

Original

Association between Early Postoperative Sodium Change and Postoperative Delirium after General Anesthesia

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Background: Postoperative delirium (POD) is a frequent neuropsychiatric complication after surgery under general anesthesia and is associated with adverse outcomes. Although perioperative dysnatremia has been linked to POD, most studies relied on static sodium measurements and failed to capture early postoperative dynamics. We investigated whether early postoperative sodium change is associated with late-onset POD.

Methods: This retrospective single-center cohort study included adults undergoing surgery under general anesthesia between July 2021 and December 2025. A Day-3 landmark design ensured temporal precedence between exposure and outcome. Perioperative sodium change (ΔNa) was defined as the difference between preoperative baseline sodium and the most recent sodium value within 48 hours after surgery and was categorized as decrease (≤ -3 mmol/L), stable (-3 to $+3$ mmol/L), or increase ($\geq +3$ mmol/L). Late-onset POD occurring on postoperative days 3 through 7 was identified using the Intensive Care Delirium Screening Checklist and antipsychotic prescriptions. Multivariable logistic regression and restricted cubic spline models were applied.

Results: Among 18,424 patients, both perioperative sodium increase and decrease were independently associated with higher odds of late-onset POD, as compared with stable sodium levels. Baseline preoperative sodium was not associated with POD. Spline analyses showed a U-shaped association between ΔNa and POD, with the lowest risk was near $\Delta\text{Na} = 0$ mmol/L. Findings were consistent across sensitivity and subgroup analyses.

Conclusions: Early postoperative sodium fluctuations were associated with increased risk of late-onset POD. Monitoring of perioperative sodium trajectories may aid in stratifying early postoperative risk.

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Introduction

Postoperative delirium (POD) is one of the most common neuropsychiatric complications after surgery under general anesthesia and is consistently associated with adverse clinical outcomes, including prolonged hospitaliza-

tion, functional decline, institutionalization, and increased mortality^{1–4}. Recent large-scale studies have further demonstrated that POD in older adults undergoing major surgery is associated with significantly increased risks of death, major postoperative complications, and

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nonhome discharge⁵. Importantly, accumulating evidence suggests that late-onset POD, which develops after initial postoperative stabilization, is more strongly associated with prolonged hospitalization and mortality than is transient early delirium⁶. Because late POD emerges after the immediate perioperative period, identifying early postoperative risk factors that precede its onset is of particular clinical relevance for perioperative management and patient prognosis.

A wide range of perioperative risk factors for delirium have been reported, including advanced age, cognitive impairment, systemic inflammation, anemia, hypoalbuminemia, and electrolyte disturbances⁷. Among these, serum sodium plays a central role in neuronal excitability and osmotic homeostasis. Both hyponatremia and hypernatremia have been associated with delirium in general inpatient and perioperative settings^{8,9}. Several observational studies have reported that perioperative dysnatremia is independently associated with POD, even after adjustment for age and comorbidity burden¹⁰. However, most existing studies rely on preoperative or single time-point sodium measurements, which do not adequately reflect the dynamic physiological changes that occur during the early postoperative period¹¹. During the first 48 hours after surgery, perioperative fluid administration, blood loss, inflammatory responses, and hemodynamic instability can result in rapid fluctuations in serum sodium levels. Such changes may induce acute osmotic shifts across the blood-brain barrier, potentially increasing cerebral vulnerability and susceptibility to delirium¹².

To appropriately evaluate the prognostic significance of early postoperative sodium fluctuations, a time-structured analytic framework that ensures temporal precedence of sodium exposure before delirium onset is required¹³. In this study, we examined the association between early postoperative sodium dynamics and subsequent late-onset POD in patients undergoing surgery under general anesthesia. In the present Day-3 landmark design, perioperative sodium change (ΔNa)—defined as the difference between preoperative baseline sodium and the most recent sodium value within 48 hours after surgery—was evaluated in relation to delirium occurring between postoperative days 3 and 7. We hypothesized that both increased and decreased early postoperative sodium levels would be independently associated with increased risk of late-onset POD. By focusing on routinely available laboratory data, this study aimed to provide a clinically implementable framework for early postoperative risk stratification in anesthetic and perioperative care.

Materials and Methods

Study Design and Setting

This retrospective, observational, single-center cohort study was conducted using routinely collected inpatient data from Nippon Medical School Hospital. Clinical data were obtained from the Diagnosis Procedure Combination (DPC) database, electronic medical records, and the operating room information system. The DPC database includes information on patient demographics, comorbidities, and procedural data, while laboratory test results and delirium assessments were extracted from electronic medical records. Surgical characteristics and intraoperative variables were obtained from the operating room information system. The study protocol was approved by the Ethics Committee of Nippon Medical School (Tokyo, Japan; approval no. M-2024-227), and the study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained using an opt-out approach, in line with institutional policy for retrospective studies that analyze routinely collected clinical data.

Study Population

All adult patients who underwent surgery under general anesthesia at the study hospital between July 2021 and December 2025 were eligible for inclusion. To minimize confounding related to pre-existing delirium or acute critical illness at admission, we excluded patients who underwent emergency surgery in the operating room on the day of admission and those receiving delirium-related psychotropic medications preoperatively.

Day-3 landmark analysis (LM3) was used to ensure appropriate temporal ordering between exposure and outcome. Patients who remained alive and delirium-free through postoperative day 3 were included in the risk set. Patients who died, were discharged, or developed delirium before postoperative day 3 were excluded. Patients who died after the landmark day without developing delirium were retained in the analysis and censored at the date of death.

Postoperative day 3 was selected as the landmark because it allowed assessment of perioperative sodium exposure over the first 48 hours after surgery and because it excluded the immediate postoperative stabilization phase, thereby reducing confounding from acute physiological instability.

Outcome Definition

The primary outcome was late-onset postoperative delir-

ium, defined as delirium occurring on postoperative days 3 through 7. Delirium was identified using either an Intensive Care Delirium Screening Checklist (ICDSC) score ≥ 4 or a psychiatrist prescription of antipsychotic medication (haloperidol, risperidone, quetiapine, or olanzapine).

Delirium screening was conducted using a standardized, hospital-wide protocol. Trained nursing staff performed daily ICDSC assessments at 15:00 during the first 7 postoperative days. Patients identified as high-risk or delirious were evaluated and managed in collaboration with physicians and pharmacists. ICDSC item scores were routinely recorded in the electronic medical record and extracted electronically for analysis.

Exposure: Perioperative Sodium Change

Laboratory data were obtained from electronic medical records. Preoperative serum sodium was defined as the measurement closest to the surgical start time within 60 days before surgery. Postoperative serum sodium was defined as the most recent measurement obtained within 48 hours after the start of surgery.

The primary exposure, perioperative sodium change (ΔNa), was calculated as postoperative sodium minus preoperative sodium. ΔNa was categorized into three prespecified groups based on clinically meaningful thresholds: Increase: $\Delta\text{Na} \geq +3$ mmol/L, Stable: $-3 < \Delta\text{Na} < +3$ mmol/L, Decrease: $\Delta\text{Na} \leq -3$ mmol/L.

The stable group served as the reference category in all categorical analyses.

Covariates

Baseline covariates included age, sex, body mass index, and comorbidities derived from the DPC database. Surgical characteristics included the American Society of Anesthesiologists (ASA) physical status classification, operation time, estimated blood loss, and intraoperative input-output balance, extracted from the operating room information system.

Patients were also classified according to admission to the intensive care unit (ICU) on the day of surgery, reflecting institutional practice for major surgery or the need for intensive postoperative monitoring.

All covariates were defined at the postoperative Day-3 landmark unless otherwise specified.

Statistical Analysis

Baseline characteristics were summarized using descriptive statistics. Categorical variables are presented as counts and percentages, and continuous variables as me-

dians with interquartile ranges. In the primary analysis, late-onset postoperative delirium was treated as a binary outcome. Multivariable logistic regression models were used to estimate adjusted odds ratios (ORs) and 95% confidence intervals for the association between ΔNa categories and delirium, with the stable sodium group as reference. The primary multivariable model adjusted for age, sex, comorbidities, and surgical factors, including operation time as the primary indicator of surgical invasiveness. To assess robustness with respect to perioperative burden and fluid exposure, a secondary model was constructed in which intraoperative net fluid balance was included instead of operation time, while all other covariates were held constant. Missing data were handled using complete-case analysis. The outcome, landmark eligibility, and ΔNa exposure were not imputed. A prespecified sensitivity analysis was conducted using an alternative definition of perioperative sodium change, categorizing ΔNa using a cutoff of ± 2 mmol/L.

To explore potential nonlinear associations, ΔNa was additionally modeled as a continuous variable using restricted cubic splines with knots placed at the 5th, 35th, 65th, and 95th percentiles of the ΔNa distribution. Linear constraints were applied to the tails, and adjusted ORs were estimated relative to $\Delta\text{Na} = 0$ mmol/L. Nonlinearity was assessed using likelihood ratio tests comparing the spline model with a model including only the linear term. Prespecified subgroup analyses were performed to evaluate potential effect modification by age (<75 vs ≥ 75 years), sex, ICU admission on the day of surgery, and ASA physical status (<3 vs ≥ 3). Interaction terms between ΔNa and each subgroup variable were included in the models and assessed using likelihood ratio tests.

All statistical tests were two-sided, and P values < 0.05 were considered statistically significant. All analyses were performed using R software.

Reporting Guideline

This study is reported in accordance with the STROBE guidelines for observational studies.

Results

Study Population and Baseline Characteristics

Between July 2021 and December 2025, a total of 28,360 adult patients underwent surgery under general anesthesia at the study institution (Figure 1). After excluding patients with a postoperative length of stay shorter than 3 days ($n = 6,296$), delirium occurring within postoperative days 0–2 ($n = 757$), admission to the Emergency and

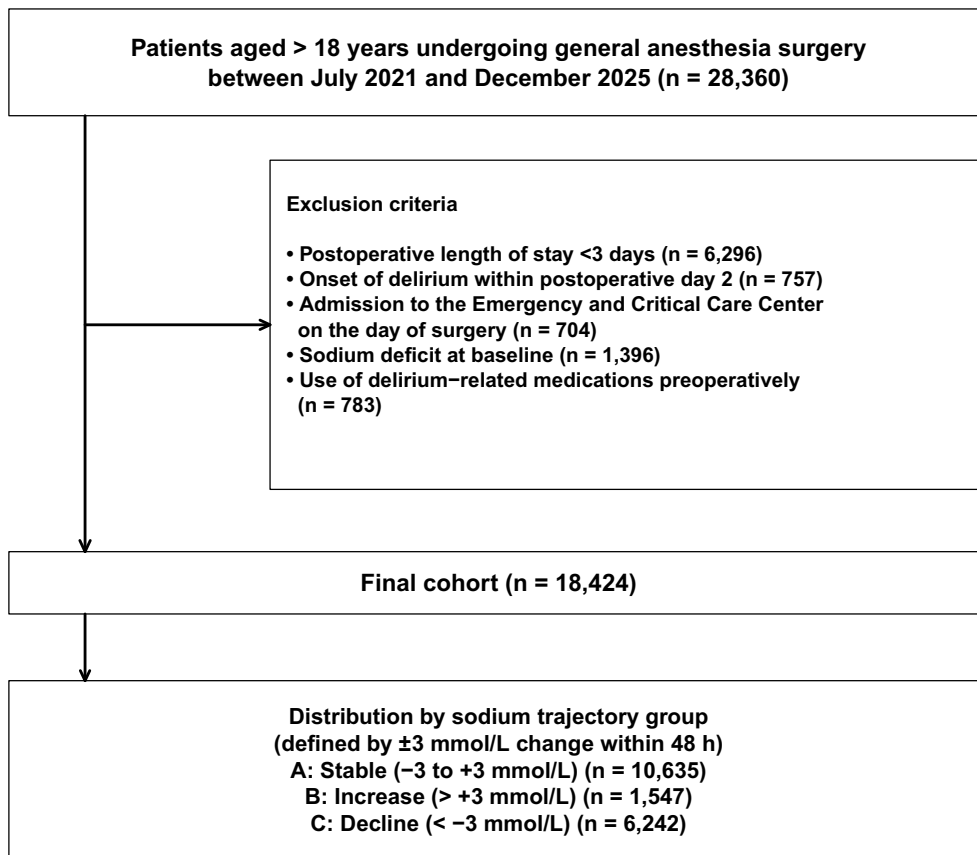


Figure 1 Study flow diagram

Flow diagram of patient selection. Among 28,360 adult patients who underwent surgery under general anesthesia between July 2021 and December 2025, patients were excluded based on pre-defined criteria, including postoperative length of stay <3 days, delirium onset within postoperative day 2, admission to the Emergency and Critical Care Center on the day of surgery, baseline sodium deficit, and preoperative use of delirium-related medications. The final analytic cohort comprised 18,424 patients. Patients were classified into three perioperative sodium trajectory groups according to changes in serum sodium within 48 hours after surgery: stable (−3 to +3 mmol/L), increase (>+3 mmol/L), and decrease (<−3 mmol/L).

Critical Care Centre on the day of surgery (n = 704), baseline sodium deficit (n = 1,396), and preoperative use of delirium-related psychotropic medications (n = 783), the final analytic cohort consisted of 18,424 patients. Based on perioperative sodium change within 48 hours after surgery, patients were categorized into three groups: stable sodium (−3 to +3 mmol/L; n = 10,635), sodium increase (> +3 mmol/L; n = 1,547), and sodium decrease (< −3 mmol/L; n = 6,242).

Baseline Characteristics

Baseline characteristics, stratified by perioperative sodium trajectory, are summarized in **Table 1**. Patients in the sodium increase group more frequently underwent emergency surgery, had higher ASA physical status, and were more often admitted to the ICU on the day of surgery. This group also had higher prevalences of neuro-

logical comorbidities, dementia, alcohol overuse, prior delirium, and use of delirium-risk medications. In addition, operation time, intraoperative fluid administration, net fluid balance, blood loss, and postoperative organ support during postoperative days 0–2 were greater in the sodium increase group.

In contrast, patients in the sodium decrease group were older but less likely to undergo emergency surgery and had lower frequencies of neurological comorbidities and delirium-related risk factors. Perioperative fluid administration and postoperative organ support were generally lower in the sodium decrease group than in the sodium increase group. Individual serum sodium values at baseline and within 48 hours after surgery are illustrated in **Supplementary Figure 1**, demonstrating minimal fluctuation in the stable group and consistent upward or downward shifts in the increase and decrease groups, re-

Table 1 Baseline characteristics, by perioperative sodium trajectory

Variable	Overall (n = 18,424)	Stable Δ Na (−3 to +3 mmol/L) (n = 10,635)	Increase Δ Na (≥ +3 mmol/L) (n = 1,547)	Decrease Δ Na (≤ −3 mmol/L) (n = 6,242)	Missing, n (%)
Late-onset POD, n (%)	314 (1.7)	132 (1.2)	70 (4.5)	112 (1.8)	
Age, years	67 [52, 76]	64 [49, 75]	67 [53, 77]	70 [58, 78]	
Male sex, n (%)	8,680 (47.1)	4,995 (47.0)	754 (48.7)	2,931 (47.0)	
Body mass index, kg/m ²	22.8 [20.4, 25.6]	22.8 [20.4, 25.7]	22.5 [20.3, 25.4]	22.9 [20.5, 25.5]	425 (2.3%)
ICU admission on day of surgery, n (%)	2,753 (14.9)	1,382 (13.0)	356 (23.0)	1,015 (16.3)	
Emergency surgery, n (%)	1,900 (10.3)	1,069 (10.1)	403 (26.1)	428 (6.9)	
ASA physical status ≥3, n (%)	3,677 (20.0)	1,966 (18.5)	384 (24.8)	1,327 (21.3)	
Organic brain disease, n (%)	4,171 (22.6)	2,436 (22.9)	525 (33.9)	1,210 (19.4)	
Dementia, n (%)	3,740 (20.3)	2,195 (20.6)	452 (29.2)	1,093 (17.5)	
Alcohol overuse, n (%)	3,604 (19.6)	2,124 (20.0)	438 (28.3)	1,042 (16.7)	
History of delirium, n (%)	3,674 (19.9)	2,159 (20.3)	443 (28.6)	1,072 (17.2)	
Delirium-risk medication [†] , n (%)	4,654 (25.3)	2,731 (25.7)	533 (34.5)	1,390 (22.3)	
Preoperative sodium, mmol/L	141 [140, 143]	141 [139, 142]	139 [136, 141]	142 [141, 144]	
Albumin, g/dL	4.1 [3.8, 4.4]	4.2 [3.8, 4.4]	4.0 [3.4, 4.3]	4.1 [3.8, 4.4]	535 (2.9%)
Blood urea nitrogen, mg/dL	14.7 [11.7, 18.7]	14.4 [11.5, 18.2]	15.2 [11.7, 20.6]	15.1 [12.1, 19.0]	
C-reactive protein, mg/dL	0.11 [0.04, 0.41]	0.10 [0.04, 0.37]	0.20 [0.05, 2.05]	0.11 [0.04, 0.37]	848 (4.6%)
Creatinine, mg/dL	0.76 [0.63, 0.94]	0.75 [0.62, 0.93]	0.79 [0.62, 1.05]	0.76 [0.64, 0.93]	
Hemoglobin, g/dL	12.9 [11.7, 14.0]	13.0 [11.8, 14.1]	12.5 [10.9, 13.8]	12.8 [11.6, 13.9]	3 (0.0%)
Potassium, mmol/L	4.2 [3.9, 4.4]	4.2 [3.9, 4.4]	4.2 [3.9, 4.5]	4.2 [3.9, 4.4]	3 (0.0%)
White blood cell count, ×10 ³ /μL	5.9 [4.9, 7.3]	6.0 [4.9, 7.3]	6.6 [5.3, 8.95]	5.8 [4.8, 7.0]	3 (0.0%)
Operation time, min	150 [99, 232]	144 [94, 226]	152 [94, 261]	158 [110, 237]	
Intraoperative net fluid balance, mL	1,200 [775, 2,081]	1,100 [734, 1,900]	1,200 [729, 2,235]	1,380 [867, 2,293]	
Total fluid administration, mL	1,450 [950, 2,600]	1,300 [900, 2,400]	1,550 [950, 3,200]	1,650 [1,050, 2,800]	
Estimated blood loss, mL	14 [0, 104]	10 [0, 86]	20 [0, 168.5]	20 [0, 133]	
Postoperative days 0–2					
Renal replacement therapy, n (%)	1,092 (5.9)	601 (5.7)	119 (7.7)	372 (6.0)	
Mechanical ventilation, n (%)	1,350 (7.3)	667 (6.3)	237 (15.3)	446 (7.1)	
Mechanical circulatory support, n (%)	348 (1.9)	167 (1.6)	82 (5.3)	99 (1.6)	

Δ Na indicates the difference between preoperative baseline sodium and the most recent sodium value within 48 hours after surgery.

[†]Delirium-risk medications include benzodiazepines, anticholinergics, opioids, and other centrally acting agents.

spectively.

Association between Δ Na Categories and Late-Onset Delirium

Multivariable logistic regression analyses are presented in **Table 2**. As compared with patients with stable perioperative sodium levels, those with increased and decreased sodium within 48 hours after surgery had significantly higher odds of late-onset postoperative delirium occurring between postoperative days 3 and 7. These associations remained statistically significant after adjustment for demographic characteristics, comorbidities, and surgical factors. Baseline preoperative serum sodium concentration was not significantly associated with delirium risk in either multivariable model. In addition to perioperative sodium trajectory, older age, male sex, ICU admission on the day of surgery, emergency surgery, and higher ASA physical status were consistently associated

with increased odds of postoperative delirium. Longer operation time and greater intraoperative net fluid balance were also independently associated with delirium risk, reflecting different dimensions of perioperative burden.

Sensitivity analyses using an alternative definition of perioperative sodium change (± 2 mmol/L) yielded results consistent with the primary analysis (**Supplementary Table 1**). Both sodium increase and sodium decrease remained associated with an increased risk of late-onset postoperative delirium, with similar effect sizes and directions.

Nonlinear Dose-Response Relationship

When perioperative sodium change was modeled as a continuous variable using restricted cubic splines, a significant nonlinear association between Δ Na and late-onset postoperative delirium was observed (**Figure 2**).

Table 2 Association between perioperative sodium change (ΔNa) and late-onset postoperative delirium

Variable	OR (95% CI)	p value	OR (95% CI)	p value
Na trajectory (48 h): Increase vs Stable	1.485 (1.049–2.102)	0.026	1.754 (1.244–2.474)	0.001
Na trajectory (48 h): Decline vs Stable	1.381 (1.049–1.817)	0.021	1.318 (1.002–1.733)	0.048
Baseline sodium (mmol/L)	0.992 (0.956–1.029)	0.663	1.012 (0.975–1.049)	0.534
Age (years)	1.039 (1.029–1.050)	<0.001	1.032 (1.022–1.041)	<0.001
Male sex	1.483 (1.152–1.908)	0.002	1.488 (1.158–1.914)	0.002
ICU admission	3.684 (2.799–4.850)	<0.001	4.553 (3.442–6.023)	<0.001
Organic brain disorder	1.373 (0.823–2.291)	0.224	1.979 (1.201–3.259)	0.007
Dementia	1.711 (0.764–3.832)	0.192	1.575 (0.678–3.658)	0.291
History of delirium	0.560 (0.236–1.329)	0.188	0.479 (0.194–1.185)	0.111
Emergency surgery	7.795 (5.743–10.579)	<0.001	4.558 (3.426–6.065)	<0.001
ASA-PS ≥ 3	1.608 (1.236–2.091)	<0.001	1.440 (1.104–1.878)	0.007
Operation time (per 60 min)	1.294 (1.243–1.347)	<0.001		
In-out balance (per 1 L)			1.246 (1.181–1.314)	<0.001

Values are adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Late-onset postoperative delirium was defined as delirium occurring between postoperative days 3 and 7. Perioperative sodium trajectory was defined as change in serum sodium from the preoperative baseline to the most recent value within 48 hours after surgery. Model 1 was adjusted for demographic variables, comorbidities, ICU admission on the day of surgery, emergency surgery, ASA physical status, and operation time. Model 2 included the same covariates as Model 1, with intraoperative in–out fluid balance replacing operation time. Stable sodium trajectory (-3 to $+3$ mmol/L) served as the reference category.

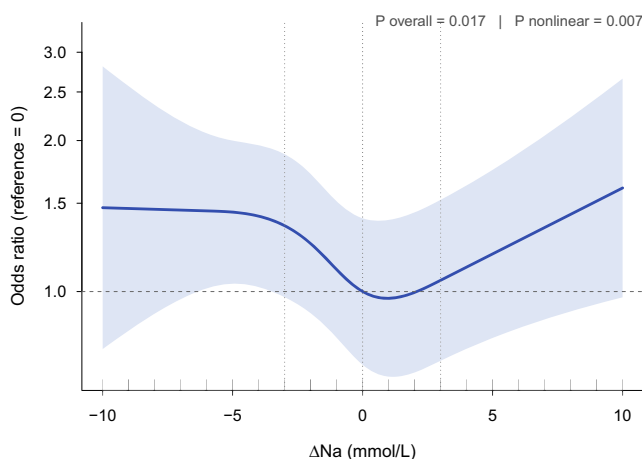


Figure 2 Nonlinear association between perioperative sodium change and late-onset postoperative delirium. Restricted cubic spline analysis showing the association between perioperative sodium change (ΔNa) within 48 hours after surgery and the odds of late-onset postoperative delirium occurring between postoperative days 3 and 7. Odds ratios are shown relative to $\Delta\text{Na} = 0$ mmol/L. The solid line represents the adjusted odds ratio, and the shaded area indicates the 95% confidence interval. Vertical dashed lines denote spline knot locations. A significant U-shaped association was observed (P for nonlinearity = 0.007), indicating increased delirium risk with both sodium increase and decrease, as compared with stable sodium levels.

The estimated odds of delirium were lowest when perioperative sodium change was close to zero and increased progressively as sodium levels deviated in either the negative or positive direction, demonstrating a U-shaped dose-response relationship.

This nonlinear association remained robust in a sensitivity analysis in which operation time was replaced with intraoperative net fluid balance as an alternative indicator of surgical invasiveness (**Supplementary Figure 2**), indicating that the overall pattern was not dependent on the specific representation of perioperative burden.

Subgroup Analyses

Prespecified subgroup analyses are shown in **Figure 3**. No significant effect modification was observed for age, sex, or ICU admission on the day of surgery. In contrast, a significant interaction was identified for ASA physical status. Patients with an ASA physical status of 3 or higher exhibited a more pronounced U-shaped association between perioperative sodium change and delirium risk, whereas this association was attenuated among patients with lower ASA physical status.

Discussion

In this retrospective cohort study using a Day-3 landmark design, we found that early postoperative sodium dynamics were independently associated with the risk of late-onset postoperative delirium among patients under-

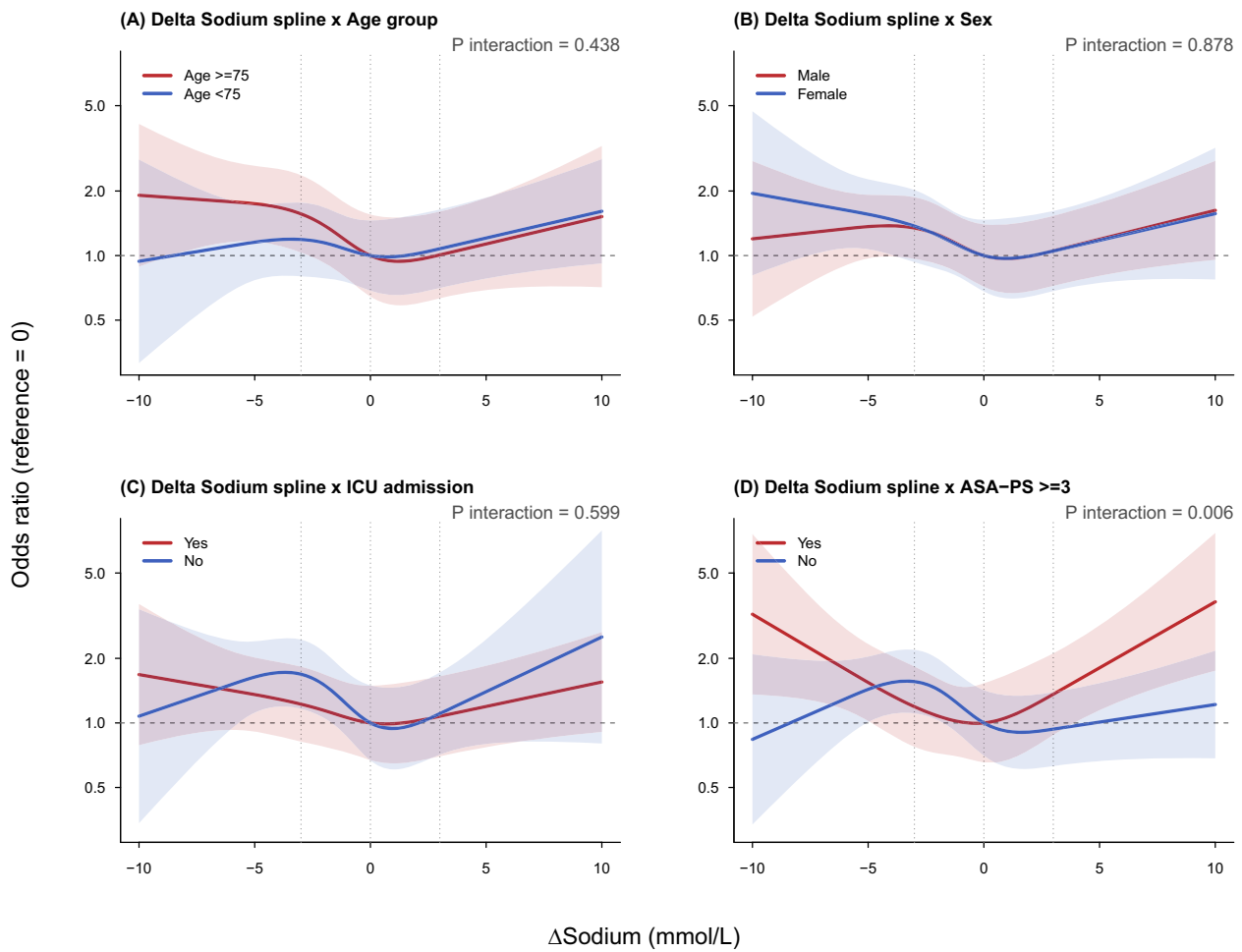


Figure 3 Subgroup analyses of the association between perioperative sodium change and delirium risk. Restricted cubic spline analyses stratified by prespecified subgroups: (A) age (<75 vs ≥75 years), (B) sex, (C) intensive care unit (ICU) admission on the day of surgery, and (D) American Society of Anesthesiologists physical status (ASA-PS <3 vs ≥3). Adjusted odds ratios for late-onset postoperative delirium are shown relative to $\Delta\text{Na} = 0$ mmol/L. Shaded areas represent 95% confidence intervals. P values indicate interaction tests between perioperative sodium change and each subgroup variable. A significant interaction was observed only for ASA-PS (P interaction = 0.006), with a more pronounced U-shaped association among patients with ASA-PS ≥3.

going surgery under general anesthesia. Both increases and decreases in serum sodium within the first 48 hours after surgery were associated with higher odds of delirium occurring between postoperative days 3 and 7, whereas baseline preoperative sodium concentration was not associated with delirium risk. Importantly, these associations were robust across multiple analytical approaches, including alternative definitions of sodium change, different representations of surgical invasiveness and perioperative fluid exposure, and nonlinear spline modelling. Taken together, these findings indicate that early postoperative sodium trajectories, rather than static sodium measurements, capture clinically relevant physiological perturbations that precede the development of postoperative delirium.

The U-shaped association observed between periopera-

tive sodium change and late-onset postoperative delirium is biologically plausible in light of current knowledge of delirium pathophysiology. Serum sodium plays a critical role in neuronal excitability, osmotic homeostasis, and cerebral volume regulation, and abrupt sodium fluctuations can induce neuronal dysfunction through osmotic stress, altered synaptic transmission, and disruption of blood-brain barrier (BBB) integrity^{9,14}. Accumulating evidence suggests that BBB dysfunction and subsequent neuroinflammatory activation are central mechanisms in the development of postoperative delirium, particularly in older surgical patients^{15,16}. During the early postoperative period, surgical stress, anesthesia, systemic inflammation, and perioperative fluid shifts may collectively increase cerebral vulnerability, even in the absence of overt preoperative electrolyte abnormalities¹⁷. Within this vul-

nerable physiological milieu, dynamic perioperative sodium fluctuations may therefore reflect acute physiological stress that amplifies susceptibility to delirium, rather than acting as isolated electrolyte disturbances. Our findings support this framework by demonstrating that early postoperative sodium trajectories precede development of late-onset delirium more consistently than static sodium values.

Most previous studies of the association between serum sodium and delirium relied on preoperative or single time-point measurements^{8,18}. While such static assessments may capture chronic illness burden or baseline frailty, they are insufficient to reflect the acute physiological stress encountered during the immediate postoperative period⁷. In contrast, perioperative sodium trajectories integrate the cumulative effects of surgical stress, perioperative fluid management, and early postoperative recovery processes¹². By applying a Day-3 landmark design, our analysis ensured temporal precedence of sodium exposure before delirium onset and reduced confounding from early postoperative instability. Notably, the observation that sodium dynamics within the first 48 hours were associated with delirium occurring several days later suggests that early postoperative electrolyte disturbances may contribute to a cascade of cerebral vulnerability that evolves beyond the immediate postoperative phase. This temporal dissociation supports the conceptualization of postoperative delirium as a dynamic pathophysiological process rather than a discrete acute event^{6,19}.

From a clinical perspective, perioperative sodium dynamics represent a scalable and pragmatic tool for postoperative delirium risk stratification. Serum sodium is routinely measured as part of standard perioperative care, and evaluating changes over time requires no additional testing or specialized resources. Monitoring early postoperative sodium trajectories may therefore facilitate timely identification of patients at increased risk for late-onset delirium, enabling targeted preventive strategies such as enhanced neurological surveillance, optimization of fluid and electrolyte management, and minimization of deliriogenic medications^{20,21}. Emerging interventional evidence further supports the clinical relevance of sodium dynamics. A recent randomized study demonstrated that modulation of perioperative sodium balance through preoperative hypertonic saline administration was associated with a reduced incidence of postoperative delirium, suggesting that perioperative sodium handling may represent a modifiable risk factor rather than a pas-

sive marker of illness severity²².

Several important limitations should be acknowledged. First, the single-center retrospective design limits the generalizability of the findings, as perioperative management strategies, fluid protocols, and delirium screening practices may vary across institutions. Second, although a landmark design was used to ensure temporal ordering between sodium exposure and delirium onset, this was an observational study, and residual confounding from unmeasured factors—such as intraoperative hemodynamics, anesthetic depth, and postoperative sedation—cannot be fully excluded. Intraoperative hemodynamic variables and anesthetic drug doses were not comprehensively captured and may partially mediate or confound the observed associations. Third, delirium was identified using ICDSC scores recorded in routine clinical practice and supplemented by antipsychotic prescriptions. Although this approach likely improves sensitivity for clinically relevant delirium, misclassification remains possible, particularly for hypoactive or transient episodes. Fourth, perioperative sodium measurements were based on clinically obtained laboratory tests rather than protocolized sampling, resulting in variability in measurement timing and potential exposure misclassification. Fifth, perioperative sodium change was derived from the most recent postoperative value within 48 hours and the closest preoperative value within 60 days, which may not fully capture rapid or transient sodium fluctuations. Sixth, although spline modelling enabled exploration of nonlinear associations, the number of patients with extreme ΔNa values was limited, leading to greater uncertainty at the tails of the dose-response curves. Finally, although postoperative day 3 was selected as a clinically motivated landmark, alternative landmark definitions may yield different effect estimates. These limitations should be considered when interpreting the present findings.

Conclusion

Perioperative sodium fluctuations within the first 48 hours after surgery, regardless of direction, were independently associated with an increased risk of late-onset postoperative delirium. The observed U-shaped relationship suggests that maintaining sodium stability during the early postoperative period may be clinically important. Routine monitoring of perioperative sodium trajectories may enhance early risk stratification, particularly among physiologically vulnerable patients. External validation in multicenter cohorts will be essential before these findings can be broadly implemented in routine

clinical practice.

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Data Availability: The data underlying this study contain sensitive individual-level patient information and are subject to institutional and ethical restrictions. Therefore, the data are not publicly available and cannot be shared outside the study institutions. Requests for access to de-identified data may be considered by the corresponding author upon reasonable request and with approval from the institutional ethics committee.

Supplementary Material: Supplementary material associated with this article is available at https://doi.org/10.1272/jnms.JNMS.2026_93-508.

References

- Zhao B, Ji HS, Xu CY, et al. Incidence and risk factors of postoperative delirium after pancreatic cancer surgery: a retrospective study. *Surg Today*. 2023;53:736–42.
- Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet*. 2014;383:911–22.
- Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA*. 2010;304:443–51.
- Ni Y, Yang X, Yang Y, Zhang H, Peng S. Incidence and factors associated with postoperative delirium after primary total joint arthroplasty in older adults: a systematic review and meta-analysis. *Front Med (Lausanne)*. 2025;12:1664605.
- Lander HL, Dick AW, Joynt Maddox KE, et al. Postoperative delirium in older adults undergoing noncardiac surgery. *JAMA Netw Open*. 2025;8:e2519467.
- Lee H, Ju JW, Oh SY, Kim J, Jung CW, Ryu HG. Impact of timing and duration of postoperative delirium: a retrospective observational study. *Surgery*. 2018;164:137–43.
- Wilson JE, Mart MF, Cunningham C, et al. Delirium. *Nat Rev Dis Primers*. 2020;6:90.
- Hong L, Shen X, Shi Q, et al. Association between hypernatremia and delirium after cardiac surgery: a nested case-control study. *Front Cardiovasc Med*. 2022;9:828015.
- Verbalis JG, Goldsmith SR, Greenberg A, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am J Med*. 2013;126(10 Suppl 1):S1–42.
- Wang LH, Xu DJ, Wei XJ, Chang HT, Xu GH. Electrolyte disorders and aging: risk factors for delirium in patients undergoing orthopedic surgeries. *BMC Psychiatry*. 2016;16:418.
- Pennington Z, Bomberger TT, Lubelski D, Benzel EC, Steinmetz MP, Mroz TE. Preoperative hyponatremia and perioperative complications in cervical spinal fusion. *World Neurosurg*. 2020;141:e864–72.
- Spasovski G, Vanholder R, Allohli B, et al. Clinical practice guideline on diagnosis and treatment of hyponatremia. *Nephrol Dial Transplant*. 2014;29(Suppl 2):i1–39.
- Hernan MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol*. 2016;183:758–64.
- Lerner DP, Shepherd SA, Batra A. Hyponatremia in the neurologically ill patient: a review. *Neurohospitalist*. 2020;10:208–16.
- Devinney MJ, Wong MK, Wright MC, et al. Role of blood-brain barrier dysfunction in delirium following non-cardiac surgery in older adults. *Ann Neurol*. 2023;94:1024–35.
- Lascola CD, Cotter SF, Klinger RY, et al. Blood-brain barrier permeability and cognitive dysfunction after surgery - a pilot study. *J Clin Anesth*. 2023;86:111059.
- Cerejeira J, Firmino H, Vaz-Serra A, Mukaetova-Ladinska EB. The neuroinflammatory hypothesis of delirium. *Acta Neuropathol*. 2010;119:737–54.
- Teo CB, Gan MY, Tay RYK, Loh WJ, Loh NW. Association of preoperative hyponatremia with surgical outcomes: a systematic review and meta-analysis of 32 observational studies. *J Clin Endocrinol Metab*. 2023;108:1254–71.
- Oh ES, Fong TG, Hsieh TT, Inouye SK. Delirium in older persons: advances in diagnosis and treatment. *JAMA*. 2017;318:1161–74.
- Hsieh TT, Yue J, Oh E, et al. Effectiveness of multicomponent nonpharmacological delirium interventions: a meta-analysis. *JAMA Intern Med*. 2015;175:512–20.
- Mart MF, Williams Roberson S, Salas B, Pandharipande PP, Ely EW. Prevention and management of delirium in the intensive care unit. *Semin Respir Crit Care Med*. 2021;42:112–26.
- Xu F, Li Y, Wang X, et al. Effect of pre-infusion of hypertonic saline on postoperative delirium in geriatric patients undergoing shoulder arthroscopy: a randomized controlled trial. *BMC Anesthesiol*. 2023;23:405.