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# The C-reactive protein (CRP)-albumin-lymphocyte (CALLY) index exhibits an L-shaped association with all-cause mortality in rheumatoid arthritis patients: a retrospective cohort study

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## Abstract

**Background** The C-reactive protein (CRP)-albumin-lymphocyte (CALLY) index is a novel biomarker reflecting inflammation, nutrition, and immune status, and its potential clinical significance and prognostic role in patients with rheumatoid arthritis (RA) has not been reported.

**Aim** The objective of this study was to investigate whether CALLY is associated with all-cause mortality in RA patients.

**Methods** The characteristics of 1101 RA patients and 18,047 non-RA individuals were collected from the National Health and Nutrition Examination Survey (NHANES) database between 1999 and 2010. The CALLY index is calculated as albumin × lymphocyte count / (CRP × 10). Multivariable Cox regression models were used to assess the association between the CALLY index and all-cause mortality in RA patients. Restricted cubic spline (RCS) analysis was applied to evaluate potential linear or nonlinear relationships between the CALLY index and mortality. Kaplan-Meier survival curves were used to assess survival probabilities across different CALLY levels in RA patients.The final analysis was conducted on July 10, 2024.

**Results** Multivariable logistic regression analysis indicated that a low CALLY index was significantly associated with RA patients when compared to non-RA individuals, with an odds ratio (OR) of 0.74 (95% CI: 0.65–0.83). Cox regression models revealed that RA patients with a higher CALLY index showed a decreased risk of all-cause mortality, with a hazard ratio (HR) of 0.62 (95% CI: 0.51–0.77). RCS analysis demonstrated a L-shaped relationship between the CALLY index and survival outcomes of RA patients. Segmented regression identified an optimal cutoff value for the CALLY

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index at 12.79, where values below this threshold were inversely correlated with all-cause mortality risk. Subgroup analysis suggested a synergistic interaction between a high Log-CALLY index, male, and age below 60 years. Kaplan-Meier survival curve analysis showed significantly higher survival rates in the high CALLY group compared to the low CALLY group ($P=0.0012$).

**Conclusions** The CALLY index is a valuable biomarker for evaluating the prognosis of patients with RA, and a lower CALLY index indicates an increased long-term mortality risk in RA patients, which suggests the importance of comprehensive assessment for inflammatory status and immune function.

**Clinical trial number** Not applicable.

**Keywords** Rheumatoid arthritis, CALLY, All-cause mortality, NHANES, Retrospective cohort study

## Introduction

Rheumatoid arthritis (RA) is an autoimmune disease primarily affecting the joints, characterized by persistent inflammation and multi-organ injuries, with the potential to cause significant disability and deformity [1, 2]. The global prevalence of RA is estimated to rise from 17.6 million in 2020 to 31.7 million in 2050 [3]. A large-scale multicenter study conducted in the United Kingdom (UK) in 2018 indicates that mortality of RA patients is decreased, but it remains 1.32 times higher than non-RA individuals. Additionally, the average age of death among RA patients is 77.33 years, which is lower than the 79.09 years observed in non-RA populations [4]. The development and severity of RA are linked to levels of inflammation [5], nutritional status [6] and immune function [7].

A 2024 review study synthesized current clinical research on prognostic biomarkers in rheumatoid arthritis (RA), highlighting that despite significant advancements, there remains a paucity of large-scale, readily accessible, or broadly applicable biomarkers for predicting RA prognosis [8]. C-reactive protein (CRP), recognized as a systemic inflammation marker in RA, exerts direct effects on osteolytic destruction and radiographic progression. It is further implicated in RA-associated comorbidities, including interstitial pneumonia, metabolic syndrome, and cardiovascular diseases. CRP reduction correlates with attenuated disease activity [9]. Malnutrition adversely impacts quality of life in elderly populations with chronic conditions [10]. Disease-related malnutrition is linked to disability, increased short- and long-term mortality, and impaired recovery [11]. Notably, malnutrition demonstrates a robust association with elevated all-cause mortality risk in RA patients [12]. Lymphocytes, as principal mediators of adaptive immune responses, exhibit distinct alterations in RA pathogenesis. Evidence indicates elevated plasmablast percentages in active RA patients [13]. Furthermore, dynamic changes in peripheral blood T lymphocyte subsets serve as predictive indicators of disease progression in RA [14]. Consequently, clinical scoring systems that integrate inflammatory nutritional status and immune response are more effective in guiding the management of patients with RA.

The accurate identification and quantification of inflammatory level, nutritional status, and immune function in RA are essential for the early prediction of prognosis across diverse populations, thus supporting more effective disease management of RA. The CALLY index, consisting of C-reactive protein (CRP), peripheral blood lymphocyte count, and albumin, was first proposed by professor Hiroya [15], and mainly used for a comprehensive evaluation of inflammatory nutritional status and immune system. It is calculated through the results of routine blood tests and standard biochemical analysis, and exhibits the advantages of fast speed, high efficiency, easy promotion, and low cost.

Several blood inflammatory composite indices derived primarily from routine blood tests, including the systemic immune-inflammation index [16], the pan-immune-inflammation index [17] and the neutrophil-lymphocyte ratio [18], have been reported in RA patients. However, a composite index that comprehensively assesses inflammation, immune function, and nutritional status for RA remains unavailable, and most prior studies are based on small sample sizes. The CALLY index is a potential candidate, widely applied in oncology as a prognostic indicator for malignancies, such as cancer of liver, colorectal, ovarian, and breast, and in non-neoplastic diseases such as angina [19], COPD [20], ulcerative colitis [21], and other conditions [15, 22–24]. Unlike SII or NLR, which focus solely on inflammatory cells, the CALLY index uniquely integrates albumin (nutrition), lymphocytes (immunity), and CRP (inflammation), offering a multidimensional assessment of RA pathophysiology.While its potential clinical significance and prognostic role in patients with RA remain undefined. In this study, we used the National Health and Nutrition Examination Survey (NHANES) database to investigate the effect of CALLY index on RA patients.

## Methods

### Study population

The data utilized in this study were obtained from NHANES database between 1999 and 2010. This database is designed to assess the health and nutritional status of the U.S. population (http://www.cdc.gov/nchs/nhanes.htm). Data of RA patients and non-RA individuals were collected through household interviews that gathered information on participants' demographic, socioeconomic, and dietary factors, as well as medical and health conditions. Biological specimens, such as serum and urine, were collected by medical personnel in mobile examination centers, alongside standardized medical and physical examinations. Informed consent was obtained from all participants at the time of recruitment. Participants needed to meet the inclusion criteria, which included being at least 20 years of age, having a diagnosis of RA or other arthritis, and providing complete data on blood count, blood biochemistry, arthritis types, and survival status. Individuals with incomplete or missing data were excluded. Ultimately, 1,101 RA participants were collected for analysis (Fig. 1).

### Definition of main research variables

In the survey data, participants were asked, "Has a doctor ever said you had arthritis?" Those who answer "Yes" were categorized as having arthritis. Further classification was based on responses to the question, "Which type of arthritis was it?" Participants who answered "rheumatoid arthritis" were classified as having RA, while those who reported other types, such as osteoarthritis, psoriatic arthritis, or other forms of arthritis, were classified as non-RA. Participants who answer "No" were categorized as non-RA, and those with missing or other responses were excluded from the analysis.

The calculation formula for CALLY index is albumin × lymphocytes / (CRP × 10), and albumin is measured in g/L, lymphocytes in 10^3/μL, and CRP in mg/dL. Given that the CALLY index was a skewed variable, and a base-10 logarithmic transformation was applied. The primary

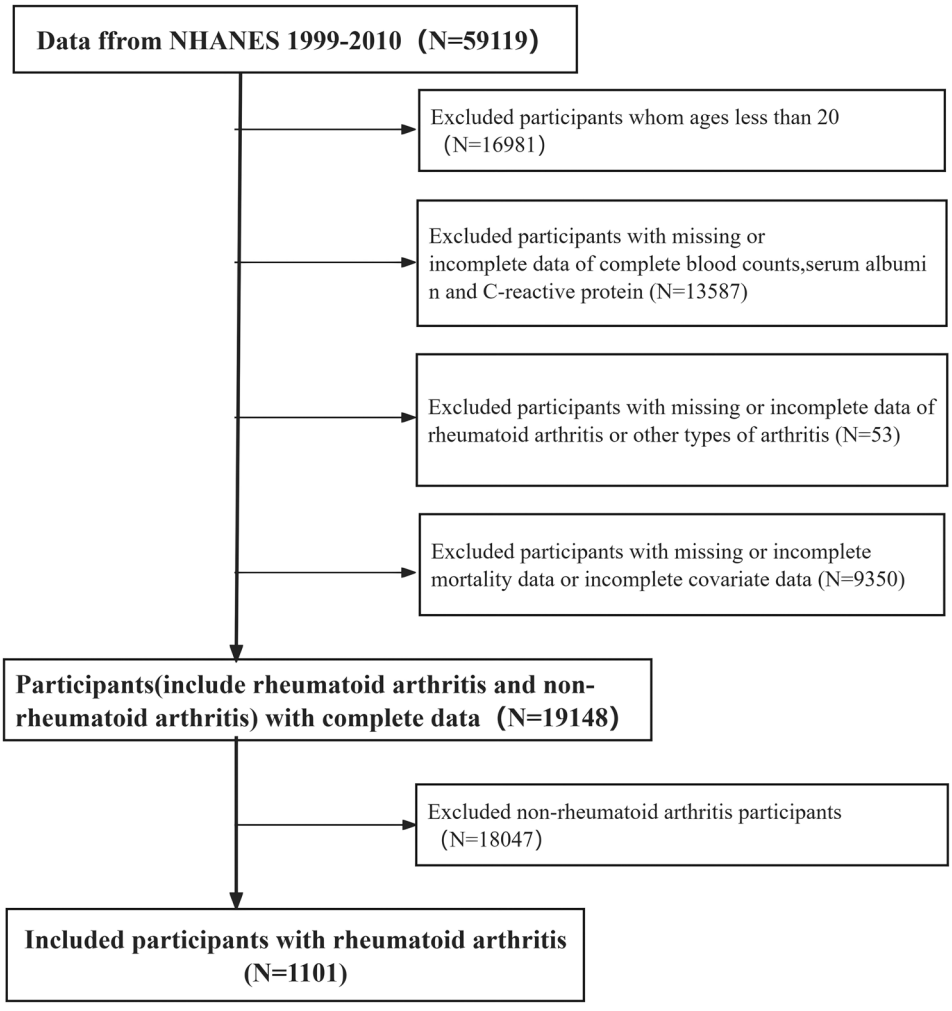


**Fig. 1** Flow chart of participants selection

outcome was all-cause mortality, which was obtained from the National Death Index (NDI) database (https://www.cdc.gov/nchs/datalinkage/mortality-public.htm). Follow-up time for each participant was determined from the date of participation to the date of death or to the final update date of the NDI database (December 31, 2019).

### Definition of covariates and data processing methods

Based on clinical knowledge regarding RA, causes of death, and other factors, potential confounders were identified as covariates. These include age (20–60 years, ≥ 60 years), gender (female, male), body mass index (BMI, $kg/m^2$), race (Mexican American, Hispanic American, non-Hispanic White, non-Hispanic Black, other races [including multiracial]), education level (1. Less than 11th grade [including Less than 9th grade, 9-11th grade (including 12th grade with no diploma)], 2. High school graduate/GED or equivalent, 3. College or AA degree or above [including Some college or AA degree, College graduate or above]), marital status (1. Married or living with partner [including Married, Living with partner], 2. Other [including Widowed, Divorced, Separated, Never married]), annual household income (categorized as less than $24,999, $25,000 to $64,999, and $65,000 or more), smoking status (defined as having smoked more than 100 cigarettes in total), diabetes (indicated by answering "Yes" to "Doctor told you have diabetes" in the survey), hypertension (indicated by answering "Yes" to "Ever told you had high blood pressure" in the survey), and alcohol use (defined as having consumed at least 12 alcoholic beverages [12 oz. beer, 5 oz. wine, or 1.5 oz. liquor] in one's lifetime or within the past year, acknowledging variations in alcohol-related questions and responses across different survey years). Drug use is defined as answering "Yes" to any of the following questions: "Ever used marijuana or hashish," "Ever used cocaine/ heroin/ methamphetamine," or "Ever use a needle to inject illegal drugs." Chronic heart disease is defined as answering "Yes" to either "Ever told you had congestive heart failure" or "Ever told you had coronary heart disease." Chronic respiratory diseases are defined as answering "Yes" to any of the following questions: "Ever been told you have asthma," "Ever told you had emphysema," or "Ever told you had chronic bronchitis." Stroke is defined as answering "Yes" to the question "Ever told you had a stroke." Malignancy is defined as answering "Yes" to the question "Ever told you had cancer or malignancy."

### Statistical analysis

The analysis was conducted using R software (version 4.2.1) and Fendrine Statistics software (version 1.92). A two-sided $P$ value < 0.05 was considered statistically significant. Continuous variables were described as means ± standard deviations and analyzed using the Mann-Whitney U test. Categorical variables were presented as numbers (percentages) and compared using chi-square tests or Fisher's exact tests. The effects of the CALLY index on primary variables were evaluated using logistic regression models (odds ratios [OR] and 95% confidence intervals [CI]) and Cox regression models (hazard ratios [HR] and 95% CI). Four models were constructed based on clinical significance and literature-derived confounding factors. ("Model 1: Unadjusted; Model 2: Adjusted for age and sex; Model 3: Further adjusted for BMI, smoking, and comorbidities; Model 4: Fully adjusted for all covariates in Table 1.")The association between the CALLY index and all-cause mortality in RA was examined using multivariable Cox regression models, and subgroup analyses were performed. Restricted cubic spline (RCS) analyses were employed to assess whether there was a linear or nonlinear relationship between the CALLY index and mortality. A segmented regression model was used to determine the optimal CALLY index cut-off value associated with significant survival outcomes. Kaplan-Meier survival curves were utilized to analyze survival probabilities of RA patients at different CALLY index levels.

## Results

### Baseline data of the study population

Among the respondents from 1999 to 2010, 1,011 RA patients and non-RA individuals ($n$ = 18047) were included after excluding those with missing data. Based on the follow-up outcomes, the patients were divided into the survival group and the death group. The death group had an average age of 69.7 ± 10.9 years and a median follow-up time of 98.0 months. In the death group, the proportion of individuals with a history of disease or adverse lifestyle habits was higher, and the CALLY index was significantly lower compared to the survival group (Table 1).

### Relationship between CALLY index and all-cause mortality in patients with RA

In both univariate logistic analysis (Supplement Table 1, crude) and multivariate logistic analysis (Supplement Table 1, model 4), the odds ratios (ORs) for RA were all less than 1.0 compared to non-RA individuals ($P$ values < 0.05), which indicates that a lower CALLY index may be a risk factor for RA patients, with the adjusted OR being 0.74 (95% CI:0.65–0.83). Next we collected follow-up mortality datas from the NDI database for a retrospective cohort study. The study included 1101 RA patients, of whom 441 were deceased (Table 1). In the follow-up cohort, with a median follow-up time of 137.0 months, both unadjusted models (Table 2, crude) and covariate-adjusted models (Table 2, model 4) showed that RA patients with a higher CALLY index have a lower risk

**Table 1** Characteristics of the study participants

| Characteristics | Total | Alive | Deceased | *p* |
|---|---|---|---|---|
| **N(%)** | 1101(100.0) | 660(59.95) | 441(40.05) | |
| **Sex, n(%)** | | | | 0.008 |
| Male | 466 (42.3) | 258 (39.1) | 208 (47.2) | |
| Female | 635 (57.7) | 402 (60.9) | 233 (52.8) | |
| **Age, Mean ± SD** | 60.8 ± 14.3 | 54.9 ± 13.2 | 69.7 ± 10.9 | < 0.001 |
| **Race, n (%)** | | | | < 0.001 |
| Mexican American | 179 (16.3) | 126 (19.1) | 53 (12) | |
| Other Hispanic | 72 (6.5) | 56 (8.5) | 16 (3.6) | |
| Non-Hispanic White | 528 (48.0) | 278 (42.1) | 250 (56.7) | |
| Non-Hispanic Black | 294 (26.7) | 184 (27.9) | 110 (24.9) | |
| Other Race - Including Multi-Racial | 28 (2.5) | 16 (2.4) | 12 (2.7) | |
| **Education level, n(%)** | | | | < 0.001 |
| Less than 11th grade (Includes 12th grade with no diploma) | 439 (39.9) | 234 (35.5) | 205 (46.5) | |
| High school graduate/GED or equivalent | 264 (24.0) | 142 (21.5) | 122 (27.7) | |
| College or AA degree or above | 398 (36.1) | 284 (43) | 114 (25.9) | |
| **Marital status, n(%)** | | | | < 0.001 |
| Married or Living with partner | 477 (43.3) | 259 (39.2) | 218 (49.4) | |
| Other | 624 (56.7) | 401 (60.8) | 223 (50.6) | |
| **Annual household income, n (%)** | | | | < 0.001 |
| ≤$24,999 | 521 (47.3) | 272 (41.2) | 249 (56.5) | |
| $25,000 to $64,999 | 391 (35.5) | 236 (35.8) | 155 (35.1) | |
| ≥$65,000 | 189 (17.2) | 152 (23) | 37 (8.4) | |
| **Hypertension, n(%)** | | | | < 0.001 |
| No | 476 (43.2) | 320 (48.5) | 156 (35.4) | |
| Yes | 625 (56.8) | 340 (51.5) | 285 (64.6) | |
| **Diabetes, n(%)** | | | | < 0.001 |
| No | 871 (79.1) | 545 (82.6) | 326 (73.9) | |
| Yes | 230 (20.9) | 115 (17.4) | 115 (26.1) | |
| **Chronic respiratory diseases, n (%)** | | | | 0.471 |
| No | 829 (75.3) | 502 (76.1) | 327 (74.1) | |
| Yes | 272 (24.7) | 158 (23.9) | 114 (25.9) | |
| **Chronic heart disease, n (%)** | | | | < 0.001 |
| No | 933 (84.7) | 602 (91.2) | 331 (75.1) | |
| Yes | 168 (15.3) | 58 (8.8) | 110 (24.9) | |
| **Drug use, n (%)** | | | | < 0.001 |
| No | 921 (83.7) | 512 (77.6) | 409 (92.7) | |
| Yes | 180 (16.3) | 148 (22.4) | 32 (7.3) | |
| **Stroke, n (%)** | | | | < 0.001 |
| No | 998 (90.6) | 618 (93.6) | 380 (86.2) | |
| Yes | 103 (9.4) | 42 (6.4) | 61 (13.8) | |
| **Malignancy, n (%)** | | | | < 0.001 |
| No | 940 (85.4) | 586 (88.8) | 354 (80.3) | |
| Yes | 161 (14.6) | 74 (11.2) | 87 (19.7) | |
| **Smoking, n(%)** | | | | 0.03 |
| No | 440 (40.0) | 281 (42.6) | 159 (36.1) | |
| Yes | 661 (60.0) | 379 (57.4) | 282 (63.9) | |
| **Alcohol uses, n(%)** | | | | 0.018 |
| No | 403 (36.6) | 223 (33.8) | 180 (40.8) | |
| Yes | 698 (63.4) | 437 (66.2) | 261 (59.2) | |
| **BMI(kg/m$^2$),Mean ± SD** | 30.3 ± 7.2 | 31.0 ± 7.4 | 29.4 ± 6.9 | < 0.001 |
| **HGB(g/dL), Mean ± SD** | 13.9 ± 1.5 | 14.0 ± 1.5 | 13.8 ± 1.6 | 0.094 |
| **ALB(g/L), Mean ± SD** | 41.6 ± 3.4 | 41.8 ± 3.2 | 41.2 ± 3.7 | 0.012 |
| **GLB(g/L), Mean ± SD** | 31.1 ± 5.4 | 30.9 ± 5.1 | 31.4 ± 5.7 | 0.106 |

**Table 1** (continued)

| Characteristics | Total | Alive | Deceased | *p* |
|---|---|---|---|---|
| **ALT(U/L), Median (IQR)** | 21.0 (16.0, 28.0) | 21.0 (16.0, 28.0) | 20.0 (15.0,28.0) | 0.006 |
| **Scr(umol/L), Median (IQR)** | 74.3 (61.9, 90.2) | 70.7 (61.9, 86.6) | 79.6 (65.4,97.2) | < 0.001 |
| **CRP(mg/dL), Median (IQR)** | 0.3 (0.1, 0.8) | 0.3 (0.1, 0.7) | 0.4 (0.2, 0.8) | 0.019 |
| **CALLY index(IQR)** | 41.1(17.2,104.4) | 45.9(18.9,115.4) | 28.6(12.4,66) | < 0.001 |
| **Log - CALLY** | 1.6 ± 0.6 | 1.7 ± 0.6 | 1.4 ± 0.6 | < 0.001 |
| **Follow-up time(month)(IQR)** | 137.0(111.0,193.0) | 152.0(130.0,210.0) | 98.0(54.0,144.0) | < 0.001 |

1,101 RA participants were included in this study. Abbreviations used are as follows: BMI, body mass index; HGB, hemoglobin concentration; ALB, serum albumin concentration; GLB, serum globulin concentration; ALT, alanine aminotransferase concentration; Scr, serum creatinine concentration; CRP, C-reactive protein concentration; CALLY index, CRP-albumin-lymphocyte index

**Table 2** Association of CALLY index with all-cause mortality risk in RA patients

| Model | HR(95% CI) | *p* value | Adjusted covariates |
|---|---|---|---|
| Crude | 0.70(0.59,0.83) | < 0.001 | No |
| Model 1 | 0.62(0.52,0.75) | < 0.001 | Crude + age + gender + smoking + alcohol use |
| Model 2 | 0.61(0.50,0.73) | < 0.001 | Model1 + race + education + marital status + household income + drug use |
| Model 3 | 0.61(0.50,0.73) | < 0.001 | Model2 + hypertension + diabetes + Chronic heart disease + Chronic respiratory diseases + stroke + cancer or malignancy |
| Model 4 | 0.62(0.51,0.77) | < 0.001 | Model3 + BMI + serum creatinine concentration + Alanine aminotransferase concentration + serum globulin concentration + haemoglobin concentration |

After excluding cases with missing values, a total of 1,101 participants were collected. A p-value of < 0.05 is considered statistically significant

of death compared to those with a lower CALLY index. After adjusting for covariates, the hazard ratio (HR) was 0.62 (95% CI: 0.51–0.77), indicating a 38% reduction in all-cause mortality risk (Table 2, model 4).

### Prognostic role of the CALLY index in RA

To further investigate the relationship between the CALLY index and the prognosis of RA, RCS analysis is performed. The results revealed an L-shaped association between Log-CALLY and RA, with a reference inflection point at Log-CALLY = 1.107 (Fig. 2). Below a CALLY index of 12.79, higher values were correlated with reduced all-cause mortality risk in RA. When the CALLY index was greater than 12.79, there was no significant correlation between the CALLY index and RA, indicating a threshold effect.

### Subgroup analysis

Subgroup analysis stratified by gender, age, education level, household income, disease history, BMI, and personal history consistently demonstrated a significant association between a lower CALLY index and an elevated risk of all-cause mortality in RA patients (Supplement Table 2). Significant interaction effects were observed for gender ($P = 0.038$) and age ($P = 0.002$). Additionally, multiplicative interactions indicated that the multiplicative scale for Log-CALLY > 1.107 with gender yields a regression coefficient of 1.57 (95% CI: 1.05–2.37, $P = 0.03$) (Table 3), while the multiplicative scale with age yields a coefficient of 1.99 (95% CI: 1.18–3.37, $P = 0.01$) (Table 3). These findings suggest a synergistic effect between a higher Log-CALLY index and both male and age under 60 years old.

### KM curve

The results of the RCS analysis allow for the division of the CALLY index into two categories: a high CALLY index group (above 12.79, Log-CALLY above 1.107) and a low CALLY index group (below 12.79, Log-CALLY below 1.107). Kaplan-Meier analysis showed that the survival rate is significantly higher in the high CALLY group compared that in the low CALLY group ($P = 0.0012$) (Fig. 3). These results indicated that a lower CALLY index was consistently and independently associated with an elevated risk of all-cause mortality in adult RA patients in the United States (US) either as a continuous or categorical variable.

## Discussion

This large-scale retrospective cohort study aimed to investigate CALLY index potential clinical significance and prognostic role in patients with RA. It is observed that RA patients exhibit a lower CALLY index values compared to non-RA individuals after adjusting for various covariates. Furthermore, lower CALLY index values were associated with an increased risk of all-cause mortality in RA patients. Hypoalbuminemia reflects both chronic inflammation (negative acute-phase reactant) and protein-energy wasting, while lymphopenia indicates T-cell exhaustion and impaired pathogen surveillance. The synergy of these factors may accelerate cardiovascular events and infections, the leading causes of death in RA. These results indicate that the CALLY index may serve as a valuable tool in managing mortality risk in RA patients due to its simplicity and ease of assessment. It is important to emphasize that the CALLY index

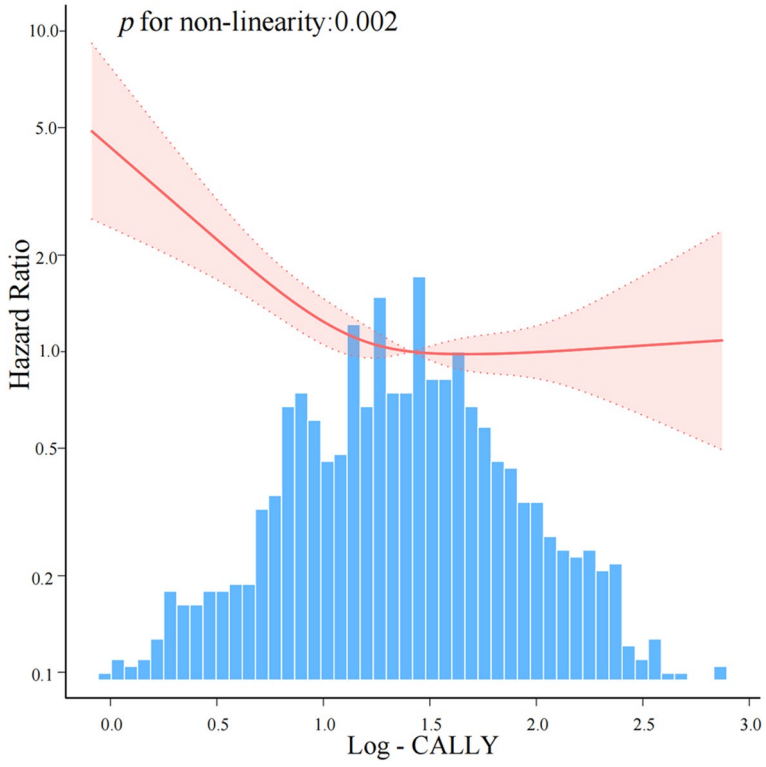


**Fig. 2** Restricted cubic spline (RCS) analysis was used to examine the relationship between Log-CALLY and all-cause mortality risk in RA patients. The CALLY index data range from the 0.5th percentile to the 99.5th percentile

**Table 3** Multiplicative interaction analysis

| Variables | Age<60 | | Age>60 | | *p* for interaction | Multiplicative scale |
|---|---|---|---|---|---|---|
| | HR 95% CI | *p* value | HR 95% CI | *p* value | | |
| N(events) | 454(73) | | 647(368) | | | |
| Log-CALLY | 0.28(0.16,0.48) | <0.001 | 0.70(0.55,0.88) | 0.003 | **0.002** | |
| **Subgroups** | | | | | | |
| Log-CALLY<1.107 | 1(Reference) | | 1(Reference) | | | |
| Log-CALLY>1.107 | 0.34(0.2,0.59) | <0.001 | 0.73(0.57,0.94) | 0.015 | **0.009** | 1.99(1.18,3.37),$^{P}$=0.01 |
| **Variables** | **Man** | | **Female** | | ***p* for interaction** | **Multiplicative scale** |
| | **HR 95% CI** | ***p* value** | **HR 95% CI** | ***p value*** | | |
| N(events) | 635(233) | | 466(208) | | | |
| Log-CALLY | 0.54(0.4,0.73) | <0.001 | 0.75(0.56,1.02) | 0.067 | **0.038** | |
| **Subgroups** | | | | | | |
| Log-CALLY<1.107 | 1(Reference) | | 1(Reference) | | **0.033** | |
| Log-CALLY>1.107 | 0.56(0.4,0.73) | <0.001 | 0.82(0.6,1.12) | 0.215 | | 1.57(1.04,2.37),$^{P}$=0.03 |

The interaction effects between the CALLY index, gender, and age were analyzed. A p-value of < 0.05 is considered statistically significant

is a composite measure, encompassing inflammation, immune function and nutritional status.

Similar to many other composite indices, a lower CALLY index was associated with an increased RA risk. These composite indices, which primarily utilize routine blood test values, include the systemic immune-inflammation index [16], the neutrophil-lymphocyte ratio [18], the albumin-CRP ratio [25], the platelet-lymphocyte ratio [26], and the pan-immune-inflammation index [17]. These indices focus on specific components of inflammation, immune function or nutritional status but fail to provide a comprehensive assessment of all three aspects. In contrast, the CALLY index integrates lymphocytes to represent immune function, CRP to reflect inflammation levels, and albumin level to indicate nutritional status.

In recent years, with the improvement of medical level, the mortality rate of RA patients has decreased, but it is still significantly higher than that of non RA populations [4]. Therefore, identifying mortality risk factors is

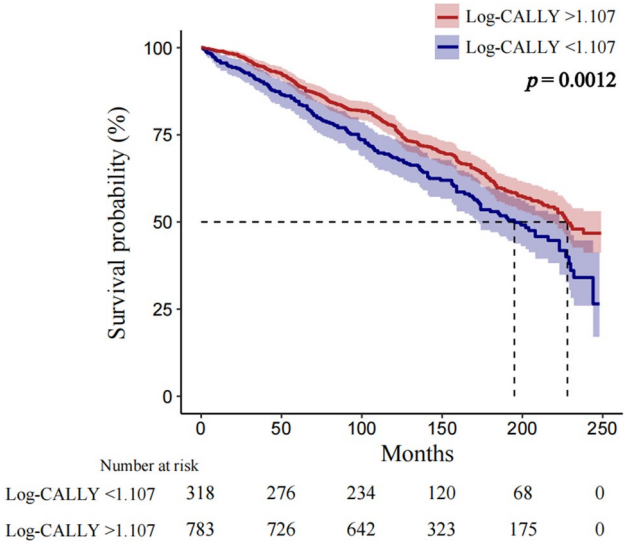


**Fig. 3** Kaplan-Meier (KM) curves of all-cause mortality risk in RA patients associated with different CALLY index values

essential in the long-term management of RA. Clinical studies on RA prognosis have identified older age, multiple comorbidities, and reduced use of conventional disease-modifying antirheumatic drugs (cDMARDs) and biologic DMARDs (bDMARDs) as factors contributing to poor outcomes [27]. Cohort studies indicate that older age, male, smoking, and especially ACPA positivity are associated with an increased overall mortality risk in RA patients [28]. This suggests that the elevated mortality risk in RA patients is related to multiple factors. Elevated levels of CRP [29]and NLR [18] are associated with an increased risk of mortality in RA patients, suggesting that high inflammation and immune status contribute to mortality risk in this population. Research on nutritional status and RA mortality risk has shown that RA patients with a BMI ≥ 30 kg/m$^2$ exhibit higher disease activity and reduced treatment responsiveness, regardless of whether they receive cDMARDs or bDMARDs compared to those with a lower BMI [30]. Conversely, other studies have reported that malnutrition is linked to an increased risk of all-cause mortality in RA patients [12, 31]. Therefore, we further investigated the relationship between the CALLY index and all-cause mortality in RA patients. And we found that the CALLY index was negatively correlated with a reduced risk of all-cause mortality in RA patients when CALLY is below 12.79 after adjusting for significant covariates. These results indicate that management of RA patients should focus on monitoring peripheral blood lymphocyte (PBMC) counts and serum albumin levels while striving to control systemic inflammation and reduce CRP levels. Subgroup analysis revealed CALLY index had interactive effects with age and gender. A higher CALLY index is associated with a reduced risk of RA mortality in patients under the age of 60 or male. Therefore, the CALLY index assessment should be prioritized in these demographic groups.

In addition, among the 1,101 RA patients monitored, the median follow-up period is 137 months. Of the 441 patients who died, the primary causes of death are heart disease (28.34%) and malignant tumors (22.22%) (Supplement Fig. 1), and both of which are associated with systemic inflammation levels, immune function and nutritional status.

This study utilizes data from the NHANES, incorporating a cohort study with follow-up survival status. The large sample size and consideration of numerous covariates facilitate control over potential confounding effects. However, this study has many limitations. Firstly, the small number of deaths from various causes restricts statistical analysis, precluding further examination of the correlation between CALLY and specific causes of death. Secondly, being a retrospective cohort study, the results indicate only that the CALLY index is associated with RA mortality risk.

## Study limitations

Given the retrospective design, this research is subject to inherent constraints in differentiating overlapping clinical presentations (such as infectious diseases and hepatic disorders). The absence of standardized exclusion criteria reflects these operational limitations. However, we must acknowledge the inherent limitations of cross-sectional NHANES data. Moreover, the information may be subject to recall bias and other potential confounding factors, which could introduce residual confounding effects. Despite these challenges, we have thoroughly discussed the limitations in the manuscript and have been cautious in interpreting and drawing conclusions from our findings.

## Conclusions

In summary, our study demonstrates that the CALLY index is associated with a high risk of RA. A lower CALLY index is linked to an increased risk of all-cause mortality in RA. The relationship between the CALLY index and RA mortality follows an L-shaped curve, with a reference value of 12.79 (Log-CALLY of 1.107). We propose a CALLY < 12.79 as a red flag for intensified multidisciplinary management, including nutritional support (e.g., protein supplementation), infection prophylaxis, and inflammatory activity monitoring. This relationship is more pronounced in individuals younger than 60 years old and in males. Therefore, in the management of RA patients, it is crucial to comprehensively evaluate the patients' nutritional status, inflammation levels, and immune function to identify those at high mortality risk as early as possible.

**Abbreviations**

| | |
|---|---|
| CALLY index | C-reactive protein (CRP)-albumin-lymphocyte index |
| RA | Rheumatoid arthritis |
| NHANES | National Health and Nutrition Examination Survey |
| CRP | C reactive protein |
| NDI | National Death Index |
| HR | Hazard ratio |
| OR | Odds ratio |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41927-025-00499-7.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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**Author contributions**
JL Z, YH L, B Y and X L designed the research. JL Z, YH L, JY Z, GH L, P L, QY C, H Z, SM L, CL Z, B Y and X L collected, analyzed the data, and drafted the manuscript. JL Z, JY Z, B Y and X L revised the manuscript. All authors contributed to the article and approved the submitted version.

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**Data availability**
Publicly available datasets were analyzed in this study. This data can be found here: https://www.cdc.gov/nchs/nhanes/index.htm.

## Declarations

**Ethics approval and consent to participate**
The portions of this study involving human participants, human materials, or human data were conducted in accordance with the Declaration of Helsinki and were approved by the NCHS Ethics Review Board. The patients/participants provided their written informed consent to participate in this study.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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**References**

1. Di Matteo A, Bathon JM, Emery P. Rheumatoid arthritis. Lancet. 2023;402(10416):2019–33.
2. Brown P, Pratt AG, Hyrich KL. Therapeutic advances in rheumatoid arthritis. BMJ. 2024;384:e070856.
3. Collaborators GBDRA. Global, regional, and National burden of rheumatoid arthritis, 1990–2020, and projections to 2050: a systematic analysis of the global burden of disease study 2021. Lancet Rheumatol. 2023;5(10):e594–610.
4. Abhishek A, Nakafero G, Kuo CF, Mallen C, Zhang W, Grainge MJ, Doherty M. Rheumatoid arthritis and excess mortality: down but not out. A primary care cohort study using data from clinical practice research datalink. Rheumatology (Oxford). 2018;57(6):977–81.
5. Hoffmann MH, Kirchner H, Kronke G, Riemekasten G, Bonelli M. Inflammatory tissue priming: novel insights and therapeutic opportunities for inflammatory rheumatic diseases. Ann Rheum Dis. 2024.
6. Nikiphorou E, Philippou E. Nutrition and its role in prevention and management of rheumatoid arthritis. Autoimmun Rev. 2023;22(7):103333.
7. Weyand CM, Goronzy JJ. Immunometabolism in the development of rheumatoid arthritis. Immunol Rev. 2020;294(1):177–87.
8. Neto M, Mendes B, Albuquerque F, da Silva JAP. Novel biomarkers in RA: implication for diagnosis, prognosis, and personalised treatment. Best Pract Res Clin Rheumatol. 2024:102021.
9. Pope JE, Choy EH. C-reactive protein and implications in rheumatoid arthritis and associated comorbidities. Semin Arthritis Rheum. 2021;51(1):219–29.
10. Rasheed S, Woods RT. An investigation into the association between nutritional status and quality of life in older people admitted to hospital. J Hum Nutr Diet. 2014;27(2):142–51.
11. Schuetz P, Seres D, Lobo DN, Gomes F, Kaegi-Braun N, Stanga Z. Management of disease-related malnutrition for patients being treated in hospital. Lancet. 2021;398(10314):1927–38.
12. Tian P, Xiong J, Wu W, Shi S, Chen A, Chen K, Chen W, Wu A, Liao Y. Impact of the malnutrition on mortality in rheumatoid arthritis patients: A cohort study from NHANES 1999–2014. Front Nutr. 2022;9:993061.
13. You H, Cheng M, Ma C, Zheng W, Jiang Y, Chen D, Tang Y. Association among B lymphocyte subset and rheumatoid arthritis in a Chinese population. J Orthop Surg Res. 2021;16(1):732.
14. Tan J, Chen J. Changes in peripheral blood T lymphocyte subsets predict disease progression in patients with rheumatoid arthritis. Am J Transl Res. 2022;14(2):1068–75.
15. Iida H, Tani M, Komeda K, Nomi T, Matsushima H, Tanaka S, Ueno M, Nakai T, Maehira H, Mori H, et al. Superiority of CRP-albumin-lymphocyte index (CALLY index) as a non-invasive prognostic biomarker after hepatectomy for hepatocellular carcinoma. HPB (Oxford). 2022;24(1):101–15.
16. Liu B, Wang J, Li YY, Li KP, Zhang Q. The association between systemic immune-inflammation index and rheumatoid arthritis: evidence from NHANES 1999–2018. Arthritis Res Ther. 2023;25(1):34.
17. Tutan D, Dogan AG. Pan-Immune-Inflammation index as a biomarker for rheumatoid arthritis progression and diagnosis. Cureus. 2023;15(10):e46609.
18. Zhou E, Wu J, Zhou X, Yin Y. The neutrophil-lymphocyte ratio predicts all-cause and cardiovascular mortality among U.S. Adults with rheumatoid arthritis: results from NHANES 1999–2020. Front Immunol. 2023;14:1309835.
19. Ye J, Chen L, Xu D, Li R, Lan R, Chen S, He X, Lin M. Inverse association between CALLY index and angina pectoris in US adults: a population-based study. BMC Cardiovasc Disord. 2025;25(1):94.
20. Ding Y, Liu Y, Yu J, Cai C, Fu L, Zhu J, Yang S, Jiang Y, Wang J. The association between the CALLY index and All-Cause mortality in patients with COPD: results from the cohort study of NHANES 2007–2010. Int J Chron Obstruct Pulmon Dis. 2025;20:159–69.
21. Su K, Xiao S, Wang M, Wang K, Fan Q, Sha S, Cheng Y, Liu X, Shi H. Predictive value of albumin to fibrinogen ratio and CALLY index for diagnosis of ulcerative colitis and mucosal healing after Vedolizumab treatment. J Inflamm Res. 2025;18:589–600.
22. 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. 2024;12:1395134.

23. Wang W, Gu J, Liu Y, Liu X, Jiang L, Wu C, Liu J. Pre-Treatment CRP-Albumin-Lymphocyte index (CALLY index) as a prognostic biomarker of survival in patients with epithelial ovarian Cancer. Cancer Manag Res. 2022;14:2803–12.
24. Zhuang J, Wang S, Wang Y, Wu Y, Hu R. Prognostic value of CRP-Albumin-Lymphocyte (CALLY) index in patients undergoing surgery for breast Cancer. Int J Gen Med. 2024;17:997–1005.
25. Yang WM, Zhang WH, Ying HQ, Xu YM, Zhang J, Min QH, Huang B, Lin J, Chen JJ, Wang XZ. Two new inflammatory markers associated with disease activity score-28 in patients with rheumatoid arthritis: albumin to fibrinogen ratio and C-reactive protein to albumin ratio. Int Immunopharmacol. 2018;62:293–8.
26. Erre GL, Paliogiannis P, Castagna F, Mangoni AA, Carru C, Passiu G, Zinellu A. Meta-analysis of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratio in rheumatoid arthritis. Eur J Clin Invest. 2019;49(1):e13037.
27. Crowson CS, Atkinson EJ, Kronzer VL, Kimbrough BA, Arment CA, Peterson LS, Wright K, Mason TG 2nd, Bekele DI, Davis JM. Comorbidity clusters in patients with rheumatoid arthritis identify a patient phenotype with a favourable prognosis. Ann Rheum Dis. 2024;83(5):556–63. 3rd et al.
28. Heckert SL, Maassen JM, le Cessie S, Goekoop-Ruiterman YPM, Guler-Yuksel M, Lems W, Huizinga TW, Bergstra SA, Allaart CF. Long-term mortality in treated-to-target RA and UA: results of the best and IMPROVED cohort. Ann Rheum Dis. 2024;83(2):161–8.
29. Videm V, Houge IS, Liff MH, Hoff M. Inflammation mediates approximately one quarter of excess relative all-cause mortality in persons with rheumatoid arthritis: the Trondelag health study. Sci Rep. 2022;12(1):18599.
30. Dubovyk V, Vasileiadis GK, Fatima T, Zhang Y, Kapetanovic MC, Kastbom A, Rizk M, Soderbergh A, Zhao SS, van Vollenhoven RF, et al. Obesity is a risk factor for poor response to treatment in early rheumatoid arthritis: a NORD-STAR study. RMD Open. 2024;10(2).
31. Baker JF, Billig E, Michaud K, Ibrahim S, Caplan L, Cannon GW, Stokes A, Majithia V, Mikuls TR. Weight loss, the obesity paradox, and the risk of death in rheumatoid arthritis. Arthritis Rheumatol. 2015;67(7):1711–7.

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