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Glycemic variability and its association with short and long term clinical outcomes in critically ill patients with cerebral hemorrhage

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Cerebral hemorrhage is a major cause of mortality and disability. This study investigates the association between glycemic variability (GV) and short- and long-term clinical outcomes such as poor outcomes at discharge, mortality at 90 days and 1 year and intensive care unit (ICU) /hospital length of stay (LOS) in ICU patients with critically ill cerebral hemorrhage. This retrospective analysis examined 732 ICU patients with non-traumatic cerebral hemorrhage from the Medical Information Mart for Intensive Care (MIMIC)-IV database. GV was quantified as the ratio of standard deviation to mean glucose during ICU stay. To assess associations between GV and clinical outcomes (poor outcomes at discharge, 90-day and 1-year mortality, ICU/hospital LOS), the study employed logistic regression, Cox proportional hazards models, and linear regression. Additionally, non-linear relationships were explored through restricted cubic spline analysis. The investigation further incorporated subgroup and sensitivity analyses to ensure robustness of findings. To evaluate the incremental predictive value of GV, the study utilized receiver operating characteristic (ROC) curve analysis, net reclassification improvement, and integrated discrimination improvement, thereby providing a comprehensive assessment of GV's clinical utility. Higher GV was significantly associated with increased risk of poor outcomes at discharge and 90-day and 1-year mortality in both patient groups. GV showed a linear association with poor outcomes at discharge but a non-linear association with 90-day and 1-year mortality. GV thresholds of ≥ 0.11 for non-traumatic cerebral hemorrhage increased mortality risks. Cohort showed non-linear relationships between GV and ICU/hospital LOS. GV's impact was stronger in non-hypertensive and male patients. Adding GV to existing severity scores improved their predictive ability for adverse outcomes. In patients with non-traumatic cerebral hemorrhage admitted to the ICU, GV demonstrates an independent association with poor outcomes over both short-term and long-term time horizons. Furthermore, GV is associated with extended durations of both ICU and overall hospital stays in this patient population. These findings underscore the importance of glycemic control in this patient population and suggest that GV could be a valuable prognostic indicator and potential therapeutic target.

Keywords Glycemic variability, Insulin resistance, Cerebral hemorrhage, Glucose homeostasis, Metabolic diseases

Cerebrovascular diseases, such as cerebral hemorrhage and infarction, are major global causes of mortality and disability, impacting around 15 million individuals each year, resulting in 5 million deaths and 5 million cases of permanent disability[1–4]. Managing these patients in the intensive care unit (ICU) is challenging due to multi-

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organ dysfunction and complex treatment needs[5], highlighting the need to identify factors affecting prognosis to improve outcomes and reduce healthcare burdens.

Insulin resistance (IR), common in cerebrovascular disease patients, reflects systemic inflammation and metabolic disturbances, leading to blood glucose fluctuations that exacerbate metabolic dysfunction and worsen clinical outcomes[6–8]. While prior research has extensively explored glycemic thresholds[9,10]—such as levels exceeding 10.5 mmol/L (190 mg/dL) being linked to increased in-hospital mortality[11]. Research on glycemic variability (GV)'s role in non-traumatic cerebral hemorrhage patients remains limited. GV, defined as fluctuations in blood glucose over time, a less-explored metric in non-traumatic cerebral hemorrhage, provides dynamic insight into glucose control and complements existing evidence on glycemic thresholds[12]. Studies consistently show that critically ill patients exhibit significant attenuation of insulin sensitivity, intensifying GV and complicating the metabolic landscape of severe illness[13,14]. Elevated GV has been associated with adverse outcomes, including increased mortality, prolonged hospital stays, and higher complications in critically ill patients[15–18].

In evaluating ICU patient prognosis, both short- and long-term indicators are crucial. Short-term indicators, like poor discharge outcomes, provide immediate feedback, while long-term measures, such as survival rates, reveal sustained impacts of care[19,20]. ICU and hospital length of stay (LOS) also reflect medical resource use and recovery. While GV's impact on outcomes has been linked to oxidative stress and inflammation, most studies focus on diabetic populations or short-term outcomes[21,22]. This study investigates GV's association with discharge outcomes, 90-day and 1-year mortality, and LOS, aiming to complement existing evidence on glucose management in critically ill patients.

Methods

Data source and study population

This study used data from the Medical Information Mart for Intensive Care (MIMIC) IV (version 2.2, https://physionet.org/content/mimiciv/2.2/), a clinical database of 76,943 ICU admissions for 53,150 patients[23]. These patients received care at Beth Israel Deaconess Medical Center between 2008 and 2019, prior to the COVID-19 pandemic. To ensure confidentiality, all personal identifiers were removed. Due to the de-identification of patient data, the institutional review board waived the need for individual consent. Data extraction was performed by Shuhuai Zou (ID: 55774871).

Inclusion criteria

Study eligibility criteria included:

(a) A confirmed diagnosis of non-traumatic cerebral hemorrhage, as defined by the International Classification of Diseases (ICD) coding system (Ninth or Tenth Revision).
(b) Admission to an ICU during hospitalization.

Exclusion criteria

Patients were excluded if they met any of the following:

(a) Insufficient glucose data (fewer than three measurements during ICU stay)[24–26].
(b) Multiple ICU admissions (two or more separate ICU stays).
(c) Inability to obtain the modified Rankin Scale (mRS) score at discharge records.
(d) Presence of extreme values in the collected data, which were considered outliers and could potentially skew the results.

This study adhered to the ethical principles of the Declaration of Helsinki (1964) and its amendments. Ethical approval was obtained from the institutional review board. This study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[27], ensuring adherence to rigorous methodological standards for observational research.

Data collection and processing

Data for this study were extracted from the database using Structured Query Language (SQL) and processed with PostgreSQL and Navicat Premium. Extracted variables included demographics, vital signs, comorbidities, severity scores, laboratory parameters, medical history, and clinical outcomes. Baseline characteristics were derived from data collected within the first 24 h of ICU admission, while GV was calculated as the ratio of the standard deviation (SD) to the mean of all glucose measurements during ICU stays.

Patients were stratified into four groups based on GV quartiles (Q1–Q4) following established methods from prior research[28]. Missing data (< 20%) were addressed using the random forest algorithm, ensuring robust data processing. Detailed methods, including data extraction, variable definitions, missing data patterns (Additional File 1: Figure S1), and stratification procedures, are provided in Additional File 1.

Primary and secondary outcomes

The main outcome was poor outcomes at discharge[29–31], including death or severe disability, defined as a mRS score of 3–6 (0 = no symptoms, 6 = death) at discharge. Two independent senior neurosurgical experts (associate professor level or above) evaluated each patient's mRS score based on discharge records. Outcomes were dichotomized into 'Yes' (mRS 3–6, poor outcome at discharge) or 'No' (mRS 0–2, favorable outcome). In cases of disagreement, a third senior neurosurgeon (professor level) made the final decision, resulting in a definitive 'Yes'

or 'No' outcome (Additional File 2: Table S1). Secondary outcomes were 90-day and 1-year mortality, as well as ICU and hospital LOS.

Statistical analyses

Baseline characteristics were summarized using appropriate descriptive statistics for continuous and categorical variables. Kaplan-Meier survival analysis and log-rank tests were used to compare survival probabilities across GV quartiles at 90 days and 1 year. Multiple regression models were applied to evaluate the associations between GV and clinical outcomes, including poor discharge outcomes, mortality, and LOS. Adjustments for potential confounders were made across three models, guided by clinical relevance and prior evidence. Non-linear relationships were explored using restricted cubic splines (RCS), and model performance was assessed using Area Under Curve (AUC), net reclassification improvement (NRI), and integrated discrimination improvement (IDI) metrics. Robustness was evaluated through sensitivity analyses, including multiple imputation methods and subgroup analyses. Statistical significance was set at two-tailed $P<0.05$. Analyses were performed using R version 4.2.2. Detailed descriptions of statistical methods, variable selection, model specifications, and robustness testing are provided in Additional File 1 and Additional file 2: Tables S2-S7.

Results

Patient selection and cohort characteristics

The study cohort included 732 patients with non-traumatic intracerebral hemorrhage, with a median age of 71 years (IQR: 60–81), comprising 396 males (396/732 [54.1%]) and 336 females (336/732 [45.9%]). The patient selection process is outlined in Fig. 1, and baseline characteristics stratified by GV quartiles are summarized in Table 1.

Patients in higher GV quartiles had a significantly higher prevalence of comorbidities such as diabetes, respiratory failure, chronic kidney disease, kidney failure, and sepsis (all $P<0.05$). Additionally, higher GV was associated with increased disease severity scores (APSIII, OASIS, SAPSII, and CCI) and elevated BUN levels (all $P<0.001$).

Clinical outcomes progressively worsened with increasing GV levels. Poor outcomes at discharge and mortality rates at 90 days and 1 year were all significantly higher in patients with elevated GV, as shown in Table 1. ICU and hospital length of stay were also prolonged in higher GV quartiles ($P<0.001$).

Further stratification by gender and clinical outcomes is presented in Additional File 2: Tables S8 and S9, respectively. Notably, GV was significantly higher in patients with poor outcomes at discharge, 90-day mortality, and 1-year mortality compared to those without these outcomes, consistent with findings illustrated in Fig. 2.

Survival analysis

Kaplan-Meier survival analysis demonstrated significant differences in cumulative mortality across GV quartiles at both 90-day and 1-year time points, with higher GV quartiles associated with significantly lower survival probabilities (Fig. 3, $P<0.05$). Detailed survival curves and log-rank test results are provided in Additional File 1: Figure S2.

Regression analyses

The regression analyses identified significant associations between GV and poor outcomes at discharge, as well as 90-day and 1-year mortality, as summarized in Table 2. These associations were consistent across all three models, even after adjusting for demographic and clinical factors. For poor outcomes at discharge, higher GV was significantly associated with increased risk, with an OR per standardized unit increase in GV of 1.43 (95% CI: 1.08–1.97, $P=0.020$) in Model 3. Quartile analysis indicated a clear trend (P for trend $=0.005$), with patients in the highest quartile (Q4) showing more than double the risk compared to the lowest quartile (Q1) (OR: 2.37, 95% CI: 1.31–4.39). Similarly, GV was significantly associated with 90-day mortality, with a HR per standardized unit increase of 1.19 (95% CI: 1.08–1.30, $P<0.001$) in Model 3, and quartile analysis showed a significant trend (P for trend <0.001), with Q4 demonstrating almost double the mortality risk compared to Q1 (HR: 1.94, 95% CI: 1.35–2.79). For 1-year mortality, GV continued to show significant associations, with an HR per standardized unit increase of 1.15 (95% CI: 1.05–1.26, $P=0.002$) in Model 3, and patients in Q4 exhibited a significantly higher risk compared to Q1 (HR: 1.78, 95% CI: 1.27–2.48, $P<0.001$).

Additional File 2: Table S10 shows the relationship between GV and LOS in ICU and hospital across three models. GV as a continuous variable was not significantly associated with ICU LOS, but higher quartiles (Q2, Q3, Q4) were linked to longer ICU stays (Model 3: β for Q2 $=2.73$, Q3 $=3.34$, Q4 $=3.09$, all $P<0.001$). Higher quartiles of GV were also linked to longer hospital stays, though the association was weaker for Q4 in Model 3 (β for Q2 $=3.86$, $P=0.014$; Q3 $=5.11$, $P=0.001$; Q4 $=3.11$, $P=0.054$). These results indicate a clear relationship between higher GV and increased LOS in ICU and hospital settings, highlighting the importance of managing GV to reduce LOS and improve outcomes.

Restricted cubic spline analysis

We conducted RCS analysis to investigate potential nonlinear associations between GV and clinical outcomes. This analysis employed four knots (5th, 35th, 65th, and 95th percentiles). Significant associations were consistently observed across all models in all examined outcomes ($P<0.05$).

The relationship between GV and poor outcomes at discharge was primarily linear (Fig. 4), with no significant non-linear relationships detected (P-nonlinear >0.05). This linear association remained after adjusting for confounders. In contrast, GV and 90-day mortality showed significant non-linear components (P-nonlinear <0.05), indicating a complex association. The association between GV and 1-year mortality is demonstrated, with all models showing significant non-linear relationships (P-nonlinear <0.05). Inflection

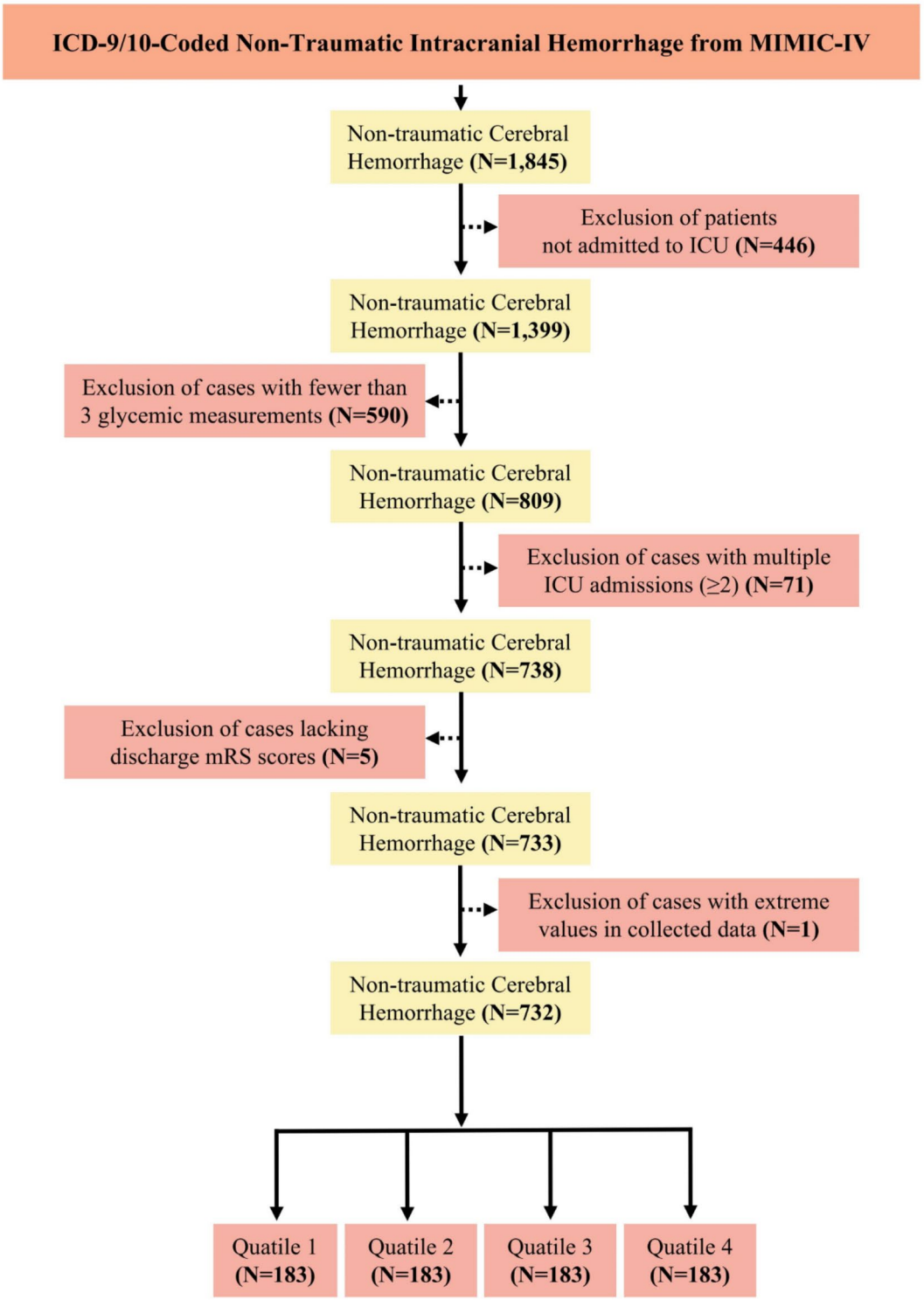

Fig. 1. Flow chart of patient selection process. *ICD-9/10* International Classification of Diseases, Ninth and Tenth Revision; *MIMIC-IV* Medical Information Mart for Intensive Care IV; *ICU* intensive care unit; *mRS* modified ranking scale.

points defining critical thresholds for GV and mortality are provided in Additional File 2: Table S11. Model 3 identified an inflection point at 0.11 GV for 90-day mortality. For GV ≥ 0.11, the adjusted HR per SD was 1.21 (95% CI: 1.10–1.32, $P < 0.001$), indicating increased 90-day mortality risk. For 1-year mortality, the adjusted HR per SD was 1.17 (95% CI: 1.07–1.29, $P < 0.001$), indicating increased long-term mortality risk.

The analysis was extended to hospital outcomes (Additional File 1: Figure S3). The RCS curves showed significant nonlinear relationships between GV and both ICU and hospital LOS (P-nonlinear < 0.05). These

Characteristic	Overall, *N* = 732	Q1, *N* = 183	Q2, *N* = 183	Q3, *N* = 183	Q4, *N* = 183	*P*-value
GV	0.15 (0.11, 0.21)	0.08 (0.05, 0.09)	0.13 (0.12, 0.14)	0.17 (0.16, 0.19)	0.28 (0.24, 0.37)	**< 0.001**
Demographic						
Age	71 (60, 81)	72 (61, 83)	70 (60, 81)	69 (57, 80)	70 (61, 80)	0.200
Gender						0.110
Male	396 (54.1%)	91 (49.7%)	104 (56.8%)	110 (60.1%)	91 (49.7%)	
Female	336 (45.9%)	92 (50.3%)	79 (43.2%)	73 (39.9%)	92 (50.3%)	
Race						**0.014**
Asian	30 (4.1%)	4 (2.2%)	8 (4.4%)	8 (4.4%)	10 (5.5%)	
Black	76 (10.4%)	18 (9.8%)	24 (13.1%)	18 (9.8%)	16 (8.7%)	
White	424 (57.9%)	128 (69.9%)	86 (47.0%)	107 (58.5%)	103 (56.3%)	
Hispanic/Latino	21 (2.9%)	5 (2.7%)	5 (2.7%)	4 (2.2%)	7 (3.8%)	
Other/Unknown	181 (24.7%)	28 (15.3%)	60 (32.8%)	46 (25.1%)	47 (25.7%)	
Vital signs						
SBP	137 (123, 152)	134 (120, 146)	139 (125, 155)	138 (123, 151)	139 (122, 155)	0.080
DBP	73 (64, 84)	72 (64, 83)	74 (65, 86)	77 (66, 89)	70 (61, 83)	**0.028**
HR	81 (70, 93)	78 (70, 91)	81 (71, 92)	82 (69, 94)	81 (72, 94)	0.782
RR	18.0 (16.0, 21.0)	18.0 (15.0, 21.0)	18.0 (16.0, 21.0)	18.0 (15.0, 22.0)	18.0 (16.0, 21.0)	0.788
First GCS	12.0 (7.0, 14.0)	14.0 (9.0, 15.0)	11.0 (7.0, 14.0)	12.0 (8.0, 14.0)	10.0 (6.0, 14.0)	**< 0.001**
Comorbidities						
Hypertension						**0.015**
Yes	493 (67.3%)	119 (65.0%)	138 (75.4%)	126 (68.9%)	110 (60.1%)	
No	239 (32.7%)	64 (35.0%)	45 (24.6%)	57 (31.1%)	73 (39.9%)	
Diabetes						**< 0.001**
Yes	171 (23.4%)	27 (14.8%)	35 (19.1%)	31 (16.9%)	78 (42.6%)	
No	561 (76.6%)	156 (85.2%)	148 (80.9%)	152 (83.1%)	105 (57.4%)	
AF						0.904
Yes	173 (23.6%)	46 (25.1%)	43 (23.5%)	40 (21.9%)	44 (24.0%)	
No	559 (76.4%)	137 (74.9%)	140 (76.5%)	143 (78.1%)	139 (76.0%)	
HF						0.100
Yes	73 (10.0%)	16 (8.7%)	15 (8.2%)	15 (8.2%)	27 (14.8%)	
No	659 (90.0%)	167 (91.3%)	168 (91.8%)	168 (91.8%)	156 (85.2%)	
CHD						0.543
Yes	50 (6.8%)	9 (4.9%)	13 (7.1%)	12 (6.6%)	16 (8.7%)	
No	682 (93.2%)	174 (95.1%)	170 (92.9%)	171 (93.4%)	167 (91.3%)	
Copd						0.773
Yes	25 (3.4%)	7 (3.8%)	5 (2.7%)	5 (2.7%)	8 (4.4%)	
No	707 (96.6%)	176 (96.2%)	178 (97.3%)	178 (97.3%)	175 (95.6%)	
RF						**< 0.001**
Yes	222 (30.3%)	31 (16.9%)	56 (30.6%)	58 (31.7%)	77 (42.1%)	
No	510 (69.7%)	152 (83.1%)	127 (69.4%)	125 (68.3%)	106 (57.9%)	
CKD						**0.014**
Yes	94 (12.8%)	17 (9.3%)	25 (13.7%)	17 (9.3%)	35 (19.1%)	
No	638 (87.2%)	166 (90.7%)	158 (86.3%)	166 (90.7%)	148 (80.9%)	
KF						**0.011**
Yes	112 (15.3%)	16 (8.7%)	29 (15.8%)	28 (15.3%)	39 (21.3%)	
No	620 (84.7%)	167 (91.3%)	154 (84.2%)	155 (84.7%)	144 (78.7%)	
Anemia						0.062
Yes	121 (16.5%)	20 (10.9%)	32 (17.5%)	30 (16.4%)	39 (21.3%)	
No	611 (83.5%)	163 (89.1%)	151 (82.5%)	153 (83.6%)	144 (78.7%)	
Sepsis						**0.012**
Yes	24 (3.3%)	2 (1.1%)	2 (1.1%)	10 (5.5%)	10 (5.5%)	
No	708 (96.7%)	181 (98.9%)	181 (98.9%)	173 (94.5%)	173 (94.5%)	
Tumor						0.143
Yes	25 (3.4%)	10 (5.5%)	6 (3.3%)	2 (1.1%)	7 (3.8%)	
No	707 (96.6%)	173 (94.5%)	177 (96.7%)	181 (98.9%)	176 (96.2%)	
Severity scores						
Continued						

Characteristic	Overall, *N* = 732	Q1, *N* = 183	Q2, *N* = 183	Q3, *N* = 183	Q4, *N* = 183	*P*-value
APSIII	43 (30, 57)	36 (27, 46)	42 (30, 53)	43 (33, 55)	52 (38, 73)	**< 0.001**
OASIS	35 (29, 41)	32 (28, 38)	35 (29, 40)	36 (30, 41)	38 (31, 43)	**< 0.001**
SAPSII	33 (26, 40)	31 (26, 38)	32 (25, 38)	31 (25, 39)	36 (29, 43)	**< 0.001**
SOFA-1 h	1.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	0.261
SIRS	2.00 (2.00, 3.00)	2.00 (2.00, 3.00)	3.00 (2.00, 3.00)	2.00 (2.00, 3.00)	3.00 (2.00, 3.00)	**< 0.001**
CCI	6.00 (5.00, 8.00)	6.00 (5.00, 7.00)	6.00 (5.00, 8.00)	6.00 (4.00, 7.00)	7.00 (5.00, 9.00)	**< 0.001**
Laboratory parameters						
RBC	4.10 (3.60, 4.50)	4.10 (3.60, 4.50)	4.20 (3.70, 4.50)	4.10 (3.70, 4.50)	3.99 (3.50, 4.40)	**0.025**
WBC	10.4 (8.2, 12.9)	9.7 (7.8, 12.1)	10.7 (8.5, 13.4)	10.1 (8.2, 12.3)	10.9 (8.7, 13.8)	**0.009**
Platelet	206 (163, 254)	208 (170, 249)	203 (166, 249)	203 (161, 247)	211 (161, 267)	0.846
Glu Mean	130 (114, 152)	120 (107, 137)	128 (113, 146)	128 (116, 144)	152 (129, 183)	**< 0.001**
Number of Glucose Measurements	9 (4,16)	5 (3, 10)	10 (5, 18)	10 (6, 18)	9 (4, 18)	**< 0.001**
PT	12.40 (11.70, 13.50)	12.24 (11.75, 13.40)	12.16 (11.60, 13.20)	12.50 (11.80, 13.55)	12.84 (11.75, 13.85)	**0.047**
APTT	28.1 (26.2, 30.2)	28.2 (26.4, 30.0)	27.9 (26.5, 29.9)	28.0 (25.6, 29.8)	28.5 (25.8, 30.9)	0.428
Aniongap	15.00 (13.00, 17.00)	15.00 (13.00, 16.51)	15.00 (13.00, 17.00)	15.00 (13.00, 17.00)	15.00 (13.00, 17.00)	0.749
Bicarbonate	23.45 (22.00, 25.00)	24.00 (22.00, 26.00)	24.00 (22.00, 25.00)	23.07 (21.00, 25.00)	23.00 (21.00, 25.00)	0.279
BUN	16 (12, 21)	15 (12, 19)	15 (12, 21)	16 (12, 20)	18 (14, 25)	**< 0.001**
Sodium	139.2 (137.0, 142.0)	140.0 (138.0, 142.0)	140.0 (137.0, 142.0)	139.4 (137.5, 141.0)	139.0 (137.0, 141.0)	**0.044**
Potassium	3.90 (3.60, 4.20)	3.90 (3.60, 4.20)	3.90 (3.50, 4.20)	3.90 (3.50, 4.20)	3.90 (3.60, 4.40)	0.339
Calcium	2.20 (2.10, 2.27)	2.22 (2.15, 2.27)	2.20 (2.11, 2.30)	2.18 (2.10, 2.27)	2.18 (2.07, 2.25)	**0.015**
Chloride	103.0 (101.0, 106.0)	103.2 (101.0, 106.0)	103.0 (100.0, 106.0)	104.0 (101.0, 106.0)	103.0 (100.0, 106.0)	0.410
Creatinine	80 (62, 97)	79 (62, 89)	80 (62, 97)	80 (62, 97)	80 (69, 115)	**0.038**
Hemoglobin	12.30 (11.00, 13.50)	12.50 (10.95, 13.50)	12.50 (11.30, 13.50)	12.50 (11.35, 13.70)	11.90 (10.50, 13.10)	**0.006**
MCH	30.43 (29.00, 31.80)	30.40 (29.35, 31.60)	30.50 (28.90, 31.75)	30.50 (28.95, 32.05)	30.30 (29.00, 31.60)	0.860
MCHC	33.40 (32.40, 34.30)	33.20 (32.50, 34.15)	33.50 (32.50, 34.40)	33.50 (32.40, 34.60)	33.30 (32.25, 34.10)	0.250
INR	1.10 (1.10, 1.20)	1.10 (1.10, 1.20)	1.10 (1.09, 1.20)	1.10 (1.10, 1.20)	1.12 (1.10, 1.30)	0.113
Medical history						
Antidiabetic						**< 0.001**
Yes	614 (83.9%)	136 (74.3%)	154 (84.2%)	163 (89.1%)	161 (88.0%)	
No	118 (16.1%)	47 (25.7%)	29 (15.8%)	20 (10.9%)	22 (12.0%)	
Antithrombotic						0.485
Yes	173 (23.6%)	51 (27.9%)	41 (22.4%)	40 (21.9%)	41 (22.4%)	
No	559 (76.4%)	132 (72.1%)	142 (77.6%)	143 (78.1%)	142 (77.6%)	
Outcomes						
Poor outcomes at Discharge						**0.003**
Yes	600 (82.0%)	134 (73.2%)	153 (83.6%)	153 (83.6%)	160 (87.4%)	
No	132 (18.0%)	49 (26.8%)	30 (16.4%)	30 (16.4%)	23 (12.6%)	
90 Day Death						**< 0.001**
Yes	248 (33.9%)	56 (30.6%)	52 (28.4%)	49 (26.8%)	91 (49.7%)	
No	484 (66.1%)	127 (69.4%)	131 (71.6%)	134 (73.2%)	92 (50.3%)	
90-day Survival Time	90 (19, 90)	90 (42, 90)	90 (42, 90)	90 (66, 90)	90 (6, 90)	**< 0.001**
1 Year Death						**< 0.001**
Continued						

Characteristic	Overall, *N* = 732	Q1, *N* = 183	Q2, *N* = 183	Q3, *N* = 183	Q4, *N* = 183	*P*-value
Yes	293 (40.0%)	68 (37.2%)	62 (33.9%)	66 (36.1%)	97 (53.0%)	
No	439 (60.0%)	115 (62.8%)	121 (66.1%)	117 (63.9%)	86 (47.0%)	
1-year Survival Time	365 (19, 365)	365 (42, 365)	365 (42, 365)	365 (66, 365)	90 (6, 365)	**< 0.001**
ICU LOS	5 (3, 9)	4 (3, 5)	6 (4, 11)	6 (3, 11)	5 (3, 10)	**< 0.001**
Hospital LOS	9 (5, 15)	7 (4, 11)	11 (7, 16)	11 (7, 17)	8 (5, 16)	**< 0.001**

Table 1. Baseline characteristics of patients according to quartiles of glycemic variability. Q1: [0.0045,0.105); Q2: [0.105,0.150); Q3: [0.150,0.215); Q4: [0.215,1.300]. *GV* glycemic variability, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *RR* respiratory rate, *GCS* Glasgow Coma Scale; *AF* atrial fibrillation, *HF* heart failure, *CHD* Coronary heart disease, *COPD* chronic obstructive pulmonary disease, *RF* respiratory failure, *CKD* chronic kidney disease, *KF* kidney failure, *APSIII* Acute Physiology Score III, *OASIS* Oxford Acute Severity of Illness Score, *SAPSII* Simplified Acute Physiology Score II, *SOFA* Sequential Organ Failure Assessment,, systemic inflammatory response syndrome, *CCI* Charlson Comorbidity Index, *RBC* red blood cell, *WBC* white blood cell, *Glu* glucose, *PT* prothrombin time, *APTT* activated partial thromboplastin time, *BUN* blood urea nitrogen, *MCH* mean corpuscular hemoglobin, *MCHC* mean corpuscular hemoglobin concentration, *INR* International Normalized Ratio, *LOS* length of stay, *ICU* intensive care unit.

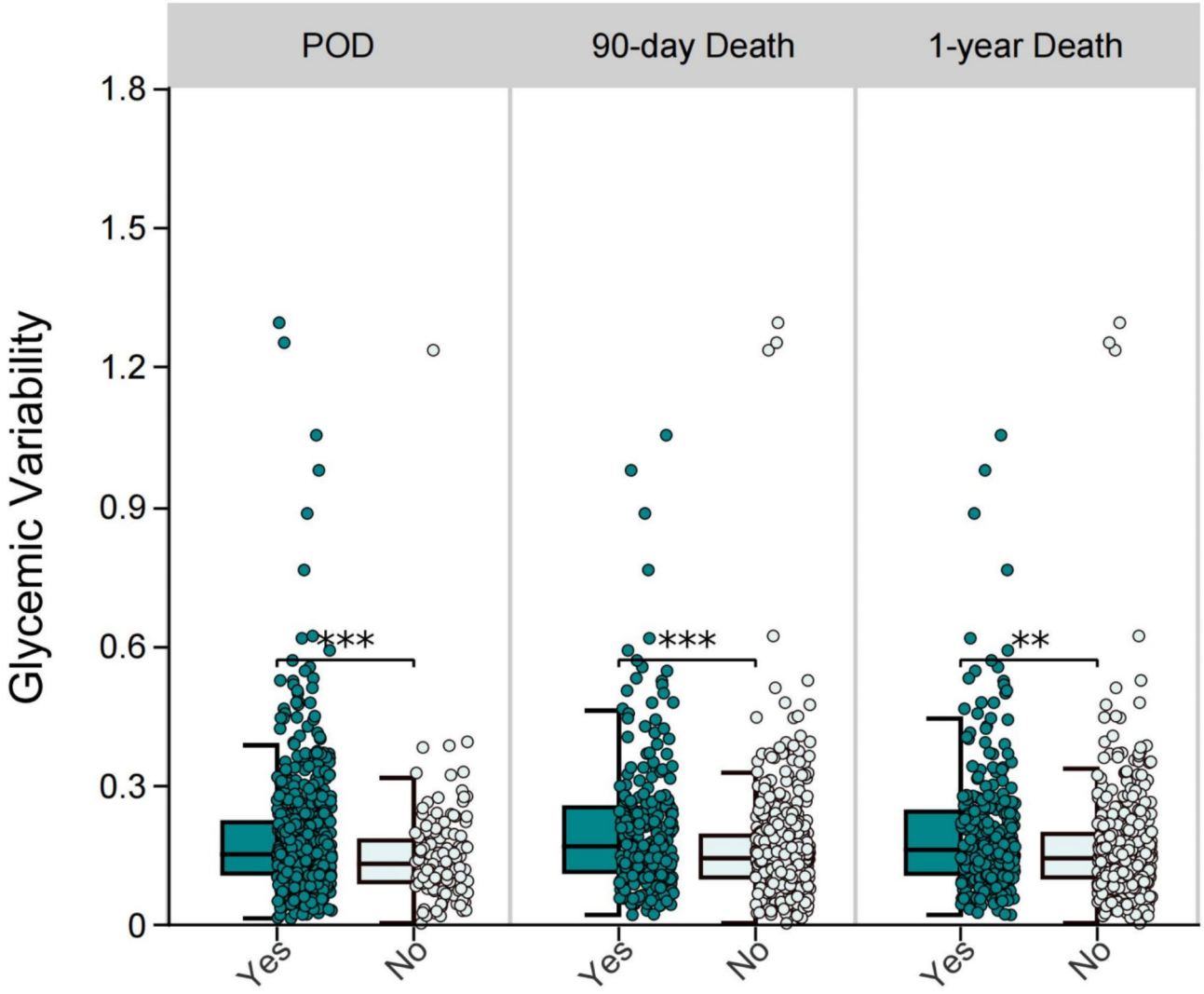

Fig. 2. Impact of glycemic variability on outcomes. ** $P < 0.01$; *** $P < 0.001$. *POD* poor outcomes at discharge, *CI* cerebral infarction; Yes, Survivor; No, Non-survival.

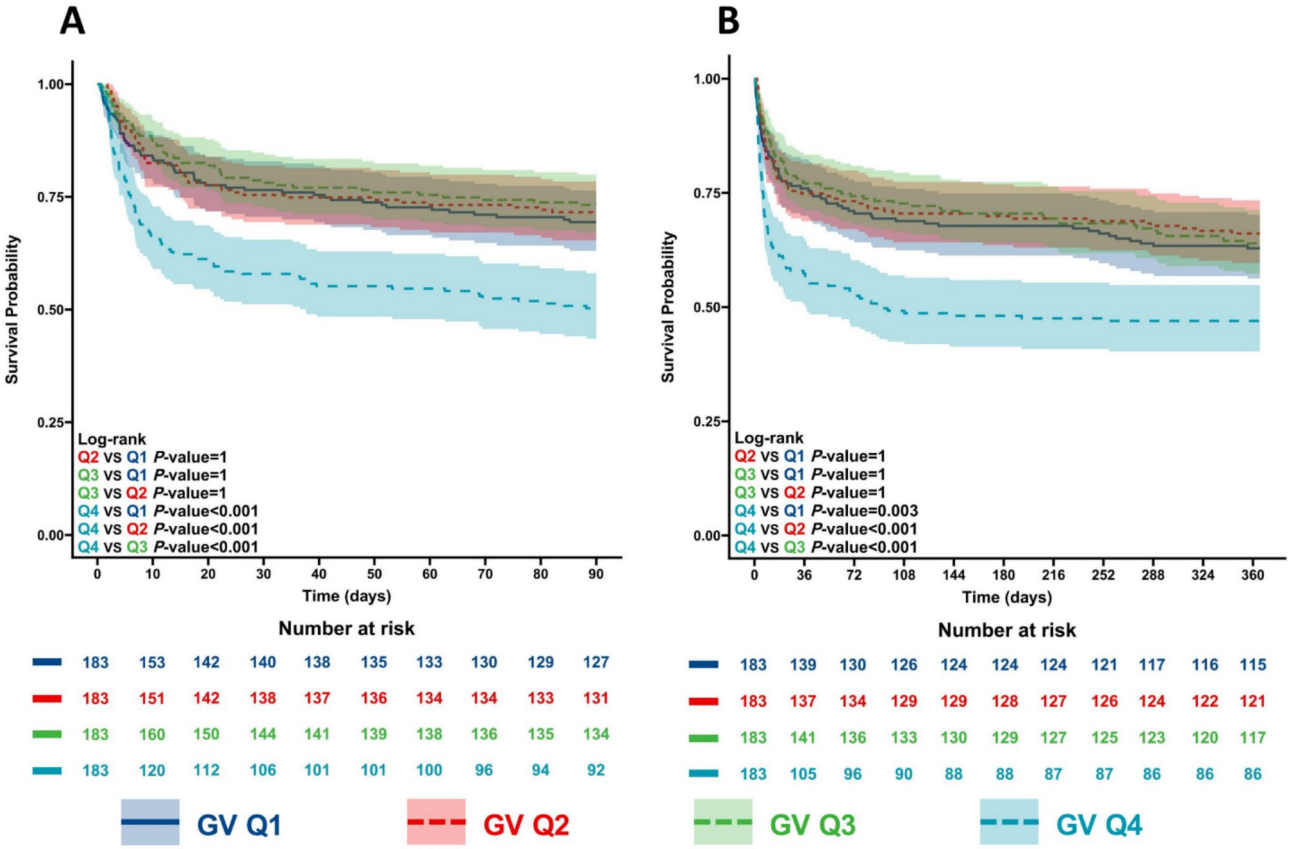

Fig. 3. Kaplan–Meier survival analysis curves for 90-day and 1-year mortality. Kaplan–Meier curves illustrating the cumulative probability of all-cause mortality stratified by glycemic variability (GV) quartiles: (**A**) 90-day mortality, (**B**) 1-year mortality. GV Quartile Ranges: Q1: [0.0045, 0.105) ; Q2: [0.105, 0.15) ; Q3: [0.15, 0.215) ; Q4: [0.215, 1.3]. *GV* glycemic variability.

findings highlight the importance of precise GV management to improve survival, with identified thresholds guiding clinical vigilance.

Predictive capacity and incremental value of GV

The predictive capacity and incremental value of GV for poor discharge outcomes, 90-day, and 1-year mortality were evaluated using AUC, NRI, and IDI metrics. GV demonstrated modest predictive performance and provided incremental improvement when incorporated into existing scoring tools. Detailed results are provided in Additional File 1: Figure S4 and Additional File 2: Table S12-S13.

Subgroup analyses

We assessed the risk stratification capacity of GV across subgroups. Subgroups were stratified by gender, age, hypertension, diabetes, and AF. Increased GV was linked to higher risk of adverse outcomes across subgroups (Fig. 5). The impact of GV on poor discharge outcomes appeared more pronounced in patients without hypertension [adjusted OR (95% CI): 2.03 (1.14–3.61), $P = 0.017$] compared to those with hypertension [adjusted OR (95% CI): 1.17 (0.85–1.61), $P = 0.330$]. However, given the multiple comparisons and the absence of consistent interactions across other analyses, this finding should be interpreted with caution (P for interaction = 0.046). Similar results were seen in males for 90-day mortality [adjusted HR (95% CI): 1.41 (1.21–1.65), $P < 0.001$ for males vs. 1.12 (0.98–1.29), $P = 0.099$ for females; P for interaction = 0.035]. These findings highlight the differential impact of GV on outcomes across subgroups, providing insights for tailoring glucose management in clinical practice.

Sensitivity analyses

Sensitivity analyses demonstrated consistent associations between GV and poor discharge outcomes, 90-day and 1-year mortality, as well as ICU/hospital LOS across multiple imputation methods, confirming the robustness of our findings. Detailed results, including subgroup analyses and confidence intervals, are provided in Table 2, Additional File 1: Figures S5-S9 and Additional File 2: Tables S10, S14–S21.

Categories	Model 1			Model 2			Model 3		
	OR/HR Per unit/SD of GV	95% CI	*P*	OR/HR Per unit/SD of GV	95% CI	*P*	OR/HR Per unit/SD of GV	95% CI	*P*
Poor outcomes at discharge									
GV (standardized)	1.47	1.14, 1.98	**0.006**	1.48	1.14, 1.99	**0.006**	1.43	1.08, 1.97	**0.020**
Quartile	*P* for trend: <**0.001**			*P* for trend: <**0.001**			*P* for trend: **0.005**		
Q1	–	–		–	–		–	–	
Q2	1.86	1.13, 3.13	**0.017**	1.79	1.06, 3.06	**0.030**	1.86	1.08, 3.26	**0.028**
Q3	1.86	1.13, 3.13	**0.017**	1.98	1.18, 3.38	**0.011**	1.87	1.09, 3.27	**0.025**
Q4	2.54	1.49, 4.46	<**0.001**	2.55	1.47, 4.51	<**0.001**	2.37	1.31, 4.39	**0.005**
90-day mortality									
GV (standardized)	1.20	1.11, 1.31	<**0.001**	1.21	1.11, 1.32	<**0.001**	1.19	1.08, 1.30	<**0.001**
Quartile	*P* for trend: <**0.001**			*P* for trend: <**0.001**			*P* for trend: <**0.001**		
Q1	–	–		–	–		–	–	
Q2	0.91	0.63, 1.33	0.633	0.90	0.61, 1.31	0.576	0.89	0.60, 1.33	0.579
Q3	0.84	0.58, 1.24	0.389	0.88	0.60, 1.30	0.531	0.86	0.58, 1.27	0.448
Q4	1.92	1.38, 2.68	<**0.001**	1.90	1.36, 2.66	<**0.001**	1.94	1.35, 2.79	<**0.001**
1-year mortality									
GV (standardized)	1.17	1.07, 1.27	<**0.001**	1.17	1.08, 1.27	<**0.001**	1.15	1.05, 1.26	**0.002**
Quartile	*P* for trend: <**0.001**			*P* for trend: <**0.001**			*P* for trend: <**0.001**		
Q1	–	–		–	–		–	–	
Q2	0.89	0.63, 1.26	0.516	0.89	0.62, 1.25	0.493	0.89	0.62, 1.27	0.514
Q3	0.94	0.67, 1.31	0.704	0.99	0.70, 1.39	0.955	0.96	0.68, 1.36	0.818
Q4	1.73	1.27, 2.36	<**0.001**	1.73	1.26, 2.36	<**0.001**	1.78	1.27, 2.48	<**0.001**

Table 2. Regression analyses for the occurrence of poor outcomes at discharge and 90-day/1-year mortality. OR for Logistic regression and HR for Cox regression; Poor Outcomes at Discharge (Logistic regression); 90-day and 1-year mortality (Cox regression) Q1: [0.0045,0.105); Q2: [0.105,0.15); Q3: [0.15,0.215); Q4: [0.215,1.3]; Model 1: no covariates were adjusted Model 2: adjusted for Gender, Age, and Race Model 3: adjusted for Gender, Age, Race, SBP, DBP, HR, RR, Hypertension, Diabetes, AF, Copd, Spesis, Tumor, Antidiabetic, Antithrombotic, WBC, Platelet, APTT, Sodium, Potassium, MCHC, INR. *GV* glycemic variability, *OR* odds ratio, *CI* confidence interval, *HR* hazard ratio. *SAE* serious adverse events, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *RR* respiratory rate, *AF* atrial fibrillation, *Copd* chronic obstructive pulmonary disease, *WBC* white blood cell, *APTT* activated partial thromboplastin time, *MCHC* mean corpuscular hemoglobin concentration, *INR* international normalized ratio.

Discussion

This investigation uniquely examines the relationship of GV with short-term outcomes (poor discharge outcomes, 90-day mortality), long-term outcomes (1-year mortality), and hospital resource utilization (ICU and hospital LOS). This approach provides a holistic perspective on the impact of GV across temporal and clinical dimensions in this critical patient population.

Our findings show that in critically non-traumatic cerebral hemorrhage patients, higher GV levels, especially in the highest quartile, were significantly linked to increased risk of poor outcomes at discharge, 90-day and 1-year mortality, and prolonged ICU and hospital LOS, even after adjusting for confounders. GV had independent associations with these adverse outcomes, highlighting its potential as a crucial prognostic indicator. GV showed a linear association with poor discharge outcomes and non-linear relationships for mortality. Significant non-linear relationships were found between GV and both ICU and hospital LOS. Adding GV to baseline severity scores improved predictive value for adverse outcomes, as shown by enhancements in clinical scoring tools. These findings were robust across multiple sensitivity analyses.

Expanding the Understanding of glycemic variability in non-traumatic cerebral hemorrhage

Cerebrovascular diseases are major contributors to long-term disability and mortality globally, imposing significant economic burdens and affecting patients' quality of life[32]. GV has recently emerged as a crucial prognostic factor in critical illnesses, including non-traumatic cerebral hemorrhage. Its significance has been demonstrated in various ICU populations. For example, Lu et al.[33] reported that each SD increase in GV was linked to a 5% increase in mortality risk in sepsis patients. GV is also an independent predictor of diabetes-related complications[34]. In cerebrovascular patients, Cai et al.[26] found significant associations between GV and severe consciousness disturbance, in-hospital mortality, and cognitive decline. While these studies highlighted GV's importance, they focused mainly on short-term outcomes. Our study extends this by investigating GV's relationship with poor outcomes, 90-day and 1-year mortality, and LOS in ICU and hospital settings, providing a deeper understanding of GV's immediate and long-term impacts on this high-risk population.

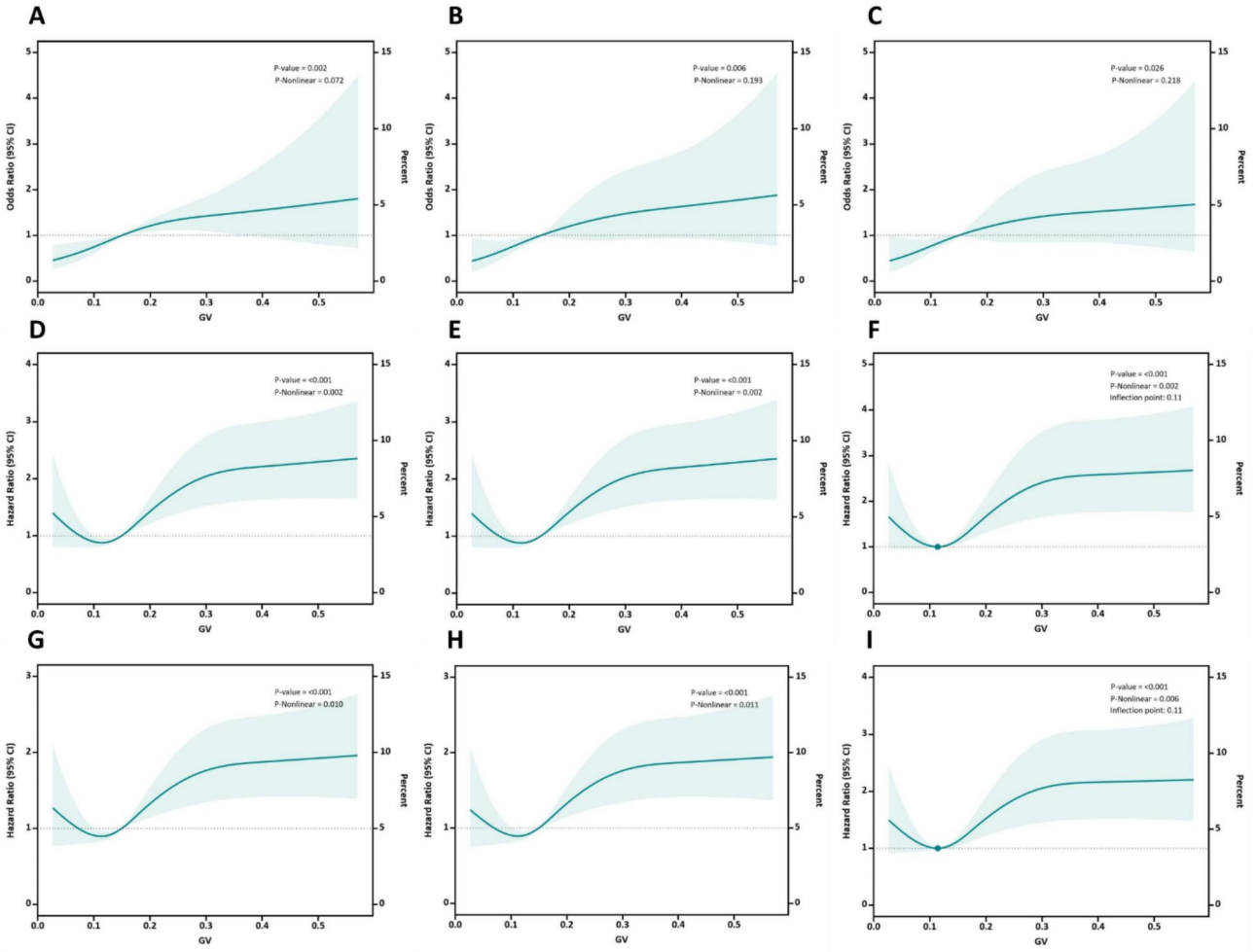

Fig. 4. RCS curves for the relationship between GV and clinical outcomes. RCS Curves of GV and OR/HR: (**A**–**C**) RCS curves for Poor Outcomes at Discharge in Model 1, Model 2, and Model 3, respectively; (**D**–**F**) RCS curves for 90-day mortality in Model 1, Model 2, and Model 3, respectively; (**G**–**I**) RCS curves for 1-year mortality in Model 1, Model 2, and Model 3, respectively; *GV* glycemic variability, *OR* odds ratio, *HR* hazard ratio, *RCS* restricted cubic spline, *ICU* intensive care unit.

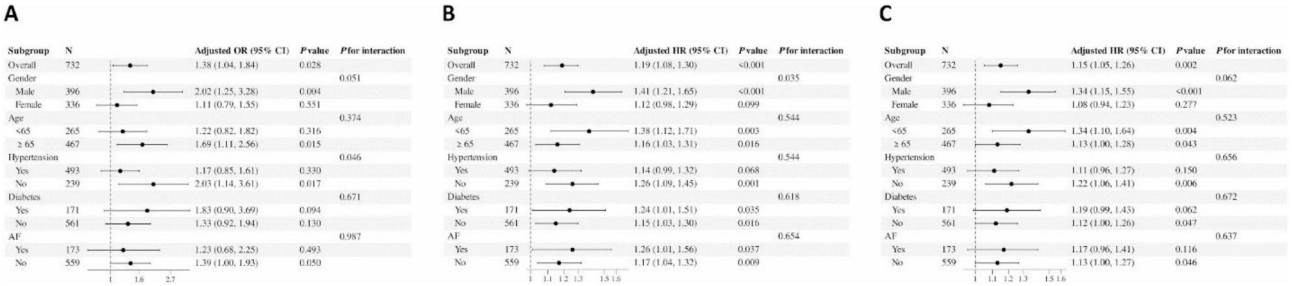

Fig. 5. Subgroup analyses for the association of glycemic variability with clinical outcomes. (**A**) Association between GV and Poor Outcomes at Discharge; (**B**) Association between GV and 90-day mortality; (**C**) Association between GV and 1-year mortality. *GV* glycemic variability; *HR* hazard ratio; *CI* confidence interval; *BMI* body mass index; *AF* atrial fibrillation.

Comparison with previous studies and novel insights into glycemic variability -outcome relationships

Our study extends Cai et al.[26] by elucidating complex relationships between GV and outcomes in non-traumatic cerebral hemorrhage patients. GV showed a linear relationship with poor outcomes and non-linear associations

with mortality. Cohort showed significant non-linear relationships between GV and ICU/hospital LOS. Methodological differences, including direct GV analysis versus logarithmic CV and variations in outcome definitions, may explain the divergence from previous findings. These results suggest the need for tailored glucose control approaches based on disease type and outcomes. Both studies highlight the complexity of GV-outcome relationships, emphasizing the need for further research in diverse populations.

This study identifies a significant non-linear association between GV and hospital stay in non-traumatic cerebral hemorrhage patients ($P < 0.001$, P-nonlinear < 0.05), with distinct inflection points that provide clinically meaningful thresholds for risk stratification. Additionally, GV ≥ 0.11 was associated with significantly increased 90-day and 1-year mortality risks, extending previous findings on the positive correlation between LogGV and hospital stay[26]. Our findings align with those from a study on the Triglyceride-glucose (TyG) index in critically ill patients[35], where TyG was positively associated with LOS for hospital survivors ($\beta = 1.36$, $P = 0.008$) and ICU survivors ($\beta = 0.87$, $P = 0.004$). These findings suggest that glucose metabolism dysregulation, including GV and TyG, may be linked to prolonged hospitalization, possibly involving oxidative stress, inflammation, and increased complications[36,37]. Consistent results across different metrics and populations underscore the importance of glucose homeostasis in critical illness outcomes and hospital resource use.

Based on the data presented in Fig. 3; Table 2, and Additional File 2 Table S11, the observed non-linear increase in the RCS plots may be influenced by variability in data density and measurement frequency at the extremes of the GV distribution. This suggests that the primary findings likely reflect a linear association between higher GV and increased mortality risk, rather than a true hockeystick-like relationship. Notably, a similar nonlinear pattern was reported in Cai et al.'s study[26], highlighting the need for careful interpretation of RCS analyses, particularly when variability at extreme values may impact the observed trends.

Subgroup analysis suggested that GV may have a greater impact on adverse outcomes in non-hypertensive hemorrhage patients. This finding could be partially explained by the potential link between insulin resistance, hyperinsulinemia, and aldosterone regulation in hypertensive patients[38], as well as more pronounced glucose fluctuations in individuals with insulin resistance[7]. However, given the exploratory nature of this analysis and the possibility of chance findings due to multiple comparisons, these results should be interpreted with caution. It is also plausible that hypertensive patients benefit from regular interventions to mitigate glucose fluctuations, while normotensive patients may be more susceptible to the adverse effects of GV. Similarly, GV appeared to have a greater impact on 90-day mortality in males, which might be attributed to estrogen's protective effect on insulin sensitivity in women and higher insulin resistance in men[39–41]. Nonetheless, further studies are needed to validate these observations and interactions in independent cohorts and to explore potential mechanisms underlying the differential impact of GV in hypertensive and non-hypertensive patients, as well as between males and females.

Pathophysiological mechanisms of glycemic variability in poor outcomes among patients with non-traumatic cerebral hemorrhage

The brain's vulnerability to glucose fluctuations is due to its high energy demands and metabolic rate, increasing sensitivity to glycemic variations and oxidative stress[42]. In non-traumatic cerebral hemorrhage patients, especially in ICU, GV can negatively impact prognosis through various interconnected mechanisms.

At the subcellular level, GV affects mitochondrial function, including the electron transport chain, ATP production, and the balance between fusion and fission, leading to mitochondrial fragmentation and reduced energy efficiency[43]. Additionally, GV induces endoplasmic reticulum (ER) stress, activating the unfolded protein response (UPR). Sustained ER stress may exacerbate cellular injury, intensify inflammation, and oxidative stress via JNK and NF-κB pathways[22]. These mechanisms interact, creating a complex network in which oxidative stress and inflammation amplify endothelial dysfunction and blood-brain barrier disruption. GV also promotes plaque formation, affects platelet function, and coagulation factor activity in atherosclerosis[21,22]. In ICU non-traumatic cerebral hemorrhage patients, the critical condition activates the sympathetic nervous system, raising blood glucose levels. Factors like therapeutic interventions, stress, infections, and nutritional support further influence glucose fluctuations, complicating glucose management and necessitating more frequent monitoring and individualized treatment strategies.

Strengths and limitations

This study found an independent association between GV and both short-term outcomes and long-term (90-day and 1-year mortality) in ICU patients with non-traumatic cerebral hemorrhage, emphasizing its prognostic value. Limitations of this study include its retrospective design, which may introduce potential selection bias, and the reliance on the MIMIC-IV database, which lacks key ICH-specific characteristics such as size, location, presence of intraventricular extension, and pre-ICH mRS scores. The absence of these critical variables limits our ability to fully adjust for potential confounders, potentially affecting the robustness of the observed associations between GV and clinical outcomes. Additionally, the use of non-continuous glucose measurements may bias GV calculations and limit their precision. Future research should focus on prospective studies incorporating standardized, continuous glucose monitoring and datasets that include comprehensive ICH-specific variables. Such studies could also investigate the underlying mechanisms linking GV to adverse outcomes, including oxidative stress, inflammation, and endothelial dysfunction, to provide deeper insights into its role in critically ill patients with ICH.

Conclusion

This study shows GV's role in cerebral hemorrhage prognosis, with higher GV linked to increased adverse events, mortality, and longer stays. Established GV thresholds (0.11) aid risk stratification, and adding GV improves

scoring systems' predictive power. GV monitoring and individualized treatment are crucial, and future research should validate these findings, explore mechanisms, and assess targeted GV interventions.

Data availability

The datasets generated and analyzed in this study are presented within the manuscript or supplementary materials, with additional information available from the corresponding author upon reasonable request.

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Author contributions
Dong Wang: Conceptualization, Methodology, Writing - Original Draft Preparation; Chang He and Shuhuai Zou: Data Curation, Formal Analysis, Visualization; Lizheng Yu and Biyuan Han: Investigation, Resources, Validation; Liming He, Ankang Liu, and Yingying Hong: Software, Writing - Review & Editing; Qianfeng Li: Writing - Review & Editing, Supervision, Project Administration, Funding Acquisition.

Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
This study was conducted in full compliance with the principles outlined in the Declaration of Helsinki. The utilization of the MIMIC-IV database (https://physionet.org/content/mimiciv/2.2/) was sanctioned by the Institutional Review Board of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. Given that the MIMIC-IV database is a publicly accessible resource, the requirement for specific ethical approval and individual informed consent for this study was waived. This waiver is in accordance with standard procedures for research involving de-identified, publicly available datasets.

Additional information
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