

The C-reactive protein to albumin ratio is a novel prognostic factor in patients with stable coronary artery disease following percutaneous coronary intervention

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Abstract

Background

Previous studies have shown that both C-reactive protein (CRP) and albumin (Alb) are the prognostic factors of cardiovascular. However, the prognostic value of C-reactive protein to albumin ratio (CAR) in patients with stable coronary artery disease (SCAD) is unclear.

Methods

This was a retrospective cohort study that continuously enrolled 204 patients with newly diagnosed SCAD between October 2014 and October 2017; the mean follow-up time was 793.75 ± 430.26 days. The Cox proportional hazard model was used to evaluate the prognostic value of CAR in patients with SCAD.

Results

In the Kaplan–Meier analysis, the long-term MACE (major adverse cardiac events) free survival rate of patients with high CAR levels decreased significantly ($P = 0.015$). Of the note, after adjusting for other covariates in multivariate analysis, CAR was still independently positively correlated with poor prognosis in SCAD patients (HR = 1.03, 95% CI: 1.01–1.06, $P = 0.02$, P for trend = 0.024). Additionally, we identified a nonlinear association between CAR and poor prognosis of SCAD by the generalized additive model (GAM). Then, through the two-piecewise linear regression model, we calculated that the inflection point of CAR was 3.933 (log-likelihood ratio test $P = 0.02$). When $CAR \leq 3.933$, there was a positive correlation between CAR and MACE in patients with SCAD (HR: 1.48, 95% CI: 1.10–1.99, $P = 0.009$). While on the right hand of the inflection point ($CAR > 3.933$), the positive correlation between the two tends to be saturated (HR: 1.01, 95% CI: 0.97–1.05, $P = 0.64$).

Conclusions

This study indicated an association between higher CAR levels and increased risk of MACE in patients with SCAD for the first time, and measurement of CAR at admission may be a valuable predictor of the prognostic outcome in patients with SCAD treated by the percutaneous coronary intervention.

Background

SCAD has become one of the most common chronic diseases in the world. This condition can directly or indirectly cause damage to the human body, promote various complications, endanger health, increase the risk of mortality, and is associated with severe economic and disease burdens. The Global Burden of Disease Study 2017 highlighted that non-communicable diseases accounted for 73.4% of deaths and SCAD was a key contributor to this mortality [1]. Therefore, it is particularly important to explore and

prevent the risk factors contributing to the poor prognosis of SCAD. The root cause of SCAD was identified to be atherosclerosis. The pathological mechanism underlying the initiation and progression of atherosclerosis and induction of plaque instability is considered to be caused by inflammation produced by immune cells [2–3]. In previous studies, inflammatory markers such as CRP, hypersensitive CRP, and interleukin-6 have been shown to be reliable long-term prognostic factors for SCAD [4–6]. And we noticed that when the body is in an inflammatory state, the rate of Alb synthesis is reduced, which results in a series of malignant clinical events [7]. It is widely acknowledged that Alb is a critical protein throughout the body, involved in the transport of things such as growth hormones or therapeutic drugs to their targets, and the presentation of surface antigens during viral or bacterial infections. Normal Alb levels are therefore essential for the body to maintain health. Recently, others have highlighted that there was also strong correlation between Alb and cardiovascular disease [8, 9]. Therefore, both inflammatory cytokines and Alb can be used to predict the prognosis of cardiovascular disease, but is there a better index to replace both CRP and Alb? A new inflammatory indicator: the CRP to Alb ratio (CAR), was found to aid in the assessment of acute coronary syndrome severity, coronary flow status, and could predict the prognostic outcome in ST-elevation myocardial infarction patients, which can better reflect the body's inflammatory status [10–12]. However, the prognostic value of CAR in patients with SCAD is unclear. Therefore, we conducted this secondary data analysis based on previously published data to explore the association between the CAR and poor prognosis of SCAD patients [9]. The findings from such a study may indicate a convenient and useful marker for the further prognosis risk appraisal of SCAD patients.

Methods

Study design and population

We download raw data uploaded by Suzuki and his colleagues [9] from the "DATADRYAD" database (www.datadryad-d.org). According to the Dryad Terms of Service, we could use these data for secondary analysis based on different research hypotheses and quote Dryad packets (Dryad data package: Suzuki et al. (2019), <https://doi.org/10.5061/dryad.fn6730j>). The study design used here has been described in a previous study [9]. In brief, this was a retrospective cohort study that continuously enrolled patients with newly diagnosed SCAD (except old myocardial infarction) and hospitalized in Shinonoi General Hospital between October 2014 and October 2017. All patients received elective percutaneous coronary intervention (PCI) treatment, excluding patients with malignant tumors. Since ethical approval and informed consent were obtained in previous studies, this study no longer requires ethical research approval. Based on the original data provided by Suzuki *et al.*, we carried out further data collation. First, replace the missing data with NA: aspartate transaminase (AST, $n = 1$), alanine aminotransferase (ALT, $n = 1$), hemoglobin A1c (HBA1c, $n = 14$), triglyceride (TG, $n = 4$), total cholesterol (TC-Chol, $n = 33$), high-density lipoprotein cholesterol (HDL, $n = 6$), and CRP ($n = 8$). The items containing CRP or Alb missing data were deleted ($n = 8$). Then, CAR was calculated as the concentration of CRP divided by the concentration of Alb. The clinical follow-up data was provided by hospital. To explore the prognostic

impact of CAR on SCAD patients, we defined the study endpoint using any MACE that occurred during the follow-up, including all-cause death, non-fatal myocardial infarction, and non-fatal stroke.

Data Collection

Routine blood chemistry tests were conducted after admission, including measurements for hemoglobin (Hb), Alb, estimated glomerular filtration rate (eGFR), CRP, AST, ALT, HbA1c, TC-Chol, TG, HDL-Chol and low-density lipoprotein cholesterol (LDL-Chol). The concentrations of Alb and CRP were determined using a LABOSPECT008 automatic analyzer (Hitachi Ltd, Tokyo, Japan). The measurement range of Alb analysis was 1.0–8.0 g/dl, the coefficient of variation was 5%, the minimum detection limit was 0.1 g/dl, and the lowest detection value of CRP was 0.01 mg/dl. Clinical baseline data and general conditions of patients after admission were recorded by trained doctors; this data included age, sex, body weight, height, systolic blood pressure (SBP), diastolic blood pressure (DBP), left ventricular ejection fraction (LVEF), diabetes mellitus (DM), atrial fibrillation (AF), hypertension (HT), peripheral artery disease (PAD), old cerebral infarction (OCI), past smoker, drug applications, and types of coronary artery lesions and stents.

Definitions

Coronary angiography and PCI procedures were performed following standard guidelines, and all patients were given aspirin and thienopyridines at least two days before PCI. During the process of PCI, the intervention strategy and stent selection were decided by the operator and the patient after consultation. The diagnosis of SCAD needed to meet one of the following criteria: (1) coronary angiography confirmed $\geq 90\%$ epicardial coronary artery stenosis. (2) evidence of stress-induced ischemia via any clinical stress-testing modality and (3) exercise-induced chest pain with coronary angiography confirmed coronary artery stenosis $\geq 75\%$.

Statistical analysis

To better understand the association between CAR and the poor prognosis of patients with SCAD, the population was divided into three equal groups according to the percentage; the continuous variable distributions were expressed as the means and standard deviation, while the categorical variable was expressed as % or n. The Kolmogorov-Smirnov test was used to measure the normal distribution of values. Differences between the mean and proportion of each group were compared, one-way ANOVA or Kruskal-Wallis H test (nonparametric variables) were used for continuous variables, chi-square test was used for categorical variables. Cumulative endpoint event survival curves were determined by the Kaplan–Meier method and event curves of disparate outcomes were compared by using the log-rank test. The Cox proportional hazard regression model analyzed the prognostic value of CAR in SCAD, and the adjusted hazard ratio (HR) to estimate the 95% confidence interval (CI) was used to evaluate the prognostic risk. Before the variables were included in the multivariate regression equation, collinearity between variables was tested using multiple linear regression based on the variance inflation factor (VIF)

[13]. Variables with VIF > 5 were considered as showing severe multicollinearity. According to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement, we also display the results of the unadjusted (crude model), minimum adjustment analysis (model I), and full adjustment analysis (model II) [14]. The goodness of fit for each model was evaluated by the $-2\log$ likelihood. Model discrimination was evaluated utilizing the concordance index (C index). In order to avoid bias caused by differences in CAR groups, we carried out a sensitivity analysis by treat CAR as a categorical variable and calculated the P for trend. Furthermore, the GAM was used to identify the nonlinear association between CAR and the poor prognosis of patients with SCAD. If a nonlinear correlation was observed, a two-piecewise linear regression model was used to calculate the threshold effect of CAR on the poor prognosis of SCAD according to the smoothing curve, and the inflection point was calculated automatically by the recursive method and the maximum model likelihood was used at the inflection point. Also, we used the Cox proportional hazard model to analyze the consequences of each subgroup (age, BMI, Hb, LDL-Chol, and PAD). For continuous variables, we converted them into categorical variables according to the clinical entry point, and each stratification was adjusted according to all factors except the stratification factor itself. Likelihood ratio tests inspected the interactions of subgroups. R package V.3.4.3 (<http://www.r-project.org>; 2020-02-03 The R Foundation), Empower (R) (www.empowerstats.com; X&Y Solutions Inc.) and SPSS (V.23.0) were used to perform all statistical analyses. $P < 0.05$ was the criterion for significance.

Results

Baseline features and population studied

Selected patients (204 patients) were diagnosed with SCAD for the first time (mean age, 72 years; male, 69%). The CRP and Alb concentrations of all patients were assessed at admission between October 2014 and October 2017. We divided patients into three equal groups according to the CAR. Eight patients without CAR noted were excluded from the study. Of the 196 remaining patients enrolled in the study, 66 patients were placed into the high-level CAR group, 65 patients were placed in the low-level CAR group, and 65 were placed in the middle-level CAR group. Table 1 summarizes the baseline clinical characteristics of the cohort. We found that in the group with the highest CAR, participants were generally older and had higher CRP concentrations but lower levels of eGFR, LVEF, HbA1c, and HDL-Chol. Moreover, there were no significant differences in medication history, coronary artery disease types, or concomitant diseases among these diverse groups. All participants were followed up for an average of 793.75 ± 430.26 days. During the follow-up period, 18 people died. Among them, 6 died of cardiovascular causes, 3 had a non-fatal myocardial infarction, and 11 had stroke events. Additionally, in order to assess the power of our study, we conducted post-hoc power analysis. Using GPower version 3.1.9.7, we showed that a sample size of 196 respondents yielded a power of 100%, an effect size (f) of 44.295, and a significance level of 0.05 (two-sided).

Table 1
Baseline Characteristics of participants (N = 196)

Variables	CAR			P-value
	Low(n = 65)	Middle(n = 65)	High(n = 66)	
Age (years)	69.46 ± 9.92	74.03 ± 9.80	75.02 ± 9.88	0.003
Sex, male, n (%)	48 (73.85%)	45 (69.23%)	43 (65.15%)	0.558
BMI (kg/m ²)	23.40 ± 3.69	23.68 ± 3.88	23.61 ± 4.15	0.722
Past smoker, n (%)	37 (56.92%)	32 (49.23%)	28 (42.42%)	0.252
Hb(g/dL)	14.23 ± 1.65	13.74 ± 2.30	12.73 ± 1.80	< 0.001
ALB (g/dL)	4.19 ± 0.34	3.94 ± 0.52	3.63 ± 0.56	< 0.001
CRP (mg/dL)	0.03 ± 0.01	0.12 ± 0.05	1.19 ± 1.60	< 0.001
CAR, x100	0.24 ± 0.10	0.91 ± 0.34	9.93 ± 13.99	< 0.001
eGFR(mL/min/1.73 m ²)	66.65 ± 22.43	59.37 ± 25.21	56.50 ± 25.92	0.013
AST (U/L)	24.54 ± 10.15	23.78 ± 8.58	25.67 ± 13.82	0.859
ALT (U/L)	22.09 ± 13.00	19.89 ± 9.99	20.56 ± 13.76	0.533
T-Chol (mg/dL)	189.64 ± 33.65	189.28 ± 31.70	175.64 ± 40.46	0.066
HDL-Chol (mg/dL)	53.84 ± 11.73	50.00 ± 14.68	46.06 ± 12.28	0.004
TG (mg/dL)	130.03 ± 91.86	134.55 ± 84.80	131.98 ± 88.03	0.938
LDL-Chol (mg/dL)	112.35 ± 24.95	110.12 ± 25.88	107.24 ± 33.36	0.597
HBA1c (%)	6.26 ± 0.80	6.30 ± 0.92	6.24 ± 0.89	0.872
SBP (mmHg)	137.12 ± 14.93	134.89 ± 21.80	137.27 ± 23.89	0.864
DBP (mmHg)	78.38 ± 10.75	74.82 ± 14.32	79.24 ± 14.70	0.137
LVEF (%)	65.63 ± 6.58	63.18 ± 9.92	60.80 ± 11.84	0.013
Basic Disease				
OCI, n (%)	8 (12.31%)	12 (18.46%)	13 (19.70%)	0.482
PAD, n (%)	14(21.54%)	16 (24.62%)	20 (30.30%)	0.505
AF, n (%)	7 (10.77%)	9 (13.85%)	10 (15.15%)	0.750
HT, n (%)	50 (76.92%)	47 (72.31%)	49 (74.24%)	0.832
DLP, n (%)	36 (55.38%)	29 (44.62%)	31 (46.97%)	0.434

Variables	CAR			P-value
DM, n (%)	28 (43.08%)	22 (33.85%)	20 (30.30%)	0.290
Lesional characteristics				
Multivessel lesions, n (%)	17 (26.15%)	18 (27.69%)	16 (24.24%)	0.903
Bifurcation lesions, n (%)	39 (60.00%)	28 (43.08%)	30 (45.45%)	0.112
LMT, n (%)	3 (4.62%)	6 (9.23%)	4 (6.06%)	0.557
Ostial lesions, n (%)	10 (15.38%)	10 (15.38%)	8 (12.12%)	0.827
Calcified lesions, n (%)	4 (6.15%)	13 (20.00%)	11 (16.67%)	0.062
CTO, n (%)	7 (10.77%)	2 (3.08%)	3 (4.55%)	0.151
Stent type				0.028
BMS, n (%)	7 (10.77%)	0 (0.00%)	4 (6.06%)	
DES, n (%)	58 (89.23%)	65 (100.00%)	62 (93.94%)	
Medication				
Aspirin, n (%)	65 (100.00%)	64 (98.46%)	65 (98.48%)	0.606
Thienopiridines, n(%)	63 (96.92%)	65 (100.00%)	65 (98.48%)	0.360
Warfarin, n (%)	3 (4.62%)	1 (1.54%)	1 (1.52%)	0.434
DOAC, n (%)	5 (7.69%)	7 (10.77%)	9 (13.64%)	0.546
Ezetimibe, n (%)	2 (3.08%)	0 (0.00%)	1 (1.52%)	0.360
PPI, n (%)	39 (60.00%)	41 (63.08%)	48 (72.73%)	0.279
Statins, n (%)	40 (61.54%)	33 (50.77%)	30 (45.45%)	0.172
ACEI, n (%)	7 (10.77%)	5 (7.69%)	7 (10.61%)	0.800
ARB, n (%)	25 (38.46%)	25 (38.46%)	36 (54.55%)	0.100
Beta-blockers, n (%)	12 (18.46%)	23 (35.38%)	17 (25.76%)	0.090
MRA, n (%)	1 (1.54%)	6 (9.23%)	4 (6.06%)	0.160

Variables	CAR	P-value
Values are n(%) or mean \pm SD. Abbreviations: BMI = body mass index, Hb = hemoglobin, Alb = serum albumin, CRP = C-reactive protein, CAR = CRP/Alb, eGFR = estimated glomerular filtration rate, ALT = alanine aminotransferase, AST = aspartate transaminase, T-Chol = total cholesterol, TG = Triglyceride, HDL-Chol = high-density lipoprotein cholesterol, LDL-Chol = low density lipoprotein cholesterol, HbA1C = hemoglobin A1c, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, LVEF = left ventricular ejection fraction, OCI = old cerebral infarction, PAD = peripheral artery disease, AF = Atrial fibrillation, HT = hypertension, DLP = Dyslipidemia, DM = diabetes mellitus, DOAC = direct oral anticoagulants, PPI = proton pump inhibitor, ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin-receptor blocker, MRA = mineralocorticoid receptor antagonist, BMS = bare metal stent, DES = drug-eluting stent, LMT = left main trunk lesions, CTO = chronic total occlusion.		

The association between CAR and the poor prognosis of SCAD

The univariate analysis results are reported in Table 2. Univariate analysis showed that age, BMI, Hb, LDL-Chol, CAR, PAD, and warfarin use were positively correlated with the poor prognosis of SCAD. Then the significant variables ($P < 0.05$) in univariate analysis and non-collinear variables (except collinear variables body weight and TC-Chol) were incorporated into the multivariate regression model. In this study, the Cox proportional hazard regression model was used to evaluate the association between CAR and the poor prognosis of SCAD. We evaluated the adjusted and unadjusted models separately (Table 3). In the crude model, there was a positive correlation between CAR and the poor prognosis of SCAD (HR = 1.03, 95% CI:1.01–1.06, $P < 0.001$), while the result of the minimum adjusting model (model I, adjusted for age, BMI, PAD) showed no significant changes compared to crude model (HR:1.03, 95% CI:1.01–1.05, $P = 0.018$). And after adjusting the full model (model II, adjusted for age, BMI, Hb, LDL-Chol, PAD, and warfarin), we could still see a positive correlation between them (HR = 1.03, 95% CI:1.01–1.06, $P = 0.02$). For the sensitivity analysis, we disposed of CAR as a categorical variable. In model II, we found that patients with a high CAR level increased the MACE risk by 2.76 times compared with a low CAR level (P for trend = 0.024). And in Kaplan–Meier analysis (Fig. 1), the long-term MACE-free survival rate of patients with high CAR levels decreased significantly ($P = 0.015$). Furthermore, the goodness of fit statistics of the two models were 235.158 and 216.411; respectively, the model II had the best model fit. And the C index for the two models were 0.751 and 0.79 (Table 4), which means that model I and model II predict each outcome fairly well.

Table 2
The results of univariate analysis.

Variables	HR (95%CI)	P-value
Age	1.06 (1.02,1.11)	0.01
Sex(male)	1.08 (0.49, 2.4)	0.85
BMI	0.83 (0.74,0.92)	< 0.01
Past smoker	0.49 (0.22,1.08)	0.08
Hb	0.66 (0.55,0.79)	< 0.01
CAR, x100	1.03 (1.01,1.06)	< 0.01
eGFR	0.99 (0.98,1.01)	0.27
AST	1.01 (0.98,1.04)	0.59
ALT	0.99 (0.95,1.02)	0.49
HDL-Chol	0.99 (0.96,1.02)	0.53
TG	1.00 (1.00,1.01)	0.84
LDL-Chol	0.98 (0.97,1.00)	0.02
HBA1c	1.20 (0.88,1.63)	0.26
LVEF	0.99 (0.95,1.02)	0.47
OCI	2.12 (0.93,4.81)	0.07
PAD	2.45 (1.16,5.16)	0.02
AF	2.06 (0.83,5.11)	0.12
HT	1.01 (0.43,2.38)	0.98
DLP	0.53 (0.25,1.16)	0.11
DM	0.65 (0.29,1.48)	0.31
Aspirin	0.15 (0.02,1.09)	0.06
Thienopiridines	0.63 (0.08,4.65)	0.65
Warfarin	4.60 (1.09,19.47)	0.04
Stains	0.68 (0.32,1.44)	0.31
Multivessel lesions	1.14 (0.50,2.58)	0.76
Bifurcation lesions	0.70 (0.33,1.49)	0.36
Abbreviations: HR: Hazard ratio; CI: confidence intervals; other abbreviations as in Table 1.		

Table 3
Association between CAR and SCAD in different models.

Variable	Crude Model		Model I		Model II	
	HR (95%CI)	<i>P</i>	HR (95%CI)	<i>P</i>	HR (95%CI)	<i>P</i>
CAR	1.03 (1.01,1.06)	< 0.001	1.03 (1.01,1.05)	0.018	1.03 (1.01,1.06)	0.020
CAR(percentage)						
Low	Reference		Reference		Reference	
Middle	1.26 (0.39,4.14)	0.700	1.1 (0.33, 3.63)	0.880	0.93 (0.26,3.31)	0.100
High	3.32 (1.21,9.07)	< 0.001	2.89 (1.04,8.02)	< 0.01	2.76 (0.96,7.92)	0.060
<i>P</i> for trend		0.011		0.021		0.024
Crude model: we did not adjust other Variables; Model I adjust for: age, BMI and PAD; Model II adjusts for age, BMI, Hb, LDL-Chol, PAD, and Warfarin; Abbreviations: HR: Hazard ratio; CI: confidence intervals; <i>P</i> = <i>P</i> -value.						

Table 4. Goodness-of-fit statistics and discrimination of the two multivariable cox regression models.

Model diagnostic measure	Model I	Model II
Goodness of fit		
-2log likelihood	235.158	216.411
Discrimination		
C index	0.751	0.79
C index: concordance index.		

Analysis of nonlinear relationships between CAR and the poor prognosis of SCAD

In this present research, CAR was a continuous variable; we also used the GAM to identify the nonlinear relationship between CAR and the poor prognosis of SCAD. Figure 2 represents a curvilinear relationship (adjusted for age, BMI, Hb, LDL-Chol, PAD, and warfarin) between the MACE risk of CAR and SCAD. The inflection point of CAR calculated by the two-piecewise linear regression model was 3.933 (log-likelihood ratio test $P = 0.02$). As we anticipated, there was a positive correlation between CAR on the left side of the inflection point ($CAR \leq 3.933$) and poor prognosis of SCAD (HR:1.48, 95% CI:1.10–1.99, $P = 0.009$). On the right hand of the inflection point ($CAR > 3.933$), the positive correlation between the two tends to be saturated (HR:1.01, 95% CI:0.97–1.05, $P = 0.64$; Table 5).

Table 5
The result of the two-piecewise linear regression model.

	MACE (HR,95%CI)	P-value
Fitting model by standard linear regression	1.03 (1.01, 1.06)	0.02
Fitting model by two-piecewise linear regression		
The inflection point of CAR	3.933	
≤3.933	1.48 (1.10, 1.99)	0.009
>3.933	1.01 (0.97, 1.05)	0.64
P for log-likelihood ratio test		0.02
The model I and Modle II adjusted age, BMI, Hb, LDL-Chol, PAD, and Warfarin. Abbreviations: MACE: major adverse cardiovascular events; HR: Hazard ratio; CI: confidence intervals.		

Subgroup Analyses

We further explored other risks that could contribute to the association between CAR and MACE in patients with SCAD, and estimated the factors that might affect the results by using subgroup analysis. Here, we used age, BMI, Hb, LDL-Chol, and PAD as stratified variables; each stratification was adjusted according to all the stratification factors, except for the stratification factor itself. The Cox proportional hazard model was used to explore the robustness of the results of each subgroup, and the effects of these variables were observed (Table 6). Through the likelihood ratio test of the interaction between subgroups, we noted no statistical significance for any stratified variables (P for interaction > 0.05). These results further support the stable independent association between CAR and poor prognosis of SCAD.

Table 6

The effect size of CAR on SCAD in prespecified and exploratory subgroups in each subgroup.

Variables	No. of participants	HR (95%CI)	P-value	P for interaction
Age (year)				0.67
<70	73	1.09 (0.84, 1.41)	0.51	
≥70	117	1.03 (1, 1.06)	0.07	
BMI (kg/m ²)				0.8
<24	109	1.03 (1.01, 1.06)	0.009	
≥24	81	1.01 (0.81, 1.26)	0.96	
LDL-Chol (mg/dL)				0.64
<120	122	1.03 (0.99, 1.05)	0.06	
≥120	68	1.09 (0.85, 1.41)	0.5	
Hb(g/dL)				0.35
<12	36	1.01 (0.98, 1.05)	0.41	
≥12	154	1.07 (0.96, 1.19)	0.2	
PAD				0.54
NO	140	1.04 (1.01, 1.07)	0.01	
YES	50	1.07 (0.99, 1.15)	0.1	
Note 1: The above model adjusted for age, LDL-Chol, PAD, Hb, and BMI.				
Note 2: In each case, the model is not adjusted for the stratification variable.				
Abbreviations: HR: Hazard ratio; CI: confidence intervals;				

Discussion

In this work, we retrospectively analyzed the prognostic ability of CAR in 196 eligible SCAD patients. As far as we know, this was the first study to investigate the association between CAR and MACE risk in patients with SCAD. Our results show that there was an independent positive correlation between CAR and the poor prognosis of patients with SCAD (HR = 1.03, 95%CI: 1.01–1.06, $P = 0.02$, P for trend = 0.024). This association was independent of other risk factors, and there was a nonlinear relationship. We used a two-piecewise linear regression model to calculate that the inflection point of CAR was 3.933 (log-likelihood ratio test $P = 0.02$).

CRP is a clinically used inflammatory marker to assess the inflammatory state of disease. In cardiovascular disease, CRP stimulates inflammatory cells to promote atherosclerotic plaque formation. This is achieved by increasing the expression of endothelial adhesion molecules and inhibiting production of endothelial nitric oxide, which can result in the instability of atherosclerotic plaques [15]. CRP also has a similar effect in cerebrovascular diseases and high CRP levels often indicate poor prognosis [16]. Alb is often used to evaluate the nutritional status of the body [17]. Previous studies found that Alb concentrations were linked to the poor prognosis of patients with SCAD [9]. In these instances, low Alb levels could be related to poor syntax score and lower prognostic nutritional index [18, 19].

In recent years, CAR has attracted much attention as a novel predictor of coronary artery disease severity and prognosis [10–12, 18]. We hypothesized that CAR might have prognostic value for predicting the prognosis of patients with SCAD. What is exciting is that our research confirmed that there was an independent positive correlation between CAR and the poor prognosis of patients with SCAD (HR = 1.03, 95%CI:1.01–1.06, $P = 0.02$, P for trend = 0.024). Also, CAR was more objectively determined than traditional prognostic factors such as sex, age, BMI, etc., and is an easily quantifiable and inexpensive prognostic factor for patients with SCAD. Effectively controlling the occurrence and development of inflammation is essential in the prevention and treatment of cardiovascular disease, but a deeper understanding of the pathogenesis of the cardiovascular disease is necessary. In the article *"Inflammation and Atherosclerosis: The End of a Controversy"* written by Dr. Hansson GK [20], it was also mentioned that more attention should be paid to the preventive effect of anti-inflammatory chemicals on cardiovascular diseases and the clinical research of inflammation and atherosclerosis. Thankfully, several targeted anti-inflammatory drugs are currently being tested [21, 22]. The results have suggested that reducing inflammation could reduce the incidence of recurrent cardiovascular events, but their long-term efficacy needs further observation. In addition, many randomized controlled trials have shown that statins not only reduce lipid concentrations but they also have anti-inflammatory effects. This reduction in inflammation can effectively improve the clinical outcome of patients with coronary artery disease (CAD) [23–25]. Combined with our research and practice, we suggest that patients diagnosed with SCAD should strictly carry out secondary prevention of CAD. In particular, the use of statins should be adjusted to an appropriate dose according to CAR, blood lipid levels, and other biochemical indicators. In order to reduce the risk of residual MACE, CAR indicators should be regularly monitored. We will continue to expand the scope of our research and carry out multi-center research to confirm our findings further to identify potential mechanisms and associations.

Limitations

Although we thought our findings were valid, our research still had some limitations. First, our cases were mainly from a single medical center, which will limit the external applicability of the results. Second, we only measured the CRP and Alb at admission and doesn't consider dynamic changes in these levels over time. Third, although transaminase levels were normal in some people in our cohort, the study did not rule outpatients with liver failure. Finally, this study was a secondary analysis based on a previous study and the data had been screened by Suzuki et al. [9], due to the raw data limitation, we were unable to obtain

details about the patients treated with PCI. Moreover, the differences in the mode of operation, the operator's proficiency, X-ray exposure time, and other factors cannot be evaluated, which may lead to some information bias. We will further explore the association of CAR with the poor prognosis of patients with SCAD by collecting our data in the future.

Conclusion

Our study showed that there was an independent positive correlation between CAR and the poor prognosis of patients with SCAD. The measurement of CAR at admission might be beneficial for early stratification and intervention to prevent MACE.

Abbreviations

CRP: C-reactive protein; Alb: albumin; CAR: C-reactive protein to albumin ratio; SCAD: stable coronary artery disease; MACE: major adverse cardiac events; GAM: generalized additive model; PCI: percutaneous coronary intervention; AST: aspartate transaminase; ALT: alanine aminotransferase; HbA1c: hemoglobin A1c; TG: triglyceride; TC-Chol: total cholesterol; HDL-Chol: high-density lipoprotein cholesterol; Hb: hemoglobin; eGFR: estimated glomerular filtration rate; LDL-Chol: low-density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure; LVEF: left ventricular ejection fraction; DM: diabetes mellitus; AF: atrial fibrillation; HT: hypertension; PAD: peripheral artery disease; OCl: old cerebral infarction; HR: hazard ratio; CI: confidence interval; VIF: variance inflation factor; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology; C index: concordance index; CAD: coronary artery disease;

Declarations

Ethics approval and consent to participate

Research ethics approval and informed consent from participants were obtained in previous studies, so research ethics approval is no longer required for this study.

Consent for publication

Not applicable.

Availability of data and materials

Data can be downloaded from the 'DATADRYAD' database (www.Datadryad.org, <https://doi.org/10.5061/dryad.fn6730j>).

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conceptualization, Methodology: Guotai Sheng and Yang Zou. Project administration: Guotai Sheng.

Software: Yang Zou and Xiaohua Chen. Visualization: Yang Zou and Hui Zeng. Supervision: Guotai Sheng, Mingchun Zhong, Hui Zeng and Xiaohua Chen. Writing-Original draft preparation: Yang Zou. Writing- Reviewing and Editing: Yang Zou, Guotai Sheng, Mingchun Zhong, Hui Zeng and Xiaohua Chen. The author(s) read and approved the final manuscript.

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Figures

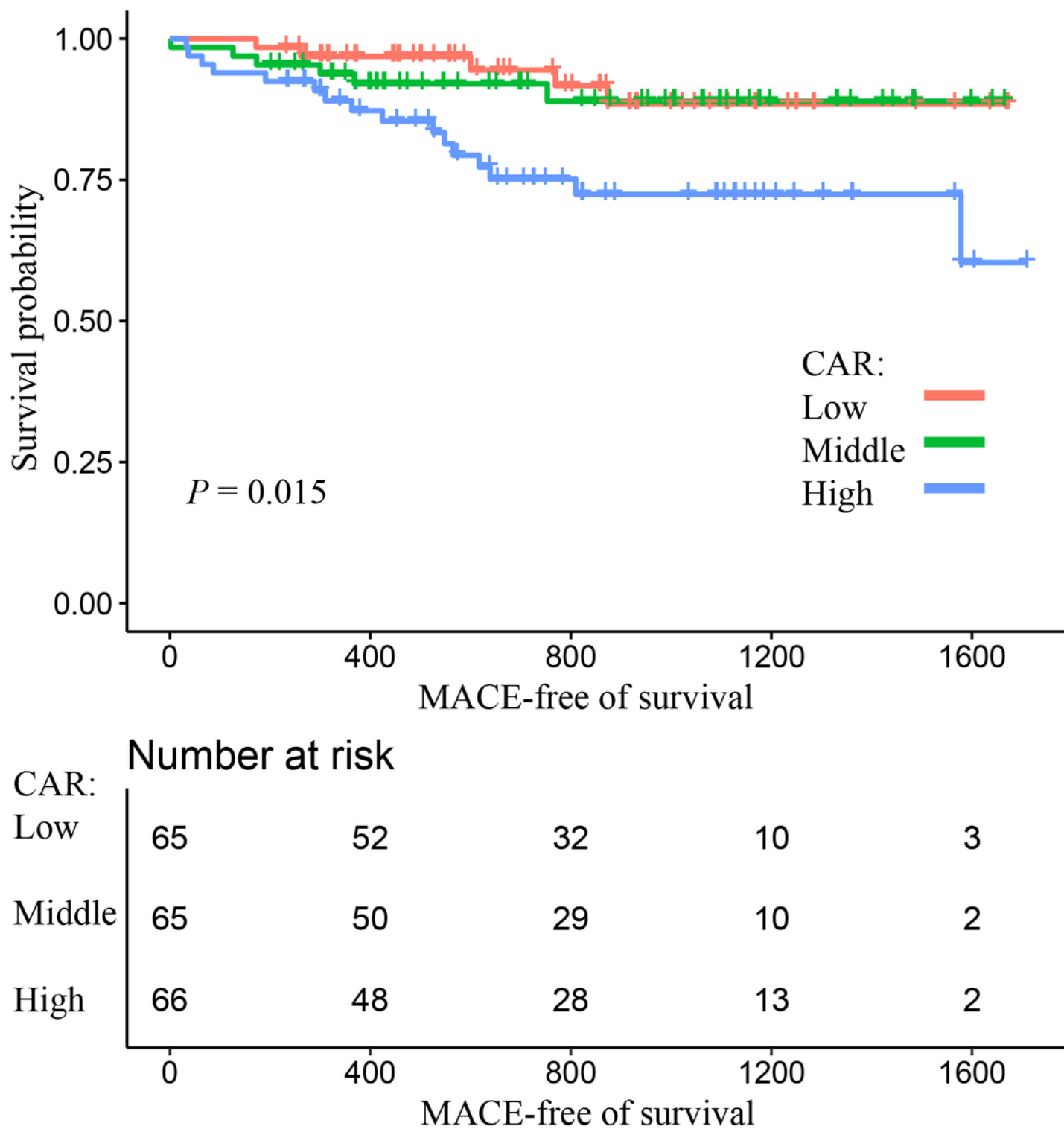


Figure 1

Kaplan–Meier analysis for cumulative MACE-free survival with low CAR level, meddle CAR level and high CAR level.

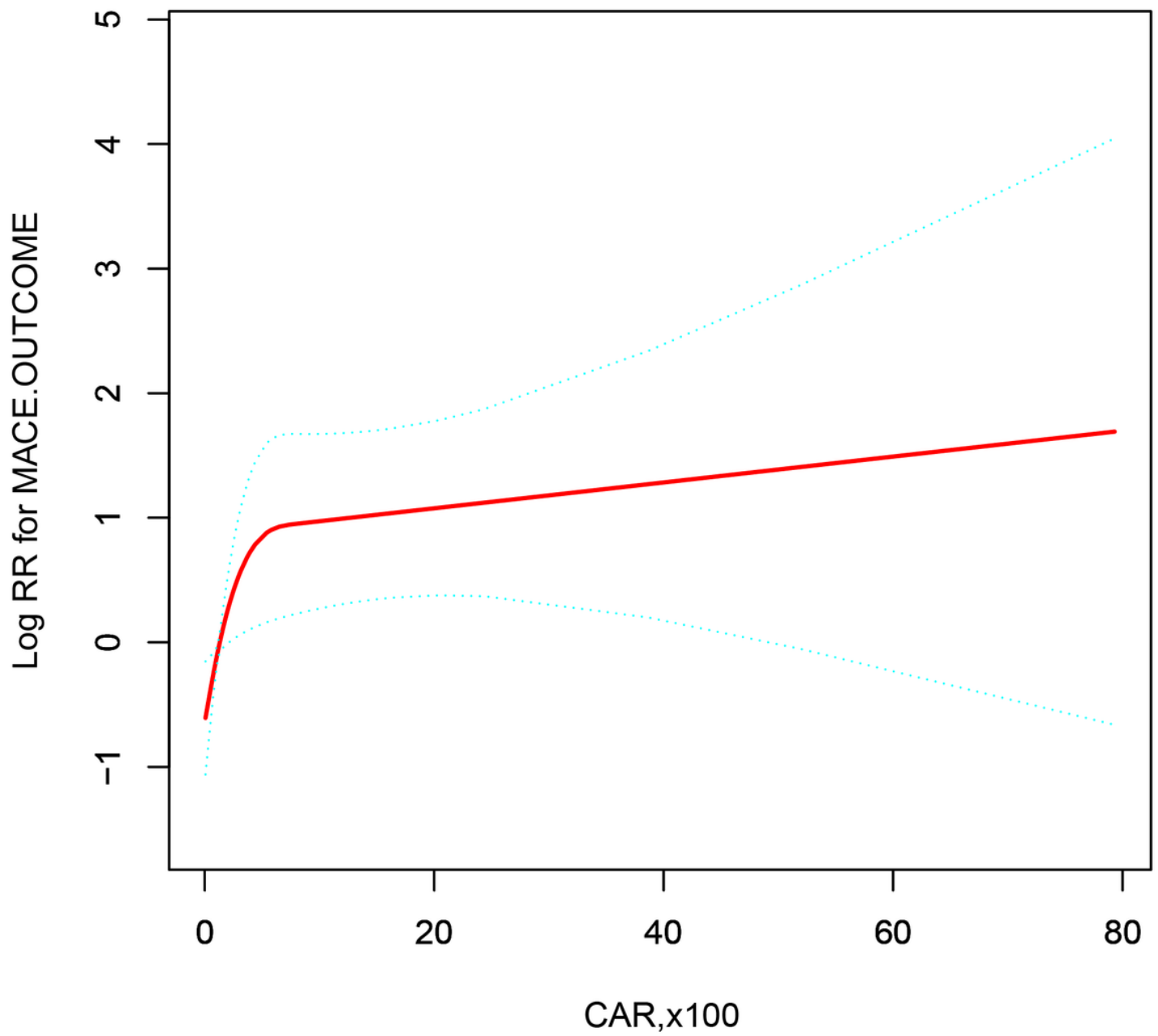


Figure 2

The nonlinear relationship between CAR and the poor prognosis of SCAD (adjusted for age, BMI, Hb, LDL-Chol, PAD, and Warfarin).