

# Association Apo B/Apo a-I Ratio and Prognostic Nutritional Index with 90-Day Outcomes of Acute Ischemic Stroke

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**Background:** The relationship between insulin resistance-related indices and the outcomes of acute ischemic stroke (AIS) is still unclear. This study aimed to explore the association between the Apo B/Apo A-1 ratio and the Prognostic Nutritional Index (PNI) with the 90-day outcomes of AIS.

**Methods:** A total of 2011 AIS patients with a 3-month follow-up were enrolled in the present study from January 2017 to July 2021. Multivariate logistic regression modeling was performed to analyze the relationship between Apo B/Apo A-1 ratio, PNI, and AIS poor outcomes. The mediating effect between the three was analyzed using the Bootstrap method with PNI as the mediating variable.

**Results:** Among the 2011 included AIS patients, 20.3% had a poor outcome. Patients were categorized according to quartiles of Apo B/Apo A-1 ratio and PNI. Multivariate logistic regression revealed that the fourth Apo B/Apo A-1 ratio quartile had poorer outcomes than the first quartile (OR 1.75, 95%CL 1.21–2.53,  $P=0.003$ ), and the fourth PNI quartile exhibited a lower risk of poor outcomes than the first quartile (OR 0.40, 95%CL 0.27–0.61,  $P<0.001$ ). PNI displayed a significant partially mediating effect (21.4%) between the Apo B/Apo A-1 ratio and poor AIS outcomes.

**Conclusion:** The Apo B/Apo A-1 ratio is a risk factor for poor AIS outcomes, whereas PNI acts as a protective factor. The association between the ApoB/ApoA-1 ratio and poor AIS outcomes was partially mediated by PNI.

**Keywords:** insulin resistance, Apo B/Apo A-1 ratio, prognostic nutritional index, acute ischemic stroke, outcomes

## Introduction

Stroke is one of the leading causes of disability and death worldwide.<sup>1</sup> Insulin resistance (IR) has been shown to be independently associated with poor outcomes in acute ischemic stroke (AIS).<sup>2</sup> It can lead to disorders of lipid metabolism and promote the formation of atherosclerosis.<sup>3,4</sup> Apo B is atherogenic,<sup>3</sup> whereas Apo A-1 is antiatherogenic,<sup>4</sup> and the Apo B/Apo A-1 ratio may reflect the balance between antiatherosclerosis and atherogenicity.<sup>5</sup> The Apo B/Apo A-1 ratio has also been suggested to be an independent predictor of stroke mortality,<sup>6</sup> and elevations in the Apo B/Apo A-1 ratio may increase the risk of stroke occurrence.<sup>7</sup> In addition, the ratio has been shown to be an independent predictor of IR in different races.<sup>8</sup> Recent studies have also confirmed that the Apo B/Apo A-1 ratio is positively associated with insulin resistance.<sup>9,10</sup> Malnutrition is a risk factor for poor stroke outcomes,<sup>11</sup> but assessing nutritional status is cumbersome. Prognostic Nutritional Index (PNI) provides a simple and effective nutritional assessment index<sup>12</sup> and has been strongly

associated with outcomes in cancer and acute coronary syndrome.<sup>13,14</sup> Newer studies suggest lower PNI is also a significant risk factor for rehospitalization.<sup>15</sup> Moreover, PNI has been shown to be independently associated with poor 90-day outcomes in stroke patients or in patients after thrombolysis in stroke.<sup>16,17</sup> Recent reports have shown that malnutrition early in life may be associated with the development of insulin resistance.<sup>18</sup> This suggests a correlation between insulin resistance, malnutrition and poor outcomes in patients with AIS, but no study has yet revealed a specific relationship between these three.

Although both PNI and the Apo B/Apo A-1 ratio have been associated with poor outcomes in AIS, we did not find any study has explored the relationship between the two and poor outcomes in AIS. Therefore, this study aimed to investigate the correlation between Apo B/Apo A-1 ratio, PNI, and poor outcomes of AIS.

## Methods

### Study Design and Participants

Data from the Jiangsu Provincial Hospital Stroke Center were collected from January 2017 to July 2021, and an observational cohort study of 2599 patients with AIS was conducted. The inclusion criteria were as follows: 1. Attended the hospital within 72h of AIS onset (counted from the time last seen as asymptomatic); 2. Acute ischemic lesions on brain imaging; 3. Laboratory tests were completed within 24 hours of admission. The exclusion criteria were as follows: 1. Modified Rankin score (mRS) > 2 before onset; 2. Inadequate laboratory tests; 3. Transient ischemic attack (TIA); 4. Emergency treatment with thrombolysis or endovascular thrombectomy; 5. Severe mental disorders and other serious systemic diseases with a life expectancy of less than 3 months; 6. Failed to follow up at 90 days.

### Data Acquisition

Venous blood samples were collected within 24 h of admission after fasting for at least 8 hours. PNI was calculated as follows:  $PNI = \text{albumin (g/L)} + 5 \times \text{total lymphocyte counts (} 10^9/\text{L)}$ .

### Clinical Assessment and Outcome Measurements

The severity of the neurological deficits was assessed at admission using the National Institutes of Health Stroke Scale (NIHSS) score. The primary outcome was the modified Rankin Scale (mRS) 3 months after the onset of symptoms. An mRS score of 0–2 was defined as a favorable outcome (functional independence), whereas scores  $\geq 3$  were considered poor outcomes. The assessments were all performed by neurologists, who were unaware of the subjects' characteristics at 3 months of symptom onset and assessed the mRS in the outpatient clinic after 90 days.

This study was approved by the Institutional Research Review Board of the Affiliated Hospital of the Nanjing University of Chinese Medicine and was conducted in accordance with the Declaration of Helsinki (2017NL-012-01).

### Statistical methods

Categorical variables were presented as frequencies (percentages), and continuous variables were presented as mean (standard deviation) or median (interquartile range). The differences between groups for categorical variables were analyzed using Pearson's chi-squared test. In contrast, the difference between two groups of continuous variables was evaluated by the *t*-test or the Wilcoxon rank sum test, depending on whether the data conformed to a normal distribution. Comparisons between three or more groups were carried out using ANOVA (parametric test) or the Kruskal–Wallis test (nonparametric test). Logistic regression models were used to analyze the association between the Apo B/Apo A-1 ratio, PNI, and poor outcomes in AIS, and confounders were selected based on the univariate analysis results and previous literature reports. Adjusted models included model 2 (adjusted for age and sex) and model 3 (further adjusted for past history, NIHSS on admission, and TOAST typing), while subgroup analyses were performed to draw forest plots. The dose-response relationship between the Apo B/Apo A-1 ratio and PNI on poor outcomes in AIS was explored using the restricted cubic spline (RCS) plots. To further explore the effects of the Apo B/Apo A-1 ratio and PNI on AIS outcomes, the mediating effect between the three was analyzed using the Bootstrap method with PNI as the mediating variable, Apo B/Apo A-1 ratio as the independent variable, and poor AIS outcomes as the dependent variable. All tests were two-sided, and a P value of 0.05 was considered statistically significant. All analyses were performed by the R statistical

program (<http://www.R-project.org>, The R Foundation), the Free Statistics analytic platform and Statistical Package for the Social Sciences 25.0.

## Results

### Baseline Information

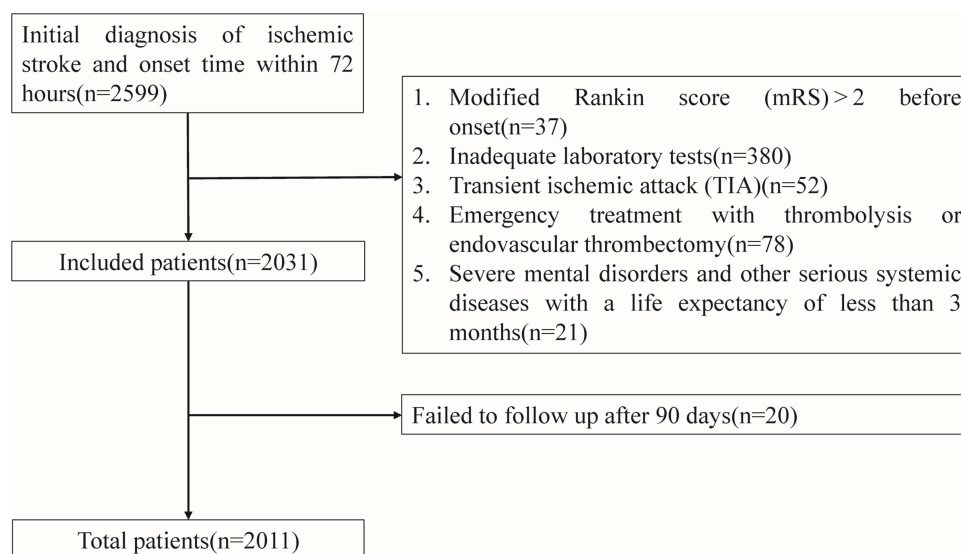
A total of 2599 patients with AIS were screened, of which 608 patients were excluded and 2011 patients were included in the final study. The inclusion flow chart is shown in [Figure 1](#). Baseline characteristics of the study participants are provided in [Table 1](#). The study population included 1342 (66.7%) males and had a mean age of 68.5 years. Moreover, the patients were grouped according to the Apo B/Apo A-1 ratio quartiles. The median NIHSS score was 3. Patients in the 4th quartile of the Apo B/Apo A-1 ratio were younger, more likely to be male, were at a greater risk of poor outcomes, had a greater likelihood of previous stroke, atrial fibrillation, or coronary artery disease, and were more likely to be smokers. Laboratory tests in patients from the 4<sup>th</sup> quartile of the Apo B/Apo A-1 ratio revealed higher levels of LDL, Apo B, TC, and TG, while exhibiting lower levels of HDL, Apo A-1, albumin, and PNI levels. In OCSF typing, patients in the 4<sup>th</sup> quartile of Apo B/Apo A-1 ratio were more likely to have PACI and POCI compared to patients in the 1<sup>st</sup> quartile of Apo B/Apo A-1 ratio. There was no significant difference in Toast typing.

### Values of PNI with Different Apo B/Apo a-1 Ratio Levels

After quartiles of Apo B/Apo A-1 ratio, the PNI values of each group were compared ([Figure 2](#)). This indicates that as the levels of Apo B/Apo A-1 ratio increase, PNI gradually decreases. Moreover, there is a statistically significant difference between the 4 groups ( $P < 0.05$ ).

### Regression Analysis of the Apo B/Apo a-1 Ratio and PNI with Poor Outcomes of AIS

First, univariate regression analyses indicated that age, sex, diabetes mellitus, stroke or TIA, atrial fibrillation, coronary artery disease, smoking, alcohol consumption, NIHSS, white, medium, lymphatic, mono, LDL, Apo A-1, cholesterol, triglycerides, albumin, PNI, and Apo B/Apo A-1 ratio were significantly associated with poor outcomes ([Table S1](#)). Multifactorial logistic regression analyses were performed between Apo B/Apo A-1 ratio, PNI, and poor outcomes, adjusting for potential confounders based on the univariate analyses and previous literature ([Table 2](#)). The results showed that ApoB/ApoA-1 was positively associated with the risk of poor outcomes when ApoB/ApoA-1 was considered a continuous variable. When the patients were categorized into ApoB/ApoA-1 quartiles, the risk of poor outcomes tended to rise with increasing ApoB/ApoA-1 ratio. When PNI was considered a continuous variable, it was negatively associated



**Figure 1** Study flowchart of patients selected.

**Table 1** Baseline Characteristics of Apo B/Apo a-I Ratio Quartiles

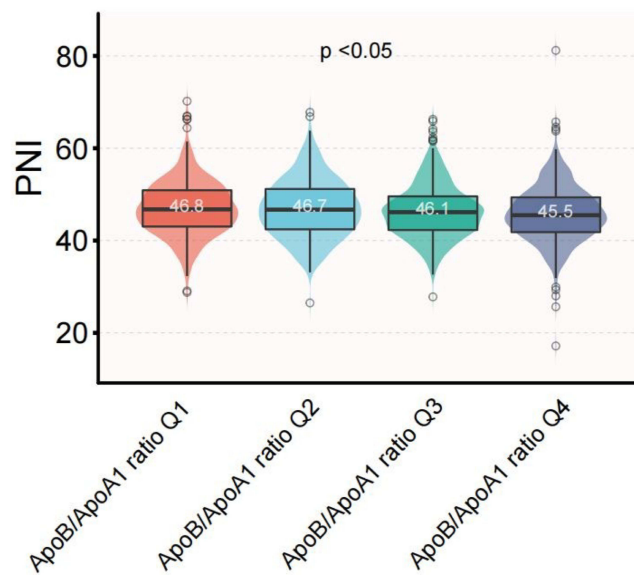
|  | Total<br>(n = 2011) | Apo B/Apo A-I Ratio<br>Quartile 1 (n = 502) | Apo B/Apo A-I Ratio<br>Quartile 2 (n = 466) | Apo B/Apo A-I Ratio<br>Quartile 3 (n = 535) | Apo B/Apo A-I Ratio<br>Quartile 4 (n = 508) | p       |
|--|---------------------|---|---|---|---|---------|
| Age, Mean ± SD, year                       | 68.5 ± 12.1         | 70.3 ± 12.5                                 | 68.8 ± 11.3                                 | 68.4 ± 12.0                                 | 66.5 ± 12.5                                 | < 0.001 |
| Male, n (%)                                | 1342 (66.7)         | 320 (63.7)                                  | 292 (62.7)                                  | 357 (66.7)                                  | 373 (73.4)                                  | < 0.001 |
| Drinking, n (%)                            | 382 (19.0)          | 87 (17.3)                                   | 77 (16.5)                                   | 113 (21.1)                                  | 105 (20.7)                                  | 0.154   |
| Smoking, n (%)                             | 578 (28.7)          | 127 (25.3)                                  | 126 (27)                                    | 154 (28.8)                                  | 171 (33.7)                                  | 0.023   |
| Admission NIHSS, Median (IQR)              | 3(1,5)              | 3(1,5)                                      | 2(1,4)                                      | 2(1,5)                                      | 3(1,5)                                      | < 0.001 |
| 90 days mRS≥3, n (%)                       | 409 (20.3)          | 97 (19.3)                                   | 76 (16.3)                                   | 113 (21.1)                                  | 123 (24.2)                                  | 0.019   |
| Medical History                            |                     |   |   |   |   |         |
| Hypertension, n (%)                        | 1565(77.8)          | 393 (78.3)                                  | 381 (81.8)                                  | 403 (75.3)                                  | 388 (76.4)                                  | 0.079   |
| Diabetes Mellitus, n (%)                   | 781 (38.8)          | 186 (37.1)                                  | 173 (37.1)                                  | 219 (40.9)                                  | 203 (40)                                    | 0.474   |
| Stroke, n (%)                              | 617 (30.7)          | 200 (39.8)                                  | 140 (30)                                    | 143 (26.7)                                  | 134 (26.4)                                  | <0.001  |
| Atrial Fibrillation, n (%)                 | 159 (7.9)           | 59 (11.8)                                   | 33 (7.1)                                    | 39 (7.3)                                    | 28 (5.5)                                    | 0.002   |
| Coronary Heart Disease, n (%)              | 286 (14.2)          | 99 (19.7)                                   | 54 (11.6)                                   | 70 (13.1)                                   | 63 (12.4)                                   | <0.001  |
| Hyperlipidemia, n (%)                      | 114 (5.7)           | 24 (4.8)                                    | 23 (4.9)                                    | 36 (6.7)                                    | 31 (6.1)                                    | 0.473   |
| Medicine Use During Hospitalization, n (%) |                     |   |   |   |   |         |
| Antihypertensive, n (%)                    | 1452 (72.2)         | 366 (72.9)                                  | 360 (77.3)                                  | 364 (68)                                    | 362 (71.3)                                  | 0.012   |
| Hypoglycemic, n (%)                        | 733 (36.4)          | 176 (35.1)                                  | 163 (35)                                    | 206 (38.5)                                  | 188 (37)                                    | 0.594   |
| Anticoagulant, n (%)                       | 532 (26.5)          | 137 (27.3)                                  | 109 (23.4)                                  | 144 (26.9)                                  | 142 (28)                                    | 0.38    |
| Antiplatelet, n (%)                        | 1873 (93.1)         | 456 (90.8)                                  | 435 (93.3)                                  | 501 (93.6)                                  | 481 (94.7)                                  | 0.097   |
| Lipid Lowering, n (%)                      | 1940 (96.5)         | 477 (95)                                    | 451 (96.8)                                  | 518 (96.8)                                  | 494 (97.2)                                  | 0.229   |
| TOAST subtypes, n (%)                      |                     |   |   |   |   | 0.009   |
| Large Artery Atherosclerosis               | 672 (33.4)          | 159 (31.7)                                  | 131 (28.1)                                  | 198 (37)                                    | 184 (36.2)                                  |         |
| Small Artery Occlusion                     | 1271 (63.2)         | 319 (63.5)                                  | 315 (67.6)                                  | 323 (60.4)                                  | 314 (61.8)                                  |         |
| Cardiogenic Embolism                       | 62 (3.1)            | 22 (4.4)                                    | 17 (3.6)                                    | 14 (2.6)                                    | 9 (1.8)                                     |         |
| Other/undetermined                         | 6 (0.3)             | 2 (0.4)                                     | 3 (0.6)                                     | 0 (0)                                       | 1 (0.2)                                     |         |
| OCSF subtypes, n (%)                       |                     |   |   |   |   | < 0.001 |
| TACI                                       | 99 (4.9)            | 30 (6)                                      | 16 (3.4)                                    | 29 (5.4)                                    | 24 (4.7)                                    |         |
| PACI                                       | 594 (29.5)          | 125 (24.9)                                  | 119 (25.5)                                  | 174 (32.5)                                  | 176 (34.6)                                  |         |
| POCI                                       | 568 (28.2)          | 128 (25.5)                                  | 126 (27)                                    | 151 (28.2)                                  | 163 (32.1)                                  |         |
| LACI                                       | 750 (37.3)          | 219 (43.6)                                  | 205 (44)                                    | 181 (33.8)                                  | 145 (28.5)                                  |         |
| Laboratory tests                           |                     |   |   |   |   |         |
| WBC, Mean ± SD,10 <sup>9</sup> /L          | 7.1 ± 2.4           | 7.0 ± 2.6                                   | 7.0 ± 2.3                                   | 7.1 ± 2.3                                   | 7.2 ± 2.4                                   | 0.346   |
| Neutrophil, Mean ± SD,10 <sup>9</sup> /L   | 4.7±2.2             | 4.7±2.5                                     | 4.7±2.2                                     | 4.8±2.1                                     | 4.8±2                                       | 0.773   |
| Monocyte, Mean ± SD,10 <sup>9</sup> /L     | 0.5 ± 0.2           | 0.5 ± 0.2                                   | 0.5 ± 0.2                                   | 0.5 ± 0.2                                   | 0.5 ± 0.2                                   | 0.126   |
| Lymphocyte, Mean ± SD,10 <sup>9</sup> /L   | 1.7 ± 0.7           | 1.6 ± 0.7                                   | 1.7 ± 0.7                                   | 1.7 ± 0.7                                   | 1.7 ± 0.8                                   | 0.009   |
| HDL, Mean ± SD, mmol/L                     | 1.2 ± 0.3           | 1.4 ± 0.3                                   | 1.3 ± 0.3                                   | 1.2 ± 0.3                                   | 1.1 ± 0.2                                   | < 0.001 |
| Apo A-I, Mean ± SD, g/L                    | 1.2 ± 0.2           | 1.3 ± 0.3                                   | 1.2 ± 0.2                                   | 1.1 ± 0.2                                   | 1.0 ± 0.2                                   | < 0.001 |
| Apo B, Mean ± SD, g/L                      | 0.9 ± 0.3           | 0.6 ± 0.2                                   | 0.8 ± 0.1                                   | 0.9 ± 0.2                                   | 1.1 ± 0.3                                   | < 0.001 |
| LDL, Mean ± SD, mmol/L                     | 2.7 ± 0.9           | 1.9 ± 0.6                                   | 2.6 ± 0.7                                   | 2.9 ± 0.7                                   | 3.3 ± 0.9                                   | < 0.001 |
| TC, Mean ± SD, mmol/L                      | 4.3 ± 1.1           | 3.6 ± 0.9                                   | 4.2 ± 0.9                                   | 4.5 ± 1.0                                   | 4.9 ± 1.1                                   | < 0.001 |
| TG, Mean ± SD, mmol/L                      | 1.6 ± 1.3           | 1.2 ± 1.3                                   | 1.5 ± 0.9                                   | 1.7 ± 1.6                                   | 1.8 ± 1.0                                   | < 0.001 |
| ALB, Mean ± SD, g/L                        | 38.1 ± 4.4          | 39.0 ± 4.3                                  | 38.6 ± 4.5                                  | 37.8 ± 4.2                                  | 37.1 ± 4.4                                  | < 0.001 |
| PNI, Mean ± SD                             | 46.5 ± 6.1          | 47.0 ± 6.0                                  | 46.9 ± 6.3                                  | 46.3 ± 5.9                                  | 45.8 ± 6.2                                  | 0.005   |

**Abbreviations:** NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale. TACI, total anterior circulation infarction; PACI, partial anterior circulation infarction; POCI, posterior circulation infarction; LACI, lacunar infarction; WBC, white blood cell; HDL, high-density lipoprotein; Apo A-I, apolipoprotein A-I; Apo B, apolipoprotein B; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglyceride; ALB, albumin; PNI, Prognostic Nutritional Index.

with the risk of poor outcomes; when PNI was analyzed as a quartile, a tendency for decreased risk of poor outcomes was observed with increasing PNI.

## Analysis of the Linear Relationship Between the Apo B/Apo a-I Ratio, PNI, and Poor Outcomes of AIS

Fitted curves were plotted in order to exclude hidden nonlinear relationships. RCS was used to explore the dose-response relationship between the Apo B/ApoA-1 ratio, PNI, and poor outcomes of AIS (Figure 3). A linear dose-response relationship was found between the Apo B/ApoA-1 ratio, PNI and poor outcomes of AIS.



**Figure 2** The violin plot of Apo B/Apo A-I ratio quartiles and PNI values ( $P < 0.05$ ).

## Subgroup Analysis of Apo B/Apo a-I Ratio, PNI and Poor Outcomes of AIS

In addition, forest plots were used to determine whether the effects of Apo B/ApoA-1 ratio and PNI on poor AIS outcomes were consistent across age, sex, and the presence of hypertensive, diabetes, stroke, atrial fibrillation, and coronary artery disease (Figure 4). Similar associations were found in all subgroups, and all interactions between subgroups were non-significant for poor outcomes at a significance level of  $P < 0.05$ . The increase in the Apo B/ApoA-1 ratio on poor outcomes of AIS was more pronounced in those who were older, had diabetes, and had coronary artery disease.

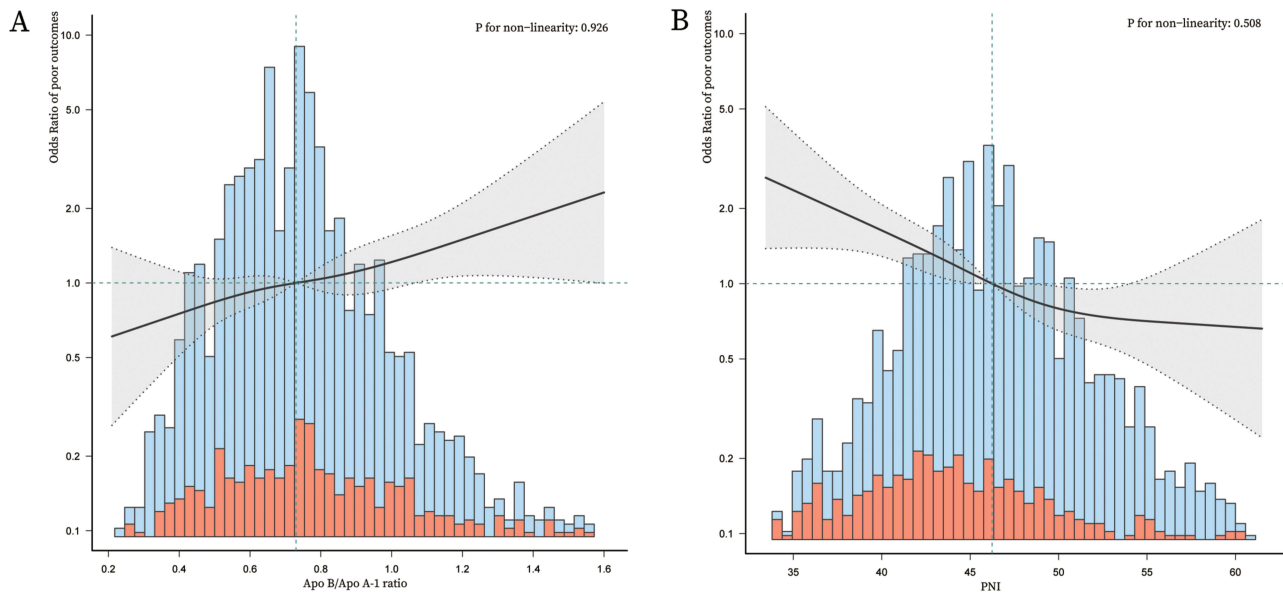
## The Association Between Apo B/Apo a-I Ratio and Poor AIS Outcomes Was Mediated by PNI

Considering that both the Apo B/Apo A-1 ratio and PNI were significantly associated with poor outcomes in AIS, mediation analyses were performed to investigate their relationship (Figure 5). When PNI was set as the mediating

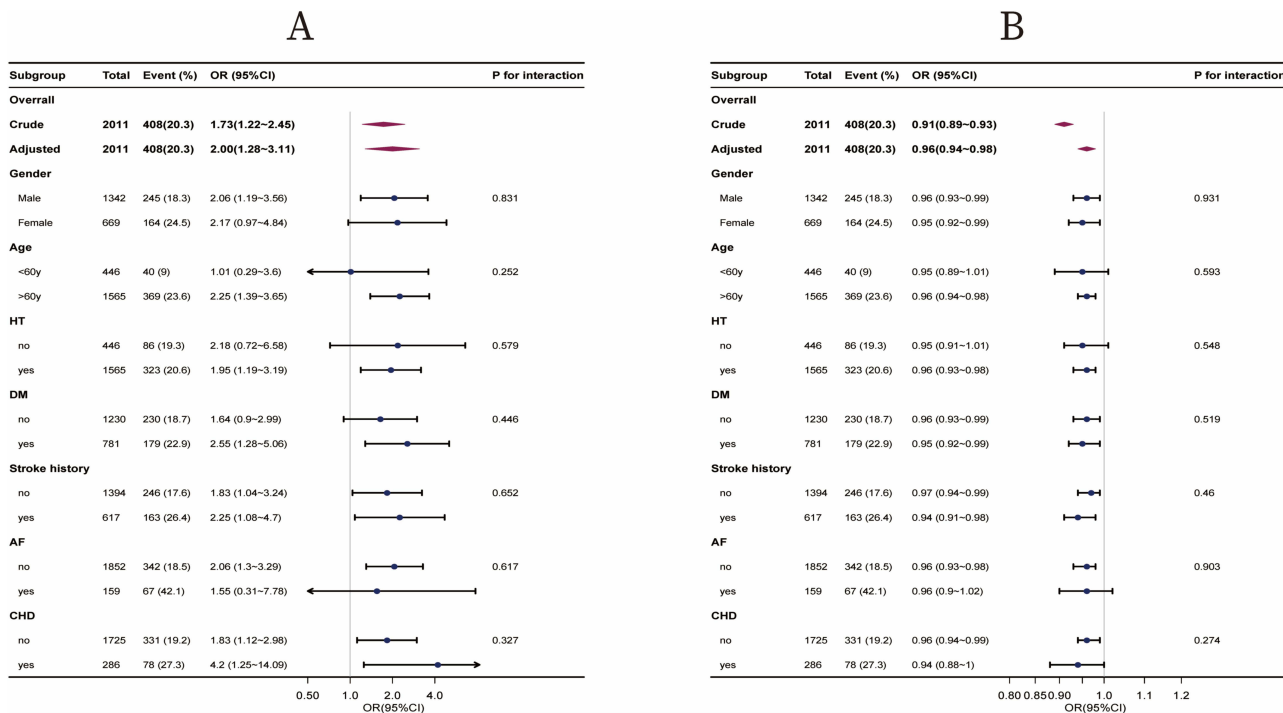
**Table 2** Association of the Apo B/ApoA-I Ratio and PNI with Poor Outcomes in AIS

|                                 | Model 1         | P      | Model 2         | P      | Model 3         | P      |
|---------------------------------|-----------------|--------|-----------------|--------|-----------------|--------|
| Apo B/Apo A I ratio(continuous) | 1.73(1.22–2.45) | 0.002  | 2.39(1.62–3.50) | <0.001 | 1.99(1.28–3.11) | 0.002  |
| Apo B/Apo A I ratio(categories) |                 |        |                 |        |                 |        |
| Q1                              | REF             | 0.02   | REF             | <0.001 | REF             | 0.016  |
| Q2                              | 0.81(0.58–1.13) | 0.222  | 0.89(0.64–1.26) | 0.515  | 1.12(0.75–1.67) | 0.581  |
| Q3                              | 1.12(0.83–1.52) | 0.471  | 1.27(0.92–1.73) | 0.143  | 1.40(0.96–2.02) | 0.082  |
| Q4                              | 1.33(0.99–1.80) | 0.06   | 1.70(1.24–2.33) | 0.001  | 1.75(1.21–2.53) | 0.003  |
| PNI (continuous)                | 0.91(0.89–0.93) | <0.001 | 0.93(0.91–0.95) | <0.001 | 0.96(0.94–0.98) | <0.001 |
| PNI (categories)                |                 |        |                 |        |                 |        |
| Q1                              | REF             | <0.001 | REF             | <0.001 | REF             | <0.001 |
| Q2                              | 0.52(0.39–0.69) | <0.001 | 0.61(0.46–0.81) | 0.001  | 0.58(0.41–0.81) | 0.001  |
| Q3                              | 0.37(0.27–0.50) | <0.001 | 0.47(0.34–0.64) | <0.001 | 0.57(0.40–0.82) | 0.003  |
| Q4                              | 0.21(0.15–0.29) | <0.001 | 0.30(0.21–0.43) | <0.001 | 0.40(0.27–0.61) | <0.001 |

**Note:** The first quartile of the Apo B/Apo A-I ratio and the first quartile of PNI were set as the reference groups. The associations between Apo B/Apo A-I ratio and PNI and poor outcomes in patients with AIS were examined by univariate and multivariate logistic regression models. Model I was a univariate analysis, model II adjusted for age and sex, and model III was further adjusted for previous hypertension, previous diabetes mellitus, previous stroke, previous atrial fibrillation, previous coronary artery disease, previous hyperlipidemia, and NIHSS and TOAST typing on.

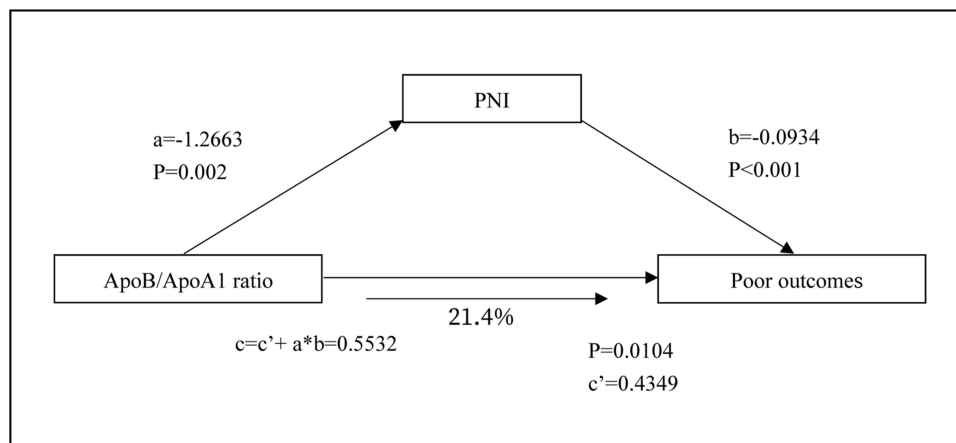


**Figure 3** **A** The relationship between the Apo B/Apo A-I ratio and poor outcomes; **B** The relationship between PNI and poor outcomes. The dose–response relationship between the Apo B/Apo A-I ratio and poor outcomes (adjusted for age, sex, prior hypertension, prior diabetes mellitus, prior stroke, prior atrial fibrillation, prior coronary artery disease, prior hyperlipidemia, and NIHSS and TOAST typing on admission). The regression line formed by the solid line represents the odds ratio, the bandwidths by the dashed line represents the confidence intervals, the blue bars represent the distribution of the total acute ischemic stroke patients, and the red bars represent the distribution of acute ischemic stroke patients with poor outcomes.



**Figure 4** **(A)** Correlation between the Apo B/Apo A-I ratio and poor outcomes in different subgroups; **(B)** Correlation between PNI and poor outcomes in different subgroups. Forest plots based on subgroup analyses (adjusted for age, sex, prior hypertension, prior diabetes mellitus, prior stroke, prior atrial fibrillation, prior coronary artery disease, prior hyperlipidemia, and NIHSS and TOAST typing on admission). HT, hypertensive; DM, diabetes mellitus; AF, atrial fibrillation; CHD, coronary heart disease.





**Figure 5** Mediation analysis of PNI on the relationship between the Apo B/Apo A-1 ratio and poor outcomes. a, regression coefficients of the relationship between the Apo B/Apo A-1 ratio and PNI; b, regression coefficients of the relationship between PNI and poor outcomes, with Apo B/Apo A-1 and PNI as independent variables; c, regression coefficients of the relationship between Apo B / Apo A-1 ratio and poor outcomes; c', regression coefficients of the relationship between Apo B / Apo A-1 ratio and poor outcomes, with Apo B/Apo A-1 ratio and PNI as independent variables. The percentage differences in coefficients (1-c/c') are shown.

variable, a significant partial mediating effect (21.4%) was observed on the Apo B/Apo A-1 ratio for poor outcomes in AIS.

## Discussion

Previous studies on the Apo B/Apo A-1 ratio and PNI have focused on cardiovascular and oncological directions. PNI has been used to predict the prognosis of a variety of tumors,<sup>19,20</sup> whereas the Apo B/Apo A-1 ratio is strongly associated with cardiovascular disease.<sup>21,22</sup> To the best of our knowledge, our study is the first to report the strong association between these two and poor stroke outcomes. Our study demonstrated that both the Apo B/Apo A-1 ratio and PNI were independently associated with poor outcomes. Apo B/Apo A-1 ratio is an independent risk factor for poor outcomes in AIS, with a higher Apo B/Apo A-1 ratio reflecting an increased risk of poor outcomes in AIS. This relationship is more prominent in patients who are older and have hypertension, diabetes mellitus, and coronary artery disease. In contrast, PNI is an independent protective factor against poor outcomes in AIS. In addition, the Apo B/Apo A-1 ratio is associated with an increased risk of poor outcomes in AIS that is partially mediated by PNI.

A large study including 5362 participants revealed that the Apo B/Apo A-1 ratio is independently associated with the development of diabetes and that the Apo B/Apo A-1 ratio is likely to be an independent risk factor for the development of IR.<sup>23</sup> A higher Apo B/Apo A-1 ratio reflects the presence of IR, which is found in most patients with T2D and which is strongly associated with dyslipidemia and cardiovascular disease.<sup>24</sup> Our study confirms that the Apo B/Apo A-1 ratio is strongly associated with poor outcomes in patients with AIS in both diabetic and coronary artery disease populations, which further confirms the reliability of the Apo B/Apo A-1 ratio as a surrogate for IR in patients with AIS. Furthermore, IR can contribute to poor outcomes in AIS through its involvement in inflammatory responses, activation of oxidative stress, and neuronal damage.<sup>25</sup> Both Apo B and IR are reliable predictors of atherosclerosis.<sup>26</sup> Apo A-1 has a significant specific anti-atherosclerotic effect early in stroke onset,<sup>27</sup> and also has a significant inhibitory effect on inflammation.<sup>28</sup> Elevated Apo B/Apo A-1 ratio reflects enhanced inflammatory response and atherosclerosis formation. The association between IR and higher Apo B/Apo A-1 ratios in patients with poor AIS outcomes may be attributed to the fact that both are involved in poststroke inflammation and atherosclerosis formation.

The present study also confirms that lower PNI is strongly associated with poor AIS outcomes. Assessment of nutritional status is overly complex and cumbersome. The calculation of PNI is based on albumin and lymphocyte levels. Albumin is widely used to determine the nutritional status and also has anticoagulant and oxygen radical scavenging properties.<sup>29</sup> Recent studies have shown that albumin is an independent predictor of poor outcomes in AIS.<sup>30</sup> Lymphocytes play an important role in the inflammatory response after stroke onset. The activation of Treg cells, a subpopulation of T lymphocytes, reduces the inflammatory response and exerts neuroprotective effects.<sup>31,32</sup>

The coexistence of higher Apo B/Apo A-1 and lower PNI reflects the coexistence of organismal malnutrition and IR. Moreover, the mediation analysis of this study revealed that the higher Apo B/Apo A-1 ratio in patients with poor AIS outcomes was partly mediated by lower PNI. Although traditional vascular risk factors (eg, hypertension, diabetes mellitus) are thought to contribute to poor outcomes in patients with AIS, recent studies have found that the residual risk of cardiovascular events cannot be eliminated even with aggressive interventions against the aforementioned traditional risk factors,<sup>33</sup> and that improving IR reduces the risk of poor outcomes in AIS.<sup>34</sup> These findings suggest that IR may play a key role in AIS outcomes. Previous studies have suggested that overnutrition leads to IR, but our study indicates that malnutrition may mediate the progression of IR in patients with AIS. The underlying mechanisms remain unclear, but there may be several reasons. Firstly, lowering albumin levels may lead to an increase in oxidative stress, which in turn exacerbates insulin resistance.<sup>35</sup> Secondly, lower albumin levels also exacerbate inflammation, further aggravating IR.<sup>36</sup> As IR promotes inflammation,<sup>37</sup> the two form a vicious cycle. Moreover, the lowering of the Treg cells results in the elevation of pro-inflammatory cell's, which leads to the development of insulin resistance.<sup>38</sup>

Nevertheless, the shortcomings of this study should be acknowledged. First, the Apo B/Apo A-1 ratio was used to reflect IR, which may not provide a comprehensive assessment of insulin resistance, and the relationship between IR and AIS outcomes should be further explored by testing glucose clamp in patients. Second, this was a single-center clinical review study, and the possibility of selection bias should be considered. The results should be confirmed by a multicenter prospective study in the future. Finally, the patients' blood indices were only measured at admission, whereas dynamic monitoring may further elucidate the relationship between the Apo B/Apo A-1 ratio, PNI, and poor outcomes.

## Conclusion

To the best of our knowledge, this study is the first to report the effect of the Apo B/Apo A-1 ratio on poor AIS outcomes is partially mediated by PNI. These findings indicate that the Apo B/Apo A-1 ratio and PNI on admission in patients with AIS are strongly associated with poor outcomes, and that early intervention may improve patient outcomes.

## Abbreviations

AIS, Acute ischemic stroke; PNI, Prognostic Nutritional Index; IR, Insulin resistance; mRS, Modified Rankin Score; TIA, Transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; RCS, Restricted cubic spline; ROC, Receiver operating characteristic; TACI, Total anterior circulation infarction; PACI, Partial anterior circulation infarction; POCI, Posterior circulation infarction; LACI, Lacunar infarction; WBC, White blood cell; HDL, High-density lipoprotein; Apo A-1, Apolipoprotein A-1; Apo B, Apolipoprotein B; LDL, Low-density lipoprotein; TC, Total cholesterol; TG, Triglyceride; ALB, Albumin; HT, Hypertensive; DM, Diabetes mellitus; AF, Atrial fibrillation; CHD, Coronary heart disease.

## Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Affiliated Hospital of Nanjing University of Chinese Medicine (2017NL-012-01). Informed consent was obtained from participants or their legal representatives.

## Consent for Publication

All the authors agree to publish.

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## Author Contributions

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

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## Disclosure

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

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