Article

Intraoperative Electroencephalogram Frontal Low Alpha Power for Predicting Postoperative Delirium in Elderly Patients after Orthopedic Surgery: A Prospective Cohort Study

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AIM: Postoperative delirium (POD) is a common complication with significant adverse effects in elderly patients. Electroencephalography (EEG) provides a promising approach for predicting the risk of POD. This study aims to elucidate the correlation between intraoperative EEG spectrum and the incidence of POD in elderly patients undergoing orthopedic surgery.
METHODS: A single-center prospective observational cohort study was conducted at Zhongda Hospital, Southeast University, from September 2022 to March 2023, registered on Chinese Clinical Trail Registry (ChiCTR2300069548). Among the 172 patients who underwent orthopedic surgery, 125 completed the study with available data. Preoperative baseline cognitive function was assessed using the mini-mental state examination (MMSE). An intraoperative 4-channel EEG was recorded. Total power spectra and power spectral density for beta, alpha, theta, and delta bands were calculated. Spectral edge frequency, burst suppression ratio, and patient state index were directly extracted from the EEG monitor. The primary outcome was POD, assessed using a 3-minute Diagnostic Interview for Confusion Assessment Method (CAM)-Defined Delirium scale or the CAM for the Intensive Care Unit. Patients were divided into POD and non-postoperative delirium (non-POD) groups. Logistic regression analysis was conducted to evaluate the independent predictive effect of intraoperative spectral distribution and other quantitative EEG data for POD.
RESULTS: The incidence of delirium within 72 hours after surgery was 8.8%. Compared to the non-POD group, the POD group showed significantly lower absolute power in the beta [0.06 (0.03, 0.09) dB *vs* 0.14 (0.08, 0.26) dB, $p < 0.001$], alpha [0.41 (0.25, 0.71) dB *vs* 1.24 (0.55, 2.57) dB, $p = 0.008$], and theta [0.77 (0.44, 1.01) dB *vs* 1.19 (0.72, 2.02) dB, $p = 0.035$] bands. Logistic regression analysis identified several independent risk factors for POD, including lower intraoperative alpha power [odds ratio (OR) 10.210, 95% confidence interval (CI) 1.233–84.568, $p = 0.031$], advanced age (OR 7.713, 95% CI 1.022–58.204, $p = 0.048$), preoperative anemia (OR 6.636, 95% CI 1.091–40.358, $p = 0.040$), and preoperative depression (OR 10.089, 95% CI 1.029–98.909, $p = 0.047$). In contrast, higher preoperative MMSE scores appeared to be a protective factor for POD (OR 0.130, 95% CI 0.021–0.820, $p = 0.030$).
CONCLUSIONS: Intraoperative EEG frontal low alpha power demonstrated a significant independent association with POD in elderly patients after orthopedic surgery. This parameter may serve as an intraoperative neurophysiological marker of cerebral vulnerability to POD. Additionally, advanced age, lower preoperative MMSE scores, preoperative anemia, and preoperative depression were independent risk factors for POD.
CLINICAL TRIAL REGISTRATION: Chinese Clinical Trial Registry (ChiCTR2300069548).

Keywords: postoperative delirium; electroencephalogram spectrum; elderly patients; orthopedic surgery

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Introduction

Postoperative delirium (POD) is an acute disturbance of consciousness that commonly occurs within 24 to 72 hours post-surgery. It manifests as sudden onset disorientation, altered consciousness, and cognitive impairment [1]. POD often leads to adverse clinical outcomes, increasing the risk of postoperative complications, readmission rates, reoperation rates, and even mortality [2]. Demographic projections indicate that by 2030, individuals aged 60 years and above will constitute over 20% of the global population [1, 3]. Concurrently, the prevalence of orthopedic conditions in the elderly (including degenerative joint diseases and fragility fractures) will continue to rise, leading to an increased demand for surgical interventions. Study has predicted that the number of hip replacement surgeries will double by 2030 [4]. In non-cardiac surgeries, the incidence of POD is higher among elderly orthopedic patients. Domestic guidelines indicate that the overall incidence of POD in non-cardiac surgery patients aged 65 and above is 11.1%. This incidence increases to 15.2% in spine and joint surgeries [5]. POD assessment mainly relies on delirium assessment scales, which are often subjective, time-consuming, and require significant resources. Furthermore, there is a critical lack of effective predictors for POD. Consequently, identifying reliable predictive indicators and implementing effective interventions remains a significant challenge for clinical healthcare professionals.

The precise mechanisms underlying POD remain unclear. Risk factors for POD include advanced age, pre-existing cognitive impairments, anesthesia and surgical stress, dependence on psychotropic medications, and sleep disturbances [5, 6]. Although there are currently no effective treatments for POD, early identification of POD risk can significantly improve patient prognosis.

Electroencephalography (EEG) is a non-invasive neurophysiological monitoring technique used clinically to study brain activity and diagnose neurological disorders. Processed EEG (pEEG) monitors have recently been widely used for intraoperative anesthesia depth monitoring [6]. The pEEG index is a quantitative parameter that translates EEG signals into numerical values to monitor the depth of anesthesia [7]. Examples of such indices include the bispectral index (BIS) and patient state index (PSI). However, study has shown that while pEEG indices are suitable for assessing anesthesia depth, they have limitations in analyzing the actual brain functional state. Quantitative EEG (qEEG) provides a more precise method for assessing brain functional states by quantifying the absolute power and frequency of various brain wavebands [8]. Recent qEEG studies have identified specific intraoperative EEG abnormalities that correlate with an increased risk of POD, including increased delta and theta activity [8], decreased alpha and beta activity [9], increased burst suppression (BS) [10], and reduced EEG coherence [11]. Notably, these association have been predominantly observed in cardiac surgeries [12, 13]. However, there is a paucity of research focused on orthopedic surgery.

The primary objective of this study is to examine the correlation between intraoperative EEG spectral characteristics and POD in elderly patients undergoing orthopedic surgery. This research aims to establish a foundation for identifying predictive EEG biomarkers that can assess the risk of POD. The ultimate goal is to improve patient outcomes by enabling early detection and intervention strategies for POD.

Materials and Methods

Study Design and Setting

This single-center, prospective, observational cohort study included 125 elderly patients who underwent elective orthopedic surgeries, including lumbar, knee, hip, and femoral surgeries, at Zhongda Hospital, Southeast University, from September 2022 to March 2023. The study was approved by the Human Ethics Committee of Zhongda Hospital, Southeast University (Ethics Approval Number: 2022ZDSYLL210-P01) and was registered in the Chinese Clinical Trial Registry (ChiCTR2300069548), (https://www.chictr.org.cn/hvshowproject.html?id=226458&v=1.2). All participants provided written informed consent. This study was conducted in accordance with the principles outlines in the Declaration of Helsinki.

The inclusion criteria were as follows: Patients aged 65 years or older and classified as American Society of Anesthesiologists (ASA) physical status II–III. Additionally, patients were scheduled for elective single-site orthopedic surgery involving arthroplasty (total hip arthroplasty, total knee arthroplasty, femoral head replacement) and transforaminal lumbar interbody fusion under general anesthesia.

The exclusion criteria were as follows: Patients with visual or auditory impairment, history of dialysis, previous open-heart or pulmonary surgery, long-term use of benzodiazepines or antipsychotics, or preexisting preoperative neurocognitive dysfunction. Additionally, patients or their families who refused to provide informed consent were excluded from participation.

Data Collection

Baseline data included demographics (sex, age, height, weight, body mass index, education level, ASA classification), smoking and alcohol consumption history, laboratory tests, surgical and anesthesia details (type of surgery, duration of surgery, duration of anesthesia, intraoperative anesthetic dosage), and postoperative follow-up indicators [length of stay, Intensive Care Unit (ICU) admission].

Baseline cognitive function was assessed using the mini-mental state examination (MMSE) scale [14] at the patient's bedside one day before surgery. The MMSE evaluates six cognitive domains: temporal orientation, spatial orientation, arithmetic ability, short-term memory, attention, and language. Preoperative pain levels were evaluated using the Numeric Rating Scale one day before surgery. The scale ranges from 1 to 10, with higher values corresponding to more severe pain: mild (1–3), moderate (4–6), and severe (7–10). Anxiety and depression were evaluated using the Hospital Anxiety and Depression Scale [15], with scores above 7 indicating potential significant anxiety or depression. The age-adjusted Charlson Comorbidity Index scale [16] was conducted to evaluate the presence and severity of comorbid conditions. Anemia was defined as a hemoglobin (Hb) level below 13 g/dL in men and below 12 g/dL in women. All assessments were conducted by the same anesthesiologist, who was professionally trained in administering these scales.

Perioperative Management and Monitoring

Patients followed standard preoperative fasting guidelines and did not receive preoperative medications. Upon admission to the operating room, peripheral intravenous access was established, and continuous physiological monitoring was initiated, comprising electrocardiogram, SpO_2, invasive blood pressure, temperature, and EEG.

General anesthesia induction included midazolam (approval number: H19990027, Enhua Pharmaceutical Co., Ltd., Xuzhou, China) (1–2 mg), sufentanil (approval number: H20054171, Yichang Renfu Pharmaceutical Co., Ltd., Yichang, China) (0.3–0.6 µg/kg), propofol (approval number: 21091531, Yangtze River Pharmaceutical Group Co., Ltd., Taizhou, China) (2–3 mg/kg), and cisatracurium (approval number: H20060869, Jiangsu Hengrui Pharmaceuticals Co., Ltd., Lianyungang, China) (0.2 mg/kg) or rocuronium (approval number: H20213778, Guangdong Sunho Pharmaceutical Co., Ltd., Zhongshan, China) (0.6 mg/kg). Once muscle relaxation was achieved, tracheal intubation was performed using a video laryngoscope. The ventilator settings were adjusted as follows: tidal volume was set to 6–8 mL/kg, a respiratory rate was adjusted to 10–16 breaths per minute, and the inspiratory-to-expiratory ratio was maintained at 1:2. The fraction of inhaled oxygen concentration was titrated between 40% and 80% to achieve an end-tidal CO_2 level of 35–45 mmHg. Anesthesia was maintained using a continuous infusion of remifentanil (approval number: H20143314, Jiangsu Hengrui Pharmaceuticals Co., Ltd., Lianyungang, China) (0.05–2 µg/kg/min) and sevoflurane inhalation (approval number: H20150020, Maruishi Pharmaceutical Co., Ltd., Osaka, Japan). No additional anesthetics, such as propofol or dexmedetomidine, were administered. The initial concentration of sevoflurane was 1 minimal alveolar concentration (MAC) and subsequently adjusted based on the PSI between 25 to 50, ensuring an appropriate depth of anesthesia. Every 40–60 minutes during the surgery, a supplemental dose of muscle relaxant at 1/3 to 1/5 of the induction dose was administered. Intraoperative blood pressure was maintained within 20% of baseline values using vasoactive drugs as needed. Fluid administration was guided by hemodynamic parameters to ensure adequate tissue perfusion. All anesthetic drugs were discontinued at the end of the surgery, and patients were transferred to either the post-anesthesia care unit or ICU for recovery.

EEG Monitoring and Processing

EEG data were acquired continuously throughout the surgery using the SedLine monitor (7362A-RDS7, Masimo Corporation, Irvine, CA, USA). Before data collection, the patient's forehead was cleansed with alcohol-soaked gauze to ensure electrode impedance below 8 kOhm and inter-channel differences below 5 kOhm. Electrodes were placed at Fp1, Fp2, F7, and F8, with the ground electrode at Fpz and the reference electrode 1 cm above Fpz. The sampling rate was 178 Hz. For each patient, a 2-minute EEG epoch of continuous, artifact-free EEG data, was selected approximately one hour after the start of the surgery. This epoch was extracted from a stable segment of the recording, free from motion, electrocautery artifacts and burst suppression (BS). Visual inspection was performed to manually identify EEG segments suitable for analysis, ensuring the absence of artifacts.

The raw EEG data, spectral edge frequency (SEF), BS ratio, and PSI were directly extracted from the SedLine monitor. Burst suppression duration was calculated according to previous study [17]. Spectral analysis was performed using customized MATLAB scripts based on EEGLAB (v2022.1, University of California, San Diego, CA, USA) and the Chronux toolbox in MATLAB R2022b (9.13.0, © 1984–2022 The MathWorks, Inc, Natick, MA, USA). The parameters for spectral analysis were set as follows: sliding window length T = 2 s with 1.9 s overlap, time-bandwidth product TW = 3, number of tapers K = 5, notch filter setting at 48–52 Hz, and band-pass filter range of 0.5–45 Hz. Signals from the Fp1, Fp2, F7, and F8 channels were averaged and weighted, and the power spectral density for beta (12.1–30 Hz), alpha (8–12 Hz), theta (4–7.9 Hz), and delta (1–3.9 Hz) bands were calculated.

Outcome Measures

The primary outcome of this study was the incidence of POD. Trained investigators utilized the validated Chinese version of the 3D Confusion Assessment Method (3D-CAM) [18] scale or the Confusion Assessment Method (CAM) for the ICU [19] for intubated patients. Delirium assessment was conducted twice daily, between 8–10 am and 6–8 pm, for 3 days following surgery [20]. POD was diagnosed if one or more positive event(s) were obtained out of 6 tests performed within 3 days postoperatively. In cases where delirium was suspected outside the designated assessment times, researchers promptly visited the ward to conduct additional evaluations.

Sample Size Calculation

This study is a prospective cohort study. Based on relevant literature, the intraoperative alpha power in patients with cognitive dysfunction constitutes approximately 5% of the total EEG power (P_1 = 0.05), while in cognitively normal patients, it accounts for about 57% (P_0 = 0.57) [21]. With α = 0.05 and β = 0.2, ensuring a statistical power of 80% for a two-sided test, the calculated sample size is n = 11. This indicates that at least 11 patients with delirium need to be observed. Given that the incidence of POD incidence in elderly orthopedic patients has previously been reported to range from 5% to 38% [22], we estimate an incidence rate

Table 1. Characteristics and perioperative data of patients between non-POD and POD.

	Non-POD N = 114	POD N = 11	$t/Z/\chi^2$	p
Gender			0.056	0.812
Male	42 (36.8%)	5 (45.5%)		
Female	72 (63.2%)	6 (54.4%)		
Age (years)	71 [68, 77]	80 [75, 83]	–3.270	0.001
Age group (years)			7.705	0.006
65–74	75 (65.8%)	2 (18.2%)		
≥75	39 (34.2%)	9 (81.8%)		
Education			0.031	0.984
Primary	70 (61.4%)	7 (63.6%)		
Secondary	34 (29.8%)	3 (27.3%)		
Tertiary	10 (8.8%)	1 (9.1%)		
BMI (kg/m^2)	24.34 ± 3.60	22.33 ± 4.28	1.746	0.083
Preoperative pain			0.823	0.364
Mild	72 (63.2%)	9 (81.8%)		
Moderate-severe	42 (36.8%)	2 (18.2%)		
Smoking	17 (14.9%)	2 (18.2%)	0.023	0.880
Drinking	17 (14.9%)	1 (9.1%)	0.006	0.940
CHD	18 (15.8%)	1 (9.1%)	0.023	0.880
Hypertension	73 (64.0%)	8 (72.7%)	0.060	0.806
Diabetes	26 (22.8%)	3 (27.3%)	0.000	1.000
MMSE	26 [23.75, 28]	22 [18, 24]	–3.485	<0.001
MMSE			8.917	0.003
<25	36 (31.6%)	9 (81.8%)		
25–30	78 (68.4%)	2 (18.2%)		
ACCI	4 [3, 5]	4 [3, 6]	–1.282	0.200
Anxiety	4 (3.5%)	1 (9.1%)		0.374
Depression	2 (1.8%)	3 (27.3%)		0.005
WBC ($\times 10^9$/L)			5.755	0.056
3.5–9.5	101 (88.6%)	7 (63.6%)		
>9.5	11 (9.6%)	3 (27.3%)		
<3.5	2 (1.8%)	1 (9.1%)		
RBC ($\times 10^{12}$/L)			2.304	0.129
4.3–5.8	42 (36.8%)	1 (9.1%)		
<4.3	72 (63.8%)	10 (90.9%)		
Anemia	19 (16.7%)	6 (54.5%)	6.785	0.009
CRP (mg/L)			4.107	0.043
0–3	89 (78.1%)	5 (45.5%)		
>3	25 (21.9%)	6 (54.5%)		
ALB (g/L)			12.196	0.002
>40	51 (44.7%)	1 (9.1%)		
30–40	61 (53.5%)	8 (72.7%)		
<30	2 (1.8%)	2 (18.2%)		
ASA classification			6.982	0.008
II	73 (64.0%)	2 (18.2%)		
III	41 (36.0%)	9 (81.8%)		
Surgery type			6.100	0.014
Arthroplasty	35 (30.7%)	8 (72.7%)		
TLIF	79 (69.3%)	3 (27.3%)		
Remifentanil (mg)	0.73 [0.52, 0.91]	0.61 [0.52, 0.81]	–0.967	0.333
Sevoflurane (mL)	25.00 [25.54, 30.36]	24.11 [18.75, 31.70]	–0.336	0.737
Surgery duration (min)	140 [114.5, 170]	135 [100, 185]	–0.336	0.737
Anesthesia duration (min)	165 [135, 195]	173 [125, 210]	–0.105	0.917

Table 1. Continued.

	Non-POD N = 114	POD N = 11	$t/Z/\chi^2$	p
ICU admission	6 (5.3%)	4 (36.4%)		0.005
LOS (d)	10 [8, 12.25]	12 [9, 14]	–1.078	0.281
Preoperative LOS (d)	3 [2, 5]	4 [3, 5]	–0.613	0.540
Postoperative LOS (d)	6.5 [5, 8]	7 [6, 11]	–0.725	0.468

Continue variables are presented as mean ± SD or median (IQR). Counting data are presented as numbers and percentages. POD, postoperative delirium; non-POD, non-postoperative delirium; ACCI, age-adjusted Charlson Comorbidity Index; ALB, albumin; ASA, American Society of Anesthesiologists; BMI, body mass index; CHD, coronary heart disease; CRP, C-reactive protein; ICU, Intensive Care Unit; IQR, interquartile range; LOS, length of stay; MMSE, mini-mental state examination; RBC, red blood cell; SD, standard deviation; TLIF, transforaminal lumbar interbody fusion; WBC, white blood cell.

of 10%. Consequently, a total of 110 patients were required for the study. Accounting for a 10% dropout rate, the study should recruit at least 123 patients.

Statistical Analysis

The statistical analysis was conducted using SPSS 26.0 software (IBM Corporation, Armonk, NY, USA). Descriptive statistics were calculated for all variables. Normally distributed continuous data are presented as mean ± standard deviation (SD), while non-normally distributed data are reported as median and interquartile range. Categorical data are described using percentages. Continuous variables were compared using the Mann-Whitney *U* test or Student's *t*-test, while categorical variables were analyzed using Fisher's exact test or the chi-square test. Receiver operating curve (ROC) analysis was conducted to assess sensitivity, specificity, and optimal cutoff values for intraoperative EEG spectrum parameters (spanning delta to beta bands), SEF, and MMSE score, based on Youden's index, in relation to clinically defined POD categories.

Factors demonstrating statistically significant differences in univariate analysis were included into a logistic regression model, with a significance level set at $\alpha = 0.05$. To address multicollinearity, we used variance inflation factor (VIF) derived from linear regression. A given predictor was removed from the logistic regression model if the VIF between the variable and other predictor variables was greater than 5, while the factor with the smallest *p*-value was selected. A forward stepwise multivariate logistic regression was conducted to identify independent risk factors associated with POD. A p-value < 0.05 was considered statistically significant.

Results

Patient Population

A total of 172 patients were initially recruited for the study. Among them, 8 patients changed their anesthesia method, 1 patient died within three days post-surgery, 1 patient underwent additional surgeries due to multiple traumatic fractures, and 37 patients had incomplete EEG data. Among them, the EEG records of 20 patients were unintentionally deleted during equipment maintenance because researchers did not export the data promptly. Additionally, 9 patients had incomplete records due to electrode malfunctions. Furthermore, there was high electrode impedance in 8 patients' EEG records. Ultimately, 125 patients were included in the study. Based on the assessment scales, patients were divided into the POD group (11 patients) and the non-postoperative delirium (non-POD) group (114 patients), with a POD incidence rate of 8.8%. The screening process is illustrated in Fig. 1.

The patient characteristics and perioperative data are summarized in Table 1. Fig. 2 illustrates the ROC curves using various indicators to predict POD after orthopedic surgery. ROC curve analysis for POD showed an optimal cut-off value for intraoperative alpha power of 0.735 Hz, with a sensitivity of 0.675, specificity of 0.818, and area under the curve (AUC) of 0.744; 95% confidence interval (CI), 0.573–0.916, $p = 0.005$ (Table 2). Based on this cut-off value, patients were classified into two groups: low alpha power group (<0.735 Hz) and high alpha power group (≥0.735 Hz). The cut-off values for delta, theta, beta power, and SEF were also calculated, and patients were classified based on these values. Similarly, the cut-off value for MMSE was established at 24.5 for predicting POD risk, with a sensitivity of 0.684, specificity of 0.818, and AUC of 0.817. Patients were divided into two groups based on their MMSE scores: those with MMSE scores below 25 and those with MMSE scores between 25 and 30. Comparative analysis revealed that the POD group exhibited significantly higher mean age ($p = 0.001$) and a greater proportion of patients with an ASA score of III ($p = 0.008$) relative to the non-POD group. The POD group also had lower preoperative MMSE scores ($p < 0.001$), a higher preva-

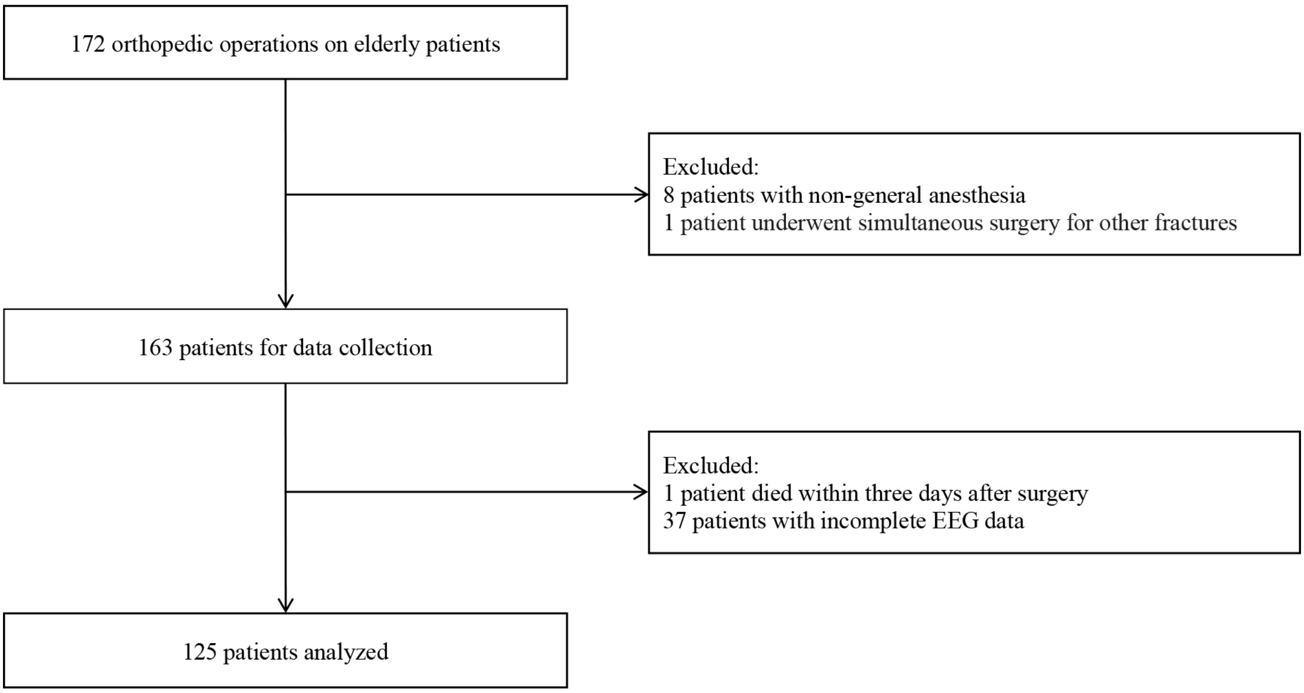

Fig. 1. Flow diagram of the participant selection process for the trial. EEG, electroencephalography.

Table 2. Predictive value of various indicators for postoperative delirium after orthopedic surgery.

Indicators	AUC	Standard error	Optimal cut-off value	Sensitivity	Specificity	*p* value	95% CI
Delta power	0.614	0.087	2.800	0.640	0.636	0.188	0.444–0.784
Theta power	0.693	0.080	1.200	0.491	0.818	0.016	0.536–0.850
Alpha power	0.744	0.088	0.735	0.675	0.818	0.005	0.573–0.916
Beta power	0.807	0.055	0.105	0.658	0.909	<0.001	0.700–0.913
SEF	0.663	0.083	12.125	0.588	0.727	0.049	0.501–0.826
MMSE	0.817	0.062	24.5	0.684	0.818	<0.001	0.696–0.938

AUC, area under curve; CI, confidence interval; SEF, spectral edge frequency.

lence of preoperative anemia (p = 0.009) and hypoalbuminemia (p = 0.002), and higher C-reactive protein (CRP) levels (p = 0.043). Additionally, POD patients showed a higher incidence of depression (p = 0.005) and arthroplasty (p = 0.014), and were more likely to require ICU (p = 0.005). The two groups did not show any significant differences regarding preoperative comorbidities, preoperative pain scores, smoking and alcohol history, surgery and anesthesia duration, or length of hospital stay ($p > 0.05$). Moreover, the consumption of remifentanil and sevoflurane did not differ significantly between the two groups ($p >$ 0.05). A comparative analysis of characteristics and perioperative data between patients excluded from and included in the study revealed no significant differences across all variables examined (**Supplementary Table 1**).

EEG Power Spectral Analysis

Intraoperative EEG power spectral analysis showed that patients in the POD group exhibited significantly lower bilateral SEF compared to the non-POD group [SEF_L (10.01 $\pm$ 3.63 Hz *vs* 12.59 $\pm$ 3.57 Hz, p = 0.024), SEF_R (10.09 $\pm$ 3.74 *vs* 12.31 $\pm$ 3.43 Hz, p = 0.044)]. Additionally, the POD group had significantly reduced power in the beta, alpha, and theta bands relative to the non-POD group ($p <$ 0.05). Although the delta band power was also lower in the POD group, this difference did not reach statistical significance. No significant differences were observed in the PSI, BS duration, or BS percentage between the two groups (p $>$ 0.05) (Table 3).

Fig. 3 illustrates the intraoperative frontal group spectrograms over a single EEG window of 120 ms, comparing the non-POD group with the POD group. The custom-written MATLAB code was employed to assess the statistical significance of the differences in power within various frequency bands. Fig. 3A depicts the spectrogram of the non-POD group, displaying the power distribution across time and frequency, with time (seconds) arranged along the x-axis and frequencies (Hz) arranged along the y-axis. Fig. 3B presents the corresponding spectrogram for the POD group, highlighting notable differences in power distribu-

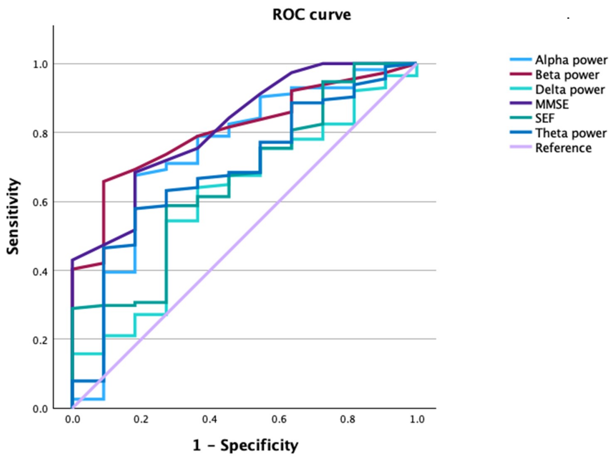

Fig. 2. ROC diagram of each indicator for diagnosis of POD after orthopedic surgery. MMSE, mini-mental state examination; ROC, Receiver operating curve; SEF, spectral edge frequency. The SPSS software SPSS (26.0, IBM, Armonk, NY, USA) was used to create the image.

tion when compared to the non-POD group. Fig. 3C directly compares the POD and non-POD groups, emphasizing the altered power dynamics observed in the POD group. Fig. 3D further elucidates these differences through a subtraction of the two groups' power spectrograms, thereby highlighting the specific frequency bands exhibiting significant power variations.

Risk Factors for POD

The results of the multivariate logistic regression analysis for POD risk factors are presented in Table 4. After adjusting for potential confounding factors that were statistically different between the groups, such as ASA, albumin (ALB), CRP, depression, ICU admission, and surgery type, forward stepwise logistical analysis indicated that among the EEG spectral monitoring data, only lower intraoperative absolute alpha power [odds ratio (OR) 10.210, 95% CI = 1.233–84.568, $p = 0.031$] was an independent risk factor for POD. Additionally, advanced age (OR 7.713, 95% CI 1.022–58.204, $p = 0.048$), preoperative anemia (OR 6.636, 95% CI 1.091–40.358, $p = 0.040$), and preoperative depression (OR 10.089, 95% CI 1.029–98.909, $p = 0.047$) were also independent risk factors for POD. In contrast, higher MMSE scores (OR 0.130, 95% CI 0.021–0.820, $p = 0.030$) appeared to be a protective factor against POD. RBC count was manually excluded from the regression model due to its VIF exceeding 5 when considered alongside Hb. Beta power and SEF were also removed from the regression model due to their multicollinearity with alpha power. The VIF values for all statistically significant variables in the univariate analysis are presented in **Supplementary Table 2**.

Discussion

In this study, intraoperative lower intraoperative absolute alpha power, advanced age, lower preoperative MMSE scores, preoperative anemia, and preoperative depression were independently associated with POD, indicating the ability of intraoperative EEG spectral characteristics to identify patients with a higher risk to develop POD during an early stage of anesthesia.

The prevalence of POD among elderly orthopedic surgery patients was 8.8%, which is lower than the internationally reported range of 12%–51% [1]. This lower incidence may be attributed to the limitations inherent in a single-center study. The majority of the included surgeries were lumbar fusion surgeries (69.3%), with knee and hip surgeries comprising only 22.8% of the sample, which may have relatively higher POD incidence rates. Yang JS *et al.* [22] reported a 7.4% incidence of POD following lumbar fusion surgery, while Kwon YS *et al.* [23] found a 5.9% incidence of POD using clinical database analysis for the same type of surgery. A systematic review and meta-analysis of 44 studies involving 104,572 participants undergoing hip fracture surgery found that the incidence of POD was 16.93% [24]. In contrast, a recent multicenter randomized controlled trial conducted in China among elderly orthopedic surgery patients found a 5.1% incidence of POD in the general anesthesia group [25]. Differences in perioperative management, including anesthesia protocols, pain management, and postoperative care, may have contributed to the lower incidence of POD observed in the study center. Variations in diagnostic criteria and assessment methods can also lead to differences in reported incidence rates, with standardized tools and consistent assessment timing impacting detection. Additionally, the study design and data collection methods, including sample size and inclusion criteria, can influence the results.

This study found that only low absolute alpha power during intraoperative EEG monitoring was independently associated with POD in elderly orthopedic patients. Alpha waves typically appear when the brain is in a relaxed state (awake with eyes closed), with maximal amplitude observed in the occipital cortex. However, the administration of sedative anesthetics like propofol, induces a characteristic shift in alpha waves topography, with attenuation in occipital regions and predominance in frontal areas. Research suggests that this unique anteriorization of alpha waves is due to thalamocortical synchronization induced by anesthetic sedatives, possibly related to the action on γ-Aminobutyric acid subtype A receptors, as these drugs commonly target this receptor [11]. Given that EEG recordings were obtained from the frontal region, alpha power serves as a reliable indicator of cerebral functional status under general anesthesia.

In this study, intraoperative absolute alpha power was significantly diminished in the POD group compared to the non-POD group, with the maximal difference peaking around 12 Hz. Additionally, density spectral array anal-

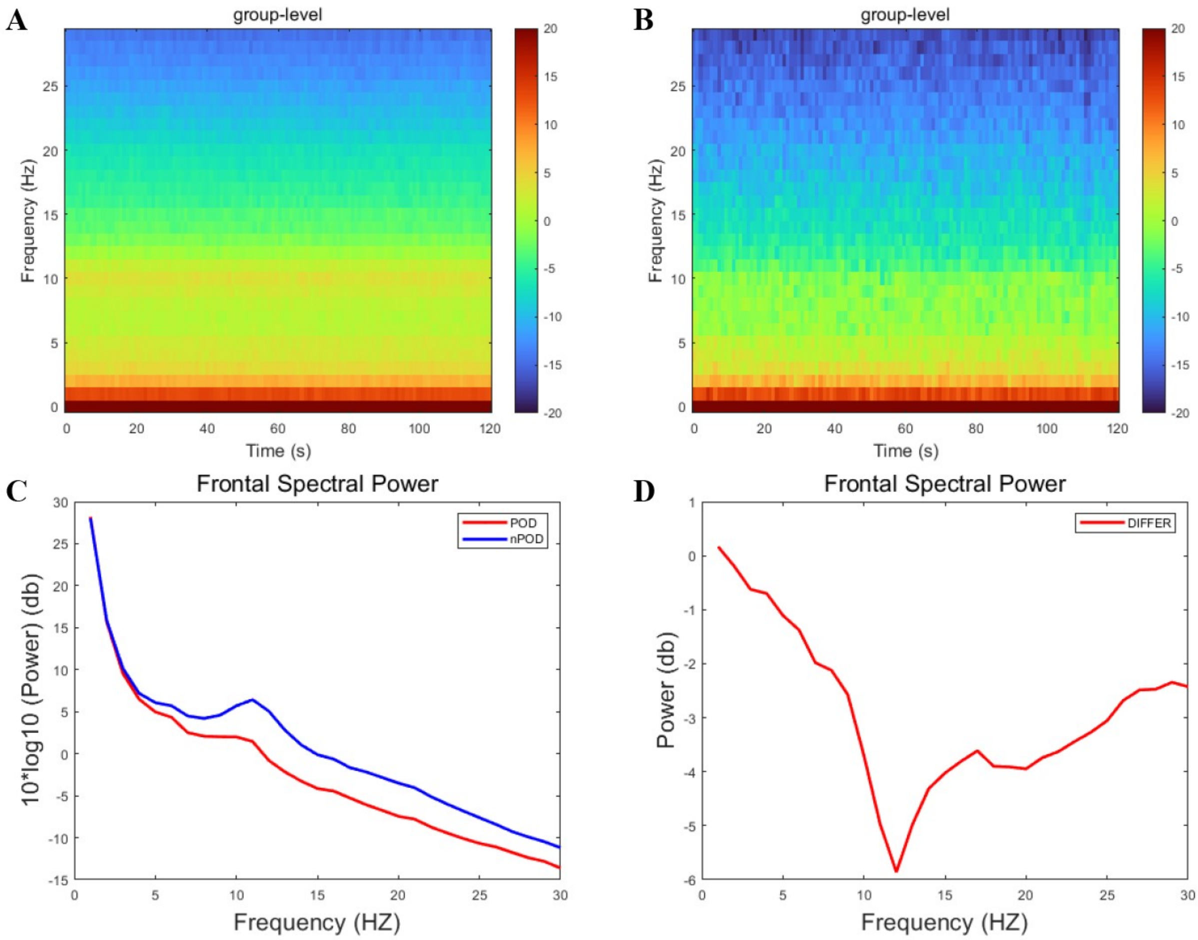

Fig. 3. Intraoperative frontal group spectrograms. Intraoperative frontal group spectrograms over a single EEG window of 120 ms comparing non-POD (n = 114) (A) with POD group (n = 11) (B). A custom-written Matlab code (R2022b, MathWorks Inc, Natick, MA, USA) was used to assess the statistical significance of the difference in power within different frequency bands. In the spectrograms, time (s) is arranged along the x-axis and frequencies (Hz) are arranged along the y-axis. (C) POD group compared to the non-POD group, (D) Subtraction of two groups of power. POD, postoperative delirium; non-POD, non-postoperative delirium. MATLAB (R2022b, MathWorks Inc, Natick, MA, USA) was used to create the image.

ysis revealed markedly reduced activity of low-frequency slow waves in the POD group compared to the non-POD group. The observed decrease in alpha power during general anesthesia may indicate a compromised brain function, potentially increasing the risk of POD. This finding aligns with previous research by Shao YR *et al*. [26], who found a strong correlation between low frontal alpha power and the "fragile brain" model under anesthesia. This model involves aspects of brain metabolism, cognition, and aging, suggesting that increased brain fragility correlates with a higher risk of postoperative cognitive dysfunction (POCD). This hypothesis suggests that low alpha power may serve as a common EEG indicator of fragile brain function. Corroborating evidence from additional study has demonstrated a significant correlation between low intraoperative alpha power and preoperative cognitive impairment [2]. Furthermore, Shao YR *et al*. [26] observed that patients who subsequently developed delirium postoperatively showed a greater decrease in alpha power during surgery. Therefore, we believe that low intraoperative alpha power is a characteristic EEG feature in patients with fragile brain function and is strongly associated with the occurrence of POD, making it a potential predictor of POD.

The statistical analysis in this study indicated that the POD group exhibited a longer duration and a higher percentage of BS during surgery compared to the non-POD group, although these differences were not statistically significant. BS may be caused by increased cortical excitability, depletion of extracellular calcium ions, and activity of adenosine triphosphate-gated potassium channels, leading to subsequent suppression [27]. This phenomenon is frequently observed in states of deep anesthesia and in the presence of neurological disorders. Several studies suggest that prolonged durations of BS may increase the incidence of POD

Table 3. Intraoperative EEG parameter of patients between non-POD and POD.

	Non-POD N = 114	POD N = 11	$t/Z/\chi^2$	p
Delta power (dB)	3.91 (2.29, 5.73)	2.66 (2.02, 5.59)	–1.242	0.214
Delta power			2.183	0.140
Low	41 (35.96%)	7 (63.64%)		
High	73 (64.04%)	4 (36.36%)		
Theta power (dB)	1.19 (0.72, 2.02)	0.77 (0.44, 1.01)	–2.105	0.035
Theta power			2.862	0.091
Low	47 (41.23%)	8 (72.73%)		
High	67 (58.77%)	3 (27.27%)		
Alpha power (dB)	1.24 (0.55, 2.57)	0.41 (0.25, 0.71)	–2.667	0.008
Alpha power			8.495	0.004
Low	37 (32.46%)	9 (81.82%)		
High	77 (67.54%)	2 (18.18%)		
Beta power (dB)	0.14 (0.08, 0.26)	0.06 (0.03, 0.09)	–3.349	$<$0.001
Beta power			11.257	0.001
Low	39 (34.21%)	10 (90.91%)		
High	75 (65.79%)	1 (9.09%)		
(delta+theta)/(alpha+beta)	4.04 (2.05, 6.37)	6.05 (3.74, 22.81)	–1.913	0.056
SEF_L (Hz)	12.59 ± 3.57	10.01 ± 3.63	2.278	0.024
SEF_L			4.251	0.039
Low	41 (35.96%)	8 (72.73%)		
High	73 (64.04%)	3 (27.27%)		
SEF_R (Hz)	12.31 ± 3.43	10.09 ± 3.74	2.031	0.044
SEF_R			2.377	0.123
Low	23 (20.18%)	5 (45.45%)		
High	91 (79.82%)	6 (54.55%)		
SEF (Hz)	12.45 ± 3.45	10.05 ± 3.66	2.184	0.031
SEF			2.862	0.091
Low	47 (41.23%)	8 (72.73%)		
High	67 (58.77%)	3 (27.27%)		
PSI	39.06 (33.21, 47.26)	46.27 (36.28, 47.90)	–0.886	0.376
Burst suppression duration (s)	9.40 (3.16, 42.84)	16.40 (5.70, 44.02)	–0.713	0.476
Burst suppression percent	0.12 (0.03, 0.52)	0.23 (0.08, 0.65)	–0.693	0.489

Continues variables are presented as mean ± SD or median (IQR). Counting data are presented as numbers and percentages. PSI, patient state index; SD, standard deviation; SEF, spectral edge frequency.

[27, 28, 29]. However, some researchers also suggest that pharmacologically induced BS can significantly decrease the cerebral metabolic rate of oxygen, potentially exerting neuroprotective effects [30]. There are also studies that have reported no clear relationship between BS and POD [31, 32]. The causal link between intraoperative BS and POD, as well as the validation of interventions aimed at reducing or eliminating BS to decrease the incidence of POD, still require further research.

Study utilizing frontal EEG-based BIS monitors to measure anesthetic depth measurement has demonstrated correlations between POD and low BIS values [33]. A previous review indicated that light anesthesia was associated with a decrease in POD in comparison with deep anesthesia [34]. In our study, although delirium patients exhibited a higher trend in PSI, there was no significant difference in PSI between the two groups. Additionally, there was no significant difference in the consumption of anesthetic drugs between the two groups. Therefore, we conclude that patients who developed delirium in this study did not undergo deeper anesthesia.

Multivariate logistic regression analysis indicated that a low preoperative MMSE score is an independent risk factor for POD. This finding suggests that patients with preexisting cognitive impairment are more likely to develop POD. A meta-analysis by Cao SJ *et al.* [35], which included one randomized controlled trial, two retrospective cohort studies, and 18 prospective cohort studies, found that patients with perioperative MMSE decline had higher rates of POD, in-hospital mortality, and one-year mortality. The study's

Table 4. Multivariable logistic regression analysis for POD.

Variables	Regression coefficient	SE	*p*	OR (95% CI)
Age (years)				
65–74			Reference	Reference
≥75	2.043	1.031	0.048	7.713 (1.022–58.204)
Alpha power				
High			Reference	Reference
Low	2.323	1.079	0.031	10.210 (1.233–84.568)
MMSE				
<25			Reference	Reference
25–30	–2.041	0.940	0.030	0.130 (0.021–0.820)
Anemia	1.892	0.921	0.040	6.636 (1.091–40.358)
Depression	2.311	1.165	0.047	10.089 (1.029–98.909)

CI, confidence index; OR, odds ratio; SE, standard error.

conclusions highlighted the value of MMSE in risk stratification and prognostic assessment of elderly surgical patients. Similarly, another study [36] also identified low MMSE scores as a consistent risk factor for increased POD and proposed its incorporation into a high-performing predictive model for screening out high-risk patients. However, Liu J *et al.* [37] reported no statistical difference in preoperative cognitive impairment as assessed by MMSE between the POD and non-POD groups. They suggested that educational level might confound MMSE scores, leading to significant bias.

Advanced age remains a significant predictor of POD, consistent with other reports. A systematic review and meta-analysis published in 2021 identified age as an independent predictor of POD following total hip and knee arthroplasty [38]. Travica N *et al.* [39] found a grade III association between preoperative age and an increased risk of POCD. The exact mechanisms linking advanced age and POD are not fully understood, but one theory suggests that aging increases the brain's vulnerability to stress [20, 40].

Additionally, perioperative anemia was found to be an independent risk factor for POD, consistent with previous studies [41, 42, 43]. The prevailing hypothesis posits that low Hb concentration reduces cerebral oxygen delivery, a key element in the pathophysiology of POD [44]. A retrospective study by Elsamadicy AA *et al.* [45] showed that lower preoperative Hb levels in elderly male patients undergoing spinal fusion surgery correlated with longer hospital stays, increased incidence of POD, and higher rates of non-incisional infections and hematoma formation. Similarly, a prospective observational study by Tahir M *et al.* [46] indicated that preoperative anemia could increase the risk of POD by nearly threefold. Conversely, a study by Myint PK *et al.* [47], which examined elderly patients admitted to five emergency surgical hospitals in the United Kingdom, found no association between anemia and POD after reviewing. The association between preoperative Hb levels and POD may be influenced by other factors such as age, comorbidities, type, and duration of surgery. Further research is needed to fully understand the relationship between preoperative Hb levels and POD and to identify additional potential risk factors contributing to POD development.

In this study, we also found that among delirium patients, a higher proportion of patients underwent arthroplasty instead of lumbar interbody fusion. A meta-analysis including 5364 patients receiving hip surgery suggested the accumulated incidence of delirium was 24.0% [48], while another meta-analysis involving 50 cohort studies reported the pooled incidence rate of POD was 7% following spine surgery [49]. It was demonstrated that the occurrence of POD varied across different types of operations, aligning with our findings.

This study has several limitations. First, as an observational study, it utilized clinical data from only one hospital with a small sample size, which may introduce selection bias. Second, the study lacks information on postoperative complications, which could be a significant factor influencing POD. Third, the study only analyzed intraoperative EEG components and did not account for relevant EEG changes before and after surgery, resulting in a lack of dynamic comparison. Fourth, the study only followed up POD data for 3 days, rather than longer periods such as 5 or 7 days, which may lead to an underestimation of POD incidence. Finally, larger multicenter studies are necessary to externally validate these findings and further optimize the results.

Conclusions

In elderly orthopedic patients, individuals who developed POD exhibited a reduced absolute alpha power on EEG during the operation. Intraoperative EEG monitoring emerges as a potentially valuable and straightforward tool for predicting the development of POD. Specifically, low intraoperative alpha power has been identified as an independent risk factor for POD. Additionally, preoperative cognitive impairment, advanced age, preoperative anemia, and preoperative depression have been described as independent predictors of POD occurrence.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding authors on reasonable request.

Author Contributions

YCD, XDQ, and JS conceptualized and designed the study, CLS and KKS collected and assembled data, QRL and XDQ analyzed and interpreted data. YCD and JS participated in drafting the manuscript, and all authors contributed to critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was approved by the Human Ethics Committee of Zhongda Hospital, Southeast University (Ethics Approval Number: 2022ZDSYLL210-P01). All participants provided written informed consent. This study was conducted in accordance with the principles outlines in the Declaration of Helsinki.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.62713/aic.3641.

References

[1] Ortman JM, Velkoff VA, Hogan H. An aging nation: the older population in the United States. 2014. Available at: https://searchworks.stanford.edu/view/13763375 (Accessed: 18 June 2024).

[2] Guessous K, Touchard C, Glezerson B, Levé C, Sabbagh D, Mebazaa A, *et al*. Intraoperative Electroencephalography Alpha-Band Power Is a Better Proxy for Preoperative Low MoCA Under Propofol Compared with Sevoflurane. Anesthesia and Analgesia. 2023; 137: 1084–1092.

[3] Chen LK. Urbanization and population aging: Converging trends of demographic transitions in modern world. Archives of Gerontology and Geriatrics. 2022; 101: 104709.

[4] Zhao J, Liang G, Hong K, Pan J, Luo M, Liu J, *et al*. Risk factors for postoperative delirium following total hip or knee arthroplasty: A meta-analysis. Frontiers in Psychology. 2022; 13: 993136.

[5] Fong TG, Inouye SK. The inter-relationship between delirium and dementia: the importance of delirium prevention. Nature Reviews. Neurology. 2022; 18: 579–596.

[6] Rasulo FA, Claassen J, Romagnoli S. Broad use of processed EEG: ready for prime time yet? Intensive Care Medicine. 2024; 50: 1350–1353.

[7] Bonatti G, Iannuzzi F, Amodio S, Mandelli M, Nogas S, Sottano M, *et al*. Neuromonitoring during general anesthesia in non-neurologic surgery. Best Practice & Research: Clinical Anaesthesiology. 2021; 35: 255–266.

[8] Vlisides PE, Li D, Maywood M, Zierau M, Lapointe AP, Brooks J, *et al*. Electroencephalographic Biomarkers, Cerebral Oximetry, and Postoperative Cognitive Function in Adult Noncardiac Surgical Patients: A Prospective Cohort Study. Anesthesiology. 2023; 139: 568–579.

[9] Sumner M, Deng C, Evered L, Frampton C, Leslie K, Short T, *et al*. Processed electroencephalography-guided general anaesthesia to reduce postoperative delirium: a systematic review and meta-analysis. British Journal of Anaesthesia. 2023; 130: e243–e253.

[10] Mohamad Faizal NS, Tan JK, Tan MM, Khoo CS, Sahibulddin SZ, Zolkafli N, *et al*. Electroencephalography as a tool for assessing delirium in hospitalized patients: A single-center tertiary hospital experience. Journal of Central Nervous System Disease. 2024; 16: 11795735241274203.

[11] Wiegand TLT, Rémi J, Dimitriadis K. Electroencephalography in delirium assessment: a scoping review. BMC Neurology. 2022; 22: 86.

[12] Khalifa C, Lenoir C, Robert A, Watremez C, Kahn D, Mastrobuoni S, *et al*. Intra-operative electroencephalogram frontal alpha-band spectral analysis and postoperative delirium in cardiac surgery: A prospective cohort study. European Journal of Anaesthesiology. 2023; 40: 777–787.

[13] McDevitt WM, Gul T, Jones TJ, Scholefield BR, Seri S, Drury NE. Perioperative electroencephalography in cardiac surgery with hypothermic circulatory arrest: a narrative review. Interactive Cardiovascular and Thoracic Surgery. 2022; 35: ivac198.

[14] Chun CT, Seward K, Patterson A, Melton A, MacDonald-Wicks L. Evaluation of Available Cognitive Tools Used to Measure Mild Cognitive Decline: A Scoping Review. Nutrients. 2021; 13: 3974.

[15] Johnsen NF, Jensen SN, Christensen KB, Pedersen SS, Helmark C, Zwisler AD, *et al*. Screening for anxiety and depression in clinical practice: translating scores from World Health Organization-5/Anxiety Symptom Scale-2/Major Depression Inventory-2 to Hospital Anxiety and Depression Scale. European Journal of Preventive Cardiology. 2023; 30: 1689–1701.

[16] Harrison JE, Weber S, Jakob R, Chute CG. ICD-11: an international classification of diseases for the twenty-first

century. BMC Medical Informatics and Decision Making. 2021; 21: 206.

[17] Pawar N, Barreto Chang OL. Burst Suppression During General Anesthesia and Postoperative Outcomes: Mini Review. Frontiers in Systems Neuroscience. 2022; 15: 767489.

[18] Ramaswamy R. The 3D-CAM 3-minute interview has 92% sensitivity and 95% specificity for detecting delirium in various care settings. Annals of Internal Medicine. 2023; 176: JC107.

[19] Miranda F, Gonzalez F, Plana MN, Zamora J, Quinn TJ, Seron P. Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) for the diagnosis of delirium in adults in critical care settings. The Cochrane Database of Systematic Reviews. 2023; 11: CD013126.

[20] Li YW, Li HJ, Li HJ, Zhao BJ, Guo XY, Feng Y, *et al*. Delirium in Older Patients after Combined Epidural-General Anesthesia or General Anesthesia for Major Surgery: A Randomized Trial. Anesthesiology. 2021; 135: 218–232.

[21] Koch S, Feinkohl I, Chakravarty S, Windmann V, Lichtner G, Pischon T, *et al*. Cognitive Impairment Is Associated with Absolute Intraoperative Frontal α-Band Power but Not with Baseline α-Band Power: A Pilot Study. Dementia and Geriatric Cognitive Disorders. 2019; 48: 83–92.

[22] Yang JS, Lee JJ, Kwon YS, Kim JH, Sohn JH. Preoperative Inflammatory Markers and the Risk of Postoperative Delirium in Patients Undergoing Lumbar Spinal Fusion Surgery. Journal of Clinical Medicine. 2022; 11: 4085.

[23] Kwon YS, Kim JH, Lee JJ, Seo EM. The Relationship between Perioperative Blood Transfusion and Postoperative Delirium in Patients Undergoing Spinal Fusion Surgery: Clinical Data Warehouse Analysis. Medicina (Kaunas, Lithuania). 2022; 58: 268.

[24] Wu J, Yin Y, Jin M, Li B. The risk factors for postoperative delirium in adult patients after hip fracture surgery: a systematic review and meta-analysis. International Journal of Geriatric Psychiatry. 2021; 36: 3–14.

[25] Li T, Li J, Yuan L, Wu J, Jiang C, Daniels J, *et al*. Effect of Regional vs General Anesthesia on Incidence of Postoperative Delirium in Older Patients Undergoing Hip Fracture Surgery: The RAGA Randomized Trial. JAMA. 2022; 327: 50–58.

[26] Shao YR, Kahali P, Houle TT, Deng H, Colvin C, Dickerson BC, *et al*. Low Frontal Alpha Power Is Associated with the Propensity for Burst Suppression: An Electroencephalogram Phenotype for a "Vulnerable Brain". Anesthesia and Analgesia. 2020; 131: 1529–1539.

[27] Lobo FA, Vacas S, Rossetti AO, Robba C, Taccone FS. Does electroencephalographic burst suppression still play a role in the perioperative setting? Best Practice & Research: Clinical Anaesthesiology. 2021; 35: 159–169.

[28] Ma O, Crepeau AZ, Dutta A, Bliss DW. Anticipating Postoperative Delirium During Burst Suppression Using Electroencephalography. IEEE Transactions on Biomedical Engineering. 2020; 67: 2659–2668.

[29] Tang CJ, Jin Z, Sands LP, Pleasants D, Tabatabai S, Hong Y, *et al*. ADAPT-2: A Randomized Clinical Trial to Reduce Intraoperative EEG Suppression in Older Surgical Patients Undergoing Major Noncardiac Surgery. Anesthesia and Analgesia. 2020; 131: 1228–1236.

[30] Liang TY, Peng SY, Ma M, Li HY, Wang Z, Chen G. Protective effects of sevoflurane in cerebral ischemia reperfusion injury: a narrative review. Medical Gas Research. 2021; 11: 152–154.

[31] Sieber FE, Neufeld KJ, Gottschalk A, Bigelow GE, Oh ES, Rosenberg PB, *et al*. Effect of Depth of Sedation in Older Patients Undergoing Hip Fracture Repair on Postoperative Delirium: The STRIDE Randomized Clinical Trial. JAMA Surgery. 2018; 153: 987–995.

[32] Koch S, Blankertz B, Windmann V, Spies C, Radtke FM, Röhr V. Desflurane is risk factor for postoperative delirium in older patients' independent from intraoperative burst suppression duration. Frontiers in Aging Neuroscience. 2023; 15: 1067268.

[33] Abbott TEF, Pearse RM. Depth of Anesthesia and Postoperative Delirium. JAMA. 2019; 321: 459–460.

[34] Li Y, Zhang B. Effects of anesthesia depth on postoperative cognitive function and inflammation: a systematic review and meta-analysis. Minerva Anestesiologica. 2020; 86: 965–973.

[35] Cao SJ, Chen D, Yang L, Zhu T. Effects of an abnormal mini-mental state examination score on postoperative outcomes in geriatric surgical patients: a meta-analysis. BMC Anesthesiology. 2019; 19: 74.

[36] Hu XY, Liu H, Zhao X, Sun X, Zhou J, Gao X, *et al*. Automated machine learning-based model predicts postoperative delirium using readily extractable perioperative collected electronic data. CNS Neuroscience & Therapeutics. 2022; 28: 608–618.

[37] Liu J, Li J, He J, Zhang H, Liu M, Rong J. The Age-adjusted Charlson Comorbidity Index predicts postoperative delirium in the elderly following thoracic and abdominal surgery: A prospective observational cohort study. Frontiers in Aging Neuroscience. 2022; 14: 979119.

[38] Zhou Q, Zhou X, Zhang Y, Hou M, Tian X, Yang H, *et al*. Predictors of postoperative delirium in elderly patients following total hip and knee arthroplasty: a systematic review and meta-analysis. BMC Musculoskeletal Disorders. 2021; 22: 945.

[39] Travica N, Lotfaliany M, Marriott A, Safavynia SA, Lane MM, Gray L, *et al*. Peri-Operative Risk Factors Associated with Post-Operative Cognitive Dysfunction (POCD): An Umbrella Review of Meta-Analyses of Observational Studies. Journal of Clinical Medicine. 2023; 12: 1610.

[40] Che J, Sun Y, Deng Y, Zhang J. Blood-brain barrier disruption: a culprit of cognitive decline? Fluids and Barriers of the CNS. 2024; 21: 63.

[41] Chou MY, Wang YC, Peng LN, Liang CK, Chu CS,

Liao MC, *et al*. Intraoperative blood transfusion predicts postoperative delirium among older patients undergoing elective orthopedic surgery: A prospective cohort study. International Journal of Geriatric Psychiatry. 2019; 34: 881–888.
[42] van der Zanden V, Beishuizen SJ, Scholtens RM, de Jonghe A, de Rooij SE, van Munster BC. The Effects of Blood Transfusion on Delirium Incidence. Journal of the American Medical Directors Association. 2016; 17: 748–753.
[43] Oldroyd C, Scholz AFM, Hinchliffe RJ, McCarthy K, Hewitt J, Quinn TJ. A systematic review and meta-analysis of factors for delirium in vascular surgical patients. Journal of Vascular Surgery. 2017; 66: 1269–1279.e9.
[44] Jin Z, Hu J, Ma D. Postoperative delirium: perioperative assessment, risk reduction, and management. British Journal of Anaesthesia. 2020; 125: 492–504.
[45] Elsamadicy AA, Adogwa O, Ongele M, Sergesketter AR, Tarnasky A, Lubkin DET, *et al*. Preoperative Hemoglobin Level is Associated with Increased Health Care Use After Elective Spinal Fusion (≥3 Levels) in Elderly Male Patients with Spine Deformity. World Neurosurgery. 2018; 112: e348–e354.
[46] Tahir M, Malik SS, Ahmed U, Kozdryk J, Naqvi SH, Malik A. Risk factors for onset of delirium after neck of femur fracture surgery: a prospective observational study. SICOT-J. 2018; 4: 27.
[47] Myint PK, Owen S, McCarthy K, Pearce L, Moug SJ, Stechman MJ, *et al*. Is anemia associated with cognitive impairment and delirium among older acute surgical patients? Geriatrics & Gerontology International. 2018; 18: 1025–1030.
[48] Yang Y, Zhao X, Dong T, Yang Z, Zhang Q, Zhang Y. Risk factors for postoperative delirium following hip fracture repair in elderly patients: a systematic review and meta-analysis. Aging Clinical and Experimental Research. 2017; 29: 115–126.
[49] Luo M, Wang D, Shi Y, Yi Q, Wang Z, Zhou B, *et al*. Risk factors of postoperative delirium following spine surgery: A meta-analysis of 50 cohort studies with 1.1 million participants. Heliyon. 2024; 10: e24967.