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Research article

The association between C-reactive protein to albumin ratio and adverse outcomes in acute ischemic stroke patients: A study in the Korean population

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ABSTRACT

Introduction: Our study aimed to explore the relationship between the C-reactive protein to albumin ratio (CAR) and adverse outcomes at 3 months in Korean patients with acute ischemic cerebral infarction.

Methods: This study focused on a sample of 1654 individuals with acute ischemic stroke (AIS), who received medical treatment at a reputable hospital in South Korea between January 2010 and December 2016. We used multivariate logistic regression models to show the effect of CAR admission on 3-month adverse outcomes in patients with AIS, as well as generalized additive modeling (GAM) and two-stage linear regression modeling to explore whether there was a linear relationship.

Results: A total of 1654 patients with acute ischemic cerebral infarction were enrolled in the study, and the CAR was determined to be associated with poor results for patients with AIS after 3 months. with correction for potential confounders (odds ratio [OR], 1.23; 95 % confidence interval [CI], 1.08–1; $p < 0.001$). A nonlinear relationship was found between the CAR and adverse outcomes at 3 months for patients with AIS, with a threshold of approximately 0.6. The effect sizes, CIs, and p-values above and below the threshold were 1.39 (1.25–1.55, $p < 0.001$) and 1.08 (0.81–1.43, $p = 0.60$).

Conclusions: The adverse outcomes of patients with AIS at three months were independently correlated with the CAR. In addition, there was a nonlinear relationship between adverse outcomes and the CAR, with the CAR increasing the risk of adverse outcomes at 3 months for patients with AIS when the CAR was less than 0.6.

1. Introduction

Acute ischemic stroke (AIS) is widely recognized as one of the leading causes of disability and mortality worldwide. It is the third most prevalent cause of disability and the second most common cause of death globally [1]. A staggering 12.2 million AIS cases were reported in 2019 alone, which tragically led to 6.6 million deaths [2]. Numerous studies have demonstrated that up to 80 % of stroke patients present with limb dysfunction, whereas the incidence of speech, language, and visual impairments ranges between 20 % and

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60 % [3,4]. Stroke also imposes a substantial economic burden on society, and with the continuous growth and aging of the population, corresponding costs are anticipated to surge significantly [1,5]. As such, accurately predicting the functional outcomes of patients with ischemic stroke is essential for optimizing poststroke recovery dynamics and creating customized treatment plans. Numerous factors influence the outcomes of stroke, including age, smoking, diabetes mellitus, coronary heart disease, hyperlipidemia, hypertension, and stroke etiology [6].

Compared to C-reactive protein (CRP) or albumin alone, the novel C-reactive protein-to-albumin ratio (CAR), has been suggested to be a more valuable predictor of inflammatory status and prognosis in various clinical contexts [7–11]. To our knowledge, data on the relationship between the CAR and adverse short-term outcomes in patients with acute ischemic stroke are scarce.

The major goal of this study was to explain the association between the CAR and poor outcomes three months after AIS, providing clinicians with detailed insights for the construction of optimal stroke treatment plans.

2. Methods

2.1. Study design

This was a cohort investigation using data collected from January 2010 to December 2016. The data were obtained from a prospective registry system at a single-center facility in South Korea.

2.2. Data sources

The data used in this paper came from a study by Kang MK et al., published in PLoS ONE [12]. This article is openly available and published in line with the Creative Commons Attribution License. This license grants unrestricted permission to use, distribute and reproduce the article in any medium, provided that the original author and source are properly acknowledged. We express our sincere gratitude to the authors for kindly sharing their data.

2.3. Participants

The initial investigation successfully recruited a total of 2084 individuals diagnosed with AIS. Blood samples from each patient were obtained from the first blood drawn on admission according to the hospital procedure. The original study criteria for exclusion were as follows: (i) individuals without laboratory information recorded or dysphagia testing within 24 h of admission, (ii) those who lacked a modified three-month Rankin scale (mRS) score post-hospitalization, and (iii) those whose CRP data were missing (Fig. 1). The aforementioned investigation was approved by the Institutional Review Board at Seoul National University Hospital. Furthermore, the IRB granted a waiver for obtaining patient consent, as evidenced by IRB No. 1009-062-332. Therefore, there was no need to obtain ethical approval for this secondary analysis.

2.4. Covariates

The C-reactive protein/albumin ratio (CAR) was a continuous variable calculated by dividing the serum CRP concentration (mg/dl) by the serum albumin concentration (g/dl). The CAR was then divided into quartiles and categorized as follows: Q1: <0.016, Q2: 0.016–0.041, Q3: 0.041–0.147, and Q4: ≥ 0.147.

The outcome variable was the adverse outcome of AIS patients at 3 months, which was assessed using the modified Rankin scale (mRS) score. Data collection involved structured interviews via telephone or during outpatient visits. The outcome variable was dichotomous: favorable outcome (mRS score ≤ 2) and unfavorable outcome (mRS score ≥ 3) [13].

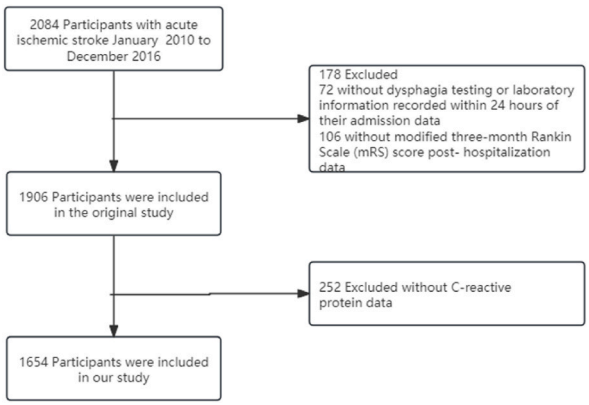

Fig. 1. Flow diagram of the study participants.

In our study, the selection of covariates was conducted by considering previous studies and incorporating our clinical knowledge and expertise. (i) Categorical variables included age, sex, smoking status, previous stroke/TIA, hypertension, diabetes mellitus (DM), hyperlipidemia, atrial fibrillation (AF), coronary heart disease, and stroke etiology (large artery atherosclerosis, small vessel occlusion, cardiogenic embolic type, other determined, or undetermined). (ii) Continuous variables included body mass index (BMI), serum triglyceride (TG), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), creatinine (Cr), and total cholesterol (TC) levels.

Data were gathered from the primary study. Clinical baseline characteristics were collected. Patients were divided into three groups according to age, (<50 years, 50–80 years, and ≥80 years) in consideration of the impact of stroke incidence and advanced age on prognosis), sex, body mass index (BMI), smoking (last cigarette in 6 months), hypertension disease, diabetes, dyslipidemia, cardiac disease (atrial fibrillation or coronary heart disease), and previous stroke/transient ischemic stroke (TIA). To assess initial neurological severity, the National Institutes of Health Stroke Scale (NIHSS) score was determined at the time of admission. TC, TG, LDL, HDL, Cr, CRP, and albumin were obtained from electronic medical records. Furthermore, stroke subtype categorization was conducted on the basis of the Trial of Org 10172 in the Acute Stroke Treatment (TOAST) classification system. Due to the limited occurrence of missing data for each variable, no imputation method was implemented.

2.5. Statistical analysis

The data collected for analysis were organized into two main categories: categorical variables and continuous variables. Frequencies (percentages) were used to describe the categorical variables. Continuous categories are displayed as the means ± standard deviations. Variables that were not distributed normally are presented as the median ± interquartile range (IQR).

Odds ratios (ORs) and 95 % confidence intervals (CIs) were calculated via logistic regression models to evaluate the correlation between the CAR and unfavorable outcomes following AIS. Sensitivity analysis was performed by dividing the CAR into quartiles and assessing the p-value for trends to test the robustness of the results. To examine the complex relationship between the CAR and adverse outcomes in AIS patients, four models were created: a crude model (unadjusted); a modified model solely accounting for sociodemographic factors (age, sex, BMI, smoking); a moderately adjusted model based on sociodemographic variables and past medical history (age, sex, BMI, smoking, previous stroke/TIA, hypertension, DM, hyperlipidemia, AF, coronary heart disease, and stroke mechanism); and a fully adjusted model (age, sex, BMI, smoking, previous stroke/TIA, hypertension, DM, hyperlipidemia, AF,

Table 1
Baseline characteristics according to 3-month outcomes with AIS.

Variables	Favorable outcome (n = 1165)	Unfavorable outcome (n = 489)	*P*-value
Sex, n (%)			<0.001
male	760 (65.24)	255 (52.15)	
female	405 (34.76)	234 (47.85)	
Age, years, n (%)			<0.001
< 50 years	112 (9.61)	21 (4.29)	
50–80 years	913 (78.37)	339 (69.33)	
≥ 80 years	140 (12.02)	129 (26.38)	
Smoking, n (%)	495 (42.49)	148 (30.27)	<0.001
BMI, Mean ± SD	23.74 ± 3.14	22.82 ± 3.50	<0.001
Previous stroke/TIA, n (%)	210 (18.03)	142 (29.04)	<0.001
Hypertension, n (%)	728 (62.49)	335 (68.51)	0.020
Diabetes Mellitus, n (%)	343 (29.44)	182 (37.22)	0.002
Hyperlipidemia, n (%)	442 (37.94)	158 (32.31)	0.030
Atrial fibrillation, n (%)	208 (17.85)	153 (31.29)	<0.001
Coronary heart disease, n (%)	137 (11.76)	56 (11.45)	0.859
Stroke mechanism, n (%)			<0.001
LAA	386 (33.13)	143 (29.24)	
SVO	250 (21.46)	56 (11.45)	
CE	271 (23.26)	160 (32.72)	
Other determined	79 (6.78)	70 (14.31)	
Undetermined	179 (15.36)	60 (12.27)	
Baseline NIHSS score, n (%)			<0.001
< 6 scores	963 (82.66)	155 (31.70)	
6–13 scores	154 (13.22)	175 (35.79)	
≥14 scores	48 (4.12)	159 (32.52)	
TC, Mean ± SD	182.20 ± 43.58	173.37 ± 46.54	<0.001
TG, (mg/dl), M (IQR)	97 (73, 132)	86.(63, 115)	<0.001
HDL-c, (mg/dl), M (IQR)	44 (36, 53)	43 (33, 54)	0.071
LDL-c, (mg/dl), M (IQR)	105.(81, 130)	101 (70, 129)	0.003
Cr, (mg/dl), M (IQR)	0.90 (0.76, 1.09)	0.86 (0.70, 1.10)	0.051
Albumin, (g/dl), Mean ± SD	4.08 ± 0.39	3.85 ± 0.48	<0.001
CRP, (mg/dl), M (IQR)	0.13 (0.06, 0.37)	0.37 (0.11, 2.34)	<0.001
CRP/Albumin ratio, M (IQR)	0.03 (0.01, 0.09)	0.09 (0.03, 0.62)	<0.001

Abbreviation: IQR, interquartile range; SD, standard deviation; TC, total cholesterol; TG, serum triglyceride; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; BMI, body mass index; TIA, transient ischemia attack; LAA, large artery atherosclerosis; SVO, small vessel occlusion; CE, cardioembolism; Cr, creatinine; CRP, c-reactive protein.

coronary heart disease, Stroke mechanism, TC, TG, HDL, LDL-C, HDL-C, Cr, and baseline NIHSS score. Each model included both univariate and multivariate binary logistic regression analyses.

Sophisticated techniques were used to examine potential nonlinearity in the correlations between the CAR and unfavorable outcomes. These techniques include the use of generalized additive models (GAMs) and complex smooth curve fitting techniques such penalized splines. When nonlinearity was found, a recursive process was used to determine the inflection point. As a result, a two-part binary logistic regression model (BLRM) was developed and placed on either side of this critical intersection.

All findings presented closely followed the STROBE statement. Data processing and analysis were performed using R software (available at http://www.R-project.org), along with Zstats v0.90 (www.medsta.cn/software). Significance was determined at the level of $p < 0.05$ [14].

3. Results

3.1. Characteristics of the participant

This study included 1654 participants after missing date were removed. The baseline characteristics table (Table 1) presents key findings related to the distribution of favorable and unfavorable outcomes among different demographic and clinical variables. Notably, there was a significant association between sex and outcome ($p < 0.001$), with a greater proportion of males experiencing favorable outcomes than females. Age also demonstrated a significant association with outcome ($p < 0.001$), as individuals aged 50–80 years presented a greater likelihood of unfavorable outcomes than did those <50 years or ≥ 80 years of age. Additionally, previous stroke history, atrial fibrillation, stroke mechanism, initial total NIHSS score, smoking status, and various laboratory parameters (including total cholesterol, triglyceride, creatinine, low-density lipoprotein, high-density lipoprotein, CRP, albumin levels, and the CRP/albumin ratio) were significantly associated with outcomes. These findings emphasize the importance of considering these baseline characteristics when evaluating outcomes and tailoring interventions for stroke patients.

3.2. Multivariate analyses

Four distinct models were created using a binary logistic regression model (BLRM).to examine the connection between the CRP/albumin ratio and the probability of unfavorable outcomes in patients with AIS. The unadjusted model revealed a 58 % increase in the odds of adverse outcomes in AIS patients per unit increase in the CAR (OR = 1.58, 95 % CI: 1.39, 1.79; $p < 0.001$). Similarly, both the partially adjusted model and the fully adjusted model suggested that as the CAR increased, the 3-month adverse prognosis of acute cerebral infarction subsequently increased: Model 1 (OR, 1.50; 95 % CI: 1.33, 1.70; $p < 0.001$), Model 2 (OR, 1.40; 95 % CI: 1.23, 1.58; $p < 0.001$), and Model 3 (OR, 1.23; 95 % CI: 1.08, 1.40; $p < 0.001$) (Table 2).

3.3. Sensitivity analyses

We transformed the CAR into an interquartile variable to further explore the relationship between the CAR and prognosis 3 months after acute cerebral infarction. In model 3, the adjusted OR for adverse outcomes in patients with AIS in Q1, Q2, and Q3 were 0.43 (95 % CI: 0.86–0.43), 0.51 (0.35–0.74), and 0.61 (0.43–0.86), respectively, with Q4 as a reference. In patients with AIS, the CAR was positively associated with an unfavorable prognosis, which was statistically significant in all the models (Table 3, trend $p < 0.001$).

To ensure the reliability of our results, we excluded stroke patients with NIHSS scores ≥14 (207 participants) at the onset of stroke before conducting multivariable logistic regression analyses. The CAR was independently associated with adverse outcomes in AIS patients at 3 months (all adjusted, OR = 1.25, 95 % CI: 1.08, 1.44, $p < 0.001$) (Supplementary Table S1).

Table 2
Association between CAR and 3-month adverse outcomes.

Variables	Unadjusted model		Model 1		Model 2		Model 3	
	OR (95 % CI)	*P*-value	OR (95 % CI)	*P*-value	OR (95 % CI)	*P*-value	OR (95 % CI)	*P*-value
CRP/Albumin ratio	1.58 (1.39–1.79)	<0.001	1.50 (1.33–1.70)	<0.001	1.40 (1.23–1.58)	<0.001	1.23 (1.08–1.40)	<0.001
Q4 (≥0.147)	Reference		Reference		Reference		Reference	
Q3 (0.041–0.147)	0.39 (0.29–0.52)	<0.001	0.40 (0.30–0.54)	<0.001	0.44 (0.32–0.60)	<0.001	0.61 (0.43–0.86)	0.026
Q2 (0.016–0.041)	0.29 (0.21–0.39)	<0.001	0.32 (0.23–0.43)	<0.001	0.38 (0.27–0.52)	<0.001	0.51 (0.35–0.74)	0.009
Q1 (<0.016)	0.23 (0.16–0.31)	<0.001	0.23 (0.17–0.32)	<0.001	0.28 (0.20–0.40)	<0.001	0.43 (0.86–0.43)	<0.001

OR: Odds Ratio, CI: Confidence Interval. The CAR was then divided into quartiles and categorized as follows: Q1: <0.016, Q2: 0.016–0.041, Q3: 0.041–0.147, and Q4: ≥0.147, where Q4 was the reference group.
Model1: Adjust: Sex, Age, BMI.
Model2: Adjust: Sex, Age, BMI, Previous stroke/TIA, Hypertension, Diabetes Mellitus, Hyperlipidemia, Smoking, Atrial fibrillation, Coronary heart disease, Stroke mechanism.
Model3: Adjust: Sex, Age, BMI, Previous stroke/TIA, Hypertension, Diabetes Mellitus, Hyperlipidemia, Smoking, Atrial fibrillation, Coronary heart disease, Stroke mechanism, Baseline NIHSS total, total cholesterol, serum triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and creatinine.

Table 3
Effect of Standardized CAR on adverse outcomes of AIS patients at 3 months: Adjusted Odds Ratios from Segmented Logistic Regression Analysis.

Characteristic	OR per SD[a]	95 % CI[a]	p-value
CRP/Albumin ratio (<0.6)	1.39	1.25, 1.55	<0.001
CRP/Albumin ratio (≥0.6)	1.08	0.81, 1.43	0.60
Log - likelihood ratio test	<0.001		

ORs were adjusted for Sex, Age, BMI, Previous stroke/TIA, Hypertension, Diabetes Mellitus, Hyperlipidemia, Smoking, Atrial fibrillation, Coronary heart disease, Stroke mechanism, Baseline NIHSS total, total cholesterol, serum triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and creatinine.

[a] OR = Odds Ratio, CI = Confidence Interval.

3.4. Threshold effect analysis

We found a nonlinear dose–response relationship between the CAR and adverse outcomes in patients with AIS (Fig. 2). We discovered that the CAR threshold was 0.6 by using a two-piecewise linear regression model. Nest, segmented regression was run independently on each group (CAR <0.6 and CAR ≥0.6), with Table 3 displaying the outcomes. According to Table 3 and Fig. 2, the unfavorable outcomes for patients with AIS increased quickly below the cutoff point (OR, 1.39; 95 % CI, 1.25–1.55; p < 0001). The estimated dose–response curve was consistent with a horizontal line above the threshold (CAR ≥0.6, OR, 1.08; 95 % CI, 0.81–1.43; p = 0.60).

3.5. Subgroup analysis

Subgroup analyses were performed to assess the impact of the CAR on adverse outcomes in patients with AIS in distinct subgroups (Fig. 3). The associations between the CAR and adverse outcomes in patients with AIS was coordinated in the subgroups as follows: sex (female vs. male; P-interaction = 0.164); age (<50 years vs. 50–80 years vs. ≥ 80 years; p-interaction = 0.349); diabetes mellitus (p-interaction, 0.233); hypertension (p-interaction, 0.276); hyperlipemia (p-interaction, 0.709); previous stroke/TIA (p-interaction, 0.57); and smoking (p-interaction, 0.344), Notably, in the baseline NIHSS score subgroups, there were no significant group differences between strokes of different severities and 3-month adverse stroke prognoses (<6 scores vs. 6–13 scores vs. ≥14 scores; P-interaction = 0.536). Therefore, the correlation between the CAR and negative outcomes in patients with AIS remains strong and consistent.

4. Discussion

In this retrospective cohort study, the CAR was independently associated with adverse outcomes in AIS patients at 3 months (all adjusted, OR = 1.21, 95 % CI: 1.06, 1.39, p < 0.001), was unaffected by significant covariates or confounders, and the association was dependent.

Moreover, a nonlinear association between the CAR and the risk of an adverse outcome for AIS patients at three months poststroke was revealed via using a generalized additive model. Nevertheless, when the CAR was below the 0.6 threshold, we found a positive correlation between the CAR and the risk of an adverse outcome for AIS patients at three months (OR, 1.39; 95 % CI, 1.25–1.55; p <

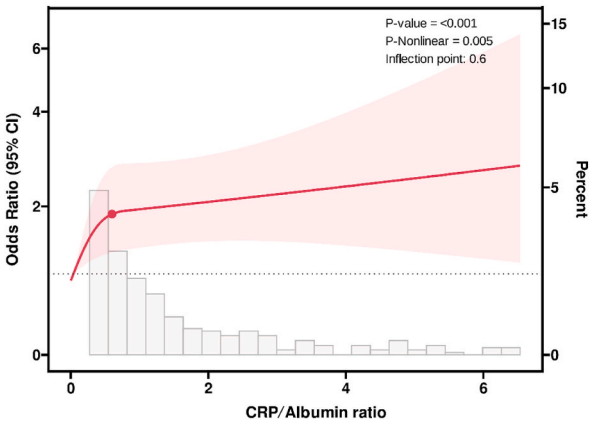

Fig. 2. Association between CAR and adverse outcomes of AIS patients at 3 months with the RCS function. Model with 3 knots located at 10th, 50th and 90th percentiles. The x-axis shows the value of the c-reactive protein to albumin ratio. Y-axis represents the OR to present adverse outcomes of AIS patients at 3 months for any value of CRP/Albumin ratio compared to individuals with reference value (50th percentile) of CRP/Albumin ratio. The logistic regression was adjusted for Sex, Age, BMI, Previous stroke/TIA, Hypertension, Diabetes Mellitus, Hyperlipidemia, Smoking, Atrial fibrillation, Coronary heart disease, Stroke mechanism, Baseline NIHSS total, TC, TG, HDL-c, LDL-c, and Cr.

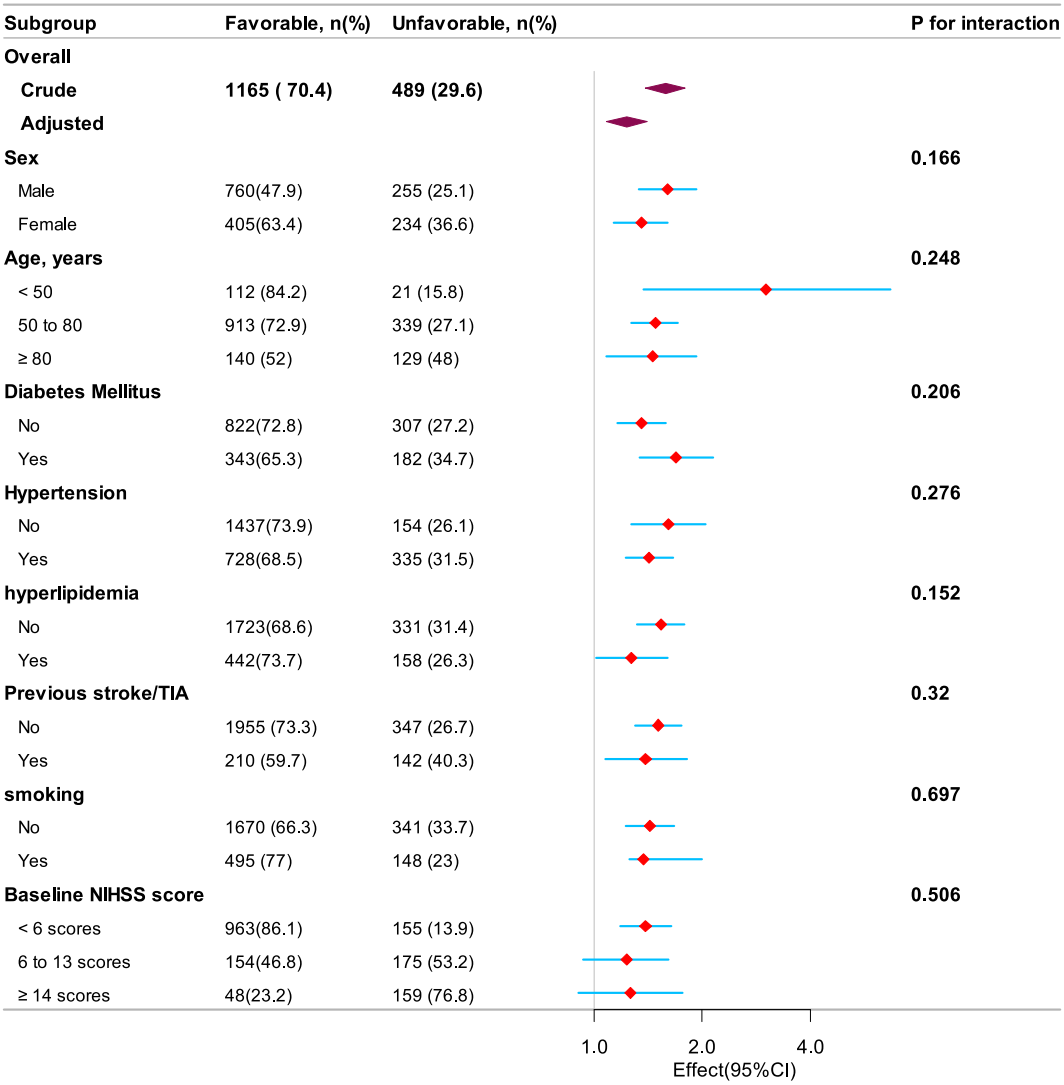

Fig. 3. Subgroup analyses of the CAR and 3-month outcomes after acute ischemic stroke. Taking into account the different effects of age, stroke severity at onset, and previous stroke history on stroke prognosis, age was classified into 3 subgroups (<50 years, 50–80 years, and ≥80 years), baseline NIHSS scores were classified into 3 subgroups (<6 scores, 6–13 scores, and ≥14 scores), and 2 subgroups were classified according to the presence of a history of stroke/TIA. Each stratification was meticulously adjusted to account for various factors. These factors included Sex, Age, BMI, Previous stroke/TIA, Hypertension, Diabetes Mellitus, Hyperlipidemia, Smoking, Atrial fibrillation, Coronary heart disease, Stroke mechanism, Baseline NIHSS total, TC, TG, HDL-c, LDL-c, and Cr.

0.001). However, when the CAR was above the threshold, there was no statistical significance, indicating that a threshold effect was present (OR, 1.08; 95 % CI, 0.81–1.43; p = 0.60).

Growing evidence suggests that systemic inflammation plays a key role in many pathophysiologic processes ranging from cardiovascular disease to cognitive decline [15,16]. CRP is an acute-phase protein synthesized by the liver in response to inflammatory cytokines (such as interleukin-1 and TNF) and is one of the most commonly used nonspecific indicators of inflammation, with a half-life of approximately 19 h [17]. CRP has been identified as a sensitive serum marker for predicting adverse outcomes of cardiovascular events, and its levels are influenced by genetic polymorphisms [18]. Notably, a cohort study confirmed the association of CRP with the risk of first cardiovascular events and mortality [19]. Although the exact mechanism is not clear, CRP is closely associated with the onset, development and regression of AIS. The results of clinical studies have shown that CRP levels are elevated within the first 48 h after onset and remain high for 3–6 months after AIS [20,21]. CRP may exacerbate cerebral cell damage by facilitating the advancement and progression of atherosclerosis, activating the complement system, suppressing fibrinolytic mechanisms, and enhancing thrombosis [22].

Albumin is the most abundant plasma protein in the body and plays an important role in all aspects of life [23–25]. Radhika Nair et al. reported that the serum albumin concentration was a potential predictor of functional outcomes following acute ischemic stroke

[26]. Furthermore, research has shown that decreased levels of serum albumin may contribute to the progression of atherosclerosis by reducing antioxidant effects and anti-inflammatory capacities [27,28]. Hypoproteinemia is often indicative of malnutrition which affects the prognosis of stroke patients [29]. In addition, prior research has demonstrated that individuals with hypoalbuminemia are at an elevated risk of experiencing complications subsequent to a stroke, with pneumonia being a predominant concern. These complications not only present a substantial threat to patients survival but also hinder their capacity to recover functionality [30].

The CRP/albumin ratio (CAR), a new inflammatory parameter, is more sensitive and specific than the values of these two markers alone in the prediction of various systemic inflammatory states and patient prognosis [8,9]. Inflammation plays an important role in atherosclerosis, which affects the prognosis of cardiovascular disease [31–33]. Recent research has indicated that the CAR serves as a novel inflammatory marker reflecting the inflammatory status associated with cardiovascular disease [34,35]. Like acute coronary syndrome, we found that the CAR was strongly associated with poor short-term prognosis in patients with acute cerebral infarction. As far as we are aware, this is the first report that investigates the correlation between the CAR and unfavorable 3-month outcomes of patients with AIS. When the CAR is less than 0.6, increase the risk of poor prognosis at 3 months for AIS patients, may be because of the patients with cerebral infarction combined with infections, poor nutritional status and other complications, for the acute cerebral infarction combined with infections and other complications, the risk of poor prognosis is increased, therefore, active control of infections, appropriate nutritional support may improve the poor prognosis of acute cerebral infarction at 3 months.

Our study, has several limitations. First, this study used a retrospective design, featured a modest sample size, and depended on the experience of a single center. Second, the outcome variable only included a 3-month short-term prognosis for cerebral infarction and did not include a one or even many-year long-term prognosis due to limitations in the original data. Third, only baseline CRP and albumin levels were obtained upon admission; further assessments may reveal changes that may have additional predictive value. Fourth, the raw data included only C-reactive protein, and did not include inflammatory markers such as the erythrocyte sedimentation rate, procalcitonin, or interleukin 6. Therefore, the study failed to explore the potential impact of other inflammatory markers on these findings. Fifth, considering that the study population was limited to one single-center institution in Korea, the study population may not be representative of other regions, limiting the generalizability of the results. We should consider this in the subsequent phase of our real-world research. To verify the causal association between the CAR and adverse outcomes in AIS patients, future studies should concentrate on randomized controlled trials.

5. Conclusions

There was a nonlinear relationship between the C-reactive protein-to-albumin ratio (CAR) and adverse outcomes in AIS patients at 3 months, and CRA increased the risk of adverse outcomes at 3 months poststroke in patients with AIS when the CAR ratio was less than 0.6.

CRediT authorship contribution statement

Dandan Yu: Visualization, Software, Investigation. **Guixiang Guo:** Validation, Resources, Project administration. **Fangchao Wan:** Validation, Methodology, Data curation. **Bohong Hu:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization.

Data availability

The data of the current study can be obtained by supplementary materials. Further inquiries can be directed to contacting the original author (https://doi.org/10.1371/journal.pone.0228738).

Ethical approval

This article was a secondary analysis using existing data that came from a study by Kang MK et al., published in PLoS ONE. The institutional review board of Seoul National University Hospital approved the study protocol and waived the need for patient consent (IRB NO. 1009-062-332).

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Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e39212.

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