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ORIGINAL RESEARCH

Intraoperative Sleep Spindle Activity and Postoperative Sleep Disturbance in Elderly Patients Undergoing Orthopedic Surgery: A Prospective Cohort Study

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Purpose: This study aimed to investigate the relationship between intraoperative sleep spindle activity and postoperative sleep disturbance (PSD) in elderly orthopedic surgery patients.

Patients and Methods: In this prospective observational cohort study, we collected intraoperative electroencephalography (EEG) data from 212 elderly patients undergoing orthopedic surgery from May 2023 to December 2023. We used the Athens Insomnia Scale to assess sleep quality on postoperative day (POD) 1 and POD 3 and analyzed the correlation between intraoperative sleep spindle activity and PSD through logistic regression.

Results: The incidence of PSD was 65.6% on POD 1 and 41.9% on POD 3. On the first day, there were no significant differences in intraoperative sleep spindle characteristics between PSD and non-postoperative sleep disturbance (non-PSD) patients. However, by the third day, PSD patients showed lower sigma power compared to non-PSD patients, as well as lower spindle density in the bilateral frontopolar (Fp1/Fp2) and bilateral temporal (F7/F8) channels, with shorter average spindle duration ($P < 0.05$). Multivariate logistic regression analysis suggested that the average spindle density in F7/F8 channels (OR 0.543, 95% CI 0.375–0.786; $P = 0.001$) was an independent risk factor for PSD on POD 3. Furthermore, Mini-Mental State Examination (MMSE) could independently predict PSD on POD 1 (OR 0.806, 95% CI 0.656–0.991; $P = 0.041$) and POD 3 (OR 0.701, 95% CI 0.562–0.875; $P = 0.002$). Pain on movement and at rest were independently associated with PSD on POD 1 (OR 1.480, 95% CI 1.200–1.824; $P < 0.001$) and POD 3 (OR 1.848, 95% CI 1.166–2.927; $P = 0.009$), respectively.

Conclusion: Intraoperative mean spindle density in the F7/F8 channels was an independent risk factor for PSD on POD 3 in elderly patients undergoing orthopedic surgery. MMSE and postoperative pain also independently increased the risk of PSD.

Keywords: postoperative sleep disturbance, sleep spindle, electroencephalography spectrum, elderly patients, orthopedic surgery

Introduction

Postoperative sleep disturbance (PSD) refers to patients' sleep structure and quality changes in the early postoperative period. It is a common postoperative complication[1,2] with clinical manifestations such as sleep deprivation, circadian rhythm disruption, and abnormal sleep architecture, with an incidence rate ranging from 15% to 72%.[3,4] It is currently believed that one of the primary mechanisms leading to PSD is the complex stress response caused by factors such as trauma,[5] pain stimulation,[3] inflammation, and blood loss during surgery,[5] which persists postoperatively.[6] This results in autonomic nervous system dysfunction, such as the sustained activation of locus coeruleus noradrenergic neurons,[7,8] excitation of arousal-promoting neural pathways, and a lowered arousal threshold,[9] making postoperative sleep more susceptible to external disturbances such as ward noise.[10] In addition, PSD can be influenced by various factors including

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anxiety, depression, pain, pre-existing sleep disorders, type and complexity of surgery, anesthesia, and cognitive impairment, all of which can interfere with restorative sleep during recovery.

With the increasingly severe aging trend in China, the population over 65 years old exceeded 200 million by the end of 2022, accounting for about 14.2% of the total population.[11] Due to the decline in physiological functions across various systems,[12,13] elderly patients are a high-risk group for PSD,[14,15] which is often accompanied by neurocognitive abnormalities.[16] Orthopedic surgeries constitute a large and growing proportion of procedures performed on elderly patients, driven by the increasing incidence of degenerative musculoskeletal diseases and age-related fragility in aging populations.[12,15] These surgeries often present unique postoperative challenges, including significant trauma, heightened pain,[3] mobility restrictions, and enforced postures,[17] which can significantly affect sleep quality and cognitive function, making PSD particularly prevalent among orthopedic surgery patients.[18] PSD can increase the risk of complications related to respiration, circulation, and neurocognition in surgical patients,[19] worsening their prognosis, and is even associated with increased postoperative mortality in elderly patients.[19] Therefore, under the concept of enhanced recovery after surgery,[20] perioperative sleep issues in elderly patients have garnered significant attention.[21] While there have been studies focused on developing predictive models and other prediction indicators for PSD risk in adults,[22] including the elderly, there remains a need for more simple and universally reliable biomarkers tailored specifically for elderly patients.

Sleep spindles, also known as sigma rhythms, are defined by the American Academy of Sleep Medicine as brain waves with a frequency of 11–16 hz, a duration of ≥0.5 seconds (usually 0.5–2 seconds), with maximum amplitude at the center, resembling a spindle shape.[23] The density of sleep spindles is positively correlated with the duration of N2 sleep in humans[24] and is characteristic of this stage, having a certain genetic trait,[23] associated with anxiety and depression as well as other psychiatric disorders.[25] Current research suggests that the main functions of sleep spindles include protecting sleep and reflecting neurocognitive functions.[23] Anesthesia and sleep share common molecular targets and neural circuits,[26] and they are two neurophysiological states that induce EEG spindles. Recent studies on the sleep-protective role of sleep spindles mainly focus on the physiological sleep state,[23,27] while the correlation between sleep spindles under anesthesia and PSD remains unclear.

Thus, this study aims to explore the correlation between intraoperative sleep spindles and PSD in elderly patients undergoing orthopedic surgeries, hoping to reduce the incidence of PSD by increasing intraoperative sleep spindle activities in the future.

Materials and Methods

This single-center, prospective cohort study was approved by the Human Ethics Committee of Zhongda Hospital, Affiliated with Southeast University (Ethics number: 2021ZDSYLL354-P01) and registered in the Chinese Clinical Trial Registry (ChiCTR2300069548), complied with the Helsinki Declaration.

Participants

The study enrolled patients who underwent elective orthopedic surgery under general anesthesia at Zhongda Hospital, Southeast University, from May 2023 to December 2023. Inclusion criteria were: (1) age ≥65; (2) ASA II–III; (3) planned orthopedic surgery of grade III or IV (including spine, femur, and large joints) under general anesthesia. Exclusion criteria included: (1) pre-existing diagnosed sleep-related disorders (including obstructive sleep apnea); (2) alcohol or psychiatric drug dependence or long-term use of antipsychotic drugs; (3) severe preoperative neurocognitive impairment; (4) blindness, deafness, inability to speak Chinese, or other communication barriers; (5) severe organ dysfunction (including heart, lung, liver, and kidney) or multiple organ dysfunction syndrome; (6) unplanned transferred to the ICU postoperatively or unplanned secondary surgery during hospitalization. Written informed consent was obtained from all participants.

The incidence of PSD in elderly patients undergoing non-cardiac general anesthesia surgery was supposed to be approximately 42%, as reported.[4,28] Based on the preliminary observations of our research group, the expected odds ratio (OR) for PSD in relation to sleep spindle activity was 0.5. Using the Logistic Regression sample size calculation module

in the PASS software, with $\alpha = 0.05$, $\beta = 0.2$, and the R-squared value at 0.6, it can be determined that a minimum of 170 cases must be included. If a sample dropout rate of 20% is accounted for, at least 213 cases would be required.

Anesthesia and Perioperative Care

Intraoperative monitoring included electrocardiography, pulse oximetry, invasive arterial blood pressure, end-tidal carbon dioxide concentration, electroencephalography (EEG), and temperature. Anesthesia was induced with midazolam, sufentanil, propofol, cisatracurium, or rocuronium for general anesthesia.

The intraoperative anesthesia maintenance strategies included sevoflurane inhalation, total intravenous maintenance with propofol, and a combined approach using both propofol and sevoflurane. Drug doses were adjusted based on EEG monitoring to maintain an appropriate depth of anesthesia, with the patient state index (PSI) between 25 and 50 intraoperatively. Every 40–60 minutes, a third of the induction dose of muscle relaxant was supplemented. Fluid infusion and blood transfusion were administered based on hemodynamic monitoring and arterial blood gas analysis. Vasopressor drugs were administered to maintain the systolic blood pressure within 20% of the baseline value.

After the surgery, patients were transferred to the post-anesthesia care unit, where neostigmine or sugammadex was routinely administered to antagonize the effect of muscle relaxants in the absence of contraindications. Nerve blocks or opioid analgesics may be administered as warranted by the level of pain following extubation.

EEG Monitoring and Data Processing

The intraoperative frontal lobe EEG data were recorded at a rate of 178 hz and obtained using the SedLine system (Masimo, Irvine, CA, USA), which includes four active channels (Fp1, Fp2, F7, and F8) with the ground electrode at Fpz and the reference electrode at Afz. Before anesthesia induction, the forehead skin was prepared with 70% alcohol wipes to decrease impedance within 8 kOhm. After the surgery, the original EEG data, real-time PSI, burst suppression (BS) duration, and other information will be extracted from the SedLine monitor.

The EEG data were processed using custom MATLAB R2022b software with EEGLAB (v2022.1) from the University of California, San Diego, and the Chronux toolbox. EEG signals tend toward stability after achieving optimal muscle relaxation, and no interfering signals such as electrooculogram or electromyogram were present. Interferences and undesirable segments attributed to electrocautery or changes in position were identified and eliminated through manual visual inspection of the intraoperative EEG recordings. We analyzed the EEG spectrogram with the following multitaper parameter: window length (T = 4 s) with an overlap of 1.9 s, time-bandwidth product (TW = 3), and number of tapers (K = 5). The energy distribution of sleep spindles in the 11–16 hz frequency range (ie, the sigma band) was analyzed to assess the overall strength of spindle activity at a macroscopic level. We averaged and weighted the signals from the Fp1, Fp2, F7, and F8 channels and calculated the power spectral density of sigma (11–16 hz) activity. In addition to sigma activity, we also analyzed the spectral power of delta (1–4 hz), theta (4–8 hz), alpha (8–12 hz), and beta (12–30 hz) bands, as these frequency ranges have been shown to play a critical role in sleep regulation.[29,30] Relative power was calculated as the ratio of the power within a specific frequency band to the total power across all frequency bands, expressed as a percentage.

Sleep spindles were identified using the A7 algorithm to detect the number of discrete spindles referring to previous research.[31] Extracted parameters included the spindle density of each channel (Fp1/Fp2/F7/F8), the average spindle density in the bilateral prefrontal regions (Fp1/Fp2) and temporal regions (F7/F8), the total spindle density across four channels, and the mean duration of the spindle. Other EEG features, including PSI, BS duration, and the percentage of BS, were also calculated.[32]

Data Collection and Measurements

Baseline data were collected, including demographic characteristics, frailty status, preoperative sleep quality, preoperative cognitive and psychological function, and pain scores. Frailty status was assessed using the Fatigue, Resistance, Ambulation, Illness, and Loss of Weight scale (scoring range from 0 to 5, with a score of ≥ 3 indicating frailty). The Pittsburgh Sleep Quality Index was used to evaluate recent one-month preoperative sleep (scoring range from 0 to 21, with higher scores denoting poorer sleep quality). Preoperative cognitive

function was assessed using the Mini-Mental State Examination (MMSE) scale (scoring range from 0 to 30, with higher scores indicating better cognitive function). The Hospital Anxiety and Depression scale was applied for evaluating anxiety and depression symptoms (scoring range from 0 to 21, with higher scores indicating more severe symptoms).

Intraoperative data were extracted from the hospital information system, including the type and timing of surgery, duration of surgery, duration of anesthesia, and anesthesia maintenance protocol.

The primary outcome was the incidence of PSD, which was assessed using the Athens Insomnia Scale (AIS).[33,34] This self-rated psychometric scale comprised 8 elements, covering aspects such as time taken to fall asleep, waking up during the night, early morning awakenings, sleep duration, sleep quality, daytime mood, daytime functioning, and daytime sleepiness. Each element was rated on a scale from 0 to 3, indicating the absence to severity of the symptom. PSD was defined as having an AIS score of 7 or higher, while non-PSD was defined as an AIS score of less than 7, assessed on postoperative day (POD) 1 and POD 3, which have been widely used in previous studies[4,35] to capture both the acute and short-term effects on sleep after surgery. Patients were categorized into the PSD and non-PSD groups based on the occurrence of sleep disturbances in the afternoon on POD 1 and POD 3. Patients were additionally classified into four groups based on their PSD status on POD 1 and POD 3 for exploratory analysis: (1) Group 1: patients without PSD on either POD 1 or POD 3, (2) Group 2: patients with PSD on both POD 1 and POD 3, (3) Group 3: patients with PSD only on POD 1, and (4) Group 4: patients with PSD only on POD 3. Postoperative delirium was assessed twice a day, both in the morning and the afternoon,[36] with the Chinese version of the 3-Minute Diagnostic Interview for Confusion Assessment Method scale, to capture potential fluctuations in the patient's cognitive state during key periods of the day. While more frequent assessments could theoretically detect additional fluctuations, we chose twice-daily assessments as they align with current clinical practice and reduce patient and staff burden.[37] If the patient was experiencing a delirium episode and was unable to complete the AIS, we would rely on information from the patient's caregiver to complete the evaluation. Meanwhile, patients were asked to rank their pain levels at rest and on movement of the last night using the Numeric Rating Scale (NRS) and recall the worst pain they experienced in the past day. Pain assessments were conducted in the afternoon on POD 1 and POD 3 for all patients. If the patient was delirious at the time of assessment, we would consult the nursing record sheet and record the patient's highest pain score within the past day. All the above scale assessments were completed by the same physician who underwent standardized training and was not involved in the experiment.

Statistical Analysis

Statistical analysis was performed using SPSS 26.0 software (IBM Corporation, Somers, NY, USA). For normally distributed continuous data, the mean and standard deviation were denoted as mean ± standard deviation, while non-normally distributed continuous data was represented by the median and the interquartile range, and categorical data was expressed as percentages (%). Continuous variables were assessed using the *t*-test or Mann–Whitney *U*-test, and comparisons of categorical variables were conducted using Fisher's exact test or the chi-square test between two groups. While ANOVA and the Kruskal–Wallis test were used for continuous variables for comparison among multiple groups. To control for the risk of Type I error due to multiple comparisons, we applied the Bonferroni correction. To account for multiple comparisons across frequency bands, we applied the Benjamini–Hochberg (BH) correction method to control the false discovery rate (FDR).[38] To identify risk factors for PSD, we used multivariate logistic regression analysis. Factors included in the model were based on their clinical relevance and evidence from prior studies. These factors included age, gender, BMI, type of surgery, anesthesia type, postoperative pain, preoperative anxiety and depression, ICU admission, and postoperative delirium. Additionally, variables that were statistically different in univariate analysis were also included in the regression model. A forward stepwise logistic regression approach was employed. Before conducting the regression analysis, multicollinearity diagnostics would be performed, whereby a variance inflation factor ≥10 would be considered indicative of collinearity, prompting the removal of the correlated indicators. A significance level of $P < 0.05$ would be considered statistically significant.

Results

Characteristics of Participants

Out of 280 initially assessed patients, 14 had their surgeries canceled, 13 lost raw EEG data, 8 were changed to regional block anesthesia, 26 were unplanned transferred to the ICU, and 7 were lost to follow-up. Ultimately, 212 patients were included in the study, with 139 in the PSD group and 73 in the non-PSD group on POD 1. On POD 3, 89 patients were classified into the PSD group, whereas 123 patients were allocated to the non-PSD group. The incidence of PSD was 65.6% on POD 1 and 41.9% on POD 3, respectively (Figure 1).

On POD 1, there were no statistically significant differences in the overall baseline characteristics between the two groups ($P > 0.05$). However, compared to the non-PSD group, the proportion of females was greater (66.9% vs 50.7%; $P = 0.021$), and the MMSE scores were lower (27.67 ± 1.74 vs 28.27 ± 1.51; $P = 0.014$) in the PSD group. Regarding the type of surgery, there was a higher proportion of spinal surgeries in the PSD group (73.4% vs 52.1%; $P = 0.005$). Moreover, compared to the non-PSD group, the PSD group exhibited higher pain scores at rest [2 (1, 2) vs 1 (0, 2); $P < 0.001$] and on movement [5 (3, 6) vs 3 (3,4); $P < 0.001$].

On POD 3, the two groups had no statistically significant differences in baseline characteristics ($P > 0.05$). However, compared to the non-PSD group, the PSD group had a higher proportion of patients classified as ASA III (37.1% vs 22.0%; $P = 0.016$) and FRAIL (unfrail/pre-frail/frail 33.7%/29.3%/37.1% vs 56.1%/24.4%/19.5%; $P = 0.003$), as well as a higher prevalence of preoperative hypertension (74.2% vs 57.7%; $P = 0.014$) and central nervous system disorders (41.6% vs 25.2%; $P = 0.012$). Patients in the PSD group were more likely to receive total intravenous anesthesia (74.2% vs 52.0%; $P < 0.005$) and a higher percentage of BS [0.281 (0.025, 1.166) vs 0.081 (0, 0.821); $P = 0.038$]. In addition, the PSD group also had higher pain scores on movement [2 (2, 3) vs 2 (1, 3); $P = 0.002$] (Table 1, Table 2).

Additionally, in Supplementary Table 1, we further compared baseline, intraoperative, and postoperative data among the four groups. Variables including age, gender, ASA, hypertension, anemia, FRAIL sore, MMSE score, surgery type, anesthesia maintenance scheme, and pain score at rest and on movement on POD 1 and POD 3 were statistically different among Groups 1 to 4.

Sigma Activity and Spectral Analysis

On POD 1, there were no significant differences in any frequency bands, including the sigma band, between the PSD and non-PSD groups ($P > 0.05$).

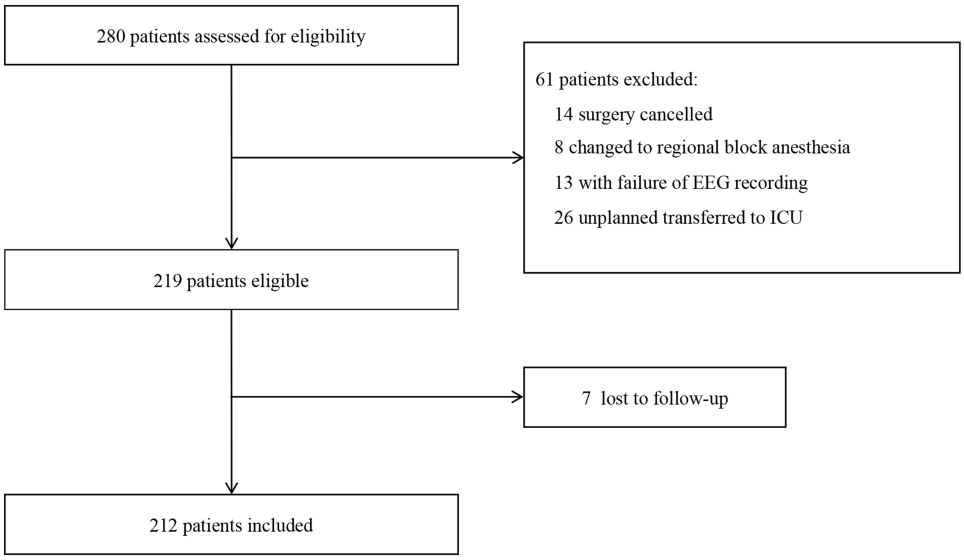

Figure 1 Flow chart showing the study design and subjects.
Abbreviations: EEG, Electroencephalogram; ICU, Intensive Care Unit.

Table 1 Characteristics of Participants

	non-PSD on POD 1 (n = 73)	PSD on POD 1 (n = 139)	*P value*	non-PSD on POD 3 (n = 123)	PSD on POD 3 (n = 89)	*P value*
Age, years	72 (68, 76)	72 (69.5, 76)	0.798	72 (69, 76)	72 (70, 77)	0.146
Gender, female, n (%)	37 (50.7%)	93 (66.9%)	0.021	70 (56.9%)	60 (67.4%)	0.121
BMI, kg/m^2	24.32 ± 3.16	24.48 ± 4.36	0.785	24.32 ± 3.83	24.58 ± 4.20	0.650
Education, n (%)						
Primary	30 (41.1%)	76 (54.7%)	0.131	59 (48.0%)	47 (52.8%)	0.182
Secondary	37 (50.7%)	57 (41.0%)		54 (43.9%)	40 (44.9%)	
Tertiary	6 (8.2%)	6 (4.3%)		10 (8.1%)	2 (2.3%)	
Smoking, n (%)	24 (32.9%)	37 (26.6%)	0.339	41 (33.3%)	20 (22.5%)	0.085
Drinking, n (%)	24 (32.9%)	32 (23.0%)	0.122	37 (30.1%)	19 (21.3%)	0.155
ASA, n (%)			0.667			0.016
II	51 (69.9%)	101 (72.7%)		96 (78.0%)	56 (62.9%)	
III	22 (30.1%)	38 (27.3%)		27 (22.0%)	33 (37.1%)	
Comorbidities, n (%)						
Hypertension	49 (67.1%)	88 (63.3%)	0.581	71 (57.7%)	66 (74.2%)	0.014
Coronary disease	13 (17.8%)	19 (13.7%)	0.424	16 (13.0%)	16 (18.0%)	0.319
Diabetes	14 (19.2%)	32 (23.0%)	0.519	25 (20.3%)	21 (23.6%)	0.569
Respiratory disease	7 (9.6%)	11 (7.9%)	0.678	12 (9.8%)	6 (6.7%)	0.437
CNS disease	24 (32.9%)	44 (31.7%)	0.856	31 (25.2%)	37 (41.6%)	0.012
Anemia	14 (19.2%)	22 (15.8%)	0.537	16 (13.0%)	20 (22.5%)	0.070
Liver disease	0 (0.0%)	7 (5.0%)	0.051	4 (3.3%)	3 (3.4%)	1.000
Kidney disease	1 (1.4%)	0 (0.0%)	0.167	0 (0.0%)	1 (1.1%)	0.871
FRAIL score			0.803			0.003
Unfrail	34 (46.6%)	65 (46.8%)		69 (56.1%)	30 (33.7%)	
Pre-frail	21 (28.8%)	35 (25.2%)		30 (24.4%)	26 (29.3%)	
Frail	18 (24.7%)	39 (28.1%		24 (19.5%)	33 (37.1%)	
MMSE score	28.27 ± 1.51	27.67 ± 1.74	0.014	28.21 ± 1.35	27.42 ± 1.98	0.002
HADS-anxiety score	4 (3, 6)	4 (3, 7)	0.588	4 (3, 5)	5 (3, 8)	0.034
HADS-depression score	3 (3, 5)	4 (3, 5)	0.404	3 (3, 5)	4 (3, 6)	0.319
Preoperative PSQI score	2 (0, 3)	2 (0, 4)	0.626	2 (0, 4)	2 (0, 4)	0.444
Preoperative pain score	3 (2, 3)	2 (2, 3)	0.673	2 (2, 3)	3 (2, 3)	0.257

Notes: Values are expressed as mean ± standard deviation, median (interquartile range), or number (percentage).
Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CNS, central nervous system; FRAIL, Fatigue Resistance, Ambulation, Illness, Loss of weight; HADS, Hospital Anxiety and Depression Scale; MMSE, Mini-Mental State Examination; POD, postoperative day; PSD, postoperative sleep disturbance; PSQI, Pittsburgh Sleep Quality Index.

On POD 3, the absolute sigma power [0.39 (0.24, 0.91) vs 0.58 (0.36, 1.09); $P < 0.001$, adjusted $P = 0.004$] and relative sigma power [5.56 (3.44, 8.55) vs 8.19 (5.81, 12.93); $P < 0.001$, adjusted $P = 0.004$] was declined in the PSD group compared to the non-PSD group. There was a significant decline of power spectral density in the frequency bands including alpha [0.88 (0.49, 1.56) vs 1.23 (0.65, 1.97); $P = 0.004$, adjusted $P = 0.007$] and beta [0.11 (0.06, 0.27) vs 0.15 (0.09, 0.27); $P = 0.010$, adjusted $P = 0.016$] among patients in the PSD group than in the non-PSD group. As for relative power, patients in the PSD group showed higher relative power of low-frequency activity (delta) (66.58 ± 13.77 vs 61.00 ± 11.95; $P = 0.002$, adjusted $P = 0.004$), lower power of alpha activities [12.06 (7.48, 18.10) vs 16.58 (12.08, 24.19); $P = 0.002$, adjusted $P = 0.004$], and lower power of high-frequency activity (beta) [1.73 (1.13, 2.62) vs 2.24 (1.53, 3.42); $P < 0.001$, adjusted $P = 0.004$] compared to the non-PSD group. (Table 3) As is shown in Supplementary Table 2, the absolute alpha, sigma, and beta power, as well as relative power across all bands, were statistically different when compared among multiple groups. Further pairwise comparison showed that Group 4 was significantly different from the other three groups.

Table 2 Intraoperative and Postoperative Data

	non-PSD on POD 1 (n = 73)	PSD on POD 1 (n = 139)	*P value*	non-PSD on POD 3 (n = 123)	PSD on POD 3 (n = 89)	*P value*
Surgery duration, min	130 (105, 160)	135 (105, 175)	0.251	135 (110, 170)	130 (100, 172)	0.385
Anesthesia duration, min	155 (135, 190)	165 (135, 205)	0.142	165 (140, 195)	155 (130, 205)	0.587
Timing of surgery, n (%)			0.390			0.191
Daytime	66 (90.4%)	120 (86.3%)		111 (90.2%)	75 (84.3%)	
Nighttime	7 (9.6%)	19 (13.7%)		12 (9.8%)	14 (15.7%)	
Surgery type, n (%)			0.005			0.368
Spine	38 (52.1%)	102 (73.4%)		82 (66.7%)	58 (65.2%)	
Hip/knee	24 (32.8%)	22 (15.8%)		29 (23.6%)	17 (19.1%)	
Others	11 (15.1%)	15 (10.7%)		12 (9.7%)	14 (15.7%)	
Anesthesia maintenance scheme, n (%)			0.332			0.005
Sevoflurane	6 (8.2%)	14 (10.1%)		15 (12.2%)	5 (5.6%)	
Propofol	41 (56.2%)	89 (64.0%)		64 (52.0%)	66 (74.2%)	
Sevoflurane + Propofol	26 (35.6%)	36 (25.9%)		44 (35.8%)	18 (20.2%)	
PSI	37.54 (32.18, 43.47)	35.35 (29.62, 42.22)	0.102	35.39 (30.38, 40.14)	35.59 (29.62, 42.63)	0.467
BS duration, min	13.54 (1.59, 52.00)	13.04 (1.08, 91.40)	0.572	7.14 (0.00, 72.76)	14.82 (2.19, 87.29)	0.055
BS percent, %	0.14 (0.01, 0.82)	0.14 (0.01, 1.10)	0.731	0.08 (0.00, 0.82)	0.28 (0.03, 1.17)	0.038
Pain score at rest	1 (0, 2)	2 (1, 2)	< 0.001	0 (0, 1)	0 (0, 1)	< 0.001
Pain score on movement	3 (3, 4)	5 (3, 6)	< 0.001	2 (1, 3)	2 (2, 3)	0.002
Postoperative delirium, n (%)	4 (5.5%)	11 (7.9%)	0.511	1 (0.8%)	9 (10.1%)	0.005

Notes: Values are expressed as median (interquartile range) or number (percentage).
Abbreviations: BS, burst suppression; POD, postoperative day; PSD, postoperative sleep disturbance; PSI, patient state index.

Table 3 Intraoperative Frontal Power Spectrum

	non-PSD on POD 1 (n = 73)	PSD on POD 1 (n = 139)	*P value*	Adjusted *P* value	non-PSD on POD 3 (n = 123)	PSD on POD 3 (n = 89)	*P value*	Adjusted *P* value
Absolute power, dB								
Total power	6.53 (4.30, 8.71)	7.23 (4.40, 10.51)	0.210	0.459	7.04 (4.45, 11.10)	7.28 (4.34, 9.93)	0.667	0.667
Delta (1–4 hz)	4.17 (2.56, 5.60)	4.15 (2.87, 6.34)	0.389	0.496	4.11 (2.58, 6.17)	4.41 (3.00, 6.21)	0.614	0.667
Theta (4–8 hz)	1.04 (0.62, 1.56)	1.23 (0.710, 1.92)	0.117	0.322	1.207 (0.74, 1.84)	1.17 (0.68, 1.92)	0.383	0.527
Alpha (8–12 hz)	0.69 (0.39, 1.51)	0.99 (0.55, 1.91)	0.063	0.231	1.23 (0.65, 1.97)	0.88 (0.49, 1.56)	0.004	0.007
Sigma (11–16 hz)	0.38 (0.2, 0.71)	0.473 (0.29, 1.04)	0.061	0.231	0.58 (0.36, 1.09)	0.39 (0.24, 0.91)	< 0.001	0.004
Beta (12–30 hz)	0.1 (0.06, 0.21)	0.15 (0.08, 0.27)	0.062	0.231	0.15 (0.09, 0.27)	0.11 (0.06, 0.27)	0.010	0.016
Relative power, %								
Rdelta	71.42 (62.16, 75.91)	68.36 (59.92, 74.62)	0.289	0.459	61.00 ± 11.95	66.58 ± 13.77	0.002	0.004
Rtheta	15.45 (12.81, 17.70)	15.91 (13.28, 18.73)	0.292	0.459	17.69 ± 3.92	17.18 ± 5.84	0.475	0.581
Ralpha	11.43 (7.67, 18.64)	13.23 (7.92, 19.24)	0.406	0.496	16.58 (12.08, 24.19)	12.06 (7.48, 18.10)	0.002	0.004
Rsigma	5.52 (3.43, 9.34)	5.87 (3.86, 9.88)	0.477	0.525	8.19 (5.81, 12.93)	5.56 (3.44, 8.55)	< 0.001	0.004
Rbeta	1.65 (1.06, 2.42)	1.88 (1.16, 2.54)	0.585	0.585	2.24 (1.53, 3.42)	1.73 (1.13, 2.62)	< 0.001	0.004

Notes: Values are expressed as mean ± standard deviation or median (interquartile range). P values were adjusted with the Benjamini–Hochberg (BH) correction method.
Abbreviations: POD, postoperative day; PSD, postoperative sleep disturbance.

Figure 2 illustrated the comparison of frontal spectral power in the frequency domain between the non-PSD group and the PSD group. Notably, no significant inter-group differences were found in terms of power spectral density of all frequency bands on POD 1 (Figure 2a). Additionally, Figure 2b demonstrated significantly lower power in the alpha (8–12 hz), sigma (11–16 hz), and beta (12–30 hz) frequency bands in the PSD group on POD 3.

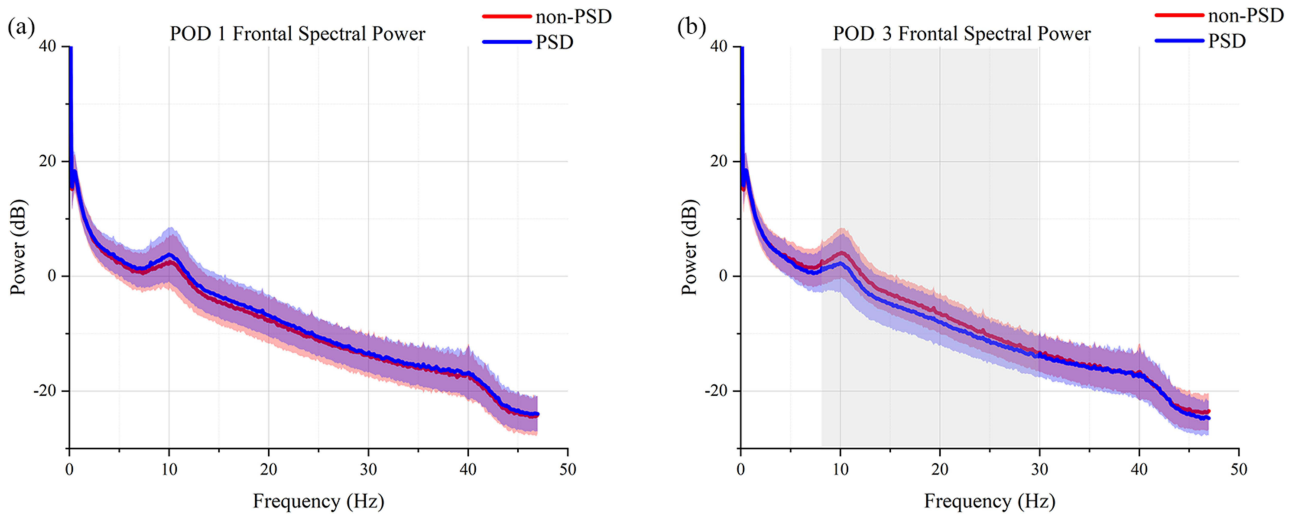

Figure 2 Intraoperative frontal power spectrum. (**a**) Comparison of frontal spectral power (dB) in the frequency domain between the non-PSD group (red) and PSD group (blue) on POD 1. (**b**) Comparison of frontal spectral power (dB) in the frequency domain between the non-PSD group (red) and PSD group (blue) on POD 3. **Abbreviations**: CI, confidence interval; POD, postoperative day; PSD, postoperative sleep disturbance.

Intraoperative Sleep Spindle Activity

No significant differences were observed in sleep spindle activity between the two groups on POD 1 ($P > 0.05$). When it comes to POD 3, the PSD group exhibited a lower average spindle density in bilateral frontopolar channels (Fp1/Fp2) [0.566 (0.000, 0.667) vs 0.623 (0.537, 0.721); $P = 0.005$] and bilateral temporal channels (F7/F8) [0.173 (0.016, 1.149) vs 0.889 (0.287, 1.913); $P < 0.001$]. Additionally, the average spindle duration was significantly shorter in the PSD group [0.683 (0.631, 0.757) vs 0.716 (0.671, 0.772); $P = 0.043$] (Table 4).

Supplementary Table 2 also compared sleep spindle activity for multiple comparisons and found that all sleep spindle densities were different among the 4 groups. Pairwise comparisons revealed that the differences were mainly between Group 4 and the other three groups.

Risk Factors for PSD

Multivariable logistic regression analysis showed that female (OR 2.032, 95% CI 1.065–3.879; $P = 0.032$), MMSE (OR 0.806, 95% CI 0.656–0.991; $P = 0.041$), spinal surgeries (OR 2.947, 95% CI 1.378–6.303; $P = 0.005$), and pain on movement (OR 1.480, 95% CI 1.200–1.824; $P < 0.001$) were independent risk factors for PSD on POD 1 (Table 5).

Table 4 Comparison of Intraoperative Discrete Sleep Spindle Activity

	non-PSD on POD 1 (n = 73)	PSD on POD 1 (n = 139)	*P value*	non-PSD on POD 3 (n = 123)	PSD on POD 3 (n = 89)	*P value*
Fp1 density	0.012 (0.000, 0.149)	0.026 (0.000, 0.258)	0.185	0.036 (0.005, 0.317)	0.011 (0.000, 0.135)	0.008
Fp2 density	0.016 (0.000, 0.172)	0.026 (0.000, 0.390)	0.207	0.064 (0.000, 0.430)	0.006 (0.000, 0.116)	0.002
F7 density	0.412 (0.041, 1.565)	0.641 (0.099, 1.808)	0.225	0.803 (0.251, 1.872)	0.138 (0.011, 1.101)	< 0.001
F8 density	0.523 (0.045, 1.408)	0.603 (0.125, 1.874)	0.185	0.971 (0.321, 1.929)	0.178 (0.020, 1.046)	< 0.001
Fp1/Fp2 mean density	0.574 (0.000, 0.726)	0.618 (0.250, 0.694)	0.735	0.623 (0.537, 0.721)	0.566 (0.000, 0.667)	0.005
F7/F8 mean density	0.510 (0.045, 1.481)	0.641 (0.136, 1.873)	0.215	0.889 (0.287, 1.913)	0.173 (0.016, 1.149)	< 0.001
Total density	1.033 (0.090, 3.416)	1.308 (0.277, 4.308)	0.269	1.923 (0.648, 4.735)	0.364 (0.043, 2.711)	< 0.001
Spindle duration	0.717 (0.654, 0.784)	0.706 (0.650, 0.755)	0.200	0.716 (0.671, 0.772)	0.683 (0.631, 0.757)	0.043

Notes: Values are expressed as median (interquartile range).
Abbreviations: POD, postoperative day; PSD, postoperative sleep disturbance.

Table 5 Multivariable Logistic Regression Analysis of PSD on POD 1

	OR	95% CI	P
Gender			
Male	1.00	Reference	
Female	2.032	1.065–3.879	0.032
MMSE	0.806	0.656–0.991	0.041
Surgery type			
Hip/knee	1.00	Reference	
Spine	2.947	1.378–6.303	0.005
Others	1.615	0.559–4.670	0.376
Pain score on movement	1.480	1.200–1.824	< 0.001

Abbreviations: CI, confidence interval; MMSE, Mini-Mental State Examination; OR, odds ratio; POD, postoperative day; PSD, postoperative sleep disturbance.

Table 6 Multivariable Logistic Regression Analysis of PSD on POD 3

	OR	95% CI	P value
F7/F8 mean density	0.543	0.375–0.786	0.001
Pain score at rest	1.848	1.166–2.927	0.009
MMSE	0.701	0.562–0.875	0.002

Abbreviations: CI, confidence interval; MMSE, Mini-Mental State Examination; OR, odds ratio; POD, postoperative day; PSD, postoperative sleep disturbance.

It also revealed that the spindle density in F7/F8 (OR 0.543, 95% CI 0.375–0.786; $P = 0.001$), MMSE (OR 0.701, 95% CI 0.562–0.875; $P = 0.002$), and pain at rest (OR 1.848, 95% CI 1.166–2.927; $P = 0.009$) were independently associated with PSD on POD 3. (Table 6) Fp1 density and Fp2 density were not included in the regression model as the collinearity was observed with Fp1/Fp2 mean density. In the same way, F7, F8, and total density were also excluded.

In addition, to validate the findings of the PSD risk factor analysis, we performed pairwise regression across four distinct patient groups with Group 1 (No PSD on POD 1 and POD 3) as the reference (Supplementary Table 3-5) and found that female (OR 3.91, 95% CI 1.43–10.47; $P = 0.008$), spine surgery (OR 4.8, 95% CI 1.46–15.84; $P = 0.010$), pain score on movement on POD 1 (OR 1.40, 95% CI 1.01–1.94; $P = 0.044$), pain score on movement on POD 3 (OR 1.84, 95% CI 1.08–3.14; $P = 0.024$), and relative sigma power (OR 0.91, 95% CI 0.84–0.99; $P = 0.025$) were independently associated with PSD among patients in Group 2 (with PSD on both POD 1 and POD 3). Additionally, female (OR 2.98, 95% CI 1.13–7.91; $P = 0.022$) and spine surgery (OR 3.12, 95% CI 1.04–9.33; $P = 0.042$) were independently associated with PSD patients in Group 3 (with PSD only on POD 1). Moreover, higher ASA grade (OR 11.17, 95% CI 2.14–58.23; $P = 0.004$), pain score on movement on POD 3 (OR 3.86, 95% CI 1.39–10.72; $P = 0.010$), and spindle density in F7/F8 (OR 0.08, 95% CI 0.01–0.43; $P = 0.004$) were independent risk factors for PSD patients in Group 4 (with PSD only on POD 3).

Discussion

Our findings indicated that the incidence of PSD on POD 1 following orthopedic surgery in elderly patients was 65.65% and decreased to around 41.98% by POD 3. On POD 3, patients in the PSD group experienced lower intraoperative sigma power, lower spindle density, and shorter average spindle durations in Fp1/Fp2 and F7/F8 channels. Logistic regression analysis also indicated that female gender, MMSE, surgery type, and pain score on movement were independent risk factors for PSD on POD 1. Similarly, the average sleep spindle density in F7/F8 during surgery, MMSE, and pain score at rest were considered independent risk factors for PSD on POD 3.

The incidence of PSD in our study was consistent with previous research.[3,39] We found no significant differences in spindle activity or other EEG-related measurements between the PSD and non-PSD groups on POD 1. Pairwise comparisons also revealed that Group 1 (non-PSD on both POD 1 and POD 3) did not differ from Group 3 (PSD only on POD 1) in intraoperative sleep spindle activity. Similarly, sleep spindle density was not an independent risk factor for patients in Group 3 and Group 2 (with PSD on both POD 1 and POD 3) compared to Group 1. Nevertheless, relative sigma activity remains a significant risk factor in Group 2. The sleep quality of surgical patients on the first night postoperatively may be affected by excessive and intense disturbances, such as noise from the bedside monitor,[40] routine vital sign collection,[41] frequent therapeutic procedures (such as passive turning),[42] interruptions by hospital staff,[43] causing patients to be forcibly awakened repeatedly during the night. This phenomenon may contribute to poor sleep on POD 1 in patients who might not have otherwise developed PSD. A study on sleep disturbance factors in postoperative monitoring units also confirmed that environmental factors on the postoperative night significantly interfere with sleep.[44] On POD 3, however, as external interference factors significantly decreased, the spindle density in all channels was significantly higher in the non-PSD group, preliminarily confirming our hypothesis that patients with lower intraoperative sleep spindle density might have a higher incidence of PSD. This finding was confirmed through pairwise comparisons, which revealed a statistically significant difference in sleep spindle activity when Group 4 (PSD only on POD 3) was compared to Group 1 (non-PSD on both POD 1 and POD 3) and Group 3 (PSD only on POD 1), respectively.

Our results demonstrate a marked reduction in intraoperative sleep spindle activity in patients who subsequently experienced PSD. The sleep spindles, which are rhythmic bursts of brain activity during NREM sleep, are critical for maintaining sleep stability.[23,45] They are generated by gamma-aminobutyric acid (GABA)ergic neurons in the thalamus, creating oscillations in brain activity at 11–16 Hz.[46] Studies indicated that sleep spindles help block external sensory information, protecting sleep from disturbances and raising the arousal threshold.[23,27] Higher sleep spindle density is associated with better sleep quality and can indicate overall sleep stability,[28,47] making them a potential biomarker.[23] In the aging process, sleep spindle activity tends to decline, while its connection to sleep quality strengthens.[48] Hence, in elderly surgical patients, sleep spindle activity might serve as a predictor of PSD. In our study, logistic regression revealed that F7/F8 mean spindle density was a significant predictor for PSD on POD 3, suggesting a stronger correlation with PSD outcomes compared to other spindle metrics. Multivariable logistic regression analysis comparing Group 4 to Group 1 further confirmed that the mean spindle density at F7/F8 was a significant predictor for patients with PSD only on POD 3. The spindle activity of F7/F8 may reflect the regulation of sleep activity by neural circuits in the region,[49] indicating that the density of spindles in these frontal regions is particularly sensitive to changes in sleep quality in postoperative patients. Among patients with Parkinson's disease, those with sleep disturbance showed reduced whole-night spindle frequency activity, quantized by sigma power (12–15 Hz).[50] Both absolute and relative spectral power were associated with the severity of excessive daytime sleepiness. A study detected the sleep spindles of 38 frequent recallers of nightmares and 25 controls for density, mean frequency, and amplitude, and found that the nightmare group showed lower slow spindle densities and higher average frequencies of total spindles.[51] The decrease in spindle activity observed during surgery may indicate that anesthetic agents and stress could disrupt the thalamic-cortical circuit needed for spindle generation. The intraoperative stress events (pain, trauma) can lead to persistent activation of locus coeruleus noradrenergic neurons,[52] which induces membrane depolarization in thalamic cortical and reticular neurons, mediating the termination of the sleep spindle and reflected in EEG as reduced spindle density and shortened spindle duration.[8]

Furthermore, we found that patients in the PSD group showed higher low-frequency activity and lower power of high-frequency activity compared to the non-PSD group. To ensure the reliability of these findings, we used the Benjamini–Hochberg correction to control for false discoveries due to multiple comparisons across frequency bands. The adjusted results remained consistent, supporting the robustness of our analysis. Previous studies have suggested that a decrease in high-frequency brain activity is associated with the loss of consciousness and deeper sleep.[53] However, some scholars have found that patients with sleep disorders often show increased delta activity and decreased alpha and beta activity, which may indicate potential neurocognitive abnormalities.[54,55] Therefore, a decrease in high-frequency brain activity and an increase in low-frequency brain activity during anesthesia may indicate vulnerability in patients' cognitive function, making them more likely to develop sleep problems.[56]

Logistic regression showed that pain scores were higher in the PSD group than in the non-PSD group on POD 1 and 3. Additionally, pain scores were significantly elevated in patients from Group 2 (with PSD on both POD 1 and POD 3) and Group 4 (with PSD only on POD 3) compared to Group 1 (without PSD on either POD 1 or POD 3). This confirms that pain significantly affects postoperative sleep quality. This finding aligns with previous studies highlighting pain as a critical factor influencing sleep patterns in postoperative patients.[57] Pain disrupts sleep continuity and affects the overall quality of sleep, leading to prolonged sleep latency and frequent awakenings.[58] On the other hand, a systematic review and meta-analysis revealed that decreased sleep quality and quantity were associated with a two- to threefold increased risk of developing a pain condition. Studies have shown that sleep disturbances can also lead to heightened pain sensitivity,[59] a phenomenon known as hyperalgesia. Moreover, lack of sleep has been linked to increased inflammatory responses in the body, leading to elevated levels of pro-inflammatory cytokines, which can enhance pain perception.[59] Addressing pain management effectively during the early postoperative period could potentially mitigate sleep disturbances and improve overall recovery outcomes.[60] Future research should explore specific pain management strategies that can be incorporated into postoperative care protocols to improve sleep quality and overall patient well-being.

Previous studies suggested that patients should be categorized by a cut-off value of MMSE < 24.[61] In our study, however, as patients with an MMSE score less than 24 were only 2.36% (5/212), MMSE was included in the logistic regression as a continuous variable. MMSE score was an independent risk factor for PSD on POD 1 and 3. These findings suggest a close link between postoperative sleep and neurocognitive outcomes. A prospective cohort study in 2015[62] found that nighttime awakening times were significantly higher in patients with postoperative delirium than in non-delirium patients. Clinical practice has also observed that sleep abnormalities are prevalent in patients with mental and cognitive disorders (eg, schizophrenia), suggesting that postoperative sleep disturbances might be a manifestation of postoperative brain dysfunction.[63] Besides sleep protection, another essential physiological role of sleep spindles is their association with learning and cognitive functions. Studies have indicated that certain general anesthetics, such as dexmedetomidine, may enhance intraoperative sleep spindle activity, potentially resulting in lower PSD and postoperative delirium rates,[64,65] which warrants further investigation in future studies.

On POD 1, female gender was identified as a risk factor for PSD. Further regression analysis also identified female gender as a risk factor for both Group 2 (patients with PSD on both POD 1 and POD 3) and Group 3 (patients with PSD only on POD 1). A prospective survey developing a nomogram for PSD in 640 patients undergoing spinal surgery reported that female was an independent risk factors associated to PSD (OR 2.067, 95% CI 1.338–3.194; $P < 0.001$).[66] Previous studies have suggested that women are more susceptible to preoperative anxiety than men,[67] possibly contributing to their increased likelihood of postoperative sleep problems. A large longitudinal study[68] on sleep found that mental health issues (eg, anxiety, depression) increase the risk of postoperative insomnia by nine times. It is important to pay particular attention to female patients, especially those with anxiety disorders.

Spine surgery patients had a significantly higher incidence of PSD on POD 1 compared to patients receiving other types of orthopedic surgery. This is further demonstrated by the regression analysis, which compared Group 2 (patients with PSD on both POD 1 and POD 3) and Group 3 (patients with PSD only on POD 1) to Group 1 (patients without PSD on either POD 1 or POD 3). These patients must lie flat without a pillow for six hours after surgery and should be turned every 2–3 hours to prevent thrombosis. Keeping patients lying flat can disrupt sleep and cause stress while gently turning them during the night can lead to frequent awakenings.[69] A retrospective analysis of data from 508 adults who underwent spine surgery revealed a significant impact of continued sleep disturbances on postoperative results.[70] This study highlighted the potential for effective interventions aimed at improving sleep quality to enhance overall recovery outcomes for spine surgery patients.

This study found that a higher proportion of propofol intravenous anesthesia was used to maintain anesthesia in patients with PSD. However, the logistic regression did not show an independent relationship between propofol and PSD. The impact of anesthesia drugs on postoperative sleep remains unclear. Most anesthetic agents do not induce spindles.[71] It is reported that spindles can be seen in deep propofol anesthesia.[72] In our study, the anesthesia depth was maintained in a proper range, with PSI 25–50. Moreover, there was no difference in PSI between non-PSD and PSD groups. Dexmedetomidine may enhance intraoperative sleep spindle activity, which was not used in our study.[64] Our findings suggest that general anesthesia with propofol maintenance had a higher incidence of PSD. Similarly, current research

suggests that propofol may disrupt sleep architecture by inhibiting the N-methyl-D-aspartic acid receptor and interfering with the secretion of orexins and melatonin.[73] In a randomized controlled trial, both propofol and sevoflurane were found to cause PSD within two weeks. While sevoflurane had a milder impact on sleep compared to propofol.[74] There are also studies reporting that propofol can alleviate sleep debt in insomnia patients and improve insomnia symptoms to some extent.[75] Moreover, we adjusted for the effect of the anesthesia maintenance scheme in regression analyses.

There are several limitations to this study. First, our experimental subjects were limited to orthopedic surgery patients, and we did not discuss other types of surgeries. Second, we did not conduct long-term postoperative follow-ups, limiting our conclusions to within 72 hours post-surgery and lacking follow-up on POD 2. Our assessment of postoperative sleep quality primarily used scales rather than objective detection equipment (eg, polysomnography), preventing us from providing a more detailed and objective evaluation of postoperative sleep. Furthermore, we only analyzed sleep spindles in the four frontal channels without further exploring the whole brain sigma activity and discrete spindle distribution. Lastly, this study was a single-center study with a relatively small sample size; future research will include multiple centers and larger sample sizes.

Conclusion

We demonstrated that the average spindle density in the temporoparietal (F7/F8) channels during surgery was independently associated with PSD on POD 3, serving as a potential biomarker for predicting PSD. We also showed that MMSE and postoperative pain independently increased the risk of PSD.

Data Sharing Statement

The original data analyzed in this study are included in the article; further inquiries can be directed to both corresponding authors.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest.

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