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GLUCOSE-TO-PLATELET RATIO AS A BIOCHEMICAL INDICATOR OF METABOLIC–COAGULATION IMBALANCE AND MORTALITY RISK IN CRITICALLY ILL PATIENTS WITH ISCHEMIC STROKE: A MIMIC-IV COHORT STUDY

ODNOS GLUKOZE I TROMBOCITA KAO BIOHEMIJSKI INDIKATOR METABOLIČKO-KOAGULACIONE NERAVNOTEŽE I RIZIKA OD SMRTNOSTI KOD KRITIČNO BOLESNIH PACIJENATA SA ISHEMIJSKIM MOŽDANIM UDAROM: KOHORTNA STUDIJA MIMIC-IV

Jie Peng[1,2], Xingzhan Zhang[2], Huanhuan Wu[2], Hongzhi Chen[2], Jianbin Guan[1], Zhanguo Liu[1,], Xingxing Liu[1,*]*

[1]Department of Critical Care Medicine, Zhujiang Hospital, Southern Medical University, Guangzhou 510280, Guangdong Province, China
[2]Department of Intensive Care Unit, The People's Hospital Medical Group of Xiangzhou, Zhuhai 519000, Guangdong Province, China

Summary

Background: Early identification of high-risk patients with ischemic stroke in the intensive care unit (ICU) remains challenging. Biochemical markers reflecting the interplay between metabolic stress and coagulation–inflammatory pathways may provide improved prognostic value. The glucose-to-platelet ratio (GPR), a composite index derived from routine laboratory parameters, has emerged as a potential indicator of systemic metabolic–coagulation imbalance; however, its prognostic significance in critically ill ischemic stroke patients has not been fully elucidated.
Methods: This retrospective cohort study was conducted using the MIMIC-IV database. Adult patients with ischemic stroke undergoing their first ICU admission and with a length of stay ≥24 hours were included (n = 3686). After excluding patients with missing exposure data, 3536 individuals were analyzed. GPR was calculated as the ratio of the first measured blood glucose (mg/dL) to platelet count ($\times 10^9$/L) within 24 hours of ICU admission. Participants were categorized into quartiles according to GPR levels. Kaplan–Meier survival analysis, multivariable Cox proportional hazards models, and restricted cubic spline analyses were employed to evaluate the association between GPR and 28- and 90-day all-cause mortality.
Results: In fully adjusted models, each unit increase in GPR was independently associated with increased risks of 28-day mortality (HR 1.11, 95% CI 1.03–1.21; P=0.009)

Kratak sadržaj

Uvod: Rana identifikacija pacijenata sa visokim rizikom od ishemijskog moždanog udara na odeljenju intenzivne nege (JIN) ostaje izazovna. Biohemijski markeri koji odražavaju interakciju između metaboličkog stresa i koagulaciono-inflamatornih puteva mogu pružiti poboljšanu prognostičku vrednost. Odnos glukoze i trombocita (GPR), kompozitni indeks izveden iz rutinskih laboratorijskih parametara, pojavio se kao potencijalni indikator sistemskog metaboličko-koagulacionog disbalansa; međutim, njegov prognostički značaj kod kritično obolelih pacijenata sa ishemijskim moždanim udarom nije u potpunosti razjašnjen.
Metode: Ova retrospektivna kohortna studija sprovedena je korišćenjem baze podataka MIMIC-IV. Uključeni su odrasli pacijenti sa ishemijskim moždanim udarom koji su prvi put primljeni na intenzivnu negu i sa dužinom boravka ≥24 sata (n = 3686). Nakon isključivanja pacijenata sa nedostajućim podacima o ekspoziciji, analizirano je 3536 osoba. GPR je izračunat kao odnos prve izmerene glukoze u krvi (mg/dL) i broja trombocita ($\times$109/L) u roku od 24 sata od prijema na intenzivnu negu. Učesnici su kategorisani u kvartile prema nivoima GPR-a. Kaplan-Majerova analiza preživljavanja, multivarijantni Koksovi modeli proporcionalnih rizika i ograničene kubne splajn analize korišćene su za procenu povezanosti između GPR-a i mortaliteta od svih uzroka u roku od 28 i 90 dana.

Address for correspondence:
Zhanguo Liu
e-mail: zhguoliu@163.com
Xingxing Liu
e-mail: alph_12129@163.com

and 90-day mortality (HR 1.09, 95% CI 1.01–1.17; P=0.019). Compared with the lowest quartile, patients in the highest GPR quartile exhibited significantly elevated risks of 28-day (HR 1.37, 95% CI 1.08–1.75; P=0.010) and 90-day mortality (HR 1.25, 95% CI 1.02–1.54; P=0.034). Kaplan–Meier curves demonstrated significantly reduced survival probabilities with increasing GPR levels (log-rank P<0.0001). Restricted cubic spline analyses confirmed a significant positive association between GPR and mortality without evidence of nonlinearity.

Conclusion: GPR was independently associated with short- and intermediate-term mortality in critically ill patients with ischemic stroke. As an accessible marker of metabolic–coagulation dysregulation, elevated GPR may help identify patients who warrant closer hemodynamic, metabolic, and organ-function monitoring.

Keywords: ischemic stroke, glucose-to-platelet ratio, biochemical marker, metabolic–coagulation imbalance, mortality

Rezultati: U potpuno prilagođenim modelima, svako poveć anje GPR-a za jednu jedinicu bilo je nezavisno povezano sa povećanim rizikom od mortaliteta u roku od 28 dana (HR 1,11, 95% CI 1,03–1,21; P=0,009) i mortaliteta u roku od 90 dana (HR 1,09, 95% CI 1,01–1,17; P=0,019). U poređenju sa najnižim kvartilom, pacijenti u najvišem kvartilu GPR-a pokazali su značajno povećane rizike od mortaliteta u roku od 28 dana (HR 1,37, 95% CI 1,08–1,75; P=0,010) i 90 dana (HR 1,25, 95% CI 1,02–1,54; P=0,034). Kaplan-Majerove krive su pokazale značajno smanjene verovatnoće preživljavanja sa povećanjem nivoa GPR-a (log-rank P<0,0001). Analize ograničenih kubičnih splajnova potvrdile su značajnu pozitivnu vezu između GPR-a i mortaliteta bez dokaza o nelinearnosti.

Zaključak: Povišeni GPR je nezavisno bio povezan sa kratkoročnim i srednjoročnim mortalitetom kod kritično obolelih pacijenata sa ishemijskim moždanim udarom. Kao pristupačan marker metaboličko-koagulacione disregulacije, povišen GPR može pomoći u identifikaciji pacijenata kojima je potrebno pažljivije praćenje hemodinamskih, metaboličkih i organskih funkcija.

Ključne reči: ishemijski moždani udar, odnos glukoze i trombocita, biohemijski marker, metaboličko-koagulacioni disbalans, mortalitet

Introduction

Ischemic stroke, caused by a blockage in cerebral arteries, is a major global contributor to mortality and chronic disability (1). Despite advancements in acute reperfusion therapy and intensive care, patients with ischemic stroke face significant short- and intermediate-term mortality risks during ICU stays (2). In addition to primary neurological damage, systemic metabolic disturbances, inflammatory responses, and coagulation abnormalities significantly influence the acute phase and progression of stroke (3–5). However, developing a straightforward and effective method to quantify these complex physiological disruptions early in the ICU remains a significant clinical challenge.

Stress-induced hyperglycemia is common in ischemic stroke patients, even those without prior diabetes diagnosis (6). Acute hyperglycemia is linked to increased infarct size, blood-brain barrier disruption, hemorrhagic transformation, and worse neurological outcomes (7). Additionally, platelet abnormalities, especially thrombocytopenia, are connected to negative post-stroke outcomes (8). Platelets are involved in inflammatory signaling, immune regulation, and endothelial repair, in addition to their functions in hemostasis and thrombosis. A reduced platelet count may indicate excessive platelet activation and consumption, reflecting dysregulation of the coagulation–inflammation axis (9). However, hyperglycemia and platelet abnormalities have usually been examined as separate risk factors, and their potential synergistic effects have not been adequately quantified.

In recent years, composite biomarkers have attracted increasing attention in risk assessment for critically ill patients. By integrating multiple routine indicators, such biomarkers may provide a more comprehensive reflection of physiological stress without increasing testing burden. The glucose-to-platelet ratio (GPR) is a composite index designed to reflect both metabolic stress and coagulation disturbances (10). Although direct evidence on GPR in other acute and critical illnesses remains limited, studies in conditions such as sepsis and acute myocardial infarction have highlighted the prognostic importance of glucose dysregulation and platelet-related abnormalities, supporting the biological rationale for integrating these two dimensions into a single marker. In ischemic stroke, however, prior research on GPR remains sparse and has mainly focused on hemorrhagic transformation rather than mortality (10). Thus, a comprehensive assessment of GPR in critically ill patients with ischemic stroke is still absent, and its association with short- and intermediate-term mortality, as well as its dose–response pattern, has not been well defined.

This retrospective cohort study examined the link between the glucose-to-platelet ratio during the initial 24 hours of ICU admission and 28- and 90-day all-cause mortality in critically ill ischemic stroke patients using the MIMIC-IV database. Multivariable Cox regression, restricted cubic spline modeling, and subgroup analyses were applied to evaluate the independence, stability, and possible nonlinear pattern of this relationship. The glucose-to-platelet ratio was examined as an accessible clinical marker for early risk assessment.

Materials and Methods

Data source and study design

This retrospective cohort study employed the MIMIC-IV database (version 3.1) and followed the STROBE guidelines for designing and reporting observational studies (11). The MIMIC-IV database, created by MIT's Laboratory for Computational Physiology in partnership with Beth Israel Deaconess Medical Center, includes deidentified clinical data from more than 70,000 ICU admissions spanning 2008 to 2022. It encompasses demographics, diagnostic codes, vital signs, laboratory results, treatments, and clinical outcomes (12).

Data extraction was conducted by the first author, Jie Peng, after completion of the required online training and receipt of authorization for database access. Structured Query Language was implemented in PostgreSQL 13.7.2, and Navicat Premium 16 was used for data extraction and management. As MIMIC-IV data is completely deidentified, the study did not include direct patient intervention or follow-up. Consequently, ethics committee approval and informed consent were waived in accordance with the Declaration of Helsinki and applicable data use agreements.

Study population

Adult patients aged 18 and older undergoing their first ICU admission were identified from the MIMIC-IV database. Patients with ischemic stroke were identified using predefined ICD-9-CM and ICD-10-CM diagnosis codes recorded in the MIMIC-IV database, including ICD-9-CM codes 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, and 436, as well as ICD-10-CM code I63.x. As this was a retrospective database study, case ascertainment relied on database-recorded diagnostic coding rather than additional manual adjudication based on bedside clinical or imaging criteria. Among patients with more than one ICU admission, only the initial ICU stay was retained for analysis. Exclusion criteria encompassed ICU stays shorter than 24 hours and absence of blood glucose or platelet measurements during the first 24 hours after ICU admission.

Data collection and variable definitions

Initial data gathered within 24 hours of ICU admission encompassed demographics (age, sex, race), comorbidities, severity scores, vital signs, lab results, and treatment measures.

Comorbidities, determined via International Classification of Diseases codes, encompassed myocardial infarction, congestive heart failure, diabetes, dementia, chronic lung disease, malignancy, hypertension, and sepsis. The overall comorbidity burden was quantified using the Charlson Comorbidity Index (CCI). Illness severity was evaluated using the SOFA score and GCS. Vital signs recorded included heart rate, respiratory rate, mean arterial pressure, body temperature, and oxygen saturation. Laboratory evaluations included counts of white and red blood cells, hemoglobin, hematocrit, and platelets, along with measurements of international normalized ratio (INR), prothrombin time (PT) and partial thromboplastin time (PTT), creatinine, blood urea nitrogen, potassium, calcium, bicarbonate, and blood glucose levels. Treatment-related variables included mechanical ventilation, continuous renal replacement therapy, vasoactive medications, and the administration of aspirin, clopidogrel, ticagrelor, statins, and insulin.

All variables were sourced from data gathered during the first 24 hours after ICU admission. When multiple measurements were available for a given variable, the first measurement obtained within this 24-hour window was used. Variables with more than 20% missing data were excluded from further analyses to reduce bias (*Supplementary Table S1*). For variables with less than 20% missing data, multiple imputation was performed using the random forest method with the mice package in R, resulting in five imputed datasets. Estimates from the imputed datasets were combined using Rubin's rules. The exposure and outcome variables were not entered into the imputation procedure (13, 14). For supplementary assessment of the imputation procedure, five continuous variables with comparatively higher missingness were selected for additional descriptive and visual evaluation as a practical plausibility check of the imputed data.

Biochemical data acquisition and definition

Biochemical parameters were systematically extracted from laboratory records within the first 24 hours following ICU admission, reflecting the early metabolic and hematological status of critically ill patients. Key biochemical variables included blood glucose, platelet count, and additional routine laboratory indices related to metabolic function, coagulation status, and systemic physiological balance, such as white blood cell count, hemoglobin, hematocrit, creatinine, blood urea nitrogen, electrolytes, and coagulation parameters (INR, prothrombin time, and partial thromboplastin time). Blood glucose levels were measured as part of routine metabolic monitoring and were considered an indicator of acute metabolic stress and neuroendocrine activation. Platelet count, obtained from standard hematological assays, was regarded as a surrogate marker reflecting coagulation activity, inflammatory response, and endothelial dysfunction. To better characterize the integrated metabolic–coagulation state, a composite biochemical index, the glucose-to-platelet ratio (GPR), was calculated by dividing

Table S1 Missing variables and their percentages.

Variable	Miss. freq	Miss. percentage %
Age	0	0
APSIII	0	0
Aspirin	0	0
Bicarbonate	1	0.0283
BUN	1	0.0283
Calcium	203	5.741
Charlson Comorbidity Index	0	0
Chloride	1	0.0283
Chronic Pulmonary Disease	0	0
Clopidogrel	0	0
Congestive Heart Failure	0	0
Creatinine	0	0
CRRT	0	0
Crrt days	0	0
DBP	252	7.1267
Dementia	0	0
Diabetes	0	0
GCS	4	0.1131
GPR	0	0
Heart Rate	4	0.1131
Hematocrit	2	0.0566
Hemoglobin	3	0.0848
Input amount	607	17.1663
INR	307	8.6821
Insulin	0	0
Liquid balance	661	18.6934
LODS	0	0
Los hospital	0	0
Los icu	0	0
Malignant Cancer	0	0
MAP	252	7.1267
Myocardial Infarct	0	0
OASIS	0	0
Output amount	74	2.0928
Platelet	0	0
Potassium	0	0
PT	307	8.6821
PTT	321	9.0781
Race	0	0
RBC	3	0.0848
Hypertension	0	0
Resp_Rate	13	0.3676
Rheumatic Disease	0	0
SBP	252	7.1267
Sepsis	0	0
Sex	0	0
SIRS	0	0
Sodium	0	0
SOFA	4	0.1131
Spo2	4	0.1131
Statins	0	0
Temperature	60	1.6968
Ticagrelor	0	0
Urine output	105	2.9695
Vasoactive	0	0
Ventilator	0	0
Ventilator hours	0	0
WBC	2	0.0566

PTT: Partial thromboplastin time, INR: International normalized ratio, PT: Prothrombin time, RR: Respiratory Rate, RBC: Red blood cell count, WBC: White blood cell count, BUN: Blood urea nitrogen, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SOFA: Sequential organ failure assessment, GCS: Glasgow Coma Scale. GPR, glucose-to-platelet ratio; MAP, mean arterial pressure; WBC, white blood cell count; RBC, red blood cell count; CRRT, continuous renal replacement therapy.

blood glucose (mg/dL) by platelet count ($\times 10^9$/L). This ratio was designed to capture the interplay between metabolic dysregulation and thrombo-inflammatory processes, providing a simplified yet biologically meaningful indicator of systemic stress response. All biochemical variables were defined based on the first available measurement within 24 hours after ICU admission to ensure temporal consistency and to reflect the early pathophysiological state. In cases of multiple measurements, the earliest recorded value was selected for analysis.

Exposure variable

The main exposure variable was the glucose-to-platelet ratio (GPR), calculated by dividing the first blood glucose value (mg/dL) within the initial 24 hours post-ICU admission by the initial platelet count ($\times 10^9$/L) during the same timeframe. GPR was evaluated in both continuous and categorical forms. Patients were categorized into GPR quartiles for analysis, using the lowest quartile (Q1) as the reference group.

Outcome

The primary outcomes were all-cause mortality at 28 and 90 days following ICU admission. Follow-up duration was defined from the time of ICU admission to death or to the relevant follow-up time point. Mortality data, covering in-hospital and up to one-year post-discharge periods, were obtained from the MIMIC-IV database (12).

Statistical analysis

Baseline characteristics were described using standard summary statistics. Continuous variables with a normal distribution are expressed as mean (standard deviation, SD) and evaluated using one-way ANOVA. Continuous variables with non-normal distribution are reported as median (interquartile range (IQR)) and assessed using the Kruskal-Wallis test. Categorical variables are presented as counts (percentages) and were compared with the χ^2 test.

Kaplan-Meier curves were used to depict 28-day and 90-day overall survival based on GPR quartiles, with between-group differences assessed using the log-rank test. Cox proportional hazards regression was used to evaluate the link between GPR and all-cause mortality, with findings expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). Three models with increasing levels of adjustment were fitted. Model 1 included no covariate adjustment. Model 2 was adjusted for demographic factors, including age, sex, and race. Model 3 incorporated demographic factors, comorbidities (e.g., myocardial infarction, heart failure, dementia, diabetes, malignancy, hypertension, sepsis), severity indices (Charlson Comorbidity Index, SOFA, GCS), treatments (e.g., mechanical ventilation, renal replacement therapy, vasoactive agents, aspirin, clopidogrel, ticagrelor, statins, insulin), vital signs (heart rate, respiratory rate, mean arterial pressure, oxygen saturation), and laboratory measures (e.g., WBC count, RBC count, hemoglobin, hematocrit, INR, prothrombin time, creatinine, BUN, potassium, calcium, bicarbonate). The selection of covariates was based on clinical relevance, existing literature, and univariable Cox proportional hazards analyses (*Supplementary Table S2*). To assess the influence of extreme exposure values, a sensitivity analysis was performed after excluding patients with GPR values below the 0.5th percentile or above the 99.5th percentile, and the fully adjusted Cox models were repeated. To thoroughly evaluate the relationship between GPR and mortality, GPR was examined as both a continuous and categorical variable, with trend tests performed.

A restricted cubic spline (RCS) was added to the fully adjusted Cox model (Model 3) to evaluate nonlinearity. In line with Harrell's regression modeling strategy, four knots were positioned at the 5th, 35th, 65th, and 95th percentiles of the GPR distribution to enhance flexibility and reduce overfitting. Nonlinearity was evaluated through likelihood ratio tests by comparing models with spline terms to those without, and the corresponding P value for nonlinearity was reported. Subgroup analyses were performed considering age, sex, diabetes, hypertension, sepsis, and insulin use, incorporating interaction terms in the models to evaluate effect modification. Statistical analyses were performed using R software (version 4.2.2), considering a 2-sided P value below .05 as statistically significant.

Results

Study population and GPR grouping

From the MIMIC-IV database, 3686 adult ischemic stroke patients were identified based on predefined inclusion and exclusion criteria, marking their first ICU admission with a minimum stay of 24 hours. After excluding 150 patients with missing blood glucose or platelet measurements within the first 24 hours of ICU admission, the final analytic cohort comprised 3,536 patients. The study flowchart and patient grouping are presented in *Figure 1*.

The study population was categorized into quartiles based on GPR, with 884 patients in each quartile. In the overall cohort, the median GPR was 0.6 (IQR, 0.5–0.9). The median GPR values within

Table S2 Univariable cox regression for 28-day all-cause mortality.

Item	HR(95%CI)	P(Wald's test)
Age (cont. var.)	1.03 (1.03,1.04)	< 0.001
Sex: Female vs male	1.15 (0.99,1.33)	0.071
Race: ref.=white		
Black	0.79 (0.61,1.02)	0.074
Others	1.25 (1.06,1.46)	0.006
Myocardial Infarct: YES vs NO	1.42 (1.19,1.68)	< 0.001
Congestive Heart Failure: YES vs NO	1.45 (1.25,1.69)	< 0.001
Dementia: YES vs NO	1.66 (1.31,2.11)	< 0.001
Chronic Pulmonary Disease: YES vs NO	1.1 (0.92,1.33)	0.292
Diabetes: YES vs NO	1.08 (0.93,1.26)	0.302
Renal Disease: YES vs NO	1.32 (1.12,1.56)	0.001
Malignant Cancer: YES vs NO	1.9 (1.54,2.35)	< 0.001
Charlson Comorbidity Index (cont. var.)	1.17 (1.14,1.19)	< 0.001
SOFA (cont. var.)	1.15 (1.12,1.18)	< 0.001
GCS (cont. var.)	0.93 (0.9,0.95)	< 0.001
Hypertension: YES vs NO	2.04 (1.64,2.53)	< 0.001
Sepsis: YES vs NO	2.55 (2.19,2.97)	< 0.001
Ventilator: YES vs NO	2.3 (1.9,2.79)	< 0.001
CRRT: YES vs NO	2.11 (1.57,2.84)	< 0.001
Vasoactive: YES vs NO	2.02 (1.74,2.35)	< 0.001
Aspirin: YES vs NO	0.71 (0.61,0.82)	< 0.001
Clopidogrel: YES vs NO	0.61 (0.48,0.79)	< 0.001
Ticagrelor: YES vs NO	0.24 (0.08,0.76)	0.015
Statins: YES vs NO	0.54 (0.46,0.62)	< 0.001
Insulin: YES vs NO	1.17 (1,1.38)	0.056
Temperature (cont. var.)	0.96 (0.86,1.06)	0.412
Heart Rate (cont. var.)	1.01 (1.01,1.02)	< 0.001
Resp_Rate (cont. var.)	1.04 (1.03,1.05)	< 0.001
MAP (cont. var.)	0.9964 (0.9925,1.0002)	0.063
Spo2 (cont. var.)	0.96 (0.94,0.98)	< 0.001
WBC (cont. var.)	1.02 (1.01,1.02)	< 0.001
RBC (cont. var.)	0.82 (0.74,0.9)	< 0.001
Platelet (cont. var.)	1.0001 (0.9993,1.0008)	0.856
Hemoglobin (cont. var.)	0.93 (0.91,0.96)	< 0.001
Hematocrit (cont. var.)	0.98 (0.97,0.99)	0.003
INR (cont. var.)	1.2 (1.14,1.27)	< 0.001
PT (cont. var.)	1.02 (1.01,1.02)	< 0.001
PTT (cont. var.)	1.001 (0.9978,1.0042)	0.53
Creatinine (cont. var.)	1.06 (1.03,1.1)	< 0.001
BUN (cont. var.)	1.01 (1.01,1.01)	< 0.001
Sodium (cont. var.)	1.0022 (0.9871,1.0176)	0.778
Potassium (cont. var.)	1.22 (1.12,1.34)	< 0.001
Chloride (cont. var.)	0.9955 (0.9829,1.0082)	0.482
Calcium (cont. var.)	0.79 (0.73,0.86)	< 0.001
Bicarbonate (cont. var.)	0.93 (0.91,0.95)	< 0.001
Liquid balance (cont. var.)	1 (1,1)	0.121
Urine output (cont. var.)	1 (1,1)	0.227
GPR (cont. var.)	1.23 (1.16,1.3)	< 0.001

PTT: Partial thromboplastin time, INR: International normalized ratio, PT: Prothrombin time, RR: Respiratory Rate, RBC: Red blood cell count, WBC: White blood cell count, BUN: Blood urea nitrogen, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SOFA: Sequential organ failure assessment, GCS: Glasgow Coma Scale. GPR, glucose-to-platelet ratio; MAP, mean arterial pressure; WBC, white blood cell count; RBC, red blood cell count; CRRT, continuous renal replacement therapy.

the quartiles were as follows: Q1, 0.4 (0.3, 0.4); Q2, 0.5 (0.5, 0.6); Q3, 0.7 (0.7, 0.8); and Q4, 1.2 (1.0, 1.7). As GPR quartiles rose, blood glucose levels showed a progressive increase, while platelet counts decreased, demonstrating a significant gradient across groups ($P<0.001$). The descriptive statistics and distributions of five selected continuous variables with comparatively higher missingness are presented in *Supplementary Table S3* and Supplementary *Figure S1*. Overall, these variables showed broadly similar summary statistics and distributional patterns before and after multiple imputation.

Baseline characteristics

Baseline characteristics varied significantly across GPR quartiles, encompassing demographics, comorbidities, disease severity, laboratory results, and treatments (*Table I*). These quartile-based comparisons provided an ordered evaluation of clinical characteristics across increasing GPR interval groups. Age differences were noted, with Q3 having the highest mean age. The high-GPR group had a significantly higher percentage of men (58.1% in Q4) compared to the low-GPR group (44.9% in Q1, $P<0.001$). While racial distribution showed statistical differences across quartiles, the overall composition was relatively stable. Patients with elevated GPR showed a significantly higher prevalence of myocardial infarction, congestive heart failure, diabetes, malignancy, hypertension, and sepsis (all $P<0.05$). The Charlson Comorbidity Index also increased with rising GPR, indicating a greater burden of comorbidity.

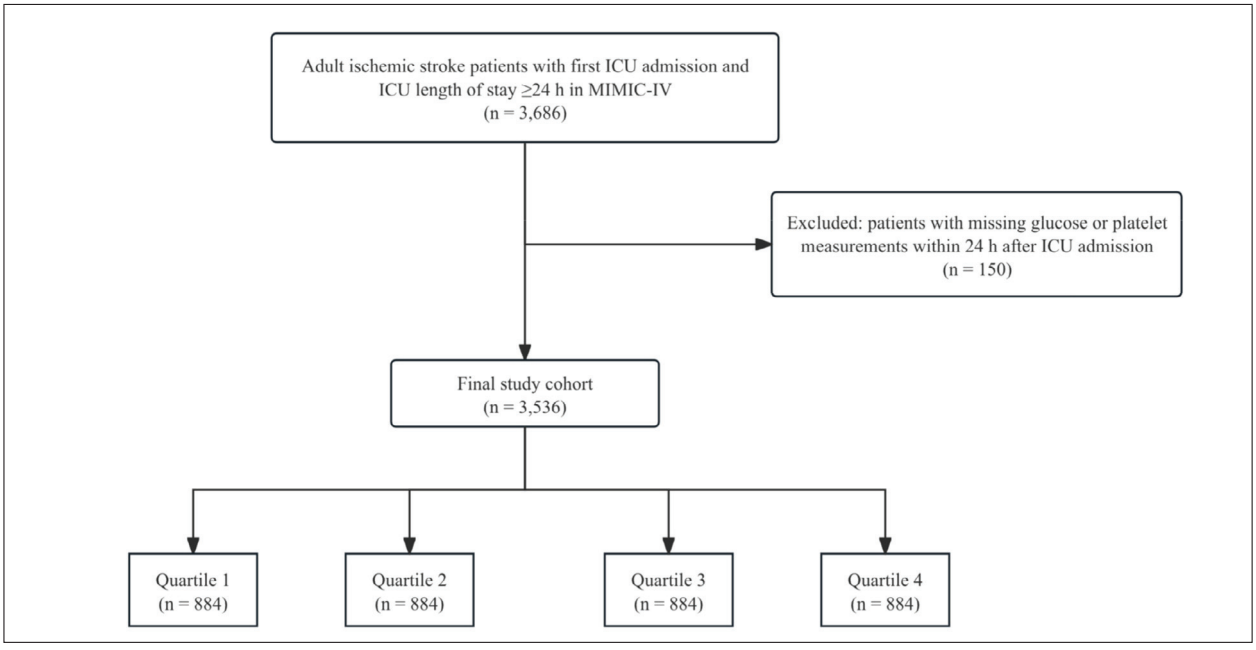


Figure 1 Flowchart of patient selection from the MIMIC-IV database.

Table S3 Descriptive statistics of selected continuous variables before and after multiple imputation.

Variable	Before imputation						After imputation					
	n	Mean	Median	SD	Minimum	Maximum	n	Mean	Median	SD	Minimum	Maximum
MAP, mmHg	3284	92.62	92	19.46	31	212	3536	92.43	92	19.53	31	212
PT, s	3229	14.83	13.1	7.44	8.3	150	3536	14.76	13.1	7.27	8.3	150
PTT, s	3215	36.21	29.6	22.49	18.4	150	3536	36.1	29.6	22.3	18.4	150
Calcium, mg/dL	3333	8.64	8.7	0.82	1.5	15.4	3536	8.63	8.7	0.82	1.5	15.4
INR	3229	1.36	1.2	0.66	0.8	15.7	3536	1.35	1.2	0.65	0.8	15.7

MAP, mean arterial pressure; PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio; SD, standard deviation.

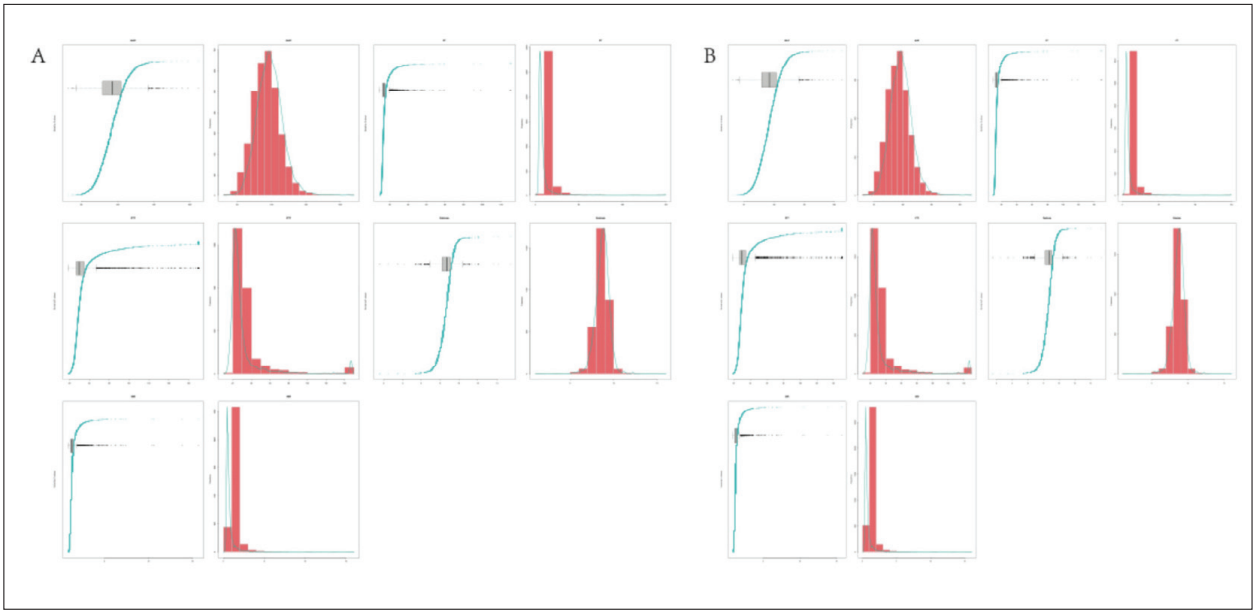


Figure S1 Distribution of selected continuous variables before and after multiple imputation.

Table I Baseline characteristics of patients stratified by quartiles of glucose-to-platelet ratio (GPR).

Characteristic	Overall (n=3536)	Q1 (n=884)	Q2 (n=884)	Q3 (n=884)	Q4 (n=884)	P value
GPR (median (IQR))	0.6 (0.5, 0.9)	0.4 (0.3, 0.4)	0.5 (0.5, 0.6)	0.7 (0.7, 0.8)	1.2 (1.0, 1.7)	**<0.001**
Demographics						
Age (years), mean±SD	70.1±14.7	68.6±15.8	69.6±15.4	72.7±13.0	69.5±14.3	**<0.001**
Sex, n (%)						**<0.001**
Male	1851 (52.3)	397 (44.9)	460 (52.0)	480 (54.3)	514 (58.1)	
Female	1685 (47.7)	487 (55.1)	424 (48.0)	404 (45.7)	370 (41.9)	
Race, n (%)						**0.035**
White	2011 (56.9)	534 (60.4)	510 (57.7)	485 (54.9)	482 (54.5)	
Black	420 (11.9)	111 (12.6)	104 (11.8)	96 (10.9)	109 (12.3)	
Other	1105 (31.2)	239 (27.0)	270 (30.5)	303 (34.3)	293 (33.1)	
Comorbidities, n (%)						
Myocardial infarction	665 (18.8)	128 (14.5)	158 (17.9)	174 (19.7)	205 (23.2)	**<0.001**
Congestive heart failure	1031 (29.2)	217 (24.5)	244 (27.6)	282 (31.9)	288 (32.6)	**<0.001**
Dementia	259 (7.3)	54 (6.1)	63 (7.1)	68 (7.7)	74 (8.4)	0.311
Chronic pulmonary disease	662 (18.7)	168 (19.0)	164 (18.6)	164 (18.6)	166 (18.8)	0.994
Diabetes	1254 (35.5)	162 (18.3)	256 (29.0)	354 (40.0)	482 (54.5)	**<0.001**
Malignant cancer	295 (8.3)	77 (8.7)	60 (6.8)	65 (7.4)	93 (10.5)	**0.023**
Hypertension	2717 (76.8)	619 (70.0)	658 (74.4)	691 (78.2)	749 (84.7)	**<0.001**
Sepsis	1482 (41.9)	284 (32.1)	317 (35.9)	352 (39.8)	529 (59.8)	**<0.001**
Charlson Comorbidity Index (mean±SD)	6.8±2.8	6.2±2.9	6.5±2.9	7.0±2.6	7.3±2.8	**<0.001**

Illness Severity scores						
SOFA score (median (IQR))	2.4 (1.0, 4.1)	1.7 (0.9, 3.0)	1.9 (0.9, 3.4)	2.5 (1.3, 4.0)	4.0 (2.5, 6.5)	**<0.001**
GCS (mean±SD)	13.9±2.2	14.0±1.8	14.0±2.0	13.8±2.4	13.7±2.5	**0.039**
Vital signs						
Temperature (°C), mean±SD	36.7±0.7	36.8±0.6	36.8±0.5	36.7±0.7	36.7±0.9	**0.013**
Heart rate (bpm), mean±SD	84.4±19.3	83.2±19.1	82.5±18.8	82.9±18.6	89.1±19.9	**<0.001**
Respiratory rate (bpm), mean±SD	19.2±5.6	18.9±5.7	18.8±5.2	19.0±5.6	20.1±5.9	**<0.001**
MAP (mmHg), mean±SD	92.4±19.5	94.1±18.4	94.1±19.6	92.1±19.2	89.4±20.5	**<0.001**
SpO2 (%), mean±SD	97.1±3.3	97.1±3.3	97.0±3.6	97.4±3.0	97.0±3.4	**0.115**
Laboratory parameters						
WBC ($\times 10^9$/L), mean±SD	11.4±7.2	11.4±6.1	11.0±5.4	11.2±5.4	12.0±10.6	**0.047**
RBC ($\times 10^{12}$/L), mean±SD	3.9±0.8	3.9±0.7	4.1±0.8	3.9±0.8	3.7±0.9	**<0.001**
Platelet ($\times 10^9$/L), mean±SD	218.7±96.4	312.6±105.0	231.5±59.1	193.4±52.1	137.2±60.6	**<0.001**
Hemoglobin (g/dL), mean±SD	11.5±2.4	11.4±2.3	12.0±2.3	11.6±2.3	11.0±2.5	**<0.001**
Hematocrit (%), mean±SD	35.2±6.8	35.1±6.3	36.7±6.4	35.3±6.7	33.5±7.4	**<0.001**
INR (mean±SD)	1.3±0.6	1.3±0.6	1.3±0.6	1.3±0.5	1.5±0.8	**<0.001**
PT (s), mean±SD	14.8±7.3	14.2±6.4	14.3±7.9	14.7±5.9	15.9±8.4	**<0.001**
PTT (s), mean±SD	36.1±22.3	34.0±17.0	35.6±22.8	36.2±22.9	38.7±25.5	**<0.001**
Creatinine (mg/dL), median (IQR)	0.9 (0.7, 1.3)	0.9 (0.7, 1.1)	0.9 (0.8, 1.2)	1.0 (0.8, 1.3)	1.1 (0.8, 1.6)	**<0.001**
BUN (mg/dL), median (IQR)	18.0 (13.0, 27.0)	16.0 (11.0, 23.0)	17.0 (12.0, 23.0)	18.5 (14.0, 28.0)	21.0 (14.0, 35.0)	**<0.001**
Sodium (mmol/L), mean±SD	139.0±4.9	138.9±4.6	139.2±4.4	139.0±4.7	139.0±5.8	0.429
Potassium (mmol/L), mean±SD	4.2±0.7	4.1±0.7	4.1±0.6	4.2±0.7	4.2±0.8	**0.037**
Chloride (mmol/L), mean±SD	103.8±5.8	103.2±5.7	103.7±5.1	103.9±5.7	104.2±6.8	**0.002**
Calcium (mg/dL), mean±SD	8.6±0.8	8.7±0.7	8.8±0.7	8.6±0.8	8.4±1.0	**<0.001**
Bicarbonate (mmol/L), mean±SD	22.7±3.9	23.1±3.6	23.2±3.5	22.7±3.8	21.8±4.4	**<0.001**
Glucose (mg/dL), mean±SD	136.2±41.7	112.0±25.0	124.7±29.9	140.7±35.7	167.2±49.6	**<0.001**
Interventions and support						
Mechanical ventilation, n (%)	2414 (68.3)	508 (57.5)	580 (65.6)	644 (72.9)	682 (77.1)	**<0.001**
Ventilator hours (median (IQR))	19.0 (0.0, 65.1)	6.4 (0.0, 38.5)	15.9 (0.0, 54.8)	21.8 (0.0, 69.0)	36.0 (4.0, 102.8)	**<0.001**
CRRT, n (%)	123 (3.5)	17 (1.9)	23 (2.6)	24 (2.7)	59 (6.7)	**<0.001**
Medications, n (%)						
Vasoactive agents	896 (25.3)	150 (17.0)	176 (19.9)	241 (27.3)	329 (37.2)	**<0.001**
Aspirin	2010 (56.8)	486 (55.0)	522 (59.0)	517 (58.5)	485 (54.9)	0.145
Clopidogrel	482 (13.6)	120 (13.6)	139 (15.7)	112 (12.7)	111 (12.6)	0.183
Ticagrelor	55 (1.6)	20 (2.3)	12 (1.4)	15 (1.7)	8 (0.9)	0.129
Statins	1961 (55.5)	463 (52.4)	536 (60.6)	510 (57.7)	452 (51.1)	**<0.001**
Insulin	2451 (69.3)	487 (55.1)	583 (66.0)	662 (74.9)	719 (81.3)	**<0.001**
Fluid balance and output						
Fluid balance (mL), median (IQR)	557.6 (-1354.8, 2732.7)	676.4 (-956.8, 2298.9)	315.0 (-1392.2, 2527.3)	478.7 (-1509.5, 2592.9)	778.1 (-1880.4, 3732.9)	**0.037**

Urine output (mL), median (IQR)	4314.0 (2075.0, 10183.8)	3820.0 (1878.8, 7660.2)	3952.5 (2000.0, 9171.2)	4319.0 (2165.8, 10556.5)	5425.5 (2317.5, 14016.2)	**<0.001**
Outcomes						
Hospital length of stay (days), median (IQR)	8.9 (5.0, 16.6)	7.9 (4.4, 14.8)	8.2 (4.6, 14.0)	8.9 (5.1, 17.3)	11.4 (6.5, 20.9)	**<0.001**
ICU length of stay (days), median (IQR)	3.4 (1.9, 6.8)	3.0 (1.7, 5.5)	3.3 (1.9, 6.3)	3.3 (1.9, 6.6)	4.3 (2.3, 8.4)	**<0.001**
Hospital mortality, n (%)	545 (15.4)	89 (10.1)	107 (12.1)	141 (16.0)	208 (23.5)	**<0.001**
ICU mortality, n (%)	336 (9.5)	52 (5.9)	68 (7.7)	96 (10.9)	120 (13.6)	**<0.001**

Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range (IQR)) according to their distribution.
Abbreviations: GPR, glucose-to-platelet ratio; IQR, interquartile range; SD, standard deviation; GCS, Glasgow Coma Scale; SOFA, Sequential Organ Failure Assessment; MAP, mean arterial pressure; WBC, white blood cell count; RBC, red blood cell count; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy.

Table II Cox proportional hazards regression analysis of the association between glucose-to-platelet ratio (GPR) and all-cause mortality.

Variable	Model 1		Model 2		Model 3	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
28-day all-cause mortality						
GPR (continuous)	1.23 (1.16–1.30)	**<0.001**	1.30 (1.23–1.38)	<**0.001**	1.11 (1.03–1.21)	**0.009**
GPR quartiles						
Q1	1 (Reference)		1 (Reference)		1 (Reference)	
Q2	1.21 (0.96–1.53)	0.112	1.17 (0.93–1.48)	0.183	1.19 (0.94–1.51)	0.15
Q3	1.56 (1.24–1.94)	**<0.001**	1.40 (1.12–1.75)	**0.003**	1.30 (1.03–1.64)	**0.027**
Q4	1.96 (1.59–2.43)	**<0.001**	1.95 (1.57–2.42)	**<0.001**	1.37 (1.08–1.75)	**0.01**
p for trend		**<0.001**		**<0.001**		**0.009**
90-day all-cause mortality						
GPR (continuous)	1.22 (1.17–1.28)	**<0.001**	1.30 (1.24–1.36)	**<0.001**	1.09 (1.01–1.17)	**0.019**
GPR quartiles						
Q1	1 (Reference)		1 (Reference)		1 (Reference)	
Q2	1.13 (0.93–1.38)	0.215	1.1(0.91–1.34)	0.327	1.13 (0.92–1.38)	0.233
Q3	1.46 (1.21–1.76)	**<0.001**	1.31 (1.09–1.59)	**0.005**	1.23 (1.01–1.49)	**0.042**
Q4	1.8 (1.5–2.15)	**<0.001**	1.78 (1.48–2.14)	**<0.001**	1.25 (1.02–1.54)	**0.034**
p for trend		**<0.001**		**<0.001**		**0.026**

Model 1: Unadjusted.
Model 2: Adjusted for age, sex, and race.
Model 3: Adjusted for age, sex, race, myocardial infarction, congestive heart failure, dementia, diabetes, hypertension, malignant cancer, Charlson Comorbidity Index, Sequential Organ Failure Assessment (SOFA) score, Glasgow Coma Scale (GCS) score, sepsis, mechanical ventilation, continuous renal replacement therapy (CRRT), vasoactive agents, aspirin, clopidogrel, ticagrelor, statins, insulin, heart rate, respiratory rate, mean arterial pressure, oxygen saturation, white blood cell count, red blood cell count, hemoglobin, hematocrit, international normalized ratio, prothrombin time, creatinine, blood urea nitrogen, potassium, calcium, and bicarbonate.

SOFA scores increased markedly across quartiles (Q1: 1.7 (0.9–3.0) vs Q4: 4.0 (2.5–6.5), P<0.001), whereas GCS scores were slightly lower in the high-GPR group. Patients with elevated GPR showed increased heart and respiratory rates, decreased mean arterial pressure, abnormal coagulation and renal function indices, reduced red blood cell count, hemoglobin, and hematocrit, along with significantly higher glucose levels (all P<0.001). Patients in the high-GPR group frequently needed mechanical ventilation, continuous renal replacement therapy, vasoactive agents, and insulin. Hospital and ICU stays were extended, with increased mortality rates in both settings for high-GPR groups.

Correlation Between GPR and All-Cause Mortality at 28 and 90 Days

Results from the multivariable Cox proportional hazards models are shown in *Table II*. The unadjusted model showed a significant association between elevated GPR and increased risks of all-cause mortality at both 28 and 90 days. These associations remained significant after adjusting for demographic factors and various potential confounders. In Model 3, treating GPR as a continuous variable, each 1-unit increase in GPR significantly raised the risk of 28-day (HR 1.11, 95% CI 1.03-1.21, P = 0.009) and 90-day all-cause mortality (HR 1.09, 95% CI 1.01–1.17, P = 0.019). When analyzed by quartiles, patients in Q3 and Q4 had significantly higher risks of short-term and intermediate-term mortality compared to Q1. Specifically, Q4 patients had a 37% higher risk of 28-day mortality (HR 1.37, 95% CI 1.08-1.75, P = 0.010) and a 25% higher risk of 90-day mortality (HR 1.25, 95% CI 1.02–1.54, P = 0.034) than those in Q1. In sensitivity analyses excluding extreme GPR values, the adjusted effect estimates remained directionally consistent with the primary analysis but with attenuated statistical significance (28-day: adjusted HR 1.11, 95% CI 0.99–1.24, P=0.072; 90-day: adjusted HR 1.09, 95% CI 0.98–1.20, P=0.098). Trend tests confirmed significant dose-response relationships between GPR quartiles and both mortality outcomes. Together with the RCS findings, these results support a graded positive association between increasing GPR levels and mortality risk.

Survival analysis and assessment of nonlinearity

Kaplan–Meier analyses indicated significant differences in survival probabilities among GPR quartiles for both 28-day and 90-day follow-up periods, with log-rank P-values below 0.0001 (*Figure 2A* and *2B*). Patients in the high-GPR groups consistently showed lower survival probabilities throughout follow-up, whereas those in the low-GPR groups had relatively higher survival curves with a more gradual decline.

Further restricted cubic spline analyses were performed to assess possible nonlinear associations between GPR and mortality risk (*Figure 3*). Significant associations were found between GPR and all-cause mortality at both 28 days (P=0.003) and 90 days (P=0.006). No significant nonlinearity was observed, with P-values of 0.665 for 28-day mortality and 0.547 for 90-day mortality.

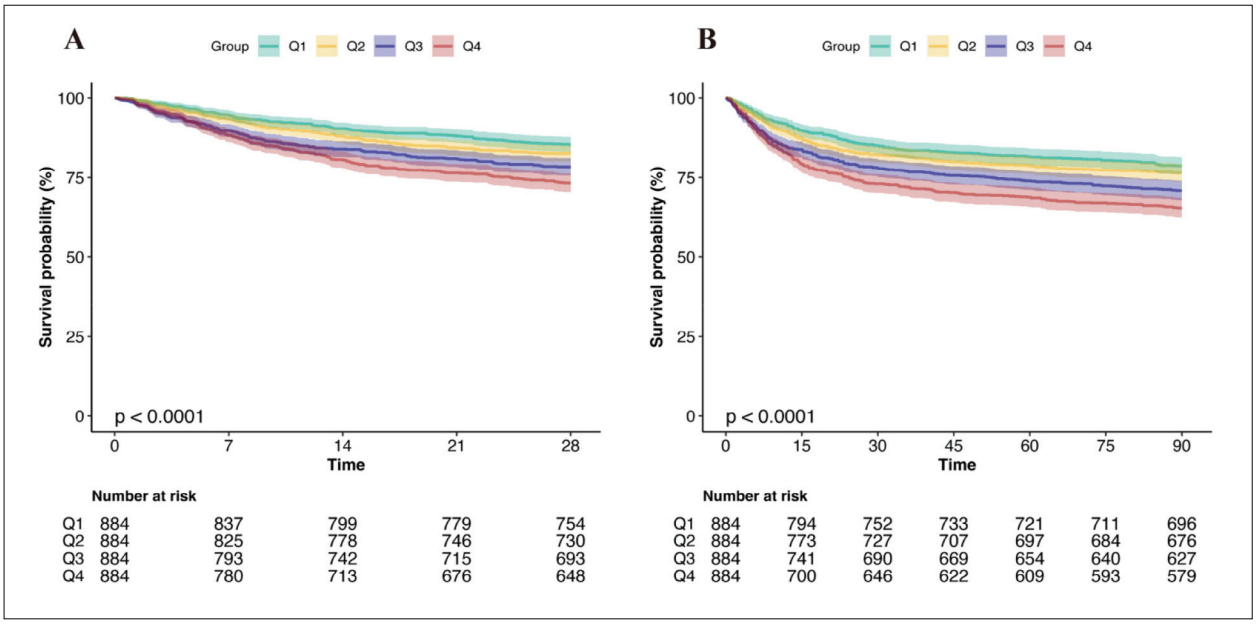


Figure 2 Kaplan–Meier survival curves for 28-day (A) and 90-day (B) all-cause mortality according to quartiles of the glucose-to-platelet ratio (GPR) in critically ill patients with ischemic stroke.

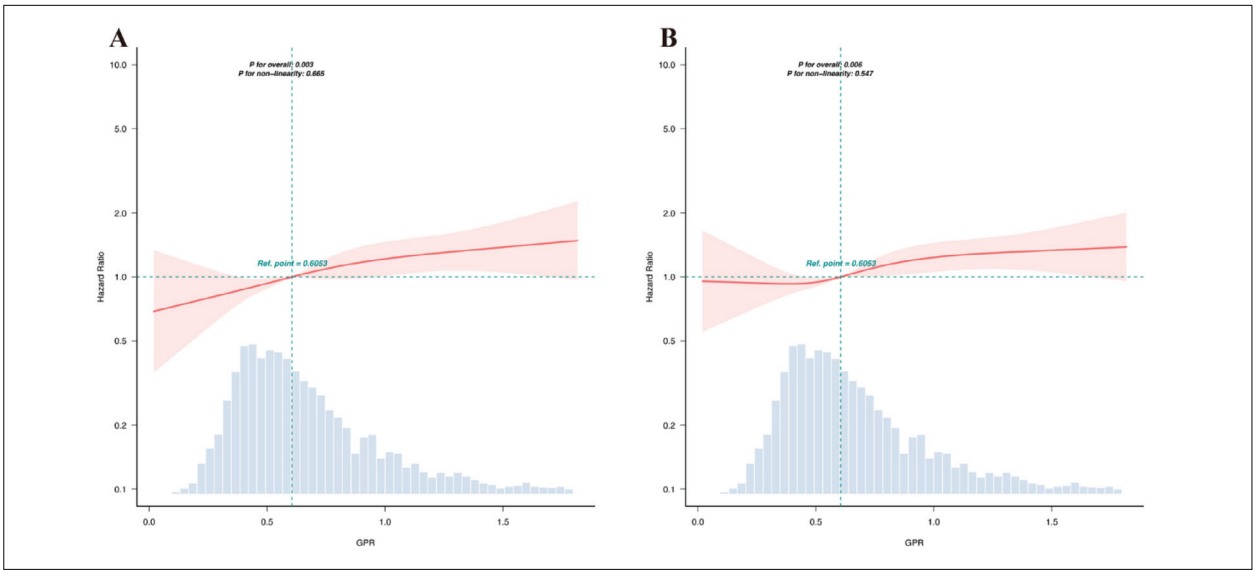


Figure 3 Restricted cubic spline analyses of the association between the glucose-to-platelet ratio (GPR) and 28-day (A) and 90-day (B) all-cause mortality in critically ill patients with ischemic stroke.

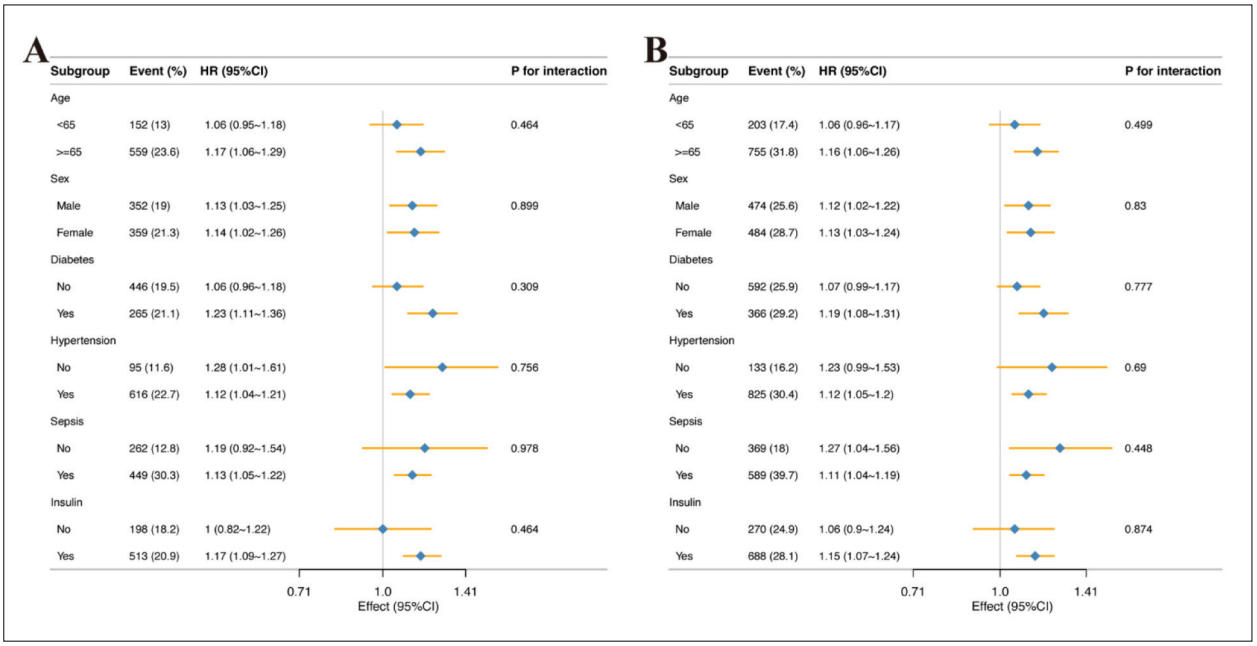


Figure 4 Subgroup analyses of the association between the glucose-to-platelet ratio (GPR) and 28-day (A) and 90-day (B) all-cause mortality in critically ill patients with ischemic stroke.

Subgroup analyses were performed according to age, sex, diabetes, hypertension, sepsis, and insulin use to evaluate the consistency of the association across clinical subgroups.

Subgroup analysis

After stratification by age, sex, presence of diabetes, hypertension, sepsis, and insulin use, the positive association between GPR and the risks of 28-day and 90-day all-cause mortality remained directionally consistent across most subgroups. No significant effect modification was identified in the interaction analyses (all P for interaction >0.05), suggesting that the association between GPR and mortality risk was relatively stable across different clinical subgroups (*Figure 4*).

Discussion

This retrospective cohort study utilizing the MIMIC-IV database identified an independent association between a higher glucose-to-platelet ratio within the first 24 hours of ICU admission and elevated 28-day and 90-day all-cause mortality risks in critically ill ischemic stroke patients. This association persisted even after controlling for demographic factors, comorbidities, severity scores, and treatment-related variables. Restricted cubic spline analysis further suggested a significant overall association between GPR and mortality risk, without evidence of a clear nonlinear threshold effect, implying that the effect of GPR on mortality may increase in a progressive manner. Subgroup analyses showed generally consistent directions of association across age groups, sexes, and major clinical subgroups, with no significant interactions, supporting the stability and potential generalizability of this indicator.

This study highlights that GPR combines blood glucose and platelet count into a single biomarker, potentially indicating both metabolic stress and coagulation-inflammation imbalance. GPR offers a more holistic assessment of the combined metabolic and coagulation disruptions in critically ill ischemic stroke patients than isolated metabolic or hematologic markers (15). In acute cerebral ischemia, metabolic derangement and microcirculatory dysfunction often occur in parallel, yet they have rarely been jointly quantified in previous studies (16), GPR offers a concise and biologically plausible quantitative measure of this complex physiological state. Research indicates that both stress hyperglycemia and platelet abnormalities are linked to negative outcomes following a stroke (17, 18). Acute hyperglycemia often arises in both diabetic and non-diabetic individuals due to the excessive activation of the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis (19). Hyperglycemia may aggravate brain injury through several mechanisms: by promoting mitochondrial superoxide overproduction and activating multiple downstream pathways that contribute to oxidative stress and endothelial dysfunction (20); by disrupting the endothelial glycocalyx, increasing blood–brain barrier permeability, and promoting microthrombosis; and by inhibiting the PI3K/Akt signaling pathway, thereby impairing endothelial repair and inducing apoptosis (21, 22). These mechanisms may collectively contribute to cerebral hypoperfusion, infarct expansion, and secondary neurological deterioration. On the other hand, thrombocytopenia may also have important pathophysiological implications in severe ischemic stroke. A reduced platelet count often reflects excessive platelet activation and consumption, including microthrombosis, disseminated intravascular coagulation, or inflammation-related bone marrow suppression. Platelets are not only central mediators of hemostasis and coagulation but also key participants in inflammatory and immune regulation. A decline in platelet count may therefore indicate both exhaustion of the coagulation system and overactivation of the immune–coagulation axis, thereby aggravating microcirculatory dysfunction and secondary inflammatory injury (23). Within the pathophysiological context of ischemic stroke, the combination of hyperglycemia and platelet depletion may represent a state of »metabolic–coagulation crisis.« An elevated GPR may therefore reflect a condition in which metabolic demand rises sharply under severe stress while microcirculatory perfusion and endothelial repair capacity continue to deteriorate (19), ultimately contributing to worsening ischemia–reperfusion injury, progression of multiple organ dysfunction, and increased short-term and intermediate-term mortality risk (16)

From a clinical perspective, these findings may have practical implications. Because blood glucose and platelet count are routinely monitored in the ICU, GPR can be calculated without additional testing costs and has good accessibility and reproducibility. Early identification of patients with markedly elevated GPR may serve as a metabolic warning signal, indicating potential hypoperfusion, inflammation–coagulation imbalance, and risk of rapid clinical deterioration. In such patients, intensified hemodynamic monitoring, optimization of metabolic management, and close tracking of dynamic organ dysfunction scores such as SOFA may be considered. Compared with commonly used composite indicators such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), which primarily reflect systemic inflammatory balance, GPR may capture a somewhat different pathophysiological dimension by integrating acute metabolic stress with platelet-related coagulation and thrombo-inflammatory status. In critically ill patients with ischemic stroke, where metabolic dysregulation, endothelial injury, and coagulation abnormalities often coexist, this feature may provide complementary clinical information for early risk assessment.

The association between GPR and mortality risk was generally consistent across clinical subgroups, suggesting that this indicator may be useful for risk stratification across different patient populations. The numerically stronger association with 28-day mortality may reflect the fact that GPR primarily captures acute systemic injury driven by early metabolic and coagulation disturbances, whereas its persistent association with 90-day mortality may also indicate longer-term impairment of metabolic regulation and cumulative microvascular injury.

It is important to recognize certain limitations. This retrospective study, conducted at a single center, may still experience residual confounding

and selection bias despite using multivariable adjustments and subgroup analyses. Second, GPR was calculated using blood glucose and platelet values obtained within the first 24 hours after ICU admission, which restricted assessment of its dynamic changes over time; future studies using longitudinal or trajectory-based GPR assessment may help determine whether temporal patterns provide additional prognostic information. Third, although sensitivity analyses excluding extreme GPR values yielded effect estimates of similar direction and magnitude, the attenuation of statistical significance suggests that robustness to outlying values should be interpreted with caution. In addition, direct prognostic comparisons between GPR and other commonly used composite indicators were not performed, and clinically important stroke-specific non-mortality outcomes, such as neurological functional recovery were not evaluated. Finally, because the study population was derived from ICUs in the United States, racial/ethnic composition and treatment practices may differ from those in Asian and other populations; further validation in multicenter, multiethnic stroke-focused cohorts with more detailed neurological outcome documentation is warranted to confirm generalizability and clarify the prognostic utility of GPR.

Conclusion

In this ICU-based cohort, elevated GPR within the first 24 hours was independently associated with higher 28-day and 90-day all-cause mortality in critically ill patients with ischemic stroke. As a readily available biomarker of metabolic–coagulation dysregulation, GPR may aid early risk stratification and prompt closer hemodynamic, metabolic, and organ-function monitoring. Further prospective multicenter studies are needed to validate its clinical utility.

Declarations

Data Availability

Data for this investigation were obtained from the publicly available MIMIC-IV database, which is accessible at https://mimic.physionet.org

Ethics approval and consent to participate

The investigation was conducted using the publicly accessible Medical Information Mart for Intensive Care (MIMIC) database, which includes deidentified health data. As the database contains anonymized information, neither individual informed consent nor further institutional review board approval was required. Database access was authorized after completion of the required Collaborative Institutional Training Initiative (CITI) program by the authors.

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None.

Author Contributions

Jie Peng conceived the study design and performed data extraction. Huanhuan Wu and Hongzhi Chen performed data processing and statistical analysis. Jie Peng and Xingzhan Zhang prepared the tables and figures. Jie Peng drafted the manuscript. Xingzhan Zhang, Huanhuan Wu, Hongzhi Chen, Jianbin Guan, Zhanguo Liu, and Xingxing Liu interpreted the data and critically revised the manuscript. All authors approved the final manuscript.

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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