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Higher CALLY index levels indicate lower sarcopenia risk among middle-aged and elderly community residents as well as hospitalized patients

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The C-reactive protein-albumin-lymphocyte (CALLY) index, which integrates albumin, lymphocytes, and C-reactive protein levels, has emerged as a novel method to assess nutritional and inflammatory statuses in patients. This study examined the correlation between the CALLY index and sarcopenia risk using two cohorts: 1804 community dwellers from the NHANES database in the United States and 139 patients from the Department of Gerontology at Kunshan Hospital, China. In the US community cohort, RCS curve analysis was used to examine the non-linear relationship between inflammatory/nutritional markers and sarcopenia, subgroup analysis was also conducted. Logistic regression was employed to evaluate the association between the CALLY index and the risk of sarcopenia in both cohorts. Results demonstrated a significant non-linear relationship between the CALLY index and the risk of sarcopenia ($P < 0.001$). Elevated levels of the CALLY index are independently linked to a decreased risk of sarcopenia in both community residents (OR = 0.35, 95% CI 0.20–0.57, Q3 CALLY index and OR = 0.26, 95% CI 0.11–0.56, Q4 CALLY index) and hospitalized patients (OR = 0.35, 95% CI 0.12–0.96). This finding identified low CALLY index as a conveniently measurable parameter, serving as a nutritional and inflammatory risk factor for sarcopenia.

Keywords CRP-albumin-lymphocyte (CALLY) index, Sarcopenia, Inflammation, Nutrition

Sarcopenia, recently acknowledged as a geriatric syndrome, predominantly manifests as a gradual reduction in skeletal muscle mass, strength, and function due to aging[1]. The incidence of sarcopenia escalates with age, affecting about 10–27% of individuals aged 60 years and older, and the prevalence rises to approximately 50% among those aged 80 and above[2,3]. The swift deterioration in muscle mass and capability associated with sarcopenia can result in numerous negative health consequences[4], such as increased risk of falls, fractures, declining functional abilities, frailty, and even mortality[5–9]. Given the increasing trend of social aging, sarcopenia undoubtedly poses a substantial barrier to healthy aging. The current diagnostic for sarcopenia requires a comprehensive evaluation of various factors, including clinical manifestations, physical examination, biochemical indicators, and imaging assessment, which complicate the diagnostic process and necessitate multidisciplinary collaboration, potentially increasing the treatment burden for patients[4,10,11]. Therefore, early detection and prompt treatment are crucial for effectively preventing or delaying the onset of sarcopenia.

Inflammation is a key factor in the onset and progression of sarcopenia[12,13]. Elevated inflammatory levels are commonly observed in patients with sarcopenia[14,15], and chronic inflammation is linked to sarcopenic characteristics such as increased muscle atrophy, weakened muscle strength, and impaired muscle function, suggesting inflammation as a possible driving force behind sarcopenia[13,16]. Several inflammatory markers have also been identified as predictors of sarcopenia. A higher platelet-to-lymphocyte ratio (PLR) have been associated with a heightened sarcopenia risk[17]. Research, including a systematic review and meta-analysis, has

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pinpointed circulating levels of C-reactive protein (CRP) and high-sensitivity C-reactive protein as potential risk factors impacting muscle health and functionality[18]. Observations also suggest that monitoring the neutrophil-lymphocyte ratio (NLR) could help in early detection of sarcopenia and muscle steatosis in patients with colorectal cancer[19]. Other indices like the systemic immune inflammation index (SII) and the systemic inflammation response index (SIRI) have also been linked to sarcopenia occurrence[20,21], though the predictive reliability of these biomarkers for sarcopenia risk remains uncertain.

Nutrition plays a vital role in the management of sarcopenia. Malnutrition is a primary contributor to sarcopenia in the elderly, with inadequate nutrient intake leading to reduced muscle protein synthesis, which is crucial in the development and progression of sarcopenia[22]. Meticulous evaluation of patients' nutritional status and implementing nutritional therapy are crucial intervention measures for sarcopenia. Therefore, assessing nutritional status may be beneficial for evaluating the risk of sarcopenia.

The CRP-Albumin-Lymphocyte (CALLY) index, derived from the combined measurement of lymphocyte count, serum albumin, and CRP levels, is a novel and comprehensive indicator for assessing both nutritional and inflammatory status. CALLY index is associated with prognostic factors such as survival and treatment response in patients with various tumors[23–26]. Despite widespread acknowledgment of the crucial roles of nutrition and inflammation in sarcopenia, the connection between the CALLY index and sarcopenia remains unexplored. This research was designed to explore the predictive capability of the CALLY index for sarcopenia occurrence and the underlying relationship between CALLY and sarcopenia, utilizing data sourced from both the community-based National Health and Nutrition Examination Survey (NHANES) database and inpatients from the Department of Gerontology, Kunshan Hospital, China.

Materials and methods

Study participants

We included two different cohorts to explore the feasibility of using CALLY values to predict sarcopenia. Data from the NHANES database during two survey cycles (2015–2016 and 2017–2018) were used to investigate the correlation between CALLY values and sarcopenia among community-dwelling individuals in the United States using big data analytics. Additionally, data from 139 patients from the Department of Gerontology, Kunshan Hospital, affiliated with Jiangsu University, China, were included to further explore whether CALLY is an independent risk factor for sarcopenia.

Participants from the NHANES who lacked relevant laboratory data on inflammatory/nutritional markers, such as the CALLY and physical examination data for sarcopenia, were excluded from further analysis. Among the initially recruited participants aged 45–79 years from 2015 to 2018, those who lacked data related to sarcopenia ($n=10898$) were first excluded. Subsequently, patients who lacked data on inflammatory/nutritional markers ($n=751$) and covariates ($n=5772$) were excluded. Finally, 1,804 participants aged 45 to 60 years were included in the final analysis (Fig. 1). The NHANES obtained approval from the Ethics Review Committee of the National Center for Health Statistics (NCHS), and all participants provided informed consent. The de-identified and anonymous data published on the NHANES website (https://www.cdc.gov/nchs/nhanes/irba98.htm) did not require additional ethical approval or informed consent for the secondary analysis.

Between October 2019 and August 2021, 139 patients aged ≥ 50 years, who were hospitalized in the Department of Gerontology at Kunshan Hospital were included in this cross-sectional study. Patients lacking relevant laboratory or sarcopenia diagnostic data were excluded. The research protocol was approved by the Institutional Review Board of the Kunshan Hospital Affiliated with Jiangsu University (approval decision number: IEC-C-011-A04-V3.0). All patients provided written informed consent before participation, and all experiments were conducted in accordance with the relevant guidelines and regulations.

Measurement of laboratory indicators

Following the NHANES CBC Profile, the UniCel DxH 800 analyzer is a quantitative automated hematology analyzer used to perform blood routine tests. CRP levels were measured using a Beckman UniCel analyzer, and albumin concentrations were measured using the DcX800 method. Peripheral blood and biochemical parameters of the Kunshan cohort, including platelets, CRP, albumin, lymphocytes, and neutrophils, were collected during hospitalization. The following formulas were used to calculate inflammatory/nutritional indicators[20,21,27,28]:

$$\mathrm{SIRI} = \text{Neutrophil count (cells/mL)} \times \text{Monocyte count (cells/mL)} / \text{Lymphocyte count (cells/mL)}$$

$$\mathrm{SII} = \text{Neutrophil count (cells/mL)} \times \text{Platelet count (cells/mL)} / \text{Lymphocyte count (cells/mL)}$$

$$\mathrm{PLR} = \text{Platelet count (cells/mL)} / \text{Lymphocyte count (cells/mL)}$$

$$\mathrm{CALLY} = \text{Serum albumin level (g/dL)} \times \text{Lymphocyte count (1000 cells/mL)} / \text{CRP (mg/dL)} / 10$$

$$\mathrm{dNLR} = \text{Neutrophil count (cells/mL)} / [\text{White blood cell count (cells/mL)} - \text{Neutrophil count (cells/mL)}]$$

Diagnostic criteria for sarcopenia

According to the guidelines established by the Foundation for the National Institutes of Health (FNIH), individuals in the NHANES database are diagnosed with sarcopenia based on an adjusted skeletal muscle mass index (ASMBMI) of <0.512 for women and <0.789 for men[29,30]. To ensure safety, pregnant women with a body weight exceeding 450 pounds or a height taller than 6 feet and 5 inches were excluded from bone density measurements.

In the Kunshan cohort, the diagnosis of sarcopenia was based on the 2019 version of the AWGS criteria[4]. Skeletal muscle mass was measured using dual-energy X-ray absorptiometry (DXA). The relative skeletal muscle mass index (RSMI) is the height-adjusted muscle mass value, calculated as follows: RSMI = ASM (Appendicular

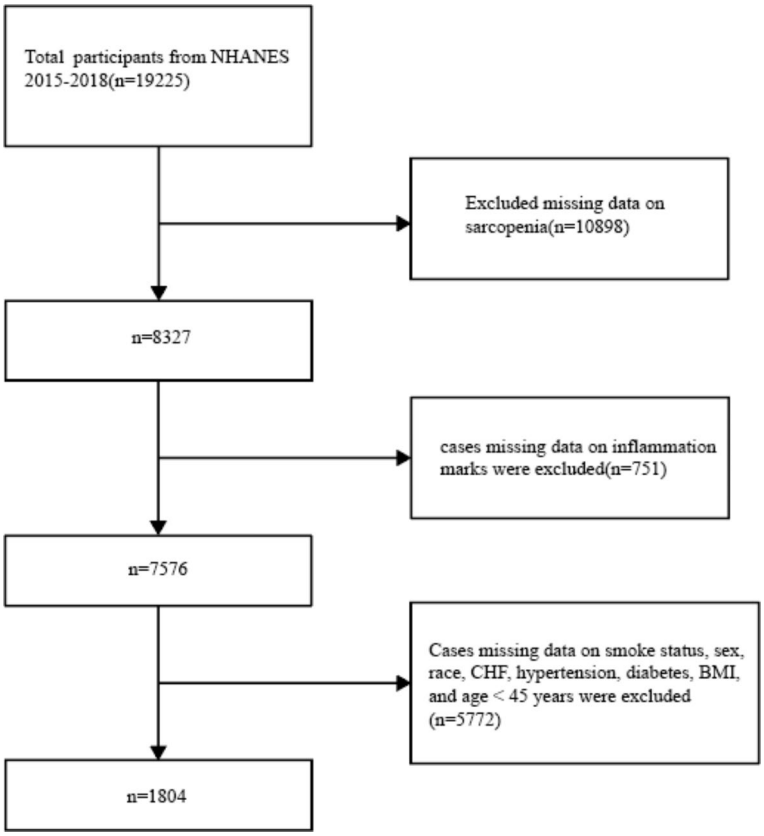

Fig. 1. Flowchart of the sample selection from NHANES 2015–2018.

Skeletal Muscle) / (height²). The cutoff values for RSMI < 7.0 kg/m² for men and < 5.4 kg/m² for women. Hand grip strength (HGS) was measured using a CAMRY EH101 electronic handheld dynamometer, with low muscle strength defined as grip strength < 28 kg for men and < 18 kg for women. Low physical performance is defined as having a walking speed of less than 1.0 m/s in the 6-meter walk test, taking more than 12 s to complete the 5-times sit-to-stand test, or scoring ≤ 9 on the Short Physical Performance Battery (SPPB). SPPB assesses physical function through gait speed, standing balance, and 5-times sit-to-stand test. The presence of one or more of these criteria indicates low physical performance. Sarcopenia is diagnosed when there is a decrease in skeletal muscle mass, grip strength, and/or low physical performance.

Covariates

Based on previous studies, clinically significant covariates were included in our study[17,20]. The NHANES demographic parameters included age, sex, race, smoking status, and body mass index (BMI). Chronic diseases, such as hypertension, diabetes, and congestive heart failure, were also considered.

Demographic parameters of the Kunshan cohort included age, sex, BMI, and smoking status. Comorbidities documented in the Kunshan cohort, including hypertension, atherosclerosis, chronic gastritis, diabetes, osteoarthritis, and chronic heart failure (CHF), were collected during hospitalization. Sarcopenia-related measurements included RSMI, HGS, the 6-m walk test, the 5-times sit-to-stand test, and SPPB, which were categorized into categorical variables based on their cutoff values.

Statistical analysis

In the NHANES cohort, restricted cubic spline (RCS) models were used to investigate the nonlinear dose-response relationship between peripheral blood-derived markers and sarcopenia occurrence. The RCS analysis was performed using three knots at the 5th, 50th, and 95th percentiles. Peripheral blood-derived markers that correlated with the risk of sarcopenia in non-linear patterns were subsequently grouped into quartiles (Q1, Q2, Q3, and Q4) according to their respective quantiles within the NHANES cohort. The CALLY values were categorized into four quartiles (Q1: CALLY ≤ 1.91; Q2: 1.91 < CALLY ≤ 4.33; Q3:4.33 < CALLY < 10; Q4: CALLY ≥ 10.00), with the first quartile (Q1) being designated as the reference quartile. Owing to the relatively small sample size of the Kunshan cohort, these biomarkers were categorized using the median value. Categorical data between/among groups were compared using the chi-square test or Fisher's exact test, as appropriate, and rank-sum tests were used for continuous variables to explore differences between groups. Spearman correlation analysis and violin plots were employed to determine the correlation between the distribution levels of CALLY values and sarcopenia measurement values, with the violin plots utilizing Wilcoxon rank-sum test. Binary logistic regression analyses were performed to determine the relationship between the CALLY index and sarcopenia.

Three logistic regression models were established for both the NHANES and Kunshan cohorts. Model 1 was an unadjusted crude model that included only the CALLY index in univariate analysis. Models 2 and 3 were multivariate analyses that incorporated the potential confounders. Model 2 was adjusted for demographic characteristics and patient comorbidities based on Model 1. Based on the results of the Spearman correlation analysis, Model 3 further extended Model 2 by incorporating adjustments for the inflammatory biomarker SII. Variance inflation factor (VIF) was utilized to assess multicollinearity in the models, the area under the receiver operating characteristic (ROC) curve (AUC) indicates better performance, the Hosmer-Lemeshow test is employed to evaluate the model's goodness-of-fit and performance. Additionally, a 1:1 propensity score matching (PSM) method was applied to the NHANES cohort to balance the sarcopenia group and the control group, thereby reducing potential bias in the observational study. Subgroup analyses were stratified by age, sex, BMI, diabetes, and hypertension to assess the sensitivity and interactions within different subgroups.

All statistical analyses were performed using R software version 4.1.0 (R Core Team, Vienna, Austria) and Statistical Product and Service Solutions software 26.0 for Windows (SPSS Inc., Chicago, IL, USA). All P-values were two-sided, and a P-value less than 0.05 indicated statistical significance.

Results

Baseline demographic characteristics of the NHANES cohort

Between 2015 and 2018, 1804 individuals selected from the NHANES database were included in the study. The participants were divided into four levels based on the quartile values of the CALLY index (Table 1). Significant differences were observed in BMI, diabetes, race, and sarcopenia distribution between the four groups. Higher CALLY levels were observed in patients without sarcopenia ($P < 0.001$), with a lower BMI ($P < 0.001$), and no

Characteristics	Total	Quartiles of CALLY index				
		Q1 (≤1.91)	Q2(1.91-4.33)	Q3(4.33-10.00)	Q4(≥10.00)	P value
N	1804	451	451	451	451	
Sarcopenia, n (%)						<0.001*
No	1601(88.7)	368 (81.6)	386 (85.6)	415 (92.1)	432 (95.8)	
Yes	203(11.3)	83(18.4)	65(14.4)	36(7.9)	19(4.2)	
Sex, n (%)						0.233
Female	944(52.3)	263 (58.4)	239 (53.0)	220 (48.8)	222 (49.3)	
Male	860(47.7)	188(41.6)	212 (47.0)	231 (51.2)	229(50.7)	
Age, years						0.114
45-55	711(39.5)	198(43.8)	165 (36.7)	150 (33.3)	198 (44.0)	
51-55	578(32.0)	119 (26.4)	140 (31.1)	169 (37.5)	150(33.2)	
56-60	515(28.5)	134(29.7)	146(32.3)	132 (29.3)	103(22.8)	
BMI, kg/m2						<0.001*
≤ 25	358(19.8)	55(12.2)	42(9.3)	80(17.8)	181(40.2)	
> 25	1446(80.2)	396(87.8)	409(90.7)	371(82.2)	270(59.8)	
Diabetes, n (%)						<0.001*
No	1605(89.0)	368(81.5)	392(86.9)	417(92.4)	428(94.8)	
Yes	199(11.0)	83 (18.5)	59 (13.1)	34 (7.6)	23 (5.2)	
Smoke status, n (%)						0.105
No	1024(56.8)	241 (53.5)	232 (51.5)	268(59.4)	283 (62.8)	
Yes	780(43.2)	210(46.5)	219(48.5)	183 (40.6)	168(37.2)	
CHF, n (%)						0.089
No	1782(98.8)	443(98.2)	443(98.2)	449(99.5)	447 (99.2)	
Yes	22(1.2)	8 (1.8)	8 (1.8)	2 (0.5)	4(0.8)	
Hypertension, n (%)						0.068
No	1259(69.8)	280 (62.1)	334 (74.1)	314(69.6)	331 (73.4)	
Yes	545(30.2)	171(37.9)	117(25.9)	137 (30.4)	120(26.6)	
Race, n (%)						<0.001*
Mexican American	154(8.5)	44 (9.8)	36(7.9)	45(10.0)	29 (6.5)	
Other Hispanic	134(7.4)	47(10.4)	29(6.4)	34(7.5)	24(5.2)	
Non-Hispanic White	1155(64.1)	262 (58.1)	315(69.8)	271(60.0)	307 (68.1)	
Non-Hispanic Black	184(10.2)	62(13.7)	43(9.6)	46(10.3)	33(7.4)	
Other Race	177(9.8)	36 (8.0)	28 (6.3)	55 (12.3)	58(12.8)	

Table 1. Basic characteristics of NHANES participants (N =1804) Values were presented as the mean ± SD, median (interquartile range), or n (%). Abbreviations: BMI, body mass index; CHF, congestive heart failure. Asterisks indicate statistical significance.

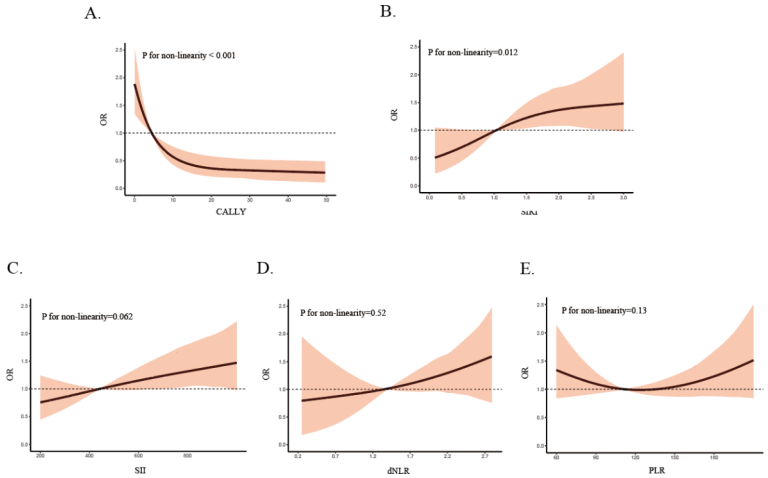

Fig. 2. Analysis of weighted restricted cubic spline regression was conducted to examine the association between inflammation markers and sarcopenia. OR and 95% CI for Model 2 were adjusted for age, sex, race, smoking status, BMI, hypertension, CHF, and diabetes. The shaded portion in the analysis represents the estimation of the 95% confidence intervals.

	Model 1		Model 2		Model 3	
CALLY	OR and 95%CI	P value	OR and 95%CI	P value	OR and 95%CI	P value
Q1	Ref	Ref	Ref	Ref	Ref	Ref
Q2	0.74(0.46-1.21)	0.225	0.75(0.43-1.31)	0.286	0.78(0.41-1.43)	0.398
Q3	0.38(0.25-0.57)	<0.001*	0.33(0.20-0.54)	<0.001*	0.35(0.20-0.57)	0.001*
Q4	0.20(0.11-0.35)	<0.001*	0.24(0.12-0.48)	0.001*	0.26(0.11-0.56)	0.002*

Table 2. The association between the CALLY index and sarcopenia among all participants in the NHANES cohort. Note: Model 1 was an unadjusted crude model; Model 2 was built upon Model 1 by incorporating adjustments for age, gender, race, smoking status, as well as comorbidities such as hypertension, diabetes, and congestive heart failure. Model 3 further extended Model 2 by incorporating adjustments for the inflammatory biomarker SII. Asterisks indicate statistical significance.

history of diabetes ($P<0.001$). Furthermore, significant differences in CALLY levels were observed between the different racial groups ($P=0.001$). Compared with patients without sarcopenia, patients with sarcopenia were older ($P=0.005$), had a lower BMI ($P<0.001$), and had a history of diabetes ($P<0.001$) and hypertension ($P=0.010$) (Supplementary Table S1). The detailed characteristics of the other covariates are summarized in Table 1 and Supplementary Table S1. To further support the relationship between CALLY index and the risk of sarcopenia, a comparative control group was established using PSM (1:1). After PSM, most baseline characteristics between the two groups showed no significant differences, with the control group comprising 178 participants and the sarcopenia group also consisting of 178 participants. However, a significant difference in CALLY values remained between the two groups. (Supplementary Table S2).

Association between the CALLY index and sarcopenia in the NHANES cohort

Weighted RCS analysis was used to model and visualize the relationship between peripheral blood-derived markers and the risk of sarcopenia. The graph demonstrates a non-linear, L-shaped association between CALLY values and the risk of sarcopenia (P for nonlinearity < 0.001) (Fig. 2A). A non-linear, relatively flat "S"-shaped dose-response relationship was also observed between the inflammatory/nutritional marker SIRI and the OR for sarcopenia (Fig. 2B, non-linear $P=0.012$), whereas the remaining inflammatory/nutritional markers, including the SII, PLR, and dNLR, did not exhibit a similar association (P for nonlinearity > 0.05) (Fig. 2C-E).

Three logistic regression models were constructed to explore the independent effect of the CALLY index on sarcopenia. The CALLY index was included in the regression models as a categorical variable and divided into four quartiles, with the first quartile of CALLY values serving as the reference (Table 2). The unadjusted Model 1 results showed that moderately and highly elevated CALLY values were associated with a reduced risk of sarcopenia, with corresponding effect sizes of OR = 0.38 (95% CI 0.25–0.57, $P<0.001$) and OR = 0.20 (95% CI 0.11–0.35, $P<0.001$), respectively. In Model 2, which was adjusted for demographic characteristics and comorbidities, the CALLY index at the third and fourth quartile levels were independently associated with a lower risk of sarcopenia, with corresponding effect sizes of OR = 0.33 (95% CI 0.20–0.54, $P<0.001$) and OR = 0.24 (95% CI 0.12–0.48, $P=0.001$), respectively.

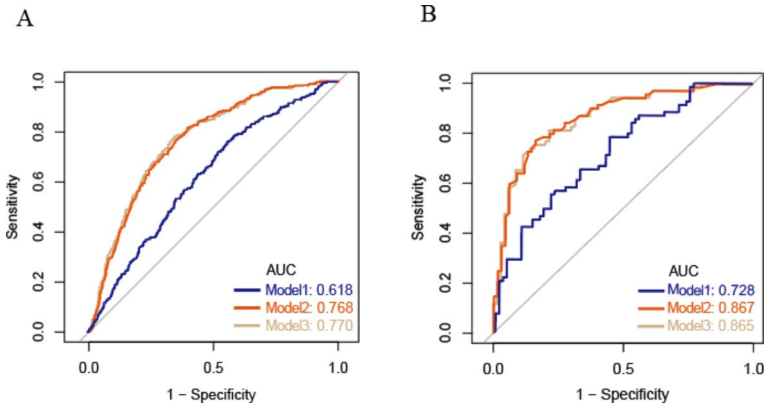

Fig. 3. ROC curves of two cohorts. A: NHANES cohort, B: Kunshan cohort. AUC, area under the curve; model 1, unadjusted model; Model 2 was built upon Model 1 by incorporating adjustments for age, gender, race, smoking status, as well as comorbidities such as hypertension, diabetes, and congestive heart failure. Model 3 further extended Model 2 by incorporating adjustments for the inflammatory biomarker SII.

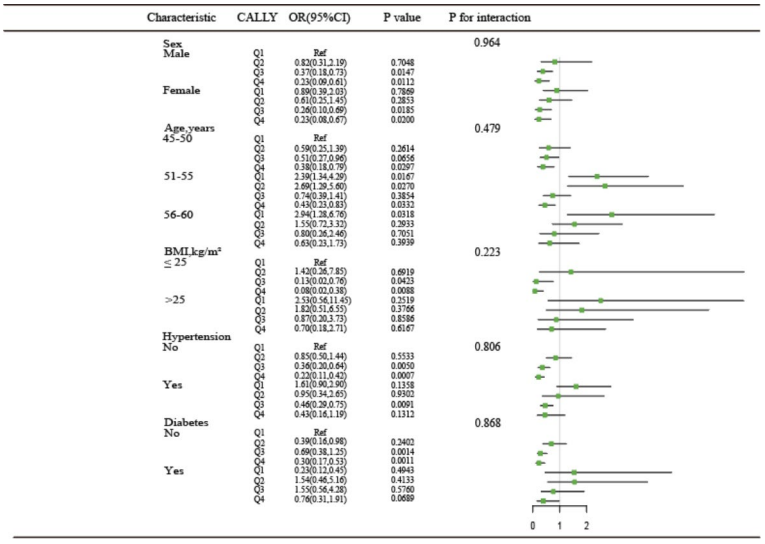

Fig. 4. The relationship between the CALLY index and Sarcopenia, stratified by sex, age, BMI, hypertension and diabetes. Abbreviations: CI, confidence interval; BMI, body mass index; CHF, congestive heart failure.

The Spearman rank correlation analysis revealed that CALLY index exhibited low to moderate negative correlations with other inflammatory/nutritional indicators ($r<0.4$). In contrast, a strong correlation was observed among the inflammatory/nutritional indicators SII, SIRI, dNLR, and PLR (Supplementary Table S3).In the fully adjusted Model 3, which included the inflammatory/nutritional marker SII in addition to the variables in Model 2, CALLY values at the third and fourth quartile levels were still negatively associated with sarcopenia risk, with corresponding effect sizes of OR = 0.35 (95% CI 0.20–0.57, $P=0.001$) and OR = 0.26 (95% CI 0.11–0.56, $P=0.002$), respectively, indicating a nonlinear negative correlation between the CALLY index and sarcopenia. While SII was not independently associated with sarcopenia risk (Table 2, Supplementary Table S4). The VIF values for Model 2 and Model 3 were less than 10 (Supplementary Table S5).

The ROC analysis for Model 2 yielded an AUC of 0.768, while Model 3 had an AUC of 0.770 (Fig. 3A). The Hosmer-Lemeshow goodness-of-fit test showed p-values of 0.63 for Model 2 and 0.27 for Model 3, respectively. The above results indicate that the model achieved good performance.

Sensitivity analysis of the NHANES cohort

After PSM, the results from three logistic regression models indicated that medium to high levels of CALLY index were associated with a decreased prevalence of sarcopenia (Supplementary Table S6). Interaction tests indicated that the relationship between the CALLY index and sarcopenia did not show statistically significant differences across the strata, suggesting that age, sex, BMI, hypertension and diabetes did not significantly influence this association (all interaction $p>0.05$) (Fig. 4). After adjusting for demographic characteristics and clinical comorbidities as confounding factors, a significant negative correlation was observed between

the third and fourth quartile levels of CALLY values and the risk of sarcopenia among participants who were female (OR = 0.26, 95% CI 0.10–0.69, $P = 0.0185$ and OR = 0.23, 95% CI 0.08–0.67, $P = 0.0200$, respectively) or male (OR = 0.37, 95% CI 0.18–0.73, $P = 0.0147$ and OR = 0.23, 95% CI 0.09–0.61, $P = 0.0112$, respectively), BMI ≤ 25 kg/m², (OR = 0.13, 95% CI 0.02–0.76, $P = 0.0423$ and OR = 0.08, 95% CI 0.02–0.38, $P = 0.0088$, respectively) and did not have hypertension (OR = 0.36, 95% CI 0.20–0.64, $P = 0.0050$ and OR = 0.22, 95% CI 0.11–0.42, $P = 0.0007$, respectively) or diabetes (OR = 0.69, 95% CI 0.38–1.25, $P = 0.0014$ and OR = 0.30, 95% CI 0.17–0.53, $P = 0.0011$, respectively), compared to those with CALLY values at the first quartile level.

Baseline characteristics of the Kunshan cohort

A total of 139 individuals hospitalized in the Department of Gerontology, Kunshan Hospital, were ultimately included in the study. The baseline characteristics of the cohort are presented in Table 3. The prevalence of sarcopenia was 49.6%, with 81 female participants and 58 male participants ($P = 0.005$). Statistically significant differences in age ($P < 0.001$) and BMI ($P < 0.001$) were between patients with and without sarcopenia. Other covariates included a history of smoking ($P = 0.597$), CHF ($P = 0.637$), hypertension ($P = 0.677$), diabetes ($P = 0.110$), osteoarthritis ($P = 0.801$), and arteriosclerosis ($P = 0.439$). Among these indicators, a statistically significant difference in chronic gastritis history was observed between patients with and without sarcopenia ($P = 0.036$). The CALLY index was lower in patients with sarcopenia than in those without ($P < 0.001$). Conversely, SII ($P < 0.001$), PLR ($P < 0.001$), and dNLR ($P = 0.034$) indicators were significantly higher in patients with sarcopenia than in those without. The SIRI indicator showed a statistically marginal significance between the groups ($P = 0.051$).

Correlation between CALLY values and sarcopenia-related measurements

The Spearman rank correlation analysis and violin plot illustrated the relationship between the distribution levels of CALLY index and sarcopenia measurement indicators. There was a significant negative correlation between CALLY values and RSMI (r = -0.401), with CALLY index decreasing as RSMI values decreased. A significant negative correlation also existed between CALLY values and the six-meter walk test (r= -0.222), where lower CALLY values were associated with poorer performance (lower speed) in the test. Poorer SPPB test performance was correlated with decreased CALLY values (r= -0.220). However, there was no significant correlation between CALLY values and grip strength or the five-times-sit-to-stand test ($p > 0.05$) (Supplementary Table S7). Similarly, the violin plot demonstrated the correlation between the distribution of CALLY values and various sarcopenia measurements. The results indicated that lower RSMI and poorer performance in the 6-meter walk test and SPPB test were associated with lower CALLY values, whereas the five-times-sit-to-stand test and grip strength levels showed no significant correlation with CALLY values (Fig. 5).

Association between the CALLY index and sarcopenia in the Kunshan cohort

CALLY values were included as categorical variables in the regression model and divided into two levels based on the median value, with CALLY values < 13 serving as the reference group. As presented in Table 4, the results of the unadjusted Model 1 showed that CALLY values were associated with sarcopenia risk, with an effect size of OR = 0.28 (95% CI 0.14–0.55, $P < 0.001$). In Model 2 adjusted for demographic characteristics and comorbidities, the CALLY index was independently associated with sarcopenia risk, with an effect size of OR = 0.33 (95% CI 0.12–0.86, $P = 0.025$).

The Spearman rank correlation analysis of the Kunshan cohort revealed results similar to those of the NHANES cohort. (Supplementary Table S8). Incorporating the inflammatory/nutritional marker SII into Model 2 formed Model 3, the CALLY index remained an independent indicator of sarcopenia, with an OR of 0.35(95% CI 0.12–0.96, $P = 0.044$). Similar to the NHANES cohort, SII was not independently related to sarcopenia risk (Table 4, Supplementary Table S9). The VIF values for Model 2 and Model 3 were less than 10 (Supplementary Table S10).

The ROC analysis for Model 2 yielded an AUC of 0.867, while Model 3 had an AUC of 0.865 (Fig. 3B). The Hosmer-Lemeshow goodness-of-fit test showed p-values of 0.93 for Model 2 and 0.88 for Model 3, respectively.

Discussion

Our study evaluated the relationship between the CALLY index and sarcopenia in two cohorts from the United States and China. We found that sarcopenia-related measurements were associated with CALLY values. After further adjustment for covariates in the logistic regression analysis, the CALLY was independently associated with sarcopenia. Moderate to high CALLY levels indicate a reduced risk of sarcopenia. The AUC and the Hosmer-Lemeshow test indicated that the models performed well. Sensitivity analysis conducted through PSM and subgroup interaction analysis validated the stability of the model.

Sarcopenia is characterized by a reduction in muscle mass along with alterations in physical function and muscle quality[10]. Sarcopenia heightens the likelihood of falls and fractures, compromises daily living activities, significantly deteriorates quality of life, and raises treatment expenses during hospital stays, thereby imposing a significant strain on the healthcare system[5,31,32]. Sarcopenia is caused by complex and interrelated pathophysiological mechanisms. Aging, malnutrition, oxidative stress, mitochondrial dysfunction, and inflammation primarily contribute to its development and progression[33]. The CALLY index is an improved scoring system that reflects the inflammatory, immune and nutritional status of patients and has emerged as a novel and promising prognostic biomarker for various types of cancers, including esophageal, gastric, and breast cancers[23,26,34]. Inflammation and malnutrition predispose to the development of sarcopenia. This study was the first to utilize CALLY values, which integrate nutritional and immunological indicators, to assess sarcopenia risk, thereby seeking a clinically simpler and more efficient tool for risk prediction.

Characteristic	Total	Non-sarcopenia	Sarcopenia	P value
N	139	70	69	
Age, years				<0.001*
≤69	51 (36.69)	38 (54.29)	13 (18.84)	
70-79	54 (38.85)	21 (30.00)	33 (47.83)	
≥80	34 (24.46)	11 (15.71)	23 (33.33)	
CALLY				<0.001*
<13	69 (49.64)	24 (34.29)	45 (65.22)	
≥13	70 (50.36)	46 (65.71)	24 (34.78)	
Sex				0.005*
Female	81 (58.27)	49 (70.00)	32 (46.38)	
Male	58 (41.73)	21 (30.00)	37 (53.62)	
Smoke status, n (%)				0.597
Never	99 (71.22)	51 (72.86)	48 (69.57)	
Ever	22 (15.83)	9 (12.86)	13 (18.84)	
Now	18 (12.95)	10 (14.29)	8 (11.59)	
CHF, n (%)				0.637
No	134 (96.40)	68 (97.14)	66 (95.65)	
Yes	5 (3.60)	2 (2.86)	3 (4.35)	
BMI, n (%)				<.001*
≤24	76 (54.68)	25 (35.71)	51 (73.91)	
>24	63 (45.32)	45 (64.29)	18 (26.09)	
Hypertension, n (%)				0.677
No	60 (43.17)	29 (41.43)	31 (44.93)	
Yes	79 (56.83)	41 (58.57)	38 (55.07)	
Diabetes, n (%)				0.110
No	103 (74.10)	56 (80.00)	47 (68.12)	
Yes	36 (25.90)	14 (20.00)	22 (31.88)	
Osteoporosis, n (%)				0.801
No	72 (51.80)	37 (52.86)	35 (50.72)	
Yes	67 (48.20)	33 (47.14)	34 (49.28)	
Atherosclerosis, n (%)				0.439
No	76 (54.68)	36 (51.43)	40 (57.97)	
Yes	63 (45.32)	34 (48.57)	29 (42.03)	
Chronic gastritis, n (%)				0.036*
No	104 (74.82)	47 (67.14)	57 (82.61)	
Yes	35 (25.18)	23 (32.86)	12 (17.39)	
SII, n (%)				<0.001*
<443.73	69 (49.64)	45 (64.29)	24 (34.78)	
≥443.73	70 (50.36)	25 (35.71)	45 (65.22)	
SIRI, n (%)				0.051
<0.95	70 (50.36)	41 (58.57)	29 (42.03)	
≥0.95	69 (49.64)	29 (41.43)	40 (57.97)	
dNLR, n (%)				0.034*
<1.66	69 (49.64)	41 (58.57)	28 (40.58)	
≥1.66	70 (50.36)	29 (41.43)	41 (59.42)	
PLR, n (%)				<0.001*
<135.60	70 (50.36)	46 (65.71)	24 (34.78)	
≥135.60	69 (49.64)	24 (34.29)	45 (65.22)	
RSMI, n (%)				<0.001*
Male≥7.0kg/m2	56(40.3)	55(78.6)	1(1.4)	
female≥5.4kg/m2				
Male<7.0kg/m2	83(59.7)	15(21.4)	68(98.6)	
female<5.4kg/m2				
HGS, n (%)				<0.001*
Male>26kg female>18kg	64(46.0)	49(70.0)	15(21.7)	
Continued				

Characteristic	Total	Non-sarcopenia	Sarcopenia	P value
Male≤ 26kg	75(54.0)	21(30.0)	54(78.3)	
Female≤18kg				
SPPB, n (%)				<0.001
> 9	76(54.7)	49(70.0)	27(39.1)	
≤9	63(45.3)	21(30.0)	42(60.9)	
6-m walk test, n (%)				0.012*
≥1.0m/s	61(52.1)	38(63.3)	23(40.4)	
<1.0m/s	56(47.9)	22(36.7)	34(59.6)	
Five times sit-to-up test, n (%)				0.001*
< 12	55(39.6)	37(52.9)	18(26.1)	
≥12	84(60.4)	33(47.1)	51(73.9)	

Table 3. General characteristics of participants with sarcopenia in the Kunshan cohort (N=139) Asterisks indicated P-values of statistical significance. Continuous variables were shown as medians and ranges, and categorical variables were reported as numbers and percentages. Abbreviations: BMI, body mass index; CHF, chronic heart failure.

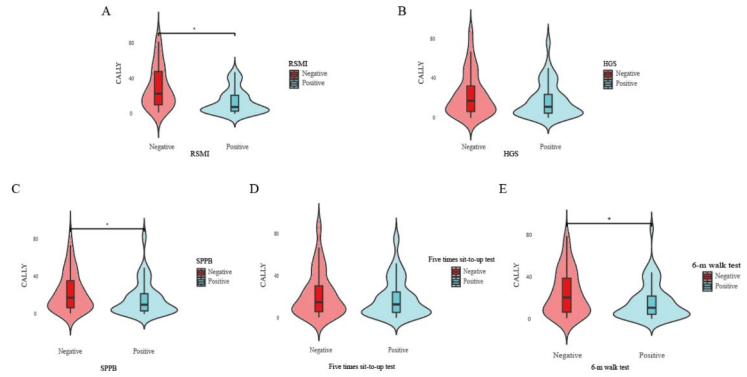

Fig. 5. Violin plots illustrating the distribution of CALLY values among participants for sarcopenia measures. The red color represented participants with negative results, and the blue color represented participants with positive results. The box plots within the violin plots showed the median and interquartile range of the CALLY values. Asterisks indicated statistically significant differences between the negative and positive groups.

	Model 1		Model 2		Model 3	
CALLY	OR and 95%CI	P value	OR and 95%CI	P value	OR and 95%CI	P value
<13	Ref	Ref	Ref	Ref	Ref	Ref
≥13	0.28 (0.14 - 0.55)	**<0.001***	0.33(0.12- 0.86)	**0.025***	0.35(0.12- 0.96)	**0.044***

Table 4. The association between the CALLY index and sarcopenia among Kunshan participants. Note: Model 1 was an unadjusted crude model; Model 2 was built upon Model 1 by incorporating adjustments for age, gender, smoking status, as well as comorbidities such as hypertension, diabetes, and chronic heart failure, osteoporosis, atherosclerosis, and chronic gastritis. Model 3 further extended Model 2 by incorporating adjustments for the inflammatory biomarker SII. Asterisks indicated statistical significance. Significant values are in bold.

Chronic, low-grade inflammation linked to aging could play a significant role in the development of sarcopenia[35]. This type of inflammation is marked by elevated levels of proinflammatory cytokines and reduced levels of anti-inflammatory cytokines[36]. Inflammation-induced pyroptosis and mitochondrial autophagy damage are important factors in sarcopenia onset and development[37].

Recent findings by Bano revealed that CRP levels were notably elevated in sarcopenia patients compared to the control group. Additionally, the study examined variations in inflammatory cytokines like IL-6 and TNF-α among sarcopenia patients, yet discovered no significant disparities[38]. However, another meta-analysis, involving 168 studies, showed that increased levels of circulating inflammatory markers (IL-6, CRP, and TNF-α) have a significant negative association with grip strength and knee extension force[39]. Notably, meta-analyses

include studies with varying sample sizes and diagnostic methods for sarcopenia, which is a major limitation. Nevertheless, compared to IL-6 and TNF-α, CRP has shown robustness in predicting outcomes across different studies. However, as a commonly used clinical indicator, CRP level is influenced by various factors, making its use for specifically diagnosing sarcopenia challenging. Therefore, the CALLY index, which combines CRP with other serum markers to comprehensively predict the risk of sarcopenia, was proposed.

Skeletal muscle regeneration relies on the activity of muscle satellite cells (MUSCs)[40]. The immune system, especially lymphocytes, is closely associated with MUSCs[41]. In vitro, lymphocytes aid in the migration and proliferation of muscle stem cells (SCs)[42]. In acute muscle injury models, they mainly recruit macrophages and CD4 + Tregs cells to promote macrophage polarization and activate MUSC proliferation through CD8 + T cells[42,43]. Aging affects the expression of CD8 + T cells and CD4 + Tregs cells[44]. The ability of aged mice to recruit CD4 + Tregs cells decreases, and MUSCs tend to proliferate rather than differentiate, leading to MUSC accumulation and loss of muscle mass. Downregulation of genes related to INF-γ expression is associated with impaired muscle regeneration in aged mice, whereas transplantation of CD8 + T cells rescued the ability of interferon-deficient mice to repair muscle damage[45]. Considering the important role of lymphocytes in muscle regeneration, the changes and subsequent effects of sarcopenia cannot be ignored.

Malnutrition is recognized as a critical risk factor for sarcopenia, particularly in individuals with disabilities or those experiencing specific health incidents like strokes, hip fractures, or cancer, which severely affect patient outcomes[22,46,47]. Therefore, recognizing the importance of nutritional status in the development, prevention, and treatment of sarcopenia is imperative. Albumin is mainly synthesized by the liver and is primarily responsible for transporting nutrients in the blood and maintaining blood volume balance[48,49]. Although evidence elucidating the direct mechanism of albumin involvement in the development of sarcopenia is lacking, a systematic review and meta-analysis have shown that there is an inverse relationship between serum albumin levels and the presence of both frailty and sarcopenia[50]. Moreover, albumin levels and sarcopenia were correlated in patients with inflammatory bowel diseases[51]. Other studies have linked serum albumin levels to diseases that predispose individuals to sarcopenia. Patients with cirrhosis are prone to sarcopenia due to disruptions in their metabolic homeostasis, and the myostatin/albumin ratio can be used to diagnose and exclude muscle atrophy[50–52]. Our findings elucidated an association between the CALLY index, which incorporates serum albumin, and sarcopenia, thereby enhancing the understanding of the role of albumin in sarcopenia and highlighting the urgent need for further mechanistic exploration in related studies.

Although there have been studies on the correlation between inflammatory markers and the risk of sarcopenia, a consensus has not yet been reached. The Western China Health and Aging Trend (WCHAT) project indicated that higher levels of SII, PLR, and NLR are linked to a heightened risk of sarcopenia in adults who are middle-aged and older[53]. Nonetheless, research focusing on sarcopenia in older adults living in communities does not endorse the use of NLR and PLR as biomarkers for sarcopenia within the Chinese demographic[54]. This discrepancy could be attributed to individual and regional differences. A cross-sectional study showed a positive correlation between SII and sarcopenia risk in individuals aged 18–59 years; however, subgroup analysis cannot ignore the interactive effects of a wide age range on the results[20]. The SIRI is closely related to osteosarcopenic obesity and its components (osteoporosis, sarcopenia, and obesity). However, data on the SIRI that independently predict the risk of sarcopenia are lacking[21]. In this research, we thoroughly assessed the relationship between sarcopenia, the CALLY index, and various other inflammatory/nutritional markers. The findings indicated that the CALLY value, which combines aspects of inflammation and nutrition, was independently associated with sarcopenia in both community residents and hospital inpatients. In contrast, other inflammatory/nutritional markers such as dNLR, PLR, SII, and SIRI did not effectively predict sarcopenia risk.

The broad applicability of the CALLY value in this study stems from the analysis of two distinct cohorts: the NHANES community sample and patients from Kunshan Hospital. This allowed for a detailed examination of the relationship between the CALLY index and sarcopenia. However, the study has certain limitations. Firstly, the inherent differences in baseline characteristics between the two cohorts—community survey participants and hospitalized patients—inevitably introduce confounding effects that may impact the results, necessitating further research for validation. Secondly, the cross-sectional design may introduce biases, preventing definitive conclusions about the causal relationship between the CALLY value and sarcopenia outcomes. Additionally, the sample size of our Kunshan cohort was relatively small, requiring further external validation to establish the predictive value of the CALLY index for sarcopenia, particularly among hospitalized patients. Despite these limitations, our findings reveal a complex connection between CALLY and sarcopenia, which could potentially guide future practical applications.

Conclusion

In conclusion, there was a significant and negative association between the CALLY index and the risk of sarcopenia among both community residents and hospital patients, indicating a multifaceted interplay between nutrition and inflammation in the development and progression of sarcopenia. This is an efficient and convenient screening tool for the clinical assessment of sarcopenia in middle-aged and older individuals.

Data availability

The NHANES obtained ethical approval from the National Center for Health Statistics (NCHS) Ethics Review Committee and ensured that all participants provided informed consent. All detailed NHANES study designs and data are publicly available at www.cdc.gov/nchs/nhanes/.The Kunshan data during the current study are not publicly available due to data privacy policy at our facility, but are available from the corresponding author on reasonable request.

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Conceptualization: ZL.G.; Formal Analysis, YJ.L., QX.W. and XL.K.; Investigation, YJ.L., QX.W. and XL.K.; Data Curation, BQ.X., YH.X. and KY.Z.; Manuscript edit, WY.Z., XY.L. and L.L. Writing – Original Draft Preparation, YJ.L., QX.W. and XL.K.; Writing – Review & Editing, YJ.L., QX.W., XL.K. and ZL.G.; Supervision, ZL.G.; Project Administration, ZL.G.; Funding Acquisition, ZL.G. All authors read and approved the final manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

Ethical approval
The Institutional Review Board (IRB) of First People's Hospital of Kunshan has reviewed the research protocol. The protocol is deemed rational and scientific, and complies with ethical standards. The IRB has approved the research protocol (approval number: IEC-C-011-A04-V3.0). The NHANES obtained ethical approval from the National Center for Health Statistics (NCHS) Ethics Review Committee and ensured that all participants provided informed consent. All detailed NHANES study designs and data are publicly available at www.cdc.gov/nchs/nhanes/.

Informed consent
Informed consent was obtained from all subjects involved in the study.

Additional information

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