International Journal of General Medicine Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Serum Glucose-Phosphate Ratio on Admission as a Potential Biomarker for Severity, Functional Outcome, and Recurrence in Acute Ischemic Stroke

Jie Li[1,*], Wenyang Ma[1,*], Wuzhuang Tang[1], Kaixuan Yang[2], Hongqiu Gu[2], Junfeng Shi[1], Feng Chen[1], Chenhan Xu[1], Shiyuan Gu[1], Yongjun Wang[2,3]

[1]Department of Neurology, The Affiliated Yixing Hospital of Jiangsu University, Yixing, People's Republic of China; [2]China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing, People's Republic of China; [3]Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Shiyuan Gu; Yongjun Wang, Email shiyuan1178@hotmail.com; yongjunwang@ncrcnd.org.cn

Background and Objective: Raised serum glucose-phosphate ratio on admission is associated with severity and poor outcome of aneurysmal subarachnoid hemorrhage and severe traumatic brain injury. However, its role in acute ischemic stroke (AIS) remains still unknown. Therefore, this prospective study aimed to investigate the association between admission serum glucose-phosphate ratio and the severity and 1-year clinical outcome of AIS.

Methods: All the patients with AIS were enrolled from the Third China National Stroke Registry III. Participants were classified into four groups according to quartiles of admission serum glucose-phosphate ratio levels. Multiple regression models and restricted cubic splines were performed to evaluate the association between serum glucose-phosphate ratio and the severity and 1-year outcome of patients with AIS.

Results: Among the 5,541 participants, the mean age was 62.3 years, and 69.4% patients were men. As the quartiles of admission serum glucose-phosphate ratio increased, the median NIHSS score raised, the percentage of moderate and severe stroke elevated, and rates of poor functional outcomes and recurrent stroke raised at one-year follow-up. After adjusting conventional risk factors, the highest admission serum glucose-phosphate ratio-level quartile group showed an association of poor functional outcome and stroke recurrence [OR (95% CI): 1.67 (1.28, 2.17) and HR (95% CI): 1.44 (1.08, 1.92), respectively], relative to the lowest group. Restricted cubic splines showed no significant nonlinear relationship between serum glucose-phosphate ratio and adverse outcomes of AIS.

Conclusion: Admission serum glucose-phosphate ratio may be a potential blood biomarker for reflecting stroke severity, predicting poor functional outcomes, and stroke recurrence.

Keywords: serum glucose-phosphate ratio, acute ischemic stroke, outcome, severity, blood biomarker

Introduction

Globally, ischemic stroke is a major cause of disabilities and mortalities, which heavily imposes an economic burden on society.[1] Thus, it is vital to identify and control stroke-related risk factors early in the treatment and secondary prevention of stroke. In recent years, the prognosis of ischemic stroke is still a research hotspot, especially regarding blood biomarkers.[2] Numerous biomarkers have been examined for predicting acute ischemic stroke (AIS) outcomes. However, many biomarkers are not yet clinically available because of high cost or access. Therefore, it is substantial to look for simple and feasible predictors based on readily available markers from clinical practice. Circulating

Received: 22 April 2024
Accepted: 16 November 2024
Published: 5 December 2024

biomarkers in blood samples are clinically prevalent, and the relationship between blood biomarkers and the prognosis of ischemic stroke has drawn more attention in recent years.[3]

Serum glucose and phosphate are two essential blood indicators commonly used and readily available in clinical practice. Hyperglycemia is common in patients with AIS. Admission hyperglycemia was associated with stroke severity,[4] and adverse clinical outcomes.[5,6] Phosphorus is one of life's most basic elements, mainly in the form of inorganic phosphate in the human body. Previous studies have found a U-shaped relationship between serum phosphate with poor functional outcome and an association between serum phosphate and unfavorable prognosis with ischemic stroke.[7] Given the potential combined effects of serum glucose and phosphate, the serum glucose-phosphate ratio as a novel blood biomarker has been used in aneurysmal subarachnoid hemorrhage (aSAH),[8] and severe traumatic brain injury (sTBI).[9] However, the effect of admission serum glucose-phosphate ratio for AIS has not been explored. Therefore, based on a nationwide prospective study, we aimed to investigate the relationship between admission serum glucose-phosphate ratio and stroke severity and 1-year clinical outcomes in patients with AIS.

Patients and Methods

Study Population

All participants with AIS were selected from the China National Stroke Registry-III (CNSR-3). The CNSR-III was a nationwide prospective registry for patients who were presented to hospitals with AIS or transient ischemic attack (TIA) from August 2015 to March 2018. A total of 15,166 AIS or TIA patients (within 7 days from the onset of symptoms) from 201 sites were recruited. Our previous studies have described specific information about the database in detail.[10] The inclusion criteria included: (1) Age ≥18 years; (2) Diagnosed with acute ischemic stroke; (3) Voluntarily sign the informed consent; Exclusion Criteria: (1) diagnosed with TIA; (2) missing serum glucose and serum phosphate values; and lost key covariates including serum hemoglobin, calcium, potassium, albumin, creatinine, or lipid value; (3) suspected non-ischemic causes of neurological symptoms; (4) lost during the 1-year follow-up (Figure 1). Accordingly, a total of 5,541 participants were enrolled in our study.

Standard Protocol Approvals and Patient Consents

This study was performed following the guidelines described by the Helsinki Declaration and was approved by the Ethical Committee of Beijing Tiantan Hospital and all other recruited participating centers approved the study protocol (IRB approval number: KY2015-001-01). Written informed consent was obtained from all participants or their legal representatives before entering this study.

Baseline Data Collection

All participants were comprehensively and precisely assessed at admission, and variables included demographics, medical history, vascular risk factors, important laboratory data, complications, and medication use. Demographics included age, gender, and body mass index (BMI). Medical history and vascular risk factors included a history of stroke, hypertension, diabetes mellitus (DM), hypercholesterolemia, coronary heart disease (CHD), atrial fibrillation, current or previous smoking, and heavier drinking. The National Institutes of Health Stroke Scale (NIHSS) score at admission and modified Rankin Scale (mRS) at discharge were recorded. Important laboratory data consisted of hemoglobin, serum glucose, serum phosphate, serum potassium, serum calcium, serum albumin, estimated glomerular filtration rate (eGFR), serum creatinine, total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C). Treatment use and complication contained antihypertensive drugs, lipid-lowering drugs, hypoglycemia drugs, and pneumonia during hospitalization. All AIS patients were categorized into five subtypes according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) type: large-artery atherosclerosis, cardioembolism, small-vessel occlusion, other determined etiology, and Undetermined.[11,12]

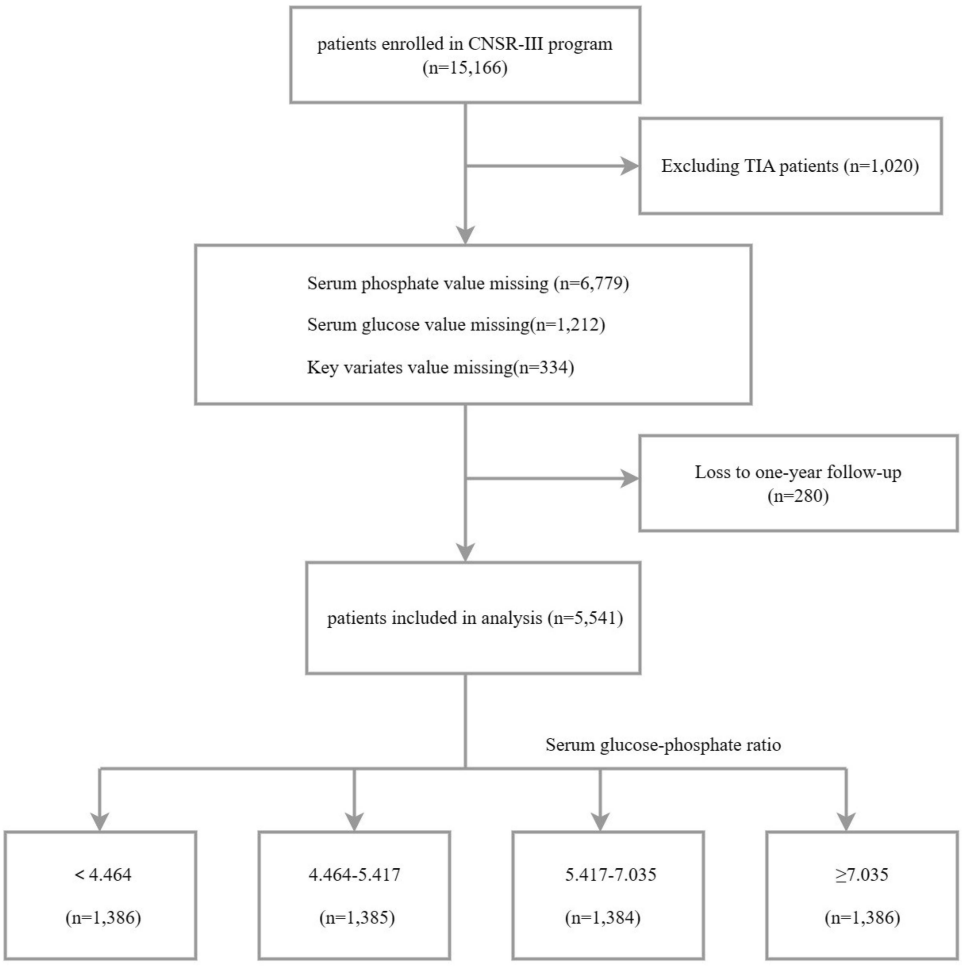

Figure 1 Flow chart of this diagram.
Abbreviation: CNSR III, China National Stroke Registry III.

Serum Phosphate and Serum Glucose Examinations

Fasting blood samples were collected in serum-separation tubes and EDTA anticoagulation blood collection tubes within 24 hours of admission. The samples were measured in the Central Laboratory of Beijing Tiantan Hospital under strict quality control standards. Serum phosphate levels were assessed with an ammonium molybdate assay using unfrozen samples. Briefly, the phosphate ions react with ammonium molybdate and then reduced to blue molybdenum which was finally colorimetric measured.[7] All measurements were performed by laboratory personnel blinded to patients' clinical situations.

Serum Glucose-Phosphate Ratio Calculation

The serum glucose-phosphate ratio was calculated as serum glucose concentration (mmol/L) divided by serum phosphate concentration (mmol/L) as the below formula.[8,9]

$$\text{The serum glucose} - \text{phosphate ratio} = \frac{\text{serum glucose concentration (mmol/L)}}{\text{serum phosphate concentration (mmol/L)}}$$

Outcome Evaluation and Stroke Severity Assessment

Patients were followed up over the telephone one year after disease onset by trained research coordinators blinded to baseline clinical status. Outcomes included poor functional outcomes, stroke recurrence, and all-cause mortality. Poor

functional outcome was defined as an mRS score of 3 to 6 [mRS score ranges from 0 (no symptoms) to 6 (death)].[7] Stroke recurrence included ischemic stroke or hemorrhagic stroke.[10] The severity of stroke patients was assessed by NIHSS score on admission and categorized into three groups: mild stroke (NIHSS score ≤5), moderate stroke (5< NIHSS score ≤10), and severe stroke (NIHSS score >10).[13]

Statistical Analyses

Continuous variables were expressed as mean ± standard deviation or median and interquartile range (IQR), as appropriate. Categorical variables were presented as frequency and percentage. Continuous variables with normal distribution were compared using Student's *t*-test. The $\chi 2$ and Fisher's exact tests were used for comparing categorical values. Univariate and multivariate logistic regression models were performed to compare the poor functional outcome at one year among the quartile groups. Univariate and multivariable Cox regression models were performed to compare the outcomes of stroke recurrence and all-cause death among the quartile groups. We further used restricted cubic spline (RCS) models for serum glucose-phosphate ratio adjusting for covariates with 5 knots at the 5th, 25th, 50th, 75th, and 95th percentiles to explore the pattern of association between serum glucose-phosphate ratio levels and risk of stroke clinical outcomes. All analyses were conducted with SAS version 9.4 software (SAS institute). All analyses were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

In brief, 5,541 (36.5%) participants with complete baseline information and one-year follow-up were enrolled in our analysis (Figure 1). The baseline characteristics of the included and excluded patients were well balanced in this analysis (Supplementary Table 1). Of all the enrolled participants, the average age was 62.3 ± 11.3 years, and 3,846 (69.4%) patients were men (Table 1). The included patients' baseline characteristics are summarized based on their serum glucose-phosphate ratio quartile in Table 1. The serum glucose-phosphate ratio ranged from 1.325 to 28.750, with a median of 5.417 and 25th-75th percentile values of 4.464 to 7.035. All patients were divided into four groups according to the serum glucose-phosphate ratio quartile. Serum glucose-phosphate ratio ranges of quartile groups were Q1 < 4.464, 4.464 ≤ Q2 < 5.417, 5.417 ≤ Q3 < 7.035, and Q4 ≥ 7.035, respectively. Compared with participants with lower serum glucose-phosphate ratio, those in higher glucose-phosphate ratio quartile groups were more likely to be older ($P < 0.001$), more male ($P < 0.001$), and more patients with slightly higher BMI ($P < 0.001$). In addition, individuals with a higher glucose-phosphate ratio were more likely to have hypertension ($P < 0.001$), DM, hypercholesterolemia ($P < 0.001$), CHD ($P < 0.001$), treatment with antihypertensive ($P < 0.001$) or hypoglycemia drugs ($P < 0.001$), or pneumonia ($P < 0.001$) during hospitalization. From the lowest to the highest quartile groups, the medians (IQR) NIHSS scores at admission were 3 [1–6], 3 [1–6], 3 [2–6], and 4 [2–7], respectively. They also had a higher stroke severity and a higher proportion in mRS (3–5 points, $P < 0.001$). History of stroke, atrial fibrillation, current or previous smoking, heavy drinker, low-density lipoprotein cholesterol, serum potassium, lipid-lowering drugs, and TOAST subtype were comparable in serum glucose-phosphate quartile groups (Table 1). Moreover, the levels of hemoglobin ($P < 0.001$), serum glucose ($P < 0.001$), total cholesterol ($P < 0.001$), and triglycerides ($P < 0.001$) increased along with the serum glucose-phosphate ratio. In contrast, serum creatinine ($P < 0.001$) and HDL decreased ($P < 0.001$) (Tables 1–3).

Table 1 Baseline Characteristics of the Patients According to Quartiles of Serum Glucose-Phosphate Ratio Level

Variables	Total (N=5,541)	Q1 (<4.464) (N=1,386)	Q2 (4.464–5.417) (N=1,385)	Q3 (5.417–7.035) (N=1,384)	Q4 (≥7.035) (N=1,386)	*P*-value
Age (Mean±SD), y	62.3±11.3	60.2±11.9	62.2±11.6	63.9±10.7	62.7±10.8	<0.001
Male, n (%)	3846 (69.4)	858 (61.9)	989 (71.4)	1027 (74.2)	972 (70.1)	<0.001
BMI (Mean±SD)	24.7±3.4	24.3±3.4	24.8±3.3	24.7±3.3	25.0±3.5	<0.001

Table 2 Baseline Medical Data of the Patients According to Quartiles of Serum Glucose-Phosphate Ratio Level

Variables	Total (N=5,541)	Q1 (<4.464) (N=1,386)	Q2 (4.464–5.417) (N=1,385)	Q3 (5.417–7.035) (N=1,384)	Q4 (≥7.035) (N=1,386)	*P*-value
Medical history, n (%)						
History of Stroke	1168 (21.1)	265 (19.1)	293 (21.2)	297 (21.5)	313 (22.6)	0.157
Hypertension	4199 (75.8)	998 (72.0)	1042 (75.2)	1065 (77.0)	1094 (78.9)	<0.001
Diabetes mellitus	1701 (30.7)	138 (10.0)	202 (14.6)	396 (28.6)	965 (69.6)	<0.001
Hypercholesterolemia	2143 (38.7)	497 (35.9)	527 (38.1)	496 (35.8)	623 (44.9)	<0.001
CHD	554 (10.0)	106 (7.6)	142 (10.3)	136 (9.8)	170 (12.3)	<0.001
Atrial fibrillation	420 (7.6)	103 (7.4)	101 (7.3)	115 (8.3)	101 (7.3)	0.699
Current or previous smoking	2472 (44.6)	617 (44.5)	620 (44.8)	642 (46.4)	593 (42.8)	0.301
Heavy drinker	882 (15.9)	196 (14.1)	244 (17.6)	226 (16.3)	216 (15.6)	0.088
Admission NIHSS, median (IQR)	3.0 (1.0–6.0)	3.0 (1.0–6.0)	3.0 (1.0–6.0)	3.0 (2.0–6.0)	4.0 (2.0–7.0)	<0.001
Admission NIHSS, n (%)						<0.001
Mild (0–5)	3976 (71.8)	1037 (74.8)	1028 (74.2)	975 (70.4)	936 (67.5)	
Moderate (6–10)	1145 (20.7)	250 (18.0)	277 (20.0)	293 (21.2)	325 (23.4)	
Severe (>10)	420 (7.6)	99 (7.1)	80 (5.8)	116 (8.4)	125 (9.0)	
Medication during hospitalization, n (%)						
Antihypertensive drugs	2538 (45.8)	600 (43.3)	603 (43.5)	634 (45.8)	701 (50.6)	<0.001
Hypoglycemia drugs	1435 (25.9)	114 (8.2)	160 (11.6)	302 (21.8)	859 (62.0)	<0.001
Lipid-lowering drugs	5258 (94.9)	1309 (94.4)	1311 (94.7)	1325 (95.7)	1313 (94.7)	0.417
Pneumonia during hospitalization, n (%)	283 (5.1)	47 (3.4)	64 (4.6)	79 (5.7)	93 (6.7)	<0.001
mRS at discharge, n (%)						<0.001
0–2	4525 (81.7)	1183 (85.4)	1159 (83.7)	1119 (80.9)	1064 (76.8)	
3–5	1015 (18.3)	203 (14.6)	225 (16.2)	265 (19.1)	322 (23.2)	
6	1 (0.0)		1 (0.1)			

(*Continued*)

https://doi.org/10.2147/IJGM.S467156 DovePress

Table 2 (Continued).

Variables	Total (N=5,541)	Q1 (<4.464) (N=1,386)	Q2 (4.464–5.417) (N=1,385)	Q3 (5.417–7.035) (N=1,384)	Q4 (≥7.035) (N=1,386)	*P*-value
TOAST, n (%)						0.060
Large-artery atherosclerosis	1418 (25.6)	324 (23.4)	340 (24.5)	391 (28.3)	363 (26.2)	
Cardioembolism	397 (7.2)	117 (8.4)	98 (7.1)	90 (6.5)	92 (6.6)	
Small-vessel occlusion	1157 (20.9)	276 (19.9)	294 (21.2)	290 (21.0)	297 (21.4)	
Other determined etiology	85 (1.5)	30 (2.2)	22 (1.6)	18 (1.3)	15 (1.1)	
Undetermined etiology	2484 (44.8)	639 (46.1)	631 (45.6)	595 (43.0)	619 (44.7)	

Table 3 Baseline Laboratory Data of the Patients According to Quartiles of Serum Glucose-Phosphate Ratio Level

Variables	Total (N=5,541)	Q1 (<4.464) (N=1,386)	Q2 (4.464–5.417) (N=1,385)	Q3 (5.417–7.035) (N=1,384)	Q4 (≥7.035) (N=1,386)	*P*-value
Laboratory parameters, (Mean±SD)						
Hemoglobin, g/L	141.3±16.7	139.1±17.2	141.1±16.2	141.6±16.5	143.4±16.7	<0.001
Serum glucose, mmol/L	6.5±2.6	4.8±0.6	5.3±0.7	6.1±1.1	9.7±3.3	<0.001
Serum phosphate, mmol/L	1.1±0.2	1.3±0.2	1.1±0.1	1.0±0.2	1.0±0.2	<0.001
Serum calcium, mmol/L	2.3±1.4	2.2±0.1	2.3±2.8	2.2±0.2	2.2±0.2	0.041
Serum potassium, mmol/L	3.9±0.4	3.9±0.4	3.9±0.4	3.9±0.4	3.9±0.4	0.099
Serum albumin, g/L	40.4±4.0	40.0±4.1	40.2±3.8	40.6±4.0	40.7±4.2	<0.001
Serum creatinine, μmol/L	74.0±31.4	75.7±45.9	74.7±23.9	74.9±25.1	70.7±25.0	<0.001
eGFR, mL/min/1.73 m2	100.2±33.7	100.2±34.6	99.6±32.8	99.2±38.3	101.9±28.4	<0.001
Total cholesterol, mmol/L	4.3±1.3	4.3±1.2	4.2±1.2	4.3±1.2	4.5±1.4	<0.001
LDL cholesterol, mmol/L	2.6±1.1	2.6±1.1	2.6±1.1	2.6±1.1	2.6±1.1	0.371
HDL cholesterol, mmol/L	1.1±0.3	1.2±0.3	1.1±0.3	1.1±0.3	1.1±0.3	0.015
Triglycerides, mmol/L	1.6±1.2	1.5±0.8	1.5±1.0	1.6±0.9	1.9±1.7	<0.001

Abbreviations: BMI, body mass index; CHD, coronary heart disease; NIHSS, National Institutes of Health Stroke Scale; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; mRS, modified Rankin Scale score; TOAST, Trial of org 10172 in acute stroke Treatment; Q, Quartiles; IQR, interquartile range; and SD, standard deviation.

Association of Serum Glucose-Phosphate Ratio with Stroke Severity

Table 2, compared with patients with lower serum glucose-phosphate ratio, patients with higher levels tended to have higher proportions of moderate to severe stroke ($P<0.001$). Figure 2 showed that, with increasing quartiles of serum glucose-phosphate ratio, the number of mild AIS patients significantly declined, and the number of moderate and severe stroke participants raised.

Serum Glucose-Phosphate Ratio Level and Clinical Outcomes at One Year

Table 4 showed the one-year incidences of clinical outcomes among the eligible participants. In the lowest serum glucose-phosphate ratio quartile group, the incidence rates of all statuses, including poor functional outcomes, recurrent stroke, and all-cause mortality, were 10.1%, 7.3%, and 1.4%, respectively. Compared Q1 with Q4, the rates of poor functional outcomes and recurrent stroke increased by serum glucose-phosphate ratio quartiles ($P = 0.002$ for poor functional outcomes; $P = 0.006$ for recurrent stroke). There was no significant difference in all-cause mortality among the groups ($P = 0.541$).

Association Between Serum Glucose-Phosphate Ratio Levels and One Year Clinical Outcomes

Multivariate regression analysis was used to evaluate the association between serum glucose-phosphate ratio and one-year clinical outcomes in AIS patients (Table 5). Compared with the participants in the lowest quartile of serum glucose-phosphate ratio (<4.464), those in the top quartile (≥7.035) had a 1.44-fold increased risk of 1-year recurrent stroke (HR, 1.44; 95% CI, 1.08–1.92) and a 1.67-fold risks of 1-year poor functional outcome (OR, 1.67; 95% CI, 1.28–2.17) after adjusting age, sex, BMI, and vascular risks (including a history of stroke, hypertension, DM, hypercholesterolemia, CHD, current or previous smoking, and heavy drinking). However, the serum glucose-phosphate ratio at admission was not significantly related to all-cause death at one year, and the adjusted HRs (95% CI) of the top (≥7.035) quartile was 1.05 (0.51–2.16, $P = 0.896$).

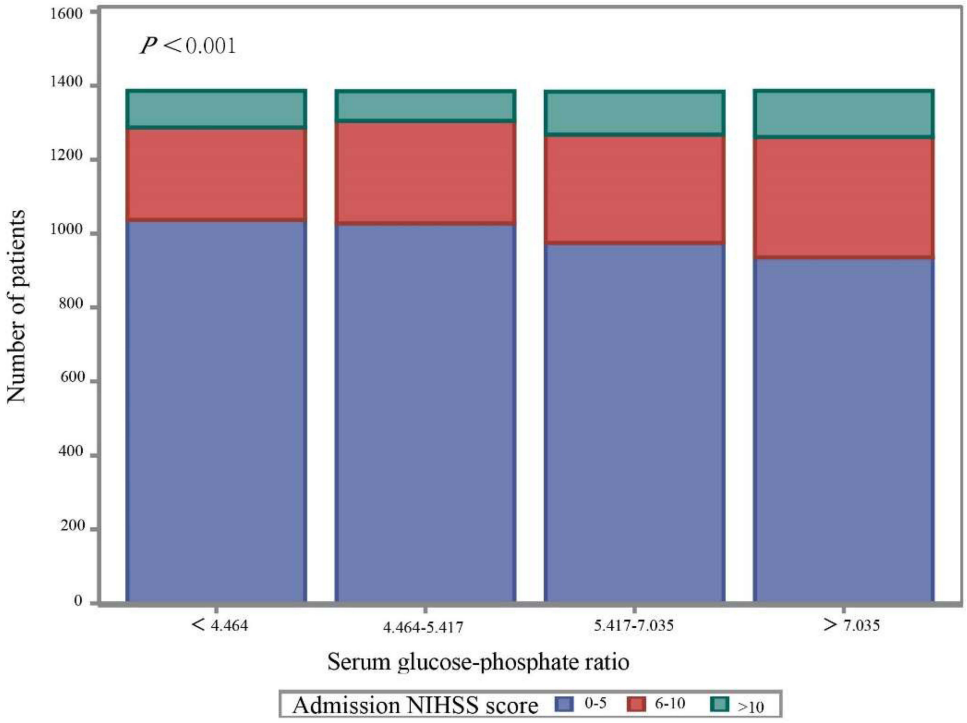

Figure 2 Relationship between serum glucose-phosphate ratio and stroke severity assessed by NIHSS score among patients with acute ischemic stroke. Patients were divided into quartiles according to serum glucose-phosphate ratio.
Abbreviation: NIHSS, National Institutes of Health Stroke Scale.

The Dose–Response Relationship Between Serum Glucose-Phosphate Ratio and Clinical Outcomes in Patients with AIS

The restricted cubic spline (RCS) was further to explore possible non-linear relationships of serum glucose-phosphate ratio and clinical outcomes in patients with AIS. Analysis of the relationship between serum glucose-phosphate ratio and poor outcome showed a significant overall *P*-value, at the same time, the non-linear association was not marginally significant (Figure 3A, *P* for overall = 0.005, *P* for non-linearity = 0.548). We did not find any non-linear association between serum glucose-phosphate ratio and recurrent stroke (Figure 3B, *P* for overall = 0.250, *P* for non-linearity = 0.563), with similar results for the relationship between serum glucose-phosphate ratio and all-cause death (Figure 3C, *P* for overall = 0.246, *P* for non-linearity = 0.274).

Discussion

This study provided valuable insights into the association between admission serum glucose-phosphate ratio and the severity and one-year clinical outcomes of AIS patients. The data highlight the potential clinical significance of this ratio as a prognostic biomarker for AIS and offer several important implications for stroke management and research.

Table 4 Outcomes According to Quartiles of Serum Glucose-Phosphate Ratio Level at One Year

Outcomes	Overall	Quartile of serum glucose-phosphate ratio				*P*-value
		Q1 (<4.464)	Q2 (4.464–5.417)	Q3 (5.417–7.035)	Q4 (≥7.035)	
Poor functional outcome, n (%)	713(12.9%)	140 (10.1%)	173(12.5%)	180(13.0%)	220 (15.9%)	0.002
Recurrent stroke, n (%)	485 (8.8%)	101(7.3%)	109(7.9%)	125(9.0%)	150 (10.8%)	0.006
All-cause mortality, n (%)	69 (1.2%)	19 (1.4%)	12 (0.9%)	19 (1.4%)	19 (1.4%)	0.540

Abbreviation: Q, quartiles.

Table 5 Association of Serum Glucose-Phosphate Ratio Levels with Clinical Outcomes

	Unadjusted	*P*-value	Model1	*P*-value	Model 2	*P*-value
	OR/HR(95% CI)		OR/HR(95% CI)		OR/HR (95% CI)	
Poor functional outcome						
Q1 (<4.464)	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2 (4.464–5.417)	1.27 (1.00–1.61)	0.048	1.19 (0.94–1.52)	0.156	1.19 (0.90–1.52)	0.161
Q3 (5.417–7.035)	1.33 (1.05–1.68)	0.018	1.18 (0.93–1.50)	0.180	1.22 (0.95–1.56)	0.119
Q4 (≥7.035)	1.68 (1.34–2.10)	<0.001	1.57 (1.25–1.98)	<0.001	1.67 (1.28–2.17)	<0.001
Recurrent stroke						
Q1 (<4.464)	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2 (4.464–5.417)	1.08 (0.83–1.42)	0.564	1.07 (0.82–1.41)	0.603	1.05 (0.80–1.38)	0.715
Q3 (5.417–7.035)	1.25 (0.96–1.62)	0.098	1.23 (0.94–1.60)	0.131	1.21 (0.92–1.59)	0.164
Q4(≥7.035)	1.52(1.18–1.95)	<0.001	1.50(1.16–1.93)	0.002	1.44(1.08–1.92)	0.013
All-cause death						
Q1 (<4.464)	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2 (4.464–5.417)	0.63 (0.31–1.30)	0.210	0.55 (0.26–1.13)	0.104	0.55 (0.26–1.13)	0.104
Q3 (5.417–7.035)	1.00 (0.53–1.90)	0.991	0.81 (0.43–1.55)	0.532	0.87 (0.45–1.67)	0.676
Q4 (≥7.035)	1.00 (0.53–1.88)	0.994	0.87 (0.46–1.65)	0.670	1.05 (0.51–2.16)	0.896

Notes: Model 1: adjusted variables included age, sex. Model 2: adjusted variables included age, sex, BMI, history of stroke, hypertension, diabetes mellitus, hypercholesterolemia, CHD, current or previous smoking and heavy drinker.
Abbreviations: BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; HR, hazard ratios; OR, odds ratios; Q, quartiles.

The current study findings suggested that AIS patients with higher serum glucose-phosphate ratios were more likely to present with moderate to severe strokes upon admission and had a greater likelihood of experiencing poor functional outcomes and recurrent strokes at the one-year follow-up. This association was in line with previous research linking hyperglycemia[14–17]and phosphate disturbances[18–23] to worsened neurological outcomes. The mechanisms involved may include: hyperglycemia, by increasing blood–brain barrier permeability and triggering post-stroke inflammation, exacerbates brain injury caused by cerebral ischemia/reperfusion[14,15]. Simultaneously, hyperglycemia may induce neurotoxicity and procoagulant states, worsening blood supply issues in the ischemic areas, and aggravating ischemic brain injury[16]. Furthermore, elevated blood glucose intensifies anaerobic glycolysis under ischemic conditions, leading to lactic acidosis. Increased blood glucose speeds up anaerobic glycolysis, causing an accumulation of lactic acid, exacerbating damage to multiple organs. The potential mechanisms between hypophosphatemia and AIS may include: firstly, lower serum phosphate levels may result in more severe strokes as phosphate plays a crucial role in energy production and the nutrition of nervous tissue. Secondly, low phosphate levels may impact brain vascular biology as phosphate is a component of cell membranes.[19] Thirdly, lower serum phosphate levels are associated with hypertension and metabolic syndrome,[24] indicating signs of malnutrition and low physical activity.

The multivariate regression analysis adjusted for relevant factors further solidified the association between high serum glucose-phosphate ratios and one-year adverse clinical outcomes. These findings imply that serum glucose-phosphate ratio can add to the predictive accuracy of clinical models for AIS prognosis, potentially helping to identify high-risk patients who may benefit from more aggressive therapeutic strategies.

The restricted cubic spline analysis provided additional insights into the dose–response relationship between serum glucose-phosphate ratio and clinical outcomes. While the overall P-values indicated significant associations, non-linear

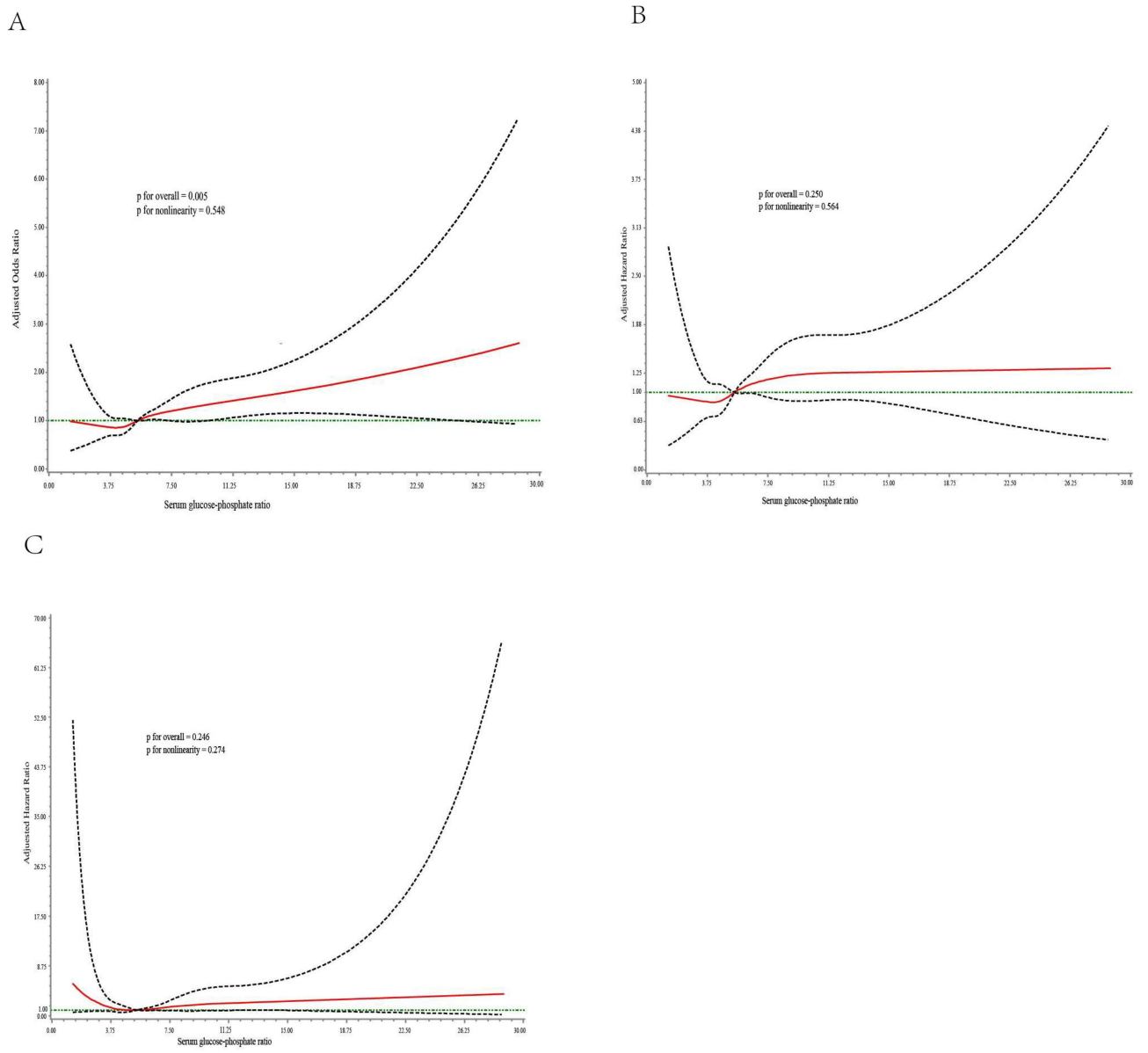

Figure 3 Restricted cubic spline analysis of the association of serum glucose-phosphate ratio levels at admission with clinical outcomes in acute ischemic stroke patients. ORs or HRs were obtained by restricted cubic spline logistic or COX regression after adjustment for confounding factors, models were adjusted for conventional risk factors (age, sex, BMI, history of stroke, hypertension, diabetes mellitus, hypercholesterolemia, CHD, current or previous smoking, and heavy drinker). Adjusted odds ratios (ORs) and hazard ratio (HRs) are indicated by the solid line, and 95% confidence intervals are indicated by the dashed lines. The knots placed were placed at the fifth, 25th, 50th, 75th, and 95th percentiles and the median value of serum glucose-phosphate ratio (5.417) as the reference point. (**A**) Poor functional outcome. (**B**) Recurrent stroke. (**C**) All-cause death.

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; HR, hazard ratios; OR, odds ratios.

relationships were not observed, suggesting that the relationship between serum glucose-phosphate ratio and poor outcome is primarily linear. This further supports the notion that serum glucose-phosphate ratio may serve as a continuous predictor of AIS outcomes.

Considering the discussion on hyperglycemia and serum phosphate levels, the combined effect of serum phosphate and glucose concentration makes the serum glucose-phosphate ratio a readily available and non-invasive biomarker for risk stratification in AIS patients. It could be potentially used to identify patients at higher risk of poor outcomes, allowing for more targeted treatment strategies and interventions. It also could be used to improve prognostication, aiding in informed decision-making regarding patient care.

However, this study has certain limitations. Firstly, the exclusion of patients due to missing key covariates and follow-up data may have introduced selection bias. Additionally, variability in acute ischemic stroke treatment protocols across participating centers may have influenced the association between serum glucose-phosphate ratio and stroke outcomes. Secondly, we only assessed the serum glucose-phosphate ratio at admission, which reflects the initial status of AIS. Future research should explore the impact of dynamic changes in this ratio on AIS progression. Moreover, while our findings may have general applicability, the predictive accuracy of this biomarker across distinct populations (eg, age groups and ethnic backgrounds) remains uncertain. Differences in metabolic conditions and neuroprotective mechanisms across age groups could alter the clinical relevance of the serum glucose-phosphate ratio. Lastly, given that this study focused on a Chinese AIS population, validation in other populations is warranted to confirm broader applicability.

This study provides a new perspective on the use of the serum glucose-phosphate ratio in AIS. Our findings indicate that this ratio not only effectively predicts stroke severity and clinical outcomes but also shows promise in assessing recurrence risk. This innovation offers clinicians a valuable tool for managing stroke patients, particularly in personalized treatment strategies. Future research should explore its applicability across different populations and treatment contexts to enhance its clinical use. Specifically, conducting longitudinal studies to assess the dynamic changes in the serum glucose-phosphate ratio over time in stroke patients could provide deeper insights into its prognostic value. Additionally, research focusing on specific populations, such as different age groups and ethnic backgrounds, will help determine the predictive accuracy of this biomarker and its relevance in diverse clinical settings.

Conclusions

In summary, our results first revealed that the baseline serum glucose-phosphate ratio was related to stroke severity and positively associated with poor functional outcomes and recurrent stroke. Future research should focus on validating the utility of serum glucose-phosphate ratio in larger and more diverse patient populations and exploring the underlying mechanisms connecting this ratio to AIS prognosis. In clinical practice, because of the convenience and availability of serum glucose and phosphate in almost all hospitals, this biomarker may become a valuable tool in assessment for AIS patients, helping clinicians identify those at higher risk for severe strokes and adverse long-term outcomes.

Data Sharing Statement

Data are available in a public, open access repository.

Acknowledgments

We appreciated all the study participants and their relatives for supporting the CNSR-III study. We also thank all the CNSR-III investigators for their contributions to patient recruitment.

Author Contributions

Jie Li and Wenyang Ma contributed equally to this work and shared first authorship. 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

Top Talent Support Program for young and middle-aged people of Wuxi Health Committee, Grant/Award Number: HB2023109; Yixing Science and Technology Projects, Grant/Award Number: 2023SF19; The Foundation of Clinical Science and Technology of Jiangsu, Grant/Award Number: Z2021001.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Ding Q, Liu S, Yao Y, et al. Global, regional, and national burden of ischemic stroke, 1990–2019. *Neurology*. 2022;98:e279–e90. doi:10.1212/WNL.0000000000013115
2. Kim JH, Kim SY, Kim B, et al. Prospects of therapeutic target and directions for ischemic stroke. *Pharmaceuticals*. 2021;14:321. doi:10.3390/ph14040321
3. 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
4. Desilles JP, Meseguer E, Labreuche J, et al. Diabetes mellitus, admission glucose, and outcomes after stroke thrombolysis: a registry and systematic review. *Stroke*. 2013;44:1915–1923. doi:10.1161/STROKEAHA.111.000813
5. Rinkel LA, Nguyen TTM, Guglielmi V, et al. High admission glucose is associated with poor outcome after endovascular treatment for ischemic stroke. *Stroke*. 2020;51:3215–3223. doi:10.1161/STROKEAHA.120.029944
6. Merlino G, Smeralda C, Gigli GL, et al. Stress hyperglycemia is predictive of worse outcome in patients with acute ischemic stroke undergoing intravenous thrombolysis. *J Thromb Thrombolysis*. 2021;51:789–797. doi:10.1007/s11239-020-02252-y
7. Zhang JF, Jing J, Meng X, et al. Serum phosphate and 1-year outcome in patients with acute ischemic stroke and transient ischemic attack. *Front Neurol*. 2021;12:652941. doi:10.3389/fneur.2021.652941
8. Zhang D, Zhuang Z, Wei Y, et al. Association of admission serum glucose-phosphate ratio with severity and prognosis of aneurysmal subarachnoid hemorrhage. *World Neurosurg*. 2019;127:e1145–e51. doi:10.1016/j.wneu.2019.04.071
9. Qiu SZ, Zheng GR, Chen B, et al. Prognostic value of admission serum glucose-phosphate ratio in predicting the 6-month outcome of patients with severe traumatic brain injury: a retrospective study. *Clin Chim Acta*. 2020;510:659–664. doi:10.1016/j.cca.2020.08.038
10. Wang Y, Jing J, Meng X, et al. The third china national stroke registry (CNSR-III) for patients with acute ischaemic stroke or transient ischaemic attack: design, rationale and baseline patient characteristics. *Stroke Vasc Neurol*. 2019;4:158–164.
11. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in acute stroke treatment. *Stroke*. 1993;24:35–41. doi:10.1161/01.STR.24.1.35
12. Xu J, Cheng A, Song B, et al. Trimethylamine N-oxide and stroke recurrence depends on ischemic stroke subtypes. *Stroke*. 2022;53:1207–1215. doi:10.1161/STROKEAHA.120.031443
13. Zhang P, Wang G, Gui Y, et al. Serum vaspin as a predictor of severity and prognosis in acute ischemic stroke patients. *Nutr Neurosci*. 2022;25:737–745. doi:10.1080/1028415X.2020.1806191
14. Guo Y, Dong L, Gong A, et al. Damage to the blood-brain barrier and activation of neuroinflammation by focal cerebral ischemia under hyperglycemic condition. *Int J Mol Med*. 2021;48:142. doi:10.3892/ijmm.2021.4975
15. Wicha P, Das S, Mahakkanukrauh P. Blood-brain barrier dysfunction in ischemic stroke and diabetes: the underlying link, mechanisms and future possible therapeutic targets. *Anat Cell Biol*. 2021;54:165–177. doi:10.5115/acb.20.290
16. Denorme F, Portier I, Kosaka Y, et al. Hyperglycemia exacerbates ischemic stroke outcome independent of platelet glucose uptake. *J Thromb Haemost*. 2021;19:536–546. doi:10.1111/jth.15154
17. Wang A, Tian X, Gu H, et al. Electrolytes and clinical outcomes in patients with acute ischemic stroke or transient ischemic attack. *Ann Transl Med*. 2021;9:1069. doi:10.21037/atm-21-741
18. Zhong C, You S, Chen J, et al. Serum alkaline phosphatase, phosphate, and in-hospital mortality in acute ischemic stroke patients. *J Stroke Cerebrovasc Dis*. 2018;27:257–266. doi:10.1016/j.jstrokecerebrovasdis.2017.08.041
19. Yamada S, Tsuruya K, Taniguchi M, et al. Association between serum phosphate levels and stroke risk in patients undergoing hemodialysis: the Q-cohort study. *Stroke*. 2016;47:2189–2196. doi:10.1161/STROKEAHA.116.013195
20. Suzuki S, Egi M, Schneider AG, et al. Hypophosphatemia in critically ill patients. *J Crit Care*. 2013;28:536.e9–19. doi:10.1016/j.jcrc.2012.10.011
21. Jia J, Guo J, Liu X, et al. Impact of serum phosphate on severity and functional outcomes after ischemic stroke in young adults. *Nutr Metab Cardiovasc Dis*. 2022;32:2553–2560. doi:10.1016/j.numecd.2022.08.008
22. Talebi A, Amirabadizadeh A, Nakhaee S, et al. Cerebrovascular disease: how serum phosphorus, vitamin D, and uric acid levels contribute to the ischemic stroke. *BMC Neurol*. 2020;20:116. doi:10.1186/s12883-020-01686-4
23. Kim J, Song TJ, Song D, et al. Serum alkaline phosphatase and phosphate in cerebral atherosclerosis and functional outcomes after cerebral infarction. *Stroke*. 2013;44:3547–3549. doi:10.1161/STROKEAHA.113.002959
24. Park W, Kim BS, Lee JE, et al. Serum phosphate levels and the risk of cardiovascular disease and metabolic syndrome: a double-edged sword. *Diabet Res Clin Pract*. 2009;83:119–125. doi:10.1016/j.diabres.2008.08.018