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Association between serum glucose potassium ratio and mortality in critically ill patients with intracerebral hemorrhage

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The effect of serum glucose-to-potassium ratio (GPR) on cerebrovascular diseases has been previously validated. However, the value of the GPR in patients with severe intracerebral hemorrhage (ICH) requiring ICU admission remains unclear. This study aimed to investigate the association between the GPR and the clinical prognosis of critically ill patients with ICH. This study identified patients with severe ICH requiring ICU admission from the Medical Information Mart for Intensive Care (MIMIC-IV) database and divided them into quartiles based on GPR levels. Outcomes included 30-day, 90-day, and 1-year mortality rates. The association between the GPR and clinical outcomes in critically ill patients with ICH was elucidated using Cox proportional hazards regression analysis and restricted cubic splines. In total, 2018 patients (53.8% male), with a median age of 70 years, were enrolled in the study. The 30-day, 90-day, and 1-year mortality rates were 23.9%, 30.1%, and 38.4%, respectively. Per multivariate Cox proportional hazards analysis, an elevated GPR was significantly associated with all-cause mortality. After adjusting for age, sex, Charlson Comorbidity Index, white blood cell count, red blood cell count, platelet count, and Glasgow Coma Scale, patients with an elevated GPR had a higher 30-day mortality (hazard ratio [HR]: 1.32; 95% confidence interval [CI]: 1.22–1.42; $P < 0.001$), 90-day mortality (HR: 1.27; 95% CI: 1.18–1.37; $P < 0.001$) and 1-year mortality (HR: 1.22; 95% CI: 1.14–1.31; $P < 0.001$) when analyzed as a continuous variable. Furthermore, analysis using restricted cubic splines demonstrated a consistent and progressive escalation in the risk of all-cause mortality with an elevated GPR. The GPR was significantly associated with short- and long-term all-cause mortality in critically ill patients with ICH. This finding demonstrates that GPR may be useful in identifying patients with ICH at a high risk of all-cause mortality.

Keywords Intracerebral hemorrhage, Glucose-to-potassium ratio, Mortality

Abbreviations

ICH	Intracerebral hemorrhage
MIMIC-IV	Medical Information Mart for Intensive Care IV
ACM	All-cause mortality
APTT	Activated partial thromboplastin time
CCI	Charlson Comorbidity Index
COPD	Chronic obstructive pulmonary disease
GCS	Glasgow Coma Scale
GPR	Glucose-to-potassium ratio
HF	Heart failure; HR, hazard ratio
ICD9	International Classification of Diseases, 9th Revision
ICD10	International Classification of Diseases, 10th Revision
PVD	Peripheral vascular disease
RF	Renal failure
ROC	Receiver operating characteristic

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SAPS	Simplified Acute Physiological Score
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sequential Organ Failure Assessment
WBC	White blood cell count

Intracerebral hemorrhage (ICH) is a pathological condition characterized by the rupture of cerebral blood vessels, resulting in blood infiltration into the brain parenchyma[1]. Globally, the incidence of ICH is approximately 3.5 million cases annually, with a notably higher prevalence in low-income countries[2]. ICH disproportionately contributes to a greater loss of disability-adjusted life years than does ischemic stroke, underscoring its profound impact on individual health outcomes and societal welfare[3–5]. The mortality rates associated with ICH are substantial, reaching 40% within the first month and 54% in 1 year, and the majority of survivors often experience functional and cognitive impairments[5–7]. Recognizing the potential for reduced mortality, clinical severity, and complications among patients with ICH through timely intervention and early outcome prediction, the identification of prognostic markers that can accurately predict adverse outcomes in ICH is important. Ideally, these markers should be simple, less invasive, cost-effective, and readily applicable in clinical settings to facilitate prompt and informed decision-making.

Serum glucose and potassium levels are vital clinical biomarkers that play a significant role in patient assessment. Elevated serum glucose levels have been consistently linked to unfavorable prognoses in ICH, as evidenced in previous studies[8,9]. Conversely, reduced serum potassium levels are reportedly not associated with poor outcomes following[10]. Furthermore, complex interactions between glucose and potassium have been documented in the literature, suggesting their interdependent nature[11,12]. Recent studies have focused on the relationship between the serum glucose-to-potassium ratio (GPR) and clinical outcomes after central nervous system injuries such as carbon monoxide poisoning[13]. These studies have demonstrated that an elevated GPR can serve as a valuable tool for assessing disease severity and independently identifying patients at risk of poor outcomes [14–17]. A retrospective study investigated the predictive potential of serum GPR in patients with ICH and concluded that it is a readily available clinical variable for predicting clinical outcomes post-ICH[15]. Although the findings regarding predictive value of GPR in ICH are promising, it is important to acknowledge their limitations. This study had a relatively small sample size and did not include long-term clinical outcomes, limiting the generalizability and comprehensiveness of the results.

We conducted an analysis utilizing data sourced from the Medical Information Mart for Intensive Care (MIMIC)-IV database to gain deeper insight into GPR's capacity as a predictive indicator of mortality among critically ill patients with ICH. Our objective is to elucidate the correlation between GPR levels and all-cause mortality (ACM) in this vulnerable population. Our investigation aims to address the lack of understanding of the prognostic value of GPR in ICH, with the ultimate goal of enhancing clinical management and facilitating prompt intervention measures for individuals at heightened risk.

Methods

Data sources

A retrospective study was conducted using extensive data from the MIMIC-IV database[18]. This publicly accessible repository encompasses the comprehensive health records of over 190,000 patients admitted to the intensive care units of the Beth Israel Deaconess Medical Center between 2008 and 2019. Jianyi Liu, the contributing author, obtained the necessary authorization to access the anonymized dataset (Record ID: 12,912,699) and oversaw the rigorous process of data extraction. Given the foundation of our research in this pre-approved and de-identified database, which has undergone rigorous institutional review board scrutiny by the Institutional Review Boards of Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology, the requirement for obtaining informed patient consent and additional ethical approval for this specific study was deemed unnecessary, adhering to the principles of ethical research practices.

Study population and data extraction

For data extraction from the MIMIC-IV database, we used PostgreSQL (version 13.7.2) in conjunction with Navicat Premium (version 16) to execute the SQL scripts. Our target population comprised adult patients (aged > 18 years) diagnosed with non-traumatic intracerebral hemorrhage (ICH) according to the International Classification of Diseases, 9th and 10th Revisions (ICD9 and ICD10), including ICD-9 code 431 and ICD-10 codes I610-I619 and I62.9[19]. Stringent exclusion criteria were used to ensure the integrity and reliability of the analysis. We excluded patients who (1) died within the initial 24 h of ICU admission, as their clinical trajectories may have been incompletely recorded or had negative survival time values; (2) had multiple ICU admissions, for which we solely considered the first admission attributed to ICH to prevent data redundancy; and (3) had crucial laboratory data, specifically glucose and potassium levels, on the first day of ICU admission, as these are essential for our analytical purposes. Subsequent to the application of these criteria, a total of 2018 participants was included in the study (Fig. 1).

Finally, we gathered the following data: (1) Demographics including age and sex; (2) Indices of clinical severity encompassing the Glasgow Coma Scale (GCS), Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiological Score (SAPS)- II, Oxford Acute Severity of Illness Score (OASIS), and Systemic Inflammatory Response Syndrome (SIRS); (3) Physiology metrics including blood pressure, heart and respiratory rates, and temperature; (4) Hematological and biochemical parameters including hemoglobin concentration (Hb), red blood cell count (RBC), platelet count, white blood cell count (WBC), activated partial thromboplastin time (APTT), glucose, potassium, and sodium levels; and (5) Existing comorbidities such as myocardial infarct, heart failure (HF), chronic obstructive pulmonary disease (COPD), peripheral vascular disease (PVD), diabetes mellitus, renal failure (RF), hepatic disorders, malignant neoplasms, and the Charlson Comorbidity Index

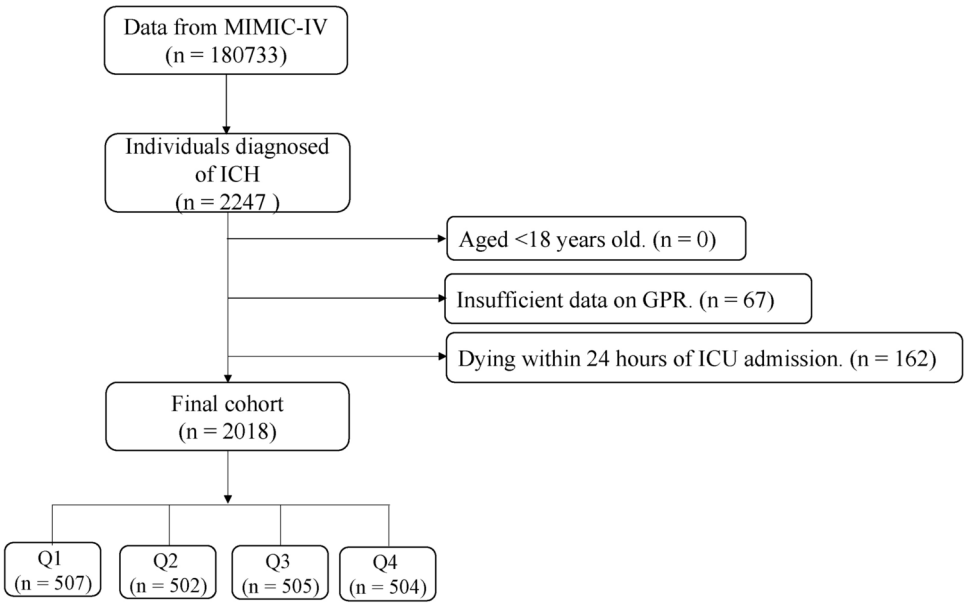

Fig.1. The flow of the enrolled patients throughout the study.

(CCI). The GPR was calculated by dividing the glucose and potassium levels (mmol/L). The analysis relied on laboratory values and scores that indicated disease severity, that were collected during the first examination within 24 h after ICU admission.

Clinical outcomes

The primary endpoint in this study was the 90-day ACM, whereas the secondary endpoints were the 30-day and 1-year ACM. Crucially, the time of death was defined as the occurrence of death within a defined period following admission to the ICU rather than merely identifying whether the number of patients decreased at a specific time point.

Statistical analyses

This study stratified participants into quartiles based on their GPR values (Q1-Q4). Quantitative variables are presented as mean ± standard deviation (SD) or as median and interquartile range (IQR), depending on the distribution of data. In contrast, qualitative variables are represented as counts and proportions. For continuous variables conforming to a normal distribution, the t-test or analysis of variance (ANOVA) was used. Conversely, the Mann–Whitney U test or Kruskal–Wallis test was used for variables that were not normally distributed. Comparisons of categorical variables across GPR quartiles were performed using Pearson's chi-square test.

Furthermore, we employed Kaplan–Meier survival analysis to ascertain the endpoint incidence rates within groups stratified by GPR levels, utilizing the log-rank test to assess the statistical significance of the differences observed. Cox proportional hazard models were used, yielding hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) to quantify the association between GPR and the study endpoints. Three models were constructed to adjust for potential confounders: model 1, unadjusted; Model 2, adjusted for age, sex, and CCI; and Model 3 incorporated variables based on clinical expertise and prior literature[20–22], including age, sex, CCI, WBC count, RBC count, platelet count and GCS. In this study, GPR was analyzed as both a continuous and ordinal variable, using the first quartile as the reference category. Trend analyses were performed across GPR quartiles. Stratification and interaction analyses dissected the influence of sex, age, presence of diabetes, and HF, employing likelihood ratio tests to probe for interactions. All analyses were conducted using R software (version 4.2.2, Foundation for Statistical Computing, Vienna, Austria), with statistical significance set at $P < 0.05$ (two-tailed).

Results

In this study, 2018 subjects with ICH in critical condition were enrolled, with a median age of 70 years (IQR: 58–81), and males constituting 53.8% (n = 1085) of the study population. The median GPR across the cohort was calculated at 1.8 (IQR: 1.4–2.31). The ACM was 23.9%,30.1%, and 38.4% for 30 day, 90 day, and 1-year, respectively.

Baseline characteristics

Table 1 lists the baseline demographic and clinical attributes stratified by GPR quartiles. Subjects were allocated into four quartiles depending upon GPR values (Q1:0.23– < 1.44; Q2:1.44– < 1.80; Q3:1.80– < 2.31; Q4:2.31–9.91). The median GPR for these quartiles were 1.26 (IQR: 1.16–1.36), 1.62 (IQR: 1.53–1.70), 2.02 (IQR: 1.91–2.15), and 2.85 (IQR: 2.52–3.56) respectively. Subjects in the highest GPR quartile had elevated GCS, OASIS, and

	Overall (n = 2018)	Q1 (n = 507)	Q2 (n = 502)	Q3 (n = 505)	Q4 (n = 504)	P-value
GPR	1.80 (1.44, 2.31)	1.26 (1.16, 1.36)	1.62 (1.53, 1.70)	2.02 (1.91, 2.15)	2.85 (2.52, 3.56)	< 0.001
Demographic						
Age (y, IQR)	70.25 (58.36, 81.06)	71.39 (60.13, 82.31)	70.24 (57.85, 81.97)	70.42 (59.51, 80.12)	68.55 (56.69, 79.52)	0.115
Male (n, %)	1085 (53.8%)	286 (56.4%)	278 (55.4%)	270 (53.5%)	251 (49.8%)	0.161
Clinical severity						
GCS	15.00 (14.00, 15.00)	15.00 (14.00, 15.00)	15.00 (14.00, 15.00)	15.00 (14.00, 15.00)	15.00 (15.00, 15.00)	0.002
SOFA	0.00 (0.00, 2.00)	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	1.00 (0.00, 2.00)	0.00 (0.00, 2.00)	0.606
SAPSII	32.00 (26.00, 40.00)	32.00 (26.00, 40.00)	31.00 (25.00, 39.00)	32.00 (26.00, 40.00)	33.00 (27.00, 40.00)	0.059
OASIS	31.00 (26.00, 36.00)	29.00 (24.00, 35.00)	30.00 (25.00, 35.00)	31.00 (26.00, 37.00)	33.00 (28.00, 37.00)	< 0.001
SIRS	2.00 (2.00, 3.00)	2.00 (1.00, 3.00)	2.00 (2.00, 3.00)	2.00 (2.00, 3.00)	3.00 (2.00, 3.00)	< 0.001
Vital signs						
Heart rate (beats/min)	78.96 (70.36, 88.33)	75.76 (67.65, 85.19)	77.96 (68.76, 87.08)	80.36 (71.19, 90.08)	81.22 (73.50, 91.27)	< 0.001
SBP (mmHg)	131.00 (122.28, 139.08)	128.00 (118.50, 136.88)	131.00 (121.96, 139.37)	131.96 (124.88, 140.65)	132.48 (123.68, 139.09)	< 0.001
DBP (mmHg)	67.45 (59.98, 75.00)	68.09 (61.10, 75.68)	68.73 (61.62, 76.43)	68.21 (60.15, 74.83)	64.79 (57.06, 72.95)	< 0.001
MBP (mmHg)	84.93 (77.93, 91.50)	84.32 (77.54, 91.26)	85.41 (78.45, 92.25)	86.40 (79.04, 91.70)	83.26 (77.00, 90.61)	0.005
Respiratory rates (breath/min)	18.27 (16.50, 20.33)	18.08 (16.38, 19.83)	18.04 (16.15, 20.06)	18.44 (16.81, 20.76)	18.50 (16.90, 20.88)	0.001
Temperature (℃)	36.94 (36.71, 37.25)	36.88 (36.69, 37.12)	36.92 (36.72, 37.22)	37.00 (36.77, 37.32)	36.98 (36.70, 37.36)	< 0.001
Laboratory Parameters						
Hb (g/dL)	12.70 (11.40, 14.00)	12.70 (11.10, 13.90)	12.80 (11.53, 14.10)	12.80 (11.60, 13.90)	12.70 (11.30, 14.00)	0.225
RBC (10^9/L)	4.23 (3.77, 4.65)	4.18 (3.69, 4.57)	4.22 (3.76, 4.67)	4.25 (3.80, 4.64)	4.23 (3.77, 4.67)	0.282
WBC (10^9/L)	9.90 (7.70, 13.17)	8.60 (6.90, 11.17)	9.60 (7.70, 12.70)	10.30 (8.00, 13.60)	11.10 (8.50, 15.00)	< 0.001
PLT (10^9/L)	209.00 (166.00, 263.00)	205.00 (165.00, 256.75)	211.00 (163.00, 266.00)	210.00 (169.00, 262.00)	212.00 (162.00, 264.00)	0.845
APTT (sec)	28.00 (25.30, 31.50)	28.90 (26.20, 32.00)	27.80 (25.20, 30.58)	27.80 (25.15, 31.50)	27.70 (24.80, 31.40)	< 0.001
Sodium (mmol/L)	139.00 (137.00, 141.00)	140.00 (137.00, 142.00)	139.00 (137.00, 141.00)	139.00 (137.00, 141.00)	139.00 (136.00, 141.00)	0.138
Glucose (mmol/L)	7.22 (5.94, 8.93)	5.39 (4.94, 5.97)	6.50 (6.00, 7.11)	7.89 (7.17, 8.61)	10.72 (9.17, 13.61)	< 0.001
Potassium (mmol/L)	4.00 (3.70, 4.40)	4.30 (4.00, 4.80)	4.10 (3.80, 4.30)	3.90 (3.60, 4.20)	3.70 (3.40, 4.10)	< 0.001
Comorbidities						
Myocardial infarct (n, %)	179 (8.9%)	48 (9.5%)	41 (8.2%)	41 (8.1%)	49 (9.7%)	0.721
Heart failure (n, %)	278 (13.8%)	81 (16.0%)	72 (14.3%)	64 (12.7%)	61 (12.1%)	0.272
PVD (n, %)	151 (7.5%)	42 (8.3%)	39 (7.8%)	45 (8.9%)	25 (5.0%)	0.084
COPD (n, %)	284 (14.1%)	91 (17.9%)	64 (12.7%)	66 (13.1%)	63 (12.5%)	0.037
Hepatic disorders (n, %)	109 (5.4%)	24 (4.7%)	24 (4.8%)	29 (5.7%)	32 (6.3%)	0.61
Diabetes mellitus (n, %)	495 (24.5%)	67 (13.2%)	68 (13.5%)	116 (23.0%)	244 (48.4%)	< 0.001
RF (n, %)	251 (12.4%)	79 (15.6%)	50 (10.0%)	58 (11.5%)	64 (12.7%)	0.048
Malignant neoplasms (n, %)	271 (13.4%)	81 (16.0%)	68 (13.5%)	65 (12.9%)	57 (11.3%)	0.178
CCI	6.00 (4.00, 8.00)	6.00 (4.00, 8.00)	5.00 (4.00, 7.00)	6.00 (4.00, 7.00)	6.00 (4.00, 8.00)	0.168
Outcomes						
30-day ACM (n, %)	482 (23.9%)	86 (17.0%)	105 (20.9%)	138 (27.3%)	153 (30.4%)	< 0.001
90-day ACM (n, %)	608 (30.1%)	121 (23.9%)	142 (28.3%)	160 (31.7%)	185 (36.7%)	< 0.001
1-year ACM (n, %)	774 (38.4%)	166 (32.7%)	185 (36.9%)	203 (40.2%)	220 (43.7%)	0.003

Table 1. Characteristics and outcomes of participants categorized by GPR.

SIRS scores, a higher incidence of diabetes and renal diseases, and increased body temperature and heart rate. Additionally, these participants had higher WBC counts and elevated APTT. Compared to subjects in the lower GPR quartile, those in the higher quartile had higher 30-day mortality (17.0% vs. 20.9% vs. 27.3% vs. 30.4%, P < 0.001), 90-day mortality (23.9% vs. 28.3% vs. 31.7% vs. 36.7%, P < 0.001), and 1-year mortality (32.7% vs. 36.9% vs. 40.2% vs. 43.7%, P = 0.003).

Clinical outcomes

The utilization of the K–M survival analysis facilitated the examination of ACM rates across different GPR quartiles, as depicted in Fig. 2. We observed that the participants.

with elevated GPR indices exhibited an increased ACM risk at 30 day, 90 day, and 1 year. The relationship between the GPR and ACM at various intervals (30 day, 90 day, and 1 year) was assessed using Cox proportional hazards modeling. The findings indicated the GPR as a significant predictor of 90-day mortality in both the initial adjusted model 2 (HR: 1.26; 95% CI: 1.17–1.35; P < 0.001) and the comprehensive adjusted model 3 (HR: 1.27; 95% CI: 1.18–1.37; P < 0.001) when analyzed as a continuous variable. Table 2 summarizes the detailed associations between GPR and ACM at 30-day, 90-day, and 1 year.

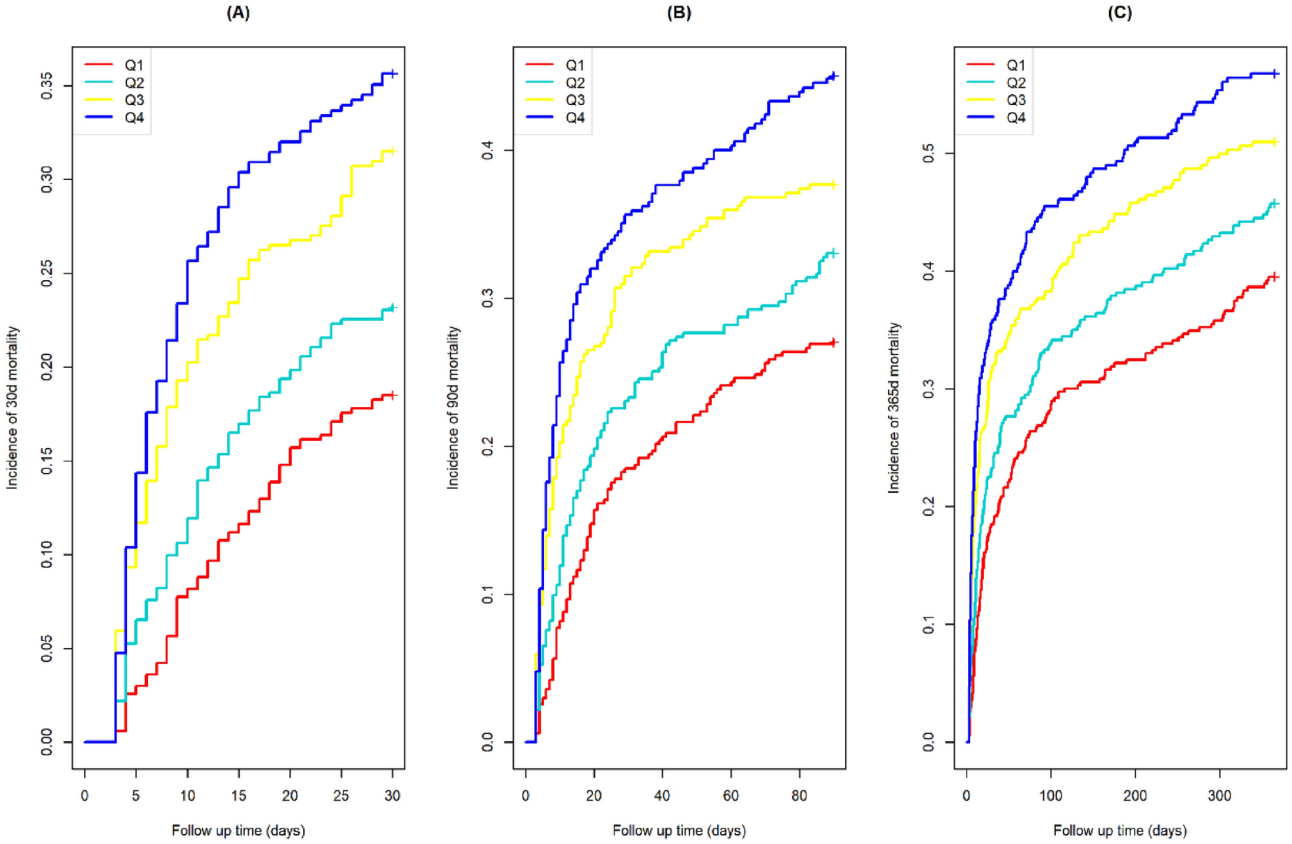

Fig. 2. Kaplan–Meier survival analysis curves for **A** 30-day, **B** 90-day, and **C** 1 year ACM.

When categorizing the GPR as an ordinal variable, subjects in the highest quartile had a significantly increased risk of 90-day ACM in the Cox proportional hazards models: the initial adjusted model 2 (HR: 1.91; 95% CI: 1.52–2.40; $P < 0.001$) and the fully adjusted model 3 (HR: 1.96; 95% CI: 1.55–2.47; $P < 0.001$), relative to those in the lowest quartile, indicating a rising trend in mortality risk with increasing GPR levels. This pattern was also mirrored in the multivariate Cox regression analyses of the 30-day and 1-year mortality rates. Additionally, RCS regression analysis did not indicate a nonlinear increase in the 30-day, 90-day and 1-year mortality risks with increasing GPR values ($P\ non-linearity = 0.064$, 0.116 and 0.153, respectively), as illustrated in Fig. 3.

Subgroup analysis

The risk stratification value of GPR for the primary endpoints was further analyzed in multiple subgroups of the enrolled patients according to sex, age, diabetes, and heart failure (Fig. 4). The GPR was significantly associated with a higher risk of 90-day mortality in patients with ICH subgroups of female (HR: 1.44; 95% CI: 1.29–1.60), those without diabetes (HR: 1.36; 95% CI: 1.24–1.50), those with heart failure (HR: 1.33; 95% CI: 1.12–1.58). Similarly, for 30-day and 1-year mortality, a significant correlation was observed with the GPR across all subgroups.

Discussion

In this study, we evaluated the correlation between GPR and ACM in critically ill patients with ICH from an American cohort. We found that elevated GPR was related to both short- and long-term ACM in these patients. Notably, even after adjusting for potential confounding factors, GPR remained robustly linked to ACM in the short and long term. The RCS regression analysis showed no nonlinear relationship between the GPR and ACM. Subgroup analyses revealed no significant changes in this relationship. Consequently, the GPR can be a potentially valuable tool in clinical decision-making and can be used as a prognostic factor for short- and long-term prognosis after ICH.

Patients with ICH commonly experience a hypermetabolic stress state in the acute phase that fosters augmented peripheral glucose uptake, utilization, and production, leading to the development of hyperlactatemia, suppression of gluconeogenesis, and insulin resistance[23]. This cascade of events establishes a hyperglycemic environment to ensure ample energy for the body's repair processes after critical illness, and are long deemed a benefical[24]. However, hyperglycemia induced by critical illness is also associated with adverse outcome. Previous studies have reported that hyperglycemia is associated with poor functional outcomes and increased mortality in ICH[25–27], with some studies suggesting a stronger relationship among non-diabetic patients[9,28]. Additionally, several studies believed that the effects of stress hyperglycemia were correlated with early ICH severity[29,30].

Categories	Model 1		Model 2		Model 3	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
30-days ACM						
Continues variable per unit	1.29 (1.20 –1.4)	< 0.001	1.31 (1.22–1.41)	< 0.001	1.32 (1.22–1.42)	< 0.001
Quartile						
Q1	Reference		Reference		Reference	
Q2	1.28 (0.96–1.70)	0.092	1.34 (1.01–1.79)	0.043	1.36 (1.02–1.81)	0.035
Q3	1.77 (1.36–2.32)	< 0.001	1.88 (1.44–2.47)	< 0.001	1.94 (1.48 – 2.54)	< 0.001
Q4	2.03 (1.56–2.65)	< 0.001	2.20 (1.68–2.86)	< 0.001	2.23 (1.71–2.91)	< 0.001
P for trend	1.27 (1.17–1.38)	< 0.001	1.30 (1.20–1.41)	< 0.001	1.31 (1.21–1.42)	< 0.001
90-days ACM						
Continues variable per unit	1.24 (1.16–1.34)	< 0.001	1.26 (1.17–1.35)	< 0.001	1.27 (1.18–1.37)	< 0.001
Quartile						
Q1	Reference		Reference		Reference	
Q2	1.23 (0.97–1.57)	0.092	1.32 (1.03–1.68)	0.026	1.34 (1.05–1.70)	0.020
Q3	1.47 (1.16–1.86)	0.001	1.58 (1.25–2.00)	< 0.001	1.63 (1.29–2.07)	< 0.001
Q4	1.76 (1.40–2.22)	< 0.001	1.91 (1.52–2.40)	< 0.001	1.96 (1.55–2.47)	< 0.001
P for trend	1.21 (1.12–1.30)	< 0.001	1.23 (1.15–1.33)	< 0.001	1.24 (1.16–1.34)	< 0.001
1-year ACM						
Continues variable per unit	1.20 (1.12–1.28)	< 0.001	1.20 (1.13–1.29)	< 0.001	1.22 (1.14–1.31)	< 0.001
Quartile						
Q1	Reference		Reference		Reference	
Q2	1.18 (0.95–1.45)	0.131	1.27 (1.03–1.57)	0.023	1.30 (1.05–1.60)	0.016
Q3	1.37 (1.11–1.68)	0.003	1.47 (1.20–1.81)	< 0.001	1.54 (1.25–1.89)	< 0.001
Q4	1.54 (1.26–1.89)	< 0.001	1.66 (1.36–2.04)	< 0.001	1.73 (1.41–2.11)	< 0.001
P for trend	1.16 (1.08–1.23)	< 0.001	1.18 (1.11–1.26)	< 0.001	1.19 (1.12–1.27)	< 0.001

Table 2. Cox proportional hazard ratios for ACM at 30-day, 90-day, and 1-year. Model 1: unadjusted; Model 2: adjusted age, sex, and CCI; Model 3: adjusted age, sex, CCI, WBC count, RBC count, platelet count, and GCS.

Similarly, serum potassium levels play a crucial role in maintaining basic cellular functions and are an important clinical blood biomarker. In a large retrospective before-after study including 10,451 ICU patients, Hessels et al. indicated that hypokalemia, hyperkalemia and potassium variability are independently associated with increased mortality[31]. Additionally, Uijtendaal et al. found that the highest mortality was seen in intensive care patients with low serum glucose concentrations combined with high serum potassium concentrations and in patients with high serum glucose concentrations combined with low serum potassium concentrations[32]. Thus, the GPR, a composite measure derived from glucose and potassium levels, has been suggested as a potential indicator of various neuropsychiatric conditions, including aneurysmal subarachnoid hemorrhage (aSAH)[14] and traumatic brain injury[33]. In a retrospective cohort study including 565 patients with aSAH, Fujiki et al. reported that GPR at admission was significantly associated with the H–K grade and Glasgow score at discharge and was a more useful prognostic factor than glucose and potassium levels alone[14]. Jung et al. found that serum GPR was an independent factor associated with 3-month mortality after aSAH[34]. An additional investigation encompassing 744 patients underscored the utility of GPR in forecasting postoperative rebleeding in non-diabetic patients with aSAH[35]. Ami et al. reported that patients with a serum GPR $\geq$ 50 at admission may be more likely to have a poor outcome after severe traumatic brain injury[33]. Demirtaș et al. advocated that GPR has a high potential as a rapid, easy preliminary marker for the exclusion of patients who will not subsequently develop delayed neuropsychiatric syndrome[13]. Furthermore, patients with high GPR levels have a significantly higher rate of hemorrhagic transformation after ischemic stroke[36]. However, there are still few studies on ICH[15]. Therefore, studies on the correlation between GPR and the risk and clinical prognosis of ICH are urgently needed. A retrospective cohort study conducted by Wu et al. showed that GPR remarkably discriminated against patients at risk of poor outcomes at 90 days after ICH[15]. Additionally, in this study, we provide evidence regarding the relationship between GPR levels and short- and long-term ACM. In critically ill patients, the predictive capacity for imminent short-term mortality outcomes may overshadow the significance of long-term survival projections. Nonetheless, for individuals who successfully navigate beyond hospital discharge, the value of an effective prognostic marker for long-term mortality cannot be overemphasized because it provides vital insights into long-term health trajectories[37]. Collectively, these studies demonstrate the prospective value of GPR as a predictive tool for the clinical outcomes of cerebrovascular diseases.

The precise pathophysiological underpinnings that delineate the correlation between GPR and etiology, as well as the progression of ICH and its associated mortality, remain unclear. Elevated intracranial pressure after ICH could directly or indirectly influence the structure and function of the hypothalamus-pituitary-thyroid and hypothalamus–pituitary–adrenal axes, leading to an increase in hydrocortisone, growth hormone, catecholamines, and glucagon[38,39]. Additionally, systemic inflammation and oxidative responses are

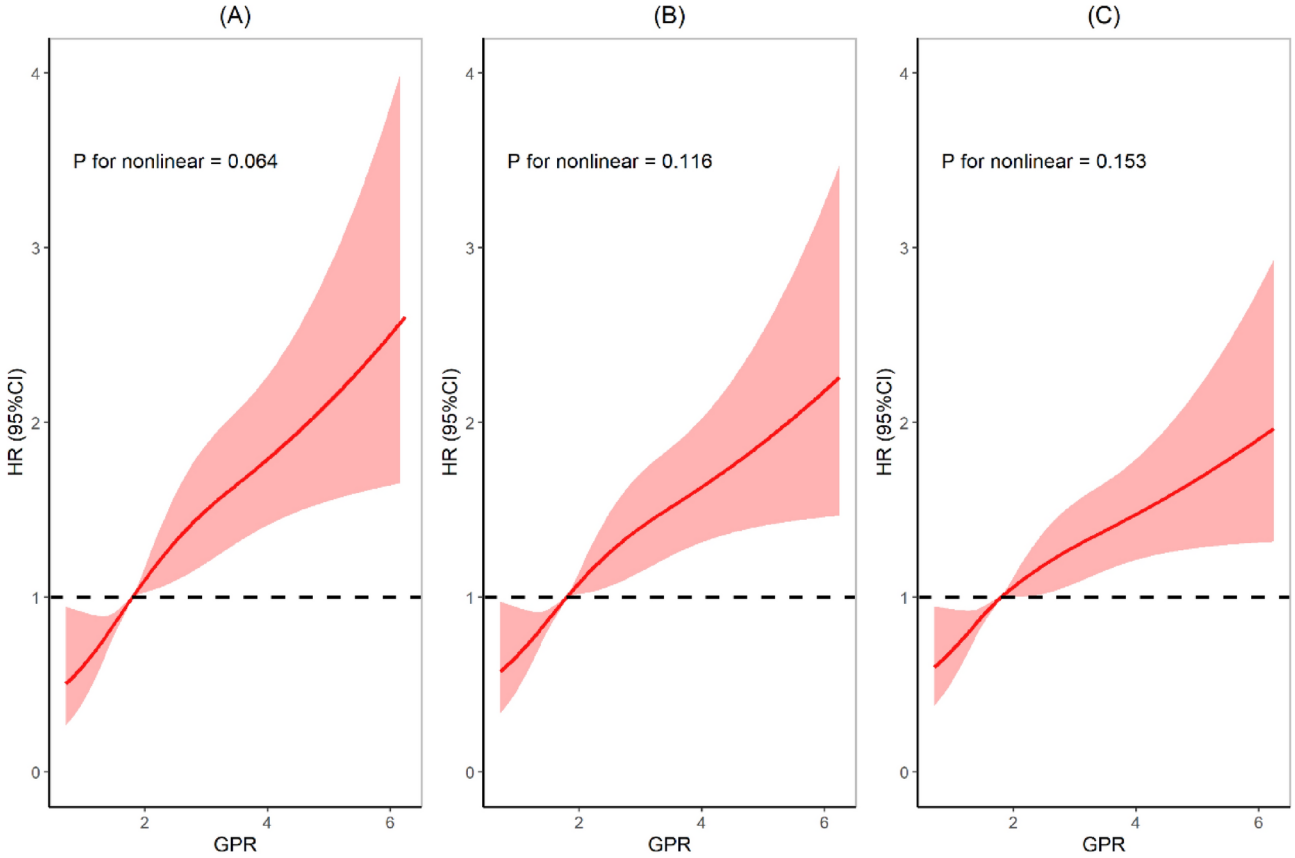

Fig. 3. Restricted cubic spline curve for **A** 30-day, **B** 90-day, and **C** 1-year ACM.

strengthened to produce more cytokines such as tumor necrosis factor-alpha and interleukin-6[40]. The complex mechanisms of these hormones and cytokines induce hyperglycemic responses and insulin resistance[41]. The regulation of sodium/potassium ATPase by high catecholamine levels and insulin secretion leads to potassium influx[42]. In addition, high cortisol levels would activate the renin–angiotensin–aldosterone system to induce low serum potassium[43]. These pathophysiological alterations collectively promote the onset and progression of cerebrovascular disorders and culminate in adverse clinical outcomes. Thus, considering the combined effects of serum glucose and potassium levels, the GPR may be a good indicator of stress injury that reflects the condition of the whole body in severe disease[16].

The principal advantage of this study is that it established a high GPR as an important predictor of increased ACM among critically ill patients with ICH in an American cohort. However, this study has some limitations. First, the retrospective design of the observational study means that causality between GPR and ACM cannot be established definitively. Although multivariate adjustments and subgroup analyses were used to account for potential confounding factors, some variables, such as the timing of ICH onset, the volume of hemorrhage and specific causes of death, were not available in the database that may influence the results, leaving room for residual confounding factors. Additionally, due to potential collinearity, diabetes was not included as a separate variable in the multivariate model, as it is already incorporated within the CCI. Second, the study only evaluated the baseline GPR and did not track its dynamic fluctuations throughout the hospital and ICU stays that could have impacted patient outcomes. This limitation means that the prognostic significance of changes in GPR during hospitalization remains unknown and requires further investigation. Third, the study was conducted at a single center, limiting the generalizability of the findings to broader populations. The predictive value of the GPR for ICH needs to be validated in larger and more diverse populations across different geographical locations. In conclusion, while this study provides valuable insights into the prognostic significance of GPR in critically ill patients with ICH, its conclusions should be interpreted with caution due to the limitations mentioned above. Thesefore, larger, diverse, and multi-center studies were required for verification in the future before the findings of the present study can be widely adopted in clinical practice.

Conclusion

GPR is strongly associated with ACM in patients with critical illness due to ICH. This significant correlation highlights the potential of the GPR as a prognostic tool for risk stratification in patients with ICH. Monitoring GPR could potentially inform clinical decision-making and disease management strategies. However, additional research is required to explore whether effective management of GPR can lead to improved clinical outcomes and prognoses in these patients.

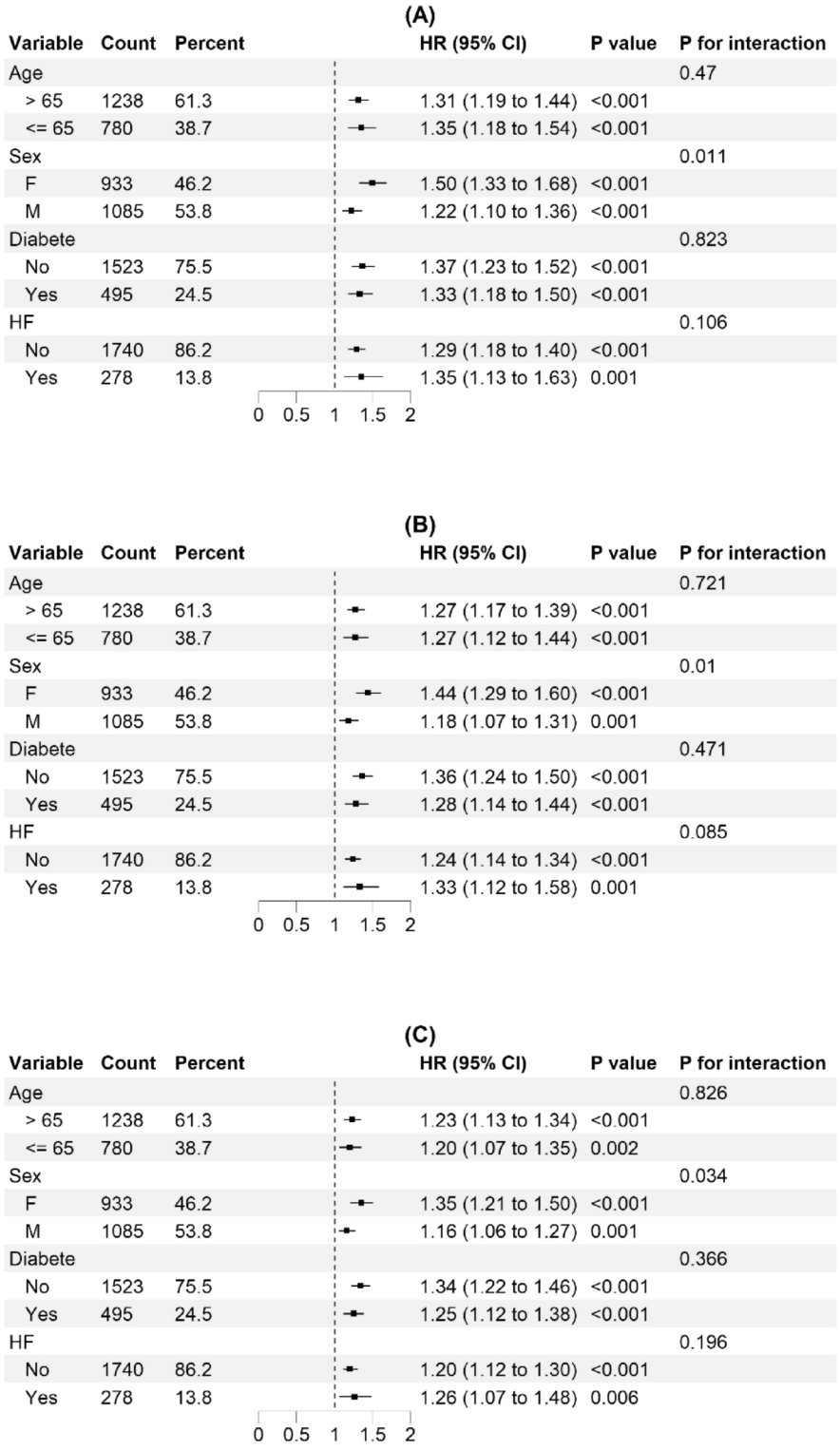

Fig. 4. Forest plots of hazard ratios for the hospital mortality in different subgroups .

Data availability

Publicly available data sets were analyzed in this study. These data can be found here: https://physionet.org/about/database/.

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Author contributions
Jianyi Liu and Yandeng Li designed the study. Jinayi Liu, Zhendong Pi, Jie Luo and Fuqun Luo extracted, collected, and analyzed data. Yizhi Guo, Zhiyuan Long and Chao Jiang prepared tables and figures. Jun Wen, Jianming Zhu and Zhihua Huang reviewed the results, interpreted data, and wrote the manuscript. All authors have contributed equally to the manuscript and approved the submission.

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Declarations

Ethics approval
Given MIMIC-IV database was approved by the Institutional Review Boards of Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology, and all protected health information was deidentified, requirement for ethical approval and informed consent was waived.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Additional information
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