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Protective role of the C-reactive protein-albumin-lymphocyte (CALLY) index for cardiovascular risk and mortality

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The C-reactive protein-albumin-lymphocyte (CALLY) index represents a novel immune-nutritional scoring system. However, the relationship between the CALLY index and cardiovascular disease (CVD) risk, as well as its association with all-cause and CVD mortality, remains to be elucidated. The binary weighted logistic regression models, Cox proportional hazards model, and Kaplan–Meier survival analysis curves were respectively used to analyze the relationship between CALLY index and outcomes. ROC curve was adopted to compare the predictive abilities of CALLY index and other inflammatory-related indexes. Moreover, restricted cubic splines (RCS) were employed to assess the potential nonlinear relationship between CALLY index and outcomes. We revealed an inverse association between CALLY index and CVD in U.S. general population (OR = 0.74, 95% CI 0.63–0.87). Moreover, elevated CALLY index was significantly associated with reduced risks of both all-cause mortality (HR = 0.62, 95% CI 0.50–0.78) and CVD mortality in CVD participants (HR = 0.68, 95% CI 0.49–0.94). RCS analysis demonstrated a linear relationship between the CALLY index and CVD in the U.S. general population and a non-linear relationship between CALLY index and all-cause and CVD mortality in CVD patients. The ROC analysis indicated that the CALLY index had a better discriminatory ability than other inflammatory-related indexes. Elevated baseline CALLY index levels were independently associated with a decreased incidence of CVD in the U.S. general population, as well as reduced risks of both all-cause mortality and CVD mortality among patients with CVD. This study suggested that the CALLY index had potential utility for risk stratification in clinical practice.

Keywords C-reactive protein-Albumin-Lymphocyte index, Cardiovascular disease, All-cause mortality, Cardiovascular mortality

Abbreviations

CALLY	The C-reactive protein-Albumin-Lymphocyte
CVD	Cardiovascular disease
RCS	Restricted cubic splines
SII	Systemic immune-inflammation index
NHR	Neutrophil-lymphocyte ratio
LHR	Lymphocyte-to-high-density lipoprotein ratio
MHR	Monocyte to HDL-C Ratio
PHR	Platelet to HDL-C Ratio
MI	Myocardial infarction
HF	heart failure
SA	Serum albumin
NCHS	National Center for Health Statistics
PIR	Poverty-Income Ratio
WBC	White blood cell

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NEU	Neutrophils
PLT	Platelet
LYM	Lymphocytes
MON	Monocyte
CRP	C-reactive protein
Alb	Albumin
HDL-C	High-density lipoprotein cholesterol
TC	Total cholesterol
TG	Triglyceride
eGFR	Estimated glomerular filtration rate
CKD	Chronic kidney disease
ROC	Receiver operating characteristic curves

Cardiovascular diseases (CVD) represent the predominant contributor to global morbidity and mortality, with the WHO projecting its continued dominance as the primary cause of mortality worldwide[1]. Extensive preclinical investigations have established a strong pathophysiological link between systemic inflammation and CVD progression. Furthermore, experimental studies utilizing well-established CVD animal models have provided compelling evidence that targeted modulation of specific immune-inflammatory pathways may offer potential therapeutic advantages[2]. Immune cells, including T cells and B cells, play crucial roles in the onset and progression of various CVDs, such as atherosclerosis, myocardial infarction, and stroke. Currently, several inflammation-related biomarkers have been employed for CVD prognosis prediction, including the systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-high-density lipoprotein cholesterol ratio (LHR), monocyte-to-HDL-C ratio (MHR), and platelet-to-HDL-C ratio (PHR). However, these individual biomarkers demonstrate limited capacity to comprehensively reflect systemic pathophysiological abnormalities. Moreover, their clinical utility requires further validation through large-scale, multicenter studies to establish robust evidence for routine clinical implementation.

Hypoalbuminemia, characterized by reduced serum albumin levels, has been observed in individuals suffering from severe myocardial infarction (MI), heart failure (HF), stroke, hip fractures, cancer, and kidney disorders[3–5]. Discovered unexpectedly in 1989, serum albumin (SA) concentration has since been established as a reliable prognostic marker for CVD[6]. The relationship between reduced SA levels and poor clinical outcomes is considered multifactorial in nature, as evidenced by previous studies[7,8]. The observed hypoalbuminemia may stem from either systemic inflammatory responses or insufficient nutritional status, both of which have been demonstrated to significantly influence CVD progression and prognosis[9,10].

The C-reactive protein-albumin-lymphocyte (CALLY) index is a novel composite biomarker that integrates the simultaneous assessment of systemic inflammation, immune response, and nutritional status[11]. It is calculated through a standardized formula: (albumin concentration [g/dL] × lymphocyte count [10^9/L])/(C-reactive protein level [mg/L]) × 10^4.[12] Several investigations have been conducted to examine the relationship between the CALLY index and disease prognosis[11–13]. These studies consistently demonstrated an inverse association between CALLY index levels and both disease incidence and mortality rates. However, the prognostic significance of the CALLY index in CVD risk prediction and mortality outcomes remains to be fully elucidated. This study aims to investigate the association between CALLY index levels and CVD incidence in the U.S. general population, while also examining its predictive value for all-cause and CVD mortality among patients with established CVD.

Methods

Study population

Our data originated from the National Health and Nutrition Examination Survey (NHANES), a comprehensive survey designed to assess the nutritional status and health conditions of the U.S. population. And the National Center for Health Statistics (NCHS) Research Ethics Review Board has approved the NHANES study. Our study examined the relationship between the CALLY index and CVD, along with all-cause and CVD mortality, using data from the NHANES spanning the years 2001 to 2018. The following groups were excluded from the study: (1) Individuals without the data of albumin, lymphocyte and C-reactive protein; (2) Individuals whose survival data were not been recorded; (3) individuals missing the data to calculate SII, NHR, LHR, MHR and PHR. Finally, 36,904 participants were enrolled into our study. The follow-up period began at each participant's NHANES examination date and continued until the date of death or the end of follow-up on December 31, 2019, whichever occurred first. Participants who were alive at the end of follow-up were right-censored at this date (NCHS Linked Mortality File description). In this study, among 4,313 participants with cardiovascular disease, 1,860 deaths occurred during follow-up. The median survival times were 107, 135, 137, and 154 months for participants in the first to fourth quartiles of the CALLY index, respectively. Figure 1 presents an overview of the participants selection process.

Data collection

Our research included four primary categories of covariates. (1) Demographic and health-related factors was collected, which comprised sex, age, race (White, Black, Mexican and other), education (less than high school, high school diploma and more than high school), marital status (married/living with partner, widowed/divorced/separated and never married), income and poverty (PIR < 1, 1–3 or > 3), smoke (no, yes), alcohol (mild, moderate and heavy), BMI (< 18.5, 18.5–25, ≥ 25) and physical activity (no or less, moderate and heavy). (2) Complete blood count and blood biochemical indicators, including white blood cell (WBC), neutrophils (NEU), platelet (PLT), lymphocytes (LYM), monocyte (MON), C-reactive protein (CRP), albumin (Alb), high-density

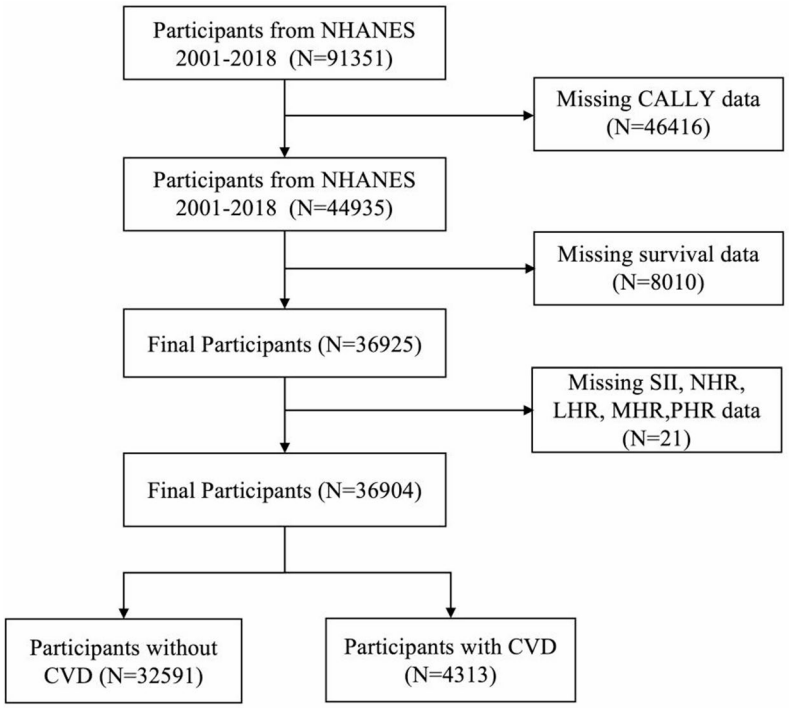

Fig. 1. Flow chart of participants in our study.

lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglyceride (TG) and estimated glomerular filtration rate (eGFR) were collected. (3) Comorbidities, including hypertension, diabetes and chronic kidney disease (CKD) were gathered.

Clinical outcomes

The primary outcomes in our study including incidence of CVD, all-cause mortality and CVD mortality. CVDs included congestive heart failure, coronary heart disease and angina pectoris. The participants was asked "Has a doctor or other health professional ever told [you/SP] that [you/s/he]…had congestive heart failure/coronary heart disease/angina pectoris/myocardial infarction/stroke?". If the answer was "yes", the individual was classified as a CVD patient. Since the diagnosis of CVD was based on self-reported data, there is a potential for misclassification.

Futhermore, we accessed the National Death Index (NDI) through the National Center for Health Statistics (NCHS) to determine the participants' survival status. And based on the international Statistical Classification of Diseases, 10th Revision (ICD-10) to identify disease-specific death.

Assessment of independent variable

The CALLY index was computed using the formula: (albumin concentration [g/dL] × lymphocyte count [10^9/L])/(CRP level [mg/L]) × 10^4, offering a comprehensive assessment of both inflammatory and nutritional conditions[14].

Additionally, we explored the association of SII, NHR, LHR, MHR, and PHR with CVD, all-cause mortality, and CVD mortality.

SII: (PLT count [10^9/L] × NEU count [10^9/L])/LYM count [10^9/L].
NHR: NEU count [10^9/L]/HDL-C mg/dL)
LHR: LYM count [10^9/L]/HDL-C (mg/dL).
MHR: MON count [10^9/L]/HDL-C (mg/dL).
PHR: PLT count [10^9/L]/HDL-C (mg/dL).

Statistical analyses

All statistical analyses accounted for the complex, multistage, stratified probability sampling design of NHANES. Sampling weights, strata, and primary sampling units (PSUs) were incorporated into all models to ensure nationally representative estimates. For the combined 2001–2018 survey cycles, multi-cycle examination weights were calculated by dividing the 2-year sample weights (WTMEC2YR) by the number of included cycles ($n = 9$). To illustrate baseline data, categorical variables were expressed as survey-weighted percentages, while continuous variables were represented as survey-weighted means. Comparisons among these groups were conducted using analysis of variance (ANOVA) or the Kruskal–Wallis test for continuous variables and the chi-square (χ^2) test for categorical variables. A two-tailed P-value of 0.05 was considered the threshold for statistical significance.

To progressively eliminate the impact of confounding factors on the occurrence of outcomes, we constructed three models. Model 1 was unadjusted. Model 2 was adjusted for sex, age, race, education, marital status and PIR. Model 3 was adjusted for sex, age, race, education, marital status, PIR, BMI, physical activity, smoke, alcohol, hypertension, diabetes and CKD. To explore the relationship between CALLY index and CVD in U.S. general population, the binary weighted logistic regression models was adopted. The Cox proportional hazards model and Kaplan–Meier survival analysis curves were used to assess the correlation of CALLY index with all-cause and CVD mortality. Stratified analysis was conducted for significant covariates, examining the impact of gender and age on the outcomes.

Furthermore, restricted cubic splines (RCS) were employed to assess the potential non-linear relationship between CALLY index and CVD, all-cause mortality, and CVD mortality. Receiver operating characteristic curves (ROC) were generated to compare the predictive abilities of the CALLY index and inflammatory-related indexes, including SII, MHR, NHR, PHR, and LHR for CVD, all-cause and CVD mortality. A subgroup analysis was performed on significant covariates, considering potential effect modifiers, including sex, age, race, education, marital status, PIR, BMI, physical activity, smoke, alcohol, hypertension, diabetes and CKD. Statistical analyses were conducted using R software (version 4.3.2).

Results

Baseline characteristics of participants

Table 1 showed the baseline characteristics of 36,904 participants with or without CVD. Compared to non-CVD participants, CVD patients tended to be male, older, Mexican, married/living with partner, individuals with more than high school education and moderate income. Moreover, CVD patients was more likely to be higher BMI, smoker and mild drinker. The biochemical indicator revealed higher WBC, PLT, LYM, MON, CRP, TG, and lower HDL-C, TC, LDL-C in these patients. Unsurprisingly, CVD patients frequently presented with comorbidities, including hypertension, diabetes, and CKD. The weighted baseline characteristics are summarized in Table S1.

To further explore the association between CALLY and CVD, we selected CVD patients from all participants. These patients were then categorized into four quartiles based on CALLY index values to examine their baseline characteristics (Table 2). Compared to lower CALLY indexes, CVD patients with higher CALLY are likely to be male, Mexican, middle-income population, and individuals who were married or living with partners. Additionally, higher PLT, LYM, HDL-C, Alb are associated with higher CALLY index in CVD patients.

The association of CALLY (log-transformed) with cardiovascular disease in all participants

When treated as a continuous variable, the CALLY index exhibited a significant inverse association with CVD in the U.S. general population ($p < 0.001$ in all models). Similarly, when analyzed as a categorical variable, participants in the highest quartile (Q4) showed a significantly reduced risk of CVD compared to those in the lowest quartile (Q1) in all adjusted models ($p < 0.001$). Moreover, in all models, a significant downward trend was observed between the CALLY index and the risk of CVD (p for trend < 0.001) (Table 3). To validate the robustness of our findings, we performed a sensitivity analysis excluding participants who died within the first 2 years of follow-up or had baseline CRP levels > 10 mg/L. The results demonstrated consistent effect estimates, confirming the stability of our primary model (Table S2). Furthermore, In the confounders-only sensitivity analysis (excluding mediators including CKD, BMI, and diabetes), the protective association of the CALLY index was more pronounced (OR = 0.62) than in the fully adjusted model (OR = 0.74) (Table S3).

Additionally, RCS analysis demonstrated a linear association between the CALLY index and CVD in the U.S. general population (P-overall < 0.001; P-nonlinear = 0.513) (Fig. 2). Compared with other inflammation-related indicators (SII, NHR, LHR, MHR, and PHR), the CALLY index achieved the highest AUC value (0.595) for CVD prediction (Fig. 3).

The association of log (CALLY) with cardiovascular disease in all participants stratified by sex and age

Furthermore, we stratified all participants by sex and age. Interestingly, after adjusted for sex, age, race, education, marital status, PIR, BMI, physical activity, smoke, alcohol, hypertension, diabetes and CKD, sex-stratified logistic regression analysis revealed a significant association between the CALLY index and the incidence of CVD in both male and female groups (Table 4). RCS analysis indicated that a CALLY index > 7.62 appeared to confer greater protective effects against CVD in females (Fig. 4A).

Furthermore, the CALLY index demonstrated an inverse association with CVD among younger participants (Table 4). RCS analysis further revealed that in this subgroup, a CALLY value exceeding 8.08 was associated with a reduced risk of CVD (Fig. 4B).

Subgroup analysis of the association between CALLY index and cardiovascular disease in all participants

To further assess the impact of CALLY index on CVD, subgroup analysis was conducted according to sex, age, race, education, marital status, PIR, BMI, physical activity, smoke, alcohol, hypertension, diabetes and CKD (Fig. 5, Table S4). The CALLY index was more closely related to CVD in participants who were female, younger, White, never married participants, smoker, heavy drinker and who did not have hypertension, diabetes and CKD.

Characteristic	Overall *N* = 36,904	No CVD *N* = 32,591	CVD *N* = 4313	*P* value
Sex (%)				< 0.001
Male	17,926 (48.57)	15,673 (48.09)	2253 (52.24)	
Female	18,978 (51.43)	16,918 (51.91)	2060 (47.76)	< 0.001
Age (years) (mean (SD))	47.71 (19.33)	45.14 (18.56)	67.10 (12.95)	
Race (%)				< 0.001
White	7073 (19.17)	6592 (20.23)	481 (11.15)	
Black	5883 (15.94)	5388 (16.53)	495 (11.48)	
Mexican	16,468 (44.62)	13,958 (42.83)	2510 (58.20)	
Other	7480 (20.27)	6653 (20.41)	827 (19.17)	
Education (%)				< 0.001
Less than high school	9307 (27.11)	7829 (26.08)	1478 (34.32)	
High school diploma	8093 (23.58)	7050 (23.49)	1043 (24.22)	
More than high school	16,925 (49.31)	15,140 (50.43)	1785 (41.45)	
Marital status (%)				< 0.001
Married/Living with partner	21,162 (58.97)	18,785 (59.49)	2377 (55.14)	
Widowed/Divorced/Separated	7642 (21.29)	5998 (18.99)	1644 (38.14)	
Never married	7085 (19.74)	6795 (21.52)	290 (6.73)	
PIR (%)				< 0.001
< 1	7041 (20.80)	6219 (20.80)	822 (20.82)	
1–3	14,530 (42.93)	12,566 (42.03)	1964 (49.75)	
> 3	12,272 (36.26)	11,110 (37.16)	1162 (29.43)	
BMI (kg/m2) (%)				< 0.001
< 18.5	645 (1.78)	595 (1.85)	50 (1.22)	
18.5–25	10,520 (29.06)	9617 (29.97)	903 (21.96)	
≥ 25	25,033 (69.16)	21,874 (68.17)	3159 (76.82)	
Physical activity (%)				< 0.001
No or less	26,602 (72.12)	22,922 (70.36)	3680 (85.38)	
Moderate	9188 (24.91)	8599 (26.40)	589 (13.67)	
Heavy	1097 (2.97)	1056 (3.24)	41 (0.95)	
Smoke (%)				< 0.001
No	19,932 (55.56)	18,195 (57.64)	1737 (40.27)	
Yes	15,945 (44.44)	13,369 (42.36)	2576 (59.73)	
Alcohol (%)				< 0.001
Mild	24,425 (66.19)	21,014 (64.48)	3411 (79.09)	
Moderate	6523 (17.68)	6102 (18.72)	421 (9.76)	
Heavy	5956 (16.14)	5475 (16.80)	481 (11.15)	
Hypertension (%)				< 0.001
No	24,749 (67.38)	23,448 (72.31)	1301 (30.21)	
Yes	11,983 (32.62)	8978 (27.69)	3005 (69.79)	
Diabetes (%)				< 0.001
No	31,585 (86.48)	28,767 (89.08)	2818 (66.57)	
Yes	4940 (13.52)	3525 (10.92)	1415 (33.43)	
CKD (%)				< 0.001
No	30,634 (83.01)	27,170 (83.37)	3464 (80.33)	
Yes	6268 (16.99)	5420 (16.63)	848 (19.67)	
WBC ($\times 10^9$/L) (mean (SD))	7.32 (3.24)	7.29 (2.42)	7.55 (6.76)	< 0.001
NEU ($\times 10^9$/L) (mean (SD))	4.33 (1.81)	4.30 (1.81)	4.51 (1.80)	< 0.001
PLT ($\times 10^9$/L) (mean (SD))	256.63 (68.63)	259.00 (67.77)	238.73 (72.33)	< 0.001
LYM ($\times 10^9$/L) (mean (SD))	2.18 (2.29)	2.18 (1.15)	2.16 (5.91)	0.516
MON ($\times 10^9$/L) (mean (SD))	0.56 (0.20)	0.56 (0.20)	0.61 (0.23)	< 0.001
CRP (mg/dL) (mean (SD))	1.51 (4.75)	1.42 (4.30)	2.21 (7.29)	< 0.001
Alb (g/dL) (mean (SD))	42.05 (3.70)	42.20 (3.70)	40.90 (3.50)	< 0.001
HDL -C (mg/dL) (mean (SD))	1.38 (0.42)	1.38 (0.42)	1.32 (0.41)	< 0.001
TC (mg/dL) (mean (SD))	193.95 (42.11)	194.97 (41.54)	186.27 (45.47)	< 0.001
TG (mg/dL) (mean (SD))	131.37 (104.61)	129.92 (106.44)	142.19 (89.12)	< 0.001
Continued				

Characteristic	Overall *N* = 36,904	No CVD *N* = 32,591	CVD *N* = 4313	*P* value
LDL-C (mg/dL) (mean (SD))	113.59 (35.78)	114.75 (35.22)	104.99 (38.68)	< 0.001
TyG (mean (SD))	5.75 (0.68)	5.72 (0.68)	5.97 (0.65)	< 0.001
eGFR mL/min/1.73 m² (mean (SD))	102.22 (74.26)	100.26 (62.47)	116.98 (132.09)	< 0.001
SII (mean (SD))	8.93 (0.79)	8.92 (0.78)	9.01 (0.87)	< 0.001
NHR (mean (SD))	2.05 (0.55)	2.04 (0.55)	2.15 (0.56)	< 0.001
MHR (mean (SD))	0.52 (0.21)	0.51 (0.20)	0.57 (0.23)	< 0.001
PHR (mean (SD))	7.56 (0.57)	7.57 (0.57)	7.50 (0.60)	< 0.001
LHR (mean (SD))	1.39 (0.43)	1.39 (0.42)	1.36 (0.48)	< 0.001
CALLY (mean (SD))	7.88 (2.41)	7.98 (2.41)	7.16 (2.31)	< 0.001

Table 1. Baseline characteristics of participants with or without cardiovascular disease (CVD) in NHANES 2001–2018. NHANES, National Health and Nutrition Examination Survey; PIR, poverty income ratio; BMI, body mass index; CKD, chronic kidney disease; WBC, white blood cell; PLT, platelet; NEU, neutrophils; LYM, lymphocyte; MON, monocyte; CRP, C-reactive protein; Alb, albumin; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; TyG, triglyceride-glucose; eGFR, estimated glomerular filtration rate; SII, systemic immune-inflammatory index; NHR, neutrophil/high-density lipoprotein (HDL-C) ratio; MHR, monocyte/HDL-C ratio; PHR, platelet/HDL-C ratio (PHR); LHR, lymphocyte/HDL-C ratio; CALLY, C-reactive protein-albumin-lymphocyte.

The relationship between log (CALLY) and all-cause and cardiovascular mortality in CVD patients

To investigate the association between the CALLY index and all-cause mortality as well as CVD mortality among patients with CVD, we conducted further analysis on this specific population. Kaplan-Meier curves demonstrated a graded reduction in the risk of all-cause and CVD mortality across increasing quartiles of the CALLY index (P for log-rank test < 0.05) (Fig. 6). Furthermore, we construed three Cox proportional hazards regression models to verified the relationship of CALLY index with all-cause and CVD mortality. As a continuous variable, CALLY index was inversely associated with all-cause and CVD mortality in CVD patients. Meanwhile, when the CALLY index was treated as a categorical variable, a significant inverse correlation was consistently observed with both all-cause and CVD mortality among CVD patients across all three models (Table 5). The sensitivity analysis demonstrated stable effect estimates for the associations between the CALLY index and both all-cause and CVD mortality after excluding participants who died during the initial 2-year follow-up period or had baseline CRP levels > 10 mg/L (Table S5-6). In the confounders-only sensitivity analysis (excluding mediators including CKD, BMI, and diabetes), the protective association of the CALLY index was more pronounced (For all-casue mortality: HR = 0.52; For CVD mortality: HR = 0.61) than in the fully adjusted model For all-casue mortality: HR = 0.54; For CVD mortality: HR = 0.68)) (Table S7-8).

RCS analysis showed a non-linear correlation between CALLY index and all-cause and CVD mortality in patients with CVD (For all-cause mortality, p-overall < 0.001, p-nonlinear = 0.002; For CVD mortality, p-overall < 0.001, p-nonlinear = 0.038) (Fig. 7). Additionally, among the indices compared, the CALLY index showed the highest AUC values for predicting all-cause mortality (AUC = 0.598) and CVD mortality (AUC = 0.605) in CVD patients. (Fig. 8).

Subgroup analysis of the association between CALLY index and all-cause and cardiovascular mortality in patients with cardiovascular disease

We stratified CVD patients into different subgroups by sex, age, race, education, marital status, PIR, BMI, physical activity, smoke, alcohol, hypertension, diabetes and CKD. Except for the PIR subgroup (For all-cause mortality: P for interaction = 0.007; For cardiovascular mortality: P for interaction = 0.003), there was no significant interaction in most subgroups. The CALLY index was closely related to all-cause and CVD mortality in PIR < 1 subgroup (Fig. 9, Table S9-S10).

Discussion

In this study, we identified a significant inverse association between the CALLY index and the risk of CVD, along with all-cause and CVD-specific mortality. Specifically, a higher CALLY index was linked to a reduced risk of CVD in the U.S. general population. Similarly, among CVD patients, elevated CALLY index levels were associated with decreased risks of both all-cause and CVD-specific mortality. These findings suggest that the CALLY index serves as a protective indicator, correlating with a lower incidence of CVD in the U.S. general population and improved survival outcomes in CVD patients. Since the diagnosis of CVD was based on self-report, there is a risk of misclassification. We acknowledge that this misclassification is likely to be non-differential, meaning that patients may either underreport or overreport their condition. Such non-differential misclassification would generally tend to attenuate the observed association strengths toward the null, rather than overestimate them.

CALLY index is an immune-inflammatory-nutritional biomarker, which reflects inflammation and immune system, and nutrition statues simultaneously. There have been several inflammatory-related indexes was associated with CVD and mortality, including SII, NHR, LHR, MHR, PHR[15–18]. However, our findings

Characteristic	All (*N* = 4313)	Q1 (*N* = 1079)	Q2 (*N* = 1078)	Q3 (*N* = 1078)	Q4 (*N* = 1078)	*P* value
Sex (%)						0.001
Male	2253 (52.24)	542 (50.23)	538 (49.91)	551 (51.11)	622 (57.70)	
Female	2060 (47.76)	537 (49.77)	540 (50.09)	527 (48.89)	456 (42.30)	0.068
Age (years) (mean (SD))	67.10 (12.95)	66.40 (12.51)	66.90 (12.98)	67.84 (13.00)	67.27 (13.29)	
Race (%)						< 0.001
White	481 (11.15)	114 (10.57)	119 (11.04)	111 (10.30)	137 (12.71)	
Black	495 (11.48)	173 (16.03)	137 (12.71)	78 (7.24)	107 (9.93)	
Mexican	2510 (58.20)	536 (49.68)	610 (56.59)	691 (64.10)	673 (62.43)	
Other	827 (19.17)	256 (23.73)	212 (19.67)	198 (18.37)	161 (14.94)	
Education (%)						0.067
Less than high school	1478 (34.32)	328 (30.48)	374 (34.73)	381 (35.44)	395 (36.64)	
High school diploma	1043 (24.22)	274 (25.46)	264 (24.51)	265 (24.65)	240 (22.26)	
More than high school	1785 (41.45)	474 (44.05)	439 (40.76)	429 (39.91)	443 (41.09)	
Marital status (%)						< 0.001
Married/Living with partner	2377 (55.14)	551 (51.11)	565 (52.41)	609 (56.55)	652 (60.48)	
Widowed/Divorced/Separated	1644 (38.14)	445 (41.28)	426 (39.52)	412 (38.25)	361 (33.49)	
Never married	290 (6.73)	82 (7.61)	87 (8.07)	56 (5.20)	65 (6.03)	
PIR (%)						< 0.001
< 1	822 (20.82)	235 (24.30)	220 (22.36)	199 (19.98)	168 (16.78)	
1–3	1964 (49.75)	503 (52.02)	495 (50.30)	491 (49.30)	475 (47.45)	
> 3	1162 (29.43)	229 (23.68)	269 (27.34)	306 (30.72)	358 (35.76)	
BMI (kg/m2) (%)						< 0.001
< 18.5	50 (1.22)	9 (0.89)	7 (0.68)	15 (1.46)	19 (1.81)	
18.5–25	903 (21.96)	167 (16.53)	184 (17.90)	218 (21.25)	334 (31.87)	
≥ 25	3159 (76.82)	834 (82.57)	837 (81.42)	793 (77.29)	695 (66.32)	
Physical activity (%)						< 0.001
No or less	3680 (85.38)	889 (82.47)	940 (87.20)	942 (87.47)	909 (84.40)	
Moderate	589 (13.67)	186 (17.25)	133 (12.34)	118 (10.96)	152 (14.11)	
Heavy	41 (0.95)	3 (0.28)	5 (0.46)	17 (1.58)	16 (1.49)	
Smoke (%)						0.266
No	1737 (40.27)	408 (37.81)	436 (40.45)	444 (41.19)	449 (41.65)	
Yes	2576 (59.73)	671 (62.19)	642 (59.55)	634 (58.81)	629 (58.35)	
Alcohol (%)						< 0.001
Mild	3411 (79.09)	766 (70.99)	844 (78.29)	890 (82.56)	911 (84.51)	
Moderate	421 (9.76)	123 (11.40)	96 (8.91)	104 (9.65)	98 (9.09)	
Heavy	481 (11.15)	190 (17.61)	138 (12.80)	84 (7.79)	69 (6.40)	
Hypertension (%)						< 0.001
No	1301 (30.21)	279 (25.88)	323 (30.02)	317 (29.49)	382 (35.47)	
Yes	3005 (69.79)	799 (74.12)	753 (69.98)	758 (70.51)	695 (64.53)	
Diabetes (%)						< 0.001
No	2818 (66.57)	626 (58.89)	694 (65.60)	717 (68.16)	781 (73.68)	
Yes	1415 (33.43)	437 (41.11)	364 (34.40)	335 (31.84)	279 (26.32)	
CKD (%)						0.218
No	3464 (80.33)	855 (79.31)	851 (78.94)	873 (80.98)	885 (82.10)	
Yes	848 (19.67)	223 (20.69)	227 (21.06)	205 (19.02)	193 (17.90)	0.28
WBC ($\times 10^9$/L) (mean (SD))	7.55 (6.76)	7.69 (2.43)	7.34 (2.05)	7.36 (2.48)	7.81 (12.90)	0.28
NEU ($\times 10^9$/L) (mean (SD))	4.51 (1.80)	4.88 (2.02)	4.55 (1.69)	4.45 (1.63)	4.17 (1.79)	< 0.001
PLT ($\times 10^9$/L) (mean (SD))	238.73 (72.33)	236.82 (73.31)	241.21 (75.41)	242.48 (72.47)	234.40 (67.70)	0.032
LYM ($\times 10^9$/L) (mean (SD))	2.16 (5.91)	1.88 (0.74)	1.94 (0.74)	2.04 (1.37)	2.77 (11.68)	0.001
MON ($\times 10^9$/L) (mean (SD))	0.61 (0.23)	0.65 (0.25)	0.59 (0.21)	0.59 (0.20)	0.59 (0.24)	< 0.001
HDL-C ((mg/dL) mean (SD))	1.32 (0.41)	1.29 (0.42)	1.31 (0.41)	1.32 (0.40)	1.37 (0.41)	< 0.001
Alb (g/dL) (mean (SD))	40.90 (3.50)	39.19 (3.72)	40.60 (3.26)	41.48 (3.17)	42.36 (2.98)	< 0.001
CRP (mg/dL) (mean (SD))	2.21 (7.29)	7.40 (13.25)	0.98 (0.54)	0.34 (0.30)	0.12 (0.46)	< 0.001
TC (mg/dL) (mean (SD))	186.27 (45.47)	179.83 (44.40)	188.65 (46.06)	189.47 (46.76)	187.13 (44.00)	< 0.001
TG (mg/dL) (mean (SD))	142.19 (89.12)	125.14 (77.15)	152.45 (91.33)	149.79 (95.06)	141.46 (89.76)	< 0.001
LDL-C (mg/dL) (mean (SD))	104.99 (38.68)	103.08 (40.21)	104.67 (37.06)	107.17 (41.65)	105.14 (35.42)	0.406
Continued						

Characteristic	All (*N* = 4313)	Q1 (*N* = 1079)	Q2 (*N* = 1078)	Q3 (*N* = 1078)	Q4 (*N* = 1078)	*P* value
TyG (mean (SD))	5.97 (0.65)	5.89 (0.68)	6.06 (0.68)	6.03 (0.62)	5.92 (0.60)	< 0.001
eGFR (mean (SD))	116.98 (132.09)	131.73 (169.52)	115.05 (132.59)	113.87 (114.65)	107.28 (100.26)	< 0.001
SII (mean (SD))	9.01 (0.87)	9.20 (0.92)	9.07 (0.86)	9.02 (0.77)	8.75 (0.85)	< 0.001
MHR (mean (SD))	0.57 (0.23)	0.62 (0.25)	0.57 (0.22)	0.56 (0.23)	0.54 (0.22)	< 0.001
NHR (mean (SD))	2.15 (0.56)	2.25 (0.59)	2.17 (0.56)	2.14 (0.54)	2.02 (0.50)	< 0.001
PHR (mean (SD))	7.50 (0.60)	7.53 (0.61)	7.53 (0.63)	7.53 (0.59)	7.44 (0.55)	< 0.001
LHR (mean (SD))	1.36 (0.48)	1.32 (0.45)	1.34 (0.43)	1.36 (0.45)	1.41 (0.58)	< 0.001

Table 2. Baseline characteristics of critical participants with CVD grouped according to CALLY index quartiles. CVD, cardiovascular disease; PIR, poverty income ratio; BMI, body mass index; CKD, chronic kidney disease; WBC, white blood cell; PLT, platelet; NEU, neutrophils; LYM, lymphocyte; MON, monocyte; CRP, C-reactive protein; Alb, albumin; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; TyG, triglyceride-glucose; eGFR, estimated glomerular filtration rate; CALLY, C-reactive protein-albumin-lymphocyte.

	Model 1			Model 2			Model 3		
Characteristic	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
CALLY	0.86	0.85, 0.88	< 0.001	0.92	0.90, 0.94	< 0.001	0.94	0.92, 0.97	< 0.001
CALLY_Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
CALLY_Q2	0.72	0.64, 0.83	< 0.001	0.77	0.67, 0.89	< 0.001	0.82	0.70, 0.96	0.015
CALLY_Q3	0.61	0.53, 0.69	< 0.001	0.66	0.58, 0.76	< 0.001	0.73	0.63, 0.85	< 0.001
CALLY_Q4	0.39	0.34, 0.45	< 0.001	0.62	0.54, 0.72	< 0.001	0.74	0.63, 0.87	< 0.001
P for Trend			< 0.001			< 0.001			< 0.001

Table 3. ORs (95% CIs) for all participants according to the CALLY (log-transformed) index. OR, odds ratio; CI, confidence interval; CALLY, C-reactive protein-albumin-lymphocyte. Model 1: unadjusted model. Model 2: adjusted for sex, age, race, education, marital status, poverty income ratio. Model 3: adjusted for sex, age, race, education, marital status, poverty income ratio, body mass index, physical activity, smoke, alcohol, hypertension, diabetes and chronic kidney disease.

demonstrated that the CALLY index exhibited superior predictive capability compared to these inflammation-related indices. This enhanced performance may be attributed to the inclusion of albumin in the CALLY index, which offered a more comprehensive evaluation of the body's overall health status.

Albumin play a crucial role in maintaining internal homeostasis. Firstly, albumin deficiency reduces the deformability of red blood cells, subsequently increasing blood viscosity[19]. In clinical practice, SA is used to maintain the permeability of capillary membranes[20]. Secondly, hypoalbuminemia impairs the vasodilatory response to nitric oxide (NO)[21]. Thirdly, hypoalbuminemia impairs toxin clearance, reduces cholesterol transport capacity, and weakens the body's anticoagulant and antioxidant defenses[22–25].

Furthermore, immune cells play an indispensable role in cardiac injury and repair processes[26]. However, the immune response to cardiac injury is highly complex and remains incompletely understood. The immune response is intricately regulated by variations in injury type, host-specific factors, and environmental conditions. The robust sterile inflammation observed in the injured heart is mediated through multiple interconnected signaling pathways[27,28]. Furthermore, diverse cell types within the immune system engage in complex interactions with each other and with resident cardiac fibroblasts, endothelial cells, and cardiomyocytes throughout the processes of cardiac injury and repair[29].

Inflammation promotes endothelial cell damage and the progression of atherosclerotic plaques, playing a critical role in the development and pathogenesis of CVD[30]. In the case of myocardial infarction, inflammation can be both beneficial and harmful. It is involved in infarct resolution, repair, and remodeling, but persistent inflammation can enlarge the infarct area and hinder cardiac recovery[31,32]. A Mendelian analysis revealed that elevated CRP levels are associated with a higher risk of hypertension and hypertensive heart disease[33].

The CALLY index has demonstrated an inverse association with the risk of several diseases. In a cross-sectional study, the CALLY index was inversely associated with the risk of cardiorenal syndrome[34]. And its predictive ability was more effectively than other inflammatory markers. Another study suggests that a higher CALLY index is associated with better prognosis in colorectal cancer patients, which is similar with our findings[35]. Ji et al. indicated that the CALLY index exhibited a protective effect against both short- and long-term major adverse cardiovascular events (MACEs) in patients with ST-segment elevation myocardial infarction (STEMI)[11]. Müller et al. identified the CALLY index as an independent prognostic factor for overall survival in patients with hepatocellular carcinoma receiving transarterial chemoembolization[36]. In our study, after stratifying all participants by sex and age, the high CALLY index (CALLY index > 7.62 or 8.08) seemed to be more protective in female and younger population. It could be attributed to the higher estrogen and progesterone levels in female.

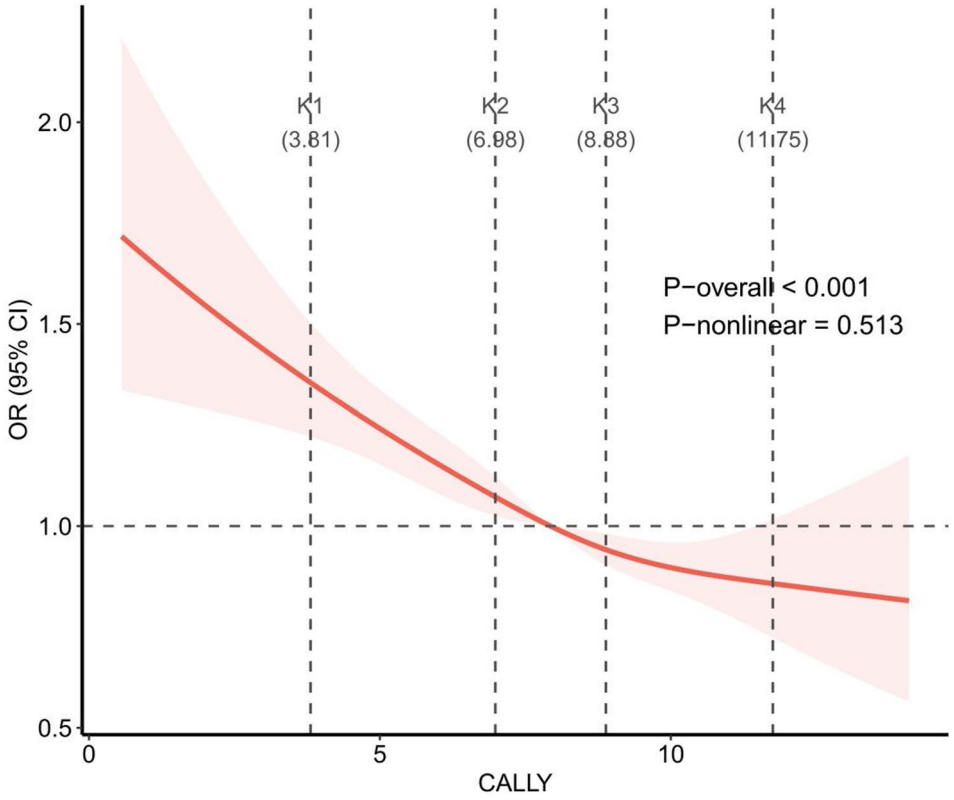

Fig. 2. RCS analysis of the association between the CALLY index and cardiovascular disease in the U.S. general population. Adjusted for sex, age, race, education, marital status, PIR, BMI, physical activity, smoke, alcohol, hypertension, diabetes and CKD, except the subgroup factors themselves.

And older adults tend to have more comorbidities, which could potentially obscure the benefits associated with a higher CALLY index. Furthermore, the patients with CVD form the U.S. general population was selected to explore the CALLY index with all-cause and CVD mortality. Kaplan-Meier curves also demonstrated a progressive reduction in the risk of all-cause and CVD mortality across higher quartiles of the CALLY index. The RCS analysis showed a non-linear relationship between CALLY index and both all-cause and CVD mortality. And Xu et al. also revealed a non-linear association of CALLY index with cardiorenal syndrome[34]. Before the CALLY index proposed in this study can be applied in clinical practice, several key issues must be addressed. Furthermore, although the ROC curve confirms that the CALLY index has better predictive performance for CVD compared to other inflammation-related indicators, its predictive capability remains limited. Therefore, this readily available composite index could be integrated with other clinically important variables in future studies to develop a multivariate predictive model. Such an approach would significantly enhance the clinical utility of the CALLY index. Future research should focus on establishing clinically applicable cut-off values for different populations, verifying its reproducibility across various laboratory platforms and reagents, and conducting comprehensive health economic evaluations to demonstrate its cost-effectiveness. Clarifying these issues is crucial for translating the CALLY index from an epidemiological tool into an effective clinical decision-support tool.

Overall, our study was the first to propose the negative association between CALLY index and both CVD and all-cause and CVD mortality in U.S. general population or patients with CVD. However, there are still several limitations in our study. Firstly, the diagnosis of CVD was from self-report of patients, which is subject to potential recall bias and misclassification. Participants may underreport or be unaware of a prior diagnosis, leading to non-differential misclassification that could attenuate the observed associations. While self-report of major cardiovascular conditions has been used and validated in large surveys, future studies with adjudicated clinical endpoints would be valuable to confirm our findings. Secondly, the evidentiary strength of cross-sectional studies is inferior to that of prospective studies and randomized controlled trials. Thirdly, Although we adjusted for numerous covariates, residual confounding is likely to persist. Key factors such as medication use, dietary habits, and comorbidity severity are not fully captured in the NHANES database, and these unmeasured confounders may influence our findings. Fourthly, some visualization and ROC plotting functions in R do not fully support complex survey weights, the graphical representations of ROC curves and survival plots were based on model-predicted probabilities, which may slightly underestimate the true sampling variability.Therefore, our findings require further validation through large-scale prospective studies in the future to enhance their robustness.

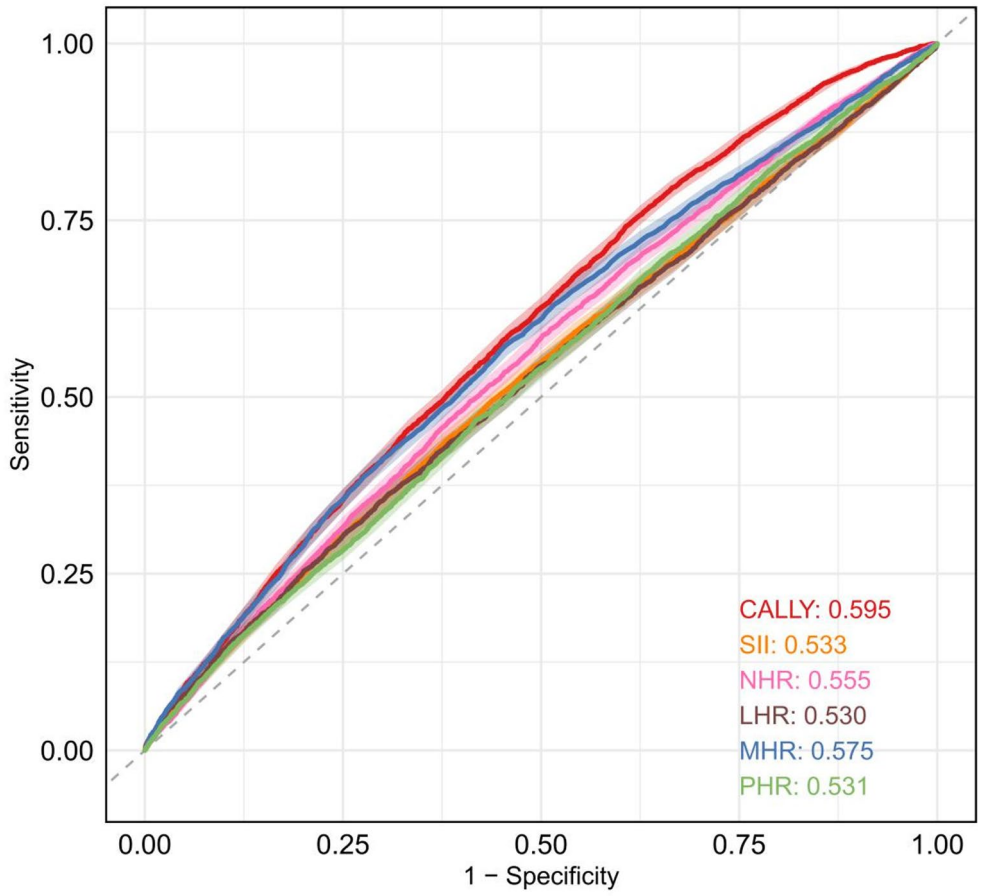

Fig. 3. Comparing the predictive ability of CALLY, SII, NHR, LHR, MHR, and PHR for cardiovascular disease in the U.S. general population using ROC curves and AUC values. Adjusted for sex, age, race, education, marital status, PIR, BMI, physical activity, smoke, alcohol, hypertension, diabetes and CKD, except the subgroup factors themselves.

Conclusion

This study confirms a significant negative correlation between the CALLY index and cardiovascular disease risk in the U.S. general population. Furthermore, among individuals with established cardiovascular disease, the CALLY index also shows significant inverse associations with all-cause mortality and cardiovascular disease-specific mortality. Compared to traditional inflammation-related indicators such as SII, NHR, LHR, MHR, and PHR, the CALLY index demonstrates stronger associations with mortality risk and better predictive performance in both the U.S. general population and patients with CVD. These findings provide compelling evidence supporting the potential clinical value of the CALLY index.

	Model 1			Model 2			Model 3		
	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Male									
CALLY	0.84	0.81, 0.86	< 0.001	0.90	0.86, 0.93	< 0.001	0.93	0.89, 0.97	< 0.001
CALLY_Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
CALLY_Q2	0.68	0.56, 0.83	< 0.001	0.75	0.59, 0.96	0.021	0.81	0.62, 1.05	0.108
CALLY_Q3	0.53	0.44, 0.64	< 0.001	0.65	0.53, 0.80	< 0.001	0.74	0.59, 0.92	0.009
CALLY_Q4	0.34	0.27, 0.42	< 0.001	0.52	0.42, 0.66	< 0.001	0.66	0.51, 0.85	0.002
P for Trend			< 0.001			< 0.001			< 0.001
Female									
CALLY	0.89	0.87, 0.91	< 0.001	0.90	0.87, 0.92	< 0.001	0.92	0.89, 0.95	< 0.001
CALLY_Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
CALLY_Q2	0.76	0.64, 0.90	0.002	0.73	0.61, 0.89	0.002	0.79	0.64, 0.98	0.034
CALLY_Q3	0.68	0.58, 0.81	< 0.001	0.63	0.52, 0.75	< 0.001	0.68	0.56, 0.84	< 0.001
CALLY_Q4	0.45	0.38, 0.54	< 0.001	0.54	0.44, 0.65	< 0.001	0.64	0.51, 0.79	< 0.001
P for Trend			< 0.001			< 0.001			< 0.001
Age < 65									
CALLY	0.86	0.85, 0.88	< 0.001	0.87	0.85, 0.89	< 0.001	0.91	0.89, 0.93	< 0.001
CALLY_Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
CALLY_Q2	0.72	0.64, 0.83	< 0.001	0.71	0.61, 0.81	< 0.001	0.77	0.66, 0.90	0.002
CALLY_Q3	0.61	0.53, 0.69	< 0.001	0.58	0.51, 0.67	< 0.001	0.67	0.58, 0.78	< 0.001
CALLY_Q4	0.39	0.34, 0.45	< 0.001	0.42	0.37, 0.49	< 0.001	0.57	0.49, 0.68	< 0.001
P for Trend			< 0.001			< 0.001			< 0.001
Age ≥ 65									
CALLY	0.96	0.93, 0.99	0.007	0.95	0.92, 0.98	0.001	0.96	0.93, 0.99	0.014
CALLY_Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
CALLY_Q2	0.85	0.75, 0.95	0.007	0.81	0.71, 0.92	0.001	0.86	0.75, 0.97	0.019
CALLY_Q3	1.04	0.91, 1.19	0.583	1.06	0.92, 1.22	0.418	1.05	0.90, 1.23	0.533
CALLY_Q4	0.93	0.84, 1.02	0.123	0.93	0.84, 1.04	0.206	0.92	0.82, 1.04	0.170
P for Trend			0.006			< 0.001			0.016

Table 4. ORs (95% CIs) for CVD according to the CALLY (log-transformed) index after stratification by sex and age. OR, odds ratio; CI, confidence interval; CALLY, C-reactive protein-albumin-lymphocyte. Model 1: unadjusted model. Model 2: adjusted for sex, age, race, education, marital status, poverty income ratio. Model 3: adjusted for sex, age, race, education, marital status, poverty income ratio, body mass index, physical activity, smoke, alcohol, hypertension, diabetes and chronic kidney disease.

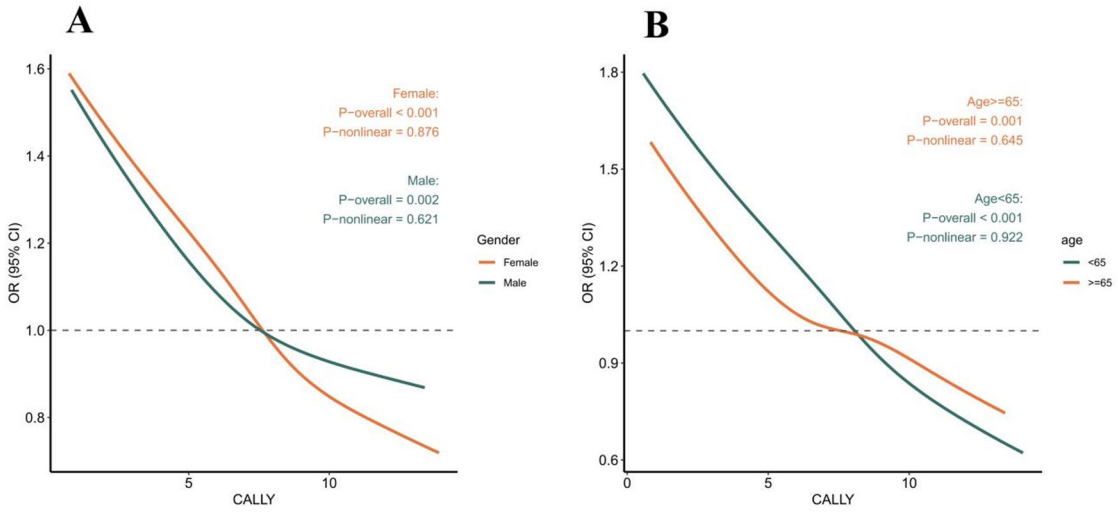

Fig. 4. The dose–response relationship between CALLY index with cardiovascular disease in U.S. general population stratified by sex (**A**) and age (**B**). Adjusted for race, education, marital status, PIR, BMI, physical activity, smoke, alcohol, hypertension, diabetes and CKD, except the subgroup factors themselves.

Subgroup	N	OR (95% CI)	P value	P for interaction
Sex				<0.001
Male	17926	0.84 (0.82, 0.85)	<0.001	
Female	18978	0.89 (0.87, 0.91)	<0.001	
Age				<0.001
<65	28252	0.84 (0.83, 0.86)	<0.001	
>=65	8652	0.94 (0.92, 0.96)	<0.001	
Race				0.013
White	7073	0.87 (0.84, 0.90)	<0.001	
Black	5883	0.86 (0.83, 0.89)	<0.001	
Mexican	16468	0.86 (0.84, 0.87)	<0.001	
Other	7480	0.85 (0.82, 0.87)	<0.001	
Education				0.207
Less than high school	9307	0.89 (0.87, 0.92)	<0.001	
High school diploma	8093	0.87 (0.84, 0.89)	<0.001	
More than high school	16925	0.88 (0.86, 0.90)	<0.001	
Marital.status				<0.001
Married/Living with partner	21162	0.90 (0.88, 0.92)	<0.001	
Widowed/Divorced/Separated	7642	0.90 (0.88, 0.92)	<0.001	
Never married	7085	0.79 (0.75, 0.82)	<0.001	
PIR				0.085
<1	7041	0.84 (0.81, 0.86)	<0.001	
1−3	14530	0.87 (0.86, 0.89)	<0.001	
>3	12272	0.89 (0.87, 0.92)	<0.001	
BMI				0.346
<18.5	645	0.82 (0.74, 0.91)	<0.001	
18.5−25.0	10520	0.82 (0.80, 0.84)	<0.001	
>=25.0	25033	0.91 (0.89, 0.92)	<0.001	
Physical.activity				0.101
No or less	26602	0.88 (0.86, 0.89)	<0.001	
Moderate	9188	0.85 (0.82, 0.88)	<0.001	
Heavy	1097	0.76 (0.64, 0.89)	<0.001	
Smoke				0.005
No	19932	0.90 (0.88, 0.91)	<0.001	
Yes	15945	0.86 (0.85, 0.88)	<0.001	
Alcohol				<0.001
Mild	24425	0.87 (0.85, 0.88)	<0.001	
Moderate	6523	0.86 (0.82, 0.89)	<0.001	
Heavy	5956	0.80 (0.77, 0.83)	<0.001	
Hypertension				<0.001
No	24749	0.88 (0.86, 0.90)	<0.001	
Yes	11983	0.94 (0.92, 0.96)	<0.001	
Diabetes				<0.001
No	31585	0.88 (0.86, 0.89)	<0.001	
Yes	4940	0.95 (0.92, 0.97)	<0.001	
CKD				<0.001
No	30634	0.85 (0.84, 0.87)	<0.001	
Yes	6268	0.96 (0.93, 0.99)	0.006	

Fig. 5. Subgroup analysis of the association between CALLY index and cardiovascular disease. Adjusted for sex, age, race, education, marital status, PIR, BMI, physical activity, smoke, alcohol, hypertension, diabetes and CKD, except the subgroup factors themselves.

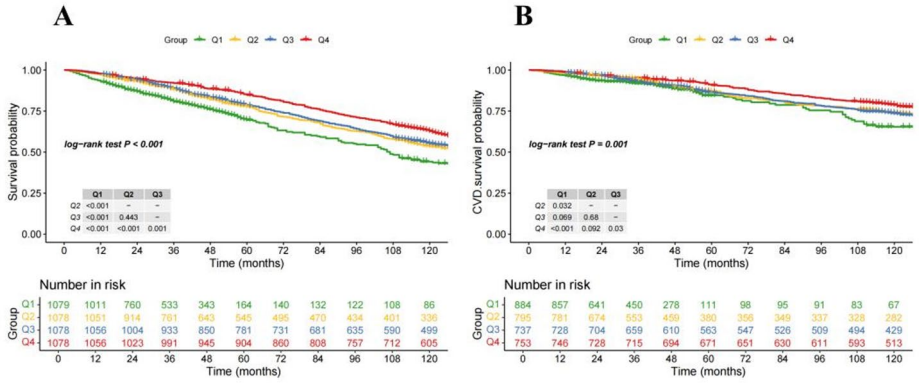

Fig. 6. Kaplan–Meier survival analysis curves for all-cause (**A**) and cardiovascular mortality (**B**). Adjusted for sex, age, race, education, marital status, PIR, BMI, physical activity, smoke, alcohol, hypertension, diabetes and CKD, except the subgroup factors themselves.

	Model 1			Model 2			Model 3		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
All-cause mortality									
CALLY	0.89	0.86, 0.92	< 0.001	0.89	0.86, 0.92	< 0.001	0.90	0.87, 0.93	< 0.001
CALLY_Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
CALLY_Q2	0.72	0.58, 0.88	0.001	0.71	0.58, 0.87	< 0.001	0.74	0.60, 0.91	0.005
CALLY_Q3	0.67	0.54, 0.82	< 0.001	0.58	0.47, 0.71	< 0.001	0.62	0.50, 0.78	< 0.001
CALLY_Q4	0.53	0.43, 0.65	< 0.001	0.50	0.41, 0.60	< 0.001	0.54	0.44, 0.66	< 0.001
P for Trend			< 0.001			< 0.001			< 0.001
Cardiovascular mortality									
CALLY	0.92	0.88, 0.97	< 0.001	0.93	0.88, 0.98	0.004	0.94	0.89, 0.99	0.030
CALLY_Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
CALLY_Q2	0.84	0.60, 1.18	0.320	0.82	0.59, 1.16	0.267	0.78	0.53, 1.14	0.198
CALLY_Q3	0.87	0.61, 1.22	0.415	0.70	0.50, 0.98	0.035	0.72	0.50, 1.03	0.070
CALLY_Q4	0.69	0.51, 0.94	0.019	0.65	0.48, 0.87	0.004	0.68	0.49, 0.94	0.021
P for Trend			0.027			0.001			0.013

Table 5. Associations between the CALLY (log-transformed) index and all-cause and cardiovascular mortality in participants with CVD. HR, hazard ratio; CI, confidence interval; CALLY, C-reactive protein-albumin-lymphocyte. Model 1: unadjusted model. Model 2: adjusted for sex, age, race, education, marital status, poverty income ratio. Model 3: adjusted for sex, age, race, education, marital status, poverty income ratio, body mass index, physical activity, smoke, alcohol, hypertension, diabetes and chronic kidney disease.

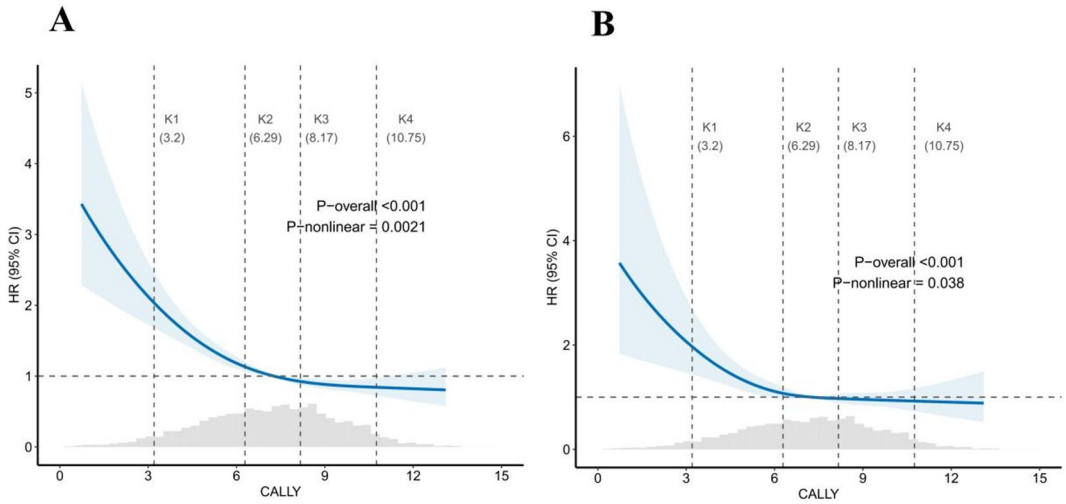

Fig. 7. RCS analysis of the association between the CALLY index and all-cause (**A**) and cardiovascular mortality (**B**) in the U.S. general population. Adjusted for sex, age, race, education, marital status, PIR, BMI, physical activity, smoke, alcohol, hypertension, diabetes and CKD, except the subgroup factors themselves.

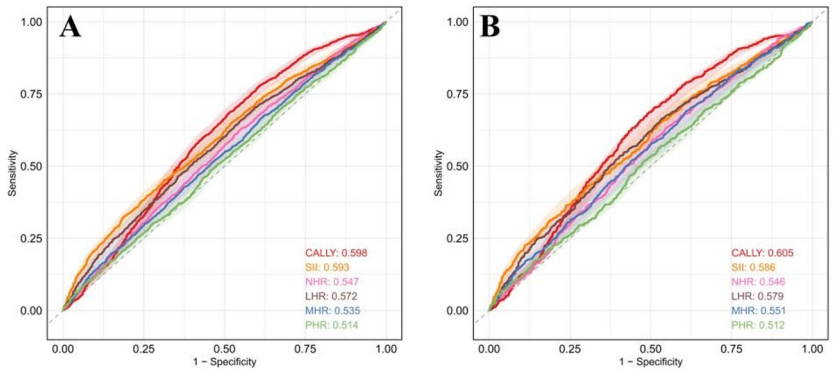

Fig. 8. Comparing the predictive ability of CALLY, SII, NHR, LHR, MHR, and PHR for all-cause (**A**) and cardiovascular mortality (**B**) in the U.S. general population using ROC curves and AUC values. Adjusted for sex, age, race, education, marital status, PIR, BMI, physical activity, smoke, alcohol, hypertension, diabetes and CKD, except the subgroup factors themselves.

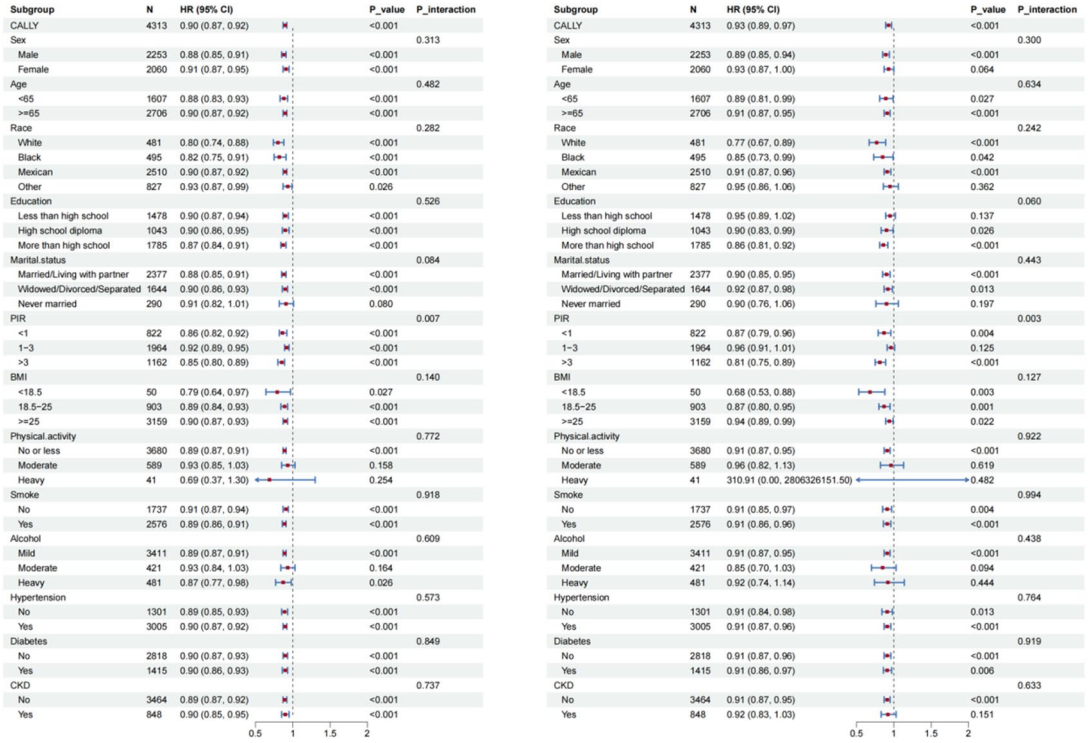

Fig. 9. Subgroup analysis of the association between CALLY index and all-cause (**Left**) and cardiovascular mortality (**Right**). Adjusted for sex, age, race, education, marital status, PIR, BMI, physical activity, smoke, alcohol, hypertension, diabetes and CKD, except the subgroup factors themselves.

Data availability

The raw data can be obtained from the official NHANES website: https://www.cdc.gov/nchs/nhanes/?CDC_AAref_Val=https://www.cdc.gov/nchs/nhanes/index.htm.

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References

1. Maffia, P. & Cirino, G. Targeting inflammation to reduce cardiovascular disease risk. *Br. J. Pharmacol.* **174**, 3895–3897 (2017).
2. Welsh, P., Grassia, G., Botha, S., Sattar, N. & Maffia, P. Targeting inflammation to reduce cardiovascular disease risk: a realistic clinical prospect? *Br. J. Pharmacol.* **174**, 3898–3913 (2017).
3. Rabbani, G., Ahn, S. N. & Review Roles of human serum albumin in prediction, diagnoses and treatment of COVID-19. *Int. J. Biol. Macromol.* **193**, 948–955 (2021).
4. Akirov, A., Masri-Iraqi, H., Atamna, A. & Shimon, I. Low albumin levels are associated with mortality risk in hospitalized patients. *Am. J. Med.* **130**, 1465e11–1465e19 (2017).
5. Chien, S. C., Chen, C. Y., Lin, C. F. & Yeh, H. I. Critical appraisal of the role of serum albumin in cardiovascular disease. *Biomark. Res.* **5**, 31 (2017).
6. Phillips, A., Shaper, A. G. & Whincup, P. H. Association between serum albumin and mortality from cardiovascular disease, cancer, and other causes. *Lancet* **2**, 1434–1436 (1989).
7. Lan, C. C., Su, W. L., Yang, M. C., Chen, S. Y. & Wu, Y. K. Predictive role of neutrophil-percentage-to-albumin, neutrophil-to-lymphocyte and eosinophil-to-lymphocyte ratios for mortality in patients with COPD: evidence from NHANES 2011–2018. *Respirology* **28**, 1136–1146 (2023).
8. Zhou, J. et al. Albumin-corrected Fructosamine predicts all-cause and non-CVD mortality among the very elderly aged 80 years or older without diabetes. *J. Gerontol. Biol. Sci. Med. Sci.* **77**, 1673–1682 (2022).
9. Liu, X. et al. The associations of plant-based protein intake with all-cause and cardiovascular mortality in patients on peritoneal Dialysis. *Nutr. Metab. Cardiovasc. Dis.* **30**, 967–976 (2020).
10. Lee, Y. T. et al. Artificial intelligence-enabled electrocardiography detects hypoalbuminemia and identifies the mechanism of hepatorenal and cardiovascular events. *Front. Cardiovasc. Med.* **9**, 895201 (2022).
11. Ji, H. et al. Prognostic significance of C-reactive protein-albumin-lymphocyte (CALLY) index after primary percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction. *Int. Immunopharmacol.* **141**, 112860 (2024).
12. Feng, J., Wang, L., Yang, X. & Chen, Q. Clinical significance of preoperative CALLY index for prognostication in patients with esophageal squamous cell carcinoma undergoing surgery. *Sci. Rep.* **14**, 713 (2024).
13. Zhang, H. et al. Superiority of CRP-albumin-lymphocyte index as a prognostic biomarker for patients with gastric cancer. *Nutrition* **116**, 112191 (2023).
14. Iida, H. et al. Superiority of CRP-albumin-lymphocyte index (CALLY index) as a non-invasive prognostic biomarker after hepatectomy for hepatocellular carcinoma. *HPB (Oxford).* **24**, 101–115 (2022).
15. Cao, Y. et al. Association of systemic immune inflammatory index with all-cause and cause-specific mortality in hypertensive individuals: results from NHANES. *Front. Immunol.* **14**, 1087345 (2023).

16. Chuang, S. M. et al. Neutrophil-to-high-density lipoprotein ratio (NHR) and neutrophil-to-lymphocyte ratio (NLR) as prognostic biomarkers for incident cardiovascular disease and all-cause mortality: A comparison study. *Am. J. Prev. Cardiol.* **20**, 100869 (2024).
17. Song, Y. et al. Combination model of neutrophil to high-density lipoprotein ratio and system inflammation response index is more valuable for predicting peripheral arterial disease in type 2 diabetic patients: A cross-sectional study. *Front. Endocrinol. (Lausanne)*. **14**, 1100453 (2023).
18. Ye, H. et al. Non-linear association of the platelet/high-density lipoprotein cholesterol ratio with bone mineral density a cross-sectional study. *Lipids Health Dis.* **23**, 300 (2024).
19. McGinley, E., Lowe, G. D., Boulton-Jones, M., Forbes, C. D. & Prentice, C. R. Blood viscosity and haemostasis in the nephrotic syndrome. *Thromb. Haemost*. **49**, 155–157 (1983).
20. Demling, R. H. Effect of plasma and interstitial protein content on tissue edema formation. *Curr. Stud. Hematol. Blood Transfus.* **53**36–52. (1986).
21. Keaney, J. F. et al. NO forms an adduct with serum albumin that has endothelium-derived relaxing factor-like properties. *J. Clin. Invest.* **91**, 1582–1589 (1993).
22. Quinlan, G. J., Martin, G. S. & Evans, T. W. Albumin: biochemical properties and therapeutic potential. *Hepatology* **41**, 1211–1219 (2005).
23. Stocker, R. et al. Antioxidant activity of albumin. -bound bilirubin - PubMed [Internet]. [cited 2024 Nov 30]. Available from: https://pubmed.ncbi.nlm.nih.gov/3475708/ *Proc Natl Acad Sci U S A*. **84**, 5918–5922 (1987).
24. Sankaranarayanan, S. et al. Serum albumin acts as a shuttle to enhance cholesterol efflux from cells. *J. Lipid Res.* **54**, 671–676 (2013).
25. Mikhailidis, D. P., Mikhailidis, A. M. & Dandona, P. Effect of human plasma proteins on stabilisation of platelet anti-aggregatory activity of Prostacyclin. *Ann. Clin. Biochem.* **19** (Pt 4), 241–244 (1982).
26. Rurik, J. G., Aghajanian, H. & Epstein, J. A. Immune cells and immunotherapy for cardiac injury and repair. *Circ. Res.* **128**, 1766–1779 (2021).
27. Suetomi, T. et al. Inflammation and NLRP3 inflammasome activation initiated in response to pressure overload by Ca2+/calmodulin-dependent protein kinase II δ signaling in cardiomyocytes are essential for adverse cardiac remodeling. *Circulation* **138**, 2530–2544 (2018).
28. Jaén, R. I. et al. Innate immune receptors, key actors in cardiovascular diseases. *JACC Basic. Transl Sci.* **5**, 735–749 (2020).
29. Epelman, S. et al. Embryonic and adult-derived resident cardiac macrophages are maintained through distinct mechanisms at steady state and during inflammation. *Immunity* **40**, 91–104 (2014).
30. Zhuang, Q. et al. Association of high sensitive C-reactive protein with coronary heart disease: a Mendelian randomization study. *BMC Med. Genet.* **20**, 170 (2019).
31. Lambertsen, K. L., Finsen, B. & Clausen, B. H. Post-stroke inflammation-target or tool for therapy? *Acta Neuropathol.* **137**, 693–714 (2019).
32. Tripathi, H. et al. Myeloid-specific deletion of lipid Plpp3 (phosphate phosphatase 3) increases cardiac inflammation after myocardial infarction. *Arterioscler. Thromb. Vasc Biol.* **43**, 379–381 (2023).
33. Kuppa, A., Tripathi, H., Al-Darraji, A., Tarhuni, W. M. & Abdel-Latif, A. C-reactive protein levels and risk of cardiovascular diseases: a two-sample bidirectional Mendelian randomization study. *Int. J. Mol. Sci.* **24**, 9129 (2023).
34. Xu, Z. et al. Associations of C-reactive protein-albumin-lymphocyte (CALLY) index with cardiorenal syndrome: insights from a population-based study. *Heliyon* **10**, e37197 (2024).
35. Yang, M. et al. Association between C-reactive protein-albumin-lymphocyte (CALLY) index and overall survival in patients with colorectal cancer: from the investigation on nutrition status and clinical outcome of common cancers study. *Front. Immunol.* **14**, 1131496 (2023).
36. Zhang, J., Zhao, Q., Liu, S., Yuan, N. & Hu, Z. Clinical predictive value of the CRP-albumin-lymphocyte index for prognosis of critically ill patients with sepsis in intensive care unit: a retrospective single-center observational study. *Front. Public. Health*. **12**, 1395134 (2024).

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YW and YZ: conceptualization, data curation, formal analysis, validation, visualization and writing–original. YT: conceptualization, project administration and writing–review & editing. YC: funding acquisition, software and supervision.

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Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
The study protocol was approved by the NHANES Institutional Review Board, and was performed in accordance with the Declaration of Helsinki, with all NHANES participants providing signed informed consent.

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