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Negative association of C-reactive protein-albumin-lymphocyte index (CALLY index) with all-cause and cause-specific mortality in patients with cancer: results from NHANES 1999–2018

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Abstract

Background The CALLY index, which is derived from C-reactive protein (CRP) content, serum albumin level, and total lymphocyte count, reflects the immune, nutritional, and inflammatory status of the body. Lack of sufficient evidence on the correlation between the CALLY index and the prognosis of cancer patients with various cancer forms. This study seeks to elucidate the association between the CALLY index and mortality from all causes as well as specific causes in cancer patients within a U.S. population.

Methods This investigation encompassed 3511 cancer-afflicted adults from the National Health and Nutritional Examination Surveys (NHANES) spanning 1999 to 2018. The CALLY index was measured at baseline only. The relationship between the CALLY index and mortality from both all causes and cancer specifically was examined using Cox proportional hazards models. Additionally, restricted cubic spline, piecewise linear regression, and various subgroup and sensitivity analyses were employed.

Results Over a median follow-up of 103 months, 1,355 deaths occurred, and the incidence of all-cause mortality for these participants was 38.34%. Our findings indicate that an elevated CALLY index correlates with a diminished risk of all-cause mortality. Upon applying a natural logarithmic transformation to the CALLY index, the comprehensively adjusted model revealed that each one-unit increment in ln CALLY corresponded to a 18% decrease in all-cause mortality risk among cancer patients (HR = 0.82, 95% CI:0.79–0.86). Analyses of mortality due to cardiac and cancer-related causes yielded consistent results, which were robust across various subgroup and sensitivity analyses.

Conclusion The CALLY index demonstrated a linear and negative association with all-cause mortality, as well as mortality caused by cancer and cardiac conditions, highlighting its significant prognostic value in patients with oncological conditions.

Keywords CALLY index, Cancer, Population-based study, NHANES, Retrospective study

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Introduction

Cancer, recognized globally as a leading cause of premature death, presents a significant barrier to further increases in life expectancy this century [1–4]. Recent estimates from global mortality data (2019) indicate that cancer is one of the four primary non-communicable diseases, accounting for 9.0 million deaths in 2016. In high-income countries, cancer has emerged as the predominant cause of premature death [5].

The CRP-albumin-lymphocyte index, abbreviated as CALLY, comprising C-reactive protein (CRP) content, serum albumin levels, and total lymphocyte count, respectively reflects inflammation level, nutritional status, and immune function of the body [6–8]. It has been shown that, the CALLY index demonstrated greater prognostic value compared to traditional colorectal cancer (CRC) prognostic factors such as NLR, PLR, SII, and mGPS. An increase in the CALLY index was linked between a significant reduction and mortality risk [9]. CALLY serves as a prognostic element in lung cancer patients, with non-small cell lung cancer patients exhibiting a low CALLY index experiencing significantly poorer overall survival compared to those with a high index [8]. Furthermore, the CALLY index has proven to be a valuable prognostic biomarker in patients with oral squamous cell carcinoma, ovarian cancer, gastric cancer, and hepatocellular carcinoma [7, 10–12].

CRP is a sensitive marker of systemic inflammation, and the cancer-associated systemic inflammatory response is a critical indicator of tumor progression. The significance of systemic inflammation in cancer progression is extensively documented, with CRP identified as a pivotal biomarker. The elevation of this protein's levels in response to inflammation underscores its value in clinical evaluations of cancer's influence on the body. Malnutrition and immunosuppression, which are common in cancer patients, also adversely affect prognosis and are reflected in biochemical indicators of albumin and lymphocytes [8, 13]. Reduced levels of these indicators not only indicate inadequate nutritional intake and reduced immunocompetence, but are also associated with increased systemic inflammation. In addition to its role in nutritional assessment, albumin is an indirect marker of systemic inflammation [14–16]. Similarly, lymphocytes play a vital part in the immune system response to cancer [17]. Whereas peripheral blood lymphocyte count is one of the important indicators for assessing the immune function of the body [18], many studies have been reported in small cell lung cancer [19], colorectal cancer [20], prostate cancer [21] and other different cancer types, higher peripheral blood lymphocyte counts are associated with better clinical prognosis.

Numerous studies have established CRP as a predictive marker for cardiovascular disease [22, 23], while higher albumin levels are independently linked to a lower risk of all-cause and CVD mortality [24]. A low lymphocyte count commonly observed during systemic inflammatory responses is linked with adverse outcomes in various heart diseases [25]. Consequently, we developed the CALLY index, incorporating CRP, albumin, and lymphocytes, to assess its correlation with all-cause mortality, cardiovascular disease mortality, and cancer mortality.

This is a retrospective study utilizing the Nhanes database and, to our knowledge, is the first research to investigate the relationship between the CALLY index and all-cause and cause-specific mortality in patients with all forms of cancer.

Methods

Study population

Data analysis utilized multiple cycles of the National Health and Nutrition Examination Survey (NHANES) spanning from 1999 to 2018 [26]. NHANES is a cross-sectional, population-based survey employing a complex, stratified, multistage probabilistic clustering design. It comprises household interviews, examinations, and laboratory measurements aimed at gathering health and nutritional information from the civilian, noninstitutionalized U.S. population. The NHANES program received approval from the National Center for Health Statistics (NCHS) Ethics Review Board, with all participants providing written informed consent. Inclusion criteria for this study included (1) participants aged 20 years and older, (2) patients with a confirmed diagnosis of cancer or malignancy, and (3) availability of CRP, albumin, and lymphocyte data necessary to calculate the CALLY index. In addition, we excluded participants without mortality status data. Ultimately, 3,511 eligible patients were screened from the NHANES data from 1999 to 2018 for analysis. The entire data selection process is depicted in Fig. 1. Data visualization and analysis were conducted using statistical software packages R 4.2.2 and EmpowerStats 4.2.

CALLY index calculation

Complete blood counts were conducted using a Coulter® DxH 800 analyzer under the supervision of trained medical personnel. CALLY index was calculated by albumin (g/L) × lymphocytes (109/L) ÷ [CRP (mg/L) × 10].

Mortality

Mortality data were sourced from the National Death Index (NDI) records up to December 31, 2019, while cause-specific mortality was ascertained using the International Classification of Diseases, 10th edition (ICD-10). Cardiovascular disease deaths were identified using ICD-10 codes I00-I09, I11, I13, and I20-I51; cancer deaths were classified under ICD-10 codes C00-C97. The

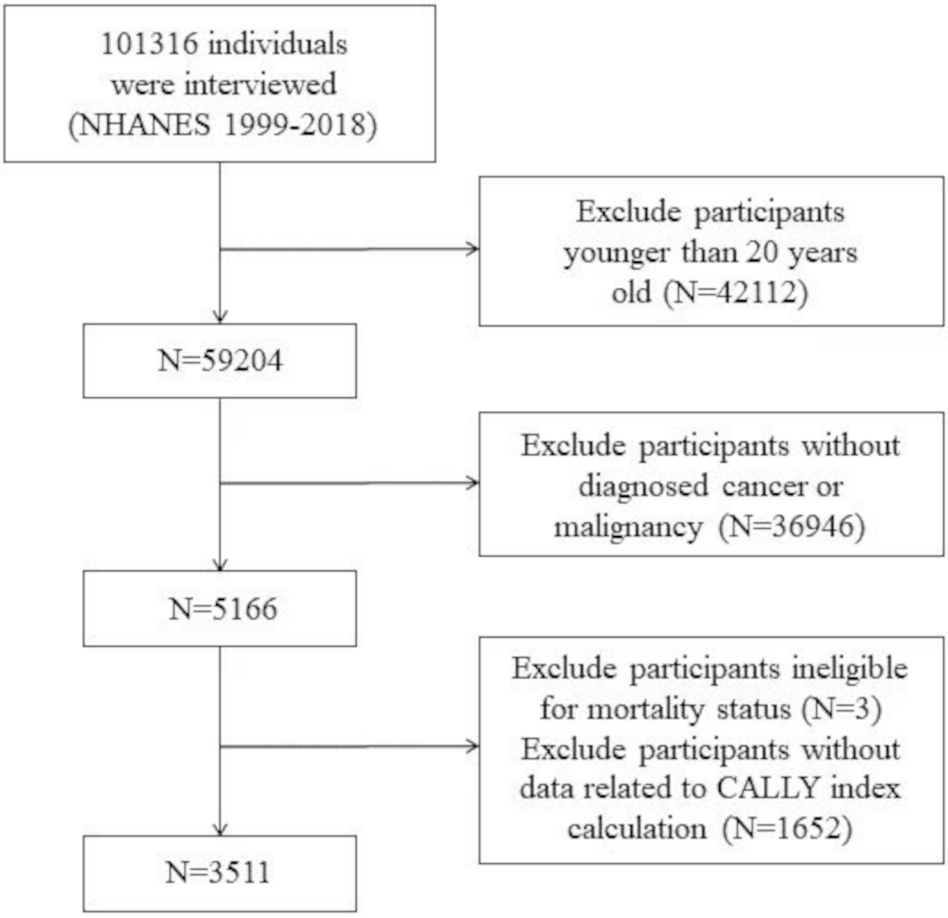

Fig. 1 Flowchart for screening participants in the NHANES database

analysis ultimately included a total of 1346 deaths, comprising 293 cardiac-related and 396 cancer-related fatalities for further examination.

Covariates

We included a variety of covariates that could have influenced the results. Age, gender, race, smoking status, alcohol consumption, types of cancer and prevalence of heart disease and kidney disease were collected by standardized questionnaires from household interviews. The prevalence of diabetes mellitus was combined with questionnaire collection and experimental values such as glycated hemoglobin (HbA1c). The prevalence of hypertension also combined questionnaire collection and measurement data, and body mass index (BMI) was collected from participants who underwent medical examinations at mobile health centers. Laboratory indicators used included blood albumin, lymphocytes, C-reactive protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol (TC), triglycerides (TG), total bilirubin (STB) and blood creatinine (Scr). Details of the definitions are given in the Supplementary Methods.

Data analysis

For the study population, continuous variables were presented as mean (standard deviation) or median (minimum-maximum), while categorical variables were displayed as percentages. Variables that showed a significance level of $p<0.05$ in univariate analysis were included in the subsequent multivariate Cox regression model. The association between the CALLY index and the risk of all-cause or cause-specific mortality was evaluated using multivariate Cox regression models, estimating hazard ratios (HR) and 95% confidence intervals (CI). Due to the left-skewed distribution of CALLY, values were natural log-transformed and categorized into quartiles for analysis, treated as both continuous and categorical variables within the models.

Model 1, which included no covariates, served as the baseline. Model 2 adjusted for demographic variables such as gender, age, race, and poverty income ratio (PIR). Model 3, a fully adjusted model, also incorporated adjustments for smoking status, alcohol consumption, body mass index (BMI), total cholesterol (TC), alanine aminotransferase (ALT), Serum creatinine (Scr), serum total bilirubin (STB), types of cancer and prevalences of

diabetes mellitus (DM), cardiovascular disease (CVD), chronic kidney disease (CKD), types of cancer and hypertension.

To test for the presence of a nonlinear relationship between CALLY and mortality, a restricted cubic spline (RCS) regression with the aforementioned multivariate adjustments was utilized. The likelihood ratio test was employed to evaluate nonlinearity, and if detected, a two-segment Cox proportional hazards regression model was established based on the inflection point. To investigate the dose-response relationship between CALLY and mortality, restricted cubic spline (RCS) regression with multivariate adjustment as described above was used. The likelihood ratio test was used to test for nonlinearity. If nonlinearity was detected, a two-segment Cox proportional risk regression model was constructed based on the inflection point.

Treatment of missing data values: mean or median interpolation was applied for continuous variables such as PIR, BMI, TC, ALT, and AST. Missing data for categorical variables such as types of cancer, smoking, drinking status, and presence of kidney disease in this study did not exceed 6% of the overall data, and missing values were labeled as unrecorded and not interpolated. The amount of missing data is shown in the Supplementary Table 1.

Sensitivity analysis

A 2-group sensitivity analysis was performed in this study. Group 1 excluded subjects with less than 2 years of follow-up (including death within 2 years) to rule out reverse causality (see Supplementary Table 8). In group 2, we performed separate interaction tests by several factors, including sex, age, whether or not they smoked, whether or not they drank alcohol, and whether or not they had diabetes mellitus, to look for whether or not there were factors influencing the relationship between the CALLY index and mortality.

Results

Baseline characteristics of study participants

Among participants across ten consecutive 2-year cycles of the NHANES (1999–2018), we excluded participants with no cancer prevalence, missing data on blood albumin, lymphocyte, and CRP concentrations, and missing follow-up data, and selected patients with diagnosed cancer aged 20 years and older. A total of 3,511 adult cancer survivors with a average age of 66.1±14.6 years were ultimately enrolled. During a median follow-up of 103 months, 1,355 deaths occurred, and the incidence of all-cause mortality for these participants was 38.34%, of which 293 died from cardiovascular disease and 396 from the cancer itself. Baseline characteristics stratified by quartiles of ln CALLY are presented in Table 1. Participants with higher levels of CALLY tended to be non-Hispanic white, have higher household poverty-to-income ratios, have no drinking habits, have no concomitant diabetes, cardiovascular disease, hypertension, or renal disease, and have lower BMI, ALT, and TG levels. The baseline characteristics according to all-cause mortality are detailed in the Supplementary Table 2.

CALLY index and mortality in Cancer patients

Table 2 shows that ln CALLY was inversely associated with the risk of all-cause mortality in model 1 ($P<0.0001$). The results of the univariate analyses using the Cox regression model are detailed in Supplementary Table 3. The results remained robust and statistically significant after adjusting for other potential confounders in Model 2 and Model 3. The HR (95% CI) was 0.83 (0.80–0.86) for Model 2 and 0.82 (0.79–0.86) for Model 3. In all models, neither CALLY as a continuous nor categorical variable affected its negative association with mortality. Specifically, the fully adjusted models showed that each unit increase in ln CALLY reduced the risk of all-cause mortality in cancer patients by 18%, as well as an 18% reduction in the risk of mortality due to cardiac (95%CI=0.74–0.90) and cancer-specific (95%CI=0.76–0.88) causes among cancer patients.

Compared with the first quartile of CALLY, patients in the fourth quartile group had a lower HR, with the Non-adjustment model (HR=0.47, 95%CI=0.40–0.56), Minimally-adjusted model (HR=0.48, 95%CI=0.40–0.57, and Fully-adjusted model (HR=0.46, 95%CI=0.38–0.56) all supported this finding, all P for interaction<0.001. Figure 2 shows a statistically significant difference in survival for different quartile ln CALLY level groups for the full mortality outcome. These statistically significant correlations persisted for mortality rates in cardiovascular disease and cancer mortality.

As shown in Fig. 3, the results of the weighted restricted cubic spline (RCS) regression analyses, adjusted for multiple potential confounders, which reaffirmed the negative linear association between the CALLY index and all-cause mortality. Similar trends have been observed for the CALLY index with respect to the CVD mortality rate and the cancer mortality rate, as shown in Supplementary Figs. 1–2. Threshold effect analyses are shown in the Supplementary Tables 4–6.

Sensitivity and subgroup analyses

To explore whether demographic characteristics, serum marker levels, or comorbidities could elucidate the relationship between ln CALLY and all-cause mortality, subgroup analyses were performed (Table 3). When analyzed stratified by the multifactorial factors described above, the results showed a significant interaction between the CALLY index and age ($P<0.0001$). The relationship

Table 1 Baseline characteristics of participants

	Q1	Q2	Q3	Q4	*P*-value
N	878	872	883	878	
Age, years	66.28 (13.58)	67.11 (14.29)	66.55 (14.74)	64.24 (15.56)	< 0.001
Family poverty income ratio	2.43(0.00–5.00)	2.68(0.00–5.00)	2.78(0.00–5.00)	2.78(0.00–5.00)	< 0.001
BMI, kg/m2	30.77 (7.41)	29.73 (6.73)	26.34 (4.84)	28.24 (5.22)	< 0.001
ALT, U/L	25.00(6.00-393.00)	21.00(7.00-177.00)	20.00(6.00-775.00)	20.00(8.00-138.00)	< 0.001
AST, U/L	22.00(9.00-310.00)	23.00(9.00-430.00)	23.00(9.00-139.00)	24.00(9.00-101.00)	< 0.001
TC, mmol/L	4.91 (1.21)	5.10 (1.11)	5.20 (1.12)	5.00 (1.05)	< 0.001
TG, mmol/L	1.45(0.18–34.56)	1.54(0.34–11.20)	1.50(0.36–16.53)	1.28(0.32–10.83)	< 0.001
STB, μmol/L	9.22 (5.00)	11.13 (4.95)	12.43 (4.95)	13.52 (5.64)	< 0.001
SCr, μmol/L	81.77(32.71-194.94)	80.44(26.50-875.20)	79.60(26.50-733.70)	79.56(26.50-282.88)	0.102
Gender, *n*(%)					0.085
Male	413 (47.04%)	398 (45.64%)	410 (46.43%)	450 (51.25%)	
Female	465 (52.96%)	474 (54.36%)	473 (53.57%)	428 (48.75%)	
Race, *n*(%)					< 0.001
Mexican American	78 (8.88%)	75 (8.60%)	55 (6.23%)	57 (6.49%)	
Other Hispanic	68 (7.74%)	35 (4.01%)	34 (3.85%)	23 (2.63%)	
Non-Hispanic White	534 (60.82%)	614 (70.41%)	658 (74.52%)	703 (80.07%)	
Non-Hispanic Black	140 (15.95%)	114 (13.07%)	108 (12.23%)	77 (8.77%)	
Other Race Including Multi-Racial	58 (6.61%)	34 (3.90%)	28 (3.17%)	18 (2.05%)	
Smoking, *n*(%)					0.677
Yes	500 (57.58%)	484 (55.50%)	499 (56.58%)	477 (54.39%)	
No	376 (42.92%)	388 (44.50%)	383 (43.42%)	400 (45.61%)	
Alcohol, *n*(%)					< 0.001
Yes	629 (76.71%)	569 (68.06%)	574 (68.09%)	597 (72.01%)	
No	191 (23.29%)	267 (31.94%)	269 (31.91%)	232 (27.99%)	
CVD, *n*(%)					< 0.001
Yes	208 (23.69%)	204 (23.39%)	167 (18.91%)	146 (16.63%)	
No	670 (76.31%)	668 (76.61%)	716 (81.09%)	732 (83.37%)	
CKD, *n*(%)					< 0.001
Yes	105 (12.03%)	67 (7.71%)	46 (5.22%)	26 (2.96%)	
No	768 (87.97%)	802 (92.29%)	835 (94.78%)	851 (97.04%)	
Diabetes, *n*(%)					< 0.001
Yes	255 (29.04%)	206 (23.62%)	169 (19.14%)	141 (16.06%)	
No	623 (70.96%)	666 (76.38%)	714 (80.86%)	737 (83.94%)	
Hypertension					< 0.001
Yes	623 (72.02%)	605 (69.94%)	606 (69.58%)	506 (59.25%)	
No	242 (27.98%)	260 (30.06%)	265 (30.42%)	348 (40.75%)	
Statues, *n*(%)					< 0.001
Alive	642 (73.12%)	509 (58.37%)	472 (53.45%)	542 (61.73%)	
Death	236 (26.88%)	363 (41.63%)	411 (46.55%)	336 (38.27%)	
Types of cancer, *n*(%)					< 0.001
Lung	35(3.99%)	24(2.75%)	10(1.14%)	11(1.25%)	
Digestive System	86(9.79%)	76(8.72%)	70(7.95%)	67(7.64%)	
Urinary System	189(21.53%)	180(20.64%)	161(18.27%)	154(17.54%)	
Head and Neck	33(3.76%)	28(3.21%)	17(1.93%)	24(2.74%)	
Reproductive system	112(12.76%)	128(14.68%)	128(14.53%)	123(14.03%)	
Breast	132(15.03%)	122(13.99%)	139(15.78%)	109(12.43%)	
Blood System	26(2.96%)	22(2.52%)	26(2.95%)	32(3.65%)	
Skin	198(22.55%)	241(27.64%)	280(31.78%)	304(34.66%)	
Central nervous system	1(0.11%)	3(0.34%)	7(0.79%)	3(0.34%)	
Bone and Soft Tissue	8(0.91%)	6(0.69%)	7(0.79%)	7(0.80%)	
Other	58(6.61%)	42(4.82%)	36(4.09%)	43(4.90%)	

Results in table: Mean (SD), Median (Min-Max) / *N*(%)

Table 2 Univariate and multivariate results by cox regression

	Q1	Q2	Q3	Q4	*P* for trend	ln CALLY
All-cause mortality						
Model1	Reference	0.75 (0.63, 0.88)	0.65 (0.56, 0.77)	0.47 (0.40, 0.56)	< 0.0001	0.82 (0.79, 0.85)
Model2	Reference	0.70 (0.59, 0.83)	0.62 (0.52, 0.73)	0.48 (0.40, 0.57)	< 0.0001	0.83 (0.80, 0.86)
Model3	Reference	0.67 (0.56, 0.80)	0.61 (0.51, 0.73)	0.46 (0.38, 0.56)	< 0.0001	0.82 (0.79, 0.86)
CVD mortality						
Model1	Reference	0.68 (0.48, 0.97)	0.58 (0.41, 0.82)	0.41 (0.29, 0.59)	< 0.0001	0.78 (0.72, 0.85)
Model2	Reference	0.70 (0.49, 1.01)	0.63 (0.44, 0.90)	0.46 (0.32, 0.67)	< 0.0001	0.82 (0.75, 0.89)
Model3	Reference	0.66 (0.45, 0.99)	0.63 (0.42, 0.94)	0.49 (0.32, 0.73)	0.0015	0.82 (0.74, 0.90)
Cancer mortality						
Model1	Reference	0.79 (0.59, 1.07)	0.66 (0.49, 0.89)	0.44 (0.32, 0.59)	< 0.0001	0.81 (0.76, 0.86)
Model2	Reference	0.86 (0.64, 1.16)	0.74 (0.55, 1.00)	0.50 (0.36, 0.68)	< 0.0001	0.84 (0.79, 0.90)
Model3	Reference	0.88 (0.63, 1.23)	0.73 (0.52, 1.03)	0.47 (0.33, 0.67)	< 0.0001	0.82 (0.76, 0.88)

Model1: Non-adjustment model, no covariates were adjusted for

Model2: Minimally-adjusted model, only adjust for age, sex, race, PIR

Model3: Fully-adjusted model, adjust for gender, age, race, PIR, BMI, smoke, alcohol, TC, ALT, Cr, STB, diabetes, hypertension, CVD, CKD and types of cancer

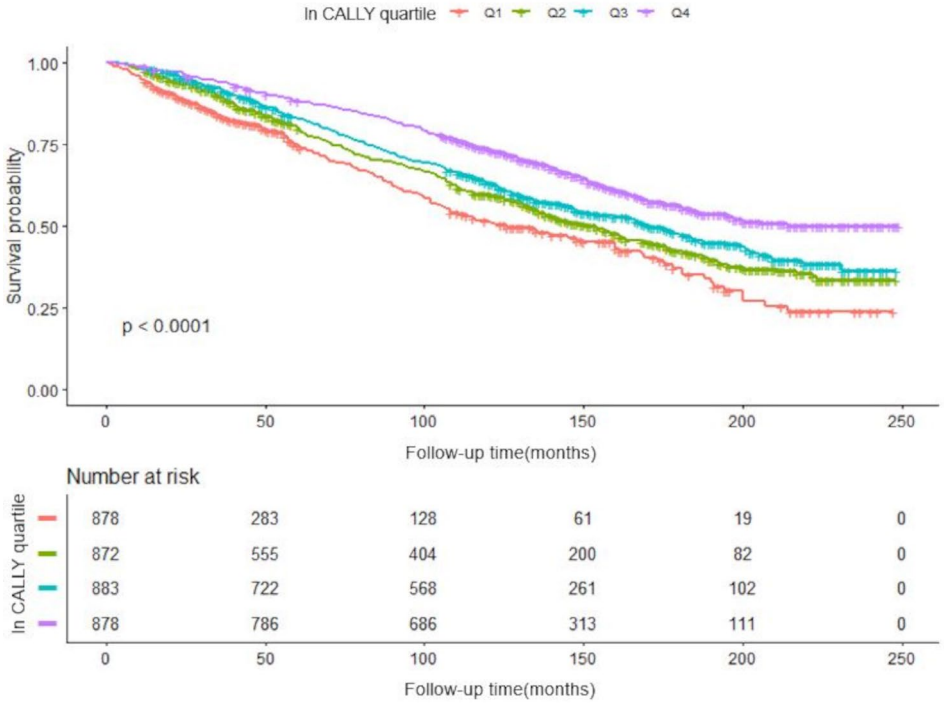

Fig. 2 Kaplan-Meier survival analysis curves illustrating significant differences in all-cause mortality rates for adult cancer patients categorized by different ln CALLY quartile groups

between the CALLY index and all-cause mortality was stable in stratified analyses for all factors except age, with *P* for interaction > 0.05. We further examined the associations between ln CALLY and all-cause and cause-specific mortality in different age subgroups, using 60 years as a cutoff. Supplementary Table 7 shows that these relationships are generally consistent with those observed in the overall population.

Discussion

In this large-scale retrospective study involving 3,511 adult cancer patients, we observed a negative linear association between CALLY levels and the risk of all-cause mortality, CVD mortality, and cancer mortality, with lower CALLY levels associated with increased risk. These findings remained robust after extensive sensitivity and stratification analyses.

Previous research has identified the CALLY index as a potential prognostic marker in various cancers, including

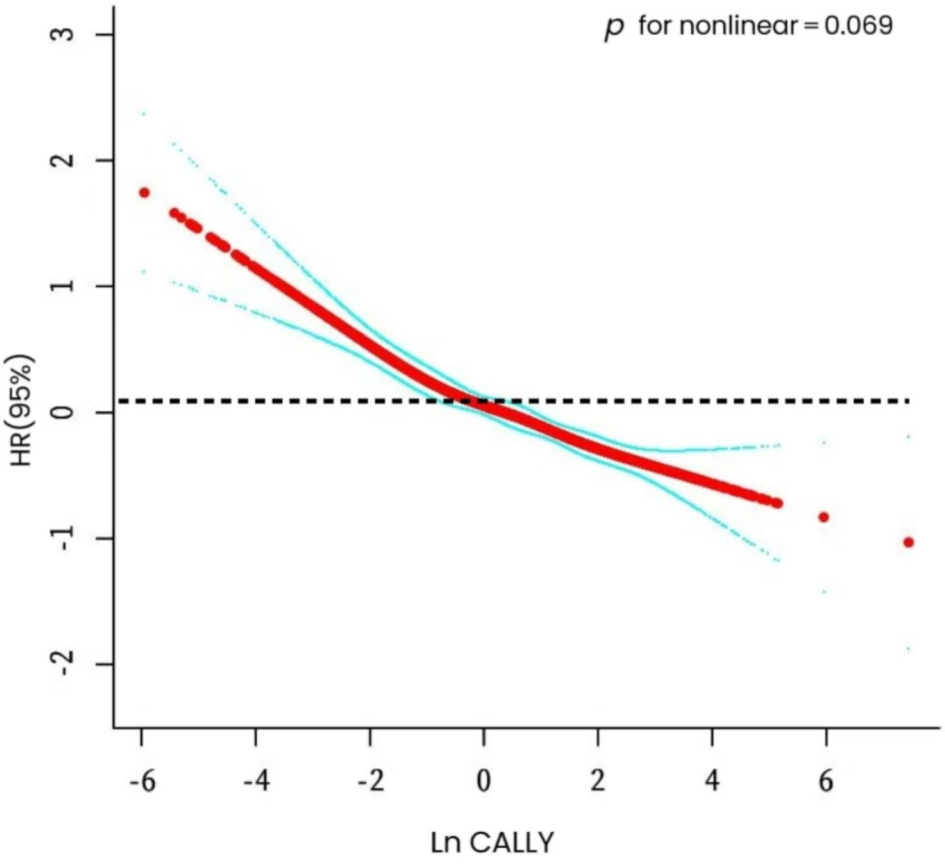

Fig. 3 Smoothed curve fitting with covariates adjusted for cancer patient follow-up data shows an approximately linear relationship between cancer patient mortality and CALLY index

colorectal [20, 27], hepatocellular [7], gastric [28], other gastrointestinal tumors [29], and lung cancer [8]. High CALLY levels have been independently linked to longer overall survival times and disease-free survival, while a low preoperative CALLY index has been recognized as a risk factor for postoperative complications, including surgical site infections. Our study corroborates these previous findings and contributes additional insights with its larger sample size. To our knowledge, this is the first research to explore the relationship between the CALLY index and both all-cause and cause-specific mortality across all cancer types, utilizing the NHANES database.

The prognosis of cancer patients is frequently linked to their immune function, nutritional status, and level of inflammation. Factors such as malnutrition, chronic uncontrolled inflammation, and autoimmune dysfunction can accelerate tumor progression and lead to cachexia in cancer patients, ultimately exerting a profound negative impact on survival and quality of life. Consequently, various indicators that reflect the immune, nutritional, and inflammatory states of patients are garnering increased attention as potential biomarkers for predicting cancer prognosis. The CALLY index, which leverages serum albumin levels, lymphocyte counts, and CRP levels as markers of nutritional status, immune function, and inflammatory response respectively, represents an enhanced scoring system for immune, inflammatory, and nutritional assessment. It is cost-effective, readily accessible, and straightforward to compute, thus offering substantial utility in clinical settings [7]. Although this study corroborates the prognostic relevance of the CALLY index in cancer, the specific mechanisms of the association between a high CALLY index and reduced mortality remain unclear.

The influence of inflammation tumors has been widely explored, but to date, the exact mechanisms by which inflammation develops into cancer are unknown. Nevertheless, inflammation does affect every stage of a tumor from onset to metastasis, and cancer cells may rely on the production of pro-inflammatory mediators to proliferate, evade the body's immunity, and promote tumor angiogenesis and metastasis. The contribution of cytokines such as tumor necrosis factor-alpha, interleukin 6, and interleukin 1 in inducing cancer cachexia is well established. Their elevated levels activate multiple pathways that promote skeletal muscle atrophy in malignant

Table 3 Subgroup analysis

Characteristic	HR	95%CI Low	95%CI High	*P* value	*P* for interaction
Age, years					< 0.0001
< 60	0.63	0.55	0.72	< 0.0001	
≥ 60	0.83	0.80	0.87	< 0.0001	
Gender, *n*(%)					0.5435
Male	0.82	0.77	0.86	< 0.0001	
Female	0.84	0.78	0.89	< 0.0001	
PIR					0.8352
< 1.3	0.82	0.75	0.89	< 0.0001	
1.3–3.5	0.84	0.79	0.88	< 0.0001	
≥ 3.5	0.82	0.75	0.89	< 0.0001	
Race, *n*(%)					0.0064
Mexican American	0.88	0.71	1.10	0.2606	
Other Hispanic	0.91	0.61	1.38	0.6719	
Non-Hispanic White	0.83	0.79	0.87	< 0.0001	
Non-Hispanic Black	0.76	0.67	0.85	< 0.0001	
Other Race Including Multi-Racial	0.43	0.28	0.67	0.0001	
BMI, kg/m2					0.1215
Low weight	0.62	0.48	0.80	0.0003	
Normal	0.84	0.79	0.90	< 0.0001	
Overweight	0.83	0.78	0.89	< 0.0001	
Obesity	0.78	0.72	0.85	< 0.0001	
Smoking, *n*(%)					0.1906
Yes	0.81	0.76	0.85	< 0.0001	
No	0.85	0.80	0.91	< 0.0001	
Alcohol, *n*(%)					0.9439
Yes	0.82	0.78	0.87	< 0.0001	
No	0.83	0.77	0.89	< 0.0001	
ALT, U/L					0.6137
< 40	0.83	0.79	0.87	< 0.0001	
≥ 40	0.85	0.76	0.96	0.0070	
AST, U/L					0.5869
< 40	0.82	0.79	0.86	< 0.0001	
≥ 40	0.85	0.75	0.97	0.0119	
TG					0.5758
< 1.7	0.82	0.78	0.86	< 0.0001	
≥ 1.7	0.84	0.78	0.90	< 0.0001	
TC, mmol/L					0.7764
< 5.2	0.82	0.78	0.86	< 0.0001	
≥ 5.2	0.83	0.77	0.89	< 0.0001	
STB, umol/L					0.5221
< 17.1	0.83	0.79	0.87	< 0.0001	
≥ 17.1	0.80	0.72	0.88	< 0.0001	
CVD, *n*(%)					0.7045
Yes	0.81	0.76	0.88	< 0.0001	
No	0.83	0.79	0.87	< 0.0001	
CKD					0.1399
Yes	0.75	0.67	0.85	< 0.0001	
No	0.83	0.80	0.87	< 0.0001	
DM					0.3517
Yes	0.85	0.79	0.92	< 0.0001	
No	0.82	0.78	0.86	< 0.0001	
Hypertension					0.6075
Yes	0.84	0.77	0.91	< 0.0001	

Table 3 (continued)

Characteristic	HR	95%CI Low	95%CI High	*P* value	*P* for interaction
No	0.82	0.78	0.86	< 0.0001	
Type of cancer					0.6163
Lung	0.59	0.51	0.69	< 0.0001	
Digestive System	0.77	0.69	0.87	< 0.0001	
Urinary System	0.85	0.79	0.91	< 0.0001	
Head and Neck	1.20	0.97	1.49	0.0929	
Reproductive system	0.80	0.70	0.92	0.0012	
Breast	0.90	0.81	0.99	0.0394	
Blood System	0.73	0.62	0.84	< 0.0001	
Skin	0.81	0.75	0.87	< 0.0001	
Central nervous system	9.62	5.51	16.80	< 0.0001	
Bone and Soft Tissue	0.18	0.13	0.26	< 0.0001	
Other	0.73	0.62	0.85	< 0.0001	

stroma [30]. The tumor microenvironment includes innate immune cells, adaptive immune cells, cancer cells and their surrounding stroma [31]. During tumor development, the inflammatory microenvironment promotes the proliferation of mutant cells [32–34]. In addition, inflammatory cells can act as a source of reactive oxygen species and reactive nitrogen intermediates, inducing DNA damage and genomic instability, thereby increasing the mutation rate [35, 36]. During cancer development, accompanied by sustained cell death and inflammatory cell infiltration, the production of a large number of cytokines, chemokines, and growth factors facilitates cell proliferation [37]. CRP serves as a typical acute-phase protein with plasma concentrations that increase rapidly and significantly in response to inflammation, infection, tissue injury, and cancer [38]. CRP transcription is regulated by various cytokines and transcription factor complexes, with IL-6 being the primary inducer of the CRP gene [39]. Serum CRP levels, which serve as the denominator of the CALLY index, reflect the systemic inflammatory response. It has been shown that high levels of serum CRP levels are associated with an immunosuppressive tumor microenvironment [40, 41], which may be one of the explanations for the relationship between high levels of serum CRP and poor prognosis in many studies [42–44].

With the advancement of modern tumor immunology, the interaction between the immune system and tumors throughout their development has become increasingly recognized [45]. It is acknowledged that drugs alone cannot entirely eliminate all tumor cells within the body, underscoring the importance of the body's own immune cells in combating residual tumor cells. Consequently, monitoring immune function is crucial for cancer prevention, tracking cancer progression, and predicting prognosis. The immune status of patients with tumors is a vital parameter for assessing prognosis and adjusting treatment strategies. Lymphocytes, as the primary immune cells of the body, play a pivotal part in immune surveillance [46]. They inhibit the proliferation, invasion, and migration of tumor cells through their cytotoxic activity and the induction of tumor cell apoptosis, thereby potentially controlling tumor growth [47]. Although lymphocyte counts are influenced by various factors, which may introduce fluctuations, they remain a valuable marker for assessing immune competence in clinical and research settings, particularly when interpreted in combination with other immune and inflammatory markers [48, 49].

Serum albumin is widely used to assess nutritional status and visceral protein synthesis. Notably, in patients with extensive diseases, serum albumin synthesis can be impeded by malnutrition and systemic inflammation. Prior research has indicated that diminished levels of albumin and lymphocytes can negatively impact prognosis across various tumor types. In a study involving 582 pancreatic cancer patients post-resection, Xu et al. [50]. reported that low serum levels of lymphocytes and albumin may predict poorer overall survival and recurrence-free survival. The Lymphocyte-Albumin (LA) index, calculated by multiplying lymphocyte count by albumin concentration, has been shown to be a prognostic marker. For example, Yamamoto et al. [51], observed that patients with stage II/III rectal cancer and low LA values had significantly reduced OS. Consistent with previous studies, Alagappan M et al. showed that low albumin levels and NLR > 5 (NLR defined as neutrophil-lymphocyte ratio) prior to radiotherapy were associated with reduced survival in patients with locally advanced pancreatic cancer treated with Stereotactic body radiotherapy [52]. Moreover, low serum albumin levels have been recognized as an independent risk factor for survival in pancreatic cancer patients [53]. Prognostic Nutritional Index (PNI) values, derived from albumin levels, have been shown to enhance survival predictions in pancreatic cancer

patients, with lower PNI levels linked to poor prognosis [54, 55].

This study has several strengths and limitations. This is a large retrospective study of the CALLY index and all-cause, cause-specific mortality in oncology patients using the Nhanes database, and to our knowledge, this study included a larger sample size than its predecessors. We adjusted for demographics and other covariates that may affect the relationship between the CALLY index and mortality to increase the confidence and generalizability of the results. Multiple sensitivity and subgroup analyses further confirmed the robustness of our results. However, this study has some limitations. First, due to database limitations, detailed cancer staging, histological information, and treatment response data were not available in our study, limiting the ability to explore differences in the correlation between CALLY and prognosis across cancers of varying severity and treatment outcomes. As a result, the generalizability of our findings may be constrained, as the prognosis can differ significantly between patients with early-stage, responsive cancers and those with advanced, refractory disease. Additionally, due to database limitations, CALLY index data could only be measured at baseline, preventing longitudinal assessment. Second, this was a retrospective study and some selection bias may exist.

Conclusion

In conclusion, we found that CALLY was linearly and negatively associated with all-cause mortality and cancer and cardiac-caused mortality. These findings suggest that CALLY has great potential to become one of the prognostic markers in oncology. This study demonstrates the importance of managing nutritional status and body inflammation levels in cancer patients, and measuring the CALLY index can help to predict prognosis and develop therapeutic strategies in daily clinical practice, but validation in large-sample, multi-center, randomized controlled trials is needed.

Abbreviations

CRP C	Reactive protein
CALLY index	C-reactive protein-albumin-lymphocyte index
NHANES	National Health and Nutritional Examination Surveys
CRC	Colorectal cancer
CVD	Cardiovascular disease
LLC	Lymphocyte count
NCHS	National Center for Health Statistics
HbA1c	Glycated hemoglobin
BMI	Body mass index
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
TC	Total cholesterol
TG	Triglycerides
STB	Total bilirubin
Scr	Blood creatinine
PIR	Poverty income ratio
CKD	Chronic kidney disease
HR	Hazard ratios
CI	95% confidence intervals
RCS	Restricted cubic spline

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

LLZ, QXJ, and QK directed the study and critically revised the manuscript for significant intellectual content. ZD was responsible for conceiving and designing the research methodology, as well as conducting the data collection, analysis, and interpretation. ZD, LYD and YYZ prepared the initial drafts of the manuscripts. All authors made substantive contributions to the manuscript and approved the version submitted for publication.

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Data availability

The dataset utilized in this study is publicly accessible and can be located at the specified link: https://www.cdc.gov/nchs/nhanes/.

Declarations

Ethics approval and consent to participate

Not applicable. This study utilized publicly available data from the National Health and Nutrition Examination Survey (NHANES), which was approved by the National Center for Health Statistics Ethics Review Board. All participants provided informed consent at the time of data collection by NHANES.

Consent for publication

Not applicable. This manuscript does not contain any individual person's data in any form.

Competing interests

The authors declare that no commercial or financial relationships that could be construed as potential conflicts of interest influenced the research conducted.

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