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Nonlinear dose-response relationship between red blood cell distribution width to platelet ratio and 90-day unfavorable outcomes in acute ischemic stroke: a prospective cohort study

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Currently, there is relatively limited research regarding the relationship between the red blood cell distribution width to platelet ratio (RPR) and the prognosis of patients with acute ischemic stroke (AIS). Therefore, this study aims to investigate the association between RPR and the incidence of unfavorable functional outcomes in AIS patients. This study utilized a prospective cohort design and included 1,682 patients who had been diagnosed with AIS and were treated at Shenzhen Second People's Hospital from January 2022 to June 2024. To evaluate the relationship between RPR and the incidence of 90-day unfavorable outcomes, a binary logistic regression model was employed. Furthermore, an additional logistic regression model that included cubic spline functions was utilized to investigate possible nonlinear associations between them. A range of sensitivity analyses and subgroup analyses were conducted to strengthen the reliability of the results. After adjusting for confounding variables, the binary logistic regression analysis demonstrated that for each 0.1 unit increase in RPR, the incidence of unfavorable outcomes at 90 days for AIS patients increased by 45.5% (OR = 1.455, 95% CI: 1.268–1.669). Additionally, the study found a nonlinear relationship between RPR and 90-day unfavorable outcomes, with an inflection point occurring at RPR = 0.33. On the left side of the inflection point, the OR for the relationship between RPR (per 0.1 unit) and 90-day unfavorable outcomes was 1.708 (95% CI: 1.403–2.080). On the right side of the inflection point, the OR for their relationship was 0.942 (95% CI: 0.630–1.410). Sensitivity analysis further confirmed the reliability of these results. This study identifies a distinct positive link between RPR and 90-day unfavorable outcomes in patients with AIS. Additionally, a non-linear relationship was observed in the relationship between them. Specifically, when the RPR value falls below 0.33, a significant positive association is noted. These findings offer valuable insights for improving rehabilitation strategies and enhancing clinical management for AIS patients.

Keywords Prognosis, Ratio of red cell distribution width to platelet count, Non-linear, Modified rankin scale score, Acute ischemic stroke

Abbreviations

NEU	neutrophil count
CHD	coronary heart disease

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HDL-c	high-density lipoprotein cholesterol
LYC	lymphocyte count
FPG	fasting plasma glucose
BMI	body mass index
FIB	fibrinogen
SVO	small vessel occlusion
HCY	homocysteine
TC	total cholesterol
ALB	serum albumin
HGB	hemoglobin concentration
TG	triglycerides
DM	diabetes mellitus
LAA	large artery atherosclerosis
LDL-C	low-density lipoprotein cholesterol
TIA	transient ischemia attack
NIHSS	National Institute of Health stroke scale
AF	atrial fibrillation
CE	cardio embolism

Acute ischemic stroke (AIS) is a major global cause of disability and mortality, representing a significant socioeconomic challenge[1,2]. Despite notable progress in the acute treatment and rehabilitation of AIS, accurately predicting neurological outcomes for affected individuals remains a considerable challenge[3]. The identification and application of dependable prognostic indicators are essential for effective risk stratification, tailoring treatment approaches, and enhancing patient outcomes[4]. Currently, key prognostic factors commonly acknowledged in AIS include age, hypertension, the underlying cause of the stroke, and diabetes mellitus (DM)[5–7].

The inflammatory response is believed to be crucial during various pathological and physiological phases of AIS. When brain tissue is damaged, pro-inflammatory chemical mediators are released, initiating a robust inflammatory response[8–10]. Research indicates that the intensity of this inflammation is significantly linked to the clinical prognosis for patients with AIS[11,12]. Recently, the ratio of red blood cell distribution width (RDW) to platelet count (RPR) has gained attention as a new inflammatory marker. Studies showed that RPR is often significantly elevated and is closely related to the severity of the inflammatory response, in several acute or chronic inflammatory diseases (such as sepsis, acute pancreatitis, systemic lupus erythematosus, etc.)[13–15]. At the same time, it has been shown to predict outcomes in several conditions, including ST-segment elevation myocardial infarction, liver fibrosis, malignancies, and chronic liver disease[16–18]. In addition, elevated RDW levels have been confirmed as a reliable indicator of systemic inflammatory status, and early studies have shown that higher RDW levels are positively correlated with poor prognosis in AIS patients[19,20]. Moreover, platelet counts appear to provide a protective effect, showing a significant negative association with poor functional outcomes[21,22]. Therefore, we hypothesize that a potential positive relationship may exist between RPR and unfavorable outcomes in AIS patients.

Regrettably, there is currently limited research examining the association between RPR and the risk of unfavorable outcomes in AIS patients. One study involving 235 AIS patients treated with intravenous thrombolysis[23] and another with 286 AIS patients who underwent mechanical thrombectomy[24]—identified a significant association between elevated RPR and short-term negative outcomes. However, both investigations utilized small sample sizes and focused on specific patient populations, and the potential nonlinear association between RPR and unfavorable outcomes was not explored. Furthermore, the studies differed in several aspects, including study design, the range of RPR values, demographic distributions of sex, definitions of functional outcomes, and adjustment variables. As a result, the association between RPR and short-term prognosis in the broader AIS population in China remains uncertain. Therefore, a prospective cohort study has been launched to explore the relationship between RPR and the risk of unfavorable outcomes in patients with AIS, which may provide valuable insights for developing rehabilitation strategies.

Methods

Study design and population

This study was a prospective cohort study. During the period from January 2022 to June 2024, patients who presented to the Stroke Center of Shenzhen Second People's Hospital and were diagnosed with AIS by computed tomography (CT) or magnetic resonance imaging (MRI) and were aged over 20 years totaled 2,106 people. Among them, 147 people refused to participate in this study, and initially, a total of 1,959 AIS patients were included.

The criteria for exclusion included the following: (i) Participants with AIS onset of more than one week($n = 91$); (ii) Participants without follow-up at 3 months post-discharge, refused to participate in follow-up, or those for whom the 90-day modified Rankin Scale (mRS) score could not be assessed during the follow-up($n = 149$); and (iii) participants with incomplete data on RDW or platelet count ($n = 25$), as well as those exhibiting extreme and abnormal RPR values (deviation exceeding three standard deviations from the mean) ($n = 12$). In total, 1,682 participants were included in the final analysis. Figure 1 illustrated the participant selection process.

Ethical approval and consent

Approval for the study was granted by the ethics review board of Shenzhen Second People's Hospital (Ethics Approval Number: 2023-305-01PJ), and the research was carried out following the ethical principles established

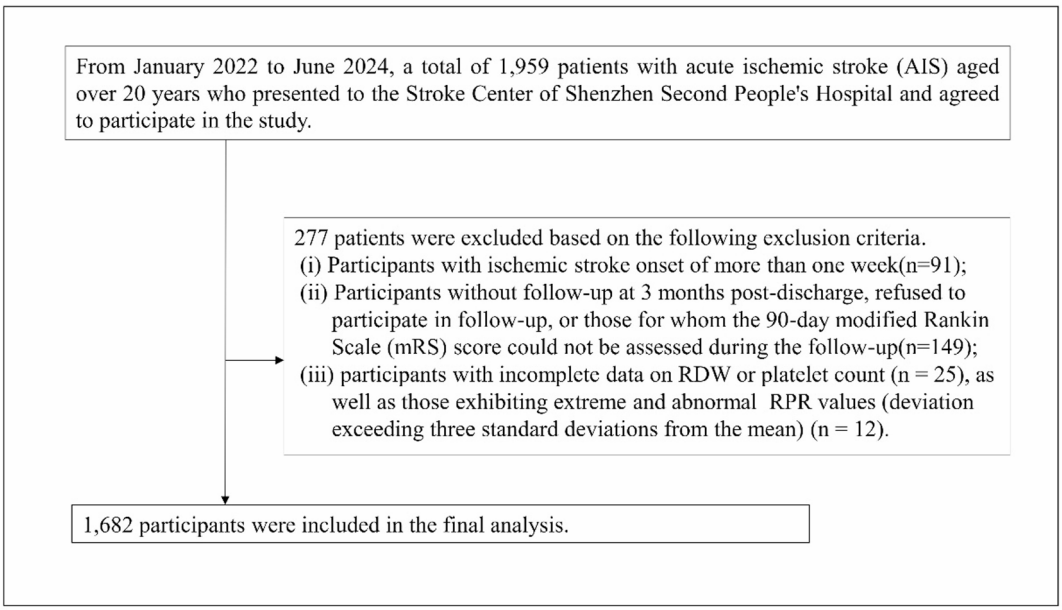

Fig. 1. Flowchart illustrating the study participants.

in the Declaration of Helsinki of 1964 and its later modifications, along with other relevant ethical guidelines. Written informed consent was secured from all participants included in this study.

Variables

Red blood cell distribution width to platelet count ratio

The RPR value is calculated using the following formula: RPR = RDW/platelet count[25]. In this formula, RDW refers to the standard deviation of red blood cell volume, measured in femtoliters (fL), and the platelet count is expressed in 10^9/L. Both RDW and platelet count are measured within 24 h after hospital admission.

Assessment of clinical outcome and follow-up

At 90 days following the onset of AIS, trained follow-up personnel, who have a thorough understanding of the mRS scoring criteria, assessed patients through face-to-face interviews or telephone interviews to collect data on patients' functional status. During these assessments, we employed the mRS to evaluate functional outcomes, which is a commonly used tool for evaluating functional recovery and independence in daily living among patients with stroke or other neurological diseases. The mRS score ranges from 0 to 6, reflecting various functional states from no symptoms to death[26]. The primary endpoint of this study was the neurological functional outcome at 90 days, classified into two categories: unfavorable (mRS ≥ 3) and favorable (mRS < 3) outcomes[27,28]. To ensure the accuracy of follow-up, we established a patient information contact database and conducted multiple phone calls to remind patients to participate in the follow-up, thus reducing the occurrence of follow-up loss.

Covariates

Covariates were chosen based on our clinical expertise and prior studies[4,29–31]. The variables identified for inclusion as covariates included: (i) categorical variables including coronary heart disease (CHD), sex, history of prior stroke or transient ischemic attack (TIA), pneumonia, hypertension, atrial fibrillation (AF), DM, smoking status, and stroke etiology; and (ii) continuous variables such as neutrophil count (NEU), age, lymphocyte count (LYC), total cholesterol (TC), the initial score on the National Institutes of Health Stroke Scale (NIHSS) upon admission, triglycerides (TG), fibrinogen (FIB), fasting plasma glucose (FPG), body mass index (BMI), homocysteine (HCY), serum albumin (ALB), low-density lipoprotein cholesterol (LDL-C), hemoglobin concentration (HGB), high-density lipoprotein cholesterol (HDL-C), and D-dimer levels.

Data gathering and measurement

At the time of admission to the hospital, specialized research coordinators systematically gathered baseline data pertaining to patients' demographic information and medical histories. This data included information on prior strokes, smoking status, AF, CHD, hypertension, and DM. Neurologists assessed stroke severity at admission using the NIHSS. Stroke subtypes were categorized based on the criteria established by the Trial of Org 10,172 in Acute Stroke Treatment (TOAST). Blood samples were gathered within 24 h following patient admission and were later examined at the laboratory of Shenzhen Second People's Hospital. Qualified technicians adhered to strict quality control protocols during laboratory evaluations, ensuring the confidentiality of patients' baseline data.

Addressing missing data

In this study, certain covariates exhibited missing data, with the corresponding counts and percentages of absent entries listed as follows: FIB (5, 0.30%), FPG (21, 1.25%), TG (40, 2.38%), HDL-c(40, 2.38%), LDL-c (40, 2.38%), TC (41, 2.44%), HCY (119, 7.07%), and NIHSS score (207, 12.30%). Missing data can undermine the statistical validity of the sample analyzed during the modeling phase. To minimize the bias resulting from these missing variables, we utilized multiple imputation techniques to address the unavailable data[32,33]. The covariates utilized in the imputation model included age, NEU, LYC, NIHSS score at the time of admission, HGB, RDW, platelet count, BMI, FIB, D-dimer, HCY, TG, HDL-c, ALB, FPG, TC, LDL-c, sex, history of previous stroke or TIA, DM, hypertension, AF, pneumonia, CHD, smoking status, and stroke etiology. The imputation procedure was executed using a linear regression method across ten iterations. The analysis of the missing data was based on the assumption of missing at random (MAR)[33].

Analysis of statistical

Baseline variables were categorized by the quartiles of RPR, facilitating the comparison of characteristics across the groups. Continuous variables with a Gaussian distribution were summarized as means and standard deviations, while non-normally distributed variables were represented using medians and interquartile ranges. Categorical data were expressed as frequencies and percentages. Both analyses of variance (ANOVA) and the Kruskal-Wallis H test were applied to continuous variables, whereas the chi-square (χ^2) test was used to evaluate differences among the RPR groups for categorical variables.

This study utilized univariate and multivariate binary logistic regression analyses to develop three distinct models examining the relationship between RPR and the incidence of unfavorable outcomes 90 days after AIS. The models consisted of: (i) Model I: no covariate adjustments; (ii) Model II: adjusted for sex, age, and BMI; and (iii) Model III: adjusted for age, smoking, BMI, CHD, sex, TG, HGB, LDL-c, D-dimer, FPG, stroke etiology, hypertension, HDL-c, DM, and initial NIHSS score.

In order to enhance the reliability of the results, we carried out multiple sensitivity analyses. Initially, RPR was transformed into a categorical variable according to its quartiles, and the trend P-value was computed to evaluate the results of RPR as a continuous variable while investigating the possibility of non-linearity. Second, to address the influence of obesity, hypertension, and DM on the prognosis of AIS patients, we conducted a sensitivity analysis by excluding individuals with a BMI greater than or equal to 28 kg/m², as well as those with hypertension and DM[34–36]. In addition, we calculated the E-value to evaluate the potential impact of unmeasured confounders on the link between RPR and 90-day unfavorable outcomes[37].

A logistic regression model using restricted cubic spline functions was employed to explore the potential non-linear association between RPR and 90-day unfavorable outcomes in AIS patients. A recursive approach was utilized to identify the inflection point if a non-linear association was detected. After identifying the inflection point, separate binary logistic regression models were developed for each side of this threshold. The likelihood ratio test was used to select the model that best represented the relationship.

Stratified binary logistic regression models were applied to conduct subgroup analyses across several categories, such as pneumonia, TG, sex, age, history of previous stroke or TIA, AF, FIB, ALB, hypertension, BMI, Smoking, and CHD. In this analysis, continuous variables like TG FIB, ALB, BMI, and age were categorized based on clinically relevant cutoffs. Specifically, TG was categorized using a threshold of 1.7 mmol/L, BMI by 28 kg/m², FIB by 4 g/L, and ALB by 35 g/L[35,38,39]. Adjustments were made for sex, LDL-c, CHD, TG, stroke etiology, age, hypertension, Scr, HDL-c, platelet count, FPG, smoking status, DM, and initial NIHSS score, while excluding the stratification variables. Likelihood ratio tests were conducted to evaluate the existence of interaction terms by comparing models that included these terms to those that did not. Finally, a receiver operating characteristic (ROC) curve was constructed to assess the predictive capability of RPR, RDW, and platelet count for unfavorable outcomes in AIS patients.

All findings were written in line with the STROBE statement[40]. Statistical analyses were executed using Empower® software (version 4.2) and R (version 3.4.3). A two-tailed p-value of less than 0.05 was considered statistically significant.

Results

Participants' characteristics

Table 1 presented the demographic and clinical characteristics of the study participants. A total of 1,682 individuals were included in the final analysis, with males accounting for 62.54% of this group. RPR demonstrated an approximately normally distributed, ranging from 0.03 to 0.62, with a mean (± standard deviation, SD) of 0.19 (± 0.09)(Fig. 2). Participants were categorized into distinct subgroups based on the quartiles of RPR: Q1(<0.14), Q2(0.14–0.18), Q3(0.18–0.23), and Q4(≥ 0.23). Compared with Q1, higher levels of RDW, FIB, and FPG, as well as lower levels of Neu, platelets, ALB, and D-dimer, were observed in participants of the higher RPR quartiles. Additionally, higher proportions of males, smokers, and incidence of pneumonia were found in the higher RPR quartiles compared to Q1, while a lower incidence of hypertension was noted.

Incidence of unfavorable outcomes 90-day in AIS patients

Table 2 presented the incidence of 90-day unfavorable outcomes in AIS patients. The findings reveal that 295 participants encountered unfavorable outcomes, leading to a total incidence rate of 17.78%. Particularly, the unfavorable outcome incidence rates for the first to fourth quartiles of RPR were 10.69%, 12.14%, 21.19%, and 27.08%, respectively.

RPR quartiles	Q1(<0.14)	Q2(0.14–0.18)	Q3(0.18–0.23)	Q4(≥ 0.23)	P-value
N	421	420	420	421	
Neu (10^9/L, mean ± SD)	5.84 ± 2.72	5.83 ± 2.83	5.04 ± 2.27	5.57 ± 3.36	< 0.001
Lyc (10^9/L, mean ± SD)	1.66 ± 0.66	1.89 ± 0.70	1.59 ± 0.61	1.43 ± 0.61	< 0.001
NIHSS score (median, quartile)	4.02(2.00–8.00)	4.10 (2.00–8.00)	4.09 (2.00–8.03.00.03)	4.30 (2.09–8.15)	0.676
HGB (g/L, mean ± SD)	140.07 ± 19.02	140.36 ± 18.61	137.76 ± 21.48	137.71 ± 22.63	0.102
BMI (kg/m2, mean ± SD)	21.78 ± 3.25	22.60 ± 3.42	23.52 ± 3.10	24.28 ± 3.26	0.017
RDW (fl., mean ± SD)	33.70 (22.80–39.00)	41.30 (39.70–43.60)	42.50 (40.60–44.70)	44.80 (42.30–47.80)	< 0.001
Platele (10^9/L, mean ± SD)	262.87 ± 102.51	259.47 ± 33.92	210.62 ± 22.78	151.12 ± 28.69	< 0.001
FIB (g/L, mean ± SD)	3.03 ± 1.43	3.36 ± 1.27	3.32 ± 1.31	3.23 ± 1.47	0.002
HCY (umol/L, mean ± SD)	14.40 (10.46–21.00.46.00)	12.90 (9.88–17.52)	13.14 (9.80–18.62.80.62)	14.00 (11.00–20.82.00.82)	0.104
ALB(g/L, mean ± SD)	38.16 ± 4.25	37.64 ± 4.22	37.34 ± 5.46	36.50 ± 4.73	< 0.001
FPG(mmol/L, mean ± SD)	6.54 ± 2.81	7.27 ± 2.90	6.86 ± 3.07	6.70 ± 2.90	0.008
TC (mmol/L, mean ± SD)	4.71 ± 1.26	4.64 ± 1.49	4.70 ± 4.66	4.37 ± 1.21	0.196
TG (mmol/L, mean ± SD)	1.45 (1.04–2.04)	1.47 (1.01–2.00.01.00)	1.35 (1.05–1.95)	1.23 (0.90–1.76)	< 0.001
HDL-c(mmol/L, median, quartile)	1.07 (0.91–1.28)	1.21 (1.02–1.43)	1.16 (0.99–1.37)	1.19 (0.99–1.43)	0.354
LDL-c(mmol/L, mean ± SD)	3.03 ± 0.96	3.10 ± 1.02	2.97 ± 1.01	2.82 ± 0.90	< 0.001
Age (years, mean ± SD)	66.29 ± 11.27	64.57 ± 11.12	68.29 ± 10.92	71.49 ± 10.94	< 0.001
D-dimer(mg/dL, mean ± SD)	1.36 (0.58–3.28)	0.65 (0.49–1.66)	0.75 (0.49–2.05)	1.31 (0.63–4.18)	< 0.001
SEX					0.010
Male	244 (57.96%)	250 (59.52%)	273 (65.00%)	285 (67.70%)	
Female	177 (42.04%)	170 (40.48%)	147 (35.00%)	136 (32.30%)	
Previous stroke/TIA (n, %)	30 (7.13%)	40 (9.52%)	37 (8.81%)	33 (7.84%)	0.605
DM (n, %)	122 (28.98%)	136 (32.38%)	129 (30.71%)	109 (25.89%)	0.198
Hypertension (n, %)	261 (62.00%)	223 (53.10%)	247 (58.81%)	222 (52.73%)	0.015
CHD (n, %)	92 (21.85%)	66 (15.71%)	88 (20.95%)	128 (30.40%)	< 0.001
AF (n, %)	45 (10.69%)	25 (5.95%)	42 (10.00%)	74 (17.58%)	< 0.001
Pneumonia (n, %)	50 (11.88%)	65 (15.48%)	60 (14.29%)	98 (23.28%)	< 0.001
Smoking (n, %)	48 (11.40%)	74(17.62%)	103 (24.52%)	121 (28.74%)	< 0.001
Stroke etiology (n, %)					0.327
SVO	135 (32.07%)	146 (34.76%)	138 (32.86%)	137 (32.54%)	
LAA	73 (17.34%)	95 (22.62%)	75 (17.86%)	96 (22.80%)	
CE	112 (26.60%)	91 (21.67%)	114 (27.14%)	94 (22.33%)	
Other determined	41 (9.74%)	26 (6.19%)	34 (8.10%)	35 (8.31%)	
Undetermined	60 (14.25%)	62 (14.76%)	59 (14.05%)	59 (14.01%)	

Table 1. Characteristics of participants at Baseline. Values are mean ± standard deviation or median (interquartile) or number (%) NEU, neutrophil count; CHD, coronary heart disease; HDL-c, high-density lipoprotein cholesterol; LYC, lymphocyte count; FPG, fasting plasma glucose; BMI, body mass index; FIB, fibrinogen; SVO, small vessel occlusion; HCY, homocysteine; TC, total cholesterol; ALB, serum albumin; HGB, hemoglobin concentration; TG, triglycerides; DM, diabetes mellitus; LAA, large artery atherosclerosis; LDL-C, low-density lipoprotein cholesterol; TIA, transient ischemia attack; NIHSS, National Institute of Health stroke scale; AF, atrial fibrillation; CE, cardio embolism; N, Number.

Relationship between RPR and 90-day unfavorable outcomes in AIS patients

To further investigate the relationship between RPR and the risk of unfavorable outcomes in AIS patients at 90 days, three distinct binary logistic regression models were developed (Table 3). In Model I, a 0.1-unit increase in RPR is associated with a 64.9% rise in the incidence of 90-day unfavorable outcomes (OR = 1.649, 95% CI: 1.456–1.867). In Model II, each 0.1-unit increase in RPR was linked to a 49.1% higher risk of 90-day unfavorable outcomes among AIS patients (OR = 1.491, 95% CI: 1.311–1.694). Similarly, Model III indicated that a 0.1-unit rise in RPR was associated with a 45.5% increase in 90-day unfavorable outcomes (OR = 1.455, 95% CI: 1.268–1.669).

Furthermore, RPR, which was initially examined as a continuous variable, was subsequently categorized for further investigation. With the lowest quartile (Q1) serving as the reference, multivariate adjustment revealed that the OR for unfavorable outcomes was 1.186 (95% CI: 0.738–1.906) in Q2, 2.497 (95% CI: 1.635–3.813) in Q3, and 2.455 (95% CI: 1.623–3.714) in Q4. Confidence interval analysis revealed that, compared with Q1, participants in Q2 showed no statistically significant difference in 90-day unfavorable outcomes, whereas those in Q3 and Q4 exhibited a significantly higher risk of unfavorable outcomes. Additionally, the trend analysis for effect size yielded statistically significant results (P for trend < 0.05) (Table 3, Model III).

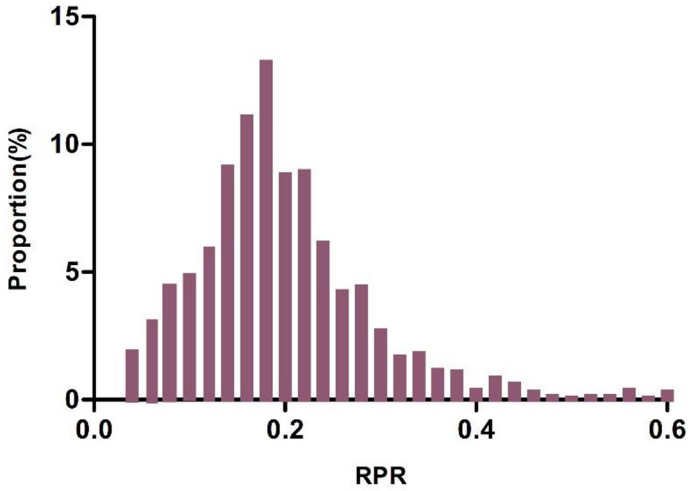

Fig. 2. Distribution of RPR. The distribution appeared approximately normal, spanning from 0.03 to 0.62, with a mean ± SD of 0.19 ± 0.09.

	Participants(*n*)	unfavorable outcome events(*N*)	Incidence of unfavorable (%)(95% CI)
Total	1682	295	17.78(15.95, 19.61)
Q1	421	45	10.69(7.73,13.65)
Q2	420	51	12.14(9.01, 15.28)
Q3	420	89	21.19(17.27, 25.11)
Q4	421	114	27.08(22.82,31.34)
P for trend			< 0.001

Table 2. Incidence rate of 90-day unfavorable outcome after AIS(%). N, Number.

Exposure	Model I (OR 95%CI) *p*	Model II (OR 95%CI) *p*	Model III (OR 95%CI) *p*
RPR (per 0.1 unit)	1.649 (1.456, 1.867) < 0.001	1.491 (1.311, 1.694) < 0.001	1.455 (1.268, 1.669) < 0.001
RPR quartiles			
Q1	Ref	Ref	Ref
Q2	1.155 (0.754, 1.768) 0.508	1.291 (0.834, 1.999) 0.251	1.186 (0.738, 1.906) 0.481
Q3	2.247 (1.525, 3.311) < 0.001	2.090 (1.403, 3.113) < 0.001	2.497 (1.635, 3.813) < 0.001
Q4	3.103 (2.129, 4.521) < 0.001	2.451 (1.658, 3.621) < 0.001	2.455 (1.623, 3.714) < 0.001
P for trend	< 0.001	< 0.001	< 0.001

Table 3. Association of RPR with 90-day unfavorable outcomes follow AIS in various models. Model I: No covariates were adjusted. Model II: sex, age, BMI, were adjusted. Model III: Stroke etiology, HGB, HDL-c, initial NIHSS score, D-dimer, BMI, TG, age, sex, FPG, CHD, hypertension, smoking, DM, and LDL-c were adjusted.

Sensitivity analysis

Multiple sensitivity analyses were conducted to enhance the validity of the findings (Table 4). First, individuals with a BMI of 28 kg/m² or higher were excluded. After adjustments for confounders, results showed a positive link between RPR and the risk of unfavorable outcomes at 90 days in AIS patients, with an OR of 1.509 (95% CI: 1.310, 1.739). Excluding those with hypertension produced similar findings, demonstrating an OR of 1.467 (95% CI: 1.198–1.797) for unfavorable outcomes at 90 days. Additionally, when patients without DM were analyzed, a significant association between RPR and 90-day unfavorable outcomes remained evident (OR = 1.708, 95% CI: 1.437–2.030).

Furthermore, the E-value was calculated to assess the potential impact of unmeasured confounding variables on the study outcomes. The determined E-value was 1.7, which surpasses the relative risk associated with unmeasured confounders and RPR (1.45). This finding suggests that unrecognized confounding factors have a negligible effect on the association between RPR and unfavorable outcomes at 90 days in AIS patients. The results from all sensitivity analyses further support the reliability of the conclusions drawn in this study.

Exposure	Model I (OR 95%CI) *p*	Model II (OR 95%CI) *p*	Model III (OR 95%CI) *p*
RPR (per 0.1 unit)	1.509 (1.310, 1.739) < 0.001	1.467 (1.198, 1.797) < 0.001	1.708 (1.437, 2.030) < 0.001
RPR quartiles			
Q1	Ref	Ref	Ref
Q2	1.131 (0.683, 1.872) 0.633	2.356 (1.081, 5.135) 0.031	1.550 (0.280, 1.080) 0.083
Q3	2.292 (1.468, 3.577) < 0.001	3.752 (1.747, 8.058) < 0.001	2.686 (1.611, 4.478) < 0.001
Q4	2.290 (1.485, 3.530) < 0.001	3.797 (1.848, 7.802) < 0.001	2.649 (1.611, 4.358) < 0.001
P for trend	< 0.001	< 0.001	< 0.001

Table 4. Association of RPR with 90-day unfavorable outcomes in AIS patients in various sensitivity analyses. Model I was sensitivity analysis in participants without BMI ≥ 28 kg/m2(n = 1,541). Stroke etiology, hypertension, HGB, LDL-c, D-dimer, age, TG, FPG, DM, HDL-c, initial NIHSS score, sex, smoking, and CHD were adjusted. Model II was sensitivity analysis in participants without hypertension(n = 729). HGB, stroke etiology, smoking, LDL-c, D-dimer, TG, HDL-c, FPG, age, initial NIHSS score, CHD, BMI, DM, and sex were adjusted. Model III was sensitivity analysis in participants without DM(n = 1,186). LDL-c, stroke etiology, BMI, HGB, Age, D-dimer, TG, FPG, initial NIHSS score, hypertension, platelet, CHD, sex, smoking, and HDL-c were adjusted. OR odds ratios; CI, confidence; Ref: reference.

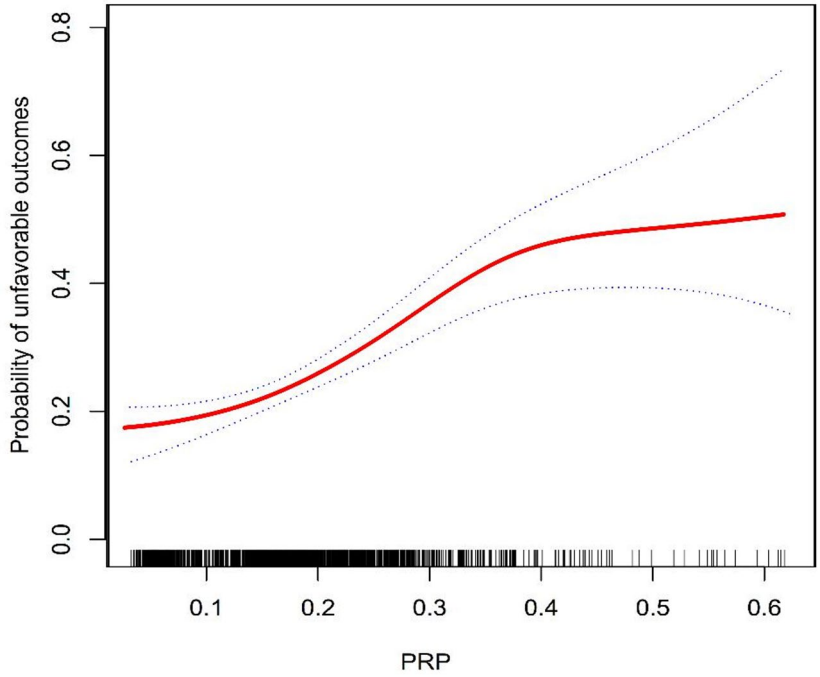

Fig. 3. The nonlinear relationship between RPR and the risk of 90-day unfavorable outcomes in AIS patients. There was a nonlinear relationship between RPR and the risk of 90-day unfavorable outcomes, with an inflection point at 0.33.

Generalized additive model (GAM) for analyzing nonlinear association between RPR and 90-Day unfavorable outcomes

Using a logistic regression model with cubic spline functions, a non-linear relationship between RPR and 90-day unfavorable outcomes was identified in AIS patients (p for nonlinearity < 0.05, Fig. 3). The analysis adjusted for several covariates, including age, hypertension, BMI, sex, HDL-c, HGB, smoking, initial NIHSS score, stroke etiology, D-dimer, TG, FPG, CHD, DM, and LDL-c. A recursive analysis identified an inflection point for RPR at a value of 0.33. Subsequently, a piecewise logistic regression model was applied to calculate OR and CI on both sides of the inflection point. On the left of this inflection point, the OR indicating the association between RPR and the risk of unfavorable outcomes at 90 days was 1.708 (95% CI: 1.403–2.080). On the right side of the inflection point, the OR was 0.942 (95% CI: 0.630–1.410), which did not achieve statistical significance (Table 5).

Results of subgroup analysis

In all predefined or exploratory subgroup analyses (Table 6), no significant interactions were found between RPR and factors such as age, sex, TG, history of stroke or TIA, CHD, AF, FIB, ALB, hypertension, BMI, smoking, and

Outcome: 90-day unfavorable outcomes	OR (95%CI) *p*-value
Fitting Model by two-piecewise linear regression	
Inflection point of RPR	0.33
< 0.33 (per 0.1 unit)	1.708 (1.403, 2.080) <0.001
≥0.33 (per 0.1 unit)	0.942 (0.630, 1.410) 0.773
P for log-likelihood ratio test	0.023

Table 5. Analysis of the relationship between RPR and 90-day unfavorable outcomes using a two-piecewise linear regression model. Age, sex, initial NIHSS score, HGB, hypertension, LDL-c, smoking, DM, D-dimer, TG, stroke etiology, HDL-c, FPG, CHD, and BMI were adjusted.

pneumonia (all $p \geq 0.05$). This suggests that these variables do not influence or modify the association between RPR and 90-day unfavorable outcomes in AIS patients.

The results of the ROC curve analysis

Additionally, we constructed an ROC curve to evaluate the predictive capability of RDW, platelet count, and RPR to assess the risk of unfavorable outcomes (Fig. 4). The areas under the curve (AUC) for each variable were as follows: platelet: 0.6712 < RDW:0.6732 < RPR:0.6844. The Youden indices for platelet, RDW, and RPR were 0.1982, 0.2321, and 0.2383, respectively, with corresponding best cut-off values of 196.2, 44.45, and 0.1987. The RPR demonstrated the highest Youden index and AUC, suggesting that its predictive ability for unfavorable prognosis in patients with AIS is superior to that of the other variables studied (Supplementary Table S1).

Discussion

This study identified an independent positive relationship between RPR and unfavorable outcomes at 90 days in patients with AIS. Furthermore, a nonlinear relationship was observed between them, with an inflection point occurring at an RPR value of 0.33. Different associations between RPR and unfavorable outcomes at 90 days were observed on both sides of this inflection point.

In recent years, RPR has emerged as a novel inflammatory biomarker. Various studies have demonstrated a strong link between RPR and the prognosis of multiple diseases, such as liver fibrosis, chronic liver disease, certain cancers, and ST-segment elevation myocardial infarction[16–18]. However, investigations into the impact of RPR on stroke prognosis are still limited. A cohort study involving 235 patients with AIS who received intravenous thrombolysis found that RPR is an independent risk factor for adverse outcomes (with adverse outcomes defined as an increase of 4 points or more in the NIHSS score within 24 hours after thrombolysis or death), determined through multivariate logistic regression analysis (OR = 2.031; 95% CI: 1.436–2.873; $P < 0.0001$)[23]. Similarly, another investigation involving 286 AIS patients who underwent mechanical thrombectomy found that each unit increase in RPR corresponded to a 67.1% rise of unfavorable outcomes at three months (defined as an mRS score of ≥ 3), with an OR of 1.671 (95% CI: 1.127–2.479; $P = 0.011$)[24]. Additionally, a study involving 2,673 critically ill AIS patients found that RPR was associated with a OR of 1.28 (95% CI: 1.02–1.59) for in-hospital all-cause mortality after adjusting for potential confounders[41]. Our study adds to the existing literature by supporting the hypothesis that elevated RPR is positively associated with short-term adverse outcomes in AIS. In contrast to prior studies, we assessed RPR as both a categorical and continuous variable, thereby reducing information loss and enabling a more precise quantification of its relationship with outcomes. Besides, we employed ROC curve analysis to evaluate the predictive performance of RPR, platelet, and RDW regarding 90-day outcomes in AIS patients. Our results demonstrate that AUC for RPR and the optimal Youden index exceed those of platelet and RDW, indicating that RPR can serve as an important predictor of adverse outcomes within 90 days post-AIS, providing critical risk assessment metrics for the development of prediction models regarding unfavorable outcomes in AIS patients. Additionally, we conducted a sensitivity analysis on participants with a BMI of less than 28 kg/m² and no history of hypertension or DM to confirm the robustness of our findings. In summary, identifying RPR as a risk factor for adverse outcomes in AIS patients and elucidating the relationship between them carries some clinical implications. Integrating RPR into routine clinical evaluations allows healthcare professionals to detect high-risk populations early, facilitating timely interventions aimed at promoting rehabilitation and ultimately reducing the incidence of unfavorable outcomes following AIS.

The specific mechanisms linking elevated RPR to poor short-term prognosis in AIS patients are not fully clear, but they likely relate to inflammation and coagulation dysfunction. Prior research has demonstrated that inflammation, coagulation abnormalities, and atherosclerosis significantly influence various pathophysiological stages of AIS[42]. Excessive inflammation can inflict damage on the endothelial lining of blood vessels, intensifying cerebral ischemic injury[9]. RDW serves as an inflammatory marker; increased RDW levels typically indicate a heightened inflammatory state in the body[20]. However, high RDW may compromise erythrocyte membrane integrity and increase their fragility[43–45]. Reduced erythrocyte deformability can impair microcirculation and oxygen delivery, thus further aggravating cerebral injury and affecting neuronal repair[46]. Studies have shown that elevated RDW values are frequently observed in AIS patients with unfavorable prognoses[47]. Moreover, during the pathogenesis of AIS, activated platelets adhere to the vascular wall at sites of ruptured atherosclerotic plaques and simultaneously release various inflammatory mediators, which further activate immune cells such as neutrophils, lymphocytes, and monocytes, and consequently lead to aggravated brain tissue injury[4849];. Research indicates that the average platelet count in deceased AIS patients is significantly lower compared to

Characteristic		OR (95%CI) *P* value	*P* for interacion
Age(years)			0.463
<60	401	1.906 (1.270, 2.861) 0.002	
60–70	552	1.353 (1.028, 1.780) 0.031	
70–80	439	1.363 (1.085, 1.712) 0.008	
≥ 80	290	1.579 (1.213, 2.056) < 0.001	
Sex			0.897
Male	1052	1.465 (1.232, 1.742) < 0.001	
Female	630	1.438 (1.151, 1.797) 0.001	
TG			0.289
< 1.7mmol/L	1119	1.405 (1.206, 1.636) < 0.001	
≥ 1.7mmol/L	563	1.691 (1.239, 2.308) < 0.001	
Previous stroke/TIA			0.062
No	1542	1.489 (1.294, 1.714) < 0.001	
Yes	140	0.680 (0.295, 1.571) 0.367	
CHD			0.490
No	1308	0.946 (0.916, 0.977) < 0.001	
Yes	374	0.963 (0.920, 1.008) 0.110	
AF			0.070
No	1496	1.361 (1.164, 1.590) < 0.001	
Yes	186	1.872 (1.361, 2.575) < 0.001	
Pneumonia			0.194
No	1409	1.568 (1.336, 1.839) < 0.001	
Yes	273	1.276 (0.979, 1.663) 0.071	
BMI			0.364
<28 kg/m^2	1541	1.509 (1.310, 1.739) < 0.001	
≥ 28 kg/m^2	141	1.867 (1.191, 2.927) 0.007	
Hypertension			0.471
No	729	1.527 (1.261, 1.850) < 0.001	
Yes	953	1.381 (1.134, 1.682) 0.0013	
FIB			0.209
<4.0 g/L	1145	1.578 (1.328, 1.876) < 0.001	
≥ 4.0 g/L	537	1.315 (1.047, 1.652) 0.019	
ALB			0.083
< 35 g/L	381	1.243 (0.996, 1.552) 0.055	
≥ 35 g/L	1301	1.596 (1.341, 1.901) < 0.001	
Smoking			0.171
No	246	1.657 (1.403, 1.956) < 0.001	
Yes	1436	1.378 (1.091, 1.741) 0.007	

Table 6. Stratified associations of RPR with 90-day unfavorable outcomes follow AIS in different sensitivity analyses by sex, TG, CHD, previous stroke/TIA, age, pneumonia, FIB, ALB, hypertension, BMI, smoking, and AF. Note 1: Above model adjusted for age, initial NHISS score, Stroke etiology, HDL-c, hypertension, CHD, LDL-c, TG, FPG, smoking, sex, DM, and Scr. Note 2: In each case, the Model is not adjusted for the stratification variable. CI, confidence; OR, odds ratios.

survivors, and lower peripheral platelet counts are often linked to larger infarct sizes and increased disease severity[50]. Therefore, RPR, which integrates RDW levels and platelet count, can more comprehensively reflect the inflammatory and coagulation status of AIS patients and, to some extent, indicate the pathophysiological processes of short-term neurological injury and repair in these patients.

Additionally, after stratifying participants based on RPR quartiles, the results of the multivariable-adjusted model indicate that OR for RPR in the Q1, Q2, and Q3, compared to the Q1, were 1.186, 2.497, and 2.455, respectively. This suggests that there is an observable trend of increasing risk for unfavorable outcomes among AIS patients from the first quartile to the third, which stopped in the fourth quartile. This observation implies a potential non-linear association between RPR and unfavorable outcomes. To test this hypothesis, we employed logistic regression with cubic splines and discovered a non-linear link between them, identifying an inflection point at an RPR level of 0.33. The results of the two-piecewise linear regression analysis showed that on the left side of the inflection point, as the RPR value increased, the incidence of 90-day unfavorable outcomes in AIS patients tended to rise. However, on the right side of the inflection point, as RPR increased, the incidence of

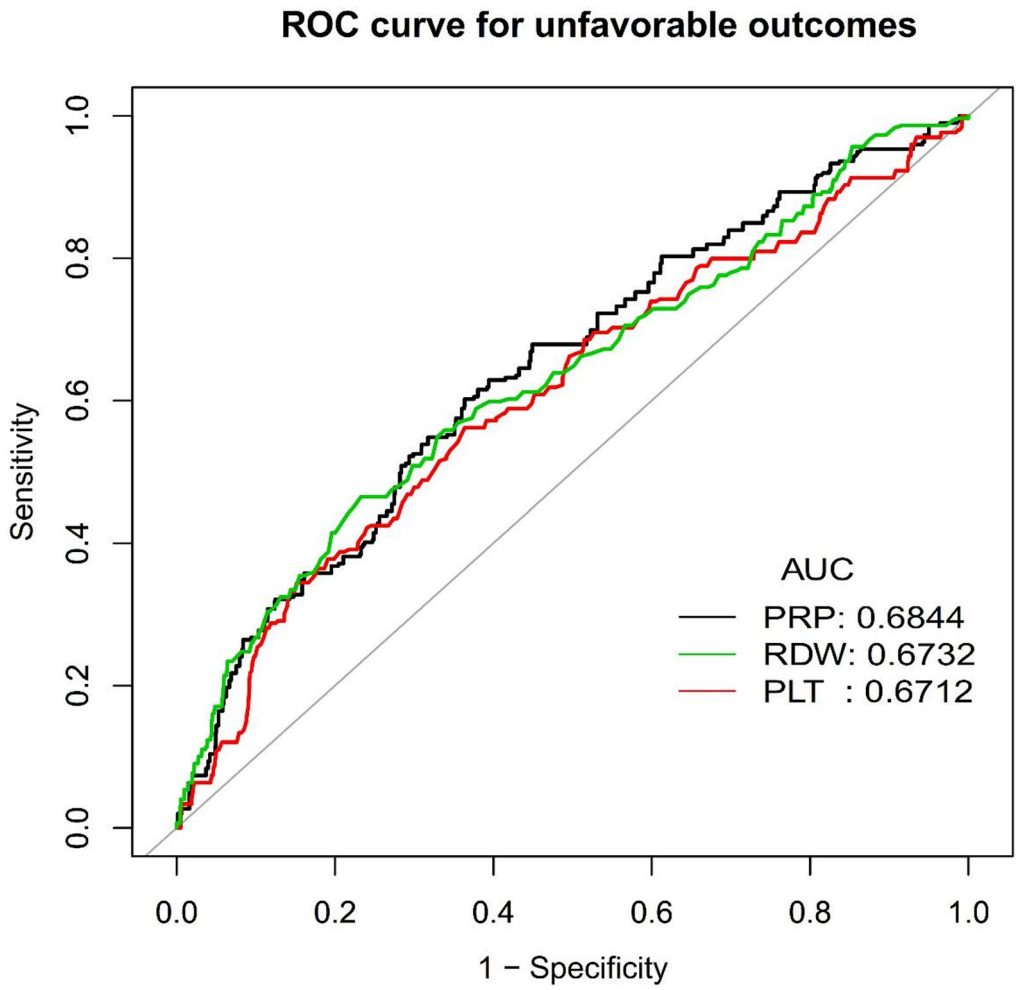

Fig. 4. The results of the ROC curve to evaluate the predictive capability of RDW, platelet count, and RPR for assessing the risk of unfavorable outcomes. The AUC values of platelet, RDW, and RPR were 0.6712, 0.6732, and 0.6844, respectively.

unfavorable outcomes showed a decreasing trend without statistical significance. Further analysis showed that participants with RPR levels greater than or equal to 0.33 exhibited higher values for age, Neu, BMI, HCY, and D-dimer compared to those with RPR levels less than 0.33. Additionally, a higher proportion of AIS patients with RPR values above 0.33 also had a history of CHD and AF (Supplementary Table S2). These factors are strongly associated with poor outcomes in AIS[51–55]. In the cohort with RPR values below 0.33, the levels of these risk factors were lower, and the effect of RPR on 90-day adverse outcomes was relatively enhanced. Conversely, when RPR surpasses 0.33, the effect of RPR on 90-day adverse outcomes was relatively attenuated due to the presence of these risk factors. This may help explain the nonlinear relationship between RPR and 90-day unfavorable outcomes in AIS patients. The discovery of this nonlinear relationship has certain clinical implications. As a simple and easily accessible hematological parameter, RPR exhibited an inflection point at 0.33, which provides a novel perspective for prognostic stratification in AIS patients. However, as an exploratory study, our results need to be externally validated in future multicenter, large-sample cohorts to confirm the general applicability and clinical reliability of this inflection point value, so as to ultimately provide valuable references for treatment strategies, rehabilitation, and reduction of complications in AIS patients.

This study offers several significant advantages. (i) It explores how RPR is associated with unfavorable outcomes in AIS patients by analyzing it as a continuous variable and as a categorical variable defined by quartiles. This dual method reduces and minimizes information loss, as well as accurately assesses the association between RPR and patient outcomes. (ii) We clarified the nonlinear link between RPR and the risk of adverse stroke outcomes and identified the inflection point, representing a significant advancement over previous research. (iii) The study utilizes imputation techniques to address missing data, thus increasing statistical power and minimizing potential biases that may result from missing covariate information. (iv) Multiple sensitivity analyses were conducted to reinforce the reliability of the results. These analyses included calculating E-values to assess the possible impact of unmeasured confounders, transforming independent variables, in addition to re-evaluating the association between RPR and short-term prognosis in AIS patients following the exclusion of individuals with hypertension, DM, and a BMI of 28 kg/m² or higher.

Several potential limitations must be considered. First, the study was a single-center study conducted solely with Chinese participants, which calls into question the applicability of the findings to other ethnic groups. In the future, we plan to collaborate with researchers both domestically and internationally to conduct further multicenter and multi-ethnic prospective studies for validation. Second, this research assessed RPR and other key parameters only at baseline, without examining how changes in RPR over time may impact the prognosis of patients with AIS. Addressing this limitation should be a vital focus for future investigations aimed at collecting more comprehensive longitudinal data on RPR fluctuations. Third, as with many observational studies, this research may be subject to uncontrolled or unmeasured confounding variables, despite having controlled for known potential confounders. However, the calculation of E-values indicates that such confounding factors are unlikely to significantly impact our findings. Finally, it is crucial to recognize that the observational nature of this study suggests an independent association between RPR and short-term outcomes in AIS patients, but it does not establish a causal relationship between them.

Conclusion

This study confirms a significant positive and nonlinear association between the RPR and 90-day unfavorable outcomes in AIS patients. Notably, when RPR is below 0.33, each 0.1-unit increase corresponds to a 70.8% higher risk of unfavorable outcomes. RPR emerges as a valuable prognostic biomarker for risk stratification in AIS patients. It provides a new perspective for improving the rehabilitation and management of stroke patients and ultimately improving their health status and quality of life, as well as providing a certain reference for future clinical studies in multicenter, large-sample cohorts.

Data availability

Due to the signing of a data security consent agreement, the provision of data is restricted, allowing only external researchers to access the data for research purposes. Researchers interested in these data can contact the corresponding author via email to obtain access. The email address is hanyong511023@163.com.

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Author contributions

Jiaqian Zhu and Yong Han initiated this research and were responsible for drafting the initial manuscript and carrying out the statistical analyses. Yong Han and liming Cao also played a significant role in designing the study and contributed to the manuscript revisions. All authors reviewed and approved the final version of the manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

Ethical approval and participant consent
This study received approval from the Ethics Review Committee at Shenzhen Second People's Hospital (Approval No. 2023-305-01PJ). Informed consent was obtained from all participants prior to their enrollment in the study.

Additional information
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