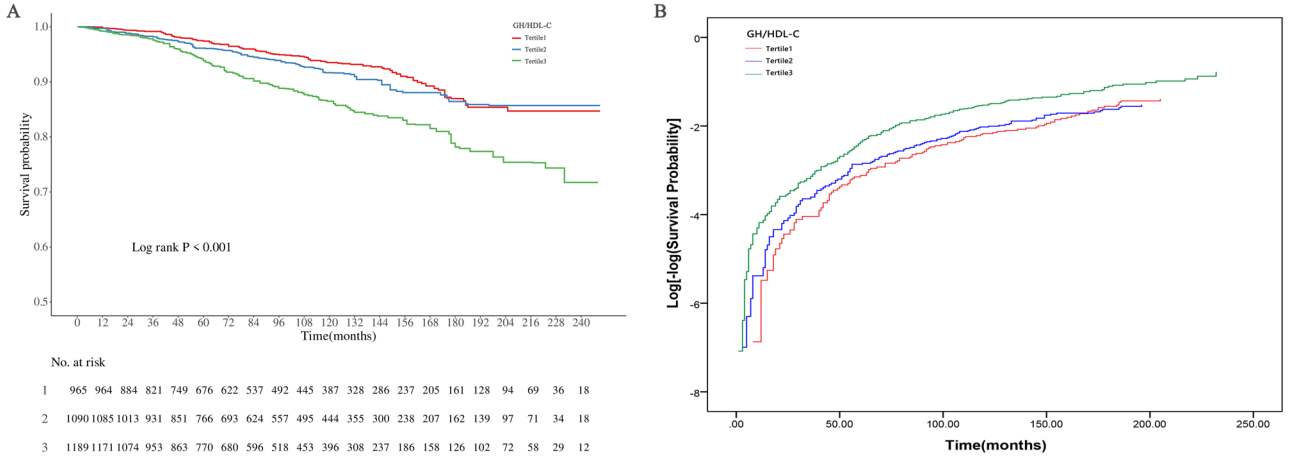


Fig. 2 **A** depicts a Kaplan-Meier survival curve with GH/HDL-C divided into three distinct categories, showing the survival rates among them. **B** illustrates the log(-log(survival)) plots for these classifications, helping to assess the proportional hazards assumption in survival data analysis

Proportional Hazards assumption, whereas age, smoking status, and CHF did not ($P < 0.05$) (Supplementary Fig. 1).

Given that age violated the Proportional Hazards assumption and was a key factor linked to CVDs, we undertook a stratified analysis by age. Individuals were segmented into three age groups (< 60 years, between 60 and 74 years, and ≥ 75 years), and this classification combined traditional age thresholds and maintained the sample size of each subgroup, thereby preventing instability in the results due to an insufficient number. Within each group, we constructed Cox proportional hazards models to investigate the association between GH/HDL-C levels and the risk of death from CVDs. To confirm the reliability of our results and maintain model stability, we created three separate models according to different covariables: Model 1 served as the crude model; Model 2 was adjusted for BMI (< 25 kg/m², 25–30 kg/m², ≥ 30 kg/m²), sex (female, male), race (non-Hispanic white and others), alcohol consumption (< 12 per lifetime, < 12/year, ≥ 12/year), hypertension, diabetes, CHD, angina, AMI, Stroke, HEI, and TC; and Model 3 further accounted for **smoking status** (never, former, and current), **CHF**, and **age** (continuous), aiming to confirm the stability of Model 2. The variance inflation factor (VIF < 5, excluding GH and HDL-C) was calculated to ensure that there is no collinearity between covariables and GH/HDL-C. We employed multivariable restricted cubic splines (RCS) with 3 degrees of freedom to examine the possible non-linear association between GH/HDL-C levels and survival status.

Further, subgroup analyses were performed to examine the consistent effect of GH/HDL-C on the risk of death due to CVDs across different subgroups among participants aged 60 to 74 years. Likelihood ratio tests were utilized to evaluate potential interaction terms, with the stratifying factors including gender, race, BMI, hypertension, diabetes, alcohol consumption and smoking status. On the other hand, we excluded cancer survivors aged ≥ 75 years who had experienced AMI and stroke, and we repeated the COX proportional hazards model analysis. This approach was intended to reinforce the stability of the indicators in predicting CVDs-related outcomes.

All statistical analyses were performed using R software (version 4.3.2) and Storm Statistical Platform (www.medsta.cn/software), with a P-value < 0.05 was deemed statistically significant.

Result

Baseline characteristics of the participants

In this study, a total of 3,244 cancer survivors were analyzed, among whom 410 individuals, representing 12.64%, died from CVDs during the follow-up period. The median age of the survivors was 60 years, while the median age of those who died from CVDs was significantly higher at 78 years, with a statistically significant difference between the two groups. In the surviving population, the median GH was 5.50%, compared to 5.70% in the CVDs-related death group, with a significant difference in median GH as well. Additionally, the survivors had higher TC and HDL-C levels compared to those who died from CVDs. The median GH/HDL-C was 4.17 (3.27, 5.24) mmol/L^-1 among survivors, while it was 4.50 (3.56, 5.83) mmol/L^-1 in the CVDs-caused death group, again showing a significant difference. Moreover, the population who died from CVDs had a greater proportion of males and non-Hispanic whites, as well as a significantly higher prevalence of previous CVDs history compared to survivors. In addition, there was a higher prevalence of BMI in the range of 25–30 kg/m² and higher rates of past smoking and drinking (< 12 times in lifetime) in the CVDs death group. (Table 1) The cohort recruited 1,425 males and 1,819 females, with patient information summarized by gender in Fig. 1.

Association between GH/HDL-C and survival status in different age groups

In cancer survivors under the age of 60, no significant association was found between GH/HDL-C levels and the risk of mortality from CVDs (Table 2). The RCS curves indicated that all models displayed relatively flat lines (Figure 3A, B and C). However, in the 60 ~ 74 age group, the RCS curves from the three models suggested a potential linear relationship between GH/HDL-C levels and the risk of CVD mortality (Figure 3D, E and F). In order to identify any possible non-linear association, we utilized knots = 4 to create the RCS curve, and the findings continued to demonstrate a linear association (P for non-linearity > 0.05) (Supplementary Fig. 2A, B, C). Further analysis using Cox proportional hazards models indicated that higher GH/HDL-C levels were associated with an increased risk of death from CVDs, with model 1 reporting an HR of 1.19 (1.09–1.30), model 2 indicated an HR of 1.15 (1.03–1.30), and model 3 revealed an HR of 1.15 (1.03–1.28) (Table 2).

Notably, among cancer survivors aged 75 and older, the RCS curve adjusted for covariates indicates a nonlinear association between GH/HDL-C and the mortality risk from CVDs, resembling a U-shape (Figure 3G, H and I). The reference value identified is 4.25 mmol/L^-1. Based on this reference, we conducted a piecewise analysis and found that when GH/HDL-C exceeds 4.25 mmol/L-1, an increase in GH/HDL-C levels leads to a significant rise in the risk of death caused by CVDs [model 1: HR 1.23 (1.09–1.39), model 2: HR 1.23 (1.10–1.38), model 3: HR 1.23 (1.09–1.39)]. Conversely, below the reference level, higher GH/HDL-C levels are associated with a slight decrease in the mortality risk from CVDs (Table 2).

Table 1 Participant baseline and variable comparison based on survival status after follow-up (weighted)

Variable	Total (*n* = 3244)	Alive(*n* = 2834)	CVDs-caused Death (*n* = 410)	*P*-value
Age, n(%)				**< 0.001**
<60years	1112 (44.04)	1093 (47.60)	19 (5.56)	
60 ~ 74years	1236 (35.98)	1140 (36.68)	96 (28.36)	
>=75years	896 (19.98)	601 (15.71)	295 (66.08)	
Gender, n(%)				**< 0.001**
Female	1819 (59.29)	1651 (60.40)	168 (47.25)	
Male	1425 (40.71)	1183 (39.60)	242 (52.75)	
Race, n(%)				**< 0.001**
Non-Hispanic White	2238 (86.84)	1887 (86.28)	351 (92.91)	
Others	1006 (13.16)	947 (13.72)	59 (7.09)	
BMI, n(%)				**0.005**
<25 kg/m^2	835 (27.95)	719 (27.84)	116 (29.16)	
25 ~ 30 kg/m^2	1209 (35.93)	1024 (35.23)	185 (43.52)	
≥30 kg/m^2	1200 (36.12)	1091 (36.93)	109 (27.32)	
Hypertension, n(%)				**< 0.001**
No	1520 (52.69)	1392 (54.78)	128 (30.13)	
Yes	1724 (47.31)	1442 (45.22)	282 (69.87)	
Diabetes, n(%)				**< 0.001**
No	2517 (82.17)	2240 (83.32)	277 (69.69)	
Yes	727 (17.83)	594 (16.68)	133 (30.31)	
Alcohol, n(%)				**< 0.001**
<12 per life	393 (9.29)	323 (8.53)	70 (17.58)	
<12/year	838 (25.38)	752 (25.63)	86 (22.64)	
≥12/year	2013 (65.33)	1759 (65.84)	254 (59.78)	
Smoke, n(%)				**< 0.001**
Current	501 (16.30)	465 (16.86)	36 (10.26)	
Nerver	1541 (47.71)	1370 (48.16)	171 (42.86)	
former	1202 (35.99)	999 (34.98)	203 (46.88)	
AMI, n(%)				**< 0.001**
Yes	282 (6.55)	191 (5.19)	91 (21.25)	
No	2962 (93.45)	2643 (94.81)	319 (78.75)	
Stroke, n(%)				**< 0.001**
Yes	237 (5.19)	155 (4.01)	82 (18.00)	
No	3007 (94.81)	2679 (95.99)	328 (82.00)	
CHF, n(%)				**< 0.001**
Yes	195 (4.74)	121 (3.41)	74 (19.07)	
No	3049 (95.26)	2713 (96.59)	336 (80.93)	
CHD, n(%)				**< 0.001**
Yes	287 (7.26)	198 (5.80)	89 (23.09)	
No	2957 (92.74)	2636 (94.20)	321 (76.91)	
Angina, n(%)				**< 0.001**
Yes	198 (4.87)	132 (3.88)	66 (15.61)	
No	3046 (95.13)	2702 (96.12)	344 (84.39)	
HEI, M(IQR)	52.84 (17.85)	52.73 (17.85)	53.92 (17.35)	**0.004**
GH(%), M(IQR)	5.50 (0.60)	5.50 (0.60)	5.70 (0.70)	**< 0.001**
TC(mmol/L), M(IQR)	5.07 (1.45)	5.09 (1.44)	4.91 (1.43)	**0.003**
HDL-C(mmol/L), M(IQR)	1.34 (0.57)	1.34 (0.57)	1.29 (0.52)	**0.022**
GH/HDL-C(mmol/L^-1), M(IQR)	4.19 (1.99)	4.17 (1.97)	4.50 (2.27)	**< 0.001**

Noting: CVDs, Cardiovascular diseases; BMI, Body Mass Index; HEI, Healthy Eating Index; GH, glycosylated hemoglobin; TC, Total cholesterol; HDL-C, High density lipoprotein cholesterol; GH/HDL-C, Glycated Hemoglobin to High Density Lipoprotein Cholesterol Ratio; AMI, Acute myocardial infarction; CHD, Coronary heart disease; CHF: Chronic Heart Failure; M(IQR), Median (interquartile range)

Table 2 The age-stratified Cox proportional hazards model, adjusted for different covariables, investigated the association between GH/HDL-C levels and the risk of CVDs mortality among cancer survivors

Variables		Model 1		Model 2		Model 3	
		HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
< 60years	GH/HDL-C	1.31 (1.19–1.45)	**< 0.001**	1.11(0.91–1.37)	0.304	1.11(0.88–1.40)	0.373
60 ~ 74years	GH/HDL-C	1.19 (1.09–1.30)	**< 0.001**	1.15 (1.03–1.30)	**0.017**	1.15 (1.03–1.28)	**0.010**
≥75years	GH/HDL-C < 4.25	0.81 (0.59–1.13)	0.215	0.64 (0.41–0.98)	**0.042**	0.64 (0.42–0.98)	**0.038**
	GH/HDL-C ≥ 4.25	1.23 (1.09–1.39)	**0.001**	1.23 (1.10–1.38)	**< 0.001**	1.23 (1.09–1.39)	**< 0.001**

Noting: HR, Hazard Ratio; CI, Confidence Interval; GH/HDL-C, Glycated Hemoglobin to High Density Lipoprotein Cholesterol Ratio; HEI, Healthy Eating Index; TC, Total cholesterol; AMI, Acute myocardial infarction; CHD, Coronary heart disease; CHF: Chronic Heart Failure.

Model 1: Crude

Model 2: Adjusted by BMI(< 25 kg/m^2, 25 ~ 30 kg/m^2, ≥ 30 kg/m^2), Gender(Female, Male), Race(Non-Hispanic White and Others), Alcohol(< 12 per life, < 12/year, ≥12/year), Hypertension, Diabetes, CHD, Angina, AMI, Stroke, HEI, TC

Model 3: Adjusted by BMI(< 25 kg/m^2, 25 ~ 30 kg/m^2, ≥30 kg/m^2), Gender(Female, Male), Race(Non-Hispanic White and Others), Alcohol(< 12 per life, < 12/year, ≥12/year), Hypertension, Diabetes, CHD, Angina, AMI, Stroke, HEI, TC, Smoking(never, former and current), CHF, Age(continuous)

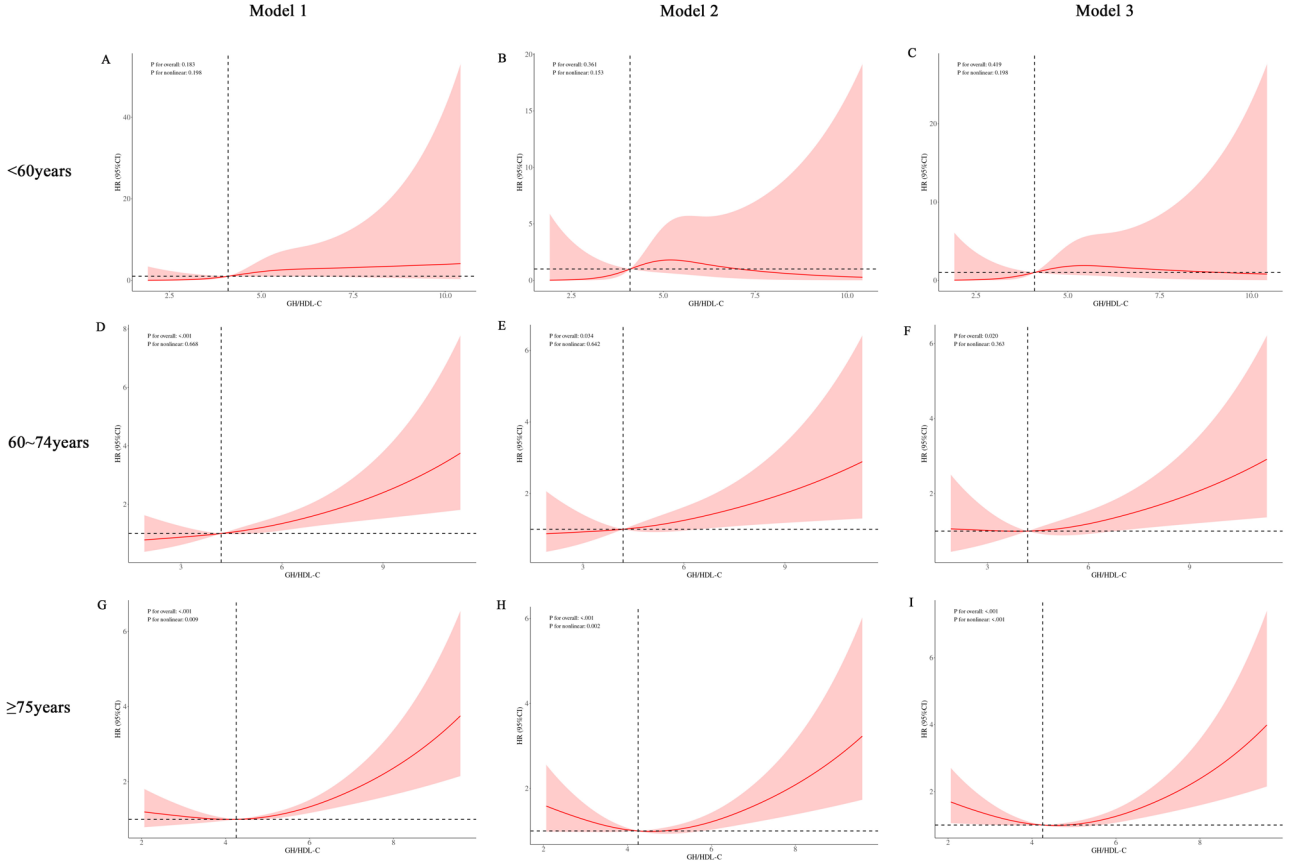


Fig. 3 The RCS plots in panels **A-C** illustrated the association between GH/HDL-C levels and the risk of CVD mortality among cancer survivors under 60 years of age, using different models. Panels **D-F** displayed the same association for cancer survivors aged 60 to 74 years, while panels **G-I** depicted the RCS plots for cancer survivors aged 75 years and older. The knots for the RCS were set at three, with Model 1 serving as the crude model, Model 2 being adjusted for factors such as BMI, sex, race, alcohol consumption, hypertension, diabetes, CHD, angina, HEI, and TC, and Model 3 further incorporating smoking status, CHF, and age to verify the stability of Model 2

Subgroup analysis and sensitive analysis

We conducted a subgroup analysis for cancer survivors aged 60 to 74, with subgroup variables including gender, race, BMI, hypertension, diabetes, alcohol consumption, and smoking status. The interaction test indicated that gender, race, BMI, hypertension, diabetes, AMI, stroke, alcohol consumption, and smoking status had no noteworthy effect on this association. Upon adjusting for covariates (BMI, Gender, Race, Alcohol consumption, along with Hypertension, Diabetes, CHD, Angina, AMI, Stroke, HEI, and TC), subgroup analysis revealed that Non-Hispanic White participants, individuals with BMI below 25 kg/m^2 or > = 30 kg/m^2, and alcohol consumers of > = 12/year faced an elevated risk of CVD mortality

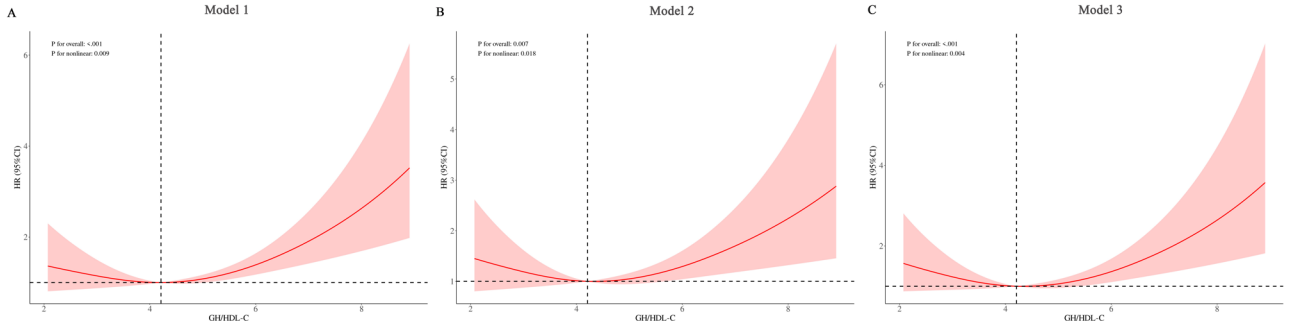


Fig. 4 The RCS plots in panels **A-C** illustrated the association between GH/HDL-C levels and the risk of CVD mortality for cancer survivors who didn't previously experience myocardial infarction or stroke aged 75 years and older

Table 3 In the subgroup of individuals aged 75 years and older, the Cox regression model, after adjusting for various covariables, investigated the association between GH/HDL-C and the mortality risk of CVDs among cancer survivors

Variables		Model 1		Model 2		Model 3	
		HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
≥75years	GH/HDL-C < 4.21	0.84 (0.55–1.28)	0.410	0.68 (0.41–1.13)	0.138	0.78 (0.44–1.36)	0.376
	GH/HDL-C ≥ 4.21	1.32 (1.15–1.51)	**< 0.001**	1.31 (1.12–1.53)	**< 0.001**	1.36 (1.16–1.59)	**< 0.001**

Noting: HR, Hazard Ratio; CI, Confidence Interval; GH/HDL-C, Glycated Hemoglobin to High Density Lipoprotein Cholesterol Ratio; HEI, Healthy Eating Index; TC, Total cholesterol; AMI, Acute myocardial infarction; CHD, Coronary heart disease; CHF: Chronic Heart Failure.

Model 1: Crude

Model 2: Adjusted by BMI(< 25 kg/m^2, 25 ~ 30 kg/m^2, ≥30 kg/m^2), Gender(Female, Male), Race(Non-Hispanic White and Others), Alcohol(< 12 per life, < 12/year, ≥12/year), Hypertension, Diabetes, CHD, Angina, HEI, TC

Model 3: Adjusted by BMI(< 25 kg/m^2, 25 ~ 30 kg/m^2, ≥30 kg/m^2), Gender(Female, Male), Race(Non-Hispanic White and Others), Alcohol(< 12 per life, < 12/year, ≥12/year), Hypertension, Diabetes, CHD, Angina, HEI, TC, Smoking(never, former and current), CHF, Age(continuous)

with increasing levels of GH/HDL-C (Supplementary Fig. 3).

For cancer survivors over the age of 75, due to the observed nonlinear relationship between GH/HDL-C and CVDs, we excluded patients with a history of AMI or stroke and reanalyzed using the Cox proportional hazards model for sensitivity analysis. The findings continued to indicate a nonlinear association between GH/HDL-C and CVDs, as suggested by the RCS curve after adjusting for covariables (Fig. 4). Furthermore, based on reference values(4.21mmol/L^-1), we proceeded with a segmented analysis, which revealed that the risk of CVDs mortality in the high-value group substantially increased with higher GH/HDL-C levels, while the low-value group showed no significant association trend (Table 3).

Discussion

Currently, the growing number of cancer survivors can be attributed to advancements in early diagnosis and cancer treatments. Therefore, it is crucial to focus on this group and assess their prognosis. In this study, we explored the association between GH/HDL-C levels and the CVDs-caused mortality risk in cancer survivors. Recognizing age as a decisive factor in CVDs risk and the impact of potential time accumulation, we did not simply include age as a covariate; instead, we conducted a stratified analysis. We divided the participants into three subgroups: <60 years, 60–74 years, and 75 years or older. The results indicated that, in the < 60 years group, the association between GH/HDL-C and long-term CVDs mortality risk was not significant. However, within the 60–74 years group, a potential linear association was observed, where higher GH/HDL-C values corresponded to increased mortality risk. For cancer survivors aged 75 and older, the association between GH/HDL-C and CVDs mortality risk appeared to be nonlinear, with the RCS curve showing a nearly U-shaped pattern. Further segmented analysis based on reference points revealed that for those above the reference point, higher GH/HDL-C levels were associated with greater mortality risk, while for those below the reference point, higher GH/HDL-C levels either corresponded to reduced mortality risk or showed no significant association.

To account for potential confounding influences, we carried out a subgroup analysis of cancer survivors aged 60 to 74. The results indicated that variables such as gender, race, BMI, hypertension, diabetes, alcohol consumption, and smoking status did not have a significant impact on the association between GH/HDL-C and the risk of mortality caused by CVDs. Despite the fact that certain subgroups did not exhibit association between GH/HDL-C and the risk of death from CVDs, this could be explained by the reduced sample size following stratification, potentially influencing the model's estimation of the association. For cancer survivors aged 75 and older, sensitivity analysis showed consistent results, revealing

that higher GH/HDL-C levels in patients above the reference value were associated with an increased risk of CVDs mortality. Our research revealed a close and complex association between GH/HDL-C levels and the risk of CVDs-caused death in cancer survivors, which offered new insights for CVDs prevention strategies in cancer survivors of different age groups. The underlying mechanisms might be explained as follows.

On one hand, diabetes serves as a high-risk factor for the development of CVDs [21], and elevated GH (HbA1c) levels in individuals with diabetes notably raise the risk of long-term mortality due to CVDs [22]. Research indicates that in non-diabetic individuals, a 3% rise in HbA1c corresponds to a 12% increase in the risk of cardiovascular events and a 10% increase in the risk of all-cause mortality [23]. Within the overall population, elevated baseline HbA1c levels are linked to a greater risk of CVDs related death [24]. Moreover, HbA1c levels demonstrate a nonlinear association with the long-term survival rates of cancer survivors [25]. The association may be attributed to several factors. Firstly, high HbA1c levels cause some vascular injury, facilitating the formation of atherosclerosis [26], and resulting in cardiovascular incidents or even mortality. Secondly, a significantly low HbA1c might reflect malnutrition or cachexia, and a persistent low glucose state can cause prolonged activation of the sympathetic nervous system, increasing oxygen consumption in the heart and potentially injuring heart muscle cells. Therefore, both excessively high and low HbA1c levels may increase the risk of developing or dying from CVDs.

On the other hand, HDL-C is recognized as a strong independent negative prognostic factor for CVDs, possessing anti-inflammatory and antioxidant properties that contribute to a reduced incidence of CVDs [27]. However, some studies suggest that U-shaped associations between levels of HDL-C and risk of all-cause and CVDs-caused mortality [28], indicating that HDL-C does not always play a protective role. Research has revealed a negative correlation between HDL-C and GH (HbA1c) [29]. For cancer patients, abnormalities in glucose and lipid metabolism represent the most prominent metabolic alterations [30]. Hence, the GH/HDL-C which incorporated two crucial markers of carbohydrate and lipid metabolism, could be a potential biomarker associated with CVDs-related mortality risk in cancer survivors, as demonstrated by our findings.

Furthermore, our study indicated that the association between GH/HDL-C levels and the risk of CVDs-caused death in cancer survivors differed across age categories. This discrepancy may be attributed to several factors: in patients under 60, there is a stronger capacity for vascular endothelial repair and compensation, which diminishes the direct association with CVDs. For patients aged 60 to 74, the risk of insulin resistance and multiple metabolic disorders significantly increases with age, particularly among cancer survivors, leading to a clearer association between GH/HDL-C and CVDs mortality risk. Lastly, in cancer survivors over 75, the likelihood of malnutrition rises, and the cumulative damage threshold of aging reaches a high level; therefore, both excessively high and low levels of GH/HDL-C may indicate an increased risk of CVDs mortality.

This study was based on a cross-sectional analysis of US participants from the NHANES database and focused on assessing the association between GH/HDL-C levels and the risk of CVDs mortality in cancer survivors. The large number of participants, long follow-up period, rational stratification and multivariable adjustment enhance the reliability of the results. However, the study does have certain limitations: Firstly, the diagnosis of cancer and the outcomes were mainly determined through physician evaluations and self-reported questionnaires, which could potentially lead to recall bias. And NHANES data offered only baseline measurements, which inadequately reflect the cumulative exposure from the baseline to the event occurrence. Secondly, although we accounted for a range of covariates in the adjusted models and performed subgroup or sensitivity analyses, the impact of unmeasured or insufficiently measured confounders (like physical activity, dietary patterns, and medications) cannot be entirely excluded. Lastly, we did not perform independent analyses categorized by the types of cancer previously experienced by the survivors, as differences in survival periods across various cancers could lead to biased results. Future efforts should focus on longitudinal studies to examine the associations between GH/HDL-C and CVDs mortality among cancer survivors.

Conclusion

In cancer survivors, GH/HDL-C was significantly associated to the CVDs mortality risk. For patients aged 60 to 74, this association demonstrated a linear trend, where increased GH/HDL-C levels lead to a higher risk of CVDs-related deaths. In those aged 75 and older, however, the association shows a non-linear U-shaped pattern.

Abbreviations

CVDs	Cardiovascular diseases
CHF	Congestive heart failure
CHD	Coronary heart disease
AMI	Acute myocardial infarction
GH	Glycated Hemoglobin (HbA1c)
HDL-C	High Density Lipoprotein Cholesterol
TC	Total Cholesterol
GH/HDL-C	Glycated Hemoglobin to High Density Lipoprotein Cholesterol Ratio
NHANES	National Health and Nutrition Examination Survey
SD	Standard deviation
IQR	Interquartile range

HR	Hazard ratio
95%CI	95% confidence intervals
BMI	Body mass index
HEI	Healthy Eating Index
RCS	Restricted Cubic Spline

Supplementary Information

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Supplementary Material 1: Figure 1: The Schoenfeld residual plots were examined for each variable to determine whether their association with the risk of CVDs death met the proportional hazards assumption, and a p-value of less than 0.05 indicated that the proportional hazards assumption was not satisfied.

Supplementary Material 2: Figure 2: Figures A-C displayed the association between cancer survivors' GH/HDL-C and CVD mortality risk for individuals aged 60 to 74 years (Knots were set to 4 during this analysis to identify possible nonlinearity).

Supplementary Material 3: Figure 3: Subgroup analysis was performed to examine the consistent effect of GH/HDL-C on the risk of death due to CVDs across different subgroups. The crude model denotes Cox univariable analysis, and the adjusted model accounts for BMI, Gende, Race, Alcohol consumption, along with Hypertension, Diabetes, CHD, Angina, AMI, Stroke, HEI, and TC.

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Author contributions
Study conception and design were carried out by XZ W and FS. FS and XJ Y were responsible for writing the manuscript. Statistical analysis was conducted by XH H and JL. The manuscript was revised by JZ and YM X, while study supervision was provided by WM Y and XZ W.

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Data availability
The datasets analyzed in this research are available from the corresponding author upon a reasonable request.

Declarations

Ethical approval
Ethical approval has been obtained from the NCHS Ethical Review Board, and all study participants provided informed consent.

Competing interests
The authors declare no competing interests.

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