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CRP-Albumin-Lymphocyte index (CALLYI) as a risk-predicting biomarker in association with osteoarthritis

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Abstract

Purpose As a novel biomarker, the C-reactive protein-Albumin-Lymphocyte Index (CALLYI) offers a comprehensive evaluation of the human body from three perspectives. However, the association between CALLYI and the incidence of osteoarthritis (OA) remains unclear. This cross-sectional study investigates the potential relationship between CALLYI and OA in US adults, develops a clinical prediction model, and validates its effectiveness.

Method The study cohort consisted of 18,624 U.S. adults who participated in the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2010. The CALLYI was calculated using the formula: albumin * lymphocytes / CRP * 10. Three weighted multiple regression models were constructed to investigate the correlation between CALLYI and OA. Restricted cubic splines (RCS) were employed to evaluate the nonlinear relationship between these two variables. Subgroup analyses were conducted to examine interactions. Univariate logistic regression, binary logistic regression, and least absolute shrinkage and selection operator (LASSO) were utilized for variable selection in the prediction model. Decision curve analysis (DCA) and receiver operating characteristic (ROC) curve analysis were applied to assess the predictive performance of the models.

Results The total sample size analyzed in this study was 18,624, of which 1,977 (10.62%) were diagnosed with OA. And the mean value of CALLYI was 5.13 (2.12,12.86). The multivariate logistic regression model revealed a negative correlation between elevated CALLYI and OA. The fully adjusted Model 3 demonstrated a significant 28% reduction in OA risk in the Q4 compared to the Q1 of CALLYI (OR = 0.72 95% CI: 0.59–0.88, $p = 0.001$). Subgroup analyses did not reveal any significant interactions ($p > 0.05$). Additionally, a significant non-linear relationship between CALLYI and OA using RCS ($p < 0.0001$). After variable screening, we constructed an OA prediction model incorporating CALLYI, and the results were visualized using a nomogram. The area under the curve (AUC) was 0.825 (95% CI: 0.817–0.834), and DCA indicated that the model holds clinical significance.

Conclusion This study, utilizing NHANES statistics, is the first to establish a nonlinear negative relationship between CALLYI and OA, with no significant interaction observed in subgroup analyses. In the OA prediction model incorporating CALLYI, we validated the effectiveness and clinical utility of this model, providing evidence that CALLYI can serve as a biomarker for OA risk prediction. Nevertheless, larger multicenter prospective cohort studies are necessary to mitigate the limitations inherent in cross-sectional designs and self-reported OA diagnoses.

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Keywords CRP-Albumin-Lymphocyte index, Osteoarthritis, National health and nutrition examination survey (NHANES)

Introduction

Osteoarthritis (OA) is one of the most prevalent orthopedic diseases worldwide, characterized by degenerative changes in articular cartilage that ultimately lead to chronic pain, joint deformity, and loss of function [1, 2]. Recent epidemiological studies indicate that by 2020, an estimated 590 million individuals globally were affected by OA, with 32 million patients in the United States alone. Furthermore, this number is projected to increase to 67 million by 2030 [3, 4]. OA not only causes physical discomfort for patients but also leads to escalating financial losses annually [5]. On the other hand, osteoarthritis usually progresses slowly [6]. If the high-risk individuals of OA can be accurately identified, diagnosed and treated in the early stage of the disease, such as repairing the damaged cartilage and bone tissue, the symptoms can be effectively relieved and the progression of the disease can be delayed. Therefore, a large number of studies on non-surgical treatment of early OA have been carried out [7, 8].

The pathogenesis of OA remains unclear; however, recent studies indicate that its development is influenced by multiple factors. Obesity, inflammation, trauma, infection, and disorders related to immunity and metabolism all identified as risk factors for [9–12]. In recent years, cross-sectional studies utilizing extensive population-based data resources to investigate the correlation between exposure factors and disease incidence have emerged as a prominent research focus. Research has confirmed that the incidence of OA is associated with factors such as smoking, selenium intake, and vitamin C intake [13, 14]. In addition, several biomarkers, including the body roundness index, hypertriglyceridemia glucose index, serum α-Klotho level, and comprehensive dietary antioxidant index, were observed to exhibit significant differences between OA patients and healthy controls [15–17]. However, given the multifaceted pathogenesis of OA, biomarkers that solely evaluate inflammation or immune function levels are insufficient for comprehensive OA prediction, potentially leading to inaccuracies. Additionally, some biomarkers have complex compositions and require intricate statistical calculations, making them unsuitable for routine clinical assessment. Therefore, our study aimed to investigate the association between a biomarker that can comprehensively assess physical status and is readily available in clinical practice, and the incidence of OA. The CRP-Albumin-Lymphocyte Index (CALLYI) proposed by Hiroya Iida et al., is a relatively novel nutritional indicator of inflammation [18]. CALLYI is calculated as AlbuminxLymphocyte , (CRPx10), incorporating assessments of the patient's nutritional status, immune function, and inflammation level. The parameters of CALLYI are routinely utilized in clinical practice, are readily obtainable, and correlate closely various pathophysiological levels in patients, which significantly enhances its practicality and applicability. Subsequent clinical studies have affirmed the utility of CALLYI in predicting the correlation and prognosis of various diseases, particularly colorectal cancer, lung cancer, and other cancers [19–22].

The National Health and Nutrition Examination Survey (NHANES) is a national cross-sectional study designed to assess the nutritional status and health of the US population [23, 24]. Noteworthy for its extensive sample size, the database is weighted to accurately reflect the demographic makeup of the U.S. population across race, gender, and age. A review of existing literature indicates that the relationship between CALLYI and OA has not been previously explored using the NHANES database. Detailed information about NHANES is freely available on its official website (http://www.cdc.gov/nchs/nhanes/index.htm). This study aims to validate the association between CALLYI and OA by analyzing NHANES data spanning from 1999 to 2010. Additionally, the performance of CALLYI as a predictive model for OA was evaluated.

Methods

Study design and population

In this investigation, data from participants in the NHANES were utilized, covering six consecutive survey cycles from 1999 to 2010 (1999–2000,2001–2002,2003–2004,2005–2006,2007–2008,2009–2010), including demographic, laboratory, and questionnaire data, comprising a total of 62,160 participants. Through a review of prior relevant literature, additional confounders that might affect the CALLYI variable were included in our analysis, such as hypertension, diabetes, coronary heart disease, stroke, smoking, alcohol consumption, and BMI [25–28]. The exclusion criteria for our study data were as follows: (1) Participants under the age of 20. (2) Missing CALLYI data. (3) Missing OA data. (4) Missing data on relevant confounding factors. The final sample size of this study was 18,624, with 1,977 participants diagnosed with OA. The design process of this study is depicted in Fig. 1.

Diagnosis of OA and definition of CALLYI

In this study, the formula used to calculate CALLYI is: Albumin (g/L)xLymphocyte (10^9/L) / (CRP (mg/L) x10). Diagnostic data for OA are obtained from the

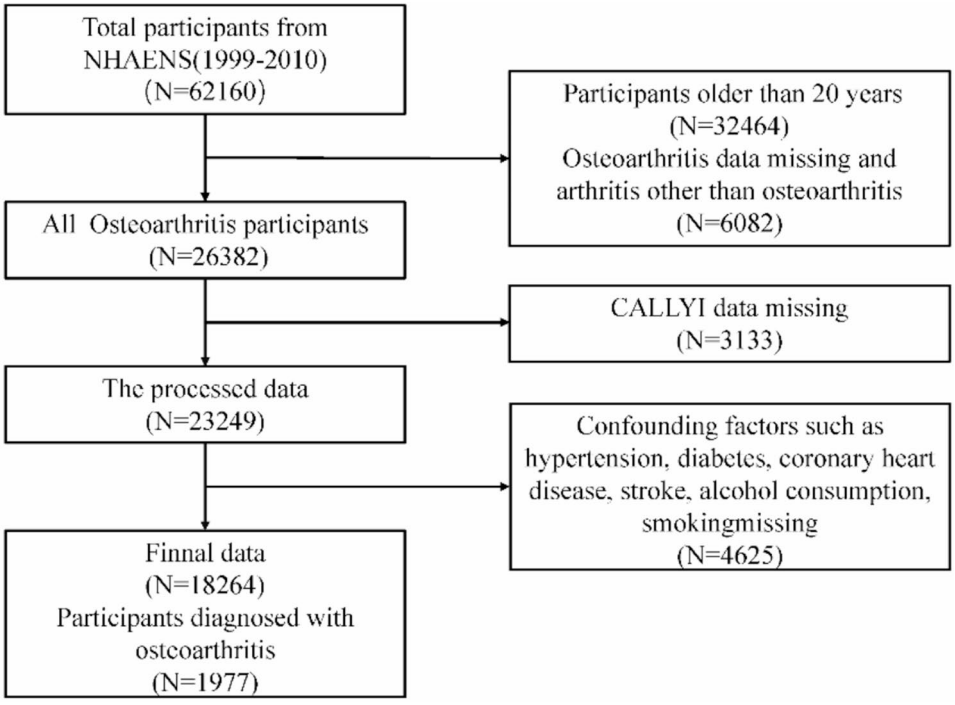

Fig. 1 This study design and screening of data from NHANES 1999–2010

questionnaire component of the NHANES, where participants are asked whether a doctor or other health professional has ever diagnosed them with arthritis, specifically identifying OA or degenerative arthritis (excluding rheumatoid arthritis, psoriatic arthritis, and other types of arthritis). Numerous studies have demonstrated that this self-reported questionnaire method yields reliable results [29, 30].

Covariates

In this study, the selection of covariates was guided by two primary considerations. First, clinical observations indicate that a significant proportion of OA patients concurrently suffer from chronic conditions such as hypertension, diabetes, and obesity. Second, a review of recently published cross-sectional studies based on NHANES data further informed our covariate selection. The covariates ultimately included in the study were gender, age, race, education level, and poverty impact ratio from demographic data, and smoking, drinking, body mass index, hypertension, diabetes, coronary heart disease, and stroke from questionnaire data. We have constructed directed acyclic graphs (Supplementary Fig. 1) to illustrate these variables in the Supplementary file. In addition, some covariates were redefined to facilitate subsequent data analysis: race (Non-Hispanic White: white, Non-Hispanic Black: black, Other Races Including Multi-Racial: multi-racial), educational level (9-11th Grade (Including 12th grade without a diploma): 9-12th Grade, High School Graduate/GED or Equivalent: 9-12th Grade, Less Than 9th Grade: <9th Grade), and BMI categorized into four groups: <18, 18–25, 25–30, and > = 30. The term "former" in alcohol and smoking data was redefined as "no". And in the diagnosis of DM, IFG and IGT were classified as "NO".

Statistical analyses

R software (version 4.3.3) (https://www.r-project.org/) was utilized for data analysis in this study. A p-value less than 0.05 was deemed statistically significant. Continuous variables, whether normally or skewed distributed, were presented as means (standard deviation), and categorical variables were expressed as weighted mean percentages. Given the goal of the NHANES to produce data representative of the U.S. population through a complex sampling design, all data were weighted according to NHANES data analysis guidelines, considering the categories and distribution characteristics of the included factors. This research employed a multivariate logistic regression model to examine the association between CALLYI and OA and to compute the odds ratio (OR) and its 95% confidence interval (CI) across three models. Model 1 involved no adjustments. Model 2 was adjusted for demographic characteristics including age, gender, race, education, and poverty impact ratio. Model 3 included adjustments for disease factors such as hypertension, diabetes mellitus, stroke, coronary heart disease, and lifestyle factors like smoking, drinking, and BMI. To ensure the robustness of the relationship between CALLYI and OA, subgroup analyses were conducted based

on sex, age, race, education, and BMI. Restricted cubic spline (RCS) curves were used to explore the potential linear or nonlinear relationship between CALLYI and OA. Subsequently, the prediction model was constructed and validated. Initially, LASSO regression was employed to screen and regress the variables, selecting an optimal λ through cross-validation. Variables were further refined by calculating OR and subsequently verified using both univariate and multivariate regression analyses to finalize the prediction model. The model's performance in terms of specificity and sensitivity was assessed via ROC curve analysis and the corresponding AUC. Additionally, decision curve analysis was conducted to evaluate the net benefit and clinical utility of the model. Finally, a nomogram was developed to visually represent the risk prediction model, assigning weighted scores to different variables based on their risk contribution, thereby quantifying the overall probability of developing OA.

Results

Baseline characteristics

Supplementary Table 1 presents the basic characteristics of the variables for the study participants. Table 1 further delineates these characteristics across the quartiles of the weighted CALLYI. The analysis included 18,624 U.S. adults, with an average age of 44.69 (standard deviation: 0.22), comprising 9,431 (50.64%) males and 9,193 (49.36%) females. The ethnic composition was predominantly non-Hispanic whites, accounting for 13,221 participants (72.39%). Supplementary Table 1 indicates that OA was more prevalent among older, well-educated, non-Hispanic white males compared to those without OA. Statistically significant differences were noted between the groups in various parameters including CRP, albumin, lymphocyte, hypertension, diabetes mellitus, stroke, coronary heart disease, smoking and drinking habits, and BMI ($p < 0.05$). The CALLY index quartiles ranged from 1 to 4, [0.017,1.917], (1.917,4.587], (4.587,11.459], (11.459,1706.4]. Additionally, the CALLY index was strongly associated with the wealth status of participants and exhibited a gradual decline with age. Higher CALLY index values correlated with fewer incidences of OA, hypertension, diabetes, coronary heart disease, and stroke ($p < 0.05$). Individuals in better health displaying higher CALLY index values.

Association between CALLYI and OA

Table 2 demonstrates that the prevalence of OA declines as the CALLYI increases, indicating a negative correlation between the CALLYI and OA prevalence. Initial unadjusted analysis (Model 1) revealed a reduction in OA prevalence in Q2, Q3, and Q4 relative to Q1 with ORs of 0.74 (95% CI: 0.65–0.85), 0.57 (95% CI: 0.49–0.67), and 0.39 (95% CI: 0.34–0.45), respectively. Model 2, incorporating demographic adjustments for gender, age, ethnicity, and education level, showed enhanced statistical significance for these groups while maintaining overall significance. Further adjustments in Model 3 for confounding factors such as smoking, alcohol consumption, BMI, hypertension, diabetes, coronary heart disease, and stroke revealed that the statistical difference for Q2 vanished. However, the results for Q3 (OR: 0.79, 95% CI: 0.67–0.93) and Q4 (OR: 0.72, 95% CI: 0.59–0.88) continued to align with the downward trend and remained statistically significant ($p < 0.05$).

Subgroup analysis between CALLYI and OA

The purpose of the subgroup analysis was to assess the reliability and stability of the association between CALLYI and OA. As presented in Table 3, variables such as sex, age, race, education level, PIR and BMI were included in the analysis. The results indicated no significant differences in the association between CALLYI and OA across these subgroups, with all p-values for interaction exceeding 0.05. This suggests that, there is no interaction between these variables and the relationship between CALLYI and OA, confirming the robustness of the described negative association.

Nonlinear relationship between CALLYI and OA

We plotted five nodes as an RCS curve, as illustrated in Fig. 2. The RCS curve revealed a significant overall trend between CALLYI and the prevalence of OA ($P < 0.05$). Moreover, this relationship was found to exhibit a significant non-linear association ($P < 0.05$). Notably, the data indicate an inverse correlation between the prevalence of OA and the CALLYI index, with higher values of the CALLYI index associated with a reduced prevalence of OA.

Variable selection for OA prediction model

Prior to constructing the prediction model, we conducted LASSO regression analysis to screen the variables. Following cross-validation, we determined the optimal λ value (λ min = 0.000419). The OR values of the variables were calculated based on the regression coefficients, and variables with OR equal to 1 were excluded. Following this, univariate logistic regression and multivariate logistic regression analyses were conducted to identify independent risk factors for OA. These variables were then incorporated into the final prediction model. Ultimately, 11 variables including age, gender, race, CALLYI, hypertension, stroke, and alcohol user—were included in the prediction model. The visualization of these results is presented in Figs. 3 and 4.

Table 1 Basic characteristics of participants by weighted CALLY index quartiles

Variable	Total	Quartiles of CALLYI				Pvalue
		Q1	Q2	Q3	Q4	
Age	44.69 (0.22)	48.30 (0.33)	46.72 (0.33)	44.61 (0.32)	40.05 (0.28)	< 0.0001
Race						< 0.0001
Black	9.75	12.73	9.80	8.61	8.33	
Mexican American	7.96	8.26	7.67	8.43	7.53	
Multi racial	5.02	3.27	4.46	5.51	6.49	
Other Hispanic	4.88	4.55	5.27	4.61	5.06	
White	72.39	71.19	72.81	72.85	72.58	
Educational level						< 0.0001
< 9th Grade	5.28	6.01	5.53	5.60	4.20	
9-12th Grade	35.77	38.88	37.25	35.09	32.58	
College Graduate or above	58.95	55.11	57.22	59.31	63.23	
Gender						< 0.0001
Female	49.36	61.94	50.86	42.73	43.93	
Male	50.64	38.06	49.14	57.27	56.07	
Poverty Impact Ratio						< 0.0001
< 1.3	18.64	21.82	18.79	16.69	17.72	
1.3–3.5	35.55	36.84	36.27	36.08	33.38	
> 3.5	45.81	41.34	44.94	47.23	48.90	
Hypertension						< 0.0001
No	67.71	55.70	62.89	69.87	79.66	
Yes	32.29	44.30	37.11	30.13	20.34	
DM						< 0.0001
No	90.83	85.01	89.41	92.62	95.15	
Yes	9.17	14.99	10.59	7.38	4.85	
Coronary heart disease						< 0.0001
No	97.21	96.06	96.48	97.72	98.31	
Yes	2.79	3.94	3.52	2.28	1.69	
Alcohol user						< 0.0001
No	26.02	33.30	27.47	23.59	21.07	
Yes	73.98	66.70	72.53	76.41	78.93	
BMI						< 0.0001
< 18	1.07	0.48	0.35	0.91	2.33	
>=30	30.80	53.37	40.01	24.30	10.44	
18–25	33.38	17.35	22.70	34.09	55.02	
25–30	34.75	28.81	36.94	40.70	32.20	
Stroke						< 0.0001
No	98.11	96.88	98.05	98.67	98.67	
Yes	1.89	3.12	1.95	1.33	1.33	
Smoke						0.25
No	76.62	77.99	76.00	76.10	76.52	
Yes	23.38	22.01	24.00	23.90	23.48	
Osteoarthritis or degenerative arthritis						< 0.0001
NO-OA	89.95	85.33	88.73	91.07	93.72	
OA	10.05	14.67	11.27	8.93	6.28	

Continuous variables are expressed as means (standard deviation): p value was calculated using a weighted linear regression model. Categorical variables are expressed as %: p value was calculated by a weighted chi-square test

DM: diabetes mellitus; BMI: body mass index; OA: osteoarthritis

An evaluation of the predictive capability of the prediction model

To evaluate the predictive performance of the CALLYI model and the OA prediction model, their respective ROC curves were plotted, and the areas under the curves (AUC) were calculated. As shown in Fig. 5, the AUC for CALLYI was 0.598 (95% CI: 0.585–0.611), while the AUC for the prediction model was 0.825 (95% CI:

Table 2 Association between CALLYI and osteoarthritis

	Model 1		Model 2		Model 3	
Character	**Pr(>|t|)**	**95% CI**	**Pr(>|t|)**	**95% CI**	**Pr(>|t|)**	**95% CI**
CALLYI Q1	ref	ref	ref	ref	ref	ref
CALLYI Q2	< 0.0001	0.74(0.65,0.85)	0.02	0.83(0.71,0.98)	0.06	0.86(0.73,1.01)
CALLYI Q3	< 0.0001	0.57(0.49,0.67)	< 0.001	0.74(0.63,0.88)	0.01	0.79(0.67,0.93)
CALLYI Q4	< 0.0001	0.39(0.34,0.45)	< 0.0001	0.67(0.55,0.81)	0.001	0.72(0.59,0.88)

Model 1 involved no adjustments

Model 2 was adjusted for demographic characteristics including age, gender, race, education, and the poverty impact ratio

Model 3 included adjustments for disease factors such as hypertension, diabetes mellitus, stroke, coronary heart disease, and lifestyle factors like smoking, drinking, and BMI

0.817–0.834), with a sensitivity of 79.8% and a specificity of 71.2%. Finally, to provide clinicians with an intuitive, clear, and user-friendly visual scoring tool, we developed a nomogram incorporating the variables from the prediction model (Fig. 4). Each variable is assigned a score reflecting its contribution to different risk factors. The total score is calculated by summing the individual scores according to the top scoring table. This score indicates the likelihood of developing OA, with higher scores corresponding to a greater probability of OA. Additionally, DCA in Fig. 5 demonstrates that the net benefit of this model exceeds that of both the "treat all" and "treat none" strategies across a wide range of threshold probabilities, indicating significant clinical utility.

Discussion

This study analyzed national survey data from NHANES for the period 1999 to 2010 to explore the relationship between CALLYI and OA. The final sample included 18,624 participants, of whom 1,977 (10.62%) were diagnosed with OA. A statistically significant inverse association between CALLYI and OA was established using multivariate logistic regression models, suggesting that higher CALLYI correlate with a reduced likelihood of OA development. This relationship was consistent across both the unadjusted Model 1 and the adjusted Model 2 and 3. No significant interactions were observed in subgroup analyses, further supporting the validity of our findings and indicating the generalizability of this association across diverse populations.

CALLYI, a relatively novel biomarker derived by assessing patient systemic nutritional status, immune function, and inflammatory responses, was initially utilized more frequently to predict cancer patient outcomes. This study represents the first attempt to integrate CALLYI with OA metrics to explore their interrelation.

The etiology and pathophysiology of OA are highly complex, influenced by numerous factors such as genetics, aging, obesity, and traum [31, 32]. Concurrent research has identified several clinicopathological variables associated with OA. Variables like serum Klotho levels and low-density lipoprotein are negatively correlated with OA. In contrast, factors like the triglyceride glucose index, weight-adjusted waist index, and dietary selenium intake have been positively linked to OA and are considered risk factors [14, 16, 33–35]. A groundbreaking study has suggested a connection between various of thyroid hormone indicators and OA, indicating a potential link between the thyroid endocrine system and cartilage differentiation and regeneration. This insight offers a novel clinical perspective for the managing and assessing OA [36].

OA a degenerative disease predominantly observed in the elderly, corroborated by the demographic data in this study (NO-OA: 42.81(0.21), OA: 61.49(0.38), $p < 0.0001$). OA features widespread inflammation of the synovium, cartilage, and subchondral bone, leading to the release of various inflammatory mediators [37]. Prolonged inflammation often coincides with chronic conditions in the elderly, such as respiratory and urinary system inflammations, which can elevate CRP levels. Elevated CRP is associated with pain and functional impairment of limbs [38–40]. Albumin, commonly used as a clinical indicator of nutritional status, is synthesized in the liver and has a prolonged half-life [41]. While direct associations between albumin and OA have not been extensively documented, numerous studies have confirmed that albumin contributes to the synthesis of several compounds that directly or indirectly affect OA progression [42, 43]. Additionally, albumin is as a critical prognostic marker in inflammatory responses, with higher levels indicating a more favorable prognosis [44]. This is relevant in clinical scenarios where exogenous albumin supplementation is necessary for patients with hypoalbuminemia. The baseline characteristics table of this study demonstrated that the NO-OA group exhibited significantly higher albumin levels compared to the OA group ($p < 0.0001$). Extensive research has focused on the role of lymphocytes in the pathogenesis of OA. Guney et al. explored the association between synovial CD30 + T lymphocyte counts and the extent of cartilage damage, highlighting a potential correlation between lymphocyte activity and joint deterioration [45]. Furthermore, investigations into the impact of Lymphocyte Activation Gene-3 (LAG-3) on regulatory T cell functions in OA have revealed compromised function in populations with high LAG-3 expression [46].

Table 3 Subgroup analysis between CALLYI quartiles and osteoarthritis

Character	Q1	Q2	Q3	Q4	*p* for interaction
Gender					0.4
Male	ref	0.76 (0.59,0.96)	0.70 (0.54,0.91)	0.49 (0.37,0.65)	
Female	ref	0.96 (0.80,1.14)	0.87 (0.73,1.05)	0.74 (0.59,0.92)	
Race					0.95
White	ref	0.82 (0.70,0.96)	0.72 (0.61,0.84)	0.57 (0.47,0.70)	
Black	ref	0.65 (0.45,0.94)	0.82 (0.55,1.23)	0.63 (0.41,0.98)	
Mexican American	ref	0.85 (0.58,1.27)	0.64 (0.38,1.08)	0.54 (0.31,0.93)	
Other Hispanic	ref	0.75 (0.31,1.77)	0.49 (0.22,1.12)	0.24 (0.07,0.79)	
Multi racial	ref	0.66 (0.31,1.43)	0.50 (0.21,1.19)	0.40 (0.17,0.94)	
Age					0.91
20-55years old	ref	0.77 (0.56,1.05)	0.72 (0.54,0.96)	0.65 (0.47,0.90)	
> 55years old	ref	0.82 (0.69,0.97)	0.74 (0.61,0.89)	0.64 (0.51,0.79)	
Educational level					0.65
College Graduate or above	ref	0.90 (0.74,1.10)	0.75 (0.61,0.92)	0.64 (0.51,0.80)	
9-12th Grade	ref	0.74 (0.59,0.92)	0.70 (0.55,0.88)	0.51 (0.36,0.72)	
< 9th Grade	ref	0.69 (0.43,1.09)	0.57 (0.32,1.02)	0.35 (0.17,0.71)	
BMI					0.31
25–30	ref	0.87 (0.69,1.10)	0.71 (0.54,0.94)	0.61 (0.46,0.82)	
> 30	ref	0.78 (0.64,0.96)	0.82 (0.66,1.04)	0.77 (0.53,1.11)	
18–25	ref	0.82 (0.51,1.31)	0.62 (0.42,0.92)	0.49 (0.35,0.69)	
< 18	ref	0.26 (0.00, 16.15)	0.10 (0.01, 0.64)	0.34 (0.08, 1.36)	
Poverty Impact Ratio					0.24
< 1.3	ref	1.43 (1.03,1.97)	1.77 (1.24,2.53)	2.21 (1.44,3.40)	
1.3–3.5	ref	1.36 (1.07,1.74)	1.39 (1.06,1.84)	1.87 (1.40,2.49)	
> 3.5	ref	1.03 (0.84,1.27)	1.28 (1.02,1.62)	1.54 (1.21,1.96)	

DM: diabetes mellitus; BMI: body mass index;

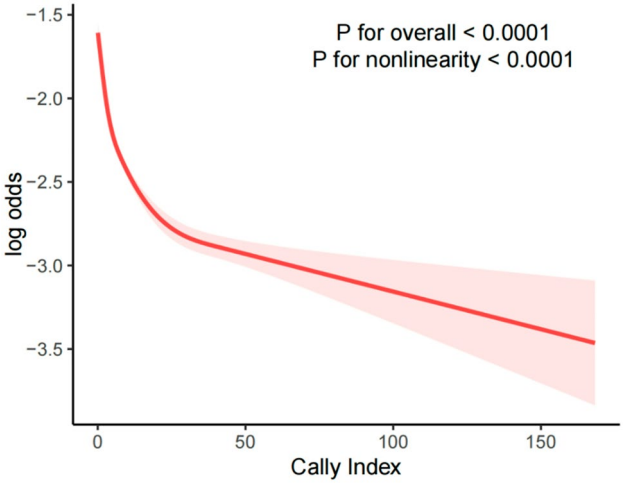

Fig. 2 Restricted cubic spline of association between CALLYI and OA

Given the critical role of lymphocytes in the immune response, lymphocyte counts are frequently used as indicators of immunocompetence. Various lymphocyte-associated biomarkers and inflammatory predictors have been identified as linked to OA progression [47]. The neutrophil/lymphocyte ratio has been recognized as a marker of OA severity and activity [48]. Additionally, the diagnostic potential of the blood monocyte-lymphocyte ratio in knee OA has been examined, along with its prognostic value in predicting patient responses to conservative treatments, demonstrated also by the monocyte-to-lymphocyte ratio in knee synovial fluid [49, 50]. The results of the aforementioned study provide a theoretical foundation for CALLYI as a potential biomarker for OA. This study confirmed a significant nonlinear negative correlation between CALLYI levels and OA. We subsequently developed and validated a prediction model incorporating CALLYI, demonstrating its clinical utility. The nomogram indicates that CALLYI assigns a score second only to age and higher than all other variables.

This study possesses several notable strengths. Firstly, it introduces CALLYI, an inflammatory nutrition indicator, as a novel predictive biomarker for osteoarthritis (OA), marking the first time this association has been proposed. Secondly, we utilized nationally representative NHANES data, incorporating a substantial dataset of 18,624 participants, including 1,977 individuals diagnosed with OA. All data were weighted in accordance with official guidelines to ensure the results are both realistic and representative. After establishing a correlation between CALLYI and OA, we developed and validated a clinical prediction model, demonstrating its effectiveness and clinical applicability. However, it is important to acknowledge that this study has certain limitations. Firstly, due to the nature of a cross-sectional study, our conclusions do not establish a causal relationship between CALLYI and OA. Secondly, while we incorporated multiple covariates based on clinical practice and relevant literature, we cannot entirely exclude all potential confounding factors. Additionally, this study's participants were exclusively from the United States, which may limit the generalizability of our findings to other populations. Lastly, the final diagnosis of

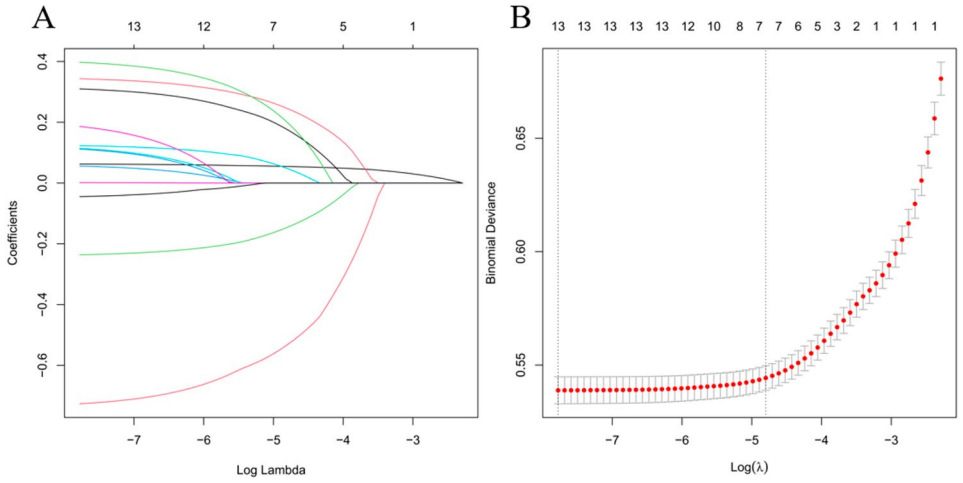

Fig. 3 The selection of variables in the OA prediction model was analyzed by LASSO regression. (**A**) Each curve in the distribution of regression coefficients represents the trajectory of a specific characteristic coefficient. (**B**) LASSO regression cross-validation profile. The red dot indicates the mean square error corresponding to the λ value, with the vertical axis representing the coefficient values. The number at the top denotes the count of nonzero coefficients in the model, while the horizontal axis shows the logarithmic value of the regularization parameter λ

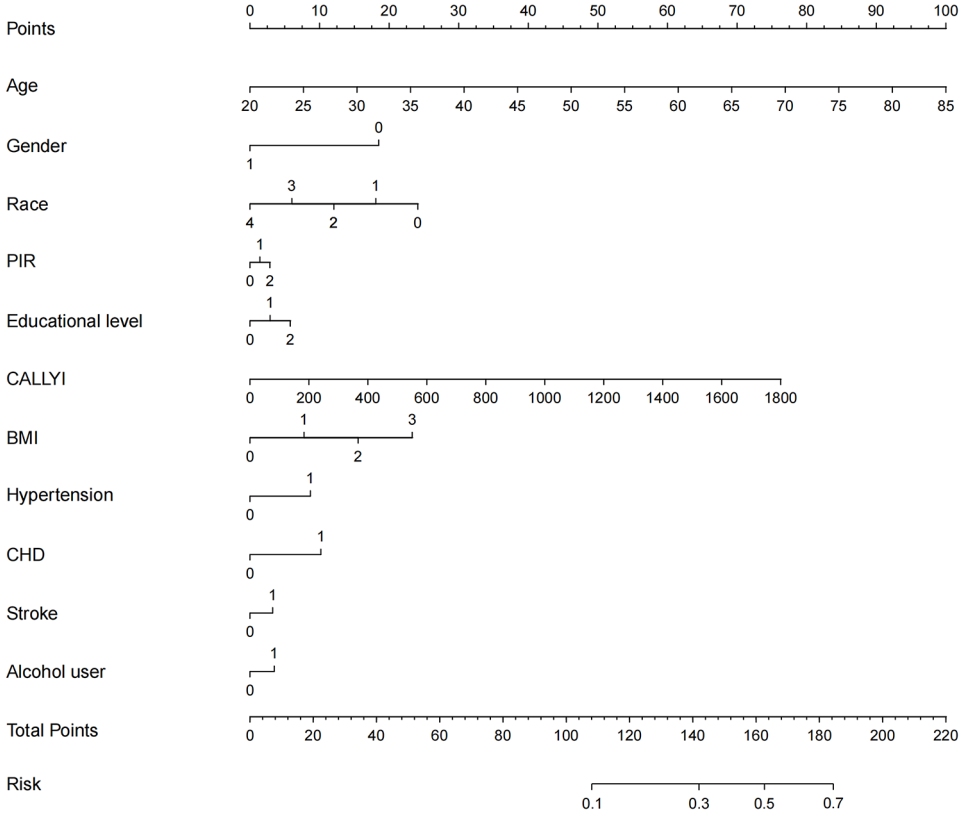

Fig. 4 The top horizontal line of the column bar is the score bar, and the sum of the scores is the risk of osteoarthritis. A total of 11 indicators were included in the risk prediction table.In the gender indicator, a value of 1 denotes male and 0 denotes female. For race indicators, the values are as follows: 0 for "White," 1 for "Mexican American," 2 for "Black," 3 for "Other Hispanic," and 4 for "Multiracial." In the poverty impact ratio (PIR), 0 indicates "1.3-3.5," 1 indicates "<1.3," and 2 indicates ">3.5." Regarding educational level, 0 represents "<9th Grade," 1 represents "9-12th Grade," and 2 represents "College Graduate or above." For BMI categories, 0 denotes "18-25," 1 denotes "25-30," 2 denotes ">30," and 3 denotes "<18." For all remaining binary indicators, 0 signifies "No" and 1 signifies "Yes."

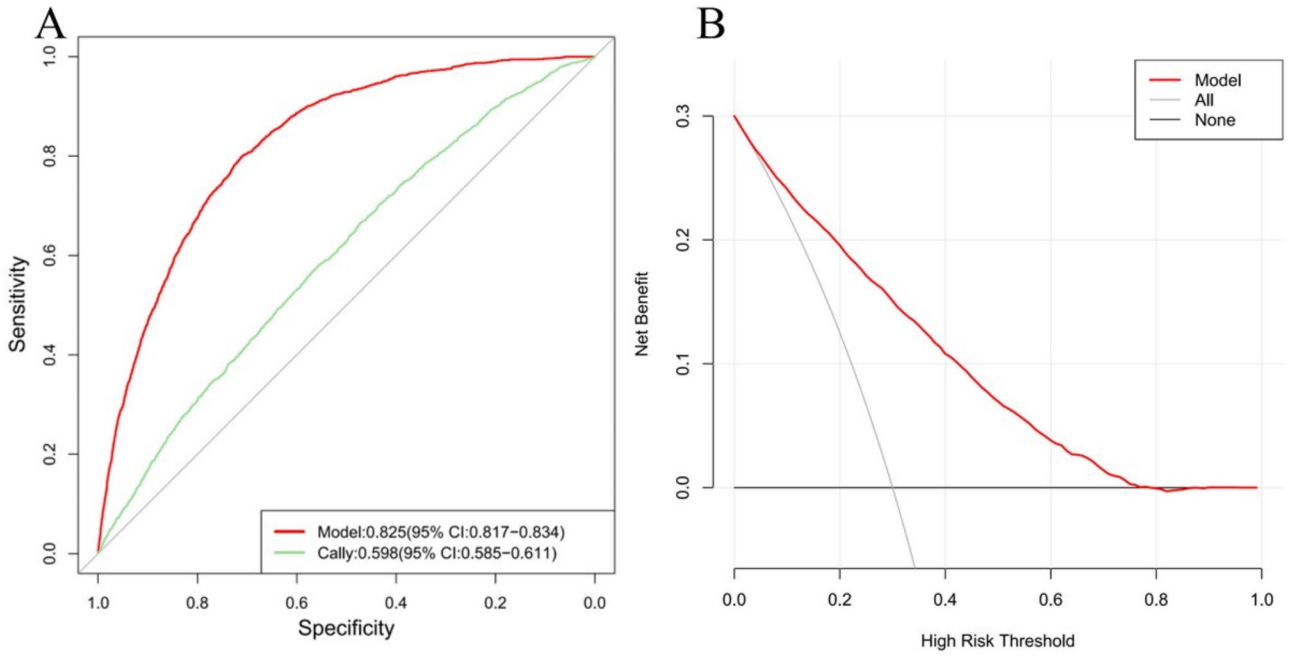

Fig. 5 (A) The ROC curve illustrates the performance of the prediction model and CALLYI, represented by red and green lines respectively. The AUC values are 0.825 (95% CI: 0.817-0.834) for the prediction model and 0.598 (95% CI: 0.585-0.611) for CALLYI. Additionally, the prediction model achieved a sensitivity of 79.8% and a specificity of 71.2%. (B) DCA shows that the red curve represents the net benefit of using the prediction model, while the black line indicates the scenario where no prediction model is utilized.

osteoarthritis was based on self-reported data from the questionnaire. Although we included a sufficient sample size and case reports, recall bias or misclassification remains a concern and may reduce the validity of the conclusions.

In conclusion, this study revealed a significant and nonlinear inverse relationship between CALLYI and the incidence of OA in US adults. We subsequently developed and validated an OA risk prediction model incorporating CALLYI, demonstrating its validity and clinical utility. Based on these findings, we propose that CALLYI, as a novel inflammatory nutritional index, holds potential as a predictive biomarker for OA. This could facilitate early identification of high-risk populations, enabling timely clinical interventions to delay disease progression.

Conclusion

This study, utilizing NHANES statistics, is the first to establish a nonlinear negative relationship between CALLYI and OA, with no significant interaction observed in subgroup analyses. In the OA prediction model incorporating CALLYI, we validated the effectiveness and clinical utility of this model, providing evidence that CALLYI can serve as a biomarker for OA risk prediction. Nevertheless, larger multicenter prospective cohort studies are necessary to mitigate the limitations inherent in cross-sectional designs and self-reported OA diagnoses.

Abbreviations

CRP	C-Reactive Protein
CALLYI	CRP- Albumin-Lymphocyte Index
NHANES	National Health and Nutrition Examination Survey
OA	Osteoarthritis
BMI	Body Measure Index
CHD	Coronary Heart Disease
DM	Diabetes Mellitus
GED	General Educational Development
OR	Odds Ratio
CI	Confidence Interval
RCS	Restricted Cubic Spline
LASSO	Least Absolute Shrinkage and Selection Operator
ROC	Receiver Operating Characteristic
DCA	Decision Curve Analysis
AUC	Areas Under the Curves
LAG-3	Lymphocyte Activation Gene-3

Supplementary Information

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Supplementary Material 1

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Author contributions

KZ and MSG designed this study and contributed to data collection and analysis, KZ drafted this manuscript, and all authors reviewed, revised, and approved this manuscript for publication.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The data used in this study were obtained from publicly available data in the NHANES database and therefore no ethical approval was required.

Consent for publication
All authors approved the final manuscript and the submission to this journal.

Competing interests
The authors declare no competing interests.

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