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# Predictive value of plasma sLRP1 for three-month clinical outcome in acute ischemic stroke and its potential pathophysiological mechanisms: A retrospective and observational study

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### Abstract

*Background & Objective:* Acute ischemic stroke (AIS) remains a leading global cause of mortality and disability; thus, accurate early prognosis is critical for guiding personalized management. Soluble low-density lipoprotein receptor-related protein 1 (sLRP1), a circulating protein implicated in neuroinflammatory regulation, has emerged as a potential biomarker in neurodegenerative and vascular pathologies. However, its prognostic significance in AIS remains undefined. This study investigated the prognostic value of admission plasma sLRP1, nuclear factor kappa B p65 subunit (NF-κB p65), and interleukin-6 (IL-6) levels regarding 90-day functional outcomes in AIS patients, while exploring potential underlying pathophysiological interrelationships. *Methods:* In this retrospective observational study, we recruited patients with first-ever AIS. Plasma sLRP1, NF-κB p65, and IL-6 levels were quantified from samples obtained at admission. The primary endpoint was poor functional outcome at 90 days, defined as a modified Rankin Scale (mRS) score of 3–6. Prognostic capabilities were assessed using univariate and multivariate logistic regression models and receiver operating characteristic (ROC) curve analyses. Correlations among the biomarkers were also evaluated. *Results:* A total of 155 AIS patients were included (median age 68.00 [IQR 60.00–75.00]; 61.29% male). Admission levels of sLRP1, NF-κB p65, and IL-6 were significantly elevated in patients with poor outcomes (all $P < 0.01$). Multivariate regression identified all three markers as independent predictors of 90-day poor functional outcomes. ROC analysis yielded an area under the curve (AUC) of 0.771 for sLRP1 alone, which improved to 0.839 when combined with NF-κB p65 and IL-6. Furthermore, sLRP1 levels were positively correlated with NF-κB p65 ($R = 0.331$, $P < 0.001$) and IL-6 ($R = 0.388$, $P < 0.001$), suggesting that sLRP1 may contribute to AIS pathophysiology by mediating cytokine release via the NF-κB inflammatory pathway.
*Conclusion:* Plasma sLRP1 represents a novel prognostic biomarker for AIS, offering potential advantages over conventional inflammatory markers. The identification of the sLRP1-NF-κB-IL-6 axis highlights a critical neuroinflammatory pathway, positioning sLRP1 as both a predictive tool and a potential therapeutic target. Integrating this biomarker panel into clinical practice could enhance early risk stratification, guide targeted anti-inflammatory interventions, and improve prognostic management in AIS.

*Keywords:* Acute ischemic stroke; sLRP1; NF-κB p65; IL-6; Prognosis; Neuroinflammation

## INTRODUCTION

Acute ischemic stroke (AIS) remains a leading cause of mortality and long-term disability worldwide, accounting for approximately 5.5 million deaths annually, with more than 50% of survivors suffering from persistent neurological

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deficits.[1] Despite advances in acute reperfusion therapies, the heterogeneity of post-stroke recovery underscores an urgent need for reliable biomarkers to predict clinical outcomes and elucidate underlying pathophysiological mechanisms.[2] Emerging evidence identifies neuroinflammation as a key driver of secondary brain injury following cerebral ischemia, mediated by complex interactions involving blood-brain barrier (BBB) dysfunction, glial activation, and cytokine cascades.[3] Within this context, the low-density lipoprotein receptor-related protein 1 (LRP1) system has recently garnered attention for its dual roles in lipid metabolism and inflammatory regulation.[4]

The soluble form of LRP1 (sLRP1), generated via the shedding of the LRP1 extracellular domain, represents a critical regulatory mechanism in inflammatory conditions and has emerged as a novel candidate biomarker for neurodegenerative diseases. In Alzheimer's disease, sLRP1 exacerbates amyloid-β accumulation by impairing peripheral clearance[5], whereas in atherosclerosis, it regulates vascular smooth muscle cell migration via matrix metalloproteinases.[6] Crucially, the NF-κB pathway—a master regulator of the inflammatory response—is activated within minutes of cerebral ischemia, promoting the production of Interleukin-6 (IL-6) and subsequently aggravating neurovascular injury.[7] Recent single-cell RNA sequencing studies have revealed a direct interaction between LRP1 and NF-κB signaling components in activated microglia[8], suggesting potential crosstalk between these systems. However, the clinical translation of these mechanistic insights remains largely unexplored, particularly regarding the combined prognostic utility of these markers in human stroke.

Current prognostic models for AIS rely primarily on clinical scales (e.g., NIHSS scores) and neuroimaging parameters[9], which often lack sensitivity to specific molecular pathophysiological processes. Although individual inflammatory markers such as IL-6 have demonstrated moderate predictive value[10], their clinical implementation is hindered by biological variability and pleiotropy. The recent TIMING trial demonstrated that multimarker panels outperform single biomarkers in predicting post-stroke recovery[11], highlighting the necessity of integrated pathophysiological approaches. We aimed to bridge this gap by investigating sLRP1 in conjunction with the canonical NF-κB/IL-6 signaling pathway, potentially offering both prognostic utility and mechanistic insights for AIS management.

## METHODS

### *Study population*

We conducted a retrospective analysis of data from patients admitted to the Department of Neurology at Jiangsu Subei People's Hospital (Affiliated Hospital of Yangzhou University), a regional medical center in central Jiangsu, China, between January 2023 and May 2024. A total of 155 patients were enrolled in the study (median age: 68 years; 38.71% female, 61.29% male). Inclusion criteria were as follows: (1) Diagnosis of first-ever acute ischemic stroke (AIS) confirmed by cranial computed tomography (CT) or magnetic resonance imaging (MRI), in accordance with the *Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke 2018*[12,13]; (2) Admission within 7 days of symptom onset; (3) Presence of focal neurological deficits (e.g., unilateral facial or limb weakness/numbness, speech disturbances) or global neurological deficits; (4) Age between 18 and 90 years. Exclusion criteria included: (1) Evidence of significant encephalomalacia on cranial CT or MRI; (2) Recurrent stroke or severe comorbidities, including severe infection, hepatic, renal, cardiac, or respiratory failure, pregnancy, or known malignancy; (3) History of Alzheimer's disease or epilepsy; (4) Coexisting autoimmune disorders, such as rheumatoid arthritis; (5) Secondary cerebral hemorrhage, intracranial/extracranial trauma, or hemorrhage associated with brain tumors; (6) Acute myocardial infarction or a history of severe adverse cardiovascular events; (7) Patients who received intravenous thrombolysis or mechanical thrombectomy at our institution or elsewhere. Eligibility screening was performed independently by two strictly trained senior neurologists. Patient data were obtained from the Neurology Brain Center Database of Jiangsu Subei People's Hospital affiliated to Yangzhou University. This database contains comprehensive demographic information, longitudinal medical records, and detailed clinical and examination data from each hospital encounter. This retrospective analysis was conducted using de-identified clinical data extracted from the institutional database, with all personal identifiers removed prior to statistical processing.

*Baseline assessments and laboratory measurements*

We systematically recorded demographic characteristics, risk factors, clinical data, blood routine indexes, biochemical indicators, and specific laboratory parameters for all study participants. Demographic data included age and gender. Documented risk factors included body mass index (BMI), smoking, alcohol drinking, hypertension, diabetes, hyperlipidemia, atrial fibrillation (AF), coronary heart disease (CHD), and peripheral vascular disease (PVD). Clinical data comprised stroke subtype classification according to the TOAST criteria (large-artery atherosclerosis [LAA], cardioembolism [CE], small-artery occlusion [SAO], and other etiologies), admission National Institutes of Health Stroke Scale (NIHSS) scores (range 0–42, with higher scores indicating greater neurological deficit severity), and admission systolic and diastolic blood pressure (BP). Blood routine indexes included blood glucose (BG), red blood cell (RBC) count, white blood cell (WBC) count, neutrophil count, lymphocyte count, monocyte count, and platelet (PLT) count. Biochemical indicators included creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), uric acid (UA), urea nitrogen (UN), glycated hemoglobin (HbA1c), homocysteine, total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). Specific inflammatory and signaling biomarkers assessed included nuclear factor kappa B p65 (NF-κB p65), interleukin-6 (IL-6), and plasma sLRP1. These three biomarkers were quantified using double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) kits, strictly following the manufacturer's instructions. All measurements were performed in duplicate by experienced technicians, and the mean values were used for analysis. Fasting venous blood samples were collected from all enrolled AIS patients on the morning of the second day of hospitalization. All other routine hematological and biochemical analyses were performed by qualified personnel in the hospital's clinical laboratory.

*Clinical outcome*

Clinical outcomes were assessed independently by two experienced neurologists. Functional status was evaluated at 3 months post-stroke using the modified Rankin Scale (mRS). A favorable clinical outcome was defined as an mRS score of 0–2, while a poor clinical outcome was defined as an mRS score of 3–6.

*Statistical analysis*

All statistical analyses were performed using SPSS software (version 27.0), R (version 4.2.3), and Python (version 3.11.4). Normally distributed continuous variables were expressed as mean ± standard deviation (SD) and compared using Student's t-test. Non-normally distributed variables were presented as medians with interquartile ranges (IQRs) and analyzed using the Mann-Whitney *U* test. Categorical variables were reported as frequencies and percentages and compared using the chi-square ($\chi^2$) test. Univariate and multivariable logistic regression models were utilized to identify independent predictors associated with 3-month functional outcomes in AIS patients. Results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Receiver operating characteristic (ROC) curve analyses were conducted to evaluate the predictive performance of sLRP1, NF-κB p65, IL-6, and their combined model. The Youden index was calculated to determine optimal cutoff values, along with sensitivity and specificity. Correlations between plasma sLRP1, NF-κB p65, and IL-6 levels were assessed using Pearson or Spearman correlation analysis, as appropriate. All statistical tests were two-sided, and a $P$-value < 0.05 was considered statistically significant.

## RESULTS

*Comparison of baseline characteristics of AIS patients with different prognosis.*

Table 1 summarizes the baseline characteristics of AIS patients stratified by functional outcome. The study cohort comprised 155 patients with a median age of 68.00 years (IQR 60.00–75.00), of whom 38.71% were female and 61.29% were male. A total of 102 patients achieved a favorable outcome (mRS 0–2) at 3 months (median age 67.00 [61.00–74.75]; 36.28% female, 63.72% male). Conversely, 53 patients experienced a unfavorable outcome (mRS 3–6) (median age 70.00 [59.00–75.00]; 43.40% female, 56.60% male). No significant differences in risk factors were observed between the two groups, with the exception of BMI ($P$ = 0.021). Admission NIHSS scores were significantly lower in the

**Table 1: Comparison of baseline characteristics of acute ischaemic stroke patients with different prognosis**

| Characteristics | Patients (N=155) | Favorable (N=102) | Unfavorable (N=53) | P-Value |
|---|---|---|---|---|
| Demographics | | | | |
| Age (years) | 68.00[60.00;75.00] | 67.00[61.00;74.75] | 70.00[59.00;75.00] | 0.799 |
| Gender, N (%): | | | | 0.490 |
| Male | 95 (61.29%) | 65 (63.73%) | 30 (56.60%) | |
| Female | 60 (38.71%) | 37 (36.28%) | 23 (43.40%) | |
| Risk factors | | | | |
| BMI (kg/m2) | 24.24±3.09 | 23.81±2.92 | 25.06±3.26 | 0.021 |
| Smoking, N (%): | | | | 0.824 |
| No | 102 (65.81%) | 66 (64.71%) | 36 (67.93%) | |
| Yes | 53 (34.19%) | 36 (35.29%) | 17 (32.08%) | |
| Alcohol drinking, N (%): | | | | 0.515 |
| No | 123 (79.36%) | 83 (81.37%) | 40 (75.47%) | |
| Yes | 32 (20.65%) | 19 (18.63%) | 13 (24.53%) | |
| Hypertension, N (%): | | | | 1.000 |
| No | 56 (36.13%) | 37 (36.28%) | 19 (35.85%) | |
| Yes | 99 (63.87%) | 65 (63.73%) | 34 (64.15%) | |
| Diabetes, N (%): | | | | 1.000 |
| No | 110 (70.97%) | 72 (70.59%) | 38 (71.70%) | |
| Yes | 45 (29.03%) | 30 (29.41%) | 15 (28.30%) | |
| Hyperlipidemia, N (%): | | | | 0.370 |
| No | 142 (91.61%) | 95 (93.14%) | 47 (88.68%) | |
| Yes | 13 (8.39%) | 7 (6.86%) | 6 (11.32%) | |
| AF, N (%): | | | | 0.259 |
| No | 139 (89.68%) | 94 (92.16%) | 45 (84.91%) | |
| Yes | 16 (10.32%) | 8 (7.84%) | 8 (15.09%) | |
| CHD, N (%): | | | | 0.251 |
| No | 134 (86.45%) | 91 (89.22%) | 43 (81.13%) | |
| Yes | 21 (13.55%) | 11 (10.78%) | 10 (18.87%) | |
| PVD, N (%): | | | | 0.275 |
| No | 146 (94.19%) | 98 (96.08%) | 48 (90.57%) | |
| Yes | 9 (5.81%) | 4 (3.92%) | 5 (9.43%) | |
| Clinical data | | | | |
| TOAST type, N (%): | | | | 0.906 |
| LAA | 82 (52.90%) | 56 (54.90%) | 26 (49.06%) | |
| CE | 54 (34.84%) | 34 (33.33%) | 20 (37.74%) | |
| SAO | 10 (6.45%) | 6 (5.88%) | 4 (7.55%) | |
| Others | 9 (5.81%) | 6 (5.88%) | 3 (5.66%) | |
| Admission NIHSS | 3.00[2.00;7.00] | 2.00[2.00;4.00] | 8.00[4.00;16.00] | <0.001 |
| Systolic BP(mmHg) | 151.78±17.90 | 151.64±19.16 | 152.06±15.36 | 0.883 |
| Diastolic BP(mmHg) | 83.97±12.44 | 82.82±12.55 | 86.19±12.04 | 0.107 |
| Blood routine indexes | | | | |
| BG(mmol/L) | 5.60[5.02;6.94] | 5.57[4.88;6.40] | 6.12[5.27;8.89] | 0.007 |
| RBC(1012/L) | 4.56[4.16;4.93] | 4.53 [4.11;4.96] | 4.56[4.24;4.93] | 0.597 |
| Leukocytes(10^9/L) | 6.46[5.54;7.94] | 6.17 [5.35;7.49] | 7.26[6.32;8.11] | 0.004 |
| Neutrophils(10^9/L) | 4.36[3.53;5.48] | 4.09[3.27;5.15] | 5.32[4.33;6.03] | <0.001 |
| Lymphocytes(10^9/L) | 1.42[1.05;1.84] | 1.47[1.07;1.92] | 1.26[0.97;1.64] | 0.012 |
| Monocytes(10^9/L) | 0.41[0.35;0.60] | 0.41[0.35;0.60] | 0.41[0.38;0.57] | 0.593 |
| PLT(10^9/L) | 186.94±59.68 | 190.31±58.12 | 180.43±62.62 | 0.342 |

**Table 1: (continued)**

| Characteristics | Patients (N=155) | Favorable (N=102) | Unfavorable (N=53) | P-Value |
|---|---|---|---|---|
| Biochemical indicators | | | | |
| Creatinine(μmol/L) | 65.00[54.20;76.60] | 64.40[53.80;74.33] | 67.10[57.90;82.60] | 0.151 |
| ALT(u/L) | 27.00[20.00;36.50] | 25.00[19.00;35.00] | 30.00[24.00;38.00] | 0.007 |
| AST(u/L) | 26.00[21.50;33.50] | 24.50[20.00;29.00] | 30.00[25.00;39.00] | <0.001 |
| UA(umol/L) | 325.15±87.77 | 327.27±84.55 | 321.09±94.35 | 0.690 |
| UN(mmol/L) | 5.34[4.56;7.06] | 5.34 [4.65;7.05] | 5.22[4.36;7.26] | 0.814 |
| HbA1c(%) | 6.10 [5.70;7.15] | 6.10[5.60;7.00] | 6.30[5.90;7.60] | 0.204 |
| Homocysteine(μmol/L) | 10.00[7.00;14.00] | 10.00[6.00;14.00] | 10.00[8.00;12.00] | 0.746 |
| TC(mmol/L) | 4.13±0.85 | 3.99±0.80 | 4.39±0.88 | 0.008 |
| TG(mmol/L) | 1.50[1.02;2.07] | 1.55 [1.11;2.09] | 1.34[0.95;1.83] | 0.177 |
| LDL-C(mmol/L) | 2.49±0.71 | 2.42±0.70 | 2.63±0.72 | 0.091 |
| HDL-C(mmol/L) | 1.01[0.83;1.24] | 0.96[0.81;1.15] | 1.21[0.96;1.51] | <0.001 |
| Laboratory parameters | | | | |
| NF-κB p65(ng/ml) | 4.10±0.64 | 3.94±0.61 | 4.41±0.57 | <0.001 |
| IL6(pg/ml) | 13.00[11.92;14.27] | 12.54[11.49;13.75] | 13.75[12.79;15.29] | <0.001 |
| sLRP1(ng/ml) | 1.95[1.69;2.23] | 1.83[1.58;2.04] | 2.22[1.94;2.38] | <0.001 |

Abbreviations: BMI, Body mass index; AF, Atrial fibrillation; CHD, Coronary heart disease; PVD, Peripheral vascular disease; TOAST, Trial of Org 10172 in acute stroke treatment; LAA, Large-artery atherosclerosis; CE, Cardioembolism; SAO, Small-artery occlusion lacunar; NIHSS, National Institutes of Health Stroke Scale; BP , Blood pressure; BG, Blood glucose; RBC, Red blood cell; PLT, Platelet; ALT, Alanine transaminase; AST, Aspartate transaminase; UA, Uric Acid; UN, Urea nitrogen; HbA1c, Glycated hemoglobin; TC, Total cholesterol; TG, Triglycerides; LDL-C, Low-Density Lipoprotein Cholesterol; HDL-C, High-Density Lipoprotein Cholesterol; NF-κB p65, Nuclear factor kappa-B p65; IL-6, Interleukin-6; sLRP1, Soluble Low-density lipoprotein receptor-related protein 1.

favorable outcome group compared to the unfavorable outcome group (2.00 [2.00–4.00] vs. 8.00 [4.00–16.00], $P < 0.001$). The distribution of stroke subtypes (TOAST classification) and admission blood pressure (systolic and diastolic) were similar between groups. Lymphocyte counts were significantly higher in the favorable outcome group (1.47 [1.07–1.92] vs. 1.26 [0.97–1.64], $P = 0.012$). In contrast, the unfavorable outcome group exhibited significantly elevated levels of BG, WBC count, neutrophil count, ALT, AST, TC, and HDL-C compared to the favorable group: BG, 5.57[4.88–6.40] vs. 6.12[5.27–8.89], $P$=0.007; Leukocytes, 6.17[5.35–7.49] vs. 7.26[6.32–8.11], $P$=0.004; Neutrophils, 4.09[3.27–5.15] vs. 5.32[4.33–6.03], $P$ <0.001; ALT, 25.00[19.00–35.00] vs. 30.00[24.00–38.00], $P$=0.007; AST, 24.50[20.00–29.00] vs. 30.00[25.00–39.00], $P$ <0.001; TC, 3.99±0.80 vs. 4.39±0.88, $P$ =0.008; HDL, 0.96[0.81–1.15] vs. 1.21[0.96–1.51], $P$ <0.001. Notably, levels of NF-κB p65, IL-6, and sLRP1 were all significantly higher in the unfavorable outcome group: NF-κB p65 (3.94 ± 0.61 vs. 4.41 ± 0.57, $P < 0.001$); IL-6 (12.54 [11.49–13.75] vs. 13.75 [12.79–15.29], $P < 0.001$); and sLRP1 (1.83 [1.58–2.04] vs. 2.22 [1.94–2.38], $P < 0.001$) (Figure 1).

*Univariate and multivariate logistic regression analysis for outcome*

We performed logistic regression analyses with the 3-month functional outcome as the dependent variable. Covariates included age, admission NIHSS scores, BG, WBC count, neutrophil count, ALT, AST, TC, HDL-C, sLRP1, NF-κB p65, and IL-6. Univariate logistic regression analysis indicated that sLRP1, NF-κB p65, and IL-6 were significantly associated with 90-day outcomes. The unadjusted odds ratios (ORs) were 32.739 (95% CI, 8.747–122.536; $P < 0.001$) for sLRP1, 3.621 (95% CI, 1.960–6.690; $P < 0.001$) for NF-κB p65, and 1.886 (95% CI, 1.449–2.456; $P < 0.001$) for IL-6. After adjusting for confounding variables in the multivariable logistic regression model, elevated levels of sLRP1, NF-κB p65, and IL-6 remained significantly associated with unfavorable functional outcomes: sLRP1 (OR, 14.273; 95% CI, 2.426–107.500; P = 0.005); NF-κB p65 (OR, 2.821; 95% CI, 1.165–7.410; P = 0.027); and IL-6 (OR, 1.589; 95% CI, 1.113–

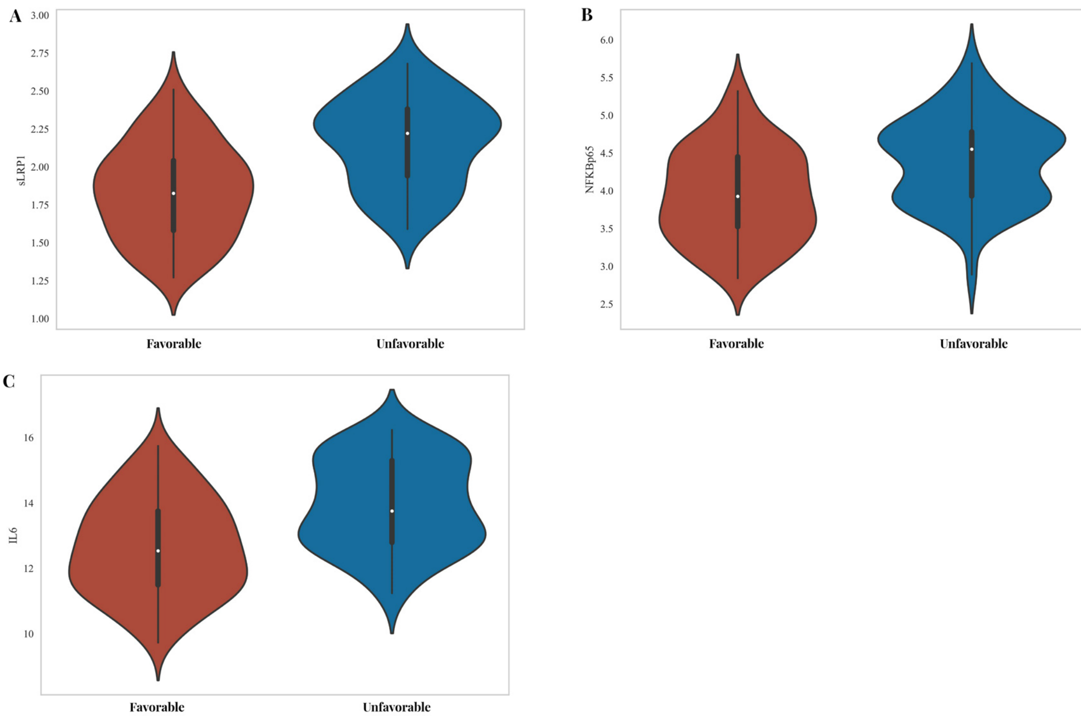


Figure 1. Comparison of sLRP1 (A), NF-κB p65(B), and IL-6 (C) among patients with different prognosis.

2.352; P = 0.014). These findings identify sLRP1, NF-κB p65, and IL-6 levels as independent risk factors for poor prognosis in AIS. Additionally, admission NIHSS scores and TC were identified as independent predictors of clinical outcome (Table 2).

*Prognostic analysis of sLRP1, NF-κB p65, and IL-6 level on patients with AIS.*

ROC curve analysis determined the predictive performance of each biomarker for 90-day functional outcomes. For sLRP1, the optimal cutoff value was 2.190, yielding a sensitivity of 58.5%, specificity of 85.3%, Youden index of 0.572, and an area under the curve (AUC) of 0.771 (accuracy: 65.8%). For NF-κB p65, the optimal cutoff was 3.630, with a sensitivity of 94.3%, specificity of 40.2%, Youden index of 0.345, and an AUC of 0.714 (accuracy: 65.8%). For IL-6, the optimal cutoff was 12.48, providing a sensitivity of 88.7%, specificity of 50.0%, Youden index of 0.387, and an AUC of 0.742 (accuracy: 65.8%). Notably, the combined model incorporating all three biomarkers demonstrated superior predictive utility, with an optimal cutoff of 0.346 (probability), sensitivity of 83.0%, specificity of 79.4%, Youden index of 0.729, and an AUC of 0.839 (accuracy: 80.0%). These results indicate that sLRP1 exhibits higher individual predictive accuracy than NF-κB p65 or IL-6, while the combined panel offers the highest prognostic value significantly outperforming any single biomarker (Table 3, Figure 2).

*Correlation analysis among the levels of plasma sLRP1 protein, NF-κB p65, and IL-6.*

Significant correlations were observed among plasma levels of sLRP1, NF-κB p65, and IL-6. Plasma sLRP1 levels were positively correlated with NF-κB p65 ($R$ = 0.331, $P$ < 0.001; Figure 3A). Furthermore, a significant positive correlation was found between sLRP1 and IL-6 ($R$ = 0.388, $P$ < 0.001; Figure 3B). Similarly, a positive correlation was identified between NF-κB p65 and IL-6 ($R$ = 0.254, $P$ < 0.001; Figure 3C).

## DISCUSSION

AIS remains a primary global cause of mortality and long-term disability, imposing a substantial burden on patients, families, and healthcare systems.[14] Accurate prognostic assessment is therefore critical for guiding personalized therapeutic strategies, optimizing resource

**Table 2: Univariate and multivariate logistic regression analysis for the outcome**

| | Univariate Analysis | | | Multivariate Analysis | | |
|---|---|---|---|---|---|---|
| | **OR** | **95%CI** | ***P*** | **OR** | **95%CI** | ***P*** |
| Age | 1.145 | 1.022-1.283 | 0.019 | 0.970 | 0.924-1.017 | 0.210 |
| Admission NIHSS | 1.193 | 1.108-1.284 | <0.001 | 1.147 | 1.067-1.248 | <0.001 |
| BG | 1.103 | 0.982-1.238 | 0.099 | 1.089 | 0.888-1.317 | 0.397 |
| Leukocytes | 1.173 | 1.008-1.365 | 0.039 | 3.180 | 0.851-13.024 | 0.092 |
| Neutrophils | 1.337 | 1.089-1.641 | 0.005 | 0.308 | 0.067-1.253 | 0.109 |
| Lymphocytes | 0.543 | 0.296-0.993 | 0.047 | 0.191 | 0.034-0.952 | 0.049 |
| ALT | 1.032 | 1.009-1.054 | 0.005 | 0.988 | 0.934-1.044 | 0.673 |
| AST | 1.072 | 1.032-1.114 | <0.001 | 1.061 | 0.981-1.156 | 0.150 |
| TC | 1.767 | 1.162-2.686 | 0.008 | 2.199 | 1.182-4.320 | 0.016 |
| HDL-C | 15.059 | 4.203-53.955 | <0.001 | 2.622 | 0.291-23.897 | 0.386 |
| sLRP1 | 32.739 | 8.747-122.536 | <0.001 | 14.273 | 2.426-107.500 | 0.005 |
| NF-κB p65 | 3.621 | 1.960-6.690 | <0.001 | 2.821 | 1.165-7.410 | 0.027 |
| IL6 | 1.886 | 1.449-2.456 | <0.001 | 1.589 | 1.113-2.352 | 0.014 |

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; BG, Blood glucose; ALT, Alanine transaminase; AST, Aspartate transaminase; TC, Total cholesterol; HDL-C, High-Density Lipoprotein Cholesterol; sLRP1, Soluble Low-density lipoprotein receptor-related protein 1; NF-κB p65, Nuclear factor kappa-B p65; IL-6, Interleukin-6.

allocation, and improving long-term patient outcomes. In this study, we evaluated the prognostic value of admission plasma sLRP1, NF-κB p65, and IL-6 levels regarding 3-month functional outcomes in AIS patients, while also exploring the underlying pathophysiological mechanisms. Our baseline comparisons and multivariable logistic regression analyses demonstrated that elevated admission levels of sLRP1, NF-κB p65, and IL-6 were significantly associated with poor 3-month outcomes, identifying them as independent risk factors for adverse prognosis. Furthermore, ROC curve analysis confirmed the robust predictive capability of these biomarkers; specifically, sLRP1 alone yielded an AUC of 0.771, while the combined panel (sLRP1, NF-κB p65, and IL-6) demonstrated enhanced predictive efficacy with an AUC of 0.839. These findings establish plasma sLRP1 as a novel prognostic biomarker for AIS and demonstrate that its integration with NF-κB p65 and IL-6 outperforms conventional inflammatory markers. Additionally, we observed significant positive correlations among plasma sLRP1, NF-κB p65, and IL-6 levels. We postulate that during the pathophysiology of AIS, sLRP1 may mediate the release of inflammatory cytokines, such as IL-6, via the NF-κB signaling pathway. This not only validates the clinical relevance of neuroinflammatory pathways to

**Table 3: The diagnostic efficacy of related indicators and their combinations for poor prognosis in patients with acute ischemic stroke**

| Prediction | AUC | *Jmax* | Cut off | *Se*（%） | *Sp*（%） | Accuracy |
|---|---|---|---|---|---|---|
| sLRP1 | 0.771 | 0.438 | 2.190 | 0.585 | 0.853 | 0.658 |
| NF-κB p65 | 0.714 | 0.345 | 3.630 | 0.943 | 0.402 | 0.658 |
| IL-6 | 0.742 | 0.387 | 12.48 | 0.887 | 0.500 | 0.658 |
| sLRP1+ NF-κB p65 +IL-6 | 0.839 | 0.624 | 0.346 | 0.830 | 0.794 | 0.800 |

Abbreviations: AUC, Area under the curve; Jmax, Maximum Youden Index; Se, Sensitivity; Sp, Specificity; sLRP1, Soluble Low-density lipoprotein receptor-related protein 1; NF-κB p65, Nuclear factor kappa-B p65; IL-6, Interleukin-6.

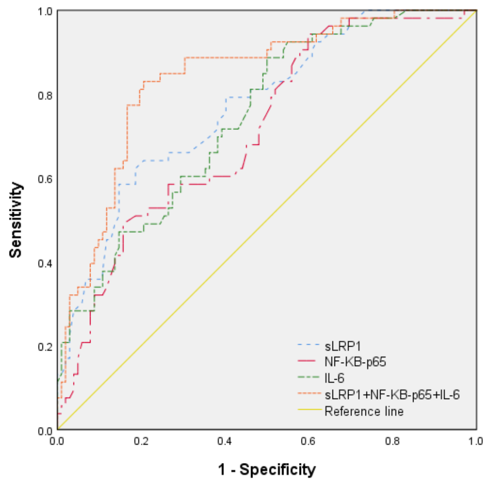


Figure 2. ROC curve analysis of the predictive value of sLRP1, NF-κB p65, and IL-6 and their comprehensive indicators on the 3-month unfavorable prognosis of patients with acute ischemic stroke.

post-stroke outcomes but also mechanistically links sLRP1 to NF-κB-mediated cytokine release, highlighting a previously unrecognized therapeutic axis for secondary neuroprotection.

LRP1 is a multifunctional receptor highly expressed in neurons, where it regulates critical physiological processes including vesicle trafficking, synaptic function, and cerebral metabolism.[4,15] It also plays a pivotal role in vascular homeostasis, influencing smooth muscle cell proliferation, vascular inflammatory markers, and the progression of atherosclerosis.[16-18] Membrane-bound LRP1 acts as a ubiquitous endocytic receptor; however, upon proteolytic shedding, it releases its extracellular domain as soluble LRP1 (sLRP1), which circulates systematically and may function as a decoy receptor or regulator of inflammatory pathways.[19,20] Previous clinical studies have associated elevated sLRP1 levels with carotid plaque inflammation, as evidenced by 18F-FDG PET (SUVmax ≥ 2.85)[21], while experimental models have linked LRP1 to the maintenance of blood-brain barrier (BBB) integrity.[22-24] In animal models of cerebral ischemia, LRP1 expression increases in the penumbra following middle cerebral artery occlusion (MCAO), and non-specific LRP antagonism has been shown to enhance functional recovery.[25,26] These findings suggest a potential protective role for LRP1 in ischemic stroke; however, emerging evidence indicates it may also drive inflammatory responses. For instance, LRP1 interacts with tissue plasminogen activator (tPA) to induce microglial activation and neuroinflammation, suggesting that tPA may exert cytokine-like effects within the central nervous system.[27] Our study corroborates these pathophysiological links, demonstrating that admission plasma sLRP1 levels are significantly associated with 3-month functional outcomes in AIS patients. Furthermore, genetic variants of LRP1 and LRP6 have been linked to various stroke-related parameters, including migraine risk and the efficacy of statins in reducing myocardial infarction risk.[17,28-31] Collectively, our findings reinforce the potential of sLRP1 as a prognostic biomarker in AIS.

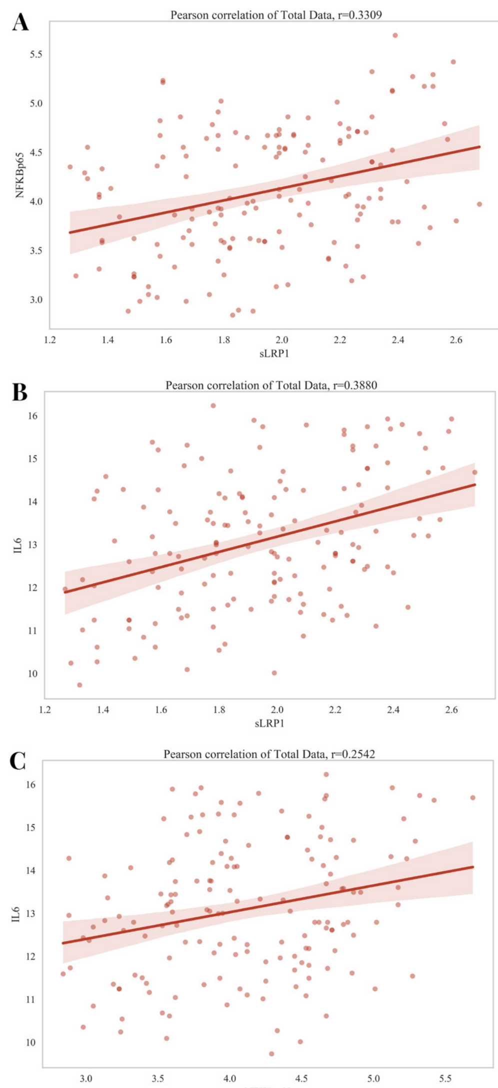


Figure 3. Correlation analysis among the levels of plasma S100A1 protein, NF-κB p65, and IL-6.

Inflammation is increasingly recognized as a pivotal determinant in the pathogenesis and progression of AIS.[32,33] Central to the post-stroke inflammatory response is the activation of the NF-κB signaling pathway and the subsequent release of proinflammatory cytokines, such as IL-6. NF-κB p65, a key subunit of the NF-κB complex, regulates the expression of numerous genes involved in inflammation, cell survival, and immune responses.[34,35] Cerebral ischemia-reperfusion initiates cascades of excitotoxicity and oxidative stress, which rapidly activate the NF-κB pathway.[36,37] Previous studies have reported that early elevations of NF-κB p65 in peripheral blood mononuclear cells correlate with larger infarct volumes and poorer functional recovery.[38] IL-6, a pleiotropic cytokine produced by immune and endothelial cells, is intimately involved in the inflammatory processes following ischemic injury.[39-41] Early elevation of IL-6 levels is associated with higher NIHSS scores, larger lesion volumes on diffusion-weighted MRI, and worse 90-day outcomes.[42-44] Mechanistically, IL-6 facilitates leukocyte recruitment, increases endothelial permeability, and induces acute-phase protein synthesis.[44,45] In the present study, we observed elevated levels of both NF-κB p65 and IL-6 in AIS patients, which were significantly associated with poor 3-month outcomes. These findings align with prior research identifying IL-6 as a robust predictor of adverse prognosis in AIS.[46,47] The NIHSS score is a well-established clinical tool for assessing neurological deficit severity and is widely utilized as a prognostic indicator. We confirmed that admission NIHSS scores are independent predictors of poor outcomes in AIS, consistent with extensive literature linking higher scores to reduced recovery potential.[48] This association likely reflects the extent of initial cerebral injury and neurological impairment, which fundamentally constrains rehabilitation trajectories and functional outcomes over the subsequent months. Additionally, we identified total cholesterol (TC) as an independent predictor of AIS prognosis. This finding is supported by evidence that vascular risk factors such as hypercholesterolemia accelerate atherosclerosis—a primary underlying etiology of AIS.[49,50]

Single biomarkers often lack the requisite sensitivity and specificity for individual prognostication. While composite scores integrating clinical scales (e.g., NIHSS) with biomarkers (e.g., IL-6) have yielded moderate predictive gains[51], their clinical utility remains limited. In contrast, our multi-marker panel comprising sLRP1, NF-κB p65, and IL-6 achieved an AUC of 0.839, significantly outperforming established biomarkers such as S100β and C-reactive protein.[52,53] Notably, this performance exceeds the benchmark for clinical utility (AUC ≥ 0.80).[54] This enhanced discriminative ability likely stems from the dual pathophysiological role of sLRP1—acting both as a mediator of blood-brain barrier (BBB) disruption and a regulator of neuroinflammatory cascades—a duality absent in conventional markers. Furthermore, the individual AUC of sLRP1 (0.771) approaches the clinical utility threshold (AUC ≥ 0.75) proposed by the Stroke Progress Review Group[55], suggesting that sLRP1 possesses substantial independent prognostic value even outside a combinatorial framework. Crucially, our multivariable model confirmed that sLRP1 predicts outcomes independently of NIHSS scores (a surrogate for infarct volume), whereas previous cohorts have observed that IL-6 levels are partially dependent on stroke severity.[56] This distinction positions sLRP1 as a unique biomarker reflecting intrinsic inflammatory activation rather than mere lesion size, consistent with preclinical evidence that LRP1 shedding precedes ischemic BBB breakdown.[57] The inclusion of baseline TC, which aligns with the "cholesterol paradox" in stroke prognosis, may further refine risk stratification.[58] Early identification of high-risk patients using this panel could guide intensive monitoring for hemorrhagic transformation, prompt consideration of anti-inflammatory or LRP1-targeted therapies, and ultimately improve recovery trajectories.

The robust correlations observed between sLRP1 and both NF-κB p65 (R = 0.331) and IL-6 (R = 0.388) translate mechanistic insights from animal models to human stroke pathology. Under physiological conditions, membrane-bound LRP1 inhibits NF-κB signaling by stabilizing IκBα. However, ischemia-induced shedding of the extracellular domain generates sLRP1, which forfeits this inhibitory capacity while simultaneously acquiring proinflammatory ligand-binding properties.[27,59] Our findings mirror this paradigm: elevated sLRP1 levels correlated significantly with NF-κB activation ($P < 0.001$), potentially driven by reduced IκBα stability or increased bioavailability of TLR4 ligands. This observation aligns with proteomic data demonstrating co-regulation of sLRP1 and IL-6 in neurodemyelinating disorders[60], though our study is the first to establish this relationship specifically within an AIS cohort. A bidirectional crosstalk likely exists, wherein IL-6 amplifies LRP1 shedding via STAT3-mediated upregulation of MMP-2/9. This mechanism, suggestive of a self-reinforcing inflammatory loop, may explain the synergistic predictive power of the biomarker panel.[61] Collectively, our results suggest that sLRP1 exacerbates cerebral inflammation by promoting NF-κB activation, thereby driving the transcription of IL-6 and other inflammatory mediators. These findings hold significant clinical implications, indicating that targeting the sLRP1 or NF-κB pathways could represent a viable therapeutic strategy to modulate inflammation and improve outcomes in AIS patients.

Several limitations of this study should be acknowledged. First, the retrospective observational design and relatively small sample size may limit the generalizability of our findings. Large-scale, multicenter prospective studies are warranted to validate the prognostic utility of these biomarkers across diverse populations. Second, although we identified significant associations between plasma sLRP1, NF-κB p65, and IL-6 levels and AIS outcomes, the precise molecular mechanisms underlying these relationships remain to be fully elucidated. Further in vivo and in vitro investigations are essential to establish causality and delineate specific signaling pathways. Third, blood sampling was restricted to the time of admission, precluding assessment of the dynamic changes in biomarker profiles during the acute and recovery phases. Longitudinal studies tracking the temporal kinetics of these markers could provide a more comprehensive understanding of their prognostic significance. Fourth, while multivariable analyses adjusted for several potential confounders, the possibility of residual confounding remains. Finally, while informative, the assessment of predictive performance using ROC curve analysis has inherent limitations. The real-world clinical applicability of this biomarker panel requires further evaluation through prospective validation studies and cost-effectiveness analyses.

In conclusion, our study demonstrates that plasma sLRP1, NF-κB p65, and IL-6 are independently associated with 3-month clinical outcomes in AIS patients, exhibiting robust prognostic performance. The combined application of these three biomarkers yields significantly enhanced predictive efficacy. Elevated levels of these markers identify patients at high risk for poor functional recovery, whereas lower levels characterize those likely to achieve favorable outcomes. The significant correlations observed among these biomarkers suggest intricate crosstalk within AIS-associated inflammatory pathways. Specifically, our data support the hypothesis that sLRP1 mediates inflammatory responses via the NF-κB pathway during AIS pathophysiology. These findings advance our understanding of stroke pathophysiology and hold substantial implications for the development of novel prognostic tools and targeted therapeutic strategies. Future investigations are warranted to validate these results and further elucidate the underlying molecular mechanisms.

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## DISCLOSURE

Ethics: The study protocol was reviewed by the Institutional Review Board of Jiangsu Subei People's Hospital, affiliated with Yangzhou University. The committee waived the requirement for formal ethical approval and informed consent. This decision was made because the study employed a retrospective design, used fully anonymized data extracted from the hospital's clinical database, and posed no more than minimal risk to participants. All patient identifiers were removed prior to data analysis to ensure complete confidentiality.

Data availability: The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

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Conflict of interest: None

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