

Association and Predictive Value of C-Reactive Protein-Lymphocyte-Albumin (CALLY) Index with Cardiovascular Disease in Patients with Cardiovascular–Kidney–Metabolic Syndrome Stage 3

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Background: Cardiovascular–kidney–metabolic (CKM) syndrome stage 3 is a high-risk condition for cardiovascular disease (CVD), characterized by intertwined metabolic dysregulation, chronic inflammation, and immune dysfunction. This study aimed to evaluate the association and predictive value of the C-reactive protein–lymphocyte–albumin (CALLY) index for CVD in this population.

Methods: In a retrospective cohort of patients with CKM stage 3, the CALLY index was calculated from baseline laboratory data. Its association with incident CVD was assessed using multivariable Cox proportional hazards models. To test robustness, sensitivity and subgroup analyses were performed. Predictive performance was evaluated by time-dependent receiver operating characteristic (ROC) analysis, integrated discrimination improvement (IDI), and net reclassification improvement (NRI).

Results: Among 826 patients followed for a median of 51 months, a higher CALLY index was independently associated with a lower risk of CVD (adjusted hazard ratio 0.37, 95% CI: 0.25–0.55). The association remained robust in sensitivity and subgroup analyses. The index demonstrated superior discrimination for CVD (area under the curve 0.806, 95% CI: 0.774–0.838). The CALLY index provided significant incremental predictive value compared to using its individual components (CRP, albumin, or lymphocyte count alone).

Conclusion: A lower CALLY index is independently associated with an increased risk of CVD in patients with CKM stage 3 and exhibits robust predictive performance. This readily available composite biomarker may aid in cardiovascular risk stratification for this high-risk group.

Keywords: cardiovascular disease, metabolic dysfunction, inflammation, biomarker

Background

In 2023, the American Heart Association (AHA) proposed a chronic condition characterized by the interaction among metabolic risk factors, chronic kidney disease (CKD), and the cardiovascular system, termed the cardiovascular kidney metabolic (CKM) syndrome.¹ The underlying pathophysiological mechanisms of CKM syndrome are mainly characterized by metabolic dysregulation, chronic inflammation, and insulin resistance which are closely linked to the onset of cardiovascular diseases (CVD).¹ In recent years, the prevalence of CKM has risen sharply worldwide, driven by increasing rates of diabetes, obesity, and aging. Based on the 2023 AHA framework, CKM disorder is categorized into stages 0 to 4. Stage 3 represents a pivotal transition in disease progression, characterized by early but potentially reversible target organ injury such as subclinical atherosclerosis, proteinuria, and early cardiac remodeling.² Without timely intervention, disease progression can accelerate rapidly. Earlier research has shown that individuals in CKM stage

3 face a markedly greater likelihood of experiencing negative cardiovascular outcomes, such as acute coronary syndrome (ACS), heart failure (HF), and stroke, in comparison to those in stages 0 through.^{3,4}

Cardiovascular events are closely associated with immune activation, nutritional status, and chronic low-grade inflammation. These factors play a central role in the pathogenesis of CVD.⁵ Prolonged activation of the IL-6 receptor pathway promotes the release of inflammatory mediators such as IL-6 and C-reactive protein (CRP). This process accelerates atherosclerosis and vascular remodeling.⁶ Aging and obesity, which are two hallmark features of CKM syndrome. They further exacerbate metabolic dysregulation and inflammation by inducing immune cell infiltration and systemic inflammatory responses.^{7,8} In CKD, persistent inflammation and immune activation similarly contribute to adverse cardiovascular outcomes.⁹ As a core pathological component of CKM, kidney injury shares overlapping mechanisms with metabolic and cardiovascular dysfunction, including oxidative stress and systemic inflammation. Previous studies have shown that higher systemic inflammation response index (SIRI) and neutrophil-to-albumin ratio (NPAR) levels are associated with a significantly higher risk of adverse cardiovascular and renal events in CKM patients.¹⁰ In clinical practice, cardiovascular risk assessment in patients with CKM, including stage 3, currently relies on established prediction models. Traditional tools such as the Framingham Risk Score (FRS) and the Pooled Cohort Equations (PCE) are primarily based on demographic and conventional cardiometabolic factors.^{1,11} More recent integrated models, such as the American Heart Association's PREVENT equations, have begun to incorporate kidney function (estimated glomerular filtration rate) to better reflect the multisystem nature of CKM.^{1,12} However, these models are not designed to capture the dynamic interplay of inflammation, immune response, and nutritional status. These are key drivers of cardiovascular pathogenesis in CKM. Consequently, there remains a lack of simple and reliable biomarkers that can simultaneously reflect inflammatory, immune, and nutritional status for cardiovascular risk assessment in CKM stage 3. This underscores an urgent need for composite biomarkers that integrate these interacting mechanisms to improve early risk stratification in CKM stage 3. Traditional predictors, such as BMI, lipid profile, and blood glucose level, are limited by their single-dimensional nature and fail to capture the complex multisystem interactions characteristic of CKM.

The CALLY index, a novel composite marker, combines CRP, albumin, and lymphocyte count to reflect the overall inflammatory, immune, and nutritional status, thereby serving as an integrated indicator of systemic health. Previous studies have shown that lower CALLY levels are independently associated with higher risks of cardiovascular and cerebrovascular events, as well as increased all-cause mortality in various populations.^{13–15} The diseases in which CALLY has been linked to cardiovascular and all-cause mortality are typically characterized by chronic inflammation and metabolic dysregulation. These pathophysiological features closely resemble those observed in CKM stage.^{13,16} These findings support further exploration of the link between CALLY and cardiovascular outcomes in CKM stage 3, as well as the potential of CALLY to identify early cardiovascular risk in this population.

Although several studies have investigated the link between CALLY and cardiovascular outcomes, its relevance and predictive value in the high-risk CKM stage 3 population remain uncertain. Patients with CKM stage 3 often present with concomitant metabolic dysregulation, persistent inflammation, and early target organ injury.^{17,18} These factors collectively increase the likelihood of cardiovascular disorders and poor prognosis. To enable early risk alerting and targeted intervention, clarifying the prognostic utility of CALLY in CKM3 is essential. Therefore, the present study aimed to investigate the association between the CALLY index and cardiovascular risk in patients with CKM stage 3. In addition, we sought to evaluate the predictive value of the CALLY index for cardiovascular outcomes in this population. We hypothesized that a lower CALLY index would be independently associated with an increased risk of cardiovascular events among individuals with CKM stage 3.

Methods

Study Data Source

This single-center retrospective cohort study was conducted at the Second Affiliated Hospital of Kunming Medical University. Data were obtained from patients who were first diagnosed with CKM stage 3 during inpatient or out patient visits at KMU between 2016 and 2025.

Study Population

All patient identifiers, including identification numbers and registration codes, were removed to ensure complete anonymity and data standardization. CKM stage 3 was defined using a stratified diagnostic approach based on the 2023 AHA framework.¹ The diagnosis was primarily established by the presence of at least one of the following three objective criteria, indicating subclinical target organ damage or very high-risk status: 1. Subclinical ASCVD: Identified by imaging evidence of atherosclerosis, including a coronary artery calcium (CAC) score ≥ 1 on non-contrast CT, or the presence of atherosclerotic plaque in the carotid, abdominal aortic, or iliac-femoral arteries as detected by ultrasound or CT angiography. 2. Subclinical HF: Determined by elevated cardiac biomarkers: NT-proBNP ≥ 125 pg/mL and sex-specific high-sensitivity troponin thresholds (hs-troponin T ≥ 14 ng/L for women and ≥ 22 ng/L for men, or hs-troponin I ≥ 10 ng/L for women and ≥ 12 ng/L for men). 3. CKD at stage G4 (eGFR 15–29 mL/min/1.73m²) or G5 (eGFR < 15 mL/min/1.73m²), or classification as “very high risk CKD” per KDIGO guidelines (defined as CKD stage G4 with UACR > 300 mg/g, or CKD stage G5). Furthermore, as a supplementary criterion to ensure a uniformly high-risk cohort, all included patients were also required to have a predicted 10-year CVD risk $\geq 20\%$, calculated using the PREVENT equations.¹¹ The risk calculation was based on the following patient variables: age, sex, smoking status, systolic blood pressure, lipid profiles, diabetes status, and estimated glomerular filtration rate (eGFR). Exclusion criteria were as follows: 1. Diagnosis of malignant tumor, acute infection, or acute kidney injury within three months before or after the first diagnosis; 2. Absence of laboratory examinations within 90 days before or after the diagnosis; 3. Missing essential information, including demographic data, chronic disease history, outcome variables, or key exposure indicators (CRP, lymphocyte count, or albumin). Furthermore, individuals who were lost to follow-up, died from any cause, had a documented history of clinical cardiovascular disease prior to the CKM stage 3 diagnosis date, or developed CVD within six months after enrollment were excluded. After strict screening, 826 eligible patients were selected for the final analysis, depicted in Figure 1. These exclusion criteria, applied relative to the baseline diagnosis date of CKM stage 3, were implemented to ensure that the CALLY index measured a stable chronic inflammatory-nutritional state and to establish a cohort suitable for assessing the risk of incident cardiovascular events.

Variables

The dataset was constructed from demographic details, medical history, vital signs, and laboratory results. Specifically, we extracted sex, age, BMI, histories of smoking, alcohol use, hypertension, and diabetes, alongside systolic/diastolic blood pressure. Laboratory data comprised hematological (Hb, WBC, neutrophil, lymphocyte counts), renal (Scr, eGFR, uric acid),

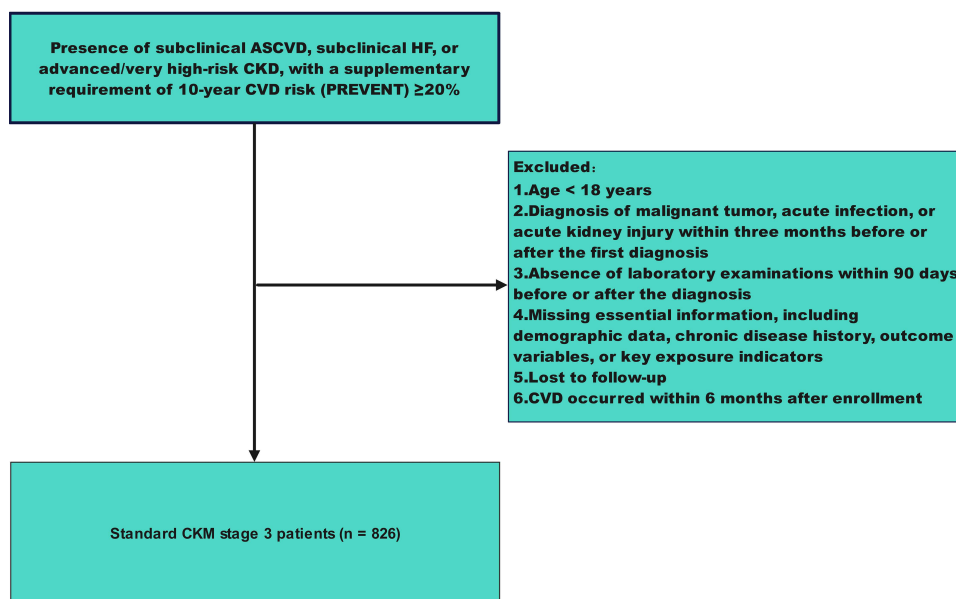


Figure 1 Flow chart for screening patients with CKM stage 3.

hepatic/nutritional (albumin), Coagulation function (APTT and fibrinogen), and metabolic parameters (lipid profile, fasting glucose for TyG index calculation). The CALLY index was computed as $ALB (g/L) \times Lym (10^9/L) / (CRP [mg/L] \times 10)$. The proportion of missing data for each variable is reported in [Supplementary Table S1](#). Variables with <5% missingness were analyzed using complete-case analysis, those with 5–20% were imputed using multiple imputation by chained equations (MICE, five iterations), and variables with >20% missingness were excluded from analysis. These thresholds were selected based on methodological recommendations for handling missing data in clinical and epidemiological research.¹⁹ The proportion of missing data for each variable are summarized in [Supplementary Table S1](#).

Outcomes

Follow-up began on the date when CKM stage 3 was first confirmed by clinical or diagnostic evaluation during hospitalization or outpatient visits within our hospital system and continued until the occurrence of a cardiovascular event or the predetermined study endpoint (September 1, 2025), whichever occurred first. Cardiovascular events were identified based on the first clinical encounter (hospitalization or outpatient visit) following the CKM stage 3 diagnosis where a new cardiovascular disease was recorded. The diagnosis was confirmed by extracting the explicit physician diagnosis documented in the corresponding clinical notes (eg, discharge summary, admission note, or outpatient progress note) and cross-referencing it with supporting objective evidence from the same episode, including imaging reports and laboratory results. Events were classified according to the relevant ICD-10 codes (I00–I09, I11, I13, and I20–I51).²⁰

Statistical Analysis

Descriptive statistics were used to summarize population characteristics and variable distributions. Normally distributed continuous variables were expressed as mean \pm standard error, while skewed data were presented as median (interquartile range). Categorical variables were presented as frequencies and percentages. Patients were divided into low and high groups based on the median value of the CALLY index. This dichotomization facilitated clinical interpretation and balanced group comparisons. Comparisons between groups were conducted with an independent-sample *t*-test for continuous data following a normal distribution, the Mann–Whitney *U*-test for skewed variables, and a chi-square test for categorical data. Statistical significance was defined as a two-tailed *P* value < 0.05. Survival rates and cumulative incidence of events were compared using Kaplan–Meier survival analysis. The association between the CALLY index and CVD risk was evaluated using multivariable Cox proportional hazards models, where the index was analyzed both as a categorical variable (median-based grouping) and as a continuous variable to preserve information and minimize bias from arbitrary categorization. Restricted cubic spline (RCS) curves were applied to illustrate the dose–response relationship between continuous CALLY levels and cardiovascular events and to examine linearity. In addition, a sensitivity analysis excluding participants with diabetes mellitus was performed to minimize potential reverse causality. Subgroup analyses were stratified by age, gender, obesity, smoking, alcohol consumption, hypertension, diabetes, and eGFR to examine the consistency of associations and potential interactions between CALLY and CVD across subgroups. To assess predictive performance, ROC curves were generated to assess how well CALLY discriminates cardiovascular events. The incremental predictive value of CALLY compared with individual biomarkers (albumin, lymphocytes, CRP) was evaluated using the integrated discrimination improvement (IDI) and net reclassification improvement (NRI) indices. A post-hoc power analysis based on the Schoenfeld approximation indicated that approximately 66 events (≈ 247 participants given the observed event rate) would be required to achieve 80% power at $\alpha = 0.05$ for the observed HR = 0.50. Our study included 221 events, providing ample statistical power. All statistical analyses were conducted using R Studio (version 4.4.3).

Result

Baseline Demographic and Clinical Characteristics

In total, 826 individuals diagnosed with CKM stage 3 were analyzed. The CALLY index was stratified by the median value into two categories, with the lower group defined as ≤ 1.60 ($n = 413$) and the higher group defined as > 1.60 ($n = 413$). The overall distribution of CALLY was 1.60 (0.81, 2.76). Baseline demographic and clinical features categorized by median CALLY are presented in [Table 1](#). Over a median follow-up period of 51 months, 221 cases of cardiovascular

Table 1 Baseline Characteristics Table Using CALLY Median Grouping

Group	Overall (n = 826)	Low (n = 413)	High (n = 413)	P-value
Age (mean (SD))	54.70±19.51	57.48±21.47	51.91±16.91	<0.001
Sex (%)				0.889
Male	321 (38.9)	160 (38.7)	161 (39.0)	
Female	505 (61.1)	253 (61.3)	252 (61.0)	
Obesity (%)				0.626
No	418 (50.6)	213 (51.6)	205 (49.6)	
Yes	408 (49.4)	200 (48.4)	208 (50.4)	
Smoke status (%)				0.353
Never	337 (40.8)	173 (41.9)	164 (39.7)	
Former	255 (30.9)	118 (28.6)	137 (33.2)	
Current	234 (28.3)	122 (29.5)	112 (27.1)	
Drink status (%)				0.414
Never	255 (30.9)	117 (28.3)	138 (33.4)	
Former	191 (23.1)	98 (23.7)	93 (22.5)	
Current	380 (46.0)	198 (47.9)	182 (44.1)	
Hypertension (%)				<0.001
No	518 (62.7)	226 (54.7)	292 (70.7)	
Yes	308 (37.3)	187 (45.3)	121 (29.3)	
Diabetes (%)				0.001
No	616 (74.6)	286 (69.2)	330 (79.9)	
Yes	210 (25.4)	127 (30.8)	83 (20.1)	
CVD Status (%)				<0.001
No	605 (73.2)	232 (56.2)	373 (90.3)	
Yes	221 (26.8)	181 (43.8)	40 (9.7)	
Time (median (IQR))	51.00 (22.00, 83.00)	48.00 (20.00, 79.00)	58.00 (25.00, 86.00)	0.017
BMI (mean (SD))	24.87±3.82	24.83±4.03	24.90±3.60	0.775
DBP (mean (SD))	74.79±11.11	75.15±12.65	74.44±9.32	0.357
SBP (mean (SD))	122.00±18.13	125.85±21.55	118.15±12.83	<0.001
NEU (median (IQR))	4.21 (3.15, 5.86)	4.85 (3.61, 6.40)	3.79 (3.00, 5.00)	<0.001
Lymph (median (IQR))	1.81 (1.40, 2.25)	1.56 (1.20, 1.95)	2.01 (1.68, 2.47)	<0.001
PLT (median (IQR))	224.00 (182.25, 270.75)	216.00 (173.00, 268.00)	229.00 (189.00, 273.00)	0.008
Alb (mean (SD))	40.60±5.26	38.76±5.41	42.44±4.41	<0.001
APTT (mean (SD))	30.46±5.32	31.27±6.44	29.63±3.69	<0.001
TT (mean (SD))	18.85±9.75	19.00±13.54	18.69±2.46	0.644
PT (mean (SD))	11.61±1.81	11.87±2.25	11.34±1.16	<0.001
FIB (mean (SD))	3.45±0.96	3.65±1.00	3.25±0.88	<0.001
WBC (median (IQR))	6.77 (5.60, 8.40)	7.20 (5.80, 8.84)	6.52 (5.44, 7.99)	<0.001
Hb (mean (SD))	130.89±20.79	125.68±22.24	136.10±17.80	<0.001
CRP (median (IQR))	4.26 (3.18, 7.29)	7.28 (5.49, 11.48)	3.31 (2.21, 3.68)	<0.001
TCHO (median (IQR))	4.74 (3.88, 5.69)	4.68 (3.73, 5.71)	4.80 (4.04, 5.66)	0.106
UA (median (IQR))	305.00 (238.13, 388.49)	326.72 (241.81, 413.00)	293.76 (236.07, 362.40)	0.006
Scr (median (IQR))	62.28 (49.73, 87.50)	65.00 (50.00, 111.00)	61.00 (49.00, 77.00)	0.001
eGFR (median (IQR))	100.81 (79.09, 120.36)	96.30 (54.00, 120.95)	102.70 (92.32, 119.96)	<0.001
TyG (mean (SD))	8.65±0.61	8.73±0.65	8.57±0.55	<0.001
LDL-C (median (IQR))	2.69 (2.10, 3.30)	2.55 (2.00, 3.21)	2.78 (2.26, 3.40)	0.001
HDL-C (mean (SD))	1.41±0.40	1.35±0.42	1.46±0.36	<0.001

Note: Data are presented as mean ± standard deviation, median (IQR), or n (%). P-values were derived from independent t-tests, Mann-Whitney U-tests, or chi-square tests, as appropriate. Statistically significant P-values ($P < 0.05$) are presented in bold font.

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; IQR, interquartile range; CVD, cardiovascular disease; NEU, neutrophil count; Lymph, lymphocyte count; PLT, platelet count; Alb, albumin; APTT, activated partial thromboplastin time; TT, thrombin time; PT, prothrombin time; FIB, fibrinogen; WBC, white blood cell count; Hb, hemoglobin; CRP, C-reactive protein; TCHO, total cholesterol; UA, uric acid; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; TyG, triglyceride-glucose index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

events were recorded, representing 26.8% of the cohort. A markedly lower rate of cardiovascular events was observed among individuals with higher CALLY levels than those with lower levels. In terms of comorbidities, the rates of hypertension and diabetes mellitus were notably reduced in the high CALLY group compared to the low CALLY group, with no significant differences observed between the groups for obesity, smoking, or alcohol consumption. For other laboratory parameters, individuals in the low CALLY group had significantly higher neutrophil counts, fibrinogen levels, and LDL-C, while hemoglobin (Hb) and HDL-C were lower in comparison to those in the high CALLY group. As shown in Table 1, patients in the low CALLY group were significantly older and had a shorter median follow-up time compared to the high CALLY group. The age difference aligns with the known interplay between aging and the inflammatory-nutritional status reflected by CALLY. The shorter follow-up in the low CALLY group is consistent with the earlier occurrence of the primary endpoint (cardiovascular events) in this group. To ensure the independent association of CALLY with CVD risk, age was adjusted for as a continuous variable in all subsequent multivariable survival analyses. These findings indicate that an elevated CALLY index correlates with a lower risk of cardiovascular events among CKM stage 3 patients.

Relationship Between CALLY and Cardiovascular Disease in CKM Stage 3

Considering the potential influence of follow-up duration on outcome occurrence, Kaplan–Meier analysis was conducted to compare the incidence of cardiovascular disease in the low and high CALLY groups. As illustrated in Figure 2, The cumulative incidence of CVD was notably lower in the high CALLY group compared to the low CALLY group. This difference was statistically significant, with a log-rank P value of less than 0.05.

Subsequently, multivariable Cox regression analysis was conducted to further assess the link between the CALLY index and cardiovascular outcomes. Prior to multivariable modeling, univariate Cox proportional hazards analyses were performed to determine the factors that have a significant relationship with the outcome. Demographic and clinical variables that were clinically relevant or statistically significant were then entered into multicollinearity diagnostics. Variables with a variance inflation factor (VIF) < 5 were considered free of serious multicollinearity and were included as covariates in the multivariable Cox model. As shown in Figure 3, the final adjusted model incorporated demographic factors (age, sex, BMI, obesity, systolic and diastolic blood pressure), medical history (CVD, hypertension, diabetes mellitus, smoking, and alcohol consumption), and laboratory parameters (hemoglobin, platelet count, neutrophil count, total cholesterol, low-density lipoprotein cholesterol, uric acid, serum creatinine, fibrinogen, and triglyceride–glucose (TyG) index).

After adjustment for these covariates, a significant inverse association was observed between CALLY and the risk of cardiovascular events. As summarized in Figure 4, the multivariable-adjusted hazard ratio for cardiovascular events in the high-level CALLY group was 0.37 (95% CI: 0.25–0.55), indicating a markedly lower risk compared with the low-level group. When CALLY was analyzed as a continuous variable, each one-unit increase was associated with an approximately 47% reduction in the risk of cardiovascular events among patients with CKM stage 3. To minimize potential reverse causality, a sensitivity analysis was conducted by excluding individuals with diabetes mellitus. As shown in Figure 4, the results remained consistent with the primary analysis, demonstrating that both categorical and continuous CALLY values were independently and inversely associated with CVD risk, even after adjustment for multiple confounding variables.

Restricted Cubic Splines and Cardiovascular Outcomes in CKM Stage 3

As shown in Figure 5, a RCS analysis was applied to examine the connection between the CALLY index and CVD risk, while also investigating the possible linearity of this association. The covariates incorporated into the model were chosen according to the results of multicollinearity analysis. The findings showed a significant inverse association between CALLY levels and the risk of new-onset CVD ($P < 0.001$). The inflection point corresponding to a HR of 1 was identified at $CALLY = 1.64$, indicating that when the CALLY value exceeded 1.64, the risk of incident CVD decreased progressively with increasing CALLY levels. Additionally, the nonlinearity examination produced a P-value > 0.05 , indicating that the association between CALLY and incident CVD was predominantly linear.

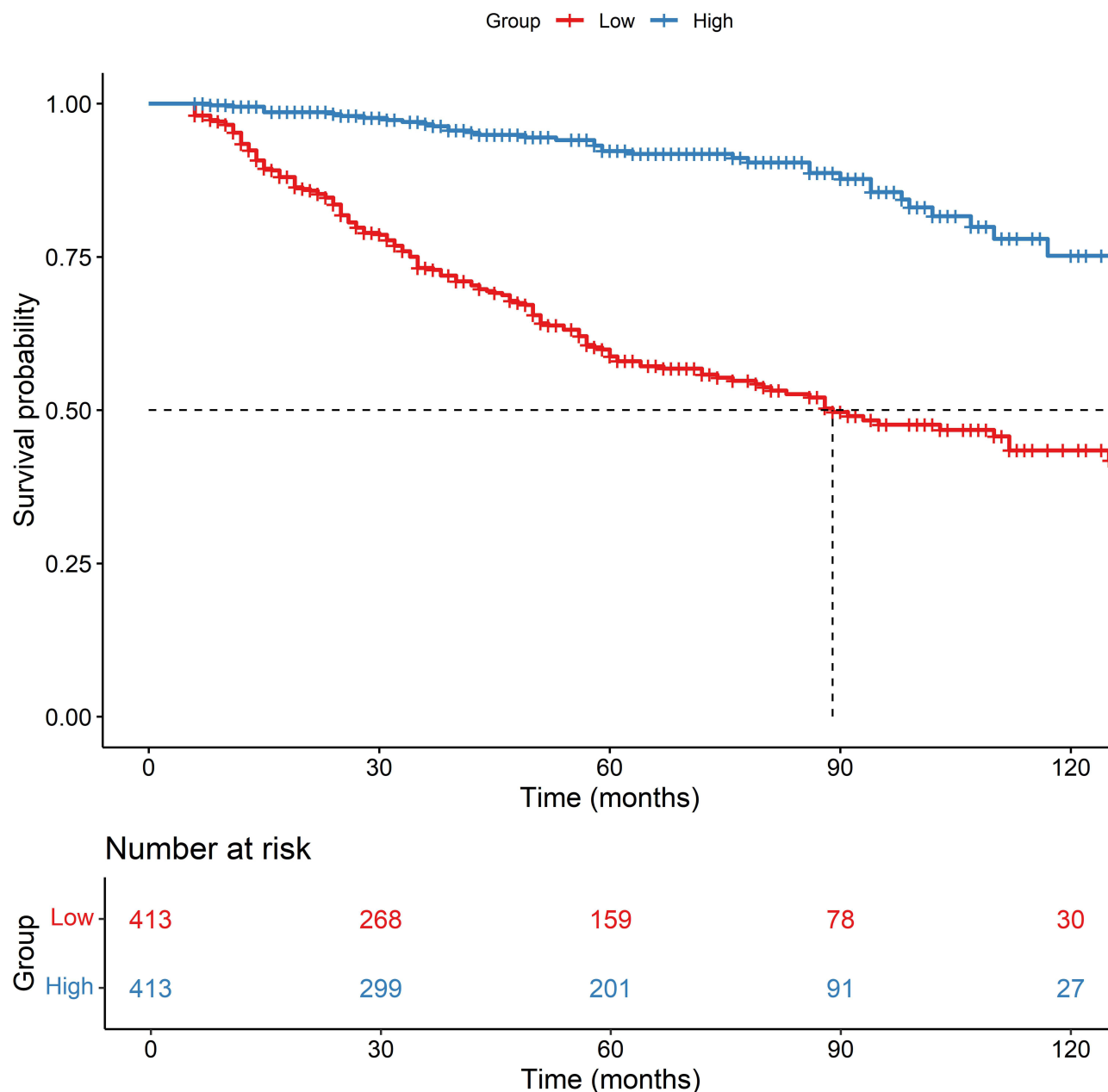


Figure 2 Kaplan-Meier analysis of Cardiovascular disease in CALLY Median groups.

Note: Log-rank $P < 0.001$.

Subgroup Analyses

Figure 6 illustrates the results of subgroup analyses carried out to explore the consistency of the association between the CALLY index and the occurrence of cardiovascular events across different patient strata. Following adjustment for potential confounders, a significant inverse association between CALLY and CVD risk was consistently observed in most subgroups. Statistically significant interaction effects were identified for a history of diabetes mellitus and for estimated glomerular filtration rate categories (eGFR >60 vs ≤ 60 mL/min/1.73m²), with both P values for interaction < 0.05 . This suggests that the strength of the association between CALLY and CVD risk may differ in the presence or absence of diabetes and across levels of kidney function, possibly reflecting the central role of inflammatory-metabolic-renal crosstalk in the pathophysiology of both CKM and the biomarkers constituting the CALLY index. No significant

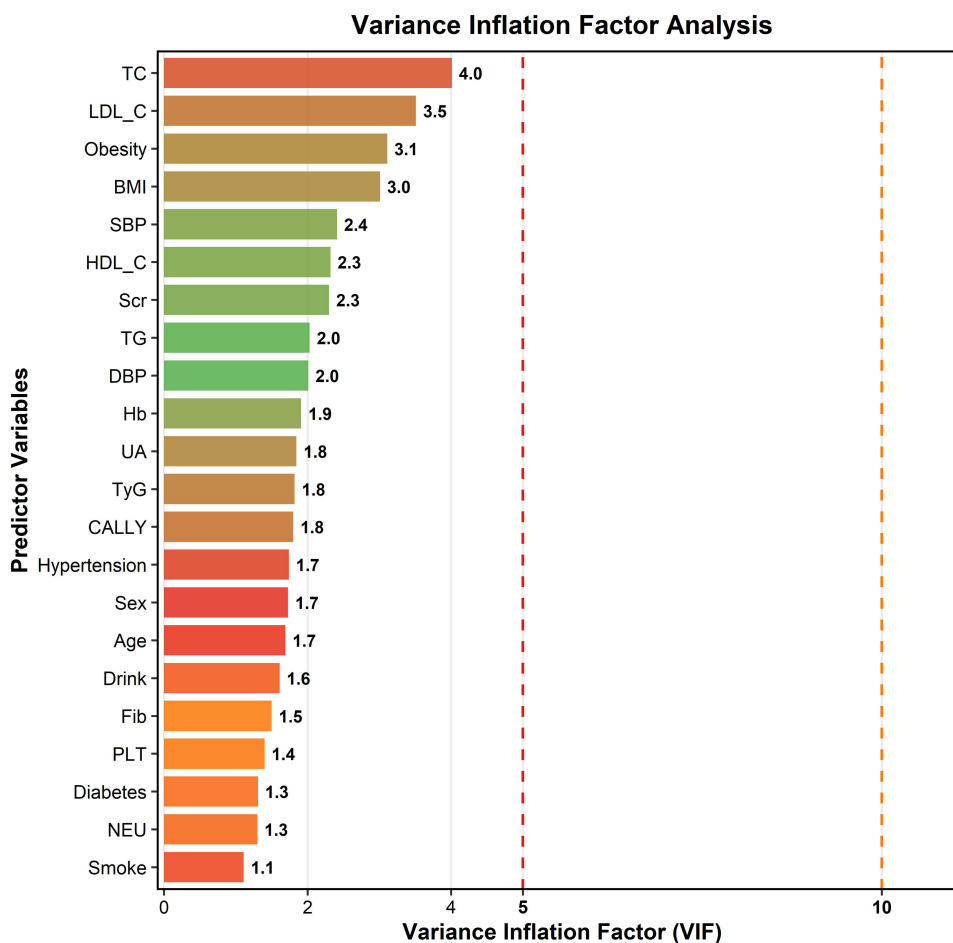


Figure 3 The covariates obtained through multicollinearity testing.

Note: Thresholds: 5=Moderate, 10=Severe collinearity.

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Hb, hemoglobin; Scr, serum creatinine; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; TC, total cholesterol; NEU, neutrophil count; PLT, platelet count; FIB, fibrinogen.

interactions were detected for other predefined subgroups, including age, sex, obesity, hypertension history, smoking status, and alcohol use (all P for interaction > 0.05).

When interpreting these subgroup findings, it is important to consider the inherent limitations in statistical power for testing interactions. The overall sample size and the distribution of clinical outcomes limit the ability to detect modest but potentially meaningful interaction effects, particularly within smaller or less frequent patient strata. Therefore, the absence of a statistically significant interaction in certain subgroups should not be definitively interpreted as evidence of no effect modification. Similarly, the observed significant interactions, while indicating heterogeneity, require confirmation in larger, dedicated studies. These analyses remain exploratory and are best viewed as generating hypotheses for future research.

Analysis of the ROC Curve and IDI/NRI for Cardiovascular Disease Outcomes in CKM Stage 3

Figure 7A and **B** illustrates the results of the ROC curve analysis, conducted to assess the predictive ability of the CALLY index for CVD outcomes. As shown in **Figure 7B**, when CRP, albumin, and lymphocyte count were analyzed individually, the areas under the curve (AUCs) were 0.706 (95% CI: 0.665–0.746), 0.717 (95% CI: 0.677–0.757), and 0.702 (95% CI: 0.659–0.744), respectively. When these three parameters were combined into the CALLY index, the AUC increased markedly to 0.806 (95% CI: 0.774–0.838), indicating superior discriminatory ability. Because time-to-

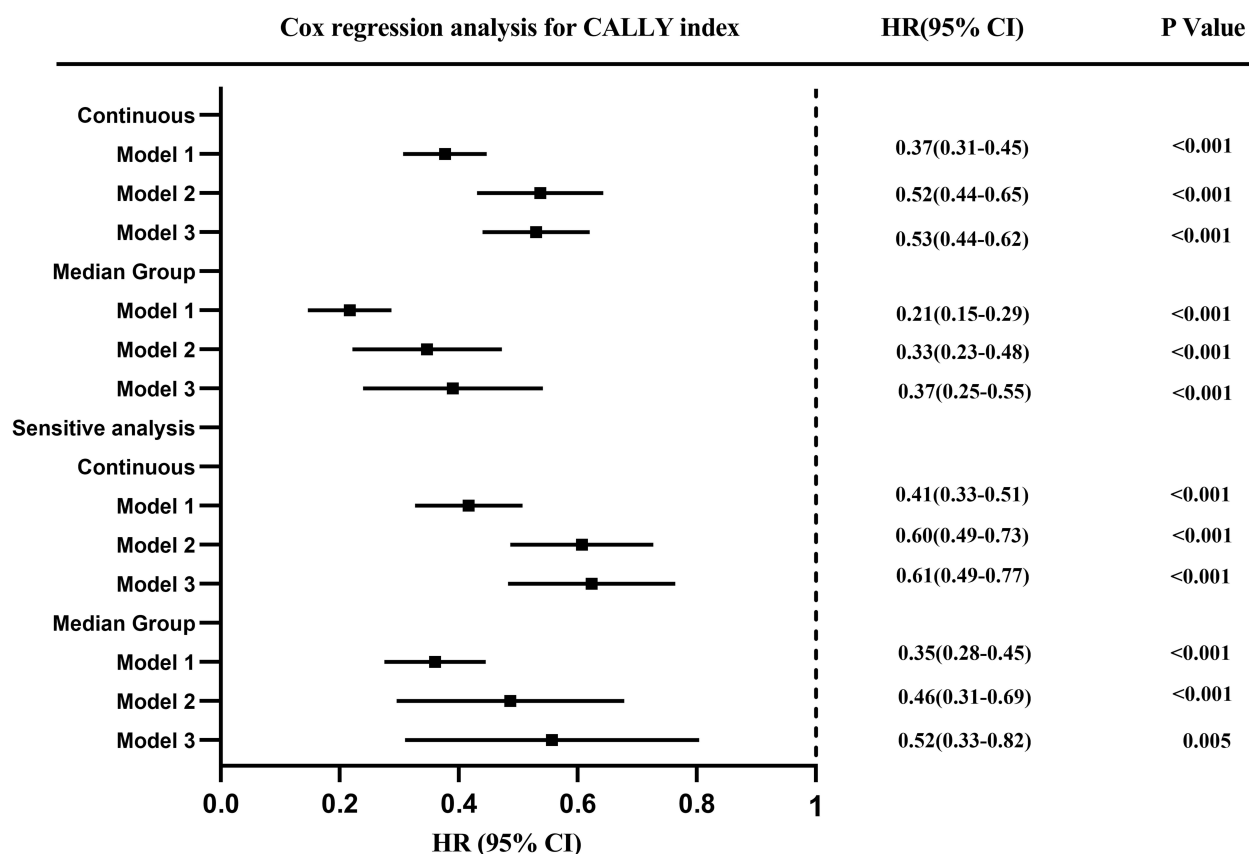


Figure 4 Univariate and covariate-adjusted Cox regression analysis. Model 1: Unadjusted for covariates. Model 2: Adjusted for gender, age, BMI, obesity, SBP, DBP, smoking history, alcohol consumption history, hypertension, and diabetes. Model 3: Based on Model 2, further adjusted for Hb, Scr, LDL, HDL, TG, TC, NEU, PLT, and FIB. **Abbreviations:** BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Hb, hemoglobin; Scr, serum creatinine; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; TC, total cholesterol; NEU, neutrophil count; PLT, platelet count; FIB, fibrinogen.

event data were incorporated in the clinical analysis, a time-dependent ROC curve was additionally constructed to evaluate whether the discriminative ability of the CALLY index differed across various follow-up durations. As illustrated in Figure 7A, the AUCs for cardiovascular events at 1, 3, and 5 years showed no significant differences. However, this apparent stability should be interpreted with caution. The decreasing number of patients at risk with longer follow-up time, inherent in our single-center cohort, reduces the precision of estimates at later time points and may affect the reliability of comparisons across time horizons. This observation underscores the need for validation in larger, multicenter cohorts with longer follow-up.

Table 2 presents the results of the calculation of both the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) to evaluate the added predictive power of the CALLY index for cardiovascular outcomes. The analyses compared models incorporating the CALLY index with those using each single biomarker (albumin, lymphocyte count, or CRP) alone. In the continuous NRI analysis, the NRI values were 0.59 (95% CI: 0.45–0.74) for albumin, 0.51 (95% CI: 0.36–0.66) for lymphocytes, and 0.73 (95% CI: 0.59–0.87) for CRP. Corresponding IDI values were 0.08 (95% CI: 0.05–0.10), 0.07 (95% CI: 0.05–0.09), and 0.08 (95% CI: 0.07–0.10), all indicating significant improvements in discrimination performance. Notably, in the categorical NRI analysis, only lymphocyte count showed a statistically significant independent improvement (NRI = 0.03, 95% CI: 0.01–0.06, P = 0.02). The improvement for albumin was at the borderline of significance (NRI = 0.03, 95% CI: –0.01–0.06, P = 0.06), while that for CRP was not significant (NRI = 0.009, P = 0.52). Collectively, these results indicate that although the CALLY index did not significantly enhance risk classification based on fixed categories, it provided significant and robust incremental predictive value for continuous risk estimation, demonstrating overall superior predictive performance compared with any single biomarker.

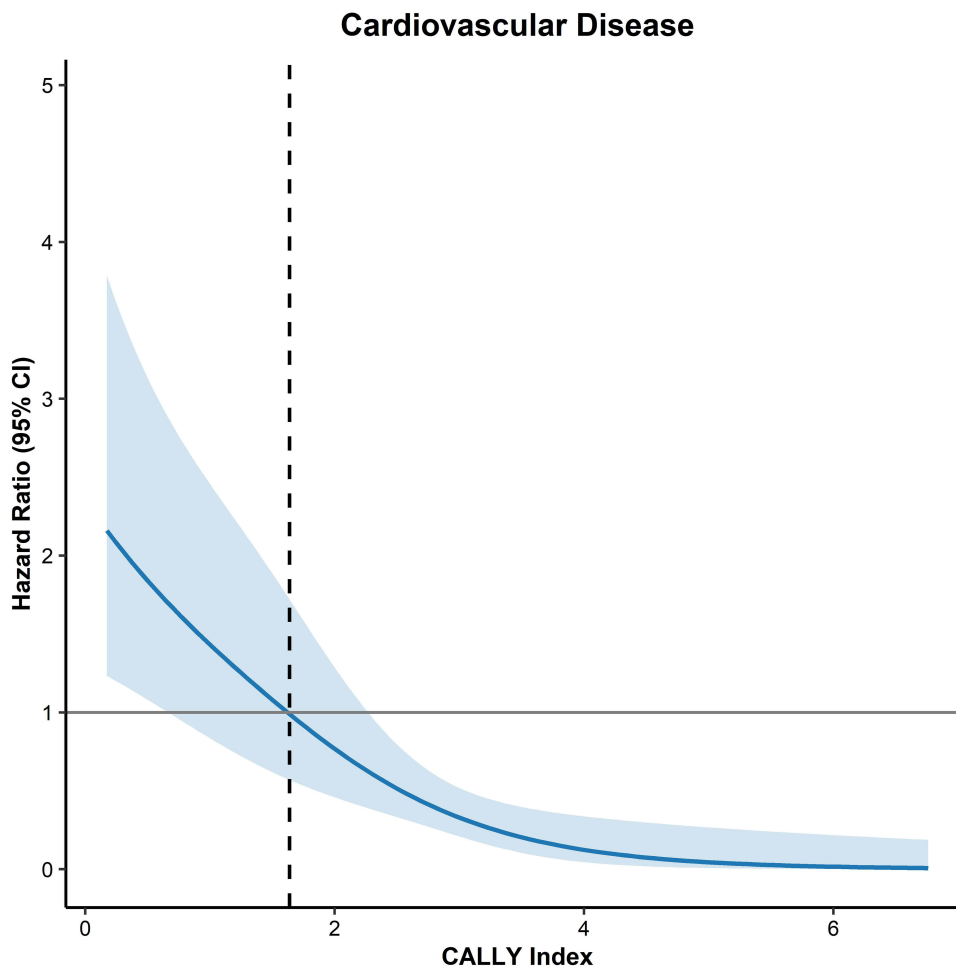


Figure 5 Restricted cubic spline plot of correlation between CALLY and CVD.

Note: P value of Overall<0.001, P value for Nonliner:0.36;Knot:1.64. The adjustment for covariates is the same as for Model 3 in Figure 4.

Discussion

To date, this is the first clinical cohort research examining the link between the CALLY index and the onset of CVD in individuals with CKM stage 3. In this study, Cox proportional hazards regression analysis, adjusted for demographic characteristics, chronic comorbidities, and laboratory parameters, demonstrated that a lower CALLY index was an independent risk factor for incident CVD in CKM stage 3 patients. Consistent results were observed in both subgroup and sensitivity analyses. Furthermore, the RCS curve analysis revealed a linear inverse relationship between CALLY levels and the risk of cardiovascular events, ROC curve analysis demonstrated that CALLY showed good predictive ability for cardiovascular outcomes. Complementary analyses of NRI and IDI further highlighted that the composite CALLY index significantly enhanced predictive accuracy compared to individual biomarkers like CRP.

The CALLY, combining factors that indicate inflammation, immune function, and nutritional status, has been initially confirmed as a predictor of negative outcomes in various populations. For example, a study published in February 2025 found a negative correlation between the CALLY index and the incidence of angina pectoris in US adults, reporting an odds ratio (OR) of 0.62 (95% confidence interval [CI]: 0.46–0.84) when comparing the highest to the lowest CALLY quartiles. Similarly, another study found that an elevated CALLY index independently lowered the likelihood of short-term negative cardiovascular outcomes in individuals with ST-segment elevation myocardial infarction.²¹ In addition, the relationship between the CALLY index and cardiovascular events as well as poor prognosis has also been validated in older adults.¹³ Although direct evidence on the link between CALLY and cardiovascular events in individuals with CKM

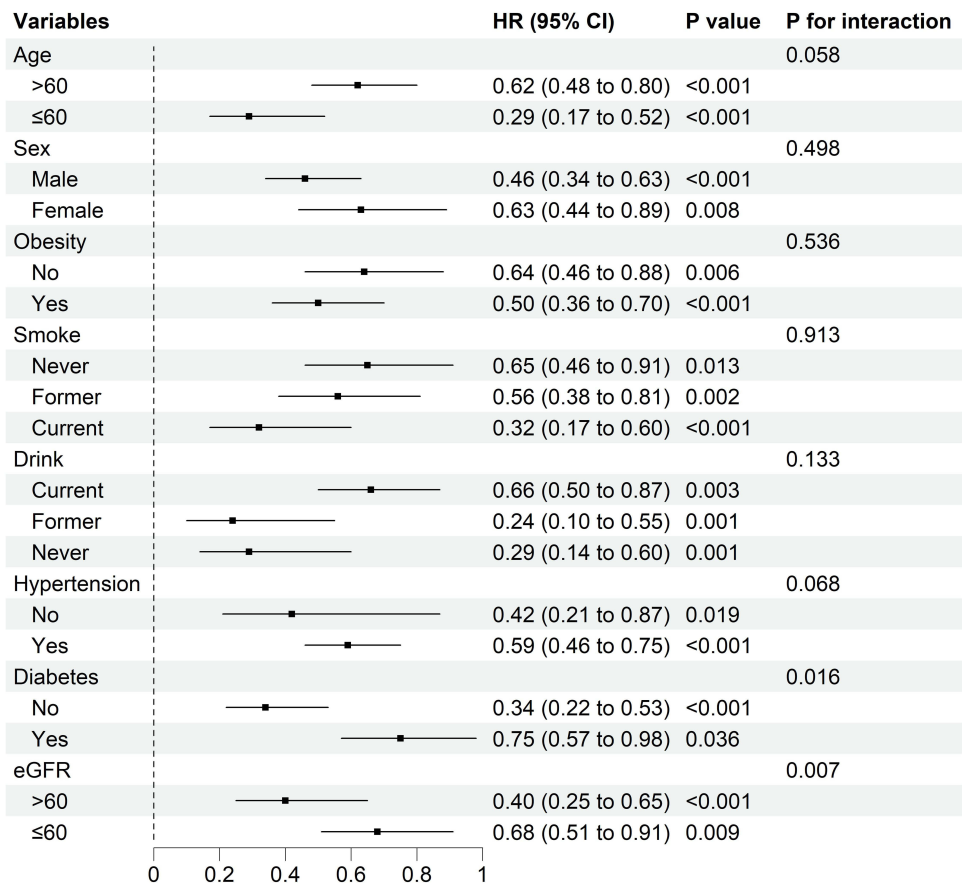


Figure 6 Subgroup analysis of the correlation between CALLY and CVD. **Note:** The adjustment for covariates is the same as for Model 3 in Figure 4. **Abbreviation:** eGFR, estimated glomerular filtration rate.

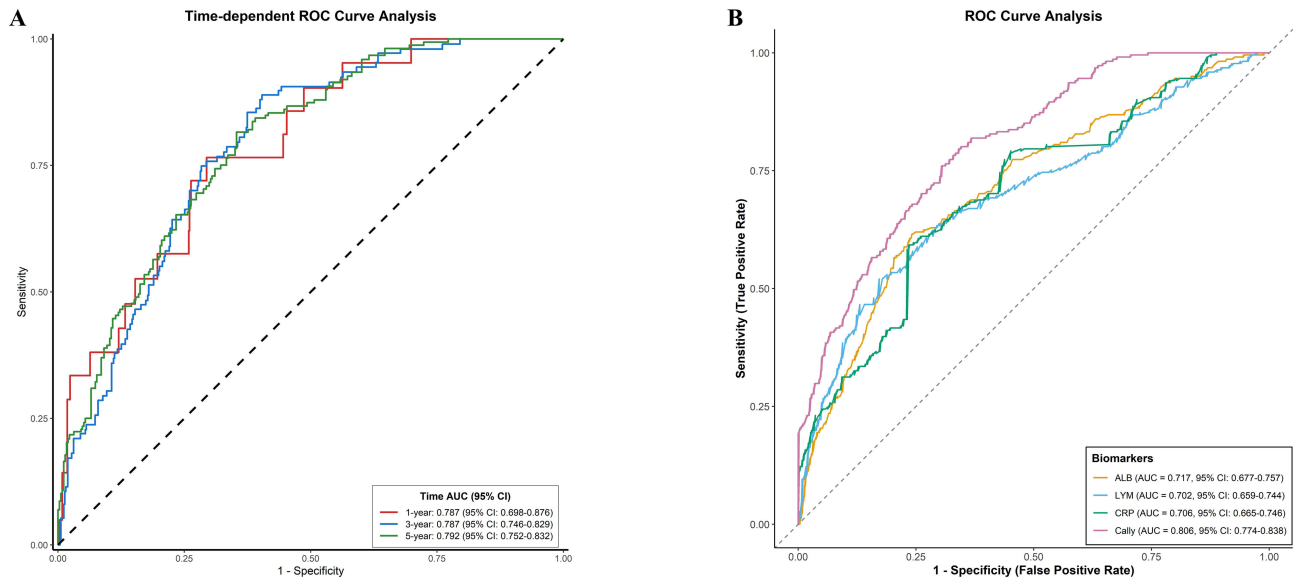


Figure 7 ROC and time-dependent ROC analyses for predicting CVD in patients with CKM stage 3. **(A)** Time-dependent ROC curve. **(B)** Conventional ROC curve. **Abbreviations:** CRP, C-reactive protein; Lym, lymphocyte count; Alb, albumin.

Table 2 CALLY's Net Reclassification Index and Integrated Discrimination Improvement Index Compared to Single Indicators

CALLY	Albumin	Lymphocyte	CRP
NRI (95% CI) (Categorical)	0.03(−0.01–0.06)	0.03(0.01–0.06)	0.009(−0.02–0.04)
P value	0.06	0.02	0.52
NRI (95% CI) (Continuous)	0.59(0.45–0.74)	0.51(0.36–0.66)	0.73(0.59–0.87)
P value	<0.001	<0.001	<0.001
IDI (95% CI)	0.08(0.05–0.10)	0.07(0.05–0.09)	0.08(0.07–0.10)
P value	<0.001	<0.001	<0.001

Note: The continuous NRI evaluates improvement in risk prediction across the entire risk spectrum, while the IDI measures the improvement in the average predicted risk difference between event and non-event groups.

Abbreviations: NRI, Net Reclassification Improvement; IDI, Integrated Discrimination Improvement.

is still limited, individuals with CKM may share similar features with the elderly population, such as metabolic dysregulation and chronic low-grade inflammation. Therefore, these prior studies provide indirect but supportive evidence for the findings of the present study, reinforcing the potential role of the CALLY index as an integrated biomarker linking inflammation, immunity, and nutrition to cardiovascular risk in CKM stage 3 patients.

The analysis further elucidates the temporal characteristics of cardiovascular risk associated with the CALLY index. The shorter median follow-up duration in the low CALLY group is concordant with the early and sustained divergence of the Kaplan-Meier survival curves, suggesting an accelerated onset of cardiovascular events. This pattern is quantitatively supported by the substantially lower hazard ratio for the high CALLY group, reflecting a delayed time-to-event distribution at the population level. Collectively, these findings indicate that the CALLY index captures not only the magnitude but also the tempo of risk progression in CKM stage 3. It should be clarified that this association characterizes a population-level risk pattern rather than providing a calibrated prediction of the exact timing of events for individual patients. Furthermore, while the discriminative ability of the CALLY index, as assessed by time-dependent ROC analysis, was observed to be relatively stable over 1 to 5 years, this observation should be interpreted with caution due to decreasing numbers at risk at longer follow-up times in our single-center cohort.

C-reactive protein (CRP) is an acute-phase reactant primarily synthesized by the liver in response to inflammatory stimuli, and its elevation reflects systemic inflammatory activation.²² CRP promotes vascular injury by inducing endothelial expression of adhesion molecules and chemokines, thereby enhancing the adhesion and migration of monocytes and lymphocytes, which contributes to endothelial dysfunction and atherosclerotic plaque formation.²³ Thus, CRP promotes plaque instability and thrombosis, increasing cardiovascular risk.²⁴ Similarly, lymphocytes, crucial elements of the adaptive immune response, influence cardiovascular events through the modulation of inflammation and plaque stability. Regulatory T cells (Tregs) exert potent anti-inflammatory effects by suppressing excessive immune responses and protecting vascular endothelium.²⁵ In contrast, pro-inflammatory T helper type 1 (Th1) cells release interferon- γ (IFN- γ) and stimulate macrophages, thereby amplifying local inflammation within atherosclerotic plaques. Meanwhile, Tregs mitigate this process by IL-10 and TGF- β , consequently, an imbalance between pro-inflammatory and anti-inflammatory immune cells may result in plaque instability. Previous studies have shown that a higher neutrophil-to-lymphocyte ratio (NLR) or reduced lymphocyte counts are independently linked to the onset of heart failure and significant cardiovascular events.²⁶ Serum albumin, traditionally considered a marker of nutritional status, also exhibits anti-inflammatory, antioxidative, and anticoagulant properties.^{27,28} It can suppress the secretion of pro-inflammatory cytokines like TNF- α and IL-6, thereby reducing endothelial injury and attenuating atherosclerosis progression.²⁹ Albumin also possesses anticoagulant and antiplatelet aggregation activities, modulating coagulation factors and platelet function to lower the risk of thrombosis.³⁰ Furthermore, as a major determinant of colloid osmotic pressure, albumin helps maintain intravascular fluid balance, prevents microcirculatory disturbances and tissue edema, and thereby protects cardiovascular function.³¹ Taken together, CRP, lymphocytes, and albumin each influence cardiovascular events through distinct yet interrelated mechanisms involving inflammation, immunity, oxidative stress, and hemostasis. These

biological functions collectively reinforce the CALLY as an all-encompassing marker that combines inflammatory, immune, and nutritional pathways, which helps explain its strong association with cardiovascular outcomes observed in this study.

In CKM stage 3 patients, persistent cardiac and renal injury, coupled with endocrine and metabolic dysregulation, may amplify the interplay among inflammation, immune dysfunction, and malnutrition. For instance, chronic inflammation can drive both immune dysregulation and malnutrition,³² while impaired nutritional status may in turn exacerbate inflammatory activity through metabolic abnormalities.³³ In the setting of CKM syndrome, the simultaneous presence of inflammation and oxidative stress accelerates renal function decline and nutritional depletion while also promoting atherogenesis, thereby perpetuating a vicious cycle of malnutrition–inflammation disequilibrium. This pathophysiological interaction parallels the malnutrition–inflammation complex syndrome (MICS), in which hypoalbuminemia and lymphopenia serve as hallmark features. The results of this study, showing that a lower CALLY index independently predicts increased cardiovascular risk, further emphasize the critical role of this composite syndrome in the development and progression of cardiovascular disease in CKM stage 3 patients.

Previous studies have shown that inflammatory markers can effectively predict cardiovascular events in long-term conditions like heart failure, diabetes, and CKD.^{34–36} Thus, similar composite indices could be useful for evaluating systemic inflammation and cardiovascular risk in CKM syndrome. For example, ratios such as the C-reactive protein/albumin ratio (CAR) and the NLR, which jointly reflect inflammation, immune status, and nutritional condition, have been independently associated with adverse outcomes and cardiovascular events across various chronic diseases.^{37,38} These findings provide a rationale for applying composite indices like CALLY in CKM syndrome.

The prognostic value of the CALLY index can be contextualized within the broader landscape of composite biomarkers in cardiometabolic disease. Several indices, such as the SIRI, SII, NPAR, and albumin to neutrophil/lymphocyte ratio (ANLR), which similarly reflect intersecting pathways of inflammation, immunity, and nutrition, have been associated with adverse cardiovascular and renal outcomes in populations with or at risk for CKM syndrome. Large-scale, nationally representative cohort studies involving these indices have demonstrated their significant and generalizable prognostic value, with reported AUCs for clinical outcomes typically in the moderate range (approximately 0.60 to 0.73).^{39–41} These studies benefit from extensive sample sizes and broad population coverage. In our more focused, single-center cohort of CKM stage 3 patients, the CALLY index demonstrated an AUC of 0.806 for incident CVD. It is crucial to interpret this numerical difference with caution. Direct comparisons are limited by substantial differences in cohort scale, design (retrospective single-center vs large national databases), and population selection. The observed AUC in our study should not be construed as evidence of superior performance but rather as a promising finding that requires validation in larger, independent, and similarly well-phenotyped cohorts. A distinctive feature of the CALLY index is its direct incorporation of CRP. Future research designed for head-to-head comparison in comparable settings is needed to determine if such compositional differences translate to varied clinical utility.

Translating a biomarker into practice requires both feasibility and clear interpretative guidance. The CALLY index holds inherent practical appeal as it is calculated from three routine, low-cost, and universally available laboratory parameters (CRP, albumin, lymphocyte count), making it easily integrable into standard clinical workflows. A critical step towards its application is defining a threshold for risk stratification. In our cohort, we observed a coherent signal: the median CALLY value (1.60) and the inflection point derived from restricted cubic spline analysis (1.64) were closely aligned. This convergence lends internal consistency to the approximate range of 1.6 as a potential transition zone associated with a shift in cardiovascular risk within our specific CKM stage 3 population. However, these specific numerical cut-offs are exploratory and derived from a single-center, retrospective cohort with a limited sample size relative to national database studies. Their generalizability and clinical utility for guiding individual patient decisions are unknown and require external validation. Establishing robust, clinically actionable thresholds is a necessary next step that must be undertaken in larger, prospective, and multiethnic cohorts using standardized.

This study possesses several notable strengths. First, to the best of our knowledge, it is the first investigation to systematically evaluate the association between the CALLY index and CVD risk in patients with CKM stage 3. The findings provide novel, population-specific evidence supporting the clinical applicability of this composite biomarker. Furthermore, subgroup analyses highlighted the stability and strength of the relationship between the CALLY index and

cardiovascular risk across various clinical strata. Importantly, the sensitivity analysis, which excluded participants with diabetes mellitus, helped mitigate potential reverse causality bias introduced by severe diabetic complications, thus improving the dependability of the findings.

Nevertheless, several limitations of this study should be acknowledged. First, the single-center, retrospective, observational design implies that findings may be influenced by local patient characteristics, clinical practices, and unmeasured confounders, which limits causal inference and may affect the generalizability of the results. Although we performed thorough multivariable adjustments, the impact of residual confounding from factors such as detailed medication history (eg, antihypertensive, antidiabetic or lipid-lowering), socioeconomic status, and specific lifestyle patterns cannot be excluded. Second, the number of incident cardiovascular events, while sufficient for the primary analysis, limits the statistical power for more nuanced analyses, including certain subgroup and interaction tests. Data on medication use were unavailable, and these agents could influence systemic inflammation, metabolic state, and ultimately cardiovascular risk, potentially affecting the observed associations. Furthermore, although we accounted for follow-up time, non-random censoring and evolution in clinical management over the study period might introduce additional unmeasured confounding. Finally, as with any observational cohort, the results demonstrate associations rather than prove causation. Future studies should include prospective, multicenter research with larger sample sizes and incorporate standardized medication data collection and broader inflammatory and metabolic biomarkers for comparison to validate and extend the clinical relevance of the CALLY index in CKM populations. Building on the present findings, the foremost priority is to address the key limitations of this single-center, retrospective study through rigorous external validation. This necessitates the design and execution of large-scale, multicenter, prospective cohort studies. Such studies are essential to confirm the association between the CALLY index and cardiovascular risk in CKM stage 3 patients across diverse populations and healthcare settings, and to establish its generalizable predictive performance. Second, given the dynamic nature of the pathways it reflects, investigating whether serial measurements of the CALLY index can track responses to therapeutic interventions and predict dynamic changes in risk would be highly valuable for personalized management. Third, as our primary endpoint was incident clinical CVD, an important next step is to evaluate the predictive value of the CALLY index for the broader composite endpoint of progression to full CKM stage 4, particularly the development of kidney failure. Exploring its utility in tracking multisystem progression could further refine risk stratification across the spectrum of CKM syndrome.

Conclusion

In patients with CKM stage 3, a lower CALLY index is independently associated with an increased risk of cardiovascular disease. The index also demonstrates robust predictive performance, highlighting its potential as a practical, integrative biomarker for cardiovascular risk stratification in this high-risk population. Prospective validation in broader cohorts is warranted to confirm these findings and assess its clinical utility.

Ethics Approval and Informed Consent

The study protocol was reviewed and approved by the Ethics Committee of the Second Affiliated Hospital of Kunming Medical University (Review Committee No.: FEY-BG-39-3.0). The requirement for informed consent was formally waived by the ethics committee because: (1) this retrospective study used fully anonymized clinical data with all personal identifiers permanently removed; (2) the research involved no interventions and posed minimal risk to participants; and (3) due to the retrospective nature and large sample size, obtaining individual consent was impracticable. This study was conducted in accordance with the Declaration of Helsinki and follows the STROBE guidelines for observational studies.⁴²

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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