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Original Article

Serum glucose-to-potassium ratio is associated with delirium and all-cause mortality in intensive care unit patients: insights from the MIMIC database analysis

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Abstract: Objectives: This study investigated the relationship between the glucose-to-potassium ratio (GPR) and intensive care unit (ICU) delirium as well as with all-cause mortality. Methods: We analyzed 32,025 first-time ICU patients from MIMIC-IV v3.1, categorized by GPR quartiles. Multivariable logistic regression, restricted cubic splines (RCS) were used to analyze the GPR-delirium relationship. The optimal GPR cutoff was determined using ROC analysis. Propensity score matching (PSM) was performed to control confounders. Cox models assessed associations with 28-, 90-, and 365-day mortality. Mediation analysis evaluated delirium's role. Results: Delirium incidence was 16.09% (n=5,152) and increased with GPR (Q1:13.93% vs. Q4:21.71%, P<0.001). After adjustment, Q4 had 58% higher delirium risk (OR=1.58, 95% CI 1.43-1.75). RCS showed a nonlinear positive association (P<0.001). The optimal GPR cutoff was 1.837 (AUC=0.829). After PSM, high GPR (≥1.837) remained a significant predictor (OR=1.43, 95% CI 1.24-1.64). High GPR was associated with high mortality at 28, 90, and 365 days (HR=1.17, 95% CI 1.08-1.28; HR=1.10, 95% CI 1.03-1.18; HR=1.11, 95% CI 1.05-1.18). Delirium mediated 19.067%, 32.218%, and 26.197% of the GPR-mortality relationship at these time points. Conclusions: Elevated GPR is associated with higher delirium risk and short- and long-term mortality in ICU patients, with delirium partially mediating this relationship. GPR may serve as a practical biomarker for early risk stratification.

Keywords: Serum glucose-to-potassium ratio, delirium, intensive care unit, mortality, medical information mart for intensive care

Introduction

Delirium is a common and serious neuropsychiatric problem in the Intensive Care Unit (ICU). It causes sudden changes in attention, awareness, and thinking. These changes happen fast and affect patient outcome. About 20% to 50% of ICU patients get delirium. For ventilated patients, this number rises to about 80% [1-3]. Many studies link delirium to longer ventilation, longer hospital stays, lasting cognitive problems, lower quality of life after discharge, and higher death risk in the hospital and long term [4, 5]. To understand the cause of delirium, procedures that put patients at risk must be identified so that patients are provided with individual attention to achieve better results. Existing interventions do not have sufficient personalization.

Available studies suggest that there are various mechanisms such as neuroinflammation, neurotransmitter dysfunction, oxidative stress, metabolic dysfunction, and low blood flow in the brain [6, 7]. Electrolyte issues and metabolic issues are unique. A high sugar level in

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blood is a typical metabolic reaction to stress in a critical illness. It is a product of catecholamines, glucocorticoids, and cytokine inflammation, which respond to extreme stress [8]. One isolated glucose reading may not be able to reflect the amount of sugar caused by stress. A clear association is still demonstrated in many studies between this condition and delirium, infection, and death [9, 10]. The most prevalent electrolyte disorders in ICUs include hypokalemia. This aggravates neuropsychiatric symptoms and increases the risk of death. It impairs neuromuscular transmission, impairs brain blood flow, and alters heart rhythm [11, 12]. The relationship between the severity of hypokalemia and delirium is yet to be further tested.

Serum glucose-potassium ratio (GPR) is a novel biomarker that reflects metabolic and electrolyte status. Nevertheless, individual glucose or potassium values are missing certain metabolic alterations under stress. They may be altered by GPR, which also can be an indication of neuroendocrine activity [13]. According to past studies, GPR is useful in predicting stroke and TBI outcomes. Increased GPR is associated with increased risk of death [14, 15]. GPR predicts poor outcomes in critically ill patients, but direct proof tying it to neurological damage is still missing. It may still work as a bedside risk tool, but one key question remains: Can GPR predict delirium and death in ICU patients? Its value as a clinical biomarker needs more testing. Studying GPR for delirium prediction has academic and practical weight.

We did a retrospective cohort study to fill this gap. A top critical care research platform, the MIMIC-IV version 3.1 database, was used. The database holds lab results, patient details, treatments and outcomes. Many machine learning and correlation studies use it [16]. We used this real-world data to look at two things: First, the link between GPR and delirium risk in ICU patients; second, the link between GPR and short- and long-term death at 28, 90 and 365 days. This work may give new evidence and practical help for delirium identification and resource use. The database has limits, such as its retrospective design, that may affect how well our results apply to other settings.

Materials and methods

Data source

This retrospective cohort study was conducted using data derived from the MIMIC-IV v3.1 database [16]. The Massachusetts Institute of Technology (MIT), Philips Healthcare and the Beth Israel Deaconess Medical Center (BIDMC) jointly developed the MIMIC-IV database. As a publicly accessible medical database, it contains detailed clinical data on over 90,000 ICU patients, covering demographic information, hospitalization records, laboratory test results, medication treatments, diagnoses, and nursing notes. The authors of this study have obtained certification for database access (certificate number: 66989309) which could qualify them to use and extract data from the database. Given that this study did not involve clinical interventions and all patient data were anonymized, informed consent from patients or approval from an ethics committee was not required.

Study population

We included patients admitted to ICU for the first time, and applied exclusion criteria: (1) Age under 18 years; (2) ICU stay under 24 hours; (3) Diagnosed with psychiatric disorders; (4) No delirium assessment performed or diagnosed with delirium within 24 hours of ICU admission; (5) Missing serum potassium or glucose values (**Figure 1**).

Definitions of GPR, delirium, and outcomes

The GPR was derived from the ratio of serum glucose to potassium levels (mmol/L) [17]. Delirium was defined as a positive Confusion Assessment Method for the ICU (CAM-ICU) assessment [18]. CAM-ICU and Richmond Agitation-Sedation Scale (RASS) scores were obtained from the MIMIC-IV v3.1 database. Delirium assessment using CAM-ICU was performed for patients with a RASS score ≥-3. The primary outcome was incident delirium during ICU hospitalization, with secondary outcomes encompassing all-cause mortality (28, 90 and 365 days).

Data extraction and processing

For the data extraction of this project, we use structured query language and navigation pre-

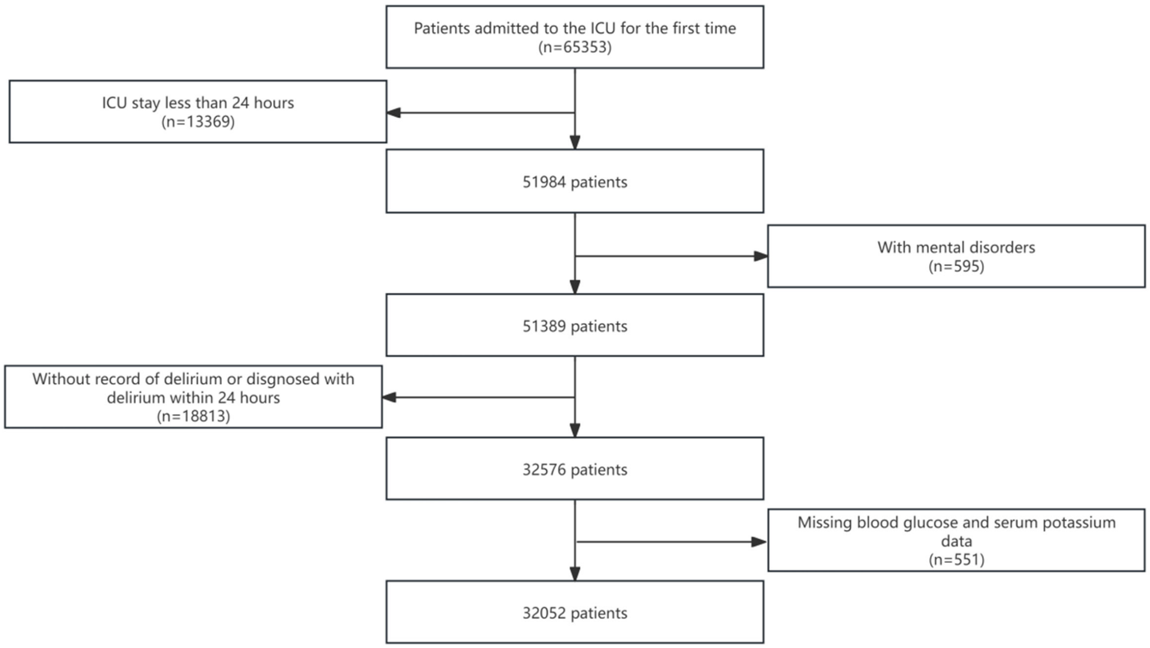


Figure 1. Research flow chart.

mium lite17 to query the MIMIC-IV version 3.1 database. The retrieved data were: (1) Basic demographic characteristics: age, gender; (2) Pre-existing comorbidities: sepsis, chronic pulmonary disease, myocardial infarction, stroke, diabetes; (3) Illness severity scores on the first day of ICU admittance: the Charlson Comorbidity Index (CCI) score and the Sequential Organ Failure Assessment (SOFA) score; (4) Vital signs before the first 24 hours in the ICU: heart rate, mean arterial pressure (MAP), respiratory rate, body temperature, and peripheral oxygen saturation (SpO_2); (5) Interventions during the ICU stay such as mechanical ventilation and administration of propofol, midazolam, or vasoactive drugs; (6) Laboratory values from the first ICU day: international normalization ratio (INR), anion gap, bicarbonate, partial thromboplastin time (PTT), calcium, BUN, potassium, Red blood cell Distribution Width (RDW), White Blood Cell count (WBC), sodium, glucose, creatine, and hemoglobin. We excluded variables having more than 20% missing data from analysis. For the rest of the variables, we used a multiple imputation technique to deal with the missing data so as to maintain the dataset and strengthen robustness in the following analysis. Missing data proportions of each variable and some more information regarding our imputation are given in Supplementary Table 1.

Statistical analysis

Continuous variables were reported as medians with IQR and compared between groups using the means comparison Mann-Whitney U test. We organized the categorical data into counts and percentages, and we used chi-square tests to see whether there were any differences between the groups. Four models were constructed: Model 1 (unadjusted) included only GPR. Model 2 made the adjustments for age, gender, vitals and comorbidities. Model 3 also contained laboratory values. Model 4 additionally controlled for severity scores and interventions. In order to avoid multicollinearity, the variables with variance inflation factor (VIF) >5 were deleted prior to final modeling [19]. RCS was used to explore a GPR-delirium association that was not linear. The ROC analysis was performed to evaluate the discriminative ability of GPR, from which the optimal cut-off value was determined. Given this threshold, PSM was done (1:1 nearest-neighbor, caliper=0.25SD), and balance was checked using Standardized Mean Difference (SMD) (<0.1 considered reasonable) [20]. Sensitivity analysis was done using univariate and multivariate regression. Interaction and subgroup analyses were done to check out effect changes across the groups we planned to use. Multivariable Cox proportional hazards models-including variables with P<0.05 from univariate screening-were fitted to evaluate the association between GPR and 28-, 90-, and 365-day all-cause mortality after ICU admission. The mediating role of delirium in the relationship between GPR and all-cause mortality (28, 90, and 365 days) was assessed using mediation analysis. The mediation model was estimated using a non-parametric bootstrap approach with 50 simulation iterations to obtain 95% confidence intervals (CIs) and *p*-values for the indirect and direct effects. The proportion mediated was calculated to quantify the contribution of the indirect path to the total effect. In this study, we performed the data analysis using SPSS 27.0 and R 4.3.3 software, with logistic regression analysis conducted in SPSS 27.0 and all other statistical analyses carried out in R 4.3.3. Significance was defined as a two-sided *p*-value <0.05.

Results

Baseline characteristics

Thirty-two thousand and twenty-five patients in the ICU were enrolled in this study at the time of their first admission. Participants were stratified into four groups according to GPR quartiles: Q1 (GPR<1.388), Q2 (1.388≤GPR<1.687), Q3 (1.687≤GPR<2.135), and Q4 (GPR≥2.135). Detailed baseline characteristics are summarized by group in **Table 1**. A total of 5,152 patients experienced delirium during their ICU stay, corresponding to an overall incidence rate of approximately 16.09%. With increasing GPR quartiles, the following clinical trends were observed. Demographics: The proportion of female patients gradually increased. Vital signs: Heart rate, MBP, respiratory rate, and body temperature showed an upward trend, while oxygen saturation significantly decreased. Comorbidities: The prevalence of sepsis, chronic pulmonary disease, myocardial infarction, diabetes and cerebrovascular disease increased significantly across higher GPR quartiles. The CCI also increased significantly. Laboratory tests: PTT, anion gap, BUN, glucose, creatinine, WBC, and RDW levels increased, whereas bicarbonate, INR, calcium, potassium, and sodium levels decreased. Treatments: The use of mechanical ventilation and midazolam rose, whereas the administration of propofol and vasoactive agents declined. Clinical outcomes: ICU length of stay was significantly prolonged. The incidence of delirium progressively increased across quartiles (13.93% in Q1 vs. 21.71% in Q4). The 28-, 90- and 365-day all-cause mortality was significantly higher in the higher GPR groups (all P<0.001).

Logistic regression analysis of the association between GPR and delirium in ICU

To examine the relationship between the GPR and delirium in ICU patients, logistic regression analyses were conducted with GPR treated both as a continuous variable and as a categorical variable according to quartiles. Four progressively adjusted models were applied to ensure the robustness of the findings. As shown in **Table 2**, when GPR was analyzed as a continuous variable, an increase in GPR was consistently associated with a higher risk of delirium across all models, indicating a stable positive relationship (P<0.001).

After being fully adjusted in Model 4, the odds ratios (95% CI) for delirium in terms of consecutive GPR quartiles, taking Q1 as the point of reference, stood at: Q2, 0.97 (0.87-1.07); Q3, 1.15 (1.04-1.27); and Q4, 1.58 (1.43-1.75). These estimations imply the risk of occurrence of delirium increases as the GPR level increases. To enforce this pattern, a formal trend test was conducted, which provided a *p*-value of trend below 0.001 in all four models, which indicated a dose-response relationship between high GPR and delirium.

Exploration of a nonlinear association between GPR and delirium

We used RCS analysis to investigate the possible nonlinear correlations between GPR and delirium. In all models, both unadjusted and adjusted, the overall relationship between the variables and the nonlinear components of the same were found to be significant (overall and nonlinear *p*-values <0.001; **Figure 2**). The resultant fitted curve showed that the risk of delirium in terms of odds ratio was less than 1 with a lower value in GPR, a sign that delirium was being guarded against. An upward rise in the odds ratio with a consistent value at the higher GPR was observed which confirmed an increase in the risk of delirium with higher levels of GPR. These findings demonstrated a clear and grad-

Table 1. Baseline characteristics of included patients

Variable	Total (n=32025)	Q1 (n=7963)	Q2 (n=8045)	Q3 (n=8002)	Q4 (n=8015)	*P*
Demographic						
Age (years)	67.12 (55.77, 77.42)	67.43 (55.34, 78.06)	66.81 (55.18, 77.09)	67.16 (56.16, 77.46)	67.10 (56.42, 76.95)	0.174
Gender: male, n (%)	18371 (57.36)	4716 (59.22)	4921 (61.17)	4557 (56.95)	4177 (52.11)	<0.001
Vital signs						
Heart Rate (bpm)	84.00 (74.00, 98.00)	81.00 (72.00, 95.00)	82.00 (73.00, 96.00)	84.00 (74.00, 98.00)	88.00 (76.00, 103.00)	<0.001
Mbp (mmHg)	84.00 (73.00, 95.50)	82.00 (72.00, 94.00)	83.00 (73.00, 94.00)	84.00 (74.00, 96.00)	85.00 (74.00, 98.00)	<0.001
Resp Rate (bpm)	18.00 (15.00, 22.00)	17.00 (15.00, 21.75)	18.00 (15.00, 22.00)	18.00 (15.00, 22.00)	19.00 (16.00, 23.00)	<0.001
Temperature (°C)	36.72 (36.44, 37.00)	36.67 (36.40, 36.94)	36.72 (36.44, 37.00)	36.72 (36.44, 37.00)	36.72 (36.44, 37.00)	<0.001
SpO_2 (%))	98.00 (96.00, 100.00)	98.00 (96.00, 100.00)	98.00 (96.00, 100.00)	98.00 (96.00, 100.00)	98.00 (95.00, 100.00)	<0.001
Comorbidities, n (%)						
Sepsis, n (%)	13595 (42.45)	3234 (40.61)	3171 (39.42)	3388 (42.34)	3802 (47.44)	<0.001
Myocardial Infarct, n (%)	5651 (17.65)	1347 (16.92)	1362 (16.93)	1330 (16.62)	1612 (20.11)	<0.001
Cerebrovascular Disease, n (%)	5520 (17.24)	1294 (16.25)	1333 (16.57)	1474 (18.42)	1419 (17.70)	<0.001
Chronic Pulmonary Disease, n (%)	7311 (22.83)	1863 (23.40)	1746 (21.70)	1769 (22.11)	1933 (24.12)	<0.001
Diabetes, n (%)		1572 (19.74)	1521 (18.91)	2000 (24.99)	4104 (51.20)	<0.001
Laboratory test						
Bicarbonate (mEq/L)	23.00 (21.00, 25.00)	23.00 (20.00, 25.00)	23.00 (21.00, 25.00)	23.00 (21.00, 25.00)	22.00 (19.00, 25.00)	<0.001
INR	1.30 (1.10, 1.50)	1.30 (1.10, 1.50)	1.30 (1.10, 1.50)	1.30 (1.10, 1.50)	1.20 (1.10, 1.50)	<0.001
Ptt (s)	30.30 (27.00, 36.20)	30.80 (27.50, 36.90)	30.30 (27.20, 35.80)	29.90 (26.80, 35.30)	30.00 (26.60, 37.10)	<0.001
Aniongap (mEq/L)	14.00 (11.00, 16.00)	13.00 (11.00, 16.00)	13.00 (11.00, 15.00)	13.00 (11.00, 16.00)	15.00 (12.00, 18.00)	<0.001
Calcium (mg/dL)	8.40 (7.90, 8.90)	8.40 (8.00, 9.00)	8.40 (7.90, 8.90)	8.40 (7.90, 8.90)	8.40 (7.90, 8.90)	<0.001
Bun (mg/dL)	17.00 (12.00, 26.00)	18.00 (13.00, 30.00)	16.00 (12.00, 23.00)	16.00 (12.00, 24.00)	19.00 (13.00, 29.00)	<0.001
Potassium (mg/dL)	4.10 (3.80, 4.50)	4.40 (4.10, 4.90)	4.10 (3.80, 4.50)	4.00 (3.70, 4.40)	3.90 (3.50, 4.40)	<0.001
Sodium (mg/dL)	139.00 (136.00, 141.00)	138.00 (136.00, 141.00)	139.00 (136.00, 141.00)	139.00 (136.00, 141.00)	138.00 (135.00, 141.00)	<0.001
Glucose (mg/dL)	125.00 (104.00, 156.00)	95.00 (86.00, 105.00)	114.00 (105.00, 125.00)	135.00 (124.00, 149.00)	191.00 (163.00, 240.00)	<0.001
Creatinine (mg/dL)	0.90 (0.70, 1.30)	1.00 (0.70, 1.40)	0.90 (0.70, 1.20)	0.90 (0.70, 1.20)	1.00 (0.70, 1.40)	<0.001
WBC (K/uL)	10.50 (7.60, 14.50)	9.60 (7.00, 13.50)	10.20 (7.50, 14.10)	10.90 (8.00, 14.60)	11.40 (8.10, 15.60)	<0.001
RDW (%)	14.00 (13.10, 15.40)	14.10 (13.20, 15.80)	13.80 (13.00,15.10)	13.80 (13.00, 15.10)	14.10 (13.20, 15.50)	<0.001
Hemoglobin (g/dL)	10.90 (9.20, 12.60)	10.50 (8.90, 12.40)	10.80 (9.10, 12.50)	11.00 (9.30, 12.70)	11.10 (9.40, 12.70)	<0.001
Disease severity score						
SOFA	1.00 (0.00, 3.00)	1.00 (0.00, 3.00)	1.00 (0.00, 3.00)	1.00 (0.00, 2.00)	1.00 (0.00, 3.00)	0.006
CCI	5.00 (3.00, 7.00)	5.00 (3.00, 7.00)	4.00 (2.00, 6.00)	4.00 (2.00, 7.00)	5.00 (3.00, 7.00)	<0.001
Intervention						
Ventilation, n (%)	24086 (75.21)	5759 (72.32)	6065 (75.39)	6146 (76.81)	6116 (76.31)	<0.001
Propofol, n (%)	12718 (39.71)	3190 (40.06)	3434 (42.68)	3189 (39.85)	2905 (36.24)	<0.001
Midazolam, n (%)	993 (3.10)	215 (2.70)	241 (3.00)	229 (2.86)	308 (3.84)	<0.001
Vasoactive, n (%)	10293 (32.14)	2681 (33.67)	2608 (32.42)	2571 (32.13)	2433 (30.36)	<0.001

Outcomes						
Los Icu (days)	2.28 (1.49, 4.15)	2.17 (1.43, 3.84)	2.16 (1.39, 3.87)	2.32 (1.50, 4.19)	2.62 (1.67, 4.97)	<0.001
Delirium, n (%)	5152 (16.09)	1109 (13.93)	1046 (13.00)	1257 (15.71)	1740 (21.71)	<0.001
28-day mortality, n (%)	2851 (8.90)	751 (9.43)	568 (7.06)	651 (8.14)	881 (10.99)	<0.001
90-day mortality, n (%)	4439 (13.86)	1176 (14.77)	938 (11.66)	1017 (12.71)	1308 (16.32)	<0.001
365-day mortality, n (%)	6665 (20.81)	1755 (22.04)	1422 (17.68)	1567 (19.58)	1921 (23.97)	<0.001

Mbp, mean blood pressure; SpO_2, saturation of the pulse oxygen; INR, international normalized ratio; PTT, Partial Thromboplastin Time; Bun, blood urea nitrogen; WBC, white blood cell count; RDW, red cell distribution width; SOFA, Sequential Organ Failure Assessment; CCI, Charlson Comorbidity Index.

Table 2. Logistic regression analysis of the association between GPR and delirium in ICU patients

Category	model 1 OR (95% CI)	*P*-value	model 2 OR (95% CI)	*P*-value	model 3 OR (95% CI)	*P*-value	model 4 OR (95% CI)	*P*-value
Continuous variable per unit	1.17 (1.14-1.20)	<0.001	1.12 (1.09-1.16)	<0.001	1.11 (1.08-1.14)	<0.001	1.13 (1.10-1.17)	<0.001
Quartile								
Q1	Reference		Reference		Reference		Reference	
Q2	0.92 (0.84-1.01)	0.086	0.94 (0.85-1.04)	0.211	0.99 (0.90-1.10)	0.893	0.97 (0.87-1.07)	0.506
Q3	1.15 (1.06-1.26)	0.002	1.11 (1.01-1.22)	0.032	1.17 (1.06-1.28)	0.002	1.15 (1.04-1.27)	0.007
Q4	1.71 (1.58-1.86)	<0.001	1.55 (1.42-1.70)	<0.001	1.57 (1.43-1.72)	<0.001	1.58 (1.43-1.75)	<0.001
P for trend		<0.001		<0.001		<0.001		<0.001

Model 1 is the base model, which includes only the GPR variable. Model 2 expands upon Model 1 by adjusting for additional variables, including age, gender, heart rate, mean blood pressure, respiratory rate, temperature, oxygen saturation, sepsis, myocardial infarction, cerebrovascular disease, chronic pulmonary disease, and diabetes. Model 3 further adjusts Model 2 by adding laboratory test result-related variables, including bicarbonate, INR, PTT, anion gap, calcium, BUN, sodium, creatinine, WBC, RDW, and hemoglobin. Model 4 was developed by further adjusting Model 3 for disease severity scores and clinical interventions, including SOFA, CCI, and the use of mechanical ventilation, propofol, midazolam, and vasoactive drugs.

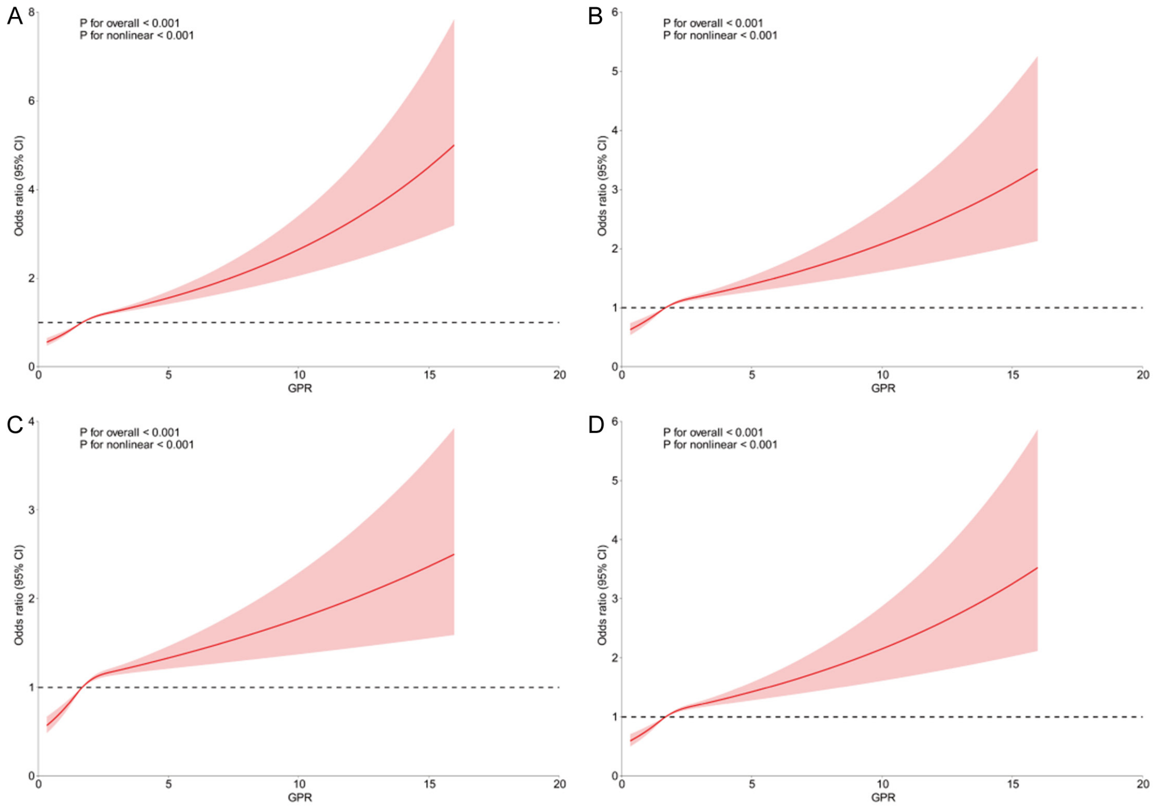


Figure 2. RCS analysis to explore the nonlinear relationship between GPR and delirium. A. Adjusted based on Model 1; B. Adjusted based on Model 2; C. Adjusted based on Model 3; D. Adjusted based on Model 4.

ed link between GPR and delirium, particularly pronounced at elevated GPR levels.

Results of ROC and logistic regression after PSM

In order to get a better idea of how well GPR predicted delirium, we calculated the model's sensitivity and specificity and created a ROC curve using the fully-adjusted model. AUC was 0.829 (95% CI: 0.822-0.835), good discrimination. In order to test whether the GPR model delivered superior predictive information versus the individual component models, we also created predictive models based on only glucose alone (Model 1) and potassium alone (Model 2), using the same fully adjusted set of variables The AUC of the glucose-only model was 0.828, and the AUC of the potassium-only model was 0.827. GPR's AUC was 0.829, which was slightly better than the AUC of the corresponding single component models (Supplementary Figure 1). The optimal cutoff value for GPR was determined to be 1.837 (**Figure 3**), with a corresponding sensitivity: 0.62 (95% CI: 0.62-0.63) and specificity: 0.49 (95% CI: 0.48-0.51). Based on this threshold, the study population was divided into these two groups below: GPR<1.837 and GPR≥1.837. PSM was then performed using this cutoff. As shown in **Figure 4**, the SMD of all covariates after PSM were < 0.1, indicating adequate balance between the two groups. After matching, 11,198 pairs of patients were retained for further logistic regression analysis. **Table 3** displays the results of univariate and multivariate logistic regression analyses after PSM. By univariate analysis, a higher GPR level was associated with a significantly elevated risk of delirium (OR=1.41, 95% CI: 1.31-1.51). After adjusting for covariates in the multivariable model, the association remained significant (adjusted OR=1.43, 95% CI: 1.24-1.64).

Subgroup analysis

In order to check for any difference in relation between GPR and delirium in different part of patients, some stratified analyses were done - both before and after the PSM - by age, gender,

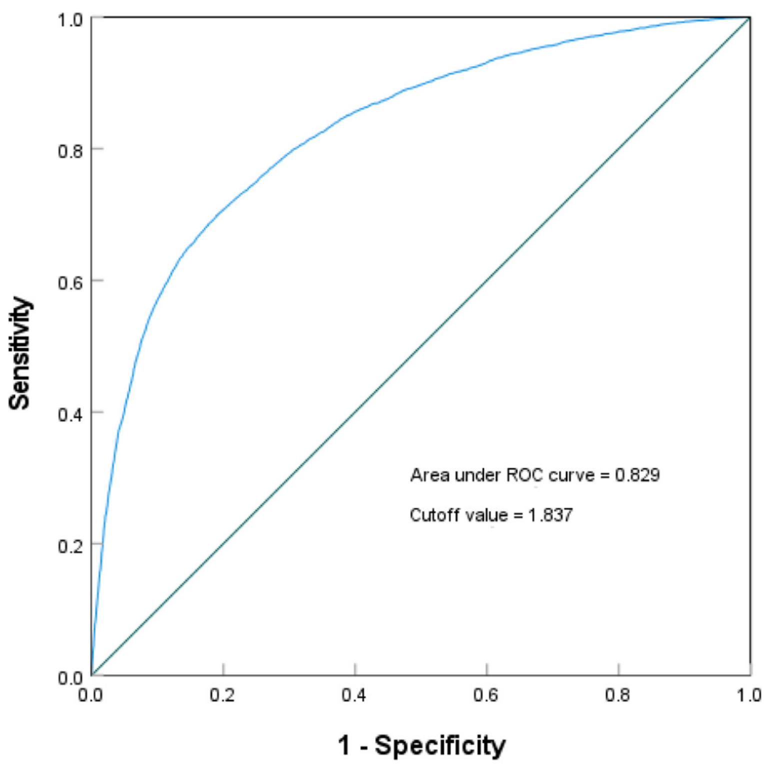


Figure 3. Result of receiver operating characteristic analysis.

sepsis, myocardial infarction, cerebrovascular accident, chronic pulmonary disease, diabetes mellitus, and principal operations such as mechanical ventilation, propofol, midazolam, and vasoactive drugs. Results are presented in **Figure 5**. In the overall cohort, and consistently before and after PSM, higher GPR remained significantly associated with increased delirium risk in all subgroups examined. Notably, interaction tests revealed that the strength of the association between elevated GPR (≥1.837) and delirium was modified by several factors. Significant interactions were detected for sepsis, cerebrovascular disease, propofol use, and vasoactive drug use by both the pre- and post-PSM analyses, indicating that the GPR-delirium association was more pronounced in patients with these conditions or treatment exposures. Interestingly, myocardial infarction showed a significant interaction before PSM, which disappeared after matching, whereas age showed no significant interaction before PSM but emerged as significant afterward. These findings imply that the initial interaction effects may have been confounded by baseline imbalances prior to PSM.

Survival analysis between GPR and 28-, 90-, and 365-day mortality

Tables 4-6 present the results of Cox proportional hazards regression analyses for all-cause mortality (28, 90, and 365 days). In the unadjusted models, the hazard ratios (HRs) with 95% CI for mortality in the high GPR group were as follows: 1.13 (1.04-1.23) for 28-day, 1.07 (1.01-1.15) for 90-day, and 1.09 (1.03-1.15) for 365-day mortality, respectively. Similar results were observed after multivariable adjustment, with the HRs and corresponding 95% CI reported as 1.17 (95% CI: 1.08-1.28), 1.10 (95% CI: 1.03-1.18), and 1.11 (95% CI: 1.05-1.18), all with *p*-values <0.05. These findings indicated that patients with increased GPR levels had a significantly increased risk of mortality. Kaplan-Meier survival curve analysis further demonstrated significant differences in survival between the two groups (**Figure 6**). The high GPR group had significantly lower survival rates at 28, 90, and 365 days compared to the low ground penetrating radar group (P<0.05).

Mediation analysis

As shown in **Figure 7**, we evaluated the mediating effect of delirium in the association between elevated GPR (≥1.837) and 28-, 90-, and 365-day mortality. The results demonstrated that in the 28-day mortality model (**Figure 7A**), the indirect effect (IE) of delirium was 0.003 (95% CI: 0.003-0.004), the direct effect (DE) was 0.012 (95% CI: 0.005-0.020), and the proportion mediated was 19.067%. In the 90-day mortality model (**Figure 7B**), the IE was 0.004 (95% CI: 0.004-0.006), the DE was 0.009 (95% CI: 0.001-0.017), and the proportion mediated significantly increased to 32.218%. In the 365-day mortality model (**Figure 7C**), the IE was 0.005 (95% CI: 0.004-0.006), the DE was 0.013 (95% CI: 0.004-0.021), and the propor-

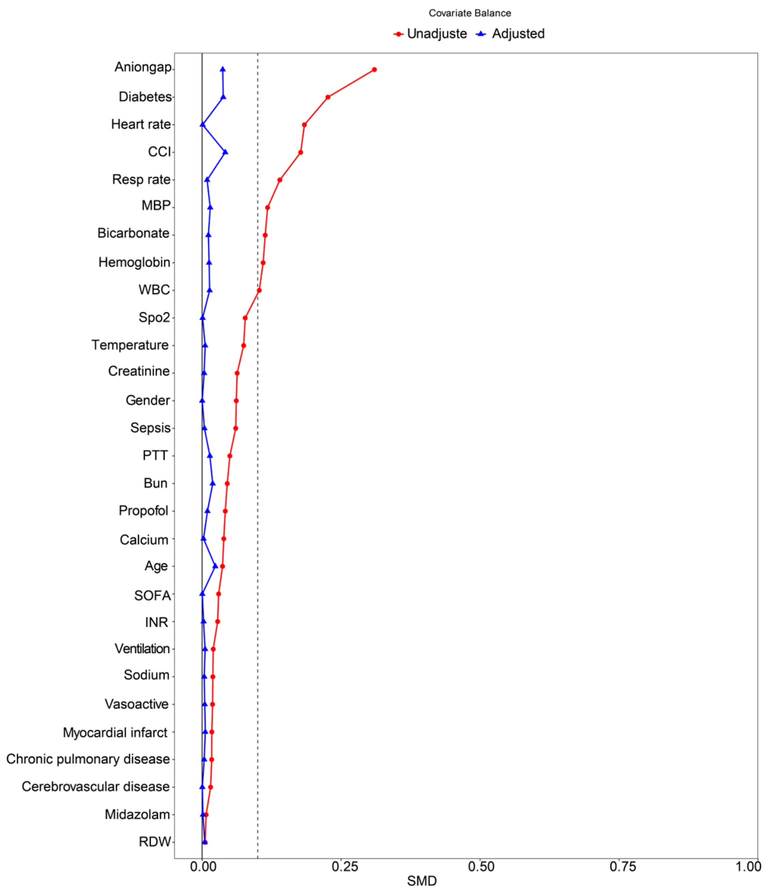


Figure 4. SMD for all variables after propensity score matching analysis. SMD: Standardized Mean Difference.

Table 3. Univariate and multivariate logistic regression before and after propensity score matching

Analysis	95% CI	*P*-value
Before PSM		
Univariate logistic regression	1.62 (1.52-1.72)	<0.001
Multivariate logistic regression	1.48 (1.38-1.59)	<0.001
After PSM		
Univariate logistic regression	1.41 (1.31-1.51)	<0.001
Multivariate logistic regression	1.43 (1.24-1.64)	<0.001

tion mediated was 26.197%. These findings suggested that GPR (≥1.837) was associated with a higher risk of 28-day, 90-day, and 365-day mortality in ICU, in part through its indirect effect mediated by delirium. In the process of all time points, we saw a consistent and significant mediating effect, which proves that delirium plays an important intermediary role in the relationship between GPR and mortality. This means delirium may be a modifiable goal to achieve better outcomes for ICU patients with high GPR.

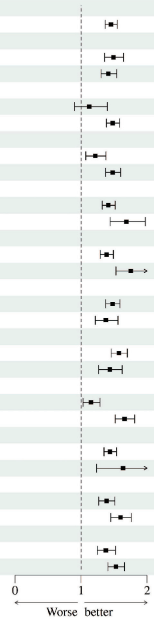
To evaluate whether the trajectory of illness severity could influence the mediation results, we conducted a sensitivity analysis that excluded patients with an ICU stay shorter than 48 hours. As shown in Supplementary Figure 2, the results remained consistent, further strengthening the evidence for delirium as a mediator in the association between GPR and mortality.

Discussion

Using the MIMIC-IV v3.1 database, glucose to phosphate ratio (GPR) was tested as a predictor of delirium and death in critically ill patients, and not only a marker of metabolic and electrolyte status. Earlier studies suggested a link between GPR and delirium [21], and our work builds on that. First, we used the newer, larger MIMIC-IV cohort, which gave more statistical power. It also made results more generalizable to real ICU populations. Second, we confirmed the link between GPR and delirium. We also discovered that GPR predicts death at 28-, 90- and 365-days. This reveals that GPR can be used more for critical care. Above all, mediation analysis revealed that delirium was partially a mediator of the GPR-death relationship. This is a new finding. It indicates that delirium mediates poor outcomes and metabolic-electrolyte imbalance. GPR is also one of the potent predictors of delirium and may be used as a combined biomarker to perform risk assessments and outcomes forecasting on the ICU. This provides new opportunities for the early identification of high-risk patients and tailored attention.

A

Variables	n (%)	GPR<1.837	GPR ≥ 1.837	OR (95%CI)	P	P for interaction
All patients	32025 (100.00)	2603/19347	2549/12678	1.45 (1.36 ~ 1.55)	<.001	
Gender						0.437
Female	13654 (42.64)	1020/7778	1157/5876	1.49 (1.36 ~ 1.64)	<.001	
Male	18371 (57.36)	1583/11569	1392/6802	1.42 (1.30 ~ 1.54)	<.001	
Ventilatiom						0.072
No	7939 (24.79)	209/4949	171/2990	1.12 (0.90 ~ 1.40)	0.302	
Yes	24086 (75.21)	2394/14398	2378/9688	1.48 (1.38 ~ 1.58)	<.001	
Sepsis						0.005
No	18430 (57.55)	652/11597	506/6833	1.22 (1.07 ~ 1.38)	0.002	
Yes	13595 (42.45)	1951/7750	2043/5845	1.48 (1.37 ~ 1.60)	<.001	
Myocardial Infarct						0.040
No	26374 (82.35)	2208/16067	2052/10307	1.41 (1.32 ~ 1.52)	<.001	
Yes	5651 (17.65)	395/3280	497/2371	1.69 (1.44 ~ 1.97)	<.001	
Cerebrovascular Disease						<.001
No	26505 (82.76)	2063/16129	1892/10376	1.39 (1.29 ~ 1.49)	<.001	
Yes	5520 (17.24)	540/3218	657/2302	1.75 (1.53 ~ 2.01)	<.001	
Chronic Pulmonary Disease						0.150
No	24714 (77.17)	1918/15062	1883/9652	1.48 (1.37 ~ 1.59)	<.001	
Yes	7311 (22.83)	685/4285	666/3026	1.38 (1.22 ~ 1.56)	<.001	
Diabetes						0.059
No	22828 (71.28)	2074/15524	1517/7304	1.57 (1.46 ~ 1.70)	<.001	
Yes	9197 (28.72)	529/3823	1032/5374	1.43 (1.27 ~ 1.62)	<.001	
Propofol						<.001
No	19307 (60.29)	778/11345	687/7962	1.15 (1.03 ~ 1.29)	0.014	
Yes	12718 (39.71)	1825/8002	1862/4716	1.66 (1.52 ~ 1.81)	<.001	
Midazolam						0.269
No	31032 (96.90)	2401/18802	2314/12230	1.44 (1.35 ~ 1.54)	<.001	
Yes	993 (3.10)	202/545	235/448	1.63 (1.24 ~ 2.16)	<.001	
Vasoactive						<.001
No	21732 (67.86)	1231/12985	1177/8747	1.38 (1.27 ~ 1.51)	<.001	
Yes	10293 (32.14)	1372/6362	1372/3931	1.60 (1.45 ~ 1.76)	<.001	
Age						0.071
<65	14328 (44.74)	1094/8684	1020/5644	1.38 (1.25 ~ 1.52)	<.001	
≥ 65	17697 (55.26)	1509/10663	1529/7034	1.53 (1.41 ~ 1.66)	<.001	



B

Variables	n (%)	GPR<1.837	GPR ≥ 1.837	OR (95%CI)	P	P for interaction
All patients	22396 (100.00)	1666/11198	2209/11198	1.42 (1.32 ~ 1.52)	<.001	
Gender						0.676
Female	10152 (45.33)	738/5075	979/5077	1.45 (1.30 ~ 1.61)	<.001	
Male	12244 (54.67)	928/6123	1230/6121	1.40 (1.27 ~ 1.54)	<.001	
Ventilation						0.083
No	5256 (23.47)	118/2598	145/2658	1.10 (0.85 ~ 1.43)	0.453	
Yes	17140 (76.53)	1548/8600	2064/8540	1.48 (1.37 ~ 1.60)	<.001	
Sepsis						0.020
No	12335 (55.08)	365/6191	457/6144	1.25 (1.08 ~ 1.44)	0.002	
Yes	10061 (44.92)	1301/5007	1752/5054	1.54 (1.41 ~ 1.69)	<.001	
Myocardial Infarct						0.091
No	18450 (82.38)	1411/9257	1806/9193	1.38 (1.28 ~ 1.49)	<.001	
Yes	3946 (17.62)	255/1941	403/2005	1.64 (1.37 ~ 1.97)	<.001	
Cerebrovascular Disease						0.006
No	18392 (82.12)	1305/9198	1655/9194	1.35 (1.25 ~ 1.47)	<.001	
Yes	4004 (17.88)	361/2000	554/2004	1.74 (1.49 ~ 2.04)	<.001	
Chronic Pulmonary Disease						0.369
No	17224 (76.91)	1225/8633	1649/8591	1.44 (1.33 ~ 1.57)	<.001	
Yes	5172 (23.09)	441/2565	560/2607	1.34 (1.16 ~ 1.54)	<.001	
Diabetes						0.361
No	14896 (66.51)	1178/7661	1493/7235	1.48 (1.35 ~ 1.61)	<.001	
Yes	7500 (33.49)	488/3537	716/3963	1.38 (1.21 ~ 1.57)	<.001	
Propofol						0.004
No	13692 (61.14)	496/6792	573/6900	1.15 (1.01 ~ 1.31)	0.030	
Yes	8704 (38.86)	1170/4406	1636/4298	1.58 (1.43 ~ 1.74)	<.001	
Midazolam						0.299
No	21661 (96.72)	1521/10839	2013/10822	1.41 (1.31 ~ 1.52)	<.001	
Yes	735 (3.28)	145/359	196/376	1.66 (1.20 ~ 2.28)	0.002	
Vasoactive						0.013
No	15261 (68.14)	800/7604	1008/7657	1.28 (1.16 ~ 1.42)	<.001	
Yes	7135 (31.86)	866/3594	1201/3541	1.58 (1.41 ~ 1.76)	<.001	
Age						0.004
<65	9906 (44.23)	716/4924	880/4982	1.27 (1.13 ~ 1.42)	<.001	
≥ 65	12490 (55.77)	950/6274	1329/6216	1.54 (1.41 ~ 1.70)	<.001	

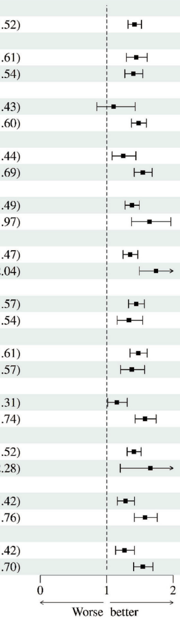


Figure 5. Subgroup analysis of the association between GPR and delirium. GPR, Glucose-to-Potassium Ratio; OR, odds ratio; CI, confidence interval.

Table 4. Association between GPR and risk of 28-day all-cause mortality

Variate	Univariable COX regression HR (95% CI)	*P*	Multivariable COX regression HR (95% CI)	*P*
GPR≥1.837	1.13 (1.04-1.23)	0.005	1.17 (1.08-1.28)	<0.001
Age	1.04 (1.04-1.04)	<0.001	1.02 (1.02-1.02)	<0.001
Gender	0.91 (0.83-0.99)	0.025	0.90 (0.83-0.99)	0.027
Heart Rate	1.01 (1.01-1.02)	<0.001	1.01 (1.01-1.01)	<0.001
Mbp	0.99 (0.99-0.99)	<0.001	1.00 (1.00-1.00)	0.682
Resp Rate	1.06 (1.05-1.06)	<0.001	1.03 (1.02-1.04)	<0.001
Temperature	0.94 (0.88-0.99)	0.036	0.92 (0.87-0.98)	0.006
Spo_2	0.95 (0.95-0.96)	<0.001	0.98 (0.97-0.99)	<0.001
Sepsis	3.08 (2.81-3.38)	<0.001	1.86 (1.68-2.06)	<0.001
Myocardial Infarct	1.19 (1.07-1.32)	0.002	0.76 (0.68-0.85)	<0.001
Cerebrovascular Disease	1.26 (1.13-1.39)	<0.001	1.43 (1.28-1.59)	<0.001
Chronic Pulmonary Disease	1.42 (1.29-1.56)	<0.001	0.94 (0.85-1.03)	0.182
Diabetes	0.94 (0.86-1.03)	0.179		
Bicarbonate	0.95 (0.94-0.96)	<0.001	1.01 (1.01-1.02)	0.022
INR	1.26 (1.23-1.29)	<0.001	1.05 (1.02-1.09)	0.003
PTT	1.01 (1.01-1.01)	<0.001	1.01 (1.01-1.01)	0.002
Calcium	0.90 (0.85-0.95)	<0.001	0.90 (0.85-0.95)	<0.001
Bun	1.02 (1.02-1.02)	<0.001	1.01 (1.01-1.01)	<0.001
Aniongap	1.09 (1.08-1.10)	<0.001	1.05 (1.03-1.06)	<0.001
Sodium	0.97 (0.96-0.98)	<0.001	0.98 (0.97-0.98)	<0.001
Creatinine	1.17 (1.15-1.20)	<0.001	0.86 (0.82-0.90)	<0.001
Wbc	1.01 (1.01-1.01)	<0.001	1.01 (1.01-1.01)	<0.001
Rdw	1.22 (1.20-1.23)	<0.001	1.12 (1.10-1.14)	<0.001
Hemoglobin	0.90 (0.89-0.92)	<0.001	1.04 (1.01-1.06)	<0.001
SOFA	1.13 (1.11-1.15)	<0.001	1.01 (0.99-1.04)	0.181
CCI	1.27 (1.26-1.29)	<0.001	1.18 (1.16-1.20)	<0.001
Ventilation	2.04 (1.80-2.31)	<0.001	1.33 (1.16-1.52)	<0.001
Propofol	1.10 (1.01-1.20)	0.029	1.16 (1.04-1.29)	0.006
Midazolam	2.08 (1.75-2.48)	<0.001	1.32 (1.10-1.58)	0.003
Vasoactive	1.80 (1.65-1.96)	<0.001	1.29 (1.16-1.43)	<0.001

Mbp, mean blood pressure; SpO_2, saturation of the pulse oxygen; INR, international normalized ratio; PTT, Partial Thromboplastin Time; Bun, blood urea nitrogen; WBC, white blood cell count; RDW, red cell distribution width; SOFA, Sequential Organ Failure Assessment; CCI, Charlson Comorbidity Index.

Strong direct evidence of the link between GPR and delirium in critically ill patients is still limited. A recent retrospective study found an initial link, but the nature of this link and its clinical meaning still needed more work. Past GPR research mostly looked at its role in predicting neurological problems and outcomes in specific critical illnesses. Demirtaş and colleagues proposed GPR as a marker for delayed neuropsychiatric problems after carbon monoxide poisoning, and they also studied its role in neurological injury pathways [22]. Other studies showed that GPR captures stress-related metabolic and electrolyte problems. It carries important prognostic information in many critical conditions. Zhou et al. found that serum GPR can predict injury severity and 6-month outcomes in acute traumatic spinal cord injury [23]. Yuan and others showed that high GPR is tied to higher short-term death in stroke patients [14, 24]. These results place GPR as a marker for poor neurological outcome. The link between GPR and delirium has not been tested in large, mixed ICU groups. It is not clear whether GPR predicts short- and long-term death in all ICU patients. It is also not clear whether delirium itself is a step between high GPR and higher death risk.

Table 5. Association between GPR and risk of 90-day all-cause mortality

Variate	Univariable COX regression HR (95% CI)	*P*	Multivariable COX regression HR (95% CI)	*P*
GPR≥1.837	1.07 (1.01-1.15)	0.042	1.10 (1.03-1.18)	0.006
Age	1.04 (1.03-1.04)	<0.001	1.02 (1.01-1.02)	<0.001
Gender	0.91 (0.85-0.97)	0.005	0.92 (0.86-0.99)	0.028
Heart Rate	1.01 (1.01-1.02)	<0.001	1.01 (1.01-1.01)	<0.001
Mbp	0.99 (0.99-0.99)	<0.001	1.00 (1.00-1.00)	0.170
Resp Rate	1.05 (1.05-1.06)	<0.001	1.03 (1.02-1.03)	<0.001
Temperature	0.96 (0.91-1.01)	0.085		
Spo_2	0.96 (0.95-0.96)	<0.001	0.98 (0.97-0.99)	<0.001
Sepsis	2.60 (2.42-2.80)	<0.001	1.72 (1.59-1.86)	<0.001
Myocardial Infarct	1.19 (1.09-1.30)	<0.001	0.77 (0.70-0.84)	<0.001
Cerebrovascular Disease	1.18 (1.09-1.29)	<0.001	1.30 (1.19-1.43)	<0.001
Chronic Pulmonary Disease	1.40 (1.30-1.52)	<0.001	0.90 (0.83-0.97)	0.008
Diabetes	1.02 (0.95-1.09)	0.635		
Bicarbonate	0.97 (0.96-0.97)	<0.001	1.02 (1.01-1.03)	<0.001
INR	1.24 (1.22-1.27)	<0.001	1.04 (1.01-1.08)	0.005
PTT	1.01 (1.01-1.01)	<0.001	1.01 (1.01-1.01)	<0.001
Calcium	0.92 (0.88-0.96)	<0.001	0.92 (0.88-0.96)	<0.001
BUN	1.02 (1.02-1.02)	<0.001	1.01 (1.01-1.01)	<0.001
Aniongap	1.08 (1.07-1.08)	<0.001	1.04 (1.03-1.05)	<0.001
Sodium	0.97 (0.96-0.97)	<0.001	0.98 (0.97-0.98)	<0.001
Creatinine	1.16 (1.14-1.18)	<0.001	0.85 (0.82-0.88)	<0.001
WBC	1.01 (1.01-1.01)	<0.001	1.01 (1.01-1.01)	<0.001
RDW	1.23 (1.21-1.24)	<0.001	1.12 (1.10-1.13)	<0.001
Hemoglobin	0.88 (0.87-0.89)	<0.001	1.00 (0.99-1.02)	0.668
SOFA	1.12 (1.10-1.13)	<0.001	1.02 (1.01-1.04)	0.009
CCI	1.29 (1.28-1.30)	<0.001	1.21 (1.19-1.23)	<0.001
Ventilation	1.68 (1.53-1.84)	<0.001	1.22 (1.11-1.35)	<0.001
Propofol	0.96 (0.90-1.03)	0.268		
Midazolam	1.92 (1.66-2.23)	<0.001	1.37 (1.17-1.59)	<0.001
Vasoactive	1.51 (1.41-1.62)	<0.001	1.23 (1.13-1.33)	<0.001

Mbp, mean blood pressure; SpO_2, saturation of the pulse oxygen; INR, international normalized ratio; PTT, Partial Thromboplastin Time; Bun, blood urea nitrogen; WBC, white blood cell count; RDW, red cell distribution width; SOFA, Sequential Organ Failure Assessment; CCI, Charlson Comorbidity Index.

From a pathophysiology viewpoint, high GPR is not just a ratio of high blood sugar and low potassium. It shows metabolic and electrolyte problems caused by body-wide stress. This double problem disrupts the central nervous system. It makes neuroinflammation, oxidative stress, energy problems, and ion imbalance worse, which may raise delirium risk [25]. The activation of HPA axis and inflammatory cytokine releases take place throughout the body as a result of stress. This damages the use of glucose and potassium simultaneously, and at the same time, strains nerve tissue. Microglia cause neuroinflammation and oxidative stress to be escalated by glucose issues. They destroy the blood-brain barrier. Such alterations impair the performance of neurons and destabilize the brain connections related to delirium [26-28]. Neuron stability is impaired by potassium issues, and the membrane potential is disrupted. The problems of glucose are energy shortage and unstable membrane potential caused by potassium problems that overwork Na+/K+-ATPase. This causes ineffective transmission of neurotransmitters [21, 29]. The weak blood-brain barrier permits the entry of peripheral inflammatory factors to the CNS. Problems with the systems of inflammation, metabolism, and

Table 6. Association between GPR and risk of 365-days all-cause mortality

Variate	Univariable COX regression HR (95% CI)	*P*	Multivariable COX regression HR (95% CI)	*P*
GPR≥1.837	1.09 (1.03-1.15)	0.002	1.11 (1.05-1.18)	<0.001
Age	1.04 (1.03-1.04)	<0.001	1.01 (1.01-1.01)	<0.001
Gender	0.92 (0.87-0.97)	0.003	0.96 (0.91-1.02)	0.217
Heart Rate	1.01 (1.01-1.01)	<0.001	1.01 (1.01-1.01)	<0.001
MBP	0.99 (0.99-0.99)	<0.001	1.00 (1.00-1.00)	0.141
Resp Rate	1.04 (1.04-1.05)	<0.001	1.02 (1.01-1.02)	<0.001
Temperature	0.97 (0.93-1.01)	0.151		
Spo_2	0.96 (0.95-0.96)	<0.001	0.98 (0.98-0.99)	<0.001
Sepsis	2.14 (2.02-2.27)	<0.001	1.51 (1.42-1.61)	<0.001
Myocardial Infarct	1.18 (1.10-1.26)	<0.001	0.77 (0.72-0.83)	<0.001
Cerebrovascular Disease	1.11 (1.03-1.19)	0.005	1.13 (1.05-1.22)	0.002
Chronic Pulmonary Disease	1.44 (1.36-1.53)	<0.001	0.90 (0.84-0.96)	<0.001
Diabetes	1.11 (1.05-1.18)	<0.001	0.68 (0.63-0.72)	<0.001
Bicarbonate	0.99 (0.98-0.99)	<0.001	1.03 (1.02-1.04)	<0.001
INR	1.23 (1.20-1.25)	<0.001	1.04 (1.01-1.07)	0.002
PTT	1.01 (1.01-1.01)	<0.001	1.01 (1.01-1.01)	0.007
Calcium	0.93 (0.90-0.97)	<0.001	0.93 (0.89-0.96)	<0.001
Bun	1.02 (1.02-1.02)	<0.001	1.01 (1.01-1.01)	<0.001
Aniongap	1.07 (1.06-1.07)	<0.001	1.04 (1.03-1.05)	<0.001
Sodium	0.97 (0.96-0.97)	<0.001	0.98 (0.97-0.98)	<0.001
Creatinine	1.16 (1.14-1.18)	<0.001	0.91 (0.88-0.94)	<0.001
WBC	1.01 (1.01-1.01)	<0.001	1.01 (1.01-1.01)	<0.001
RDW	1.23 (1.22-1.24)	<0.001	1.12 (1.10-1.13)	<0.001
Hemoglobin	0.88 (0.87-0.89)	<0.001	0.98 (0.97-0.99)	0.031
SOFA	1.09 (1.08-1.11)	<0.001	1.01 (1.00-1.03)	0.065
CCI	1.30 (1.29-1.31)	<0.001	1.25 (1.24-1.27)	<0.001
Ventilation	1.39 (1.29-1.49)	<0.001	1.06 (0.98-1.14)	0.155
Propofol	0.81 (0.77-0.86)	<0.001	0.98 (0.91-1.05)	0.538
Midazolam	1.69 (1.49-1.92)	<0.001	1.30 (1.14-1.48)	<0.001
Vasoactive	1.27 (1.20-1.35)	<0.001	1.14 (1.06-1.22)	<0.001

Mbp, mean blood pressure; SpO_2, saturation of the pulse oxygen; INR, international normalized ratio; PTT, Partial Thromboplastin Time; Bun, blood urea nitrogen; WBC, white blood cell count; RDW, red cell distribution width; SOFA, Sequential Organ Failure Assessment; CCI, Charlson Comorbidity Index.

electrolytes injure neural networks. This occurs in the prefrontal lobe and hippocampus. It causes attention and consciousness impairments which are delirium signs [30, 31]. High GPR is not only a laboratory finding, but also an indicator of associated, failing body processes. GPR is a natural component of delirium, which makes it a potential composite biomarker to check early risks in critically ill patients.

Our exercise demonstrated that high GPR is associated with delirium and increased mortality 28-, 90-, and 365-day mortality among ICU patients. GPR reflects stress and metabolic-electrolyte imbalance in the body. It can demonstrate a reduced total physical resiliency in critically ill patients [32, 33]. Delirium in this dysfunction of the multisystem can be a clinical figure of acute brain trauma as well as a possible mediator of high mortality, a manifestation of the extent of primary physiologic decompensation. No coincidental relationships between high levels of GPR and delirium and mortality underline the use of GPR as a prognostic biomarker, which reflects the cumulative effect of multiple-organ dysfunction, metabolic-electrolyte imbalances, and systemic inflammation, but not the effect of a single lab value like

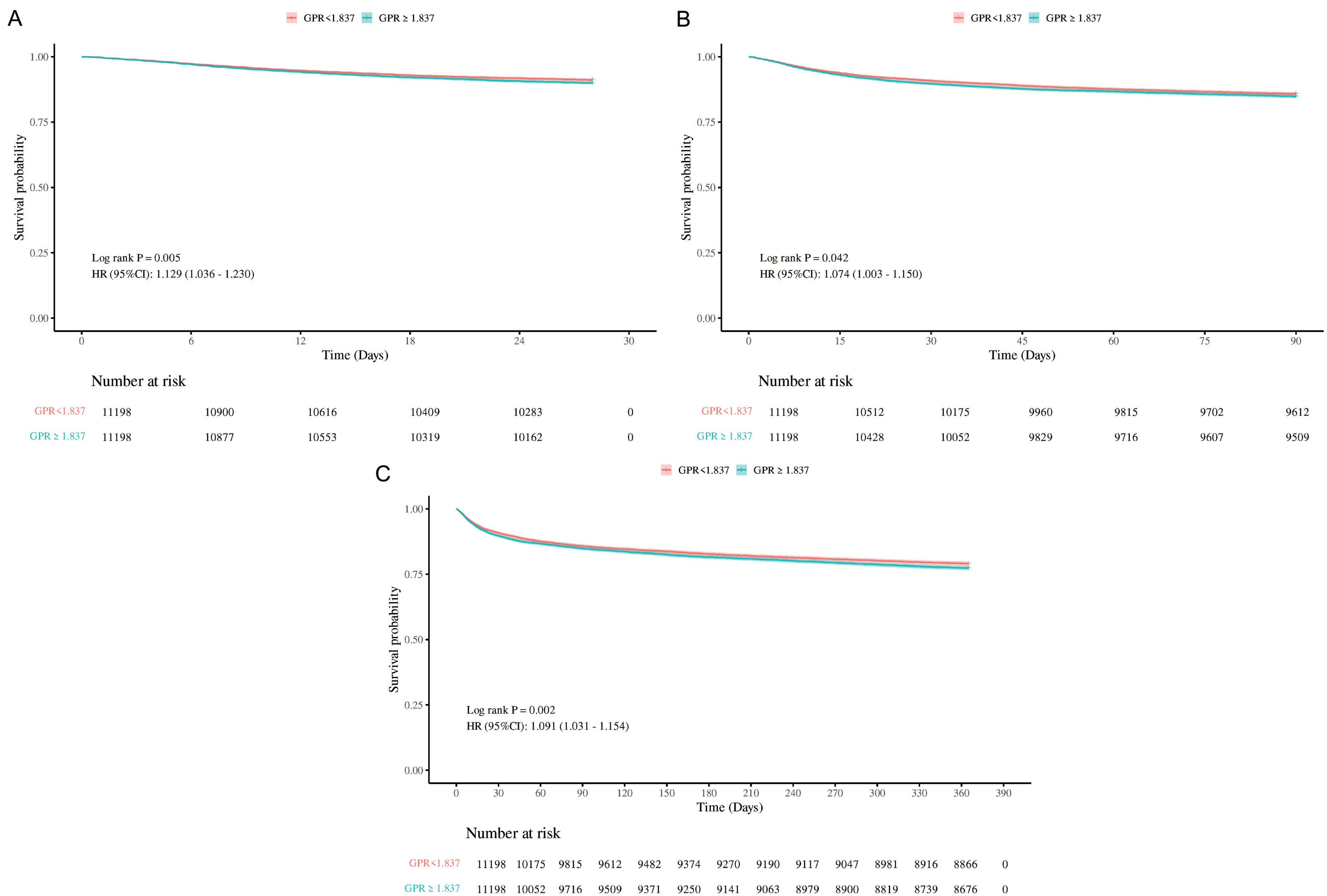


Figure 6. Kaplan-Meier (K-M) curves. A. K-M survival curve for 28-day mortality; B. K-M survival curve for 90-day mortality; C. K-M survival curve for 365-day mortality. GPR: Glucose-to-Potassium Ratio.

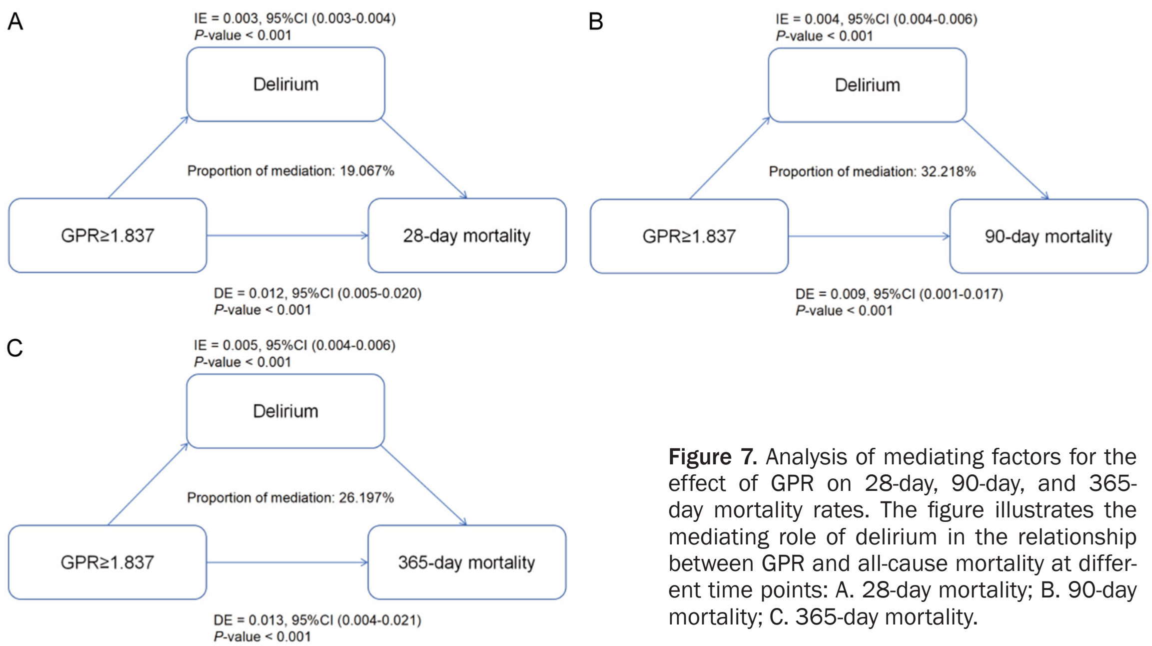


Figure 7. Analysis of mediating factors for the effect of GPR on 28-day, 90-day, and 365-day mortality rates. The figure illustrates the mediating role of delirium in the relationship between GPR and all-cause mortality at different time points: A. 28-day mortality; B. 90-day mortality; C. 365-day mortality.

hyperglycemia or hypokalemia itself [34, 35]. Early identification of high GPR patients can assist the doctor to identify high-risk individuals and treat delirium and help multi-organ maintenance. This can enhance both long-term and short-term outcomes on such patients.

According to our mediation analysis, delirium is partially behind the relationship that exists between GPR and death. The delirium mediates metabolic issues and poor patient outcome. Previous research discovered delirium to be a sensitive phenomenon in the brain due to body stressors such as infection and metabolic imbalance [2, 5]. Delirium is not only an indicator of ill health, but also it aggravates hormonal problems. It prolongs the period of ventilation and duration of stay and which leads to permanent cognitive impairments. The effects are mutually supportive and aggravate the results [36, 37]. The GPR and death connection are mediated by delirium. There is a need for early detection and rapid attention to delirium in critical care patients. This paper is an initial attempt to propose GPR as a biomarker. One of the predictors of delirium in patients in the ICU is GPR, which is a ratio based on regular laboratory tests. It is also associated with risk of short- and long-term death. GPR is a product of blood glucose and serum potassium, which are measured on a daily basis. GPR can be used to offer early risk assessment and one on one care to severely ill patients.

Nonetheless, there were a few limitations to the study: First, the study was retrospective observational, and thus there can be unmeasured confounding factors. We used propensity score matching and multivariable regression to adjust for confounders. The pathway of high GPR to delirium to higher death makes biological sense. But the study design could not prove cause and effect. Residual confounding factors may also affect the mediation analysis. Second, GPR was calculated from lab values on the first ICU day only. One time-point does not capture changes in metabolic stress and GPR over the ICU stay. These changes may hold extra prognostic information. Future studies should test if GPR trends or time-weighted values improve prediction for delirium and death. Third, delirium diagnosis came from CAM-ICU assessments in the MIMIC-IV database. CAM-ICU is a valid and common tool. We could not assess variation in its use-such as frequency, timing, or protocol adherence-because the database lacked detailed data. ICU sedation may lower delirium detection, especially for the hypoactive subtype. This may lead to misclassification of delirium outcomes. If present, such misclassification bias may have affected different patient groups stratified by GPR levels to varying degrees. Finally, our study was based on a single-center database, with study participants predominantly consisting of Western patients. This may limit the generalizability of our findings to other ethnic groups and different healthcare settings worldwide. For these reasons, prospective, multi-center studies involving diverse patient populations are needed to further validate the universal applicability and clinical utility of GPR for risk stratification in critically ill patients.

Conclusion

Elevated GPR is an independent and significant predictor of both delirium incidence and increased all-cause mortality in ICU patients. As an easily obtainable and cost-effective biomarker, GPR of critically ill patients has clinical value for early risk stratification and prognostic assessment.

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Disclosure of conflict of interest

None.

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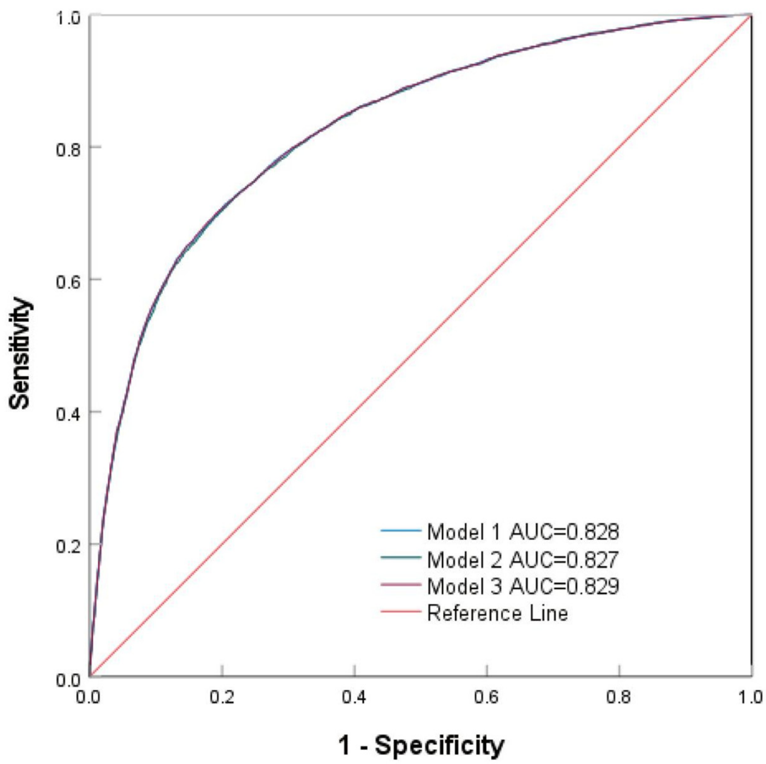
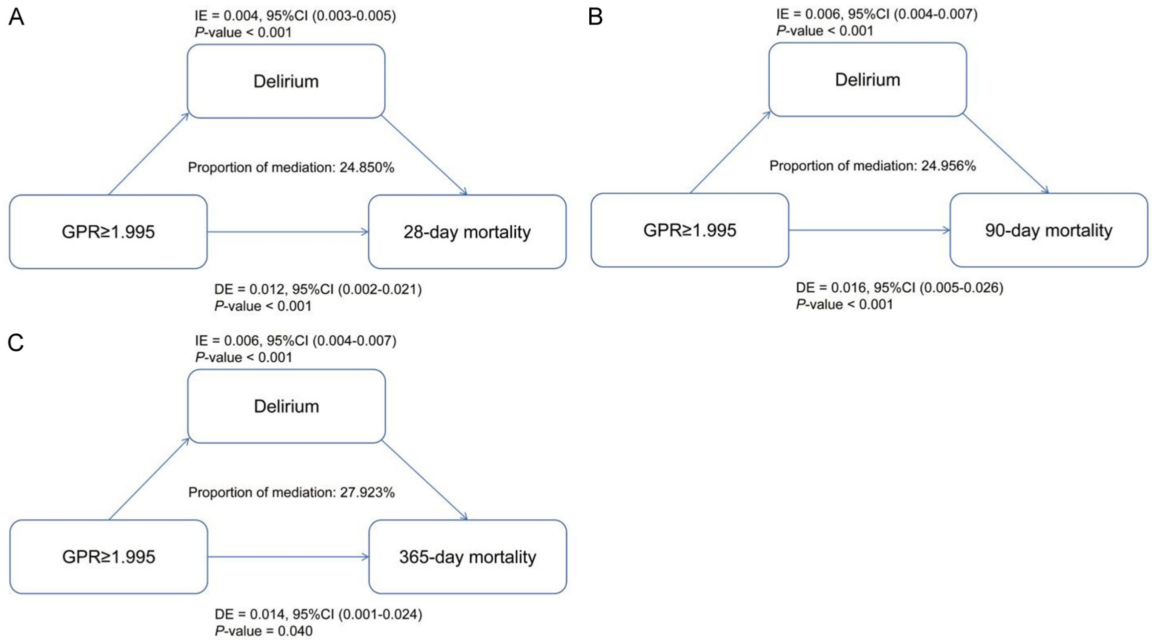
Supplementary Table 1. Missing data and multiple imputation details

Variable	Total	Missing Count	Missing Proportion (%)	Imputation Times
Demographic				
Age	32025	0	0	
Gender	32025	0	0	
Vital signs				
Heart Rate	32025	0	0	
Mbp	32025	8	0.024980484	20
Resp Rate	32025	63	0.196721311	20
Temperature	32025	829	2.588602654	20
Spo_2	32025	5	0.015612802	20
Comorbidities				
Sepsis	32025	0	0	
Myocardial Infarct	32025	0	0	
Cerebrovascular Disease	32025	0	0	
Chronic Pulmonary Disease	32025	0	0	
Diabetes	32025	0	0	
Laboratory tests				
Bicarbonate	32025	7	0.021857923	20
INR	32025	3913	12.21857923	20
Ptt	32025	4102	12.80874317	20
Aniongap	32025	10	0.031225605	20
Calcium	32025	2667	8.327868852	20
Bun	32025	13	0.040593286	20
Potassium	32025	0	0	
Sodium	32025	2	0.006245121	20
Glucose	32025	0	0	
Creatinine,(mg/dL)	32025	6	0.018735363	20
WBC, (K/uL)	32025	158	0.493364559	20
RDW, (%)	32025	165	0.515222482	20
Hemoglobin, (g/dL)	32025	158	0.493364559	20
Disease severity score				
SOFA	32025	0	0	
CCI	32025	0	0	
Intervention				
Ventilation	32025	0	0	
Propofol	32025	0	0	
Midazolam	32025	0	0	
Vasoactive	32025	0	0	
Outcomes				
Los Icu	32025	0	0	
Delirium	32025	0	0	
28-day mortality	32025	0	0	
90-day mortality	32025	0	0	
365-day mortality	32025	0	0	
SOFA	32025	0	0	
CCI	32025	0	0	

Intervention			
Ventilation	32025	0	0
Propofol	32025	0	0
Midazolam	32025	0	0
Vasoactive	32025	0	0
Outcomes			
Los Icu	32025	0	0
Delirium	32025	0	0
28-day mortality	32025	0	0
90-day mortality	32025	0	0
365-day mortality	32025	0	0



Supplementary Figure 1. Comparison of ROC curves for delirium prediction: Model 1 (Glucose), Model 2 (Potassium), and Model 3 (GPR).



Supplementary Figure 2. Sensitivity mediation analysis excluding patients with ICU length of stay less than 48 hours