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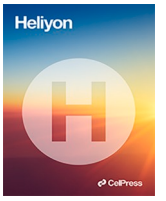

Research article

Associations of C-reactive protein-albumin-lymphocyte (CALLY) index with cardiorenal syndrome: Insights from a population-based study

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ABSTRACT

Background: Cardiorenal syndrome (CRS) is a complex condition characterized by the interplay of immune imbalance and inflammation. The C-reactive protein-Albumin-lymphocyte (CALLY) CALLY index serves as a new immune-nutritional scoring system, but its predictive value for CRS remains to be established.

Methods: In this study, we analyzed data from 27,978 participants in National Health and Nutrition Examination Survey (NHANES) from 1999 to 2010. The CALLY index was calculated as the ratio of albumin to lymphocyte, divided by C-reactive protein (CRP) multiplied by 10^4. CRS was defined by the coexistence of cardiovascular disease and chronic kidney disease (eGFR <60 mL/min/1.73 m^2). Multivariate weighted logistic regression models were employed to determine the odds ratio and 95 % confidence interval for the association between the CALLY index and CRS. Receiver operating characteristic (ROC) curves and restricted cubic spline (RCS) curves were used to assess the predictive efficacy and nonlinear relationship, respectively.

Results: The prevalence of CRS in the study population was 1.22 %. Our findings revealed a significant inverse relationship between the CALLY index and CRS risk, with lower CALLY index values being associated with a higher likelihood of CRS (OR = 0.95, 95 % CI = 0.94–0.96, P < 0.001). Participants in higher quartiles of the CALLY index showed a progressively reduced risk of CRS (P for trend <0.001). Moreover, the CALLY index demonstrated superior predictive performance compared to other inflammatory indicators, such as systemic immune-inflammation index (SII), neutrophil/high-density lipoprotein ratio (NHR), lymphocyte/high-density lipoprotein ratio (LHR), monocyte/high-density lipoprotein ratio (MHR), and platelet/high-density lipoprotein ratio (PHR) (AUC = 0.672, 95 % CI = 0.643–0.701).

Conclusions: This study underscores the significant negative correlation between the CALLY index and the risk of cardiorenal syndrome. The CALLY index emerges as a robust and independent predictor of CRS, outperforming traditional inflammatory markers. This finding highlights the potential utility of the CALLY index as a clinical tool for identifying individuals at risk for CRS.

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1. Introduction

Cardiorenal syndrome (CRS) denotes a reciprocal relationship between the heart and kidneys, where the compromised function of one, whether sudden or ongoing, can trigger a similar decline in the other [1]. More than 50 % of patients with chronic heart failure (CHF) combine with renal insufficiency. It is estimated that 20–60 % of moderate to severe renal failure patients have heart failure [2]. The high prevalence of CRS presents a significant challenge to public health and healthcare systems. Currently, the early diagnosis and prognostic assessment of CRS are not adequate, so searching for effective biomarkers is important [3].

With the development of pathophysiology, studies have revealed that a variety of pathophysiologic processes are implicated in CRS, with immune imbalance and inflammation being pivotal in both the onset and progression of the condition [4,5]. Malnutrition is prevalent in patients with CRS and negatively impacts clinical outcomes in CRS [6]. The C-reactive protein -Albumin-lymphocyte (CALLY) index serves as a new immune-nutritional scoring system, which is calculated based on albumin level multiplied by lymphocyte count divided by C-reactive protein level multiplied by 10,000 [7,8]. Previous retrospective studies have examined the association of CALLY with prognosis in patients with colorectal and hepatocellular carcinoma, and it is better than other inflammation-based biomarkers [7,9,10]. However, studies on the correlation between CALLY index and CRS are quite limited.

Albumin reflects nutritional status, lymphocyte count reflects the immune system, and C-reactive protein serves as a classic inflammatory marker. In addition to influencing CRS initiation and progression, these markers may also influence its prognosis [4,7,11]. Consequently, leveraging data from the National Health and Nutrition Examination Survey (NHANES), we investigated the potential independent link between the CALLY index and CRS, with the goal of addressing the gap in understanding risk factors and predictors for CRS and to inform the development of effective preventative measures.

2. Materials and methods

2.1. Data and study participants

We performed a cross-sectional analysis utilizing NHANES dataset spanning from 1999 to 2010. This extensive program, administered by the National Center for Health Statistics, serves as a vital source for evaluating the health and nutritional profiles of the American population. NHANES encompasses comprehensive interviews that delve into demographic characteristics, socioeconomic status, dietary habits, and various health aspects, complemented by meticulous examinations involving medical tests and blood marker evaluations conducted by qualified healthcare professionals.

From the total of 62,160 individuals who participated in the six consecutive NHANES cycles during the specified timeframe, we implemented rigorous exclusion criteria to ensure the accuracy and reliability of our analysis. This led to the exclusion of 26,781 participants under the age of 18, as they were not considered eligible for our study's focus. In addition, 4,063 individuals were excluded since insufficient data was available to calculate estimated glomerular filtration rate (eGFR), a crucial parameter for assessing

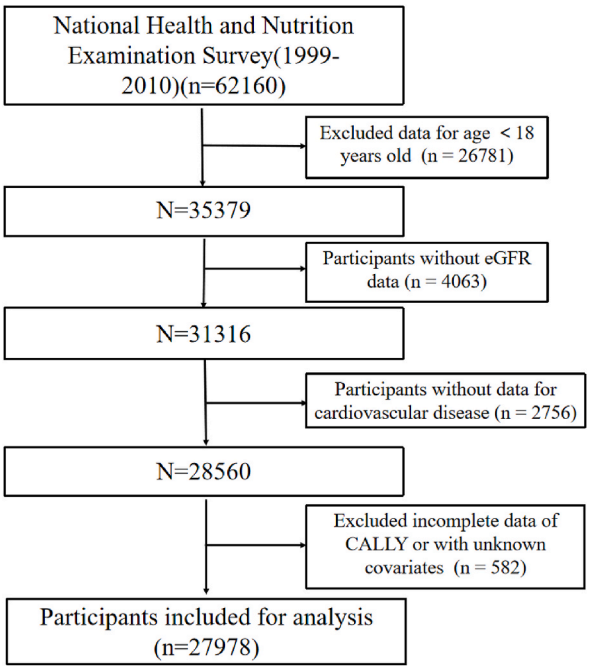

Fig. 1. Inclusion and exclusion process of the study participants. Abbreviations: NHANES, National Health and Nutrition Examination Survey; eGFR, estimated glomerular filtration rate; CALLY, C-reactive protein-albumin-lymphocyte.

chronic kidney disease (CKD). Furthermore, we excluded 2,756 participants who lacked information on cardiovascular disease (CVD), as well as 582 individuals who were missing either the CALLY index values or relevant covariates required for our analysis. The detailed selection process, including these exclusions, is illustrated in Fig. 1.

2.2. Assessment of C-reactive protein-albumin-lymphocyte index

Blood cell counts were analyzed utilizing the Coulter HMX Hematology Analyzer, with results for neutrophils, platelets, monocytes, and lymphocytes reported in standardized units of $\times 10^3$ cells per microliter. Our primary focus was on the CALLY index, a novel metric derived from preoperative albumin levels, lymphocyte counts, and CRP values. Specifically, the CALLY index was calculated as [(Albumin in g/L) * (Lymphocyte count in 1000 cells/uL)]/(CRP in mg/dL), providing a holistic evaluation of inflammatory and nutritional status [7].

Additionally, we investigated the relationship between SII, MHR, NHR, PHR, and LHR and cardiorenal syndrome.

$$CALLY\ index = \frac{\text{Albumin} \times \text{Lymphocyte}}{\text{CRP}}$$

$$\text{systemic immune} - \text{inflammation index(SII)} = \frac{\text{Platelet counts} \times \text{neutrophil counts}}{\text{lymphocyte counts}}$$

$$\text{monocyte/high} - \text{density lipoprotein ratio(MHR)} = \frac{\text{monocyte counts}}{\text{HDL} - \text{C}}$$

$$\text{neutrophil/high} - \text{density lipoprotein ratio(NHR)} = \frac{\text{neutriphil counts}}{\text{HDL} - \text{C}}$$

$$\text{platelet/high} - \text{density lipoprotein ratio(PHR)} = \frac{\text{platelet counts}}{\text{HDL} - \text{C}}$$

$$\text{lymphocyte/high} - \text{density lipoprotein ratio(LHR)} = \frac{\text{lymphocyte counts}}{\text{HDL} - \text{C}}$$

2.3. Cardiorenal syndrome ascertainment

Expanding on the previous study, CRS encompass a wide spectrum of conditions where impairments in the function of one organ—either the heart or the kidneys—can trigger dysfunction in the other [7]. This interplay can manifest as acute kidney injury in the context of acute heart failure or CKD secondary to CHF [12]. Therefore, the diagnosis of CHF and CKD concomitantly was defined as CRS. We utilized information on CHF history was collected using the standardized question: 'During the past 12 months, has a doctor or other health professional ever told you had congestive heart failure?'. And CKD was defined by the eGFR, with eGFR values below 60 mL/min per 1.73 m^2 indicating CKD. We used Creatinine and Cystatin C-based equations to estimate GFR without taking race into account [13].: eGFR = 142 × (Serum Creatinine/A) ^{B} x (0.9938) ^{Age} x C, where Serum Creatinine (Scr) denotes serum creatinine concentration (mg/dL); (1) Female C : 1.012; Scr≤0.7 mg/dL , A = 0.7 , B = −0.241; Scr>0.7 mg/dL , A = 0.7 , B = −1.2; (2) Male C : 1,Scr≤0.9 mg/dL , A = 0.9 , B = −0.302; Scr>0.9 mg/dL , A = 0.9 , B = −1.2 [14].

$$eGFR = 142 \times \left(\frac{Scr}{A}\right)^{B} \times (0.9938)^{\text{Age}} \times C$$

(1) $Female: C = 1.012; Scr \le 0.7mg/dL: A = 0.7, B = -0.241$

$Scr > 0.7mg/dL: A = 0.7, B = -1.2$

(2) $Male: C = 1.000; Scr \le 0.7mg/dL: A = 0.9, B = -0.302$

$Scr > 0.7mg/dL: A = 0.9, B = -1.2$

2.4. Covariates assessment

We incorporated demographic details, lifestyle factors, and potential confounders into our analysis as covariates. Demographic factors included age, gender, ethnicity, and educational attainment. Lifestyle factors such as smoking and alcohol consumption were also considered. Additionally, we accounted for comorbidities like hypertension and diabetes. Age was the sole continuous variable, with categorization details provided in Supplementary Table 2.

2.5. Statistical analysis

Considering the complex sampling design of the survey, we conducted weighted analyses in line with the NHANES guidelines. The statistical evaluation of the CALLY index was performed according to the database's protocols. We depicted continuous and categorical variables using mean (±SD) and percentage, respectively. The continuous CALLY index was categorized into quartiles for initial analysis. For categorical variables, we determined the p-value using the chi-squared test with Rao & Scott's second-order correction, while for continuous variables, we applied the Kruskal-Walli's rank-sum test, tailored for complex survey samples.

The association between the CALLY index and CRS was examined using three weighted linear regression models: Model 1 (unadjusted), Model 2 (adjusted for sex, age, and race), and Model 3 (further adjusted for gender, age, race, education, PIR, BMI, smoking, alcohol consumption, hypertension, diabetes, HDL, TC, and TG). Additionally, we utilized three-knot restricted cubic splines (RCS) to investigate potential non-linear relationships between the CALLY index and CRS, employing the generalized additive model to create a smooth curve based on the penalty spline approach. Segmented regression models were also used to determine whether the CALLY index and the CRS were linear or nonlinear and the Area Under the Curve (AUC) values and receiver operating characteristic (ROC)

Table 1
Weighted patient demographics and baseline characteristics of participants according to CALLY index.

Characteristic	Q1	Q2	Q3	Q4	*p*-value
	[1.71,167)	[167,400)	[400,1010)	[1010,13000]	
CALLY	90.88 ± 43.17	270.64 ± 66.77	647.76 ± 175.86	2,829.19 ± 2,272.91	<0.001[b]
Age	49.27 ± 16.98	48.60 ± 16.62	46.41 ± 16.28	41.51 ± 15.74	<0.001[b]
Gender					<0.001[c]
Female	4,494 (64.9 %)	3,790 (54.9 %)	3,202 (45.7 %)	3,015 (45.0 %)	
Male	2,499 (35.1 %)	3,191 (45.1 %)	3,794 (54.3 %)	3,993 (55.0 %)	
BMI	32.29 ± 8.03	29.65 ± 6.04	27.67 ± 5.23	24.99 ± 4.31	<0.001[b]
Race					<0.001[c]
Mexican American	1,484 (8.1 %)	1,501 (7.8 %)	1,475 (7.9 %)	1,328 (7.4 %)	
Other Hispanic	418 (4.8 %)	470 (5.6 %)	494 (5.0 %)	488 (5.0 %)	
Non-Hispanic White	3,320 (69.2 %)	3,486 (71.7 %)	3,548 (72.2 %)	3,553 (71.4 %)	
Non-Hispanic Black;	1,575 (14.0 %)	1,292 (10.6 %)	1,163 (9.0 %)	1,233 (9.2 %)	
Other race	196 (3.9 %)	232 (4.3 %)	316 (5.9 %)	406 (7.0 %)	
Education					<0.001[c]
Less Than 9th Grade	2,467 (25.2 %)	2,310 (22.2 %)	2,114 (20.6 %)	1,959 (18.5 %)	
9–11th Grade	3,440 (55.3 %)	3,401 (54.0 %)	3,450 (52.5 %)	3,344 (50.5 %)	
High school grade and more	1,086 (19.5 %)	1,270 (23.7 %)	1,432 (27.0 %)	1,705 (31.0 %)	
PIR					<0.001[c]
<1	1,141 (12.2 %)	1,446 (16.1 %)	1,198 (12.5 %)	1,153 (12.7 %)	
≥1	5,301 (87.8 %)	5,029 (83.9 %)	5,184 (87.5 %)	5,287 (87.3 %)	
Hypertension					<0.001[c]
No	4,058 (60.4 %)	4,433 (67.8 %)	4,796 (73.0 %)	5,430 (81.5 %)	
Yes	2,935 (39.6 %)	2,548 (32.2 %)	2,200 (27.0 %)	1,578 (18.5 %)	
Diabetes					<0.001[c]
No	5,854 (86.2 %)	6,059 (90.4 %)	6,231 (92.4 %)	6,452 (94.6 %)	
Yes	1,139 (13.8 %)	922 (9.6 %)	765 (7.6 %)	556 (5.4 %)	
Alcohol					<0.001[c]
Yes	4,578 (69.2 %)	4,915 (73.9 %)	5,216 (77.7 %)	5,409 (80.2 %)	
No	2,415 (30.8 %)	2,066 (26.1 %)	1,780 (22.3 %)	1,599 (19.8 %)	
Smoke					0.002[c]
Yes	3,372 (49.6 %)	3,403 (49.4 %)	3,403 (48.8 %)	3,214 (46.2 %)	
No	3,621 (50.4 %)	3,578 (50.6 %)	3,593 (51.2 %)	3,794 (53.8 %)	
Moderate-intensity activity					0.037[c]
No	4,829 (67.0 %)	4,724 (66.5 %)	4,626 (65.1 %)	4,548 (64.4 %)	
Yes	2,164 (33.0 %)	2,257 (33.5 %)	2,370 (34.9 %)	2,460 (35.6 %)	
Chronic Heart Failure					<0.001[c]
No	6,600 (95.5 %)	6,741 (97.6 %)	6,816 (98.4 %)	6,884 (98.7 %)	
Yes	393 (4.5 %)	240 (2.4 %)	180 (1.6 %)	124 (1.3 %)	
Chronic Kidney Diseases					<0.001[c]
No	6,210 (91.6 %)	6,335 (93.8 %)	6,483 (95.2 %)	6,699 (97.2 %)	
Yes	783 (8.4 %)	646 (6.2 %)	513 (4.8 %)	309 (2.8 %)	
Cardiorenal Syndrome					<0.001[c]
No	6,835 (98.3 %)	6,891 (99.2 %)	6,942 (99.6 %)	6,973 (99.7 %)	
Yes	158 (1.7 %)	90 (0.8 %)	54 (0.4 %)	35 (0.3 %)	
eGFR mL/(min·1.73m^2)	90.94 ± 20.577	92.57 ± 19.088	94.54 ± 18.477	98.13 ± 17.798	<0.001[b]
HDL (mg/dl)	51.08 ± 15.602	51.14 ± 15.397	51.83 ± 15.593	55.91 ± 16.366	<0.001[b]
TC (mg/dl)	199.71 ± 41.551	204.31 ± 42.320	201.09 ± 41.238	191.96 ± 37.920	<0.001[b]
TG (mg/dl)	156.48 ± 109.348	161.38 ± 128.488	155.02 ± 136.631	126.26 ± 107.678	<0.001[b]
Creatinine (mg/dL)	0.87 ± 0.547	0.87 ± 0.351	0.88 ± 0.281	0.87 ± 0.263	<0.001[b]
Albumin (g/L)	40.58 ± 3.566	42.51 ± 3.019	43.53 ± 2.993	44.58 ± 2.932	<0.001[b]
Lymphocyte (1000 cells/dL)	1.97 ± 0.671	2.10 ± 0.843	2.16 ± 0.791	2.21 ± 1.295	<0.001[b]
C-reactive protein (mg/dL)	1.27 ± 1.359	0.35 ± 0.156	0.16 ± 0.069	0.05 ± 0.034	<0.001[b]
PLT (1000 cells/dL)	280.30 ± 76.939	267.70 ± 66.666	260.88 ± 63.383	254.70 ± 62.270	<0.001[b]
WBC (1000 cells/dL)	7.77 ± 2.373	7.34 ± 2.148	7.15 ± 2.046	6.96 ± 2.426	<0.001[b]
Monocyte (1000 cells/dL)	0.58 ± 0.20	0.56 ± 0.18	0.55 ± 0.18	0.54 ± 0.19	<0.001[b]
Neutrophils (1000 cells/dL)	4.96 ± 1.996	4.43 ± 1.646	4.19 ± 1.537	3.94 ± 1.453	<0.001[b]

[a]Mean ± SD; n (unweighted) (%).
[b]Kruskal-Walli's rank-sum test for complex survey samples
[c]chi-squared test with Rao & Scott's second-order correction

curve analyses were used to evaluate other inflammatory markers (SII, MHR, NHR, PHR, LHR). Missing data for these variables were imputed using the modal value for categorical variables or the median for continuous ones.

To ensure the robustness of our findings, we performed several sensitivity analyses: 1) analyzing data prior to multiple imputation to assess its potential impact; 2) to mitigate the potential for over-adjustment bias when incorporating key variables as covariates after the calculation of sampling weights, we conducted an analysis without applying weights to the data.; 3) identifying cut-off points via ROC curves and dividing them into two groups for trend analysis.

All statistical analyses were performed using R software, version 4.2.0, along with relevant R packages. A p-value threshold of less than 0.05 was considered to denote statistical significance in our study.

3. Results

3.1. Baseline characteristics

In the NHANES 1999–2010 cycles, 27,978 subjects (48.2 % men) met the criteria for this cross-sectional study, with mean age of 46.13 ± 16.65 years. The baseline characteristics of the study cohort, stratified by CALLY index groups, are presented in Table 1. The majority of the participants excluded from the analysis were minors, as they were either not surveyed on relevant medical conditions or were ineligible for the assessment of the index measurements. Among the participants included in the study, the majority were white (13,907, 71.2 %), and a significant portion had achieved a high school education or higher (5,493, 25.8 %). A considerable number of individuals (3,794, 53.8 %) reported never having smoked. The Q1 group of the CALLY index, indicating the lowest values, consisted of older individuals who were more likely to smoke, be obese, and have elevated blood pressure. This group also exhibited a higher prevalence of conditions such as CHF and CKD. The prevalence of CHF and CKD among the participants was 2.3 % and 5.3 %, respectively. Statistically significant differences were observed in all baseline variables when comparing the groups categorized by the CALLY index. (all $p < 0.05$).

3.2. The relationships of CALLY index and CRS

The prevalence of CRS was 1.22 % (337 VS 27,641) among the 27,978 participants included in the study. As depicted in Supplemental Table 1, the optimal threshold value at the maximum value of Youden index is 255.3, selected through rigorous ROC analysis to ensure clinical relevance. Table 2 illustrates that after accounting for covariates, weighted logistic regression analysis indicates that a lower CALLY index is correlated with an increased likelihood of CRS (OR = 0.95, 95 % CI = 0.94–0.96, $p < 0.001$). When comparing the first quartile of the CALLY index as a reference, an increment in each subsequent quartile of the CALLY index is significantly linked to a reduced odds ratio for CRS, demonstrating a marked trend (p for trend <0.001). Fig. 2 displays the distribution of CALLY index and reveals no nonlinear association of CALLY index with CRS through RCS analysis (adjusted or unadjusted). Furthermore, the analysis revealed non-linear relationships with CRS, as evidenced by the Generalized Additive Model (GAM) and the application of smooth curve fitting techniques.

3.3. Stratification connection of CALLY index and CRS

Supplemental Figure 2 delineates our in-depth analysis of the stratified relationship between the CALLY index and CRS across various subgroups, categorized by sex, BMI, smoking status, alcohol intake, and the presence of hypertension and diabetes. The stratified analysis indicated that there were no statistically significant differences in the association between the CALLY index and CRS among any of the examined subgroups (p for interaction >0.05).

3.4. ROC analysis

To assess and compare the predictive power of CALLY with other inflammatory biomarkers, namely SII, MHR, NHR, PHR and LHR, for the prediction of CRS, we computed AUC values, as illustrated in Fig. 3. Our findings reveal that CALLY exhibited higher AUC

Table 2
Cross-sectional association between CALLY index and CRS.

Continuous or categories	Model 1		Model 2		Model 3	
	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
Cally as continuous variable	0.97 (0.96, 0.98)	<0.001	0.97 (0.96, 0.98)	0.03	0.95 (0.94, 0.96)	0.03
Low (< 255.3)						
high (≥255.3)	0.37 (0.30, 0.47)	<0.001	0.47 (0.38, 0.59)	<0.001	0.55 (0.43, 0.47)	<0.001
Q1						
Q2	0.48 (0.35, 0.66)	<0.001	0.51 (0.35, 0.66)	<0.001	0.60 (0.42, 0.85)	0.004
Q3	0.24 (0.17, 0.35)	<0.001	0.35 (0.23, 0.53)	<0.001	0.39 (0.26, 0.56)	<0.001
Q4	0.17 (0.11, 0.26)	<0.001	0.30 (0.21, 0.44)	<0.001	0.38 (0.24, 0.64)	<0.001
p for trend	<0.001		<0.001		<0.001	

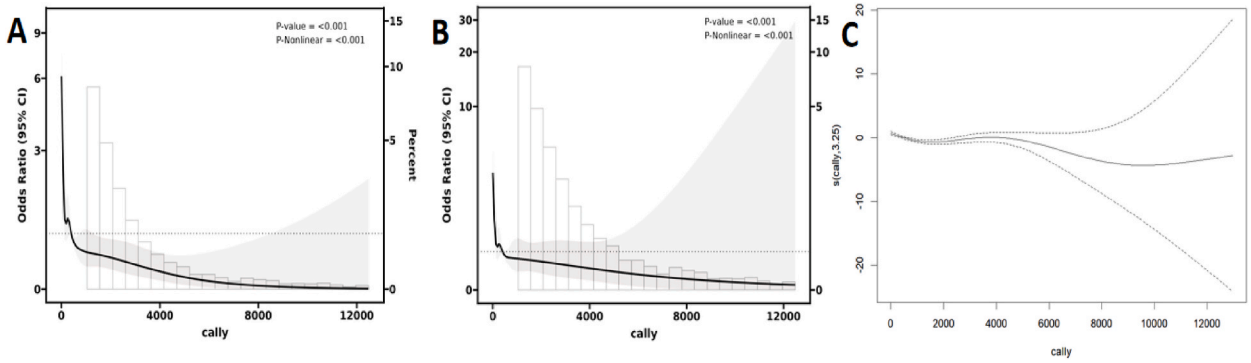

Fig. 2. Nonlinear associations of CALLY index with CRS. A. Unadjusted. B Adjusted for age, gender, education levels, race and BMI C. Generalized additive model curve; CALLY: C-reactive protein-albumin-lymphocyte; CRS cardiorenal syndrome.

values than the remaining inflammatory biomarkers, highlighting its superior performance in predicting CRS. Furthermore, Supplemental Table 3 demonstrates that the AUC values for CALLY are statistically significantly different from those of the other inflammatory biomarkers. Collectively, these findings indicate that the CALLY index demonstrates superior discriminatory power and precision in predicting CRS compared to other inflammatory biomarkers discussed. This suggests that the CALLY index could serve as a valuable clinical instrument for assessment and decision-making processes in the context of CRS.

4. Discussion

This study's findings indicate a significant and negative correlation between the CALLY index and the risk of CRS, a relationship that persists after accounting for various potential confounding factors. This suggests that the CALLY index could serve as an independent predictor for the risk of CRS. The consistency of the subgroup analyses further validated the validity of the CALLY index as a predictor of CRS risk and provided superior predictive ability compared with other inflammation-based composite indexes such as SII, NHR, LHR, MHR, and PHR.

The CALLY index is a novel inflammatory index with albumin levels, lymphocyte counts and CRP as components [7]. Albumin serves as a critical measure for evaluating nutritional status, and the deterioration of renal function not only reduces serum albumin but also diminishes its capacity to bind with uremic toxins [15]. Immune cells play an important role in cardiac injury and repair [16,

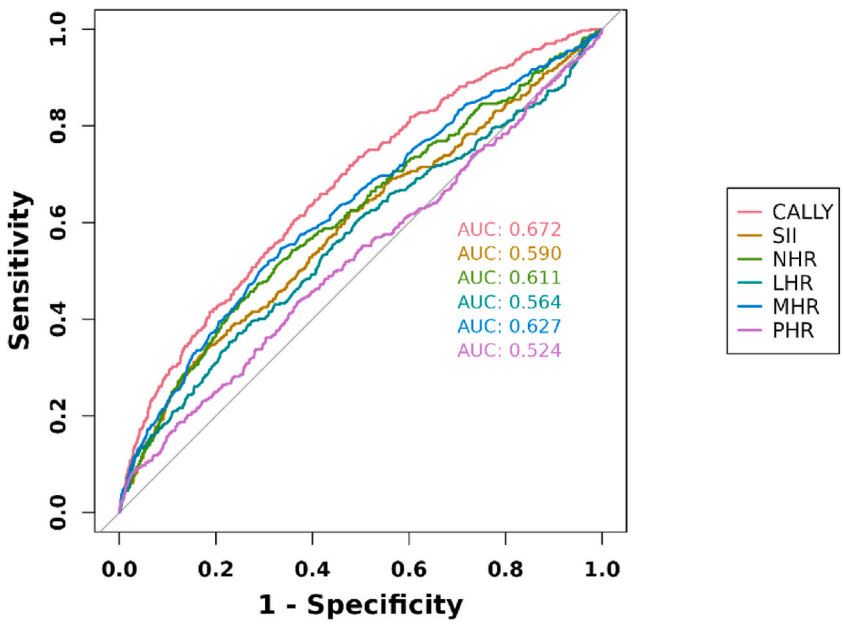

Fig. 3. ROC curves and the AUC values of the six inflammatory biomarkers (CALLY, SII, NHR, PHR, MHR, and LHR) in diagnosing CRS. CALLY: C-reactive protein-albumin-lymphocyte; SII: systemic immune-inflammation index; NHR, neutrophil/high-density lipoprotein ratio; MHR, monocyte-high-density lipoprotein ratio; LHR, lymphocyte high-density lipoprotein ratio, PHR, platelet high-density lipoprotein ratio. ROC Curve, receiver operating characteristic curve.

17]. In addition, the immune system participates in regulating the severity of kidney injury [18]. Inflammation stands out as a key mechanism in CRS and is acknowledged for its potential to induce stress on both acute and chronic cardiorenal systems [4]. Studies in mouse models of acute CRS have highlighted the significant role of inflammation in the transition from acute kidney injury to chronic kidney disease [19]. An exacerbated inflammatory state can exacerbate renal damage, and renal insufficiency has a direct impact on the clinical outcomes of both acute and chronic heart diseases [20]. CRP, recognized as a traditional marker of inflammation, has been found to be significantly correlated with an elevated cardiorenal risk [21]. Consequently, the CALLY index can be seen as a more responsive indicator that mirrors systemic immune and inflammatory reactions.

Systemic, ongoing inflammation is recognized as a pivotal initiator of both heart failure and renal impairment [22]. The SII, MHR, NHR, PHR and LHR are composite inflammatory indicators [23]. Elevated levels of SII, NHR, LHR, MHR and PHR are significantly associated with an increased risk of heart failure and chronic kidney disease [24–26]. A retrospective study has established the correlation between MHR and CRS, and MHR can be used as a tool for early prevention and intervention of CRS [10]. Presently, the CALLY index's application is predominantly in the prognostication of oncology patients [7,9]. The CALLY index was independently associated with patients with colorectal cancer [8]. Research has also uncovered a substantial negative correlation between the CALLY index and both all-cause and cardiovascular mortality rates in the elderly [27]. Moreover, a retrospective, single-center observational study has identified the CALLY index as an autonomous risk predictor for the onset of acute kidney injury (AKI) [28].

In this research, we conducted a pioneering exploration of the CALLY index's utility in forecasting outcomes for individuals afflicted with CRS. This research marks the pioneering effort to scrutinize the CALLY index's efficacy in forecasting CRS incidence, revealing its superior predictive capacity over SII, NLR, LMR, MHR, and PHR. The CALLY index, as an innovative nutritional immune-inflammatory scoring system, encompasses diminished albumin indicative of nutritional standing and hepatic functionality [29]. A decline in lymphocyte counts may be associated with immune system disequilibrium [30]. Furthermore, heightened CRP levels signify an aggravated inflammatory reaction [31]. Therefore, the CALLY index comprehensively reflects the systemic inflammatory response and provides superior ability to predict the occurrence of CRS.

This study has certain limitations. Firstly, due to its retrospective nature, the potential for bias cannot be entirely ruled out, and the cross-sectional design limits the ability to infer causal relationships. Secondly, the reliance on self-reported cardiovascular events introduces the possibility of reporting bias. Consequently, there is a need for future large-scale prospective studies to ascertain the longitudinal relationship between the CALLY index and CRS, as well as for clinical data-based studies to thoroughly evaluate the predictive and practical value of the CALLY index. In conclusion, our study revealed that the CALLY index was significantly negatively correlated with cardiorenal syndrome and was a powerful independent predictor of CRS.

5. Conclusions

This study underscores the significant negative correlation between the CALLY index and the risk of cardiorenal syndrome. The CALLY index emerges as a robust and independent predictor of CRS, outperforming traditional inflammatory markers. This finding highlights the potential utility of the CALLY index as a clinical tool for identifying individuals at risk for CRS.

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Data availability statement

The data of this study associated with your study been deposited into NHANES. The NHANES data and survey methodology are publicly available and accessible on the website (https//www.cdc.gov/nchs/nhanes/index.htm). Further inquiries can be directed to the corresponding authors.

Additional information

No additional information is available for this paper.

List of abbreviations

NHANES	National Health and Nutrition Examination Survey
SII	systemic immune-inflammation index
NHR	neutrophil/high-density lipoprotein ratio
LHR	lymphocyte/high-density lipoprotein ratio
MHR	monocyte/high-density lipoprotein ratio
PHR	platelet/high-density lipoprotein ratio
CALLY	C-reactive protein-albumin-lymphocyte
CRS	cardiorenal syndrome
CRP	C-reactive protein
RCS	Restricted cubic spline

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ROC	Receiver operating characteristic
eGFR	estimated glomerular filtration rate
CKD	chronic kidney disease
CVD	cardiovascular disease
HDL	high density lipoprotein
TG	triglyceride
TC	total cholesterol
AUC	area under the curve
GAM	Generalized Additive Model
BMI	Body mass index

CRediT authorship contribution statement

Zhehao Xu: Writing – original draft, Resources, Methodology, Investigation, Data curation. **Jiao Tang:** Writing – review & editing, Writing – original draft, Resources, Methodology, Data curation, Conceptualization. **Xin chen:** Writing – review & editing, Resources, Methodology. **Yian Jin:** Writing – original draft, Methodology, Investigation. **Huanji Zhang:** Writing – original draft, Software, Resources. **Ruiyun Liang:** Writing – review & editing, Writing – original draft, Resources, Methodology, Formal analysis, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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