# Association of Preoperative Serum Potassium With Postoperative Seizures in Patients Undergoing Elective Craniotomy

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**BACKGROUND AND OBJECTIVES:** Patients who undergo craniotomy are at risk of developing seizures during the postoperative period. Preoperative serum potassium as an important potential risk factor has not been investigated yet.

**METHODS:** We conducted a retrospective cohort study involving adults undergoing elective craniotomy at West China Hospital, from January 2011 and March 2021. The main outcome of this study was postoperative seizures in patients undergoing elective craniotomy during hospitalization. We performed univariable and multivariable logistic regression to investigate the association of preoperative serum potassium with postoperative seizures.

**RESULTS:** A total of 15 041 patients were collected after filtering by excluded criteria. The incidence of postoperative seizures was 4.87%. We identified a linear relationship between preoperative serum potassium and postoperative seizures (*P* for nonlinearity = .87). Compared with patients with serum potassium 3.5 to 4.5 mmol/L, the odds of postoperative seizures increased in patients with serum potassium ≥4.5 mmol/L (the adjusted odds ratios 1.46, 95% CI 1.10-1.93), and the odds of postoperative seizures decreased in patients with serum potassium ≤3.5 mmol/L (the adjusted odds ratios 0.73, 95% CI 0.53-1.01).

**CONCLUSION:** We found that high preoperative serum potassium level was associated with the high risk of postoperative seizures in patients undergoing craniotomy. We demonstrated that preoperative serum potassium level was the independent risk factor of postoperative seizures.

**KEY WORDS:** Elective craniotomy, Preoperative serum potassium, Postoperative seizures

Seizures are common complications during the postoperative period in patients undergoing elective craniotomy. Postcraniotomy seizures are associated with longer hospitalization, more financial burden, and a higher risk of accident trauma.[1-5] Multiple studies have demonstrated the risk factors of postoperative seizures, including hypertension, cerebral edema, the location of lesions, and the history of preoperative seizures.[6-10] Identifying more potential risk factors, such as abnormal preoperative laboratory tests, may effectively prevent and avoid postoperative seizures.

Serum potassium level is a common laboratory test in patients undergoing elective craniotomy during the preoperative period. Because of the electrophysiological properties of potassium, evidence has demonstrated that preoperative serum potassium level was an independent risk factor of postoperative malignant arrhythmia in both cardiac and noncardiac surgeries.[11-15] Although the mechanisms underlying seizures are uncertain, multiple cellular and brain network research has proved that potassium fluctuations were determinants in brain hyperexcitability.[16] Based on solid evidence from multiple experimental results, a hypothesis called the "potassium accumulation hypothesis" demonstrated that a transient extracellular potassium increase could trigger a massive neuronal depolarization, leading to brain network hyperactivity, further potassium accumulation, and seizure onset.[17,18] Normally, the potassium concentrations of extracellular fluid and serum were strictly segregated by the blood-



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brain barrier. But in certain conditions, such as craniotomy, hypertension, and inflammation, the blood-brain barrier will be impaired, leading to increased communication between serum and extracellular fluid.[19-22] Therefore, the high concentration of preoperative serum potassium may be associated with an increased incidence of postoperative seizures in patients undergoing elective craniotomy. However, the association of preoperative serum potassium with postoperative seizures in patients undergoing elective craniotomy has not been reported to date.

In this large retrospective study, we hypothesized that preoperative serum potassium was an independent risk factor of postoperative seizures, and the level of preoperative serum potassium was linearly associated with the risk of postoperative seizures in patients undergoing elective craniotomy.

# METHODS

## Study Design and Patient Selection

We retrospectively collected patients undergoing elective craniotomy referred to West China Hospital, between January 2011 to March 2021. The Institutional Review Boards of West China Hospital approved the study with a waiver of informed consent. The data of this study are available from the corresponding author upon reasonable request. Patients were eligible if they received an elective craniotomy during hospitalization. We excluded patients who met the following criteria: (1) excluding patients with emergency surgery such as intracerebral hemorrhage, subarachnoid hemorrhage, or trauma; (2) excluding patients who had seizures earlier than craniotomy, received epilepsy surgery, or had a history of epilepsy; (3) excluding patients younger than 18 years; (4) excluding patients with missing preoperative serum potassium records; and (5) excluding patients with serum potassium levels more than 7 days before surgery.

## Ethical Approval

The ethics committee of West China Hospital (No. 20211701) approved the study.

## Preoperative Serum Potassium Level

The information on preoperative serum potassium levels was collected from electronic medical databases. We extracted the information of max serum potassium level from 7 days before the craniotomy of each patient. We stratified the patients into 3 groups based on preoperative serum potassium levels (preoperative serum potassium ≤3.5 mmol/L; 3.5-4.5 mmol/L; ≥4.5 mmol/L).

## Outcomes

The main outcome of this study was postoperative seizures in patients undergoing elective craniotomy during hospitalization. The records of postoperative acute seizure events were extracted from an electronic medical record system and reviewed by a neurologist or neurosurgeon. Both general and partial epileptic seizures during the postoperative period were included in this study. We excluded patients who had seizures earlier than craniotomy, received epilepsy surgery, or had a history of epilepsy.

## Statistical Analysis

Statistical analyses were performed using R version 4.2.2 (R Foundation for Statistical Computing). Categorical variables were reported as absolute numbers (%), and continuous variables were reported as mean (±SD) or median (IQR). A 2-sided $P$ value < .05 was accepted as statistically significant.

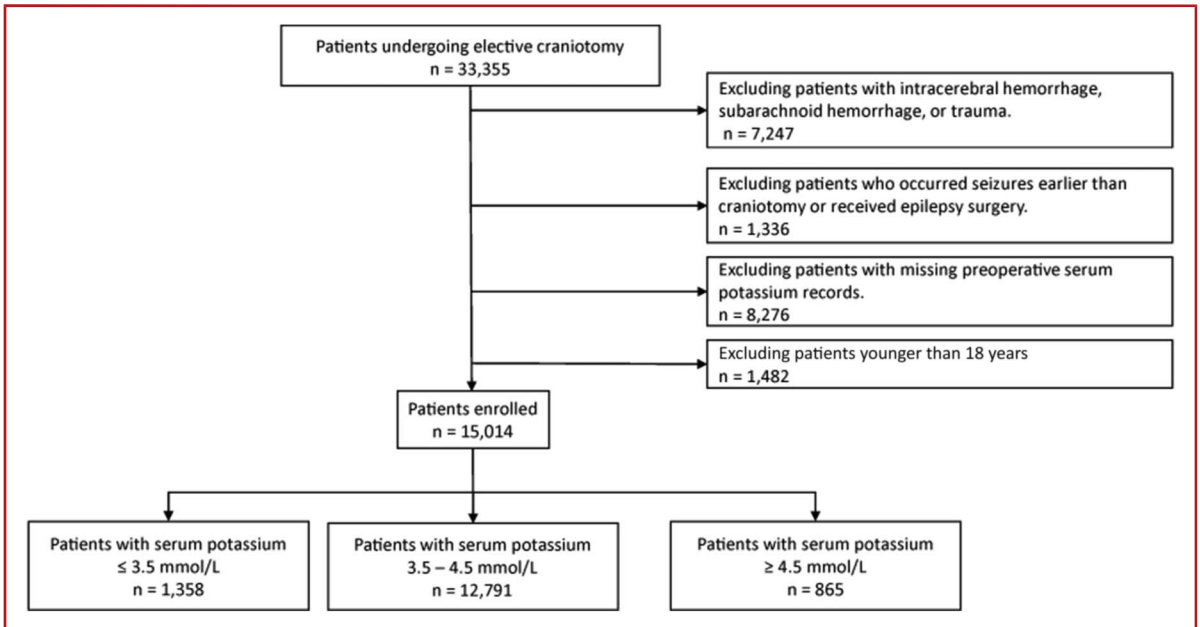


**FIGURE 1.** *The workflow of cohort formation.*



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**TABLE 1. Baseline Characteristics of Patients With Different Preoperative Serum Potassium Levels**

| Characteristics[a] | Serum potassium ≦3.5 mmol/L | Serum potassium 3.5-4.5 mmol/L | Serum potassium ≧4.5 mmol/L | *P* value |
|---|---|---|---|---|
| No. of patients | 1358 | 12 791 | 865 | |
| Demographics | | | | |
| Age, y | 52.63 (13.02) | 49.32 (13.70) | 50.45 (15.30) | <.001 |
| Female | 932 (68.6) | 7051 (55.1) | 411 (47.5) | <.001 |
| Smoking | | | | <.001 |
| Never | 1204 (88.7) | 10 478 (81.9) | 665 (76.9) | |
| Current | 78 (5.7) | 1407 (11.0) | 120 (13.9) | |
| Ever | 76 (5.6) | 906 (7.1) | 80 (9.2) | |
| Alcohol abuse | 142 (10.5) | 1847 (14.4) | 164 (19.0) | <.001 |
| Medical history | | | | |
| Hypertension | 412 (30.3) | 2072 (16.2) | 140 (16.2) | <.001 |
| Diabetes | 116 (8.5) | 935 (7.3) | 58 (6.7) | .188 |
| Coronary heart disease | 24 (1.8) | 146 (1.1) | 10 (1.2) | .13 |
| Chronic kidney disease | 18 (1.3) | 152 (1.2) | 19 (2.2) | .035 |
| Chronic liver disease | 78 (5.7) | 552 (4.3) | 35 (4.0) | .044 |
| Preoperative clinical parameters | | | | |
| ASA, >2 | 578 (42.6) | 4905 (38.3) | 395 (45.7) | <.001 |
| Glasgow Coma Scale, <15 | 74 (5.4) | 516 (4.0) | 29 (3.4) | .022 |
| Contrast agents use | 404 (29.7) | 3837 (30.0) | 266 (30.8) | .873 |
| Systolic blood pressure. mm Hg | 131.81 (19.10) | 125.94 (20.93) | 124.75 (17.76) | <.001 |
| eGFR, mL/min/1.73m$^2$ | 111.91 (19.03) | 110.28 (18.54) | 100.34 (23.25) | <.001 |
| Antiepilepsy drug use | 130 (9.6) | 1352 (10.6) | 134 (15.5) | <.001 |
| Therapy of potassium imbalances | 187 (13.8) | 1367 (10.7) | 139 (16.1) | <.001 |
| Primary diagnosis | | | | <.001 |
| Functional disease | 122 (9.0) | 801 (6.3) | 21 (2.4) | |
| Cerebrovascular disease | 180 (13.3) | 1179 (9.2) | 54 (6.2) | |
| Primary brain tumor | | | | |
| Schwannoma | 68 (5.0) | 622 (4.9) | 27 (3.1) | |
| Meningioma | 255 (18.8) | 2692 (21.0) | 200 (23.1) | |
| Craniopharyngioma | 24 (1.8) | 241 (1.9) | 18 (2.1) | |
| Glioma, WHO grades I & II | 106 (7.8) | 1268 (9.9) | 114 (13.2) | |
| Glioma, WHO grades III & IV | 145 (10.7) | 1793 (14.0) | 185 (21.4) | |
| Other brain tumors | 259 (19.1) | 2290 (17.9) | 122 (14.1) | |
| Metastasis | 45 (3.3) | 344 (2.7) | 39 (4.5) | |
| Others | 154 (11.3) | 1561 (12.2) | 85 (9.8) | |

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**TABLE 1. Continued.**

| Characteristics[a] | Serum potassium ≦3.5 mmol/L | Serum potassium 3.5-4.5 mmol/L | Serum potassium ≧4.5 mmol/L | *P* value |
|---|---|---|---|---|
| Preoperative laboratories | | | | |
| Serum sodium, mmol/L | 141.55 (4.43) | 141.08 (4.11) | 140.43 (4.95) | <.001 |
| Serum potassium, mmol/L | 3.31 (0.19) | 3.99 (0.71) | 4.73 (0.31) | <.001 |
| Glucose, mmol/L | 6.99 (2.20) | 6.50 (1.94) | 7.12 (2.54) | <.001 |
| Serum chloride, mmol/L | 104.82 (5.69) | 104.08 (4.34) | 103.50 (4.80) | <.001 |
| Serum cystatin C, mg/L | 0.78 (0.19) | 0.79 (0.16) | 0.84 (0.24) | <.001 |
| Serum albumin, g/L | 36.88 (5.31) | 38.25 (4.80) | 37.76 (5.76) | <.001 |
| Creatine, μmol/L | 62.72 (15.79) | 66.45 (15.27) | 75.51 (22.78) | <.001 |
| Intraoperative information | | | | |
| Craniotomy duration, hours | 3.51 (1.84) | 3.53 (1.77) | 3.56 (1.79) | .755 |
| Intraoperative blood loss, ml | 288.83 (472.45) | 281.57 (442.22) | 301.95 (408.71) | .379 |
| Location of lesions | | | | <.001 |
| Cerebellum | 103 (7.6) | 797 (6.2) | 39 (4.5) | |
| Frontal | 72 (5.3) | 1094 (8.6) | 111 (12.8) | |
| Insula | 2 (0.1) | 0 (0.0) | 0 (0.0) | |
| Occipital | 12 (0.9) | 132 (1.0) | 15 (1.7) | |
| Parietal | 23 (1.7) | 379 (3.0) | 28 (3.2) | |
| Stem | 7 (0.5) | 87 (0.7) | 6 (0.7) | |
| Temporal | 28 (2.1) | 375 (2.9) | 36 (4.2) | |

ASA, American Society of Anesthesiologists; eGFR, estimated glomerular filtration rate; SMD, strictly standardized mean difference; WHO, World Health Organization.
[a]Mean (SD) or n (%).

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We performed logistic regression to investigate the association of preoperative serum potassium with postoperative seizures. We used univariable logistic regression analysis to obtain univariate odds ratios and 95% CIs. Then, the multivariable logistic regression model with stepwise methods was used to determine independent risk factors from univariate analyses ($P < .10$). The cofounders of multivariable analysis included age; sex; smoking; alcohol; hypertension; diabetes mellitus; chronic kidney disease; chronic pulmonary disease; coronary heart disease; American Society of Anesthesiologists; Glasgow Coma Scale; contrast use; antiepilepsy drug use; therapy of potassium imbalanced; primary diagnosis; systolic blood pressure; intraoperative blood loss; location of lesions; preoperative laboratories included glucose; serum sodium, glucose, and chloride. We used restricted cubic spline functions to analyze the log-linearity assumption for continuous characteristics. Subgroup analyses were conducted for sex, age, alcohol consumption, smoking status, diabetes mellitus, hypertension, American Society of Anesthesiologists, Glasgow Coma Scale, intraoperative blood loss, systolic blood pressure, and estimated glomerular filtration rate.

## RESULTS

After filtering by excluded criteria, 15 014 patients undergoing elective craniotomy were included in this study (Figure 1). Baseline clinical features were reported in Table 1. The incidence of postoperative seizures was 4.87%. Patients with higher serum potassium levels (≥4.5 mmol/L) were more likely to be old, male, and have chronic kidney disease, low estimated glomerular filtration rate, and high American Society of Anesthesiologists.

We used a restricted cubic spline to visualize the dynamic association of preoperative serum potassium with postoperative seizures. We identified a linear relationship between preoperative serum potassium levels and postoperative seizures ($P$ for nonlinearity =.87, the continuous adjusted odds ratios (OR) 1.68, 95% CI 1.34-2.10) (Figure 2A). Specifically, as preoperative serum potassium levels rose, the adjusted odds ratio for postoperative seizures also increased. The incidence rate of postoperative seizures increased with elevated preoperative serum potassium



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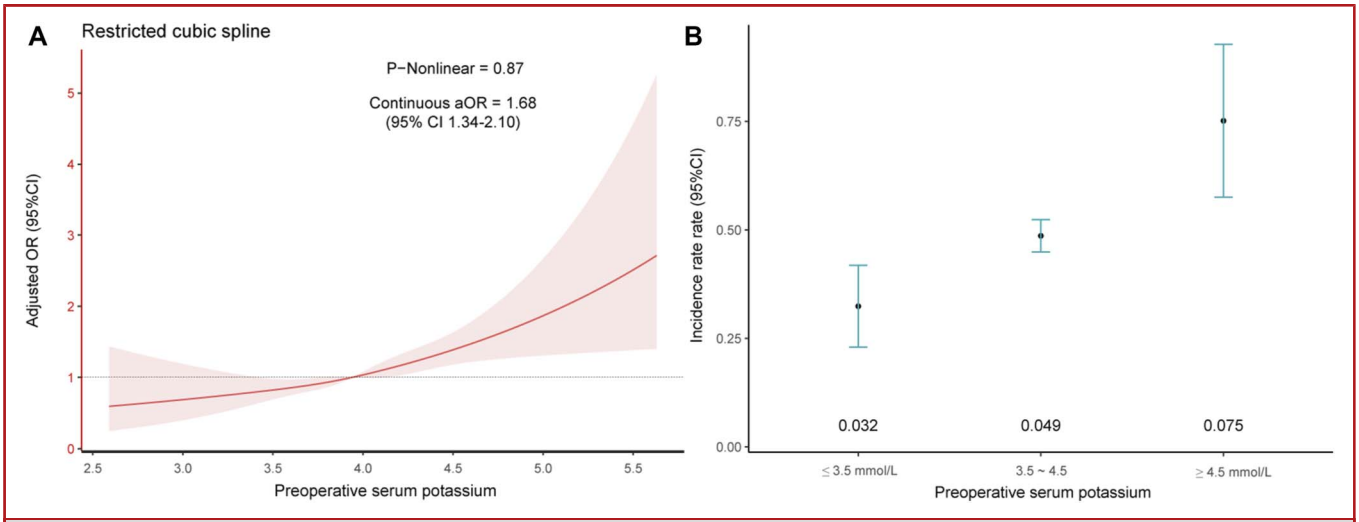


**FIGURE 2.** *The restricted cubic spline* **A** *and incidence rate* **B** *of preoperative serum potassium and postoperative seizures in patients undergoing craniotomy. OR, odds ratios.*

(Figure 2B). As presented in Table 2, compared with patients with serum potassium 3.5 to 4.5 mmol/L, the odds of postoperative seizures increased in patients with serum potassium ≥4.5 mmol/L (the adjusted OR 1.46, 95% CI 1.10-1.93), and the odds of postoperative seizures decreased in patients with serum potassium ≤3.5 mmol/L (the adjusted OR 0.73, 95% CI 0.53-1.01). Furthermore, we conducted a sensitivity analysis including cohorts with emergency procedures to validate our primary findings. Consistently with our initial results, we observed an elevated risk of postoperative seizures in patients with serum potassium levels ≥4.5 mmol/L (the adjusted OR 1.46, 95% CI 1.13-1.89).

The details of univariable and multivariable logistic regression analysis are presented in Table 3. Univariable analysis showed that risk factors of postoperative seizures included young age, male, smoking, alcohol abuse, chronic kidney disease, low Glasgow Coma Scale, high American Society of Anesthesiologists, none contrast agent use, antiepilepsy drug use, therapy of potassium imbalances, benign and malignant tumors, low blood pressure, low serum glucose, high sodium, and temporal lesion. After multivariable analyses with a bidirectional stepwise method, the independent risk factors of postoperative seizures included young age, male, chronic kidney disease, antiepilepsy drug use, therapy of potassium imbalances, benign and malignant tumor, low Glasgow Coma Scale, high American Society of Anesthesiologists, none contrast agent use, low blood pressure, low serum glucose, and temporal lesion.

We also performed the subgroup analysis and indicated no statistically significant interaction among most variables in the association of preoperative serum potassium with postoperative seizures (Figure 3).

## DISCUSSION

In this large retrospective study, we found that preoperative serum potassium level was linearly associated with the risk of postoperative seizures. These results suggested that preoperative

**TABLE 2. Unadjusted and Adjusted Associations Between Preoperative Serum Potassium and Postoperative Seizures**

| Stratify | Threshold | Events/total, n (%) | Unadjusted OR | *P* | Adjusted OR[a] | *P* |
|---|---|---|---|---|---|---|
| Continuous | NA | NA | 1.82 (1.49-2.23) | <.001 | 1.68 (1.34-2.10) | <.001 |
| Stratified by preoperative serum potassium | 3.5-4.5 mmol/L | 622/12 791 (4.9%) | 1 (Reference) | NA | 1 (Reference) | NA |
| | ≥4.5 mmol/L | 65/865 (7.5%) | 1.59 (1.22-2.07) | .001 | 1.46 (1.10-1.93) | .008 |
| | ≤3.5 mmol/L | 44/1358 (3.2%) | 0.66 (0.48-0.89) | .008 | 0.73 (0.53-1.01) | .055 |

NA, not available; OR, odds ratios.

[a]Adjusted for patient and disease factors—age; sex; smoking; alcohol; hypertension; diabetes mellitus; chronic kidney disease; chronic pulmonary disease; coronary heart disease; American Society of Anesthesiologists; Glasgow Coma Scale, contrast use; antiepilepsy drug use; therapy of potassium imbalanced; primary diagnosis; systolic blood pressure; intraoperative blood loss; location of lesions; preoperative laboratories included glucose; serum sodium, glucose, and chloride.



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**TABLE 3. Detailed Information on Univariate and Multivariate Regression**

| | Univariate analyses | | Multivariate analyses | |
|---|---|---|---|---|
| **Characteristics** | **OR (95% CI)** | ***P* value** | **OR (95% CI)** | ***P* value** |
| Demographics | | | | |
| Age | 0.97 (0.97-0.98) | <.001 | 0.97 (0.97-0.98) | <.001 |
| Sex | 0.60 (0.51-0.69) | <.001 | 0.66 (0.54-0.80) | <.001 |
| Smoking | 1.58 (1.23-2.03) | <.001 | 1.23 (0.92-1.65) | .163 |
| Alcohol abusing | 1.32 (1.09-1.61) | .005 | 1.06 (0.82-1.36) | .652 |
| Medical history | | | | |
| Hypertension | 0.63 (0.51-0.80) | <.001 | 0.89 (0.68-1.15) | .354 |
| Diabetes | 0.88 (0.65-1.18) | .385 | NA | NA |
| Chronic kidney disease | 2.08 (1.27-3.41) | .003 | 2.43 (1.44-4.09) | .001 |
| Chronic pulmonary disease | 1.37 (1.00-1.89) | .051 | 1.35 (0.97-1.88) | .075 |
| Coronary heart disease | 0.33 (0.10-1.03) | .056 | 0.44 (0.14-1.40) | .164 |
| Preoperative clinical parameters | | | | |
| American Society of Anesthesiologists | 1.20 (1.10-1.30) | <.001 | 1.15 (1.05-1.26) | .002 |
| Glasgow Coma Scale | 0.90 (0.85-0.95) | <.001 | 0.93 (0.87-0.99) | .029 |
| Estimated glomerular filtration rate | 0.86 (0.64-1.17) | .344 | NA | NA |
| Contrast agents use | 0.76 (0.64-0.91) | .002 | 0.73 (0.61-0.88) | .001 |
| Systolic blood pressure | 0.99 (0.99-1.00) | <.001 | 1.00 (1.00-1.00) | .786 |
| Antiepilepsy drug use | 4.09 (3.46-4.83) | <.001 | 3.60 (3.00-4.31) | <.001 |
| Therapy of potassium imbalances | 1.29 (1.04-1.60) | .019 | 0.74 (0.59-0.94) | .014 |
| Preoperative laboratories | | | | |
| Serum glucose | 0.93 (0.89-0.97) | <.001 | 0.94 (0.90-0.99) | .01 |
| Serum sodium | 1.04 (1.02-1.06) | <.001 | 1.03 (1.01-1.06) | .016 |
| Serum chloride | 1.03 (1.01-1.04) | .002 | 1.01 (0.99-1.03) | .248 |
| Intraoperative information | | | | |
| Craniotomy duration | 1.01 (0.86-1.19) | .888 | NA | NA |
| Intraoperative blood loss | 1.16 (0.99-1.37) | .07 | 0.92 (0.77-1.10) | .361 |
| Location of lesions | | | | |
| Temporal | 2.94 (2.20-3.95) | <.001 | 2.01 (1.47-2.75) | <.001 |
| Others | 1 (Reference) | NA | 1 (Reference) | NA |
| Primary diagnosis | | | | |
| Benign tumor | 0.72 (0.58-0.89) | .003 | 0.73 (0.58-0.91) | .005 |
| Malignant tumor | 2.40 (2.01-2.87) | <.001 | 1.72 (1.41-2.09) | <.001 |
| Cerebrovascular disease | 1.22 (0.93-1.61) | .157 | 1.17 (0.87-1.57) | .29 |
| Others | 1 (Reference) | NA | 1 (Reference) | NA |

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**TABLE 3. Continued.**

| Characteristics | Univariate analyses | | Multivariate analyses | |
|---|---|---|---|---|
| | OR (95% CI) | *P* value | OR (95% CI) | *P* value |
| Preoperative serum potassium | | | | |
| Serum potassium ≤3.5 mmol/L | 0.66 (0.48-0.89) | .008 | 0.73 (0.53-1.01) | .055 |
| Serum potassium ≥4.5 mmol/L | 1.59 (1.22-2.07) | .001 | 1.46 (1.10-1.93) | .008 |
| Serum potassium 3.5-4.5 mmol/L | 1 (Reference) | NA | 1 (Reference) | NA |

NA, not available; OR, odds ratios.

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serum potassium was the independent risk factor of postoperative seizures.

The risk factors of postcraniotomy seizures were widely reported which include older age, location of the lesion,[8] brain edema, and prophylactic application of antiepileptic drugs.[23-25] However, the influence of preoperative electrolyte management was not systematically investigated. Our results indicated that preoperative serum potassium level was linearly associated with the risk of postoperative seizures, emphasizing the importance of preoperative serum potassium management in craniocerebral surgery-related seizures. Extensive previous experimental research has consistently demonstrated that elevated potassium levels could induce brain network hyperactivity and trigger seizures. According to the "potassium accumulation hypothesis," elevating the potassium concentration induces neuronal depolarization, heightening their excitability. This elevation also alters the equilibrium potential of potassium toward depolarization. With heightened excitability, neurons escalate their firing rate, further augmenting potassium levels. Consequently, this process becomes self-sustaining. Eventually, the depolarization resulting from increased potassium could surpass a threshold, directly initiating and sustaining firing, independent of excitatory synaptic input. This lowered threshold can create a situation where neurons are more likely to synchronize their firing, leading to abnormal and uncontrolled electrical activity, which is characteristic of seizures.

During a craniotomy procedure, the blood-brain barrier always becomes compromised, leading to increased communication between the serum potassium concentration and the extracellular fluid. We hypothesize the "double hits" of having elevated preoperative serum potassium levels and undergoing a craniotomy represents a significant risk factor of postoperative seizures. Based on a large retrospective cohort, we investigated whether the preoperative serum potassium levels were associated with postoperative seizures in patients undergoing craniotomy. As shown in the results, we found preoperative serum potassium ≥4.5 mmol/L could increase the risk of postoperative seizures. The preoperative serum potassium was an independent risk factor of postoperative seizures in patients undergoing craniotomy. In addition, we also identified a dose-response relationship between preoperative serum potassium levels and postoperative seizures, which enhances causal inferences in observational studies. Therefore, controlling preoperative serum potassium could potentially prevent postoperative seizure onset in patients undergoing craniotomy. Future studies may perform prospective clinical trials to identify whether the preoperative serum potassium level was associated with an altered incidence of postoperative seizures. While our study focused on the association between elevated serum potassium (above 4.5 mmol/L) and postoperative seizures, it is important to acknowledge that hypokalemia (serum potassium below 3.5 mmol/L) can also have significant clinical implications, including adverse effects on cardiac rhythm. Optimization of serum potassium levels should be a comprehensive consideration in the management of patients undergoing craniotomy, weighing the potential risks of both hyperkalemia and hypokalemia. Achieving an appropriate balance within the therapeutic range is crucial for preventing adverse cardiac events, such as rhythm abnormalities or arrhythmias.

### Limitations

There are some limitations in this study. First, we could not infer a causal relationship between preoperative serum potassium and postoperative seizures because of the inherent limitation of the retrospective study. Second, the outcome of this study was postoperative seizures during hospitalization and did not contain delayed postoperative seizures after discharge. Third, the information on seizure history was retrieved by study participants and may cause recall bias. Fourth, the single-center outcomes may not be generalizable to other medical entities. Future studies could include various racial and ethnic groups through multicenter international collaboration. Fifth, this retrospective study relies on existing medical records and data repositories, which have inherent limitations in data availability and quality, such as incomplete documentation in medical records, or technical issues with data extraction and recording.

## CONCLUSION

In this large retrospective study, we found high preoperative serum potassium level was associated with the high risk of postoperative seizures in patients undergoing craniotomy. We



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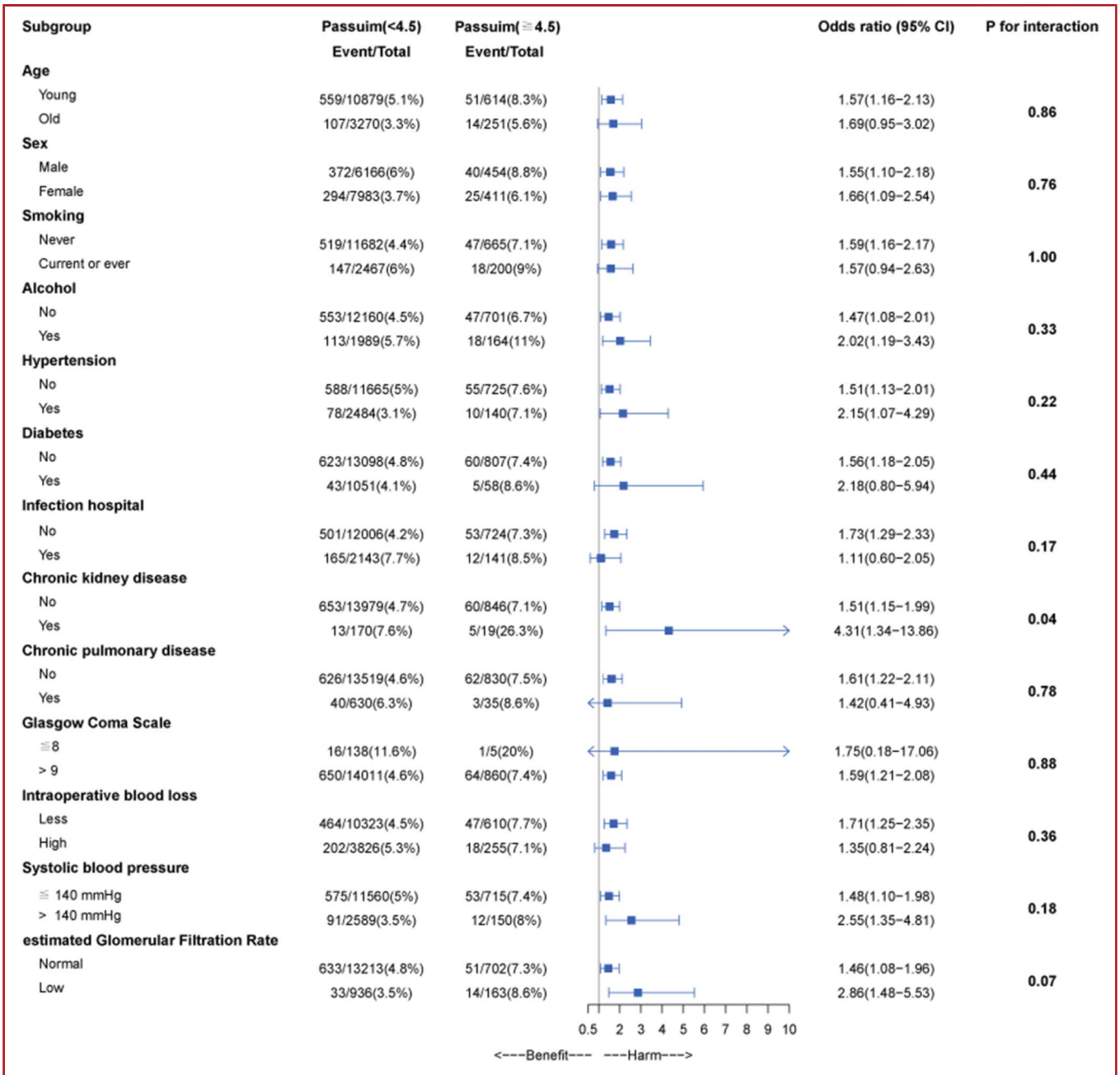


demonstrated preoperative serum potassium level was the independent risk factor of postoperative seizures.

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## Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.



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## REFERENCES


1. O'Donnell JM, Morgan MK, Heller GZ. The risk of seizure following surgery for brain arteriovenous malformation: a prospective cohort study. *Neurosurgery.* 2017; 81(6):935-948.
2. O'Donnell JM, Morgan MK, Bervini D, Heller GZ, Assaad N. The risk of seizure after surgery for unruptured intracranial aneurysms: a prospective cohort study. *Neurosurgery.* 2016;79(2):222-230.
3. Fabinyi GC, Artiola-Fortuny L. Epilepsy after craniotomy for intracranial aneurysm. *Lancet.* 1980;1(8181):1299-1300.
4. North JB, Penhall RK, Hanieh A, Hann CS, Challen RG, Frewin DB. Postoperative epilepsy: a double-blind trial of phenytoin after craniotomy. *Lancet.* 1980;1(8165):384-386.
5. Wu AS, Trinh VT, Suki D, et al. A prospective randomized trial of perioperative seizure prophylaxis in patients with intraparenchymal brain tumors. *J Neurosurg.* 2013;118(4):873-883.
6. Rozycki A, Lewin JJ 3rd, Tamargo R, Zink B, Mirski M, Gibbs H. Impact of intraoperative cefazolin on postoperative seizures after elective repair of unruptured cerebral aneurysm. *Am J Health Syst Pharm.* 2017;74(4):213-217.
7. Skardelly M, Brendle E, Noell S, et al. Predictors of preoperative and early postoperative seizures in patients with intra-axial primary and metastatic brain tumors: a retrospective observational single center study. *Ann Neurol.* 2015;78(6):917-928.
8. Garcia JH, Morshed RA, Chung J, et al. Factors associated with preoperative and postoperative seizures in patients undergoing resection of brain metastases. *J Neurosurg.* 2023;138(1):19-26.
9. Bahna M, Heimann M, Bode C, et al. Tumor-associated epilepsy in patients with brain metastases: necrosis-to-tumor ratio forecasts postoperative seizure freedom. *Neurosurg Rev.* 2022;45(1):545-551.
10. Ersoy TF, Ridwan S, Grote A, Coras R, Simon M. Early postoperative seizures (EPS) in patients undergoing brain tumour surgery. *Sci Rep.* 2020;10(1):13674.
11. Arora P, Pourafkari L, Visnjevac O, Anand EJ, Porhomayon J, Nader ND. Preoperative serum potassium predicts the clinical outcome after non-cardiac surgery. *Clin Chem Lab Med.* 2017;55(1):145-153.
12. Sanjay OP. pre-operative serum potassium levels and peri-operative outcomes in patients undergoing cardiac surgery. *Indian J Clin Biochem.* 2004;19(1):40-44.
13. Zhang B, Liu XY, Kang B, et al. Preoperative hypokalemia can increase complications after colorectal cancer surgery: a propensity score matching analysis. *BMC Cancer.* 2022;22(1):846.
14. Chu T, Wu Z, Xu A. Association between preoperative hypokalemia and postoperative complications in elderly patients: a retrospective study. *BMC Geriatr.* 2022;22(1):743.
15. Ebrahim M, Larsen PB, Hannani D, Liest S, Jørgensen LN, Jørgensen HL. Preoperative risk factors including serum levels of potassium, sodium, and creatinine for early mortality after open abdominal surgery: a retrospective cohort study. *BMC Surg.* 2021;21(1):62.
16. de Curtis M, Uva L, Gnatkovsky V, Librizzi L. Potassium dynamics and seizures: why is potassium ictogenic? *Epilepsy Res.* 2018;143:50-59.
17. Benini R, Avoli M. Altered inhibition in lateral amygdala networks in a rat model of temporal lobe epilepsy. *J Neurophysiol.* 2006;95(4):2143-2154.
18. Fertziger AP, Ranck JB, Jr. Potassium accumulation in interstitial space during epileptiform seizures. *Exp Neurol.* 1970;26(3):571-585.
19. Marchi N, Angelov L, Masaryk T, et al. Seizure-promoting effect of blood-brain barrier disruption. *Epilepsia.* 2007;48(4):732-742.
20. Pavlovsky L, Seiffert E, Heinemann U, Korn A, Golan H, Friedman A. Persistent BBB disruption may underlie alpha interferon-induced seizures. *J Neurol.* 2005;252(1):42-46.
21. Tomkins O, Friedman O, Ivens S, et al. Blood-brain barrier disruption results in delayed functional and structural alterations in the rat neocortex. *Neurobiol Dis.* 2007;25(2):367-377.
22. Tomkins O, Shelef I, Kaizerman I, et al. Blood-brain barrier disruption in posttraumatic epilepsy. *J Neurol Neurosurg Psychiatry.* 2008;79(7):774-777.
23. Wang J, Luo X, Chen C, et al. Preoperative MRI for postoperative seizure prediction: a radiomics study of dysembryoplastic neuroepithelial tumor and a systematic review. *Neurosurg Focus.* 2022;53(4):e7.
24. Horiuchi S, Kanaya K, Horiuchi T. The occurrence and relationship of postoperative seizure and de novo epilepsy after craniotomy surgery: a retrospective single-center cohort study. *Front Surg.* 2022;9:881874.
25. Wang H, Zhang K, Cao H, et al. Seizure after cranioplasty: incidence and risk factors. *J Craniofac Surg.* 2017;28(6):e560-e564.


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## COMMENTS

This large retrospective study examines the association between preoperative serum potassium level and postoperative seizures in patients undergoing elective craniotomy. Of the 15,014 patients included, the postoperative seizure rate was 4.87%. The results suggest a linear increase in risk of seizure as potassium rises above 4.5 mmol/l.

While this is an interesting observation, the authors are unable to establish a causal link between potassium and seizures. Several risk factors were identified, but I am suspicious that the retrospective nature of the study has concealed important data. For example, patients with elevated potassium preoperatively tended to be young while old age was actually a risk factor of postoperative seizures.

The authors provide no information regarding surgical treatment beyond tumor location and pathological grade. One would naturally expect a highly malignant tumor of the temporal lobe to pose a greater risk of postoperative seizure independent of potassium level. By contrast, a benign tumor of the cerebellopontine angle should pose a very low risk. Unfortunately, specific detail about this subgroup was not included, so the relationship to craniotomy per se, cannot be judged.

There are several other paradoxical findings. Patients on preoperative antiepileptic drugs are more at risk. Perhaps this means that the underlying pathology was a more concerning risk for seizures before surgery. No information was provided on which agents were used or when they were initiated. Low blood sugar would be expected to lead to hypokalemia, and yet, this was an independent predictor of postoperative seizure. Low GCS was also a risk factor, but this was crudely defined as <15. It is unknown how many of these 619 patients faced independent risk based on serious preoperative neurological compromise.

There is no argument that scrupulous attention to an electrolyte abnormalities is warranted before elective craniotomy. This study highlights the potential importance of potassium in the genesis of postoperative seizures. Further study may clarify the pathophysiology at play as it related to craniotomy.

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