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Association of persistent postoperative hyperglycemia with mortality after elective craniotomy

***Jialing He, MD,[1] Yu Zhang, MD,[2] Lu Jia, MD,[3] Xin Cheng, MD,[1] Yixin Tian, MD,[1] Pengfei Hao, MD,[2] Tiangui Li, MD,[5] Yangchun Xiao, MD,[4] Liyuan Peng, MD,[4] Yuning Feng, MD,[4] Haidong Deng, MD,[4] Peng Wang, MD,[4] Weelic Chong, MD,[6] Yang Hai, MD,[7] Lvlin Chen, MD,[4] Chao You, MD,[1] and Fang Fang, MD[1]**

[1]Department of Neurosurgery, West China Hospital, Sichuan University, Chengdu, Sichuan; [2]Evidence-Based Medicine Center, Affiliated Hospital of Chengdu University, Chengdu, Sichuan; [3]Department of Neurosurgery, Shanxi Provincial People's Hospital, Taiyuan, Shanxi; [4]Affiliated Hospital of Chengdu University, Chengdu, Sichuan; [5]Department of Neurosurgery, Longquan Hospital, Chengdu, Sichuan, China; [6]Department of Medical Oncology, Thomas Jefferson University, Philadelphia; and [7]Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania

OBJECTIVE The influence of persistent postoperative hyperglycemia after craniotomy has not yet been explored. This study aimed to investigate the hypothesis that persistent postoperative hyperglycemia is associated with mortality in patients undergoing an elective craniotomy.

METHODS This study included adult patients (age ≥ 18 years) undergoing an elective craniotomy between January 2011 and March 2021 at the West China Hospital, Sichuan University. Peak daily blood glucose values measured within the first 7 days after craniotomy were collected. Persistent hyperglycemia was defined by two or more consecutive serum glucose levels of mild, moderate, or severe hyperglycemia. Normoglycemia, mild hyperglycemia, moderate hyperglycemia, and severe hyperglycemia were defined as glucose values of ≤ 6.1 mmol/L, > 6.1 and ≤ 7.8 mmol/L, > 7.8 and ≤ 10.0 mmol/L, and > 10.0 mmol/L, respectively.

RESULTS This study included 14,907 patients undergoing an elective craniotomy. In the multivariable analysis, both moderate (adjusted OR 3.76, 95% CI 2.68–5.27) and severe (adjusted OR 3.82, 95% CI 2.54–5.76) persistent hyperglycemia in patients were associated with higher 30-day mortality compared with normoglycemia. However, this association was not observed in patients with mild hyperglycemia (adjusted OR 1.32, 95% CI 0.93–1.88). Interestingly, this association was observed regardless of whether patients had preoperative hyperglycemia. There was no interaction between moderate or severe hyperglycemia and preexisting diabetes (p for interaction = 0.65). When postoperative peak blood glucose values within the first 7 days after craniotomy were evaluated as a continuous variable, for each 1-mmol/L increase in blood glucose, the adjusted OR of 30-day mortality was 1.17 (95% CI 1.14–1.21). Postoperative blood glucose (area under the curve [AUC] = 0.78) was superior to preoperative blood glucose (AUC = 0.65; p < 0.001) for predicting mortality. Moderate and severe persistent hyperglycemia in patients were associated with an increased risk of deep venous thrombosis (adjusted OR 3.20, 95% CI 2.31–4.42), pneumonia (adjusted OR 2.77, 95% CI 2.40–3.21), myocardial infarction (adjusted OR 4.38, 95% CI 3.41–5.61), and prolonged hospital stays (adjusted OR 1.43, 95% CI 1.29–1.59).

CONCLUSIONS In patients undergoing an elective craniotomy, moderate and severe persistent postoperative hyperglycemia were associated with an increased risk of mortality compared with normoglycemia, regardless of preoperative hyperglycemia.

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KEYWORDS postoperative period; persistent hyperglycemia; mortality; elective craniotomy

Hyperglycemia is common in critical care patients and is a well-established indicator of critical care severity and a predictor of mortality.[1,2] Postsurgical patients are particularly vulnerable as they may experience an increased systemic inflammation, impaired immune response, stress response, and altered glucose metabolism.[3,4] The management degree of postoperative glucose levels may be an important effect modifier.[5] However, optimizing postoperative glucose levels remains a topic of significant controversy.[6–8] The practice of tight

ABBREVIATIONS ASA = American Society of Anesthesiologists; CCI = Charlson Comorbidity Index; ROC = receiver operating characteristic; VIF = variance inflation factor.

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* J.H., Y.Z., and L.J. contributed equally to this work.

glycemic control (6.1–7.8 mmol/L) has emerged as a plausible strategy to improve outcomes but increases the risk of hypoglycemia.[9]

Notably, hyperglycemia is even more common in patients who have undergone elective craniotomy because they often receive corticosteroids to reduce brain swelling.[10,11] Currently, no guidance exists regarding the implementation of tight glycemic control for a specific level of hyperglycemia after craniotomy.[6] A global survey reported that perceptions and practices on managing postoperative glucose in patients undergoing craniotomy are variable.[6] Variability in glycemic management might reflect a scarcity of solid clinical evidence.

Recently, we demonstrated that preoperative hyperglycemia is associated with mortality after craniotomy.[12] However, no studies have estimated the association between postoperative hyperglycemia and mortality after craniotomy.

Because of the low incidence of mortality following elective craniotomy,[13] the inability to obtain a large sample of deaths may preclude any small study from fully appreciating the possible risks associated with postoperative hyperglycemia. Although there are numerous small studies[14,15] in the literature concerning postoperative hyperglycemia and some associated morbidity (e.g., infection), none of these have been large enough to assess postoperative mortality. Moreover, the 2023 American Diabetes Association practice guideline states that whether hospitalized adults receive insulin therapy or not should be based on the severity of persistent hyperglycemia.[9] Therefore, there is a need to examine the influence of persistent hyperglycemia on mortality following craniotomy and define the optimal treatment threshold for persistent hyperglycemia using a larger sample size.

In this study, we aimed to systematically evaluate the association between persistent postoperative hyperglycemia and mortality in patients undergoing an elective craniotomy.

Methods

Study Design and Data Source

This is a single-institution retrospective cohort study of 14,907 patients undergoing an elective craniotomy. We evaluated consecutive electronic health records from the West China Hospital, Sichuan University, from January 1, 2011, to March 31, 2021. The West China Hospital Ethics Committee approved this study, and informed consent was not required.

The inclusion criterion was adult patients (age ≥ 18 years) who underwent an elective craniotomy. Excluded were patients who underwent urgent or emergency surgery, repeat craniotomy, or burr hole procedures; those with intracerebral hemorrhage, subarachnoid hemorrhage, or trauma; and those who did not have blood glucose records within the first 7 days after craniotomy. Moreover, patients with nonexistent or wrong personal identification numbers in the electronic health records were also excluded because we extracted the personal identification numbers of patients to obtain death records from the Household Registration Administration System.

Identification and Classification of Persistent Hyperglycemia

Peak daily blood glucose values, measured in the first 7 days after craniotomy, were used as an index of glycemic monitoring. Current guidelines[9,16] indicate that hyperglycemia in hospitalized adults is determined based on any blood glucose values recorded during their hospital stay. Thus, we did not distinguish between fasting glucose and nonfasting glucose. Notably, most peak daily glucose levels were measured in a nonfasting state. Based on the 2023 American Diabetes Association's current clinical practice recommendations,[9] normoglycemia, mild hyperglycemia, moderate hyperglycemia, and severe hyperglycemia were defined as glucose values of ≤ 6.1 mmol/L, > 6.1 and ≤ 7.8 mmol/L, > 7.8 and ≤ 10.0 mmol/L, and > 10.0 mmol/L, respectively. Persistent hyperglycemia was defined by two or more consecutive serum glucose levels of mild, moderate, or severe hyperglycemia. If a patient was classified as having moderate hyperglycemia in one recording and severe hyperglycemia in another, the patient was categorized as having moderate hyperglycemia. Similarly, if a patient was classified as having mild hyperglycemia in one recording and moderate or severe hyperglycemia in another, the patient was categorized as having mild hyperglycemia.

Outcomes

The primary outcome was postoperative 30-day mortality. Secondary outcomes included postoperative complications (acute kidney injury, deep venous thrombosis, pneumonia, surgical site infection, myocardial infarction) and prolonged hospital stays (defined as postoperative hospital stay ≥ 14 days).

The death records were collected from the Chinese Hukou System, a Household Registration Administration System. If a citizen dies in China, the law demands that his or her kin should contact the household registration authority and terminate the household registration within 30 days.[17] In 2021, the Seventh National Population Census revised this system. According to the National Bureau of Statistics, the missing registration rate of the Seventh National Population Census was 0.05%.[18] Thus, death records in this system are accurate, and the rate of loss to follow-up of this study is negligible.[19] The censoring date was August 15, 2021.

Statistical Analysis

Descriptive statistics were used to summarize variables as frequency (percentage) for categorical variables or mean (SD) for continuous variables. As appropriate, the differences between groups were compared using one-way ANOVA or the chi-square test. We replaced missing values with multiple imputations.

Univariate logistic regression analysis was used to assess the association between the independent predictors and overall favorable outcomes. Covariates associated with p values < 0.1 were further implemented into a backward stepwise multivariable logistic regression model. Based on clinical experience and previous reports, demographic variables (age, sex, smoking, alcohol consumption), medical history (hypertension, diabetes, chronic

liver disease, coronary artery disease), American Society of Anesthesiologists (ASA) class, Charlson Comorbidity Index (CCI), primary diagnosis, systolic blood pressure, preoperative laboratory testing values (blood glucose, albumin, lymphocyte counts, neutrophil counts, white blood cell counts), intraoperative surgery time, intraoperative blood loss, perioperative drug use (steroid, insulin), and perioperative transfusion were considered important confounders. Model discrimination (examined using C-statistics) was assessed. When the variance inflation factor (VIF) for all variables was > 5, significant multicollinearity needed to be corrected.

Propensity score matching[20,21] was performed as the sensitivity analysis with a matching ratio (normoglycemia to moderate and severe hyperglycemia) of 1:1 and a caliper distance of 0.2. Besides the variables in the primary multivariable model, we conducted sensitivity analyses to additionally adjust for the mean daily dose and duration of perioperative insulin use as well as adverse outcomes, including postoperative complications (acute kidney injury, deep venous thrombosis, pneumonia, surgical site infection, myocardial infarction) and prolonged hospital stays. Furthermore, separate analyses were conducted for nonfasting and fasting blood glucose in patients. E-values were calculated to quantify the effect of unmeasured confounding on 30-day mortality[22] and were computed with an online E-value calculator (https://www.evalue-calculator.com/evalue//).[23]

We conducted receiver operating characteristic (ROC) analyses of postoperative (peak blood glucose value within the first 7 days after craniotomy) and preoperative glucose values as a predictor of 30-day mortality, respectively. The DeLong test was used to compare the ROC curves statistically.

Restricted cubic splines were used to estimate the odds ratios of peak blood glucose values within the first 7 days after craniotomy and their association with the risk of 30-day mortality. Overall survival within 1 year was estimated using the Kaplan-Meier method. Hazard ratios were calculated by the multivariable Cox proportional hazards model and tested by the log-rank test.

We conducted subgroup analyses. Patients were divided into subgroups of normoglycemia (glucose ≤ 6.1 mmol/L) and persistent hyperglycemia (moderate and severe, glucose > 7.8 mmol/L) to explore if the association differed for subgroups classified by various baseline variables.

All statistical analyses were performed using R software version 4.2.3 (The R Foundation for Statistical Computing). Bonferroni p values < 0.01 were considered statistically significant for the subgroup analyses. In other analyses, statistical significance was defined as a 2-sided p value < 0.05.

Results

A total of 14,907 adult patients undergoing an elective craniotomy were included during the study period (eFig. 1). The baseline characteristics of these patients are presented in Table 1. Persistent mild hyperglycemia was observed in 4506 (30.2%) patients, moderate hyperglycemia in 1965 (13.2%) patients, and severe hyperglycemia in 1224 (8.2%) patients. The mean age of the study population was 50 years. Females accounted for 55.3% of the patients. Overall, 3.5%, 3.9%, 10.6%, and 46.0% of patients with normoglycemia, mild hyperglycemia, moderate hyperglycemia, and severe hyperglycemia, respectively, had diabetes (p < 0.001). Specifically, the proportion of patients with postoperative hyperglycemia was higher among patients with diabetes compared with those without diabetes (79% vs 49%). Furthermore, a significant association between diabetes and postoperative hyperglycemia was found (adjusted OR 1.98, 95% CI 1.69–2.33) (eTable 1). A higher proportion of patients with mild, moderate, and severe hyperglycemia had hypertension, chronic liver disease, or coronary artery disease compared with patients with normoglycemia. Additionally, patients with mild, moderate, and severe hyperglycemia also had higher preoperative systolic blood pressure, preoperative blood glucose, preoperative neutrophil counts, preoperative white blood cell counts, and intraoperative blood loss. Postoperative mortality at 30 days for the entire cohort was 2.0% (n = 294).

In Fig. 1, using restricted cubic spline regression analysis, we found a dose-response curvilinear association between postoperative peak blood glucose level within the first 7 days after craniotomy and 30-day mortality (p for nonlinear = 0.48). Patients with blood glucose levels > 7.8 mmol/L had an increased risk of death compared with those with levels ≤ 7.8 mmol/L (reference). There was a progressive increase in the observed rates of mortality with higher blood glucose levels.

The associations between persistent postoperative glycemic status and 30-day mortality are displayed in Table 2. Compared with normoglycemia in patients, both moderate (adjusted OR 3.76, 95% CI 2.68–5.27) and severe (adjusted OR 3.82, 95% CI 2.54–5.76) hyperglycemia were associated with higher 30-day mortality after adjusting for age, sex, diabetes, ASA class, CCI, primary diagnosis, preoperative lymphocyte counts, preoperative white blood cell counts, intraoperative surgery time, intraoperative blood loss, perioperative insulin use, perioperative steroid use, and perioperative transfusion (eTable 2). The E-values for the association between moderate or severe persistent hyperglycemia and 30-day mortality were 7.0 and 7.1, respectively. The model diagnostics showed good discrimination (C-statistic = 0.84). No obvious multicollinearity was detected in the regression model of our study (all VIFs < 5, mean VIF 1.57). Additionally, in patients with preoperative normoglycemia (≤ 6.1 mmol/L), compared with postoperative normoglycemia, mild (adjusted OR 1.94, 95% CI 1.21–3.11), moderate (adjusted OR 3.96, 95% CI 2.37–6.61), and severe (adjusted OR 4.36, 95% CI 2.30–8.25) postoperative hyperglycemia were all associated with higher 30-day mortality.

When postoperative peak blood glucose within the first 7 days after craniotomy was evaluated as a continuous variable (Table 2), for each 1-mmol/L elevation in blood glucose, the adjusted OR of 30-day mortality was 1.17 (95% CI 1.14–1.21). Box plots also showed a significant difference among patients who died within 30 days of surgery with regard to their postoperative daily glucose level using quantitative estimation (p < 0.001) (Fig. 2). Additionally, the areas under the ROC curves for predicting

TABLE 1. Baseline characteristics of the patients according to persistent postoperative glycemic status

Characteristic	Normoglycemia (n = 7212)	Mild Hyperglycemia (n = 4506)	Moderate Hyperglycemia (n = 1965)	Severe Hyperglycemia (n = 1224)	p Value	Missing Value
Demographics						
Mean age, yrs	46.9 (14.1)	49.6 (13.4)	53.7 (13.1)	57.3 (12.1)	<0.001	0 (0.0)
Female	3853 (53.4)	2486 (55.2)	1183 (60.2)	722 (59.0)	<0.001	0 (0.0)
Smoking	928 (12.9)	462 (10.3)	163 (8.3)	93 (7.6)	<0.001	0 (0.0)
Alcohol	1186 (16.4)	704 (15.6)	264 (13.4)	158 (12.9)	0.001	0 (0.0)
Medical history						
Hypertension	925 (12.8)	799 (17.7)	486 (24.7)	461 (37.7)	<0.001	0 (0.0)
Diabetes	250 (3.5)	176 (3.9)	208 (10.6)	563 (46.0)	<0.001	0 (0.0)
Chronic liver disease	346 (4.8)	243 (5.4)	118 (6.0)	110 (9.0)	<0.001	0 (0.0)
Coronary artery disease	68 (0.9)	51 (1.1)	41 (2.1)	62 (5.1)	<0.001	0 (0.0)
ASA classes IV & V	316 (4.4)	138 (3.1)	90 (4.6)	104 (8.5)	<0.001	0 (0.0)
CCI					<0.001	0 (0.0)
0	4805 (66.6)	3057 (67.8)	1263 (64.3)	469 (38.3)		
1 or 2	1962 (27.2)	1172 (26.0)	549 (27.9)	501 (40.9)		
≥3	445 (6.2)	277 (6.1)	153 (7.8)	254 (20.8)		
Primary diagnosis					<0.001	0 (0.0)
Primary brain tumor						
Schwannoma	217 (3.0)	237 (5.3)	141 (7.2)	57 (4.7)		
Meningioma	1318 (18.3)	924 (20.5)	486 (24.7)	323 (26.4)		
Craniopharyngioma	91 (1.3)	76 (1.7)	44 (2.2)	40 (3.3)		
Glioma, WHO grades I & II	730 (10.1)	503 (11.2)	221 (11.2)	108 (8.8)		
Glioma, WHO grades III & IV	1108 (15.4)	663 (14.7)	249 (12.7)	180 (14.7)		
Other brain tumors	1116 (15.5)	761 (16.9)	269 (13.7)	181 (14.8)		
Metastasis	278 (3.9)	129 (2.9)	57 (2.9)	32 (2.6)		
Vascular	895 (12.4)	508 (11.3)	257 (13.1)	170 (13.9)		
Others	1459 (20.2)	705 (15.6)	241 (12.3)	133 (10.9)		
Mean preop SBP, mm Hg	124 (16)	127 (17)	129 (35)	132 (18)	<0.001	268 (2.0)
Mean preop lab values						
Blood glucose, mmol/L	5.3 (1.4)	5.5 (1.3)	6.2 (2.0)	8.3 (3.6)	<0.001	1270 (9.0)
Albumin, g/L	42.0 (4.2)	41.9 (4.6)	41.1 (5.2)	40.2 (5.8)	<0.001	1311 (9.0)
Lymphocyte count, 10^9/L	1.7 (0.7)	1.6 (0.7)	1.6 (0.7)	1.6 (0.7)	<0.001	1374 (9.0)
Neutrophil count, 10^9/L	5.0 (3.4)	5.2 (4.0)	5.9 (4.4)	6.0 (4.3)	<0.001	1247 (8.0)
WBC count, 10^9/L	7.2 (3.5)	7.5 (3.9)	8.0 (4.4)	8.1 (4.2)	<0.001	1224 (8.0)
Mean intraop values						
Op time, hrs	3.6 (1.7)	3.5 (1.8)	3.6 (2.0)	3.5 (2.0)	<0.001	198 (1.0)
Blood loss, ml	251.8 (430.2)	275.6 (456.5)	341.8 (526.7)	361.8 (566.1)	<0.001	1711 (11.0)
Insulin treatment						
Periop insulin use	157 (2.2)	106 (2.4)	188 (9.6)	484 (39.5)	<0.001	0 (0.0)
Mean daily dose, IU/day	47.3 (96.6)	50.6 (94.8)	40.1 (53.6)	53.0 (93.1)	0.38	0 (0.0)
Mean duration, days	3.2 (3.7)	2.9 (3.8)	3.4 (4.2)	6.4 (6.6)	<0.001	0 (0.0)
Preop insulin use	57 (0.8)	23 (0.5)	39 (2.0)	136 (11.1)	<0.001	0 (0.0)
Postop insulin use	128 (1.8)	92 (2.0)	174 (8.9)	461 (37.7)	<0.001	0 (0.0)
Periop steroid use	5228 (72.5)	3267 (72.5)	1398 (71.1)	866 (70.8)	0.41	0 (0.0)
Periop transfusion	230 (3.2)	201 (4.5)	145 (7.4)	146 (11.9)	<0.001	0 (0.0)

SBP = systolic blood pressure; WBC = white blood cell.

Values are given as number of patients (%) or mean (SD) unless otherwise indicated. Normoglycemia, mild hyperglycemia, moderate hyperglycemia, and severe hyperglycemia were defined as glucose values of ≤ 6.1 mmol/L, > 6.1 and ≤ 7.8 mmol/L, > 7.8 and ≤ 10.0 mmol/L, and > 10.0 mmol/L, respectively.

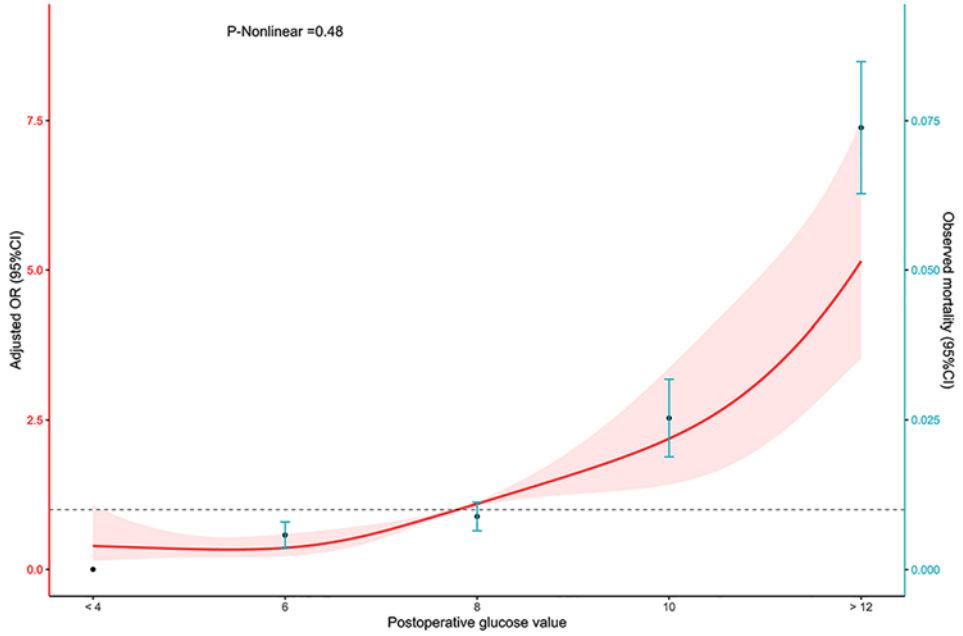

FIG. 1. Restricted cubic spline of postoperative glucose values with 30-day mortality in patients undergoing an elective craniotomy. The x-axis shows postoperative glucose values (peak blood glucose value within the first 7 days after craniotomy), and the left y-axis shows the odds ratios of postoperative 30-day mortality. The right y-axis shows the observed mortality. The model was adjusted for age, sex, diabetes, ASA class, CCI, primary diagnosis, preoperative lymphocyte counts, preoperative white blood cell counts, intraoperative surgery time, intraoperative blood loss, perioperative insulin use, perioperative steroid use, and perioperative transfusion. A blood glucose level of 7.8 mmol/L served as the reference. The *red shaded area* indicates 95% CIs. The *dots* represent the observed mortality, and the *error bars* indicate the 95% CIs for the observed mortality. Figure is available in color online only.

30-day mortality with preoperative glucose level or postoperative glucose level were 0.65 and 0.78, respectively (Fig. 3), and the postoperative glucose level was a superior predictor ($p < 0.001$, DeLong test).

In Fig. 4, we assessed the interactions between persistent postoperative glycemic status (normoglycemia vs moderate and severe hyperglycemia, > 7.8 mmol/L) and baseline variables and how they influenced postoperative 30-day mortality. There was no statistical interaction. Additionally, the association between moderate or severe hyperglycemia and 30-day mortality was seen in patients without preexisting diabetes (adjusted OR 3.61, 95% CI 2.58–5.04) but not in those with preexisting diabetes (adjusted OR 2.73, 95% CI 0.80–9.37). However, there was no interaction between moderate or severe hyperglycemia and preexisting diabetes (p for interaction = 0.65). Moreover, patients with moderate or severe persistent postoperative hyperglycemia had a higher risk of mortality regardless of whether they had preoperative hyperglycemia or received perioperative steroids.

We used Kaplan-Meier survival curves to compare the risk of mortality in patients with different persistent postoperative glycemic statuses over a 1-year period. The analysis indicated a positive association between the severity of hyperglycemia and mortality risk ($p < 0.001$, log-rank test) (Fig. 5). The multivariable Cox regression model indicated that compared with patients with normoglycemia, the adjusted hazard ratios of 1-year mortality were 1.11 for mild hyperglycemia (95% CI 0.97–1.27), 1.46 for moderate hyperglycemia (95% CI 1.23–1.72), and 1.75 for severe hyperglycemia (95% CI 1.43–2.16).

We further conducted 1:1 propensity score matching for sensitivity analyses to validate our obtained results. Baseline characteristics of propensity score–matched samples were well matched (standardized mean difference < 0.1)

TABLE 2. Unadjusted and adjusted associations between persistent postoperative glycemic status and 30-day mortality

	Glycemic Status	Glucose, mmol/L	Events/Total	Unadjusted OR (95% CI)	p Value	Adjusted OR (95% CI)	p Value
Continuous variable*	NA	Per 1.0	NA	1.20 (1.17–1.23)	<0.001	1.17 (1.14–1.21)	<0.001
Clinical threshold	Normal	<6.1	73/7212 (1%)	1 (reference)	<0.001†	1 (reference)	<0.001†
	Mild	6.1–7.8	60/4506 (1.3%)	1.32 (0.94–1.86)		1.32 (0.93–1.88)	
	Moderate	7.8–10.0	83/1965 (4.2%)	4.31 (3.14–5.93)		3.76 (2.68–5.27)	
	Severe	>10.0	78/1224 (6.4%)	6.66 (4.81–9.21)		3.82 (2.54–5.76)	

NA = not applicable.
* Peak blood glucose value within the first 7 days after craniotomy.
† p for trend.

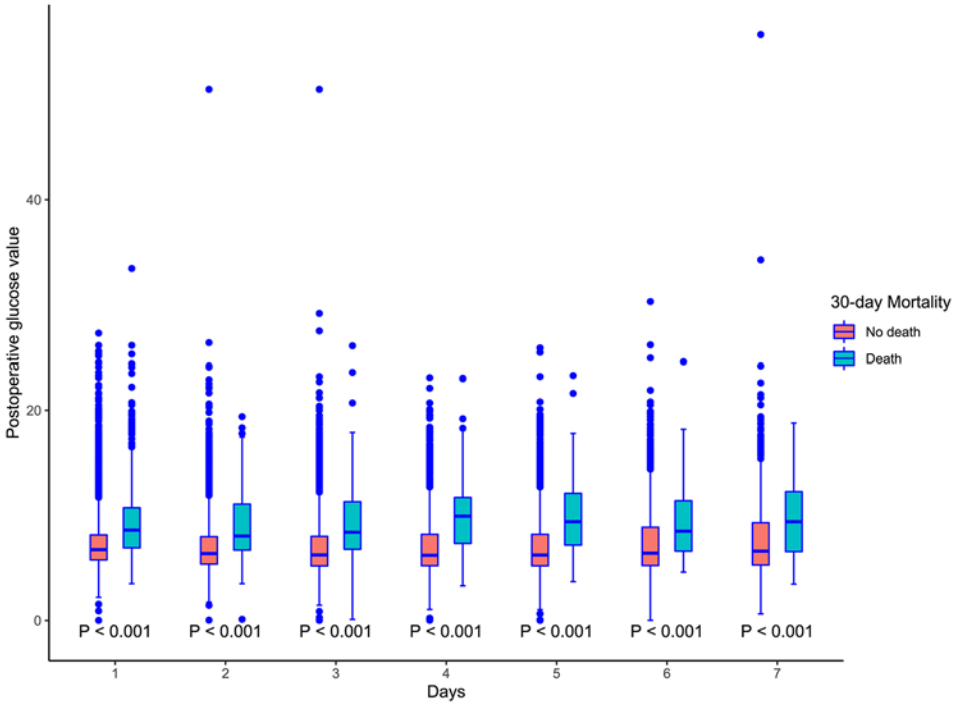

FIG. 2. Box plots showing the significant difference among patients who died within 30 days of surgery with regard to their postoperative daily glucose levels using quantitative estimation. The *lines* indicate medians; the *boxes*, interquartile ranges; the *whiskers*, maximum and minimum values; and the *circles*, outliers. Figure is available in color online only.

(eTable 3). Consistent with the primary results, moderate and severe hyperglycemia (> 7.8 mmol/L) in patients were associated with higher odds of 30-day mortality (matched OR 3.15, 95% CI 2.09–4.75).

We additionally adjusted for the mean daily dose and duration of perioperative insulin use as well as adverse outcomes in the multivariable logistic regression model (eTable 4). Moderate and severe hyperglycemia were also

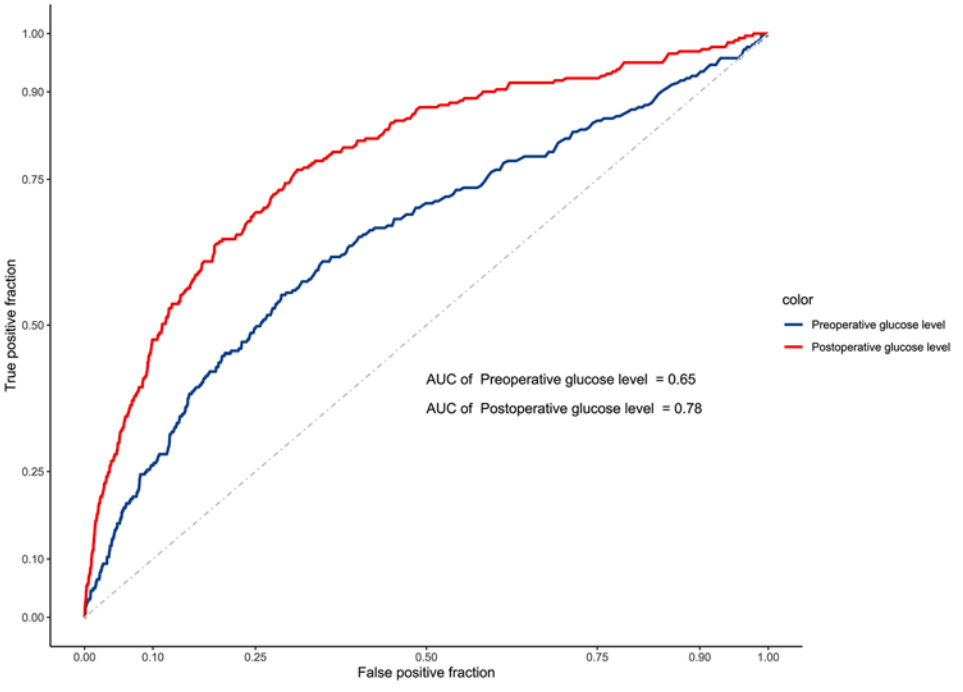

FIG. 3. ROC curves of postoperative (peak blood glucose value within the first 7 days after craniotomy) and preoperative glucose as a predictor of 30-day mortality. Figure is available in color online only.

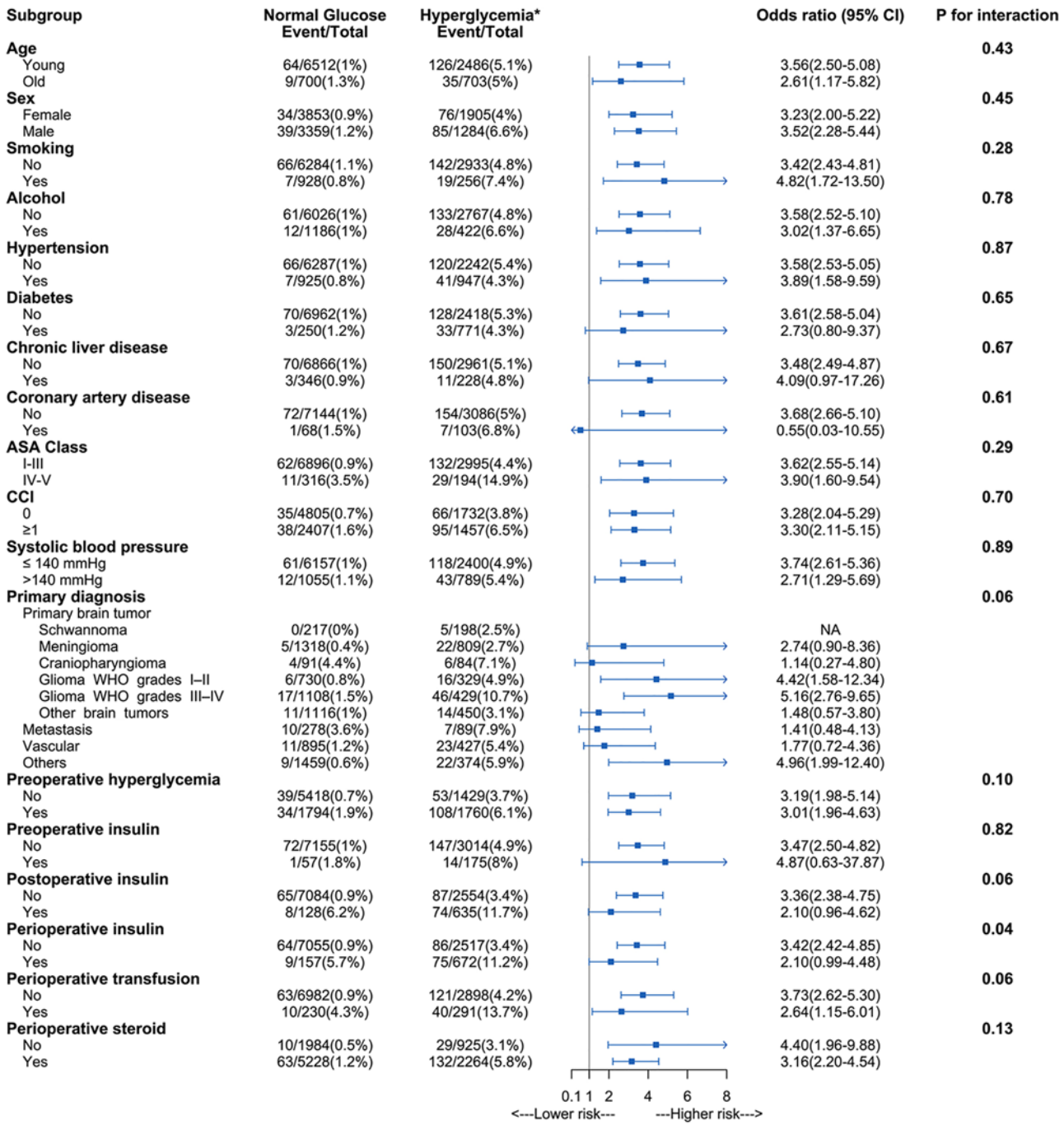

FIG. 4. Subgroup analysis of the association of moderate and severe persistent hyperglycemia with 30-day mortality. *Moderate and severe persistent hyperglycemia. Figure is available in color online only.

associated with an increased risk of 30-day mortality. Furthermore, our primary outcome remained consistent and unaffected regardless of whether fasting or nonfasting blood glucose values were considered (eTable 5).

In Table 3, moderate and severe persistent hyperglycemia was associated with an increased risk of deep venous thrombosis (adjusted OR 3.20, 95% CI 2.31–4.42), pneumonia (adjusted OR 2.77, 95% CI 2.40–3.21), myocardial infarction (adjusted OR 4.38, 95% CI 3.41–5.61), and prolonged hospital stays (adjusted OR 1.43, 95% CI 1.29–1.59) compared with those with normoglycemia. There was no statistical association of acute kidney injury and surgical site infection with moderate and severe persistent hyperglycemia.

Discussion

Our study revealed that moderate or severe persistent postoperative hyperglycemia was associated with higher

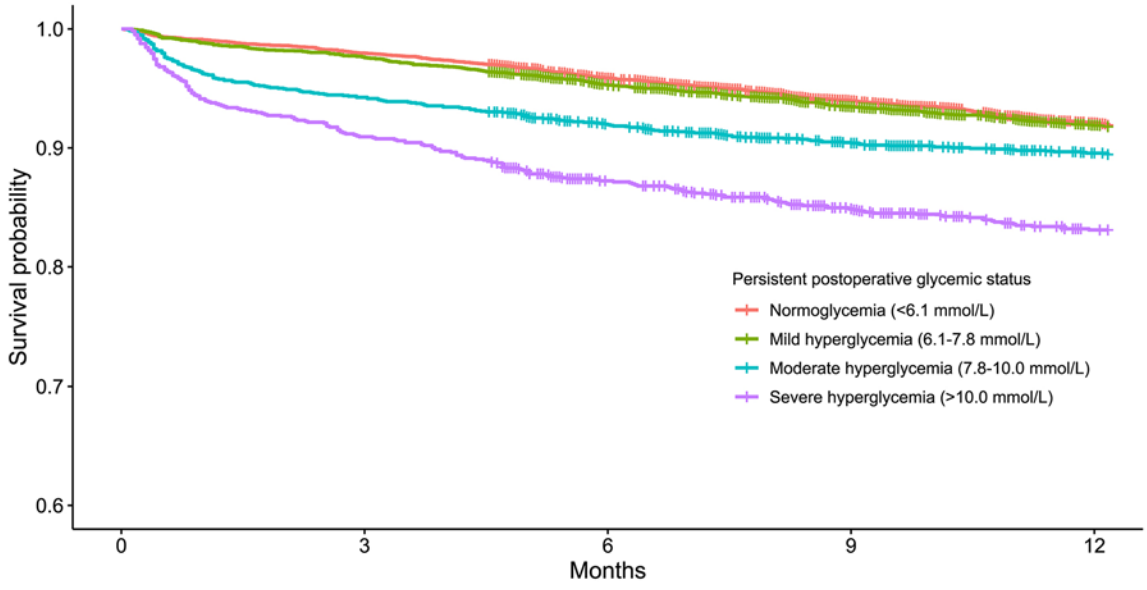

FIG. 5. Kaplan-Meier estimates for 1-year survival of patients undergoing an elective craniotomy. Figure is available in color online only.

30-day mortality compared with normoglycemia in patients after elective craniotomy. This association remained significant whether or not patients presented with preoperative hyperglycemia, and postoperative blood glucose levels were better predictors of mortality than preoperative levels. Furthermore, moderate or severe persistent hyperglycemia was also associated with an elevated risk of complications such as deep venous thrombosis, pneumonia, myocardial infarction, and prolonged hospital stays.

To our knowledge, this is the first investigation of the association of postoperative hyperglycemia with mortality following elective craniotomy. We reviewed our findings in the context of recent literature and determined that they are consistent with prior studies of patients undergoing major surgery, such as cardiac surgery[24] and intestinal surgery.[25]

In this study, the relationship between postoperative hyperglycemia and mortality was found to be independent of perioperative steroid use or the fasting status of glucose levels. Steroids were commonly administered during craniotomy, resulting in elevated blood glucose levels. However, subgroup analyses demonstrated that postoperative hyperglycemia was associated with a higher risk of mortality within 30 days, regardless of the use of perioperative steroids. Furthermore, separate analyses for fasting and nonfasting blood glucose levels yielded no significant impact on the primary outcome.

For morbidity, our findings on pneumonia[26] and prolonged hospital stay[15] were similar to those reported in prior studies of patients undergoing craniotomy. Contrary to a prior study,[14] however, we did not observe a significantly increased risk of surgical site infection. Notably, we observed some new findings on deep venous thrombosis and myocardial infarction among these patients. For example, a retrospective study of 105 children undergoing an elective craniotomy reported that postoperative hyperglycemia was associated with postoperative complications (infectious, respiratory, etc.) and longer hospital stays.[15] In a study of 224 patients undergoing craniotomy, severe intraoperative hyperglycemia (blood glucose ≥ 10.0 mmol/L) was associated with a higher risk of postoperative composite infection (lung, wound, blood, etc.).[26] Additionally, Weber et al. reported that postoperative hyperglycemia was

TABLE 3. Associations of postoperative complications and lengths of hospital stay with moderate and severe persistent hyperglycemia

Outcome	Persistent Hyperglycemia		
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p Value
Acute kidney injury	2.23 (1.71–2.90)	1.17 (0.85–1.61)	0.34
Deep venous thrombosis	4.83 (3.64–6.41)	3.20 (2.31–4.42)	<0.001
Pneumonia	4.00 (3.55–4.50)	2.77 (2.40–3.21)	<0.001
Surgical site infection	1.45 (1.13–1.87)	1.09 (0.81–1.45)	0.58
Myocardial infarction	8.03 (6.50–9.93)	4.38 (3.41–5.61)	<0.001
Prolonged hospital stays*	1.88 (1.72–2.05)	1.43 (1.29–1.59)	<0.001

* Prolonged hospital stay was defined as a postoperative hospital stay ≥ 14 days.

associated with an increased risk of surgical site infection after neurosurgery.[14]

We recently demonstrated that preoperative hyperglycemia was associated with mortality after craniotomy.[12] In the current study, we expanded on this finding by demonstrating that postoperative hyperglycemia was also associated with mortality regardless of preoperative hyperglycemia. In ROC analyses, we found that postoperative blood glucose was superior to preoperative blood glucose for predicting mortality, which was consistent with prior findings in elective colorectal surgery.[27] Taken together, the results of these two studies highlight the importance of controlling blood glucose before and after surgery. However, contrary to our previous study, the current study did not identify the adverse effect of mild hyperglycemia. This discrepancy suggested that mild hyperglycemia might be a normal response of the body after craniotomy.

The current study found that the association between moderate or severe hyperglycemia and 30-day mortality was observed only in patients without preexisting diabetes. However, patients with preexisting diabetes showed a high odds ratio (adjusted OR 2.73, 95% CI 0.80–9.37), although the association did not reach statistical significance. Furthermore, we found no influence of the interaction between hyperglycemia and preexisting diabetes on mortality (p for interaction = 0.65), which was consistent with previous studies involving patients with intracerebral hemorrhage[28] and critically ill patients.[1] These findings suggested that whether patients had preexisting diabetes or not might have no effect on the association between hyperglycemia and mortality after craniotomy. However, the absence of an association between hyperglycemia and mortality among patients with preexisting diabetes warrants further investigation in future studies.

The mechanisms underlying the association between persistent postoperative hyperglycemia and worse survival are complex and not yet fully understood. One proposed explanation is that excessive blood glucose concentration raises serum osmolality and stimulates vasopressin secretion, which might lead to tissue acidosis and electrolyte disturbances.[29] Another mechanism suggests that hyperglycemia results in an increase in oxidative stress and blood-brain barrier breakdown.[29,30] Moreover, persistent postoperative hyperglycemia may serve as a surrogate marker of an underlying causative factor for mortality. However, to measure the burden of comorbidities in patients we used the CCI score, which is commonly used within surgical medicine[31] to evaluate the risk of postoperative mortality retrospectively. Our findings remained robust after adjusting for this significant confounding factor in the multivariable logistic regression model. Therefore, the association between persistent postoperative hyperglycemia and postoperative mortality is possibly due to persistent excessive blood glucose concentration in patients, rather than the burden of comorbidities. Another possible explanation for increased postoperative mortality may be attributed to the heightened incidence of adverse outcomes associated with postoperative hyperglycemia. This hypothesis would be supported by a decrease in the strength of the association between postoperative hyperglycemia and mortality after adjusting for adverse outcomes in the multivariable analysis.

The optimal management of hyperglycemia in neurosurgery is the subject of intense debate.[6–8] A recent global survey reported that perceptions and practices of postoperative blood glucose management in patients undergoing craniotomy varied across regions.[6] This variability might arise from a lack of conclusive clinical evidence regarding the association between postoperative hyperglycemia and adverse outcomes in patients undergoing craniotomy. For example, according to the survey, neurosurgeons in North America were more concerned with patients developing a blood glucose concentration > 10.0 mmol/L during an elective craniotomy compared with their counterparts in other regions, such as Europe and South Asia. As such, neurosurgeons in North America might be more inclined to manage hyperglycemia in patients following craniotomy. However, our study revealed that a persistent elevation of random blood glucose levels > 7.8 mmol/L was associated with a higher risk of 30-day mortality. This level was lower than the treatment threshold for postoperative blood glucose of ≥ 10.0 mmol/L recommended in many guidelines,[16,32,33] emphasizing the importance for neurosurgeons to be aware of the risk of patients developing hyperglycemia after craniotomy.

Observational studies such as this one cannot establish a cause-and-effect relationship, meaning that it remains unclear whether the elevated risk of 30-day mortality observed in patients who experience hyperglycemia following craniotomy can be mitigated through intensive glucose control. In 2001, van den Berghe published a landmark randomized controlled trial[34] and found that intensive insulin therapy to maintain blood glucose levels between 4.4 and 6.1 mmol/L could reduce morbidity and mortality among patients in the surgical intensive care unit. However, subsequent multicenter large trials of tight glucose control have failed to replicate these benefits, taking into account the growing concern for iatrogenic hypoglycemia.[35,36] For neurocritical care patients, a systematic review and meta-analysis[37] of 16 randomized controlled trials compared the effects of tight glycemic control (3.9–7.8 mmol/L) with conventional glycemic control (8.0–16.7 mmol/L) among patients with traumatic brain injury, ischemic or hemorrhagic stroke, anoxic encephalopathy, CNS infections, or spinal cord injury. This analysis found that intensive insulin therapy was associated with an increased risk of hypoglycemia and did not have an influence on mortality among neurocritical care patients. Thus, the latest guidelines[9,38] published regarding intensive insulin therapy in hospitalized patients adopt a more conservative approach (7.8–10.0 mmol/L), taking into account the growing concern for iatrogenic hypoglycemia. The results of our study endorse the regular monitoring and careful consideration of elevated postoperative blood glucose levels, even in patients without preexisting diabetes. However, this study found that patients with moderate postoperative hyperglycemia (7.8–10.0 mmol/L) were still associated with an increased risk of mortality. Thus, future studies may provide additional insight into whether maintaining blood glucose levels below 7.8 mmol/L improves outcomes and clarify whether such glycemic disturbances are indicative of or potentially contribute to eventually adverse outcomes.

There are some advantages of this study. First, to our

knowledge, this study is the first to assess the effect of persistent postoperative hyperglycemia on mortality in patients undergoing an elective craniotomy. Second, the inclusion of a large sample size enabled us to achieve more precise statistical estimates of mortality, despite its low incidence rate of 2.0%. Third, we took into account various critical confounding factors, such as CCI, ASA, perioperative steroid and insulin use, intraoperative surgery time, and intraoperative blood loss, enhancing the reliability of our findings. Finally, the use of household registration data, administrated by the Chinese government, ensured the accuracy of our recorded mortality outcomes.

Our study has several limitations. First, its retrospective design introduces the possibility of unmeasured confounders, which may introduce bias to our results. However, the E-values calculated for the association between moderate or severe persistent hyperglycemia and 30-day mortality were 7.0 and 7.1, respectively, suggesting that any potential unmeasured confounders might be insufficient to alter our conclusion. Second, although HbA1c level may serve as a superior marker for evaluating the long-term glycemic status,[39] most patients in our study did not undergo routine testing for this measurement. Nonetheless, a large retrospective study indicated that HbA1c, as a reflection of antecedent glycemia, was not associated with 30-day postoperative mortality in noncardiac and cardiac surgeries.[40] Thus, the impact of not conducting HbA1c tests on our primary outcome of 30-day postoperative mortality might be negligible. Third, although we have adjusted insulin treatment in the analyses, we were unable to accurately assess the glucose metabolism of patients due to the retrospective design of our study. The existing literature suggests that the key to improved outcomes lies in controlling glucose metabolism rather than solely focusing on insulin dosage.[41] It is possible that persistent postoperative hyperglycemia indicates impaired glucose metabolism, including insulin resistance and subsequent blood glucose abnormalities.[42] Such a state has been reported in other studies of critically ill patients[43,44] and has been associated with the severity of illness[44] and mortality.[45] Lastly, despite the considerable size of our study population, the generalizability of these findings to other medical healthcare centers remains uncertain as our outcomes were derived from a single institution.

Conclusions

In this study, we found that persistent postoperative hyperglycemia, either moderate or severe, was associated with an increased risk of 30-day mortality in patients undergoing an elective craniotomy compared with normoglycemia. This association was observed in patients with or without preoperative hyperglycemia. Our findings suggest that the optimal blood glucose level for intervention in postoperative hyperglycemia might be lower than the treatment threshold of ≥ 10.0 mmol/L recommended in various guidelines.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Fang, He, Cheng, Feng. Acquisition of data: Fang, Zhang, Jia, Tian, Hao, Xiao, Chen. Analysis and interpretation of data: He, Zhang, Cheng, Hao, Li, Xiao, Hai, You. Drafting the article: He, Zhang, Cheng, Chong, Chen, You. Critically revising the article: Fang, He, Zhang, Jia, Li, Xiao, Feng, Wang, Chong. Reviewed submitted version of manuscript: Fang, He, Jia, Xiao, Deng, Wang, Hai. Approved the final version of the manuscript on behalf of all authors: Fang. Statistical analysis: He, Zhang, Cheng, Deng, Wang. Administrative/technical/material support: He, Peng, Wang. Study supervision: Fang, He, Peng, Wang, You.

Supplemental Information

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Correspondence

Fang Fang: West China Hospital, Sichuan University, Chengdu, Sichuan, China. fangfang01@scu.edu.cn.