Clinical Interventions in Aging

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Prognostic Value of Glucose-to-Potassium Ratio in Acute Ischemic Stroke Patients Undergoing Thrombolysis and Its Interaction with Inflammation

Lingling Lin[1,*], Rui Zhang[2,3,*], Jianing Wang[4,*], Yichuan Fan[2,5], Wei Xie[2,6], Bohuai Yu[2,6], Jialing Lou[2,6], Yanyi Pan[2,6], Chao Chen[7], Suwen Huang[2], Guangyong Chen[1], Yiyun Weng[2]

[1]Department of Neurology, The Third Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, People's Republic of China; [2]Department of Neurology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, People's Republic of China; [3]Renji College, Wenzhou Medical University, Wenzhou, Zhejiang, People's Republic of China; [4]Department of Neurology, The Second Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, People's Republic of China; [5]Alberta Institute, Wenzhou Medical University, Wenzhou, Zhejiang, People's Republic of China; [6]The First School of Medicine, School of Information and Engineering, Wenzhou Medical University, Wenzhou, Zhejiang, People's Republic of China; [7]Department of Nutriology, The Third Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, People's Republic of China

*These authors contributed equally to this work

Correspondence: Guangyong Chen, Department of Neurology, The Third Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, 325000, People's Republic of China, Email gychen@wmu.edu.cn; Yiyun Weng, Department of Neurology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, 325000, People's Republic of China, Email wengyiyun2012@126.com

Objective: The glucose-to-potassium ratio (GPR) has been proven to be an early predictor of central nervous system injury. Meanwhile, it has a potential interaction with the inflammatory response. Therefore, we aimed to comprehensively analyze the prognostic value of GPR for thrombolytic acute ischemic stroke (AIS) patients and its synergistic effect with the neutrophil-to-lymphocyte ratio (NLR).

Methods: AIS patients treated with thrombolysis were retrospectively enrolled at the First Affiliated Hospital of Wenzhou Medical University between February 1st, 2018, and December 31st, 2021. Cox and Logistic regression were used for evaluating the predictive value of GPR for the prognosis of AIS patients. Patients were grouped according to GPR and NLR levels to study the synergistic effect of GPR and NLR.

Results: In a cohort of 606 patients, after adjusting for significant confounding factors in a multivariate regression analysis, GPR was able to independently predict adverse outcomes such as 6-mRS [odds ratio (OR) = 1.743, 95% confidence interval (CI): 1.271–2.389, $p = 0.001$]. The synergistic analysis of GPR and NLR showed that for 6-mRS, GPR-H/NLR-L (OR = 2.888, 95% CI: 1.213–6.874, $p = 0.017$), GPR-H/NLR-M (OR = 2.757, 95% CI: 1.179–6.447, $p = 0.019$) and GPR-H/NLR-H (OR = 5.195, 95% CI: 2.320–11.634, $p < 0.001$) were significantly associated with adverse outcomes.

Conclusion: GPR independently predicts adverse outcomes in AIS patients, and its addition to the prediction model improves predictive accuracy. There's a synergistic effect between GPR and NLR on adverse outcomes.

Keywords: glucose-to-potassium ratio, neutrophil-to-lymphocyte ratio, acute ischemic stroke

Introduction

Stroke ranks as the second leading cause of death globally, accounting for approximately 7 million fatalities annually, and is the third major contributor to disability worldwide.[1] Due to the substantial rates of mortality and disability associated with stroke, which impose a significant burden on both families and society,[2] the early identification of individuals at risk for poor outcomes is crucial for the timely implementation of effective therapeutic strategies.[3,4] At present, intravenous thrombolysis continues to be the primary systemic reperfusion therapy for patients diagnosed with acute ischemic stroke

Received: 11 July 2025
Accepted: 22 October 2025
Published: 7 November 2025

(AIS).[5] Although traditional risk factors and clinical scales provide useful information, there is a pressing need for novel biomarkers that can enable early and accurate prognosis, especially during the critical emergency care phase.

In recent years, the role of biomarkers in predicting stroke outcomes has garnered significant attention.[6,7] Among these, serum glucose and potassium are two key biomarkers widely utilized in clinical practice. Glucose, as the primary energy source for cellular functions, plays a vital role in sustaining metabolic processes.[8] Potassium, the most prevalent cation in the human body, is essential for numerous physiological functions, such as nerve signal transmission, heart rhythm regulation, muscle activity, and kidney function maintenance.[9] Disruptions in serum glucose and potassium levels have been linked to an elevated risk of stroke.[10,11] Research has also revealed intricate interactions between potassium and glucose within the body.[12,13] Given the potential synergistic effects of glucose and potassium, the glucose-to-potassium ratio (GPR) has been proposed as an early prognostic indicator for central nervous system injuries, including aneurysmal subarachnoid hemorrhage (aSAH),[14] acute intracerebral hemorrhage,[15] severe traumatic brain injury,[16] and neuropsychiatric disorders following carbon monoxide poisoning.[17] However, the association between GPR and clinical outcomes in AIS remains underexplored. Notably, GPR possesses unique advantages that make it highly suitable for immediate bedside application—an unmet need in current AIS emergency care. Unlike complex prognostic tools that require specialized equipment, prolonged detection time, or additional costs, GPR is calculated using serum glucose and potassium levels—two parameters routinely measured within 30 minutes of AIS patients' emergency department (ED) arrival via point-of-care testing (POCT) or standard biochemical analyzers. This "zero extra cost, zero delay" feature means GPR can be integrated seamlessly into existing AIS workflows. While previous studies have examined the impact of GPR and inflammatory markers on AIS, the synergistic relationship between these factors has yet to be fully elucidated.[18] The neutrophil-to-lymphocyte ratio (NLR) has emerged as an inexpensive and readily accessible composite biomarker, with growing recognition as a systemic inflammatory indicator that has been extensively studied in cardiovascular diseases.[19]

Therefore, based on a retrospective cohort of AIS patients undergoing thrombolysis, we first hypothesize that: 1) GPR can independently predict adverse outcomes in this population across short-term [3-month modified Rankin Scale (mRS), early neurological deterioration (END)], medium-term (6-month mRS), and long-term (12-month mRS, 1-year mortality) follow-ups; 2) GPR and NLR exert a synergistic effect, the combination of high GPR and abnormal NLR will further elevate the risk of adverse prognosis compared to either marker alone. Correspondingly, our specific study objectives are threefold: to quantify the independent prognostic value of GPR for the aforementioned outcomes after adjusting for confounding factors; to explore and characterize the synergistic interaction between GPR and NLR in predicting these adverse outcomes, including the risk magnitude of different GPR-NLR combinations; and to validate the enhancement in prognostic performance by integrating GPR into conventional models using multiple statistical approaches.

Materials and Methods

Study Design and Population

We retrospectively enrolled 1036 adult patients with AIS who received thrombolysis at the First Affiliated Hospital of Wenzhou Medical University between February 1st, 2018, and December 31st, 2021. The inclusion criteria were as follows: 1) adult patients diagnosed with AIS based on neuroimaging results obtained from computed tomography (CT) or magnetic resonance imaging (MRI) according to World Health Organization (WHO) criteria; 2) availability of complete emergency department records accompanied by blood routine examination data within the first 24 hours post-admission, as well as follow-up data. And the exclusion criteria were as follows: 1) patients with severe liver or renal insufficiency; 2) patients with malignant tumors; 3) patients with autoimmune disease; 4) patients with pre-stroke disability [with a pre-admission mRS score of 3 or greater]. Ultimately, 606 patients were included in the analysis (Figure S1).

Data Collection

Patient's demographic data (age, sex, current smoking, current drinking), medical history [history of hypertension, diabetes mellitus, heart disease, atrial fibrillation (AF), previous stroke], laboratory data (lymphocyte, neutrophils, serum

glucose, serum potassium, serum sodium, serum chlorine), and clinical data [premorbid mRS, blood pressure, heart rate, National Institutes of Health Stroke Scale (NIHSS) score, Door-to-needle time, Impaired circulation, Trial of Org 10172 in Acute Stroke Treatment (TOAST)] were obtained from the comprehensive review of electronic medical records. The GPR was calculated as serum glucose (mmol/L)/potassium (mmol/L), using the parameters from the emergency department and the 24-hour blood routine tests.[20] Grouping was performed with the bisection and trimean methods according to the level of GPR and NLR, respectively. The GPR was classified as GPR-H (> 1.46) or GPR-L (≤ 1.46), while NLR was classified as NLR-H (> 5.16), NLR-M (2.84 < NLR ≤ 5.16), or NLR-L (≤ 2.84).

Clinical Outcomes

Poor prognosis was defined as an mRS score (range from 0 to 6) of 3 or higher, death within 1 year, or the occurrence of END.[21] END was defined as an increase of ≥ 2 points in the total NIHSS score or ≥ 1 point in the motor items of the NIHSS within 7 days of hospital admission. The primary outcome was 6-mRS, while secondary outcomes were 3-mRS, 12-mRS, END, and mortality within 1 year.

Statistical Analysis

The Kolmogorov–Smirnov (K-S) test was employed to evaluate the distribution of continuous variables. Variables following a normal distribution were summarized using the mean and standard deviation (SD), while those with a non-normal distribution were described using the median and interquartile range (IQR). For normally distributed continuous variables, *T*-tests were applied, whereas non-parametric tests were used for variables that did not follow a normal distribution. Categorical variables were analyzed using chi-square tests or Fisher's exact tests, as appropriate.

The association between GPR and different adverse outcomes was assessed using regression models appropriate to the outcome type. Cox proportional hazards regression was used for the outcome of all-cause mortality (Death) to account for the time-to-event nature of the data. Binary logistic regression was used for outcomes assessed at a fixed time point (3-mRS, 6-mRS, 12-mRS, and END). In the multivariable model, variables demonstrating statistical significance ($p < 0.05$) in the univariate analysis, such as age, gender, baseline NIHSS score, history of heart disease, history of hypertension, serum chloride levels, impaired circulation, atrial fibrillation, TOAST, and baseline mRS were incorporated. Certain variables with $p < 0.05$ were excluded from the univariate analysis due to issues of collinearity. Following this, restricted cubic splines were applied to evaluate the dose-response relationship between GPR and adverse prognosis. Subgroup analyses were conducted to ensure the consistency of findings across various subgroups. To compare the predictive performance of the original model (containing only confounding factors) and the enhanced model (including GPR), we employed Harrell's C-index, Integrated Discrimination Improvement (IDI), and Net Reclassification Improvement (NRI). Nomograms and clinical decision curves were generated to assess the impact of GPR on outcomes and to compare the net benefits between the original and enhanced models. Additionally, 3D bar charts were used to visualize the synergistic dose-response relationship between GPR and NLR in relation to adverse outcomes. The reliability of the study was further strengthened by a series of sensitivity analyses: the exclusion of participants on prognostic medications, an evaluation of heterogeneity across subgroups defined by thrombolytic agent usage, and a comparison of ROC curves using DeLong's test. Finally, a synergistic heatmap was constructed to illustrate the odds ratios between GPR, NLR, and adverse outcomes. All statistical analyses were performed using SPSS 26.0 or R 4.3.2 software, and $p < 0.05$ (two-tailed) was considered statistically significant.

Results

Baseline Characteristics

Baseline characteristics of the participants are represented in Table 1. Significant differences were observed in demographics and clinical features between the group with a poor prognosis and the group with a favorable prognosis. Among the 606 participants in this study, the median age was 68 (59.00–76.00) years. There were 73 (12.25%) patients with a history of previous stroke. Out of the total cohort, 422 (69.64%) patients had 6-mRS between 0 and 2, while 184 (30.36%) patients had 6-mRS between 3 and 6. In comparison to patients who had a favorable prognosis, the cohort with adverse outcomes exhibited

Table 1 Baseline Characteristics of Patients Grouped According to 6-mRS

Variables	Total (n = 606)	6-mRS		*p*-value
		mRS 0–2 (n = 422)	mRS 3–6 (n = 184)	
Demographics				
Age (years)	68.00 (59.00–76.00)	66.00 (57.00–73.00)	73.00 (65.00–80.00)	< 0.001
Sex, male (%)	400 (66.01)	290 (68.72)	110 (59.78)	0.037
Smoking, n (%)	235 (38.78)	171 (40.52)	64 (34.78)	0.168
Drinking, n (%)	199 (32.84)	145 (34.36)	54 (29.35)	0.212
Clinical features				
Baseline NIHSS, score	6.00 (4.00–11.00)	5.00 (3.00–8.00)	10.00 (7.00–15.00)	< 0.001
SBP (mmHg)	153.40 ± 24.56	152.83 ± 23.94	154.71 ± 25.94	0.293
DBP (mmHg)	86.00 (76.00–96.00)	86.00 (77.00–96.00)	83.00 (75.00–95.00)	0.252
Heart rate (beats/min)	77.00 (67.00–88.00)	76.00 (67.00–86.25)	80.00 (66.25–90.00)	0.087
Baseline mRS, score ≥ 1 (%)	87 (14.36)	32 (7.58)	55 (29.89)	< 0.001
Door-to-needle time (minutes)	45.00 (31.00–63.00)	46.00 (33.00–63.00)	44.00 (29.25–62.00)	0.350
Impaired circulation, Posterior (%)	98 (16.17)	79 (18.72)	19 (10.33)	0.010
Medical history				
Hypertension, n (%)	378 (62.38)	247 (58.53)	131 (71.20)	0.003
Diabetes, n (%)	123 (20.30)	83 (19.69)	40 (21.74)	0.483
Heart disease, n (%)	107 (17.66)	59 (13.98)	48 (26.09)	< 0.001
Previous stroke, n (%)	73 (12.25)	45 (10.66)	28 (15.22)	0.113
Atrial fibrillation, n (%)	41 (6.77)	22 (5.21)	19 (10.33)	0.021
Laboratory data				
Lymphocyte (10^9/L)	1.45 (1.10–1.87)	1.51 (1.18–1.92)	1.31 (0.98–1.73)	< 0.001
Neutrophils (10^9/L)	5.63 (4.33–7.65)	5.28 (4.13–6.97)	6.35 (4.97–8.70)	< 0.001
NLR	3.68 (2.52–6.23)	3.27 (2.31–5.25)	5.01 (3.07–8.21)	< 0.001
Serum glucose (mmol/l)	5.50 (4.80–7.20)	5.30 (4.70–6.70)	6.40 (5.23–8.33)	< 0.001
Serum potassium (mmol/l)	3.82 ± 0.36	3.83 ± 0.33	3.80 ± 0.42	0.213
GPR	1.46 (1.25–1.91)	1.40 (1.21–1.78)	1.71 (1.38–2.21)	< 0.001
Serum sodium (mmol/l)	140.00 (139.00–142.00)	140.00 (139.00–142.00)	140.00 (138.00–142.00)	0.059
Serum chlorine (mmol/l)	106.00 (104.00–108.00)	106.00 (104.00–108.00)	105.00 (103.00–107.00)	< 0.001
Admission hyperglycemia, n (%)	113 (18.65)	62 (14.69)	51 (27.72)	< 0.001
TOAST, n (%)				< 0.001
LAA, n (%)	400 (66.01)	283 (67.06)	117 (63.59)	
SAO, n (%)	45 (7.43)	38 (9.00)	7 (3.80)	
CE, n (%)	134 (22.11)	77 (18.25)	57 (30.98)	
Others, n (%)	27 (4.46)	24 (5.69)	3 (1.63)	

Abbreviations: NIHSS, national institute of health stroke scale; mRS, modified Rankin Scale; SBP, systolic arterial pressure; DBP, diastolic arterial pressure; NLR, neutrophil to lymphocyte ratio; GPR, glucose to potassium ratio; TOAST, Trial of Org 10172 in Acute Stroke Treatment; LAA, large artery atherosclerosis; SAO, small artery occlusion; CE, cardioembolism.

older ages [73.00 (65.00–80.00) vs 66.00 (57.00–73.00), $p < 0.001$], elevated NIHSS scores upon admission [10.00 (7.00–15.00) vs 5.00 (3.00–8.00), $p < 0.001$], a higher prevalence of hypertension [131 (71.20%) vs 247 (58.53%), $p = 0.003$], a higher incidence of heart disease [48 (26.09%) vs 59 (13.98%), $p < 0.001$], a higher proportion of patients with poor baseline mRS [55 (29.89%) vs 32 (7.58%), $p < 0.001$], a higher incidence of prior atrial fibrillation (AF) [19 (10.33%) vs 22 (5.21%), $p = 0.021$], a lower prevalence of posterior impaired circulation [19 (10.33%) vs 79 (18.72%), $p = 0.010$] and a higher incidence of previous stroke [28 (15.22%) vs 45 (10.66%), $p = 0.113$]. Furthermore, they displayed a higher level of NLR [5.01 (3.07–8.21) vs 3.27 (2.31–5.25), $p < 0.001$] and a higher level of GPR [1.71 (1.38–2.21) vs 1.40 (1.21–1.78), $p < 0.001$].

The Association Between GPR and Adverse Clinical Outcomes

Multivariate Logistic regression and Cox regression of unfavourable outcomes at 3-mRS, 6-mRS, 12-mRS, END, and Death were employed in Table 2. In unadjusted models, the GPR was independently associated with END, short,

Table 2 Regression Analysis Between GPR and Adverse Clinical Outcomes

Outcomes	Event (%)	Model 1		Model 2	
		OR/HR (95% CI)	*p*-value	OR/HR (95% CI)	*p*-value
3-mRS	199 (32.84)	1.772 (1.401–2.240)	< 0.001	1.566 (1.151–2.131)	0.004
6-mRS	184 (30.36)	1.853 (1.462–2.350)	< 0.001	1.743 (1.271–2.389)	0.001
12-mRS	174 (28.71)	1.781 (1.409–2.251)	< 0.001	1.691 (1.224–2.336)	0.001
END	55 (9.08)	1.747 (1.319–2.313)	< 0.001	1.854 (1.330–2.585)	< 0.001
Death	70 (11.55)	1.746 (1.408–2.166)	< 0.001	1.582(1.220–2.052)	0.001

Notes: Model 1: unadjusted; Model 2: adjusted for age, sex, baseline NIHSS, hypertension, heart disease, chlorine, impaired circulation, atrial fibrillation, TOAST, baseline mRS.
Abbreviations: OR, odds ratio; HR, hazard ratio; CI, confidence interval; mRS, modified Rankin Scale; NIHSS, national institute of health stroke scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment; END, early neurological deterioration.

medium, long term adverse clinical outcomes and Death [3-mRS: odds ratio (OR) = 1.772 (1.401–2.240), $p < 0.001$; 6-mRS: OR = 1.853 (1.462–2.350), $p < 0.001$; 12-mRS: OR = 1.781 (1.409–2.251), $p < 0.001$; END: OR = 1.747 (1.319–2.313), $p < 0.001$; Death: hazard ratio (HR) = 1.746 (1.408–2.166), $p < 0.001$]. After adjustment for covariates, GPR was still independently associated with these adverse clinical outcomes (3-mRS: OR = 1.566 (1.151–2.131), $p = 0.004$; 6-mRS: OR = 1.743 (1.271–2.389), $p = 0.001$; 12-mRS: OR = 1.691 (1.224–2.336), $p = 0.001$; END: OR = 1.854 (1.330–2.585), $p < 0.001$; Death: HR = 1.582 (1.220–2.052), $p = 0.001$). Restricted cubic spline exhibited a linear relationship between GPR and 6-mRS (p for overall = 0.002, p for nonlinearity = 0.199), and GPR was also linearly related to 3-mRS (p for overall = 0.030, p for nonlinearity = 0.704), 12-mRS (p for overall = 0.008, p for nonlinearity = 0.664), END (p for overall = 0.003, p for nonlinearity = 0.564), and Death (p for overall = 0.007, p for nonlinearity = 0.958), as illustrated in Figures 1 and S2.

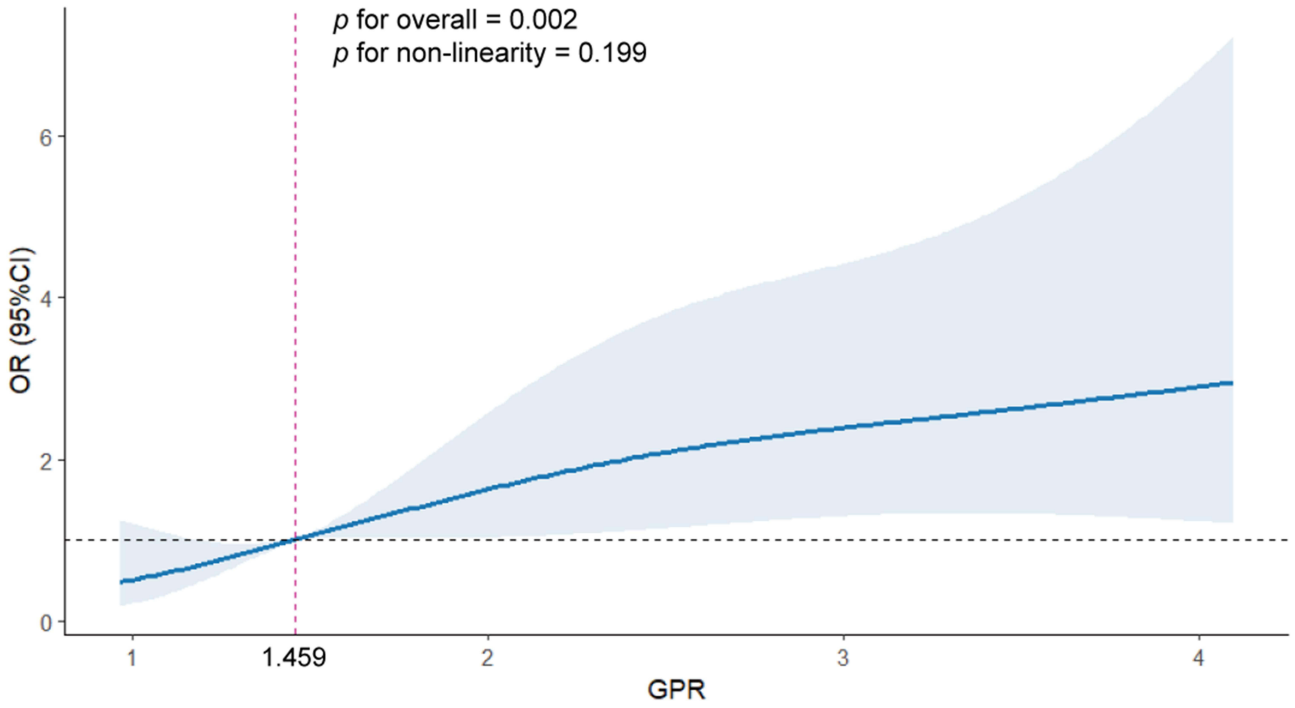

Figure 1 The association between GPR and adverse clinical outcomes (6-mRS).
Notes: Model: adjusted for age, sex, baseline NIHSS, hypertension, heart disease, chlorine, impaired circulation, atrial fibrillation, TOAST, baseline mRS.
Abbreviations: OR, odds ratio; CI, confidence interval; GPR, glucose to potassium ratio.

https://doi.org/10.2147/CIA.S553110

Evaluation of the Prognostic Value of GPR

We explored the impact of GPR on the primary outcome in the nomogram of Figure 2. Simultaneously, the net benefit difference between the model incorporating GPR and the original model with only confounding factors was compared in the clinical decision curve of Figure S3. The results all indicated that GPR significantly impacts adverse outcomes and possesses clinical predictive value. Moreover, we conducted reclassification and discrimination statistics for GPR in Table 3. Model 2 demonstrated an enhancement in the discrimination of 6-mRS with the inclusion of GPR into Model 1 (including age, sex, baseline NIHSS, heart disease, hypertension, chlorine, impaired circulation, AF, TOAST and baseline mRS), resulting in an AUC improvement of 0.007 ($p < 0.001$), NRI 48.0% ($p < 0.001$) and IDI 2.2% ($p < 0.001$). The discriminatory ability of 3-mRS [AUC improved 0.005 ($p < 0.001$); NRI 41.5% ($p < 0.001$); IDI 1.5% ($p = 0.004$)], 12-mRS [AUC improved 0.006 ($p < 0.001$); NRI 40.3% ($p < 0.001$); IDI 2.0% ($p = 0.003$)], END [AUC improved 0.072 ($p < 0.001$); NRI 46.7% ($p = 0.001$); IDI 2.6% ($p = 0.014$)] and Death [NRI 38.7% ($p = 0.002$)] was also improved in the model 2.

Subgroup Analyses

Subgroup analyses for GPR on 6-mRS, 3-mRS, 12-mRS, END, and Death were illustrated in Tables S1–S3. Subgroup analyses were conducted based on age, sex, baseline NIHSS, heart disease, hypertension, chlorine, impaired circulation, AF, TOAST, baseline mRS within the enrolled patient cohort. However, no significant interaction was observed between GPR and each interaction term. A significant multiplicative interaction between GPR and the primary outcome (6-mRS) was largely absent across most subgroups. It is noteworthy, however, that a significant interaction was evident for the combined factors of age, hypertension, baseline NIHSS, and chlorine. This observation implies that the independent association of GPR with adverse prognosis is not uniform and is significantly modified by this specific patient profile. Therefore, failure to adjust for this critical interaction may result in a potentially biased estimate of the independent prognostic value of GPR.

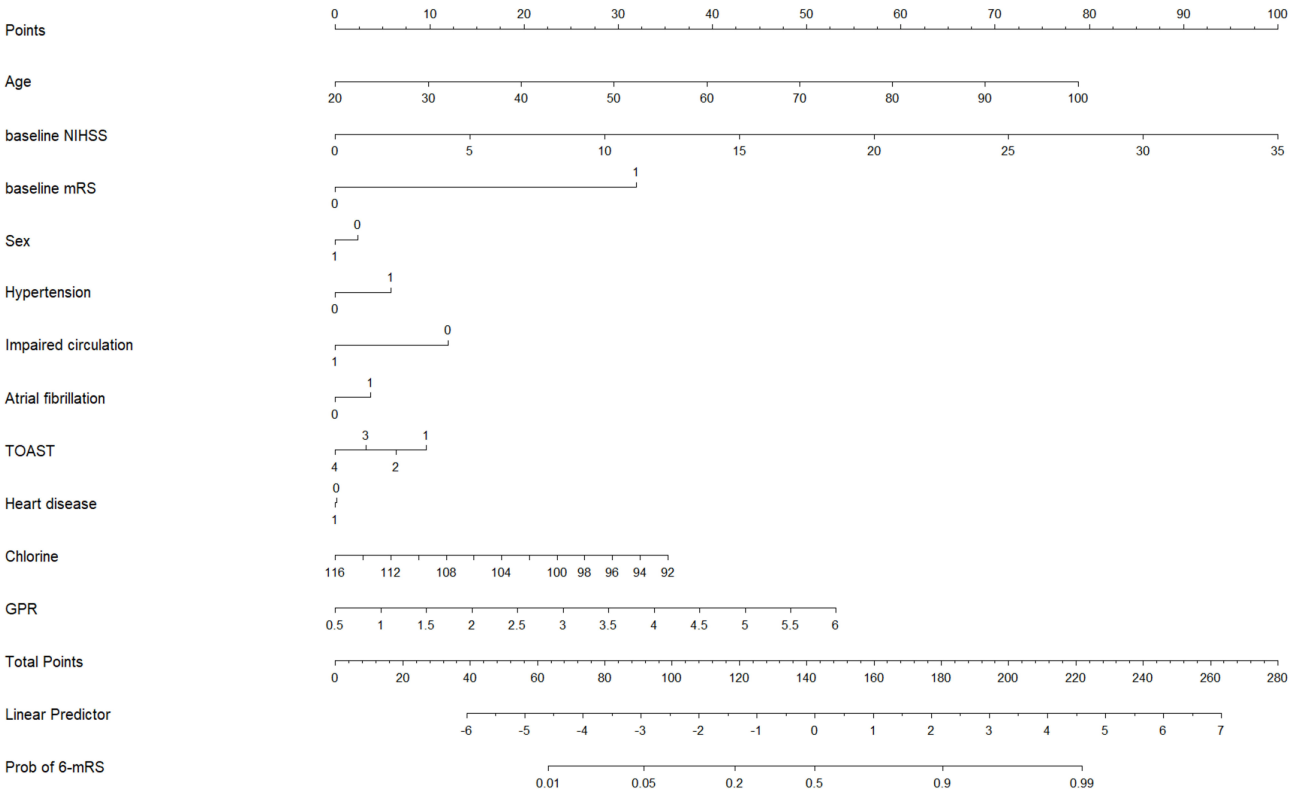

Figure 2 Line graph of the impact degree of 6-mRS.
Abbreviations: mRS, modified Rankin Scale; NIHSS, national institute of health stroke scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment; GPR, glucose to potassium ratio.

Table 3 Reclassification and Discrimination Statistics for Adverse Outcomes by GPR

	Harrell's C-ndex		NRI		IDI	
	Estimate (95% CI)	***p*-value**	**Estimate (95% CI)**	***p*-value**	**Estimate (95% CI)**	***p*-value**
3-mRS						
Model 1	0.833 (0.799–0.866)		Ref.		Ref.	
Model 2	0.838 (0.804–0.871)	< 0.001	0.415 (0.251–0.579)	< 0.001	0.015 (0.005–0.025)	0.004
6-mRS						
Model 1	0.837 (0.804–0.871)		Ref.		Ref.	
Model 2	0.844 (0.810–0.878)	< 0.001	0.480 (0.313–0.647)	< 0.001	0.022 (0.009–0.035)	< 0.001
12-mRS						
Model 1	0.845 (0.811–0.879)		Ref.		Ref.	
Model 2	0.851 (0.817–0.885)	< 0.001	0.403 (0.232–0.574)	< 0.001	0.020 (0.007–0.033)	0.003
END						
Model 1	0.626 (0.547–0.706)		Ref.		Ref.	
Model 2	0.698 (0.621–0.775)	< 0.001	0.467 (0.192–0.741)	0.001	0.026 (0.005–0.047)	0.014
Death						
Model 1	0.861 (0.833–0.901)		Ref.		Ref.	
Model 2	0.869 (0.841–0.909)	0.454	0.387 (0.141–0.633)	0.002	0.020 (−0.005–0.044)	0.112

Notes: Model 1: adjusted for age, sex, baseline NIHSS, hypertension, heart disease, chlorine, impaired circulation, atrial fibrillation, TOAST, baseline mRS; Model 2: adjusted for age, sex, baseline NIHSS, hypertension, heart disease, chlorine, impaired circulation, atrial fibrillation, TOAST, baseline mRS, GPR.

Abbreviations: CI, confidence interval; NIHSS, national institute of health stroke scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment; mRS, modified Rankin Scale; END, early neurological deterioration; NRI, net reclassification improvement; IDI, integrated discrimination improvement; Ref, reference group.

Synergistic Relationship Between GPR and NLR with Adverse Outcomes

We demonstrated the dose-response relationship between GPR and NLR and adverse outcomes in Figures 3 and S4. The incidence of overall adverse outcomes, particularly 3-mRS and 6-mRS, increased progressively with higher GPR, and this trend was further exacerbated by an elevation in NLR. In contrast, no further increase in the incidence of adverse outcomes with rising NLR was observed in the case of Death. The heat maps of adjusted odds ratios of GPR and NLR were displayed in Figures 4 and S5. For 6-mRS, the groups with GPR-H and NLR-L (OR = 2.888*), NLR-M (OR = 2.757*), as well as NLR-H (OR = 5.195***) all showed significance, the same results were observed for 3-mRS. For END, the group with GPR-H and NLR-H (OR = 3.421*) levels showed significance, the same result was observed for Death. For 12-mRS, the groups with GPR-H and NLR-M (OR = 2.441*) and NLR-H (OR = 3.993*) levels all showed significance. We demonstrated and compared the results of the synergistic analysis through color differences in Figures 4 and S5, while in Table S4, we provided further detailed explanations for the results presented in the heat maps.

Sensitivity Analysis

As presented in Table S5, after excluding participants who received critical prognostic medications (antihypertensives, hypoglycemics, lipid-lowering agents, anticoagulants, or antiplatelet drugs), the positive associations between GPR and 12-mRS and Death remained statistically significant [12-mRS: OR = 1.772 (1.108–2.835), $p = 0.017$; Death: HR = 1.692 (1.174–2.440), $p = 0.005$]. However, the outcome of 3-mRS, 6-mRS and END were inconsistent with the primary results. As detailed in Table S6, the association between GPR and adverse clinical outcomes demonstrated no difference between the 595 patients treated with alteplase and the 11 treated with urokinase, further supporting the robustness of our findings. To further evaluate the clinical relevance of GPR, Table S7 presents a direct comparison with emerging inflammatory biomarkers (MLR, PLR, AISI, and SII). Regarding the predictive value for the primary outcome of 6-mRS, although the diagnostic performance of these indicators showed no statistically significant differences, the GPR achieved the highest AUC value among all compared parameters (0.652, 95% CI: 0.605–0.700). This suggests that GPR may possess a relatively superior potential for discriminative ability in diagnosing and stratifying AIS patients.

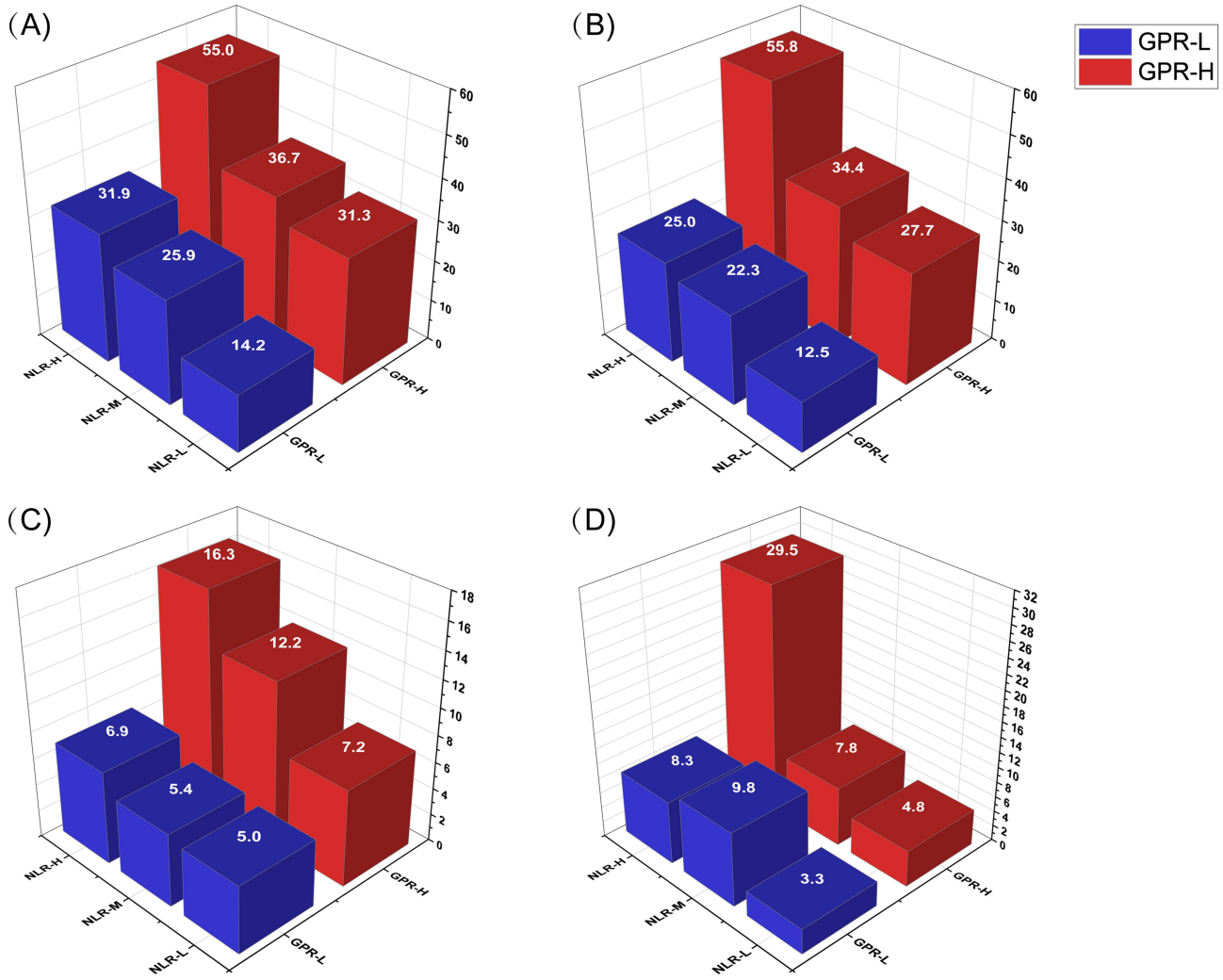

Figure 3 The dose-response relationship between GPR and NLR and adverse outcomes (**A**) the outcome is histogram of 3-mRS, (**B**) the outcome is histogram of 6-mRS, (**C**) the outcome is histogram of END, (**D**) the outcome is histogram of Death).
Abbreviations: NLR, neutrophil-to-lymphocyte ratio; GPR, glucose-to-potassium ratio.

Discussion

This retrospective cohort study investigated the relationship between GPR and the prognosis of patients with AIS, while simultaneously exploring the synergistic effect of GPR and NLR on patient prognosis. The study found that GPR demonstrated favorable prognostic performance in patients with AIS undergoing thrombolysis and exhibited beneficial clinical effects when included in the predictive model. GPR could independently predict adverse outcomes in the short, medium, and long term with high accuracy. Additionally, the synergistic analysis of GPR and NLR indicated that GPR-H/NLR-L, GPR-H/NLR-M, and GPR-H/NLR-H were associated with increased risks of poor 3-mRS and 6-mRS outcomes. This suggested that increasing NLR levels may predict a worse prognosis for 3-mRS and 6-mRS; GPR-H/NLR-M and GPR-H/NLR-H were associated with increased risks of poor END and Death outcomes, which suggested that medium-level and high-level NLR may predict a worse prognosis for END and death; and GPR-H/NLR-H was associated with increased risks of poor 12-mRS outcomes, which suggested that high-level NLR may predict a worse prognosis for 12-mRS. These discoveries implied that GPR held high predictive value in clinical practice for AIS. Therefore, simultaneously monitoring GPR and NLR levels and concentrating on the comprehensive metabolic condition of these patients might offer a more exhaustive evaluation of prognosis in AIS patients.

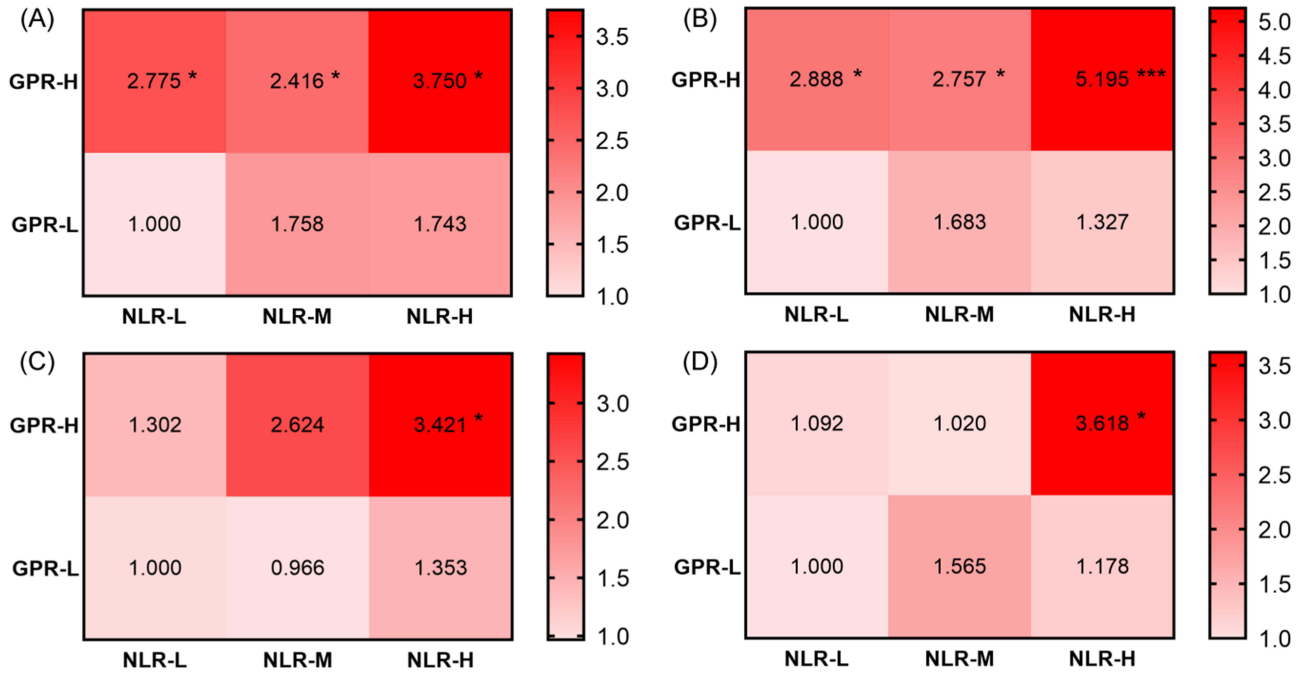

Figure 4 Heatmap of the ratio of synergistic effects between GPR and NLR (**A**) the outcome is a heatmap of 3-mRS, (**B**) The outcome is a heatmap of 6-mRS, (**C**) The outcome is a heatmap of END, (**D**) The outcome is a heatmap of Death).
Notes: Model: adjusted for age, sex, baseline NIHSS, hypertension, heart disease, chlorine, impaired circulation, atrial fibrillation, TOAST, baseline mRS. reference group: GPR-L+NLR-L. *indicates $p < 0.05$, ***indicates $p < 0.0001$.
Abbreviations: NLR, neutrophil-to-lymphocyte ratio; GPR, glucose-to-potassium ratio; ref, reference group.

Hyperglycemia is frequently observed in patients with AIS, affecting approximately 30–40% of individuals, including those without a prior diagnosis of diabetes.[22,23] This phenomenon can be attributed to the activation of the sympathetic nervous system in response to severe neurological stress, leading to the overproduction of catecholamines such as adrenaline, noradrenaline, and dopamine.[24] These compounds stimulate the release of glucagon, subsequently raising blood glucose levels.[25] Furthermore, research has demonstrated that patients with acute cerebrovascular stroke (CVS) are prone to hyperglycemia during the stress phase, with this phenomenon being particularly prominent in those with hemorrhagic stroke.[26] The clinical implications of hyperglycemia in AIS are significant. Numerous studies have demonstrated a strong association between elevated blood glucose levels and adverse outcomes in AIS patients. Zeinhom et al confirmed in 592 alteplase-treated AIS patients that admission hyperglycemia independently predicted 3-month poor outcomes (OR = 13.105, $p < 0.001$), and post-alteplase intracerebral hemorrhage (ICH) also increased this risk (OR = 7.410, $p = 0.008$).[27] Ahmed et al further found in 716 AF related embolic stroke patients that hyperglycemia was linked to severe hemorrhagic transformation (HT) subtypes, with synergistic effects with sustained AF and warfarin.[28] These align with our study: GPR integrates hyperglycemia and hypokalemia, better predicting post-alteplase outcomes than single glucose. For instance, non-diabetic individuals who experience hyperglycemia during ischemic stroke are at a higher risk of stroke recurrence within 90 days and exhibit poorer functional recovery.[29,30] Additionally, Beseoglu and Steiger[31] highlighted that hyperglycemia is associated with initial neurological severity and poorer outcomes at the 6-month follow-up.

There is no doubt that serum potassium is also particularly crucial. In addition to high serum glucose, hypokalemia is frequently observed in stroke patients (20%), as it is involved in multiple cellular functions. Under physiological conditions, potassium is actively transported into cells via the cell membrane and the sodium/potassium adenosine triphosphatase pump (Na+/K+-ATPase), which is modulated by catecholamines.[32] The activity of Na+/K+-ATPase is influenced by catecholamines, B2 adrenergic hormones, and insulin, leading to a reduction in extracellular potassium levels. Following a stroke, the surge in catecholamines further exacerbates the decline in serum potassium

concentrations.[32] Studies have also demonstrated a connection between potassium levels and mortality, indicating that higher dietary potassium intake may reduce the risk of stroke-related death.[33]

In recent years, the study of serum glucose and potassium levels has garnered significant interest among researchers. Multiple studies have established that disturbances in glucose regulation and potassium metabolism are independently linked to neurological dysfunction and cerebrovascular events.[15,34] It is worth noting that hyperglycemia encompasses not only sustained high blood glucose levels but also fluctuations, including both increases and decreases.[35] This highlights the limitations of relying solely on a single time-point measurement of serum glucose and underscores the importance of integrating it with other indicators. GPR, a novel biomarker derived from blood glucose and potassium levels, offers a straightforward and measurable approach to predicting outcomes in stroke patients.[33]

Elevated GPR levels have been linked to poorer clinical outcomes in various neurological conditions, including traumatic brain injury (TBI), ischemic stroke (IS), and ICH.[15,16,36] Furthermore, these findings suggest that GPR could serve as a potential biomarker for stress-induced injury, reflecting systemic disturbances in severe illnesses. Investigations into stress-related conditions, such as acute myocardial infarction,[37] blunt abdominal trauma,[38] pulmonary embolism,[39] and intermediate syndrome resulting from anticholinesterase poisoning,[40] consistently reveal a robust correlation between increased GPR levels and unfavorable outcomes or more severe symptoms. Under conditions of significant stress injury, activation of the sympathetic nervous system prompts the release of stress hormones, such as catecholamines, growth hormone, cortisol, and cytokines, which contribute to hyperglycemia and insulin resistance.[29,30] In AIS patients, heightened catecholamine levels and insulin secretion modulate Na+/K+-ATPase activity, leading to greater intracellular potassium uptake.[32,33] As a result, elevated GPR levels following a stroke may signal stress-induced activation and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. HPA axis dysfunction is believed to play a crucial role in the progression of energy pump failure and various signaling pathways implicated in AIS.[41] Moreover, elevated cortisol levels stimulate the renin-angiotensin-aldosterone system (RAAS), which can lower serum potassium concentrations.[42] Cortisol also increases blood glucose levels, and current evidence underscores the central role of RAAS in stroke progression.[43] Given the combined influence of serum potassium and glucose levels, the GPR index may serve as a useful tool for evaluating HPA axis and RAAS dysregulation in AIS patients. Our study further substantiated the significant association between high GPR levels and mortality, indicating that GPR has strong predictive value for short-term, medium-term, and long-term adverse outcomes in AIS patients. Through the use of nomograms, clinical decision curves, and Harrell's C-index, our research further elucidated the utility and impact of GPR in assessing clinical outcomes.

Meanwhile, in previous studies, we found that the influence of the inflammatory response on the prognosis of stroke may have the same mechanism as GPR. Following a stroke, there is an increase in the expression of pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, etc., which can induce neuronal damage and death directly through various mechanisms, including the activation of the HPA axis. The activation of the HPA axis may further intensify the inflammatory response, creating a vicious cycle. This interaction has significant implications for the prognosis and recovery of stroke patients.[44,45] Also in the study by Husain et al[46] they found that the RAAS and its primary mediator, Ang II, directly influence the progression of atherosclerosis by affecting endothelial function and inflammatory responses, thereby indirectly affecting the occurrence of AIS. To sum up, GPR and inflammatory response have the same mechanism of influence on AIS, which likely means that GPR has a synergistic effect with the inflammatory response on the poor prognosis of AIS.

The NLR is one of the most representative indicators of inflammatory response in AIS. Therefore, in our study, the NLR was used to represent the inflammatory response to explore its synergistic effect with GPR on the adverse prognosis of AIS. We observed significant differences in 3-mRS and 6-mRS scores between patients with high GPR and low, moderate, and high NLR levels, compared to those with low GPR and high NLR levels. Notably, the impact of low NLR levels was greater than that of moderate NLR levels, suggesting that both low and high NLR levels were associated with a higher likelihood of adverse outcomes. Besides, there was a significant difference in END and Death when GPR was high and NLR levels were high, which may indicate that patients with both high NLR and GPR levels are at increased risk for adverse outcomes. Regarding the 12-mRS, significant differences were observed between high GPR and both moderate and high NLR levels, indicating that patients with low NLR levels may be at a safer prognosis.

To the best of our knowledge, this is the first comprehensive study to analyze the association between GPR and END, short-term, medium-term, long-term adverse outcomes, and Death in patients with AIS who have received thrombolytic therapy, and it is also the first to investigate the synergistic role of inflammatory markers and GPR in this association. Nevertheless, several limitations should be noted. First, the small sample size and single-center design may introduce selection bias. Second, while efforts were made to mitigate confounding variables, the possibility of unaccounted confounders influencing the results cannot be entirely excluded due to the retrospective nature of the study. This includes unmeasured variables related to post-stroke treatment, such as medication dosage, specific drug types, adherence to therapy, and the nature of physical rehabilitation programs. Additionally, the study's focus on an Asian population may limit the generalizability of the findings. Finally, although the study identified a synergistic relationship between different levels of GPR and NLR and stroke prognosis, the underlying biological mechanisms require further investigation. This may necessitate the integration of genomic or metabolomic data to better understand the impact of these biomarkers on AIS.

This study holds significant clinical implications for the prognosis of AIS. The GPR clinical threshold (1.459), identified by Figure 1, represents the optimal cut-off value validated by a triple evaluation process encompassing the statistical inflection point, data distribution, and clinical outcomes. Its integration into existing prognostic models significantly enhances clinical utility by optimizing risk stratification, streamlining decision-making, and guiding individualized interventions. Particularly for the emergency assessment and long-term management of AIS patients undergoing thrombolysis, the value 1.459 serves not only as a prognostic threshold but also as an actionable signal for intervention initiation. This provides clinicians with a practical, low-cost tool for combined metabolic and inflammatory assessment, thereby supporting the evolving trend toward precision neurocritical care. By considering the GPR level, clinicians can better tailor individualized treatment plans for patients. Particularly, high-risk clusters may benefit from more aggressive glucose and potassium management to improve prognostic outcomes. Furthermore, this study suggests that future post-stroke management should incorporate a comprehensive assessment of GPR and NLR levels to help clinicians identify high-risk patients and provide appropriate interventions. Future research should involve larger, multicenter studies to validate these findings and further confirm the biological synergistic mechanisms between GPR and NLR levels and AIS. Additionally, more efforts should be made to develop specific management strategies for GPR and NLR levels to optimize individualized interventions.

Conclusions

Our study indicated that GPR independently predicts adverse outcomes in AIS patients, and elevated levels of GPR are significantly associated with poorer clinical outcomes in AIS patients. It was conspicuously associated with 3-mRS, 6-mRS, 12-mRS, END, and Death. Additionally, it had significant synergies with NLR in different adverse outcomes. The comprehensive assessment of GPR and NLR levels may hold potential value in predicting the prognosis of AIS.

Data Sharing Statement

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

Ethics Approval and Informed Consent

This study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University (KY2025-R250) and was conducted in accordance with the principles in the Declaration of Helsinki. Given the retrospective nature of this study and the use of anonymized data, the Ethics Committee waived the requirement for obtaining written informed consent. We confirmed that all the data were anonymized to ensure confidentiality.

Acknowledgments

We sincerely thank the participating hospitals, patients, their families, and colleagues who have provided valuable suggestions for this study.

Author Contributions

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

Funding

The study was supported by the National Innovation and Entrepreneurship Training Program for College Students (No. 202410343059).

Disclosure

On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. Feigin VL, Stark BA, Johnson CO. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the global burden of disease study 2019. *Lancet Neurol*. 2021;20:795–820. doi:10.1016/S1474-4422(21)00252-0
2. Ma Q, Li R, Wang L, et al. Temporal trend and attributable risk factors of stroke burden in China, 1990-2019: an analysis for the global burden of disease study 2019. *Lancet Public Health*. 2021;6:e897–e906. doi:10.1016/S2468-2667(21)00228-0
3. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2018;49:e46–e110. doi:10.1161/STR.0000000000000158
4. Zhou Y, Wu D, Yan S, et al. Feasibility of a clinical-radiomics model to predict the outcomes of acute ischemic stroke. *Korean J Radiol*. 2022;23:811–820. doi:10.3348/kjr.2022.0160
5. Berge E, Whiteley W, Audebert H, et al. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *Eur Stroke J*. 2021;6:I–lxii. doi:10.1177/2396987321989865
6. Makris K, Haliassos A, Chondrogianni M, Tsivgoulis G. Blood biomarkers in ischemic stroke: potential role and challenges in clinical practice and research. *Crit Rev Clin Lab Sci*. 2018;55:294–328. doi:10.1080/10408363.2018.1461190
7. Montellano FA, Ungethüm K, Ramiro L, et al. Role of blood-based biomarkers in ischemic stroke prognosis: a systematic review. *Stroke*. 2021;52:543–551. doi:10.1161/STROKEAHA.120.029232
8. Remesar X, Alemany M, Antonio L. Dietary energy partition: the central role of glucose. *Int J Mol Sci*. 2020;22:21. doi:10.3390/ijms22010021
9. Palmer BF. Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system. *New Engl J Med*. 2004;351:585–592. doi:10.1056/NEJMra035279
10. Johnson LS, Mattsson N, Sajadieh A, Wollmer P, Söderholm M. Serum potassium is positively associated with stroke and mortality in the large, population-based malmö preventive project cohort. *Stroke*. 2017;48:2973–2978. doi:10.1161/STROKEAHA.117.018148
11. Shi H, Ge Y, Wang H, Zhang Y, Teng W, Tian L. Fasting blood glucose and risk of Stroke: a Dose-Response meta-analysis. *Clin Nutr*. 2021;40:3296–3304. doi:10.1016/j.clnu.2020.10.054
12. McTaggart JS, Clark RH, Ashcroft FM. The role of the KATP channel in glucose homeostasis in health and disease: more than meets the islet. *J Physiol*. 2010;588:3201–3209. doi:10.1113/jphysiol.2010.191767
13. Rowe JW, Tobin JD, Rosa RM, Andres R. Effect of experimental potassium deficiency on glucose and insulin metabolism. *Metabolism*. 1980;29:498–502. doi:10.1016/0026-0495(80)90074-8
14. Fujiki Y, Matano F, Mizunari T, et al. Serum glucose/potassium ratio as a clinical risk factor for aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 2018;129:870–875. doi:10.3171/2017.5.JNS162799
15. Wu XY, Zhuang YK, Cai Y, et al. Serum glucose and potassium ratio as a predictive factor for prognosis of acute intracerebral hemorrhage. *J Int Med Res*. 2021;49:3000605211009689. doi:10.1177/03000605211009689
16. Zhou J, Yang CS, Shen LJ, Lv QW, Xu QC. Usefulness of serum glucose and potassium ratio as a predictor for 30-day death among patients with severe traumatic brain injury. *Clin Chim Acta*. 2020;506:166–171. doi:10.1016/j.cca.2020.03.039
17. Demirtaş E, Korkmaz İ, Tekin YK, Demirtaş E, Çaltekin İ. Assessment of serum glucose/potassium ratio as a predictor for delayed neuropsychiatric syndrome of carbon monoxide poisoning. *Hum Exp Toxicol*. 2021;40:207–213. doi:10.1177/0960327120945773
18. Liu Y, Qiu T, Fu Z, et al. Systemic immune-inflammation index and serum glucose-potassium ratio predict poor prognosis in patients with spontaneous cerebral hemorrhage: an observational study. *Medicine*. 2024;103:e39041. doi:10.1097/MD.0000000000039041
19. Afari ME, Bhat T. Neutrophil to lymphocyte ratio (NLR) and cardiovascular diseases: an update. *Exp Rev Cardiovasc Ther*. 2016;14:573–577. doi:10.1586/14779072.2016.1154788
20. Chen Y, Peng Y, Zhang X, et al. The blood glucose-potassium ratio at admission predicts in-hospital mortality in patients with acute type A aortic dissection. *Sci Rep*. 2023;13:15707. doi:10.1038/s41598-023-42827-2
21. Liu H, Liu K, Zhang K, et al. Early neurological deterioration in patients with acute ischemic stroke: a prospective multicenter cohort study. *Ther Adv Neurol Disord*. 2023;16:17562864221147743. doi:10.1177/17562864221147743
22. Luitse MJ, Biessels GJ, Rutten GE, Kappelle LJ. Diabetes, hyperglycaemia, and acute ischaemic stroke. *Lancet Neurol*. 2012;11:261–271. doi:10.1016/S1474-4422(12)70005-4
23. Southerland AM, Mayer SA, Chiota-McCollum NA, et al. Glucose control and risk of symptomatic intracerebral hemorrhage following thrombolysis for acute ischemic stroke: a SHINE trial analysis. *Neurology*. 2024;102:e209323. doi:10.1212/WNL.0000000000209323

24. Ogura T, Satoh A, Ooigawa H, et al. Characteristics and prognostic value of acute catecholamine surge in patients with aneurysmal subarachnoid hemorrhage. *Neurological Res*. 2012;34:484–490. doi:10.1179/1743132812Y.0000000033
25. O'Neill PA, Davies I, Fullerton KJ, Bennett D. Stress hormone and blood glucose response following acute stroke in the elderly. *Stroke*. 1991;22:842–847. doi:10.1161/01.STR.22.7.842
26. El-Fawal BM, Badry R, Abbas WA, Ibrahim AKJE. Stress hyperglycemia and electrolytes disturbance in patients with acute cerebrovascular stroke. *Egypt J Neurol Psychiat Neurosurg*. 2019;55:86.
27. Zeinhom MG, Khalil MFE, Kamel IFM, et al. Predictors of the unfavorable outcomes in acute ischemic stroke patients treated with alteplase, a multi-center randomized trial. *Sci Rep*. 2024;14:5960. doi:10.1038/s41598-024-56067-5
28. Ahmed SR, Zeinhom MG, Ebied A, et al. A multi-center study on the predictors of different subtypes of hemorrhagic transformation of brain infarction after thrombolysis in atrial fibrillation patients presented with embolic stroke. *Sci Rep*. 2025;15:15655. doi:10.1038/s41598-025-97968-3
29. Guo Y, Wang G, Jing J, et al. Stress hyperglycemia may have higher risk of stroke recurrence than previously diagnosed diabetes mellitus. *Aging*. 2021;13:9108–9118. doi:10.18632/aging.202797
30. Zonneveld TP, Nederkoorn PJ, Westendorp WF, Brouwer MC, van de Beek D, Kruyt ND. Hyperglycemia predicts poststroke infections in acute ischemic stroke. *Neurology*. 2017;88:1415–1421. doi:10.1212/WNL.0000000000003811
31. Beseoglu K, Steiger HJ. Elevated glycated hemoglobin level and hyperglycemia after aneurysmal subarachnoid hemorrhage. *Clin Neurol Neurosurg*. 2017;163:128–132. doi:10.1016/j.clineuro.2017.10.037
32. Gariballa SE, Robinson TG, Fotherby MD. Hypokalemia and potassium excretion in stroke patients. *J Am Geriatr Soc*. 1997;45:1454–1458. doi:10.1111/j.1532-5415.1997.tb03195.x
33. Khaw KT, Barrett-Connor E. Dietary potassium and stroke-associated mortality. A 12-year prospective population study. *New Engl J Med*. 1987;316:235–240. doi:10.1056/NEJM198701293160502
34. De Bernardis Murat C, Leão RM. A voltage-dependent depolarization induced by low external glucose in neurons of the nucleus of the tractus solitarius: interaction with K(ATP) channels. *J Physiol*. 2019;597:2515–2532. doi:10.1113/JP277729
35. Zhou R, Wei C, Zhao M, Sun L. Association between short-term glucose fluctuations and cognition in patients with acute ischemic stroke complicated by type 2 diabetes mellitus. *J Nutr Health Aging*. 2024;28:100252. doi:10.1016/j.jnha.2024.100252
36. Alamri FF, Almarghalani DA, Alraddadi EA, et al. The utility of serum glucose potassium ratio as a predictive factor for haemorrhagic transformation, stroke recurrence, and mortality among ischemic stroke patients. *Saudi Pharm J*. 2024;32:102082. doi:10.1016/j.jsps.2024.102082
37. Jiang F, Yang J, Zhang Y, et al. Angiotensin-converting enzyme 2 and angiotensin 1-7: novel therapeutic targets. *Nat Rev Cardiol*. 2014;11:413–426. doi:10.1038/nrcardio.2014.59
38. Plakht Y, Gilutz H, Shiyovich A. The association of concomitant serum potassium and glucose levels and in-hospital mortality in patients with acute myocardial infarction (AMI). Soroka acute myocardial infarction II (SAMI-II) project. *Int J Cardiol*. 2019;287:39–45. doi:10.1016/j.ijcard.2019.02.031
39. Katipoğlu B, Demirtaş E. Assessment of serum glucose potassium ratio as a predictor for morbidity and mortality of blunt abdominal trauma. *Ulusal travma ve acil cerrahi dergisi*. 2022;28:134–139. doi:10.14744/tjtes.2020.88945
40. Sharif AF, Fayed MM. Assessment of the serum glucose/potassium GLU/K ratio as a predictor of intermediate syndrome following acute anticholinesterase exposure. *Neurotoxicology*. 2022;89:161–173. doi:10.1016/j.neuro.2022.02.001
41. Fan X, Cao J, Li M, et al. Stroke Related Brain-Heart Crosstalk: pathophysiology, Clinical Implications, and Underlying Mechanisms. *Adv Sci*. 2024;11:e2307698. doi:10.1002/advs.202307698
42. Back C, Thiesen KL, Skovgaard K, et al. RAAS and stress markers in acute ischemic stroke: preliminary findings. *Acta Neurol Scand*. 2015;131:132–139. doi:10.1111/ane.12298
43. Paulson OB, Barry DI, Strandgaard S, Lassen NA. Does angiotensin-II protect against strokes? *Lancet*. 1986;2:927–928. doi:10.1016/S0140-6736(86)90452-6
44. Feng X, Ma X, Li J, et al. Inflammatory pathogenesis of post-stroke depression. *Aging and Disease*. 2024;16:209–238. doi:10.14336/AD.2024.0203
45. Kumari S, Dhapola R, Sharma P, Nagar P, Medhi B, HariKrishnaReddy D. The impact of cytokines in neuroinflammation-mediated stroke. *Cytokine Growth Factor Rev*. 2024;78:105–119. doi:10.1016/j.cytogfr.2024.06.002
46. Husain K, Hernandez W, Ansari RA, Ferder L. Inflammation, oxidative stress and renin angiotensin system in atherosclerosis. *J Biol Chemist*. 2015;6:209–217. doi:10.4331/wjbc.v6.i3.209