

Association of the C-reactive Protein–Albumin–Lymphocyte Index With Long-term All-cause Mortality After Percutaneous Coronary Intervention for Acute Coronary Syndrome: A Retrospective Cohort Study

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Abstract

Background

Inflammation, malnutrition, and immune dysregulation are closely linked to adverse outcomes in patients with acute coronary syndrome. The C-reactive protein–albumin–lymphocyte index combines inflammatory, nutritional, and immune parameters, but its prognostic value in patients with acute coronary syndrome undergoing percutaneous coronary intervention remains unclear.

Methods

We conducted a single-center retrospective cohort study of 388 adult patients with acute coronary syndrome who underwent percutaneous coronary intervention between January 2021 and January 2024. The C-reactive protein–albumin–lymphocyte index was calculated from admission laboratory measurements as albumin multiplied by lymphocyte count and divided by C-reactive protein. The primary outcome was all-cause mortality. Cox proportional hazards models were used to evaluate the association between the C-reactive protein–albumin–lymphocyte index and all-cause mortality. The parsimonious adjusted model included the index and age, sex, GRACE risk score, left ventricular ejection fraction, diabetes mellitus, chronic kidney disease, and multivessel disease. Dose–response, subgroup, and sensitivity analyses were also performed.

Results

During a median follow-up of 26 months, 62 deaths occurred. All-cause mortality decreased across increasing tertiles of the C-reactive protein–albumin–lymphocyte index: 29.2% in the low tertile, 13.3% in the medium tertile, and 5.4% in the high tertile. In the parsimonious adjusted model, each one-unit increase in the index was independently associated with a lower risk of all-cause mortality (hazard ratio, 0.552; 95% confidence interval, 0.368–0.827; $P = 0.004$). The association was also significant per one-standard-deviation increase and across tertiles. Restricted cubic spline analysis showed no significant departure from linearity. An exploratory two-piecewise Cox model identified a data-driven inflection point at 3.117, with a stronger inverse association below this threshold; however, this threshold should not be interpreted as a clinically validated cut-off. The association remained robust after winsorization of extreme index values, exclusion of early deaths, and imputation-based analyses.

Conclusions

Among patients with acute coronary syndrome undergoing percutaneous coronary intervention, a higher baseline C-reactive protein–albumin–lymphocyte index was independently associated with lower long-term all-cause mortality. This readily available biomarker may help identify patients at increased post-

procedural risk, although external validation and assessment of incremental prognostic value are warranted.

Introduction

Despite continuing advances in revascularization techniques and guideline-directed secondary prevention, the long-term risk of death among patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) remains substantial [1]. This persistent residual risk suggests that mechanisms beyond traditional cardiovascular risk factors may contribute importantly to long-term prognosis.

Systemic inflammation and nutritional status are increasingly recognized as key determinants of cardiovascular outcomes. These processes may influence clinical trajectories by affecting plaque stability, myocardial repair, immune–metabolic homeostasis, and overall physiological resilience [2]. In the post-PCI setting, patients experience a dynamic state in which inflammatory activation and recovery-related metabolic demands coexist. Disruption of the balance between inflammatory burden and nutritional reserve may therefore increase vulnerability to adverse long-term outcomes.

To capture the combined prognostic effects of inflammation, nutrition, and immune status, several composite hematologic indices have been developed and evaluated across cardiovascular populations [2]. Among these, the C-reactive protein–albumin–lymphocyte index (CALLY) integrates three clinically relevant domains: systemic inflammation reflected by C-reactive protein, hepatic synthetic and nutritional status reflected by albumin, and immune cell availability reflected by lymphocyte count. CALLY has shown independent prognostic value for all-cause or cardiovascular mortality in patients with cancer, stroke, chronic kidney disease, and other clinical conditions [3–6]. Related indices, including the neutrophil-to-lymphocyte ratio, prognostic nutritional index, and systemic immune-inflammation index, have also been associated with adverse cardiovascular events [7, 8]. However, the prognostic significance of CALLY specifically among patients with ACS undergoing PCI remains unclear, and direct evidence in this population is limited.

Therefore, we conducted a single-center retrospective cohort study to evaluate the independent association between baseline CALLY and all-cause mortality among patients with ACS undergoing PCI. Cox proportional hazards regression was used to quantify this association, with a parsimonious adjustment strategy informed by clinical relevance and change-in-estimate criteria. Given the observational and single-center design, this study was intended as a hypothesis-generating investigation, with the primary aim of clarifying whether CALLY provides independent prognostic information for all-cause mortality in this specific clinical setting.

Methods

Study design and population

We conducted a single-center retrospective cohort study in the Department of Cardiology at the First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine. Adult patients hospitalized for acute coronary syndrome who underwent percutaneous coronary intervention during the index hospitalization between January 2021 and January 2024 were screened through institutional clinical databases. Patients were followed from the index procedure until death or the end of the observation period. Individuals without baseline data required to calculate the C-reactive protein–albumin–lymphocyte index or without ascertainable vital status were excluded. The study was approved by the Ethics Committee of the First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine, approval number K2020-020. Because this was a retrospective study using de-identified clinical data, the requirement for written informed consent was waived.

Exposure and outcome

The primary exposure was the C-reactive protein–albumin–lymphocyte index, calculated from admission laboratory measurements as albumin in g/dL multiplied by lymphocyte count in $\times 10^9/L$ and divided by C-reactive protein in mg/L. The index was analyzed primarily as a continuous variable. For descriptive analyses and trend assessment, patients were also categorized into tertiles according to the observed distribution of CALLY: low, 0.030–0.461; medium, 0.470–1.150; and high, 1.152–9.816. The primary outcome was all-cause mortality, defined as death from any cause during follow-up. Vital status was ascertained from electronic medical records and institutional registry data.

Data collection

Baseline variables were extracted from medical records. Demographic and anthropometric variables included age, sex, and body mass index. Clinical severity and cardiac function were characterized by the GRACE risk score, left ventricular ejection fraction, and Killip class. Comorbidities included smoking status, hypertension, diabetes mellitus, hyperlipidemia, prior heart failure, and chronic kidney disease. Angiographic and procedural variables included the number of diseased vessels and the number of implanted stents. Discharge medications included statins, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, and P2Y12 inhibitors. Laboratory variables included C-reactive protein, albumin, lymphocyte count, and low-density lipoprotein cholesterol.

Statistical analysis

Continuous variables were summarized as mean $\pm$ standard deviation or median with interquartile range, as appropriate, and categorical variables were summarized as frequencies and percentages. Baseline characteristics were compared across CALLY tertiles using one-way analysis of variance for continuous variables and Pearson chi-square or Fisher exact tests for categorical variables, as appropriate. Univariable Cox proportional hazards models were used to evaluate associations between baseline variables and all-cause mortality.

Missingness was evaluated among patients with observed exposure and outcome data. Most variables had no missing data. Smoking status had one missing value, and the number of implanted stents had 36 missing values. Missing values were handled using missForest imputation across five completed datasets when variables were included in the analytic dataset. Regression estimates from imputed datasets were pooled on the log-hazard scale using Rubin's rules (Supplemental table 1).

The primary analysis evaluated the association between CALLY and all-cause mortality using Cox proportional hazards regression. Four sequential models were fitted. Model 1 included CALLY alone. Model 2 adjusted for age and sex. Model 3 adjusted for age, sex, GRACE risk score, left ventricular ejection fraction, and body mass index. Model 4 was the parsimonious adjusted model and included CALLY with age, sex, GRACE risk score, left ventricular ejection fraction, diabetes mellitus, chronic kidney disease, and multivessel disease. Covariates for the parsimonious model were selected based on clinical relevance, change-in-estimate assessment (10%) [9–11], and collinearity screening. Hazard ratios were reported per one-unit increase in CALLY and per one-standard-deviation increase in CALLY (Supplemental table 2). A tertile-based trend test was also performed. The proportional hazards assumption for CALLY was assessed using Schoenfeld residuals.

Restricted cubic spline analysis was used to assess the dose–response relationship between CALLY and all-cause mortality within the Cox model framework. Departure from linearity was evaluated using a likelihood-ratio test. Because the CALLY distribution was right-skewed, an exploratory two-piecewise Cox regression analysis was also performed. The inflection point was selected using an Akaike information criterion–minimized grid search over candidate cut-points from the 10th to 90th percentile of the exposure distribution. The two-piecewise model was compared with the linear model using a likelihood-ratio test. Because the threshold was selected in a data-driven manner and no bootstrap or profile-likelihood confidence interval for the knot was calculated, the threshold analysis was considered exploratory.

Subgroup analyses were performed to evaluate whether the association between CALLY and all-cause mortality differed across clinically relevant strata. Effect modification was assessed using likelihood-ratio tests comparing models with and without cross-product interaction terms between CALLY and the subgroup variable. These analyses were exploratory and were not adjusted for multiple comparisons.

Sensitivity analyses were performed to assess the robustness of the primary findings. First, the parsimonious Cox model was refitted after winsorizing CALLY at the 1st and 99th percentiles. Second, early deaths occurring on or before the 5th percentile of observed event times were excluded, and the parsimonious model was refitted. Third, E-values were calculated to quantify the minimum strength of association that an unmeasured confounder would need to have with both CALLY and all-cause mortality, conditional on measured covariates, to explain away the observed association.

All analyses were performed using R software. Statistical tests were two-sided, and P values less than 0.05 were considered statistically significant.

Results

Baseline characteristics

A total of 388 patients with ACS undergoing PCI were included in the analysis (Fig. 1). During a median follow-up of 26 months (range, 0.88–56 months), 62 patients died, corresponding to an overall all-cause mortality rate of 16.0% and an incidence rate of 7.3 per 100 person-years .

Baseline characteristics stratified by tertiles of the C-reactive protein–albumin–lymphocyte index (CALLY) are presented in Table 1. The distribution of CALLY was right-skewed, with a median value of 0.73 (interquartile range, 0.35–1.53) and an observed range of 0.030–9.816. Patients were categorized into low, medium, and high CALLY tertiles, with ranges of 0.030–0.461, 0.470–1.150, and 1.152–9.816, respectively.

Table 1. Baseline characteristics according to CALLY tertiles. Values are presented as mean ± SD or n (%). Patients were categorized into tertiles according to the C-reactive protein–albumin–lymphocyte index (CALLY). P values were calculated using one-way analysis of variance for continuous variables and the chi-square test for categorical variables.

Table 1
Baseline Characteristics

Variable	Overall	Low	Medium	High	Test	P value
N	388	130	128	130	-	-
CALLY tertile range	0.030–9.816	0.030–0.461	0.470–1.150	1.152–9.816	-	-
Age (years)	66.17 ± 11.51	69.14 ± 11.48	65.02 ± 11.41	64.33 ± 11.12	F = 6.832 [F]	0.001
GRACE risk score	126.76 ± 25.84	132.82 ± 26.71	124.62 ± 27.95	122.82 ± 21.55	F = 5.648 [F]	0.004
Left ventricular ejection fraction (%)	61.39 ± 7.20	60.94 ± 7.00	61.64 ± 7.04	61.60 ± 7.56	F = 0.385 [F]	0.680
Body mass index (kg/m ²)	23.89 ± 2.60	24.28 ± 3.05	23.85 ± 2.58	23.53 ± 2.05	F = 2.746 [F]	0.065
CALLY index	0.73 (0.35–1.53)	0.25 (0.16–0.35)	0.73 (0.60–0.88)	2.00 (1.53–3.19)	F = 216.128 [F]	< 0.001
CRP (mg/L)	4.48 (2.08–10.17)	5.88 (2.25–10.47)	3.65 (2.07–8.52)	4.55 (1.87–11.09)	F = 0.791 [F]	0.454
Albumin (g/dL)	3.84 ± 0.55	3.30 ± 0.37	3.85 ± 0.28	4.38 ± 0.31	F = 359.524 [F]	< 0.001
Lymphocyte count (×10 ⁹ /L)	1.56 (1.15–2.17)	1.53 (1.13–2.05)	1.56 (1.14–2.18)	1.57 (1.21–2.19)	F = 0.370 [F]	0.691
LDL-C (mmol/L)	2.78 ± 1.12	2.78 ± 1.43	2.82 ± 0.89	2.74 ± 0.98	F = 0.190 [F]	0.827
All-cause mortality	-	-	-	-	χ ² =28.566 [C]	< 0.001
No	326 (84.0%)	92 (70.8%)	111 (86.7%)	123 (94.6%)	-	-
Yes	62 (16.0%)	38 (29.2%)	17 (13.3%)	7 (5.4%)	-	-
Sex (male/female)	-	-	-	-	χ ² =0.847 [C]	0.655

Note. Baseline characteristics of study population stratified by C-reactive protein–albumin–lymphocyte index (CALLY). Continuous variables: mean ± SD; categorical variables: n (%). In the Test column, method tags are appended in square brackets: [F] one-way ANOVA F-test (> 2 groups); [T] two-sample t-test (2 groups); [C] Pearson chi-square test; [F] Fisher's exact test (when expected cell count < 5).

Variable	Overall	Low	Medium	High	Test	P value
Female	153 (39.4%)	55 (42.3%)	47 (36.7%)	51 (39.2%)	-	-
Male	235 (60.6%)	75 (57.7%)	81 (63.3%)	79 (60.8%)	-	-
Smoking status	-	-	-	-	$\chi^2=8.366$ [C]	0.079
Never smoker	191 (49.2%)	62 (47.7%)	63 (49.2%)	66 (50.8%)	-	-
Current smoker	134 (34.5%)	55 (42.3%)	39 (30.5%)	40 (30.8%)	-	-
Former smoker	63 (16.2%)	13 (10.0%)	26 (20.3%)	24 (18.5%)	-	-
Hypertension	-	-	-	-	$\chi^2=2.647$ [C]	0.266
No	116 (29.9%)	33 (25.4%)	38 (29.7%)	45 (34.6%)	-	-
Yes	272 (70.1%)	97 (74.6%)	90 (70.3%)	85 (65.4%)	-	-
Diabetes mellitus	-	-	-	-	$\chi^2=3.035$ [C]	0.219
No	277 (71.4%)	88 (67.7%)	89 (69.5%)	100 (76.9%)	-	-
Yes	111 (28.6%)	42 (32.3%)	39 (30.5%)	30 (23.1%)	-	-
Hyperlipidemia	-	-	-	-	$\chi^2=1.344$ [C]	0.511
No	368 (94.8%)	125 (96.2%)	122 (95.3%)	121 (93.1%)	-	-
Yes	20 (5.2%)	5 (3.8%)	6 (4.7%)	9 (6.9%)	-	-
Prior heart failure	-	-	-	-	$\chi^2=0.869$ [C]	0.648
No	371 (95.6%)	123 (94.6%)	122 (95.3%)	126 (96.9%)	-	-
Yes	17 (4.4%)	7 (5.4%)	6 (4.7%)	4 (3.1%)	-	-
Chronic kidney disease	-	-	-	-	$\chi^2=9.684$ [C]	0.008

Note. Baseline characteristics of study population stratified by C-reactive protein–albumin–lymphocyte index (CALLY). Continuous variables: mean $\pm$ SD; categorical variables: n (%). In the Test column, method tags are appended in square brackets: [F] one-way ANOVA F-test (> 2 groups); [T] two-sample t-test (2 groups); [C] Pearson chi-square test; [F] Fisher's exact test (when expected cell count < 5).

Variable	Overall	Low	Medium	High	Test	P value
No	370 (95.4%)	118 (90.8%)	124 (96.9%)	128 (98.5%)	-	-
Yes	18 (4.6%)	12 (9.2%)	4 (3.1%)	2 (1.5%)	-	-
Killip class	-	-	-	-	$\chi^2=5.218$ [F]	0.516
I	339 (87.4%)	109 (83.8%)	112 (87.5%)	118 (90.8%)	-	-
II	22 (5.7%)	7 (5.4%)	8 (6.2%)	7 (5.4%)	-	-
III	20 (5.2%)	10 (7.7%)	6 (4.7%)	4 (3.1%)	-	-
IV	7 (1.8%)	4 (3.1%)	2 (1.6%)	1 (0.8%)	-	-
Number of diseased vessels	-	-	-	-	$\chi^2=22.323$ [C]	0.034
2-vessel disease	134 (34.5%)	33 (25.4%)	45 (35.2%)	56 (43.1%)	-	-
3-vessel disease	122 (31.4%)	50 (38.5%)	30 (23.4%)	42 (32.3%)	-	-
4-vessel disease	110 (28.4%)	42 (32.3%)	41 (32.0%)	27 (20.8%)	-	-
Other/left main	22 (5.7%)	5 (3.8%)	12 (9.4%)	5 (3.8%)	-	-
Number of implanted stents	-	-	-	-	$\chi^2=4.946$ [C]	0.763
0	67 (17.3%)	24 (18.5%)	19 (14.8%)	24 (18.5%)	-	-
1	200 (51.5%)	68 (52.3%)	61 (47.7%)	71 (54.6%)	-	-
2	66 (17.0%)	17 (13.1%)	23 (18.0%)	26 (20.0%)	-	-
≥ 3	19 (4.9%)	6 (4.6%)	9 (7.0%)	4 (3.1%)	-	-
Statin use	-	-	-	-	$\chi^2=0.512$ [C]	0.774
No	34 (8.8%)	10 (7.7%)	13 (10.2%)	11 (8.5%)	-	-
Note. Baseline characteristics of study population stratified by C-reactive protein–albumin–lymphocyte index (CALLY). Continuous variables: mean ± SD; categorical variables: n (%). In the Test column, method tags are appended in square brackets: [F] one-way ANOVA F-test (> 2 groups); [T] two-sample t-test (2 groups); [C] Pearson chi-square test; [F] Fisher's exact test (when expected cell count < 5).						

Variable	Overall	Low	Medium	High	Test	P value
Yes	354 (91.2%)	120 (92.3%)	115 (89.8%)	119 (91.5%)	-	-
ACEI/ARB use	-	-	-	-	$\chi^2=0.571$ [C]	0.752
No	204 (52.6%)	69 (53.1%)	64 (50.0%)	71 (54.6%)	-	-
Yes	184 (47.4%)	61 (46.9%)	64 (50.0%)	59 (45.4%)	-	-
Beta-blocker use	-	-	-	-	$\chi^2=1.093$ [C]	0.579
No	217 (55.9%)	68 (52.3%)	73 (57.0%)	76 (58.5%)	-	-
Yes	171 (44.1%)	62 (47.7%)	55 (43.0%)	54 (41.5%)	-	-
P2Y12 inhibitor use	-	-	-	-	$\chi^2=3.212$ [C]	0.201
No	81 (20.9%)	31 (23.8%)	20 (15.6%)	30 (23.1%)	-	-
Yes	307 (79.1%)	99 (76.2%)	108 (84.4%)	100 (76.9%)	-	-
<p>Note. Baseline characteristics of study population stratified by C-reactive protein–albumin–lymphocyte index (CALLY). Continuous variables: mean $\pm$ SD; categorical variables: n (%). In the Test column, method tags are appended in square brackets: [F] one-way ANOVA F-test (> 2 groups); [T] two-sample t-test (2 groups); [C] Pearson chi-square test; [F] Fisher's exact test (when expected cell count < 5).</p>						

All-cause mortality decreased progressively across increasing CALLY tertiles. Mortality occurred in 38 patients (29.2%) in the low tertile, 17 patients (13.3%) in the medium tertile, and 7 patients (5.4%) in the high tertile ($P < 0.001$). Compared with patients in the higher CALLY tertiles, those in the low tertile were older and had higher GRACE risk scores. Mean age was 69.14 ± 11.48 years in the low tertile, 65.02 ± 11.41 years in the medium tertile, and 64.33 ± 11.12 years in the high tertile ($P = 0.001$). GRACE risk score also differed significantly across tertiles, with corresponding values of 132.82 ± 26.71 , 124.62 ± 27.95 , and 122.82 ± 21.55 , respectively ($P = 0.004$).

CALLY tertiles were also associated with chronic kidney disease and the extent of coronary artery disease. Chronic kidney disease was more frequent in the low CALLY tertile than in the medium and high tertiles (9.2%, 3.1%, and 1.5%, respectively; $P = 0.008$). The distribution of the number of diseased vessels also differed across tertiles ($P = 0.034$). In contrast, sex, left ventricular ejection fraction, body mass index, smoking status, hypertension, diabetes mellitus, hyperlipidemia, prior heart failure, Killip class, number of implanted stents, and discharge medications were not significantly different across CALLY tertiles.

Univariable associations with all-cause mortality

In univariable Cox regression analyses, higher CALLY was significantly associated with a lower risk of all-cause mortality (Table 2). When analyzed as a continuous variable, each unit increase in CALLY was associated with a lower hazard of death (HR, 0.439; 95% CI, 0.282–0.681; $P < 0.001$). When scaled per 1-standard-deviation increase in CALLY (1.412 units), the association remained significant (HR, 0.312; 95% CI, 0.168–0.582; $P < 0.001$).

Table 2. Univariable Cox regression analyses for all-cause mortality. Hazard ratios were estimated using univariable Cox proportional hazards models. For categorical variables, the lowest-risk or clinically conventional category was used as the reference group.

Table 2
Univariate Regression Analysis

Variable	HR	95% CI	P value
CALLY	0.439	(0.282, 0.681)	< 0.001
CALLY (per 1.412 SD)	0.312	(0.168, 0.582)	< 0.001
CALLY tertile: Low	Reference		
CALLY tertile: Medium vs Low	0.425	(0.240, 0.754)	0.003
CALLY tertile: High vs Low	0.166	(0.074, 0.372)	< 0.001
P for trend			< 0.001
Age (per year)	1.076	(1.048, 1.106)	< 0.001
GRACE risk score (per point)	1.015	(1.006, 1.025)	0.002
LVEF (per 1%)	0.996	(0.962, 1.031)	0.811
BMI (per kg/m ²)	1.013	(0.924, 1.111)	0.780
CRP (mg/L)	1.002	(0.994, 1.010)	0.615
Albumin (g/dL)	1.232	(0.777, 1.953)	0.376
Lymphocyte count (×10 ⁹ /L)	0.879	(0.638, 1.209)	0.427
LDL-C (mmol/L)	1.059	(0.815, 1.378)	0.667
Male sex	1.447	(0.862, 2.430)	0.162
Hypertension	1.376	(0.773, 2.449)	0.277
Diabetes mellitus	0.656	(0.361, 1.191)	0.166
Hyperlipidemia	0.257	(0.036, 1.854)	0.178
Prior heart failure	2.449	(0.979, 6.124)	0.055
Chronic kidney disease	1.414	(0.559, 3.578)	0.464
Statin use	1.665	(0.521, 5.322)	0.389
ACEI/ARB use	0.906	(0.549, 1.493)	0.697
Beta-blocker use	1.015	(0.615, 1.675)	0.953
P2Y12 inhibitor use	0.609	(0.349, 1.063)	0.081
Smoking: Never	Reference		
Smoking: Current	11.048	(5.899, 20.691)	< 0.001
Note. Univariate survival regression analysis for each variable with all-cause mortality as outcome.			

Variable	HR	95% CI	P value
Smoking: Former	1.291	(0.500, 3.328)	0.598
Killip class: I	Reference		
Killip class: II	1.787	(0.707, 4.512)	0.220
Killip class: III	3.712	(1.740, 7.919)	< 0.001
Killip class: IV	3.616	(1.119, 11.681)	0.032
Vessel disease: 2-vessel	Reference		
Vessel disease: 3-vessel	1.802	(0.941, 3.451)	0.076
Vessel disease: ≥4-vessel/other	1.836	(0.973, 3.462)	0.061
Stents: 0	Reference		
Stents: 1	1.228	(0.691, 2.182)	0.483
Stents: 2	0.512	(0.189, 1.388)	0.188
Stents: ≥3	0.908	(0.265, 3.106)	0.877
Note. Univariate survival regression analysis for each variable with all-cause mortality as outcome.			

A graded association was also observed across CALLY tertiles. Compared with patients in the low CALLY tertile, those in the medium tertile had a lower risk of all-cause mortality (HR, 0.425; 95% CI, 0.240–0.754; P = 0.003), and those in the high tertile had an even lower risk (HR, 0.166; 95% CI, 0.074–0.372; P < 0.001). The trend across tertiles was statistically significant (P for trend < 0.001).

Among other baseline variables, older age (HR per year, 1.076; 95% CI, 1.048–1.106; P < 0.001), higher GRACE risk score (HR per point, 1.015; 95% CI, 1.006–1.025; P = 0.002), current smoking compared with never smoking (HR, 11.048; 95% CI, 5.899–20.691; P < 0.001), Killip class III compared with class I (HR, 3.712; 95% CI, 1.740–7.919; P < 0.001), and Killip class IV compared with class I (HR, 3.616; 95% CI, 1.119–11.681; P = 0.032) were associated with all-cause mortality in univariable analyses.

Multivariable association between CALLY and all-cause mortality

The inverse association between CALLY and all-cause mortality remained consistent across sequential Cox proportional hazards models (Table 3). In the unadjusted model, each unit increase in CALLY was associated with a lower hazard of death (HR, 0.439; 95% CI, 0.282–0.681; P < 0.001). After adjustment for age and sex, the association remained statistically significant (HR, 0.559; 95% CI, 0.374–0.836; P = 0.005).

Table 3. Association between CALLY and all-cause mortality in sequential Cox proportional hazards models. Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: adjusted for age, sex, GRACE

score, LVEF, and BMI. Model 4 (parsimonious): adjusted for age, sex, GRACE score, LVEF, diabetes mellitus, chronic kidney disease, and multivessel disease.

Table 3
Multivariable Regression Analysis (Tiered Adjustment)

Model	HR	95% CI	P value	N	Events
Model 1: Unadjusted	0.439	(0.282, 0.681)	< 0.001	388	62
Model 2: Age + Sex	0.559	(0.374, 0.836)	0.005	388	62
Model 3: Age + Sex + GRACE + LVEF + BMI	0.567	(0.379, 0.848)	0.006	388	62
Model 4: Parsimonious adjusted	0.552	(0.368, 0.827)	0.004	388	62
Model 4: per SD (1.412)	0.432	(0.244, 0.765)	0.004	388	62
Model 4: P for tertile trend			< 0.001	388	62

Note. Unadjusted: exposure only. Minimally adjusted: Age, Sex. Model 3: Age + Sex + GRACE + LVEF + BMI. Model 4 (parsimonious): Age + Sex + GRACE + LVEF + Diabetes + CKD + Multivessel disease. Covariates were selected based on clinical relevance, change-in-estimate assessment, and collinearity screening. HR = hazard ratio; CI = confidence interval.

Further adjustment for age, sex, GRACE risk score, left ventricular ejection fraction, and body mass index yielded a similar estimate (HR, 0.567; 95% CI, 0.379–0.848; P = 0.006). In the parsimonious multivariable model adjusted for age, sex, GRACE risk score, left ventricular ejection fraction, diabetes mellitus, chronic kidney disease, and multivessel disease, CALLY remained independently associated with all-cause mortality (HR, 0.552; 95% CI, 0.368–0.827; P = 0.004). This corresponds to an approximately 45% lower hazard of death for each one-unit increase in CALLY.

When CALLY was modeled per 1-standard-deviation increase, the association was also significant in the parsimonious model (HR, 0.432; 95% CI, 0.244–0.765; P = 0.004). The tertile-based trend remained significant after multivariable adjustment (P for trend < 0.001). The proportional hazards assumption was not violated for CALLY, as assessed using Schoenfeld residuals (P = 0.704).

Dose–response and threshold analyses

Restricted cubic spline analysis showed no statistically significant evidence of departure from linearity for the association between CALLY and all-cause mortality (Fig. 2). The overall dose–response pattern suggested a predominantly inverse association across the observed range of CALLY values.

Because the CALLY distribution was right-skewed, an exploratory two-piecewise Cox regression analysis was further performed to evaluate potential threshold behavior (Table 5 and Supplemental Tables S8–S9). The AIC-minimized grid search identified an inflection point at CALLY = 3.117. In the linear Cox model using the original continuous CALLY exposure, the HR was 0.456 (95% CI, 0.307–0.677; P <

0.001). In the two-piecewise model, the association below the threshold was strongly inverse (HR, 0.378; 95% CI, 0.238–0.602; $P < 0.001$), whereas the association above the threshold was not statistically significant (HR, 1.452; 95% CI, 0.561–3.754; $P = 0.442$).

Table 5. Sensitivity analyses for the association between CALLY and all-cause mortality. Results are based on Model 4 (parsimonious adjustment).

Table 5 Threshold Effect Analysis			
Category	Metric	Estimate	P value
Model I (linear)	Fitting model using Cox proportional hazards model (linear exposure term)	HR = 0.456 (0.307 to 0.677)	< 0.001
Model II (piecewise)	Fitting model using two-piecewise linear Cox model: Threshold (K)	3.117	-
Model II (piecewise)	Effect 1 (< K)	HR = 0.378 (0.238 to 0.602)	< 0.001
Model II (piecewise)	Effect 2 (> K)	HR = 1.452 (0.561 to 3.754)	0.442
Model II (piecewise)	Effect difference (2 vs 1)	HR = 3.836 (1.147 to 12.837)	0.029
Model comparison	Log-likelihood ratio test (df = 1)	LR = 4.760	0.029
Note. Structured summary: Model I = linear exposure term; Model II = best-fitting two-piece spline at threshold K (minimum AIC over a grid from 10th–90th percentile of exposure, 50 cutpoints); effect difference = ratio of HRs above vs below K; model comparison = log-likelihood ratio test (df = 1). Bootstrap or profile-likelihood CI for threshold K is not computed; K is treated as a selected cut-point.			

The effect difference between the two slopes was statistically significant (HR, 3.836; 95% CI, 1.147–12.837; $P = 0.029$), and the two-piecewise model showed a better fit than the linear model by likelihood-ratio testing (LR = 4.760; $P = 0.029$). The identified threshold was stable across all five imputed datasets, with a mean knot of 3.117, standard deviation of 0.000, and coefficient of variation of 0.0000. However, because this threshold was derived from an exploratory data-driven search and no bootstrap or profile-likelihood confidence interval for the knot was computed, this value should not be interpreted as a clinically validated cut-off.

Subgroup analyses

Exploratory subgroup analyses were conducted to assess whether the association between CALLY and all-cause mortality differed across clinically relevant strata (Table 4). Overall, the inverse association between CALLY and mortality was directionally consistent across most subgroups.

Table 4. Stratified associations between CALLY and all-cause mortality. Hazard ratios represent the association within each subgroup. Interaction P values were calculated by adding a product term

between CALLY and the subgroup variable to the Cox model. Subgroup analyses were exploratory and were not adjusted for multiple comparisons.

Table 4
Stratified Analysis

Stratification Variable	Stratum	Sample size	HR	95% CI	P value	P for interaction
Age (years)	-	0	-	-	-	0.733
Sex	-	0	-	-	-	0.023
Female	Female	153	0.176	(0.055, 0.569)	0.004	-
Male	Male	235	0.593	(0.377, 0.932)	0.024	-
GRACE risk score	-	0	-	-	-	0.626
LVEF (%)	-	0	-	-	-	0.268
BMI (kg/m ²)	-	0	-	-	-	0.245
Smoking status	-	0	-	-	-	0.967
Never smoker	Never smoker	190	0.138	(0.030, 0.632)	0.011	-
Current smoker	Current smoker	135	0.617	(0.400, 0.950)	0.028	-
Former smoker	Former smoker	63	0.032	(0.001, 0.862)	0.041	-
Hypertension	-	0	-	-	-	0.704
No	No	116	0.486	(0.231, 1.024)	0.058	-
Yes	Yes	272	0.422	(0.246, 0.722)	0.002	-
Diabetes mellitus	-	0	-	-	-	0.547
No	No	277	0.463	(0.292, 0.736)	0.001	-
Yes	Yes	111	0.294	(0.081, 1.069)	0.063	-
Hyperlipidemia	-	0	-	-	-	0.823
No	No	368	0.449	(0.289, 0.697)	< 0.001	-
Note. Stratified analysis by covariates to assess effect modification for CALLY and all-cause mortality. P for interaction is from likelihood-ratio test comparing models with and without exposure × stratum interaction term.						

Stratification Variable	Stratum	Sample size	HR	95% CI	P value	P for interaction
Yes	Yes	20	0.355	(0.010, 12.127)	0.565	-
Prior heart failure	-	0	-	-	-	0.315
No	No	371	0.405	(0.250, 0.656)	< 0.001	-
Chronic kidney disease	-	0	-	-	-	0.702
No	No	370	0.427	(0.270, 0.676)	< 0.001	-
Killip class	-	0	-	-	-	0.479
I	I	339	0.495	(0.313, 0.783)	0.003	-
II	II	22	0.277	(0.042, 1.801)	0.179	-
III	III	20	0.305	(0.049, 1.882)	0.201	-
Number of diseased vessels	-	0	-	-	-	0.045
2-vessel	2-vessel	134	0.676	(0.387, 1.182)	0.169	-
3-vessel	3-vessel	121	0.534	(0.275, 1.039)	0.065	-
≥ 4-vessel/other	≥ 4-vessel/other	111	0.237	(0.079, 0.709)	0.010	-
Number of implanted stents	-	0	-	-	-	0.491
0	0	67	0.643	(0.304, 1.360)	0.248	-
1	1	237	0.377	(0.207, 0.688)	0.001	-
2	2	65	0.555	(0.151, 2.045)	0.376	-
Statin use	-	0	-	-	-	0.194
Note. Stratified analysis by covariates to assess effect modification for CALLY and all-cause mortality. P for interaction is from likelihood-ratio test comparing models with and without exposure × stratum interaction term.						

Stratification Variable	Stratum	Sample size	HR	95% CI	P value	P for interaction
No	No	34	0.084	(0.002, 3.179)	0.181	-
Yes	Yes	354	0.465	(0.301, 0.718)	< 0.001	-
ACEI/ARB use	-	0	-	-	-	0.263
No	No	204	0.354	(0.181, 0.694)	0.003	-
Yes	Yes	184	0.586	(0.326, 1.054)	0.074	-
Beta-blocker use	-	0	-	-	-	0.236
No	No	218	0.559	(0.335, 0.933)	0.026	-
Yes	Yes	170	0.308	(0.136, 0.695)	0.005	-
P2Y12 inhibitor use	-	0	-	-	-	0.116
No	No	82	0.669	(0.378, 1.183)	0.167	-
Yes	Yes	306	0.346	(0.189, 0.635)	< 0.001	-
Note. Stratified analysis by covariates to assess effect modification for CALLY and all-cause mortality. P for interaction is from likelihood-ratio test comparing models with and without exposure × stratum interaction term.						

A nominal interaction was observed by sex (P for interaction = 0.023). The association appeared stronger among female patients (HR, 0.176; 95% CI, 0.055–0.569; P = 0.004) than among male patients (HR, 0.593; 95% CI, 0.377–0.932; P = 0.024). A nominal interaction was also observed according to the number of diseased vessels (P for interaction = 0.045). The association was strongest among patients with ≥ 4-vessel or other complex disease (HR, 0.237; 95% CI, 0.079–0.709; P = 0.010), whereas the estimates were attenuated among patients with 2-vessel disease (HR, 0.676; 95% CI, 0.387–1.182; P = 0.169) and 3-vessel disease (HR, 0.534; 95% CI, 0.275–1.039; P = 0.065).

No statistically significant interactions were observed for age, GRACE risk score, left ventricular ejection fraction, body mass index, smoking status, hypertension, diabetes mellitus, hyperlipidemia, prior heart failure, chronic kidney disease, Killip class, number of implanted stents, statin use, ACEI/ARB use, beta-blocker use, or P2Y12 inhibitor use. Given the moderate sample size, limited number of events, sparse data in several strata, and absence of multiplicity adjustment, all subgroup findings should be considered exploratory.

Sensitivity analyses

The primary association was robust across prespecified sensitivity analyses. In the pooled multivariable Cox regression across five imputed datasets, the results were virtually identical across imputations, with a pooled HR of 0.552 (95% CI, 0.368–0.827; $P = 0.004$), confirming negligible between-imputation variability (Supplemental table 5).

After winsorizing CALLY at the 1st and 99th percentiles, corresponding to bounds of 0.048 and 7.086, the association between CALLY and all-cause mortality remained statistically significant and was not materially attenuated (HR, 0.456; 95% CI, 0.307–0.677; $P < 0.001$). This finding indicates that the observed association was not driven by extreme CALLY values.

The association also remained robust after excluding early events occurring on or before the 5th percentile of observed event times. After exclusion of 4 early deaths occurring within 1.78 months, the analytic sample was reduced from 388 to 379 patients. In this sensitivity analysis, higher CALLY remained significantly associated with lower all-cause mortality (HR, 0.357; 95% CI, 0.226–0.564; $P < 0.001$), supporting the robustness of the findings to potential reverse causation (Supplemental table 6, 7).

E-value analysis further supported the robustness of the primary association to unmeasured confounding (Supplemental table 3). For the parsimonious adjusted model, the E-value was 3.810 for the point estimate and 2.290 for the confidence interval limit closest to the null. Thus, an unmeasured confounder would need to be associated with both CALLY and all-cause mortality by a risk ratio of at least 2.29-fold, conditional on measured covariates, to fully explain away the observed association.

Discussion

In this single-center retrospective cohort of 388 patients with ACS undergoing PCI, a higher baseline C-reactive protein–albumin–lymphocyte index was independently associated with a lower risk of long-term all-cause mortality. This association remained statistically significant after adjustment for age, sex, GRACE risk score, left ventricular ejection fraction, diabetes mellitus, chronic kidney disease, and multivessel disease. The finding was consistent when CALLY was modeled per standard-deviation increment and across tertiles, and was further supported by sensitivity analyses using winsorized CALLY values, exclusion of early deaths, and imputation-based models (Supplemental table 4). Although an exploratory threshold analysis suggested a potential inflection point, restricted cubic spline analysis did not show significant departure from linearity; therefore, CALLY should be interpreted primarily as a continuous prognostic marker rather than as a validated categorical cut-off.

The main finding is clinically plausible and consistent with the broader concept that residual risk after ACS is not fully captured by anatomical revascularization success or traditional cardiovascular risk factors alone. Despite contemporary PCI techniques, antithrombotic therapy, lipid-lowering treatment, and guideline-directed secondary prevention, patients with ACS remain vulnerable to late mortality and

recurrent adverse events [12, 13]. Established risk tools such as the GRACE score are useful for clinical risk stratification, but they do not fully incorporate the combined effects of systemic inflammation, nutritional reserve, and immune competence [14, 15]. In this context, CALLY may provide a simple summary measure of host vulnerability, reflecting biological domains that are relevant to recovery after ACS and PCI.

To our knowledge, direct evidence regarding the prognostic role of CALLY in patients with ACS undergoing PCI remains limited. Previous studies of CALLY have mainly focused on malignant disease and other non-coronary populations. For example, Zhao et al. reported that CALLY provided prognostic information in liver cancer beyond the TNM staging system [16]. Although the disease context differs substantially from ACS, the underlying rationale is similar: a composite marker integrating inflammation, nutrition, and immune status may better capture systemic physiological reserve than any single laboratory parameter. Our study extends this concept to a post-PCI ACS population and suggests that a lower CALLY level may identify patients with a higher long-term mortality risk.

The present results also align with prior evidence supporting the prognostic value of related immune-inflammatory and nutritional indices in coronary artery disease. In patients with acute myocardial infarction treated with PCI, Balaban Koçaş et al. showed that the neutrophil-to-lymphocyte ratio, systemic immune-inflammation index, and prognostic nutritional index were associated with adverse clinical outcomes [17]. More recently, Karakurt and Karakurt reported that the global immune-nutrition-inflammation index predicted in-hospital mortality among patients with ST-segment elevation myocardial infarction [18]. Beyond these composite indices, extensive literature has linked elevated C-reactive protein, hypoalbuminemia, and lymphopenia individually to poor outcomes in cardiovascular disease [19–22]. CALLY differs from many existing indices by combining a positive acute-phase reactant, a negative acute-phase and nutritional marker, and an immune-cell component into a single ratio. This structure may explain why lower CALLY values were associated with substantially higher mortality in our cohort.

Several biological mechanisms may underlie the observed association. Elevated C-reactive protein reflects systemic inflammatory activation, which is closely related to endothelial dysfunction, plaque vulnerability, thrombotic tendency, and adverse ventricular remodeling after myocardial injury [19, 20]. Albumin is not only a marker of nutritional status and hepatic synthetic capacity but also has antioxidant, anti-inflammatory, and antithrombotic properties; lower albumin levels may therefore indicate both reduced physiological reserve and a more severe inflammatory milieu [21, 23]. Lymphopenia may reflect stress-induced immune dysregulation, neurohormonal activation, and impaired adaptive immune responses, all of which have been associated with worse outcomes in cardiovascular and critical illness settings [22, 24]. A low CALLY value thus represents the convergence of heightened inflammation, impaired nutritional reserve, and immune suppression. These processes may act synergistically to increase susceptibility to recurrent ischemic events, heart failure progression, infection, frailty-related decline, and non-cardiovascular death.

An important feature of our study is that the association persisted after adjustment for GRACE risk score and other clinically relevant covariates. GRACE is a validated and widely used prognostic tool in ACS [14, 15], and adjustment for GRACE reduces the likelihood that the observed association is merely a reflection of conventional ACS severity. The persistence of the CALLY–mortality association after accounting for GRACE, left ventricular ejection fraction, renal dysfunction, diabetes, and multivessel disease suggests that CALLY may capture a distinct dimension of risk. Nevertheless, our study did not evaluate incremental predictive performance using C-statistics, calibration metrics, net reclassification improvement, or integrated discrimination improvement. Accordingly, the findings should not be interpreted as evidence that CALLY improves clinical prediction beyond established models. Rather, they support CALLY as a biologically plausible candidate marker that warrants formal predictive validation.

The dose–response analyses require cautious interpretation. Restricted cubic spline analysis did not detect significant nonlinearity, supporting an approximately monotonic inverse association between CALLY and mortality across the observed exposure range. The exploratory two-piecewise analysis identified a data-driven inflection point at 3.117 and suggested attenuation of the association above this value. However, relatively few patients had high CALLY values, and no bootstrap or profile-likelihood confidence interval was calculated for the knot. Therefore, this threshold should not be used as a clinical cut-off. Future studies with larger sample sizes and external validation cohorts should examine whether a reproducible threshold exists or whether CALLY is best modeled continuously.

From a clinical perspective, CALLY has several attractive features. It is derived from routinely available admission laboratory tests and can be calculated without additional cost, specialized equipment, or complex procedures. If externally validated, it may help identify patients who remain at high risk despite successful PCI and standard secondary prevention. Such patients might benefit from closer follow-up, optimization of nutritional status, more intensive management of inflammatory comorbidities, or enrollment in structured cardiac rehabilitation programs. However, these implications remain speculative. Current evidence is insufficient to recommend CALLY-guided treatment decisions, and interventional studies would be required to determine whether modifying the inflammatory–nutritional–immune profile improves outcomes.

This study has several methodological strengths. First, the analysis focused on a clinically relevant and well-defined ACS population undergoing PCI. Second, the primary model used a parsimonious adjustment strategy to reduce overfitting in the context of a moderate number of events. Third, missing data were handled using imputation, and pooled estimates were consistent across completed datasets. Fourth, multiple sensitivity analyses supported the robustness of the main finding, including winsorization of extreme CALLY values and exclusion of early deaths. Finally, E-value analysis provided a quantitative assessment of the potential impact of unmeasured confounding, indicating that a moderately strong unmeasured confounder would be required to fully explain away the observed association.

Several limitations should also be acknowledged. First, this was a single-center retrospective study, which limits generalizability and cannot eliminate selection bias. Second, the sample size was moderate and the number of deaths was limited, reducing statistical power for subgroup analyses and increasing the possibility of model instability. The subgroup findings should therefore be considered exploratory. Third, although the parsimonious model adjusted for major clinical predictors, residual confounding from unmeasured factors such as frailty, socioeconomic status, inflammatory or infectious comorbidities, procedural complexity, medication adherence, and post-discharge treatment intensity cannot be excluded. Fourth, the observational design precludes causal inference. Fifth, only baseline CALLY was assessed; dynamic changes in inflammation, nutrition, and immune status after PCI were not available. Sixth, cause-specific mortality and nonfatal cardiovascular events were not analyzed, limiting mechanistic interpretation. Seventh, the study did not assess incremental predictive performance beyond established risk scores using discrimination, calibration, or reclassification metrics. Finally, no external validation cohort was available, and the findings require confirmation in larger multicenter prospective studies.

Conclusions

The higher baseline CALLY was independently associated with lower long-term all-cause mortality among patients with ACS undergoing PCI. This association was consistent across multiple modeling strategies and sensitivity analyses, suggesting that CALLY may reflect an important dimension of inflammatory, nutritional, and immune vulnerability after ACS. However, given the retrospective single-center design and the lack of external validation or incremental predictive assessment, CALLY should be regarded as a hypothesis-generating prognostic marker rather than a tool ready for clinical decision-making.

Declarations

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This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request, subject to institutional and ethical approval.

Ethics Statement

This study was approved by the Ethics Committee of the First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine (approval number: K2020-020). Given the retrospective nature of the study

and the use of de-identified clinical data, the Ethics Committee waived the requirement for written informed consent.

Conflict of Interest

There are no conflicting interests.

Author Contributions

Conceptualization: Ying-Pu Guo, Chi Chen; Data curation: Ying-Pu Guo; Formal analysis: Chi Chen; Methodology: Tao Zheng; Writing - original draft: Ying-Pu Guo; Writing - review and editing: Tao Zheng; Supervision: Tao Zheng.

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Figures

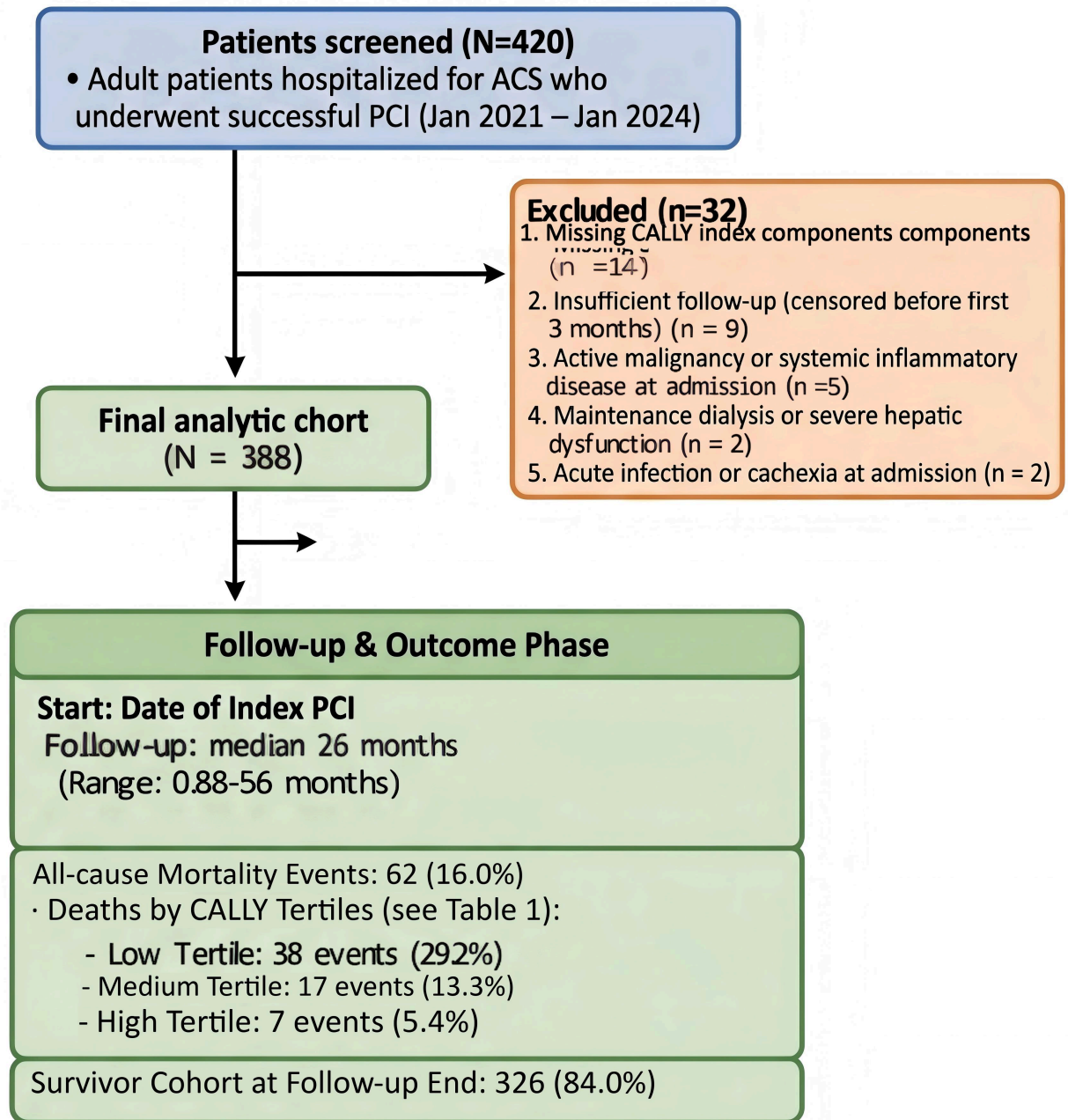
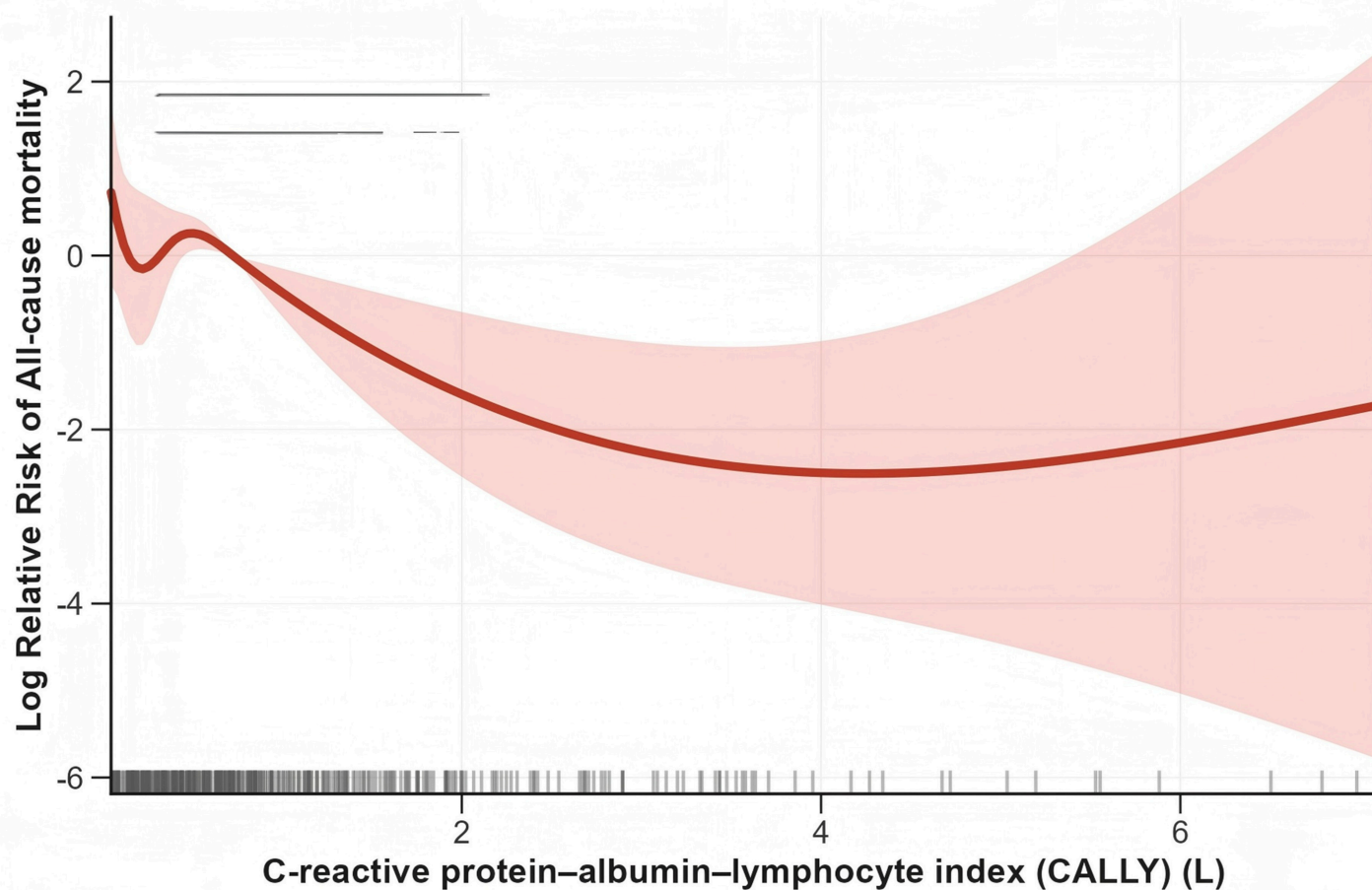


Figure 1

Study flow diagram.

All-cause mortality vs C-reactive protein–albumin–lymphocyte index (CALLY)

Adjusted for covariates | n = 387



Pointwise 95% CI for centered log-HR contrast; RCS-style natural splines + Cox PH; centered at median exposure.

Figure 2

Smooth-curve analysis of the association between CALLY and all-cause mortality using restricted cubic splines. The solid line represents the hazard ratio; the shaded area represents the 95% confidence interval. The reference value was set at the median CALLY.

Supplementary Files

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- [SupplementalTablesV2.docx](#)