International Journal of General Medicine

Dovepress

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ORIGINAL RESEARCH

# The Radio of RDW/ALB: A Cost-Effective Biomarker for Early-Stage Risk Stratification in Acute Ischemic Stroke

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**Background and Aims:** The red blood cell distribution width (RDW) to albumin (ALB) ratio (RAR) has been identified as a prognostic indicator for mortality in critically ill patients across various diseases. Nevertheless, the impact of RAR on clinical functional prognosis in Acute ischemic stroke (AIS) remains uncertain. This study aimed to evaluate the prognostic significance of RAR in AIS patients.

**Methods:** A secondary analysis was performed on a cohort study, involving 1906 AIS patients recruited from a South Korean academic hospital. Both univariate and multivariate logistic regression was employed to assess the connections between RAR and negative functional results in AIS. To explore potential non-linear relationships in this association, a generalized additive model (GAM) and smooth curve fitting were utilized. Further, a mediation analysis was performed to identify possible mediators.

**Results:** Out of the 1906 eligible patients, 546 (28.65%) were found to have an unfavorable prognosis. Patients with elevated RAR had a higher likelihood of facing a negative prognosis in AIS (all P<0.001). RAR demonstrated a dose-response relationship with the probability of poor functional prognosis. When analysis of RAR as a continuous variable, an increase in RAR was correlated with a higher risk of adverse prognosis.When RAR was analyzed as quartile variables, the highest RAR remained an independent contributing factor for both 3-month unfavorable outcomes (adjusted OR, 1.4; 95% CI: 1.0–2.1, P=0.046) and 3-month mortality (adjusted OR, 5.2; 95% CI, 2.0–13.9; p<0.001). More interestingly, the presence of a pro-inflammatory state may serve as a mediator in the connections between RAR and adverse functional outcomes.

**Conclusion:** Given its cost-effectiveness and ease of measurement, baseline RAR holds promise as a valuable biomarker for early risk assessment in AIS patients.

**Keywords:** acute ischemic stroke, RDW/ALB, adverse functional outcomes, dose-response relationship, biomarker

## Introduction

Stroke is still the second most common cause of death and the main reason for adult-onset disability worldwide, leading to substantial economic and medical challenges for both individuals and society.[1,2] From 1990 to 2019, the Global Burden of Diseases (GBD) data revealed significant increases in stroke statistics: incident strokes rose by 70%, prevalent strokes by 85%, stroke-related deaths by 43%, and DALYs by 32%.[2] In 2010 in China, the estimated prevalence of stroke was 2.6%, with an incidence rate of 505.2 per 100,000 person-years and a mortality rate of 343.4 per 100,000 person-years.[3] Acute ischemic stroke (AIS), stemming from cerebral artery occlusion or ischemic cerebral hypoperfusion, constitutes over 80% of all strokes.[4] Research has shown that 40% of AIS patients fail to achieve functional independence despite advancements in therapeutic approaches.[5] The identification of precise predictors of functional prognosis in AIS patients has the potential to optimize treatment decisions, enhance clinical care, and simplify recovery and discharge planning.[6] Hence, finding a dependable prognostic indicator to forecast the functional outlook of AIS patients is crucial.

Received: 18 August 2024
Accepted: 17 September 2024
Published: 27 September 2024

Routine blood tests often include an assessment of the red blood cell distribution width (RDW). It provides an accurate and objective reflection of the size variability of peripheral red blood cells. The typical range of RDW in most clinical laboratories falls between 11% and 15%,[7] and an elevation in RDW may indicate involvement in various detrimental biological pathways, such as inflammation,[8] oxidative stress,[9] telomere shortening,[10] nutritional deficiencies,[11] and erythropoietin deficiency or dysfunction.[12] There is evidence that elevated RDW levels are closely correlated to the occurrence and recurrence of AIS,[13–15] and higher RDW values were linked with poorer functional outcomes and higher mortality rates.[16,17] RDW can serve as an adverse biomarker for assessing stroke severity and predicting the prognosis of AIS patients.

Serum albumin (ALB), the predominant water-soluble protein in plasma, is synthesized in the liver and plays a vital role in regulating plasma colloid osmotic pressure and maintaining nutritional balance in the body.[18] The serum albumin concentration indicates the host's nutritional and inflammatory status,[19] and its reduction is linked to a higher risk of stroke and poor prognosis in AIS.[20]

The red blood cell distribution width to albumin ratio (RAR) is viewed as an innovative and informative marker that may have prognostic significance in cardiovascular and respiratory conditions.[14,21] In addition, RAR appears to be nonspecific indicators capable of effectively stratifying risk in patients with serious conditions, such as type 2 diabetes and foot ulcers,[22] acute kidney injury,[23] severe acute pancreatitis,[24] and elderly Survivors with Sepsis.[25] In the field of stroke, prior studies have suggested its ability to forecast 30-day all-cause death in severely ill patients with AIS.[26] Nevertheless, the influence of RAR on clinical functional prognosis in AIS patients remains uncertain. To fill this gap, we performed a secondary analysis utilizing information from a study group in Korea to investigate the relationship between RAR and negative functional results in patients with AIS.

# Methods

## Study Design and Data Source

A post hoc analysis was conducted on publicly available research data from a prospective cohort study by Kang, Kim, Kim et al "Geriatric nutritional risk index predicts poor outcomes in patients with acute ischemic stroke-automated undernutrition screen tool".[27] The article is freely available and released under the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction as long as the original author and source are acknowledged.[27] Here, We express our gratitude to the authors for their contribution.

## Study Population

From January 2010 to December 2016, 2084 individuals diagnosed with AIS within a week of symptom onset were included in the initial study. The criteria for exclusion were specified as: (i) no evaluation for swallowing difficulties or test results within 24 hours of being admitted to the hospital (n=72); (ii) missing a modified Rankin Scale (mRS) score 90 days after being admitted (n=106). Finally, the initial study encompassed a cohort of 1906 individuals. Given that the data of interest, such as ALB and RDW values were complete in the original study, all 1906 individuals were ultimately included in the current analysis.[27] The participant selection process is outlined in Figure 1. The initial study was carried out with the authorization of the Institutional Review Board at Seoul National University Hospital, which exempted the need for patient consent (IRB No.1009–062-332). As a result, ethical approval was deemed unnecessary for the current secondary analysis. Furthermore, the initial research adhered to the Declaration of Helsinki guidelines, ensuring all protocols complied with relevant norms and regulations, as detailed in the Declarations section.[27] This secondary analysis followed the same approach.

## Data Collection

Data on age, gender, anthropometric measurements (BMI), medical histories, and clinical and laboratory data were collected for analysis. From the electronic medical record, various laboratory parameters were extracted, including red blood cell (RBC), hemoglobin (HGB), hematocrit (HCT), white blood cell (WBC), platelet (PLT), aspartate amino-transferase (AST), alkaline phosphatase (ALP), serum total protein, blood urea nitrogen (BUN), serum creatinine (Scr), fasting blood glucose (FBG), hemoglobin A1C (HBA1c), fibrinogen (FIB), international normalized ratio (INR), and high-sensitivity C-reactive protein (Hs-CRP). Patients' medical backgrounds were extensively recorded, including past

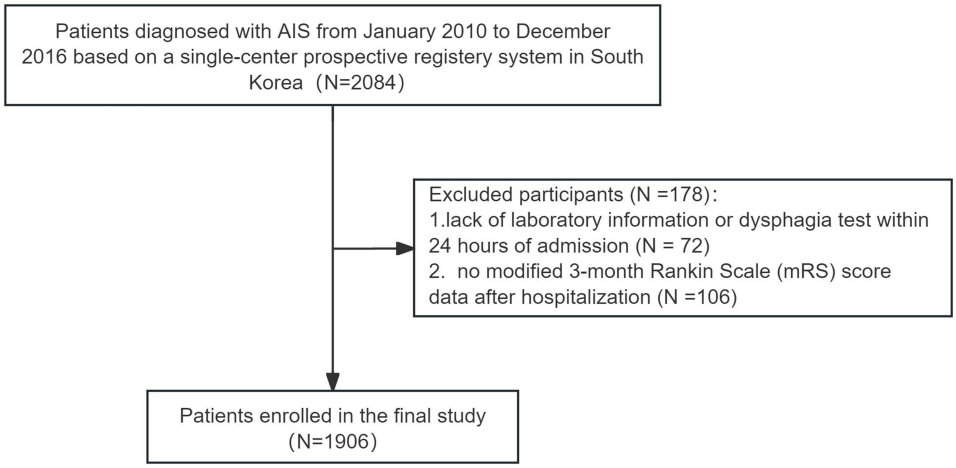


**Figure 1** Flow chart of the study.
**Abbreviations**: AIS, acute ischemic stroke; RDW, red cell distribution width; ALB, albumin.

experiences of stroke/TIA, diabetes mellitus (DM), dyslipidemia, atrial fibrillation (AF), and coronary heart disease (CHD). Furthermore, information from clinical records including pre-existing modified Rankin Scale (mRS) rating and smoking habits (last cigarette within 6 months) were gathered. Upon arrival, neurological severity was initially assessed using the National Institutes of Health Stroke Scale (NIHSS) score. The cause of the stroke was additionally classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) guidelines.[28]

RAR calculated as the ratio of RDW to ALB, is treated as a continuous variable for AIS patients within the first 24 hours of admission, with data sourced from electronic medical records.[27] For analytical purposes, RAR was divided into quartiles: Q1 (<2.98), Q2 (2.98–3.22), Q3 (3.22–3.58), and Q4 (≥3.58).

## Outcome Measures

In line with the research referenced,[27] this study primarily examined the short-term outlook following an AIS event, as indicated by the mRS score at the 3-month follow-up achieved via outpatient visits or scheduled phone calls. Patients were segregated into two distinct groups based on their respective outcomes: those exhibiting a favorable prognosis (mRS score < 3) and those with unfavorable prognoses at the 3-month mark (mRS score ≥ 3).[29] The secondary outcome was 3-month mortality, which was delineated by a mRS score of 6 at 90 days after AIS onset.

## Statistical Analysis

The baseline characteristics of all patients were categorized based on RAR quartiles. Mean and standard deviation (SD) or median (interquartile range [IQR]) were used to represent continuous variables, while categorical variables were shown as frequency or percentage. Statistical analyses included the chi-square test, one-way ANOVA, and the Kruskal–Wallis test to compare categorical, normally distributed, and non-normally distributed continuous variables, respectively.

Univariate and multivariate logistics regression models were utilized to evaluate the association between the RAR and adverse functional outcomes in patients with AIS. Three distinct models were utilized: a crude model without adjustments; model I adjusted for age and sex; and model II which built upon model I by further adjusting for BMI, history of previous stroke or TIA, hypertension, DM, dyslipidemia, smoking, AF, CHD, initial NIHSS, premorbid mRS and stroke etiology. The selection of covariates was informed by clinical expertise and scholarly literature. Odds ratios (ORs) and 95% confidence intervals (95% CI) were utilized to compute and present effect sizes. Furthermore, E values were calculated to investigate the potential presence of hidden confounding in the association between RAR and adverse results.[30]

In addition, generalized additive models (GAM) and curve-fitting techniques were employed to evaluate the nonlinear correlation between RAR and negative functional results in AIS patients. Subgroup analysis was conducted to explore the influence of RAR on unfavorable prognosis within various subgroups, including age, sex, BMI, stroke etiology, and

medical histories. The modifications and interactions within these subgroups were examined using the likelihood ratio test. In light of the recognition of the pro-inflammatory state as a potential mechanism by which RAR influences the progression of AIS, our study sought to examine the potential mediation of hs-CRP in the correlation between RAR and negative outcomes in AIS. The Sobel test was employed to evaluate the mediating effect of hs-CRP in the examined association.[31] Statistical analysis was conducted using R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc, Boston, MA), with significance set at a two-sided p-value ≤ 0.05.

# Results

## Participants Baseline Characteristics

The final analysis included 1906 participants, with 1168 (61.28%) male patients, 546 (28.65%) had an unfavorable prognosis, and 91 (4.77%) died at 3 months after AIS onset. The baseline characteristics of participants were stratified by RAR quartiles and presented in Table 1. Patients with higher RAR levels (Q3-Q4), compared to those in the low RAR (Q1-Q2), were typically older, no smokers, and have a higher prevalence of AF, CHD, and previous stroke or TIA. Additionally, they exhibited elevated baseline levels of BUN, Creatinine, AST, ALP, and FIB, but lower levels of RBC count, Hemoglobin, Hematocrit, Platelet count, ALT, and BMI. Their stroke etiology was predominantly cardio-embolic or other determined causes. Moreover, these individuals showed higher initial NIHSS scores, discharge NIHSS scores, and premorbid mRS scores, and had a greater chance of facing unfavorable functional results.

## Association Between RAR and Adverse Functional Outcomes

The unadjusted and multivariable-adjusted regression analyses were utilized to assess the prognostic value of RAR on adverse functional outcomes in AIS, as detailed in Table 2. The study findings showed that higher RAR levels, when examined as a continuous factor, were linked to increased chances of negative functional results at 3 months (odds ratio range 1.5–2.2, p<0.001) and 3-month mortality (odds ratio range 1.9–2.6, p<0.001). Moreover, examining RAR as quartile categories, while adjusting for age and gender, showed that the top RAR (Q4 compared to Q1) was associated

**Table 1** Baseline Characteristics of Participants

| Variables | Total (n = 1906) | RAR | | | | *P-value* |
|---|---|---|---|---|---|---|
| | | Q1 (<2.98) N=470 | Q2 (2.98–3.22) N=480 | Q3 (3.22–3.58) N=479 | Q4 (≥3.58) N=477 | |
| **Demographics** | | | | | | |
| Male, n(%) | 1168 (61.28) | 290 (61.70) | 318 (66.25) | 278 (58.04) | 282 (59.12) | 0.044 |
| Age(years), n(%) | | | | | | <0.001 |
| <50 | 161 (8.45) | 75 (15.96) | 34 (7.08) | 24 (5.01) | 28 (5.87) | |
| 50 to <70 | 780 (40.92) | 237 (50.43) | 225 (46.88) | 169 (35.28) | 149 (31.24) | |
| ≥70 | 965 (50.63) | 158 (33.62) | 221 (46.04) | 286 (59.71) | 300 (62.89) | |
| **Anthropometric** | | | | | | |
| BMI (kg/m2) | 23.50 ± 3.25 | 24.31 ± 3.19 | 23.69 ± 3.12 | 23.42 ± 3.21 | 22.58 ± 3.26 | <0.001 |
| **Laboratory parameters** | | | | | | |
| RBC count ($10^9$/L) | 4.32 ± 0.64 | 4.64 ± 0.48 | 4.47 ± 0.52 | 4.29 ± 0.54 | 3.90 ± 0.74 | <0.001 |
| Hemoglobin (g/dL) | 13.48 ± 2.00 | 14.54 ± 1.42 | 14.01 ± 1.53 | 13.46 ± 1.65 | 11.92 ± 2.27 | <0.001 |
| Hematocrit (%) | 40.07 ± 5.59 | 42.65 ± 4.05 | 41.49 ± 4.44 | 40.12 ± 4.73 | 36.05 ± 6.47 | <0.001 |
| WBC count ($10^9$/L) | 8.14 ± 2.89 | 8.46 ± 2.87 | 7.81 ± 2.34 | 7.97 ± 2.69 | 8.32 ± 3.49 | <0.001 |
| Platelet count ($10^9$/L) | 223.61 ± 71.31 | 237.46 ± 65.38 | 224.59 ± 58.13 | 217.69 ± 59.93 | 214.94 ± 93.97 | <0.001 |
| BUN (mg/dL) | 16.00 (12.00–20.00) | 14.00 (12.00–17.00) | 15.00 (13.00–19.00) | 16.00 (13.00–20.00) | 17.00 (13.00–23.00) | <0.001 |
| Creatinine (mEq/L) | 0.89 (0.74–1.08) | 0.86 (0.73–1.00) | 0.90 (0.76–1.08) | 0.89 (0.74–1.08) | 0.91 (0.72–1.23) | <0.001 |
| AST(U/L) | 23.00 (18.00–29.75) | 23.00 (18.25–28.00) | 22.00 (18.00–27.00) | 23.00 (19.00–30.00) | 24.00 (19.00–32.00) | <0.001 |
| ALT(U/L) | 18.00 (13.00–26.00) | 20.00 (15.00–29.00) | 18.00 (14.00–24.00) | 17.00 (13.00–26.00) | 17.00 (11.00–25.00) | <0.001 |
| ALP(U/L) | 68.00 (56.00–85.00) | 67.00 (56.00–81.00) | 67.00 (56.00–80.00) | 68.00 (55.00–85.00) | 74.00 (59.00–95.00) | <0.001 |
| Total protein (g/dL) | 7.01 ± 0.61 | 7.42 ± 0.42 | 7.15 ± 0.42 | 6.93 ± 0.46 | 6.55 ± 0.73 | <0.001 |

(*Continued*)

**Table 1** (Continued).

| Variables | Total (n = 1906) | RAR | | | | *P-value* |
|---|---|---|---|---|---|---|
| | | Q1 (<2.98) N=470 | Q2 (2.98–3.22) N=480 | Q3 (3.22–3.58) N=479 | Q4 (≥3.58) N=477 | |
| FBG (mmol/L) | 106.85 ± 38.25 | 108.98 ± 39.32 | 104.47 ± 35.71 | 105.42 ± 35.69 | 106.00 ± 36.77 | <0.001 |
| HBA1c (%) | 6.37 ± 1.15 | 6.30 ± 1.09 | 6.25 ± 0.97 | 6.35 ± 1.08 | 6.29 ± 1.02 | <0.001 |
| Hs-CRP (mg/dL) | 0.16 (0.06–0.60) | 0.12 (0.05–0.19) | 0.16 (0.06–0.27) | 0.16 (0.08–0.38) | 0.51 (0.16–3.34) | 0.267 |
| INR | 1.05 ± 0.32 | 1.03 ± 0.27 | 1.02 ± 0.20 | 1.03 ± 0.26 | 1.13 ± 0.46 | 0.484 |
| FIB (mg/L) | 334.19 ± 85.21 | 316.31 ± 62.79 | 321.04 ± 64.76 | 331.92 ± 75.41 | 366.69 ± 115.58 | <0.001 |
| RAR | 13.40 ± 1.54 | 2.80 ± 0.12 | 3.09 ± 0.07 | 3.39 ± 0.10 | 4.29 ± 0.84 | <0.001 |
| RDW($10^9$/L) | 4.02 ± 0.43 | 12.39 ± 0.50 | 12.90 ± 0.53 | 13.35 ± 0.58 | 14.93 ± 2.23 | <0.001 |
| Albumin (g/dL) | 3.39 ± 0.70 | 4.43 ± 0.20 | 4.17 ± 0.19 | 3.94 ± 0.19 | 3.53 ± 0.43 | <0.001 |
| **Comorbidities, n(%)** | | | | | | |
| Previous stroke/TIA | 402 (21.09) | 81 (17.23) | 97 (20.21) | 104 (21.71) | 120 (25.16) | 0.026 |
| Hypertension | 1211 (63.54) | 294 (62.55) | 305 (63.54) | 307 (64.09) | 305 (63.94) | 0.961 |
| Diabetes Mellitus | 614 (32.21) | 135 (28.72) | 147 (30.63) | 164 (34.24) | 168 (35.22) | 0.109 |
| Dyslipidemia | 699 (36.67) | 198 (42.13) | 188 (39.17) | 176 (36.74) | 137 (28.72) | <0.001 |
| Atrial fibrillation | 407 (21.35) | 59 (12.55) | 90 (18.75) | 113 (23.59) | 145 (30.40) | <0.001 |
| CHD | 220 (11.54) | 36 (7.66) | 48 (10.00) | 71 (14.82) | 65 (13.63) | 0.002 |
| Smoking status | 750 (39.35) | 208 (44.26) | 191 (39.79) | 183 (38.20) | 168 (35.22) | 0.038 |
| **Scoring systems** | | | | | | |
| Initial NIHSS | 3.00 (1.00–7.00) | 3.00 (1.00–5.00) | 2.00 (1.00–5.00) | 4.00 (1.50–9.00) | 5.00 (2.00–11.00) | <0.001 |
| Discharge NIHSS | 2.00 (0.00–4.00) | 1.00 (0.00–3.00) | 1.00 (0.00–3.00) | 2.00 (0.00–5.00) | 2.00 (1.00–8.00) | <0.001 |
| Premorbid mRS score, n(%) | | | | | | <0.001 |
| mRS score<3 | 1679 (88.14) | 437 (92.98) | 427 (88.96) | 411 (85.80) | 404 (84.87) | |
| mRS score ≥3 | 226 (11.86) | 33 (7.02) | 53 (11.04) | 68 (14.20) | 72 (15.13) | |
| **Stroke etiology, n(%)** | | | | | | <0.001 |
| LAA | 606 (31.79) | 172 (36.60) | 168 (35.00) | 147 (30.69) | 119 (24.95) | |
| SVO | 365 (19.15) | 100 (21.28) | 126 (26.25) | 83 (17.33) | 56 (11.74) | |
| CE | 493 (25.87) | 77 (16.38) | 109 (22.71) | 150 (31.32) | 157 (32.91) | |
| Other determined | 171 (8.97) | 39 (8.30) | 19 (3.96) | 33 (6.89) | 80 (16.77) | |
| Undetermined | 271 (14.22) | 82 (17.45) | 58 (12.08) | 66 (13.78) | 65 (13.63) | |
| **Outcomes, n(%)** | | | | | | |
| 3-month unfavorable outcomes | 546 (28.65) | 91 (19.36) | 100 (20.83) | 150 (31.32) | 205 (42.98) | <0.001 |
| 3-month mortality | 91 (4.77) | 5 (1.06) | 8 (1.67) | 13 (2.71) | 65 (13.63) | <0.001 |

**Abbreviations**: RAR, red blood cell distribution width/albumin ratio; BMI, body mass index; RBC, red blood cell; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; FBG, fasting blood glucose; Hs-CRP, Hs-C-reactive protein; INR, international normalized ratio; FIB, fibrinogen; RDW, red blood cell distribution width; TIA, transient ischemia attack; CHD, coronary heart disease; NHISS, National Institutes of Health Stroke Scale; mRS, modified rankin scale; LAA, large artery atherosclerosis; SVO, small vessel occlusion; CE, cardioembolism.

**Table 2** Relationship Between RAR and Adverse Functional Outcomes in Multiple Regression Model

| Different outcomes | Unadjusted Model | | Model I | | Model II | |
|---|---|---|---|---|---|---|
| | OR (95% CI) | *P*-value | OR (95% CI) | *P*-value | OR (95% CI) | *P*-value |
| **3-month unfavorable outcomes** | | | | | | |
| RAR | 2.2 (1.9, 2.5) | <0.001 | 2.0 (1.8, 2.4) | <0.001 | 1.5 (1.3, 1.8) | <0.001 |
| RAR(quartile) | | | | | | |
| Q1 (<2.98) | Reference | | Reference | | Reference | |
| Q2 (2.98–3.22) | 1.1 (0.8, 1.5) | 0.572 | 1.0 (0.7, 1.4) | 0.924 | 1.0 (0.7, 1.4) | 0.839 |
| Q3 (3.22–3.58) | 1.9 (1.4, 2.6) | <0.001 | 1.6 (1.2, 2.2) | 0.003 | 1.1 (0.8, 1.6) | 0.605 |
| Q4 (≥3.58) | 3.1 (2.3, 4.2) | <0.001 | 2.6 (2.0, 3.6) | <0.001 | 1.4 (1.0, 2.1) | 0.046 |
| *P* for trend | | <0.001 | | <0.001 | | 0.028 |

(*Continued*)

**Table 2** (Continued).

| Different outcomes | Unadjusted Model | | Model I | | Model II | |
|---|---|---|---|---|---|---|
| | OR (95% CI) | *P*-value | OR (95% CI) | *P*-value | OR (95% CI) | *P*-value |
| **3-month mortality** | | | | | | |
| RAR | 2.6 (2.2, 3.2) | <0.001 | 2.6 (2.1, 3.2) | <0.001 | 1.9 (1.5, 2.4) | <0.001 |
| RAR(quartile) | | | | | | |
| Q1 (<2.98) | Reference | | Reference | | Reference | |
| Q2 (2.98–3.22) | 1.6 (0.5, 4.9) | 0.428 | 1.5 (0.5, 4.6) | 0.487 | 1.3 (0.4, 4.3) | 0.644 |
| Q3 (3.22–3.58) | 2.6 (0.9, 7.3) | 0.072 | 2.2 (0.8, 6.4) | 0.132 | 1.3 (0.4, 3.8) | 0.687 |
| Q4 (≥3.58) | 14.7 (5.9, 36.8) | <0.001 | 12.7 (5.0, 32.0) | <0.001 | 5.2 (2.0, 13.9) | <0.001 |
| *P* for trend | | <0.001 | | <0.001 | | <0.001 |

**Notes**: Model I adjusted for age and sex. Model II adjusted for age, sex, BMI, history of previous stroke or transient ischemia attack, hypertension, diabetes mellitus, dyslipidemia, smoking, atrial fibrillation, coronary heart disease, initial NIHSS, premorbid mRS, and stroke etiology.
**Abbreviations**: OR, odds ratio; CI, confidence interval; RAR, red blood cell distribution width/albumin ratio.

with a higher likelihood of 3-month adverse results (adjusted odds ratio, 2.6; 95% confidence interval [CI], 2.0–3.6; p<0.001) and 3-month death (adjusted odds ratio, 12.7; 95% CI, 5.0–32.0; p<0.001). In model II, after adjusting for more confounding variables, the highest RAR remained a significant independent predictor for 3-month unfavorable outcomes (adjusted OR,1.4; 95% CI: 1.0–2.1, P=0.046) and 3-month mortality (adjusted OR, 5.2; 95% CI, 2.0–13.9; p<0.001), with a statistically significant trend observed (P<0.001).

Additionally, the E-value was computed to evaluate the potential influence of unobserved variables on the relationship between RAR and adverse prognosis in AIS. The calculated E-value of 1.75 (lower confidence limit, 1.47) suggests a lower likelihood of unmeasured confounding variables influencing the observed association in AIS.

## The Dose-Response Relationship Addressed by the generalized Additive Model

We further investigated to determine the presence of a non-linear relationship between RAR and adverse prognosis in cases with AIS. By employing the generalized additive model (GAM) and fitting smooth curves, we identified a dose-response correlation between RAR and the probability of negative results after 3 months. Our findings indicate that as RAR levels rose, the probability of experiencing unfavorable outcomes at 3 months progressively and consistently increased (Figure 2).

## Subgroup Analysis

Stratified analyses were then conducted to assess the stability of the association between RAR and unfavorable functional outcomes at 3 months in AIS patients (Figure 3 and Supplementary Table 1). The results indicated that subgroup analyses stratified by age, sex, BMI, stroke etiology, and history of chronic diseases consistently yielded similar outcomes, with no significant interactions observed (all p>0.05).

## Mediator Analysis

During the assessment of potential mediation effects on the relationship between RAR and adverse functional prognosis in AIS, it was found that hs-CRP played a crucial role as a mediator in this connection, as indicated by the Sobel test. The analysis revealed a notable indirect effect of hs-CRP on the association between RAR and the likelihood of 3-month unfavorable prognosis and 3-month mortality, with the mediation accounting for 13.51% and 15.92% of the association, respectively (Figure 4 and Table 3).

# Discussion

We herein identified that elevated RAR at baseline was significantly linked to a higher risk of negative prognosis in a cohort of 1906 patients with AIS, even after controlling for potential confounding factors. And this association

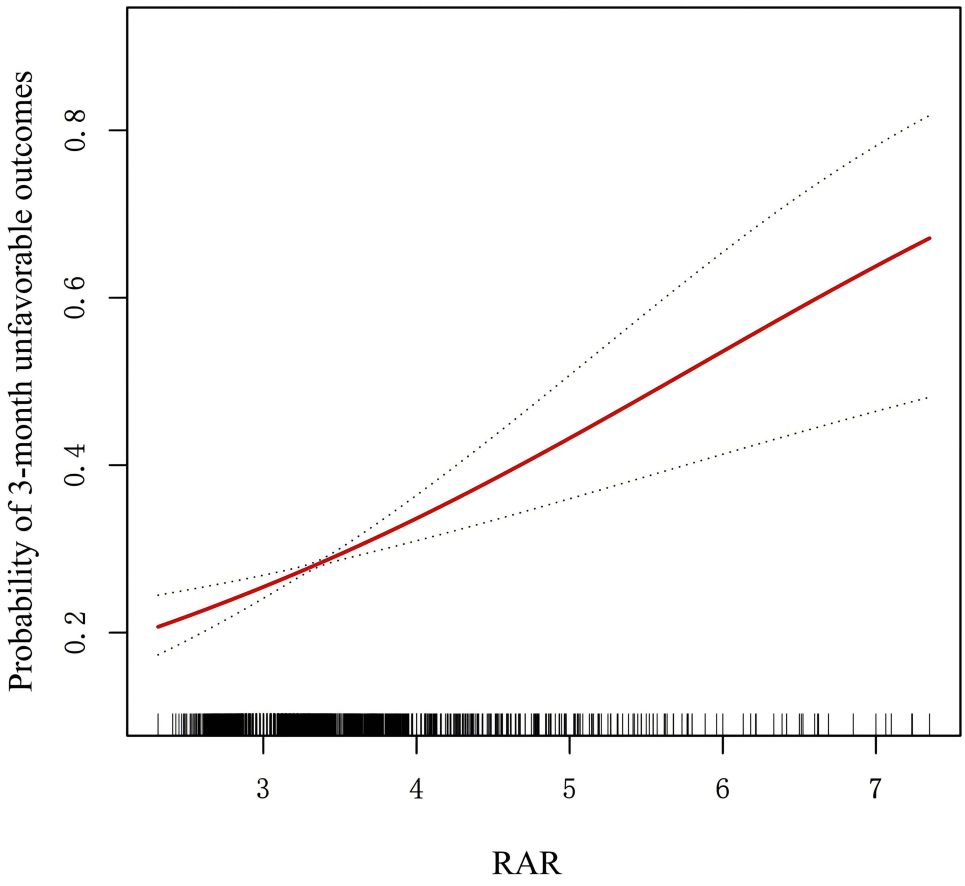


**Figure 2** The smoothing curves illustrating the relationship between RAR and the probability of 3-month unfavorable outcomes in patients with acute ischemic stroke. A dose-response relationship between RAR and probability of 3-month unfavorable outcomes was detected after adjusting for age, sex, BMI, history of previous stroke or transient ischemia attack, hypertension, diabetes mellitus, dyslipidemia, smoking, atrial fibrillation, coronary heart disease, initial NIHSS, premorbid mRS and stroke etiology.

remained consistent across subgroup analyses, with no significant interactions detected. More interestingly, our results indicate that the presence of a pro-inflammatory state may act as a mediator in the heightened connection between RAR and negative functional outcomes in AIS patients. Thus, RAR could be considered a novel, prevalent, and readily available biomarker for clinicians to evaluate the prognostic outlook of individuals with AIS.

Previous studies have verified the impact of RAR on death rates in severely ill patients with AIS. An examination of information from the MIMIC-IV Database showed that RAR was a predictive element for 30-day all-cause mortality in severe AIS patients.[26] A separate study on critically ill stroke patients from the same database demonstrated a notable correlation between baseline RAR levels and the occurrence of stroke-associated infections and mortality.[32] Nevertheless, the prognostic value of RAR has been demonstrated in various critically ill conditions, and its impact on adverse functional outcomes in AIS is not yet fully understood. The current investigation demonstrates that RAR at baseline is elevated with increasing stroke severity on initial NIHSS scores, a 1% increase in RAR is linked to a 50% elevated likelihood of adverse functional outcomes among individuals with AIS. These results support and build upon previous research indicating that a higher initial RAR is a potential predictor for stroke severity and unfavorable prognosis of AIS.

Although the current analysis yielded robust evidence indicating the predictive value of elevated RAR in adverse endpoints of AIS, the underlying mechanism remains uncertain. Oxidative stress (OS) and subsequent sub-clinical inflammation are posited as significant pathophysiological factors contributing to this clinical observation. Initially, OS leads to the overproduction of reactive oxygen species, which in turn stimulates erythropoiesis, resulting in anisocytosis and an elevation in RDW.[33] A longitudinal study involving 786 women with moderate and severe disabilities revealed a direct relationship between increasing RDW levels and heightened serum oxidant levels,[9] with ALB identified as a holistic marker of antioxidant capacity.[34] Ischemia and reperfusion injury are known to be triggers for OS.[35] The imbalance between oxidative stress injury

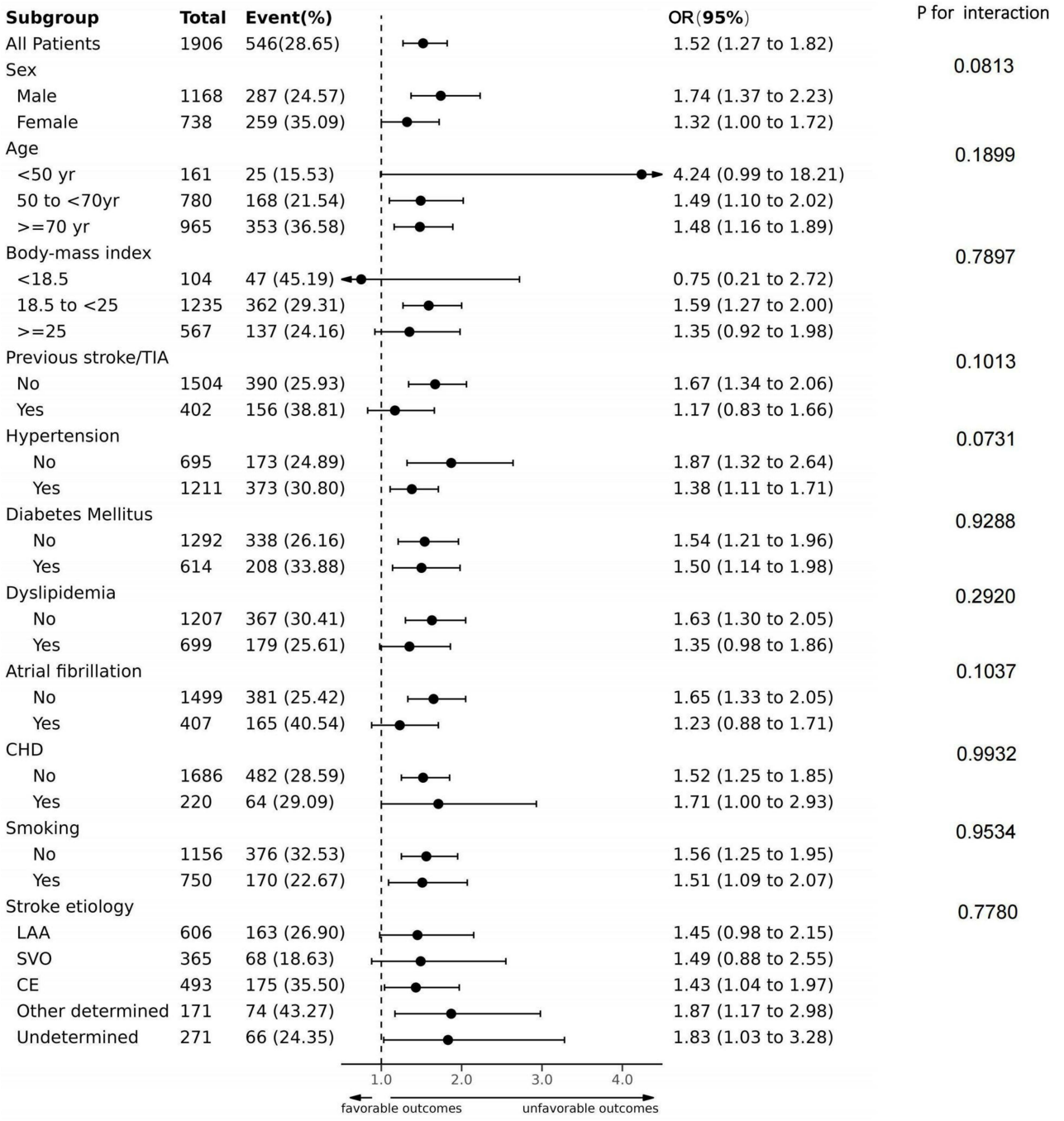


**Figure 3** Forest plot of the association between RAR and probability of 3-month unfavorable outcomes in terms of age, sex, BMI, history of previous stroke or transient ischemia attack, hypertension, diabetes mellitus, dyslipidemia, smoking, atrial fibrillation, coronary heart disease, and stroke etiology.

and levels of antioxidants has been shown to impact neuronal damage or protection in cases of cerebral ischemia and reperfusion, ultimately affecting the functional outcomes and mortality rates of AIS.[36] Thus, we speculate that higher levels of RAR may indicate an imbalance between OS damage and antioxidation, which were related to the poor functional outcomes of AIS.

Numerous studies have established a correlation between inflammation and the progression of AIS, encompassing the stages of initial ischemia, infarction, and subsequent reparative processes.[37,38] During stroke-induced inflammation, the release of diverse cytokines impacts erythropoiesis, erythropoietin (EPO) synthesis, and the suppression of erythroid progenitors, which is reflected by the elevation of RDW.[39] Moreover, previous studies have demonstrated a positive

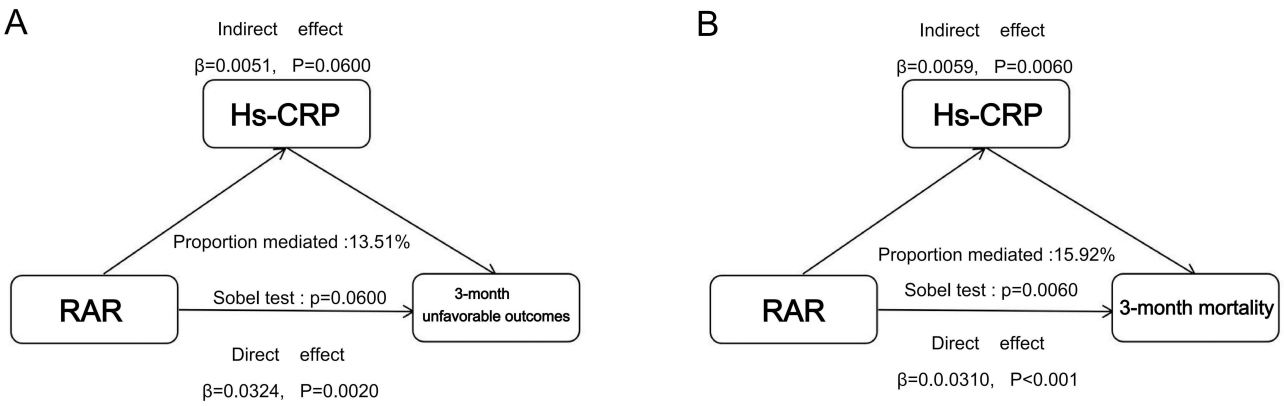


**Figure 4** Mediation analysis of the association between RAR and 3-month unfavorable outcomes (**A**) or 3-month mortality (**B**) in acute ischemic stroke.
**Abbreviations**: RAR, red blood cell distribution width/albumin ratio; Hs-CRP, high-sensitivity C-reactive protein.

correlation between RDW and plasma inflammatory biomarkers, including C-reactive protein (CRP),[8] erythrocyte sedimentation rate (ESR),[8] and interleukin (IL)-6.[40] Elevated RDW levels, even within the normal range, may exacerbate the inflammatory response, resulting in poorer outcomes following AIS.[17,41] Additionally, ALB is commonly utilized to evaluate nutritional status and systemic inflammation.[42] Low levels of albumin, known as hypoalbuminemia, have been linked to prognosis in a variety of diseases and the general population.[43] Hashem's[44] research identified ALB as a significant prognostic factor following AIS, while a separate study[45] from China utilizing a nomogram chart prediction model highlighted ALB as a predictor of mortality within 6 months of stroke onset. Therefore, the concurrent assessment of RDW and ALB may exhibit a stronger correlation with adverse outcomes in AIS compared to individual indicators.

Our study found a correlation between elevated RAR and increased hs-CRP levels, indicating a potential association between high RAR levels and a pro-inflammatory state (Supplementary Table 2). Mediation analyses revealed that hs-CRP concentrations mediated the relationship between RAR and adverse functional outcomes in AIS. The results offer additional support for the theory that the increased RAR levels may contribute to the advancement of AIS by triggering a systemic inflammatory response.

Although there is growing evidence supporting the predictive significance of RDW and ALB for cerebrovascular diseases, our study is the first to examine the novel combined biomarker, RAR for negative functional outcomes in AIS. This

**Table 3** The Mediating Effect of Hs-CRP Between RAR and 3-Month Unfavorable Outcomes/3-Month Mortality in AIS

| | Unadjusted Model | | Model I | | Model II | |
|---|---|---|---|---|---|---|
| | **Estimate** | ***P* -value** | **Estimate** | ***P* -value** | **Estimate** | ***P* -value** |
| **The mediation effect of Hs-CRP between RAR and 3-month unfavorable outcomes** | | | | | | |
| Total effect | 0.1026 (0.0851, 0.1212) | <0.001 | 0.0930 (0.0747, 0.1114) | <0.001 | 0.0375 (0.0198, 0.0564) | <0.001 |
| Mediation effect | 0.0185 (0.0111, 0.0268) | <0.001 | 0.0170 (0.0100, 0.0251) | <0.001 | 0.0051 (−0.0002, 0.0110) | 0.0600 |
| Direct effect | 0.0840 (0.0636, 0.1036) | <0.001 | 0.0761 (0.0558, 0.0964) | <0.001 | 0.0324 (0.0136, 0.0518) | 0.0020 |
| Proportion mediated | 0.1805 (0.1041, 0.2727) | <0.001 | 0.1826 (0.1018, 0.2871) | <0.001 | 0.1351 (−0.0054, 0.3739) | 0.0600 |
| **The mediation effect of Hs-CRP between RAR and 3-month mortality** | | | | | | |
| Total effect | 0.0566 (0.0407, 0.0720) | <0.001 | 0.0549 (0.0386, 0.0710) | <0.001 | 0.0369 (0.0202, 0.0537) | <0.001 |
| Mediation effect | 0.0107 (0.0052, 0.0180) | <0.001 | 0.0103 (0.0047, 0.0177) | <0.001 | 0.0059 (0.0016, 0.0121) | 0.0060 |
| Direct effect | 0.0459 (0.0306, 0.0613) | <0.001 | 0.0446 (0.0293, 0.0603) | <0.001 | 0.0310 (0.0138, 0.0483) | <0.001 |
| Proportion mediated | 0.1885 (0.0921, 0.3183) | <0.001 | 0.1868 (0.0874, 0.3230) | <0.001 | 0.1592 (0.0437, 0.3992) | 0.0060 |

**Notes**: Model I adjusted for age and sex. Model II adjusted for age, sex, BMI, history of previous stroke or transient ischemia attack, hypertension, diabetes mellitus, dyslipidemia, smoking, atrial fibrillation, coronary heart disease, initial NIHSS, premorbid mRS, and stroke etiology.

investigation holds substantial clinical significance. Firstly, RAR may serve as a straightforward yet relatively reliable parameter for risk stratification in early AIS patients, potentially even before hospital admission, within the emergency department. This could enhance the granularity of existing risk scores, thereby aiding medical personnel in making accurate clinical decisions and delivering tiered nursing care at the earliest possible stage. Secondly, due to its simplicity, rapidity, and cost-effectiveness, RAR does not necessitate specialized skills or equipment for monitoring, making it suitable for diverse clinical settings, including economically underdeveloped areas. Thirdly, our study also identifies potential targets for therapeutic intervention aimed at improving outcomes for patients with AIS. Nonetheless, this hypothesis necessitates validation in future research endeavors. Lastly, age, sex, BMI, stroke etiology, and chronic disease histories were selected for stratified analysis to analyze in more detail the impact of RAR on adverse functional outcomes in diverse AIS populations. However, the study's limitations must be recognized. Firstly, the assessment of RAR was only conducted solely at the time of admission, without considering changes over time, which warrants further investigation. Secondly, the research was carried out at a sole tertiary academic medical center, which could introduce bias in selection, highlighting the need for validation of results in future multi-center studies. Thirdly, as a secondary analysis utilizing published data, there may be unknown factors not accounted for in the data set that could have influenced the results, such as intravenous thrombolysis or endovascular thrombectomy information, details for the treatment of hemorrhagic transformation, baseline ASPECT score, onset-to-door time (ODT), and hyperglycemia medication specifics. Although based on our evaluation of the E-value, it appears that any unmeasured or uncontrolled variables had minimal impact on our findings. We will commence a new study to gather more variable information.

## Conclusions

In summary, the current study offers compelling evidence supporting the correlation between RAR levels and negative functional outcomes in AIS, with the involvement of a pro-inflammatory state mediating this association. Furthermore, a dose-response relationship was observed between baseline RAR levels and unfavorable outcomes at the 3 months in AIS patients. Overall, given its cost-effectiveness and availability as a hematological marker, baseline RAR shows promise as a valuable biomarker for early risk assessment in AIS patients.

## Abbreviations

RAR, red blood cell distribution width/albumin ratio; AIS, acute ischemic stroke; GAM, generalized additive model; BMI, body mass index; RBC, red blood cell; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; FBG, fasting blood glucose; Hs-CRP, high-sensitivity C-reactive protein; INR, international normalized ratio; FIB, fibrinogen; RDW, red blood cell distribution width; TIA, transient ischemia attack; CHD, coronary heart disease; NHISS, National Institutes of Health Stroke Scale; mRS, modified Rankin scale; LAA, large artery atherosclerosis; SVO, small vessel occlusion; CE, cardioembolism.

## Data Sharing Statement

The publicly available datasets presented in the present study were available at the website: https://journals.plos.org/plosone/.

## Ethics Approval and Consent to Participate

The studies involving human participants were reviewed and approved by the Institutional Review Board of Seoul National University Hospital. And the Institutional Review Board waived the need for informed consent (IRB No. 1009–062-332).

## Acknowledgments

As this is a secondary study, the data and methodology explanation are primarily sourced from the following study: Kim Y, Nam K-W, Jeong H-Y, Kang MK, Kim TJ, Kim SK et al (2020) "Automated undernutrition screen tool: Geriatric nutritional risk score predicts poor outcomes in individuals with acute ischemic stroke" published in *PLoS ONE* 15(2): e0228738. We are appreciative of the study's whole authorship team.

## 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.

## Funding

This research was supported by grants from the general program of Changde City Science Foundation (2020S014).

## Disclosure

The authors declare that they have no competing interests in this work.

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