

ORIGINAL ARTICLE

Preoperative resting-state electrophysiological signals predict acute but not chronic postoperative pain

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Abstract

Background: The prevalence of postoperative pain is notably high among the elderly population, which poses significant challenges for their postoperative recovery. In this study, we aimed to identify preoperative predictors for acute and chronic postoperative pain in patients undergoing lumbar spinal surgery through a longitudinal investigation.

Methods: We recruited 75 patients (mean age 68.29 ± 5.60 years) and collected their resting-state electroencephalography (EEG) data two hours before the surgery. The aperiodic and periodic signal components were extracted from the resting-state EEG using the Fitting Oscillations and One-Over-F algorithm. We also collected the preoperative pain ratings, demographic information and the Hospital Anxiety and Depression Scale from all patients. The postoperative pain ratings were collected ten times from Day 1 to Week 12 after surgery.

Results: We observed a high incidence of postoperative acute and chronic pain among older patients. Preoperative pain and peak alpha frequency in resting-state EEG were the primary predictors of acute postoperative pain. Although age is a significant predictor of chronic postoperative pain, its predictive performance is poor.

Conclusions: Overall, our study provides valuable insights into the complex pattern of preoperative EEG features, preoperative pain and age in predicting postoperative pain at different stages. Our findings highlight the significance of exploring preoperative features to identify patients who are at a higher risk of developing severe postoperative pain, which can aid in the development of more personalized and effective pain management strategies.

Significance: The heightened occurrence of postoperative pain among the elderly presents formidable obstacles to their recuperation. This study delves into identifying preoperative factors influencing acute and chronic postoperative pain. Our findings indicate that preoperative pain and peak alpha frequency are crucial predictors of acute postoperative pain. However, the predictive performance for chronic postoperative pain is limited, although age was a significant predictor of chronic postoperative pain. These insights contribute to the identification of patients at elevated risk for severe acute and chronic postoperative pain, offering valuable guidance for pre-surgical risk assessment.

Qi Han and Hailu Wang contributed equally to this work.

1 | INTRODUCTION

Postoperative pain is an important adverse outcome of surgical procedures, with 20% to 80% of patients experiencing moderate-to-severe acute pain (Mei et al., 2010) and 10% to 40% suffering from chronic pain (Babiloni et al., 2006; Zagorulko et al., 2021). Elderly patients face a notably high incidence of postoperative acute and chronic pain, posing significant challenges for their rehabilitation (Kehlet et al., 2006; Macrae, 2008; Wang et al., 2016). Identifying preoperative predictors of postoperative pain becomes crucial, as it allows healthcare professionals to anticipate pain symptoms, ultimately assisting in developing targeted postoperative care for elderly patients.

The role of neural oscillations in encoding the perception of acute, tonic and chronic pains has been well-documented (Babiloni et al., 2006; Li et al., 2023; Ploner et al., 2017; Taesler & Rose, 2016; Tu et al., 2016). Electroencephalographic (EEG) signals reflect not only oscillatory activities but also additional background activities. Oscillatory activities are periodic and exhibit frequency-specific 'narrowband' power, appearing as peaks in the power spectrum. Background activities, on the other hand, are aperiodic and distributed across all frequency bands, typically exhibiting a $1/f$ power distribution (Barry & De Blasio, 2021; Donoghue & Watrous, 2023). Recent studies have provided compelling evidence that the $1/f$ component reflects meaningful neural activity, transcending its previous characterization as mere noise (Donoghue et al., 2020). However, previous studies often overlooked the impact of aperiodic signals on neural oscillations and extracted the spectral power of EEG oscillations irrespective of background activities (Donoghue et al., 2020). This oversight is partly because these two types of activities cannot be directly isolated from EEG power spectra obtained through conventional spectral analysis (Hu & Zhang, 2019), and partly because the current understanding of the aperiodic background activities is still limited. Nevertheless, the slope of the EEG aperiodic signal has been considered as a marker for the excitatory-inhibitory balance of neural activity (Ahmad et al., 2022), which is crucial for pain processing (Peirs & Seal, 2016; Torsney & MacDermott, 2006; Xiong et al., 2017). In other words, alternations in aperiodic component of the EEG signal might reflect abnormal neural signal transmissions associated with pain processing, providing a possible predictor of the subjective intensity of pain perception. Therefore, it is necessary to decompose the power spectra into aperiodic and periodic components and explore how they relate to postoperative pain.

Here, we aimed to identify preoperative predictors of postoperative acute and chronic pain through a longitudinal

investigation involving 75 patients who underwent lumbar spinal surgery. We collected resting-state EEG data, preoperative pain ratings, demographic information and the Hospital Anxiety and Depression Scale (HADS) ratings before surgery. Postoperative pain ratings were collected at multiple time points after surgery (Figure 1a). EEG data were analysed using both conventional spectral analysis and a novel Fitting Oscillations and One-Over-F (FOOOF) algorithm to extract periodic and aperiodic components (Donoghue et al., 2020; Hill et al., 2022). These analytic strategies enabled us to compare the differences between two approaches in identifying key features associated with pain.

2 | MATERIALS AND METHODS

The clinical study was approved by the Medical Ethics Committee of the Peking University People's Hospital, Beijing China. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki. The study was registered prior to patient enrollment at the Clinical Trial Registry (<https://register.clinicaltrials.gov/>) with the registration number NCT03761576 (Date of registration: December 3, 2018). Please note that the clinical trial registry has been revised based on our previous study (Han et al., 2021), owing to the resemblance in study design and research objectives.

2.1 | Participants

A hundred patients who agreed to undergo lumbar spinal surgery at Peking University People's Hospital were recruited between November 2020 and March 2021. Inclusion criteria were (1) education levels beyond secondary school; (2) American Society of Anesthesiologist (ASA) grade I-III; and (3) preferred to use postoperative patient-controlled intravenous analgesia (PCIA). Exclusion criteria were (1) cerebrovascular diseases; (2) psychiatric diseases or psychiatric family history; (3) traumatic brain injury or post-craniotomy; (4) preoperative opioid users; and (5) planned to return to Intensive Care Unit after surgery for further observation and treatment. With these criteria (see Figure 1b), 19 patients were excluded from the study for the following reasons: previous neurological diseases ($n=10$), previous psychiatric diseases ($n=4$), opioid addiction ($n=2$), and refused to sign informed consent ($n=3$). Six additional patients were excluded from the statistical analysis due to the poor quality of EEG data. A total of 75 patients were enrolled in the present study. The detailed demographic information of all patients is summarized in Table 1.

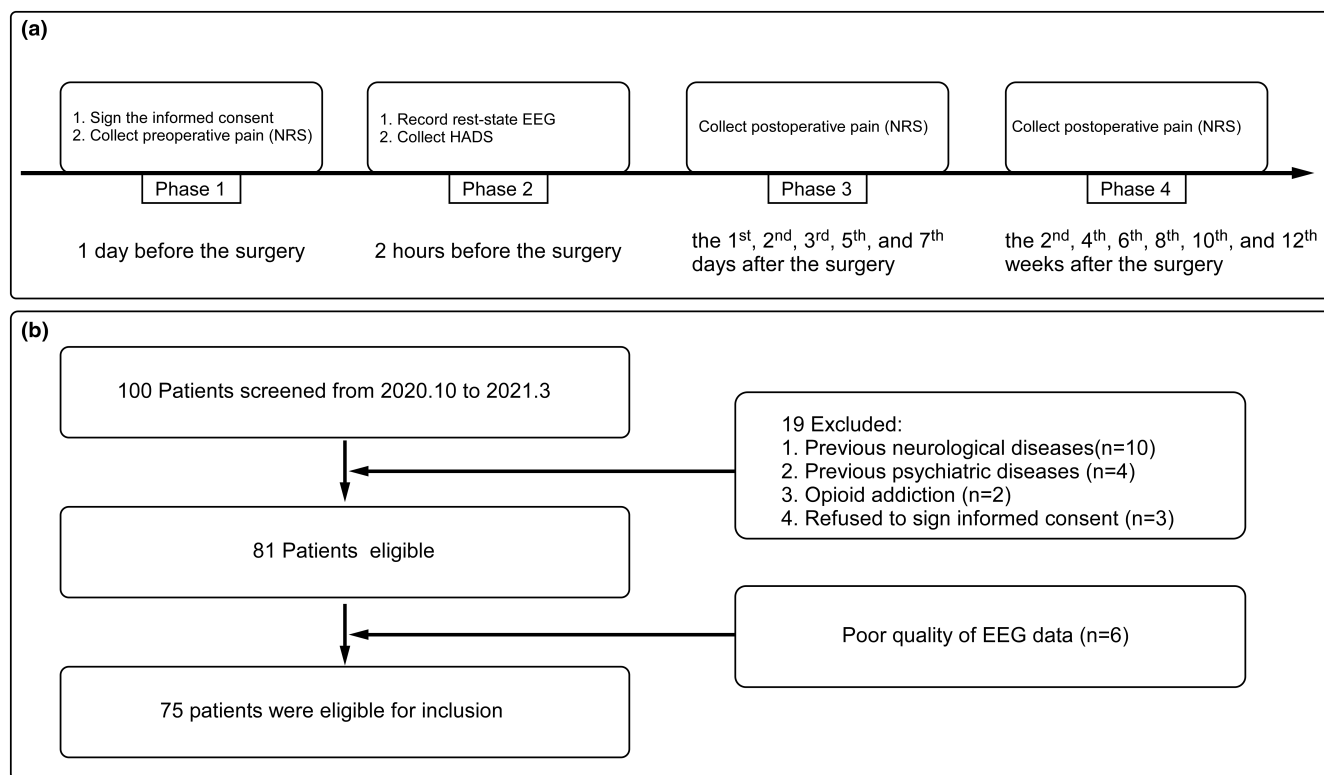


FIGURE 1 Study design and flow of patients. (a) The study is composed of four phases. The pain scores were collected before (phase 1) and after the surgery (phase 3 and phase 4). The HADS and resting-state EEG data were collected two hours before surgery (phase 2). (b) Twenty-five patients were excluded from the study, with 19 patients excluded for exclusion criteria and six patients excluded for poor EEG data quality. Seventy-five out of 100 patients were included in the analysis.

2.2 | Study design

As shown in Figure 1a, the study is composed of four phases. In phase 1, patients were instructed to sign the informed consent and assess preoperative pain one day before surgery. Patients were required to avoid smoking or drinking coffee or caffeine-containing beverages 10 hours before surgery. In phase 2, all patients were instructed to complete the HADS to measure their preoperative anxiety and depression. Then, resting-state EEG data were collected two hours before surgery (please see the following section for details about EEG data recording). In phase 3, patients underwent the surgeries conducted at approximately the same time in a day (from 8 am to 12 pm) and their postoperative pain was collected on the 1st, 2nd, 3rd, 5th and 7th days after surgery (i.e. POD1, POD2, POD3, POD5 and POD7). Specifically, the highest postoperative pain over the past 24 hours was assessed on an 11-point numerical rating scale (NRS; 0=no pain, 10=worst imaginable pain) at 15–17 o'clock on POD1 and POD2. On POD3 and POD5, the highest postoperative pain over the past 24 hours was assessed using the same NRS, but after the epidural analgesic tube was removed. On POD7, the highest postoperative pain over the past 24 hours was assessed after the drainage tube was removed. In phase 4, postoperative pain at the 2nd, 4th, 6th, 8th, 10th

and 12th weeks after surgery (i.e. POW2, POW4, POW6, POW8, POW10 and POW12) was collected from all patients by telephone follow-up. Specifically, the highest postoperative pain over the past week was assessed on the same NRS. Postoperative pain is defined as the pain occurring at either the site of incision or related anatomical areas associated with the surgery. Preoperative and postoperative NRS scores were obtained from patients at rest to avoid the influence of movement on the ratings of pain perception. Please also note that in our study, chronic postoperative pain was a persistent pain state based on Macrae's 4 point definition: (1) the pain has emerged as a consequence of clinical operation; (2) its duration is at least 2 months; (3) no other explanation exists for the pain; and (4) the pain is not a continuation of a pre-existing chronic pain condition for which the surgery was performed (Chapman & Vierck, 2017; Macrae, 2001). All patients were examined by the same investigator, and all patients were reminded that they could withdraw from the experiment at any time for any reason.

2.3 | Anaesthetic management protocol

An hour before surgery, patients received general anaesthesia according to the local clinical standards to ensure

TABLE 1 Demographic information, surgical data and behavioural results.

Variables		Patients Mean $\pm$ SD or N (%)
Age (years)		68.29 $\pm$ 5.60
Sex	Male	27 (36%)
	Female	48 (64%)
ASA	II	61 (81.3%)
	III	14 (18.7%)
Educational level	Primary	6 (8%)
	Junior high	25 (33.3%)
	Senior high	24 (32%)
	University/ College	20 (26.7%)
Preoperative NRS		5.26 $\pm$ 2.17
Anxiety score		2.65 $\pm$ 2.06
Depression score		3.71 $\pm$ 2.35
Intraoperative blood loss (ml)		322 $\pm$ 165.07
Time of operation (min)		149 $\pm$ 35.59
POD1 NRS		4.40 $\pm$ 1.51
POD2 NRS		4.34 $\pm$ 1.28
POD3 NRS		3.99 $\pm$ 1.36
POD5 NRS		3.73 $\pm$ 1.18
POD7 NRS		3.65 $\pm$ 1.30
POW2 NRS		3.20 $\pm$ 1.17
POW4 NRS		2.87 $\pm$ 1.15
POW6 NRS		2.53 $\pm$ 1.13
POW8 NRS		2.24 $\pm$ 1.19
POW10 NRS		2.00 $\pm$ 1.26
POW12 NRS		1.68 $\pm$ 1.74

Abbreviations: ASA, American Society of Anaesthesiologists; NRS, numerical rating scale; POD, postoperative day; POW, postoperative week; SD, standard deviation.

the safety of the surgery. The induction of anaesthesia was achieved using midazolam (0.02–0.04 mg/kg), propofol (1–2 mg/kg), rocuronium (0.6–1 mg/kg) and sufentanil (0.3–0.5 μ g/kg). Anaesthesia was maintained with 1% sevoflurane, propofol (0.1–0.3 μ g/kg/min) and remifentanil (0.3–0.5 μ g/kg/min) during the surgery. More sufentanil and rocuronium were supplied when needed, and the total amount of sufentanil should be no more than 0.6 μ g/kg. Flurbiprofen axetil (100 mg) was started to be administered 30 min before the end of the surgery. Along with the infusion of flurbiprofen axetil (8 mg/h), the PCIA with sufentanil (background 3 μ g/h, single dose 3 μ g, lockout 15 min, limit 15 μ g/h) was used for all patients by the end of operation.

2.4 | EEG data recording and preprocessing

During EEG data recording, patients lay in a bed with a semi-recumbent position in a silent, temperature-controlled room. EEG data were recorded using 32 Ag-AgCl electrodes placed on the scalp according to the International 10–20 system (Compumedics Neuroscan, Australia). The NuAmps amplifier (Model 7181) was set with a sampling rate of 1000 Hz and with a signal bandpass filter from 0.01 to 100 Hz. The ground electrode was positioned 10 mm anterior to Fz, and the right mastoid electrode was used as the online reference. Impedances of all electrodes during data recording were kept below 10 k Ω . EEG data were preprocessed using EEGLAB (Delorme & Makeig, 2004), an open-source toolbox running under the MATLAB environment. Specifically, EEG data were first bandpass filtered from 1 to 45 Hz, as brain oscillations at high frequencies typically suffer from a low signal-to-noise ratio due to their small magnitude and susceptibility to muscle artefacts (Ray & Maunsell, 2015). Moreover, we focused on 1–45 Hz to maintain consistency with the methodology developed by Donoghue et al. (2020), ensuring comparability of results. EEG data with high-amplitude artefacts were then manually excluded, leaving an average of 9.37 $\pm$ 1.2 min of data per patient for further analysis. Subsequently, EEG data contaminated by eye blinks, eye movements and muscle artefacts were corrected using an independent component analysis algorithm *runica* in EEGLAB (Delorme & Makeig, 2004). After preprocessing, EEG data were re-referenced to the average of all scalp electrodes.

2.5 | Power spectral density (PSD)

After EEG preprocessing, the PSD of EEG signals was calculated using the Welch's method (2-s windows, 50% overlap) from signals of each electrode separately for each patient (Donoghue et al., 2020; Hu & Iannetti, 2019; Li et al., 2020). This operation yielded an EEG power spectrum ranging from 1 to 45 Hz, in steps of 0.25 Hz, for each electrode and each patient. Then, we divided the power spectra from 1 to 45 Hz into five canonical frequency bands (Donoghue et al., 2020; Pernet et al., 2020), that is delta: 1–4 Hz, theta: 4–7 Hz, alpha: 7–14 Hz, beta: 14–30 Hz and gamma: 30–45 Hz. The total power within each frequency band was defined as the mean value of power spectra within the respective frequency range. Group-level power spectra were obtained by calculating the average of single patient power spectra at the Cz electrode, and the scalp topography of power spectra at each frequency band was computed by spline interpolation.

2.6 | Aperiodic and periodic components in PSD

Previous studies have illustrated that PSD could be conceptualized as a combination of an aperiodic component and periodic oscillations (Buzsáki et al., 2013; Donoghue et al., 2020; Gao et al., 2017). The aperiodic signal, or 1/f-like power distribution in electrophysiological signals, is commonly named as the background electrical brain activity (Bédard et al., 2006; Miller et al., 2009) and can be defined by two parameters: aperiodic exponents, indicating the slope of the power spectrum, and aperiodic offsets, representing background power levels. In principle, the power at each frequency point of PSD (i.e. total power) is composed of the power relative to the background electrical brain activity and the power of the periodic signals. Donoghue et al. (2020) demonstrated that changes in the aperiodic component can be erroneously interpreted as changes in oscillation power when focusing on a narrow frequency band of interest (Donoghue et al., 2020). However, the power of the periodic signal could be extracted after the aperiodic component was removed from PSD by performing a Gaussian fitting. In this case, features of periodic oscillations (e.g. the relative power, bandwidth and peak frequency of oscillations) could be correctly estimated without confusion from the background electrical brain activity.

According to the previous study (Donoghue et al., 2020), the power spectral density of EEG signals could be modelled as:

$$PSD = L + \sum_{n=0}^N G_n \quad (I)$$

$$L = b - \log(F^x) \quad (II)$$

$$G = h \times e^{\left(\frac{-(F-C)^2}{2w^2}\right)} \quad (III)$$

In these formulas, L is the aperiodic component, G is the periodic component, and N is the number of periodic components for Gaussian fitting. The aperiodic offset is b , F is the frequencies, and x is aperiodic exponent. The periodic relative power is h , peak frequency is C , and bandwidth is w .

The FOOOF algorithm was employed to estimate aperiodic and periodic components (Donoghue et al., 2020). Specifically, the FOOOF algorithm was performed within the frequency range from 1 to 45 Hz with the following settings: peak width limits=(1,6), max num peaks=6, min peak height=0.1, peak threshold=2, aperiodic mode='fixed'. The aperiodic exponents and aperiodic

offsets were calculated for each electrode and each patient. Although the FOOOF algorithm could extract multiple oscillatory peaks across different frequency bands, we focused the analysis on the alpha band, as only alpha peaks demonstrated high consistency across individuals and can be reliably extracted from most of the patients (70 out of 75) in our study. More importantly, there is a close link between alpha oscillations and pain perception (Ploner et al., 2017). If there were more than one peak at the range of interest (i.e. alpha oscillations), the peak corresponding to the maximal relative power was selected for the following analysis. If there were no peak was observed at the range of interest, the data was excluded from further analysis. In line with the Donoghue et al. (2020) study, features from aperiodic component (i.e. aperiodic offsets and aperiodic exponents) and periodic oscillations (i.e. peak frequency, bandwidth and relative power of alpha oscillations) were estimated from PSD at central (Cz) and occipital (Oz) electrodes, respectively, in the FOOOF analysis.

2.7 | Statistical analysis

The Spearman's rank correlation analysis was performed to explore the relationship between electrophysiological features (i.e. the total powers at different frequency bands and the features of both aperiodic and periodic components) and behavioural scores (i.e. anxiety and depression scores, preoperative pain ratings and postoperative pain ratings). This analysis would provide an intuitive illustration of the relationship between different measures and allow us to examine whether the predictors in MLR models were correlated with each other.

Moreover, multiple linear regression (MLR) analyses were conducted to build prediction models of postoperative pain (response variable) using a series of predictors, including the age of patients, anxiety and depression scores, preoperative pain, total power and the features of both aperiodic and periodic components. Each prediction model included postoperative pain ratings at a single time point as the response variable and multiple predictor variables. The 95% confidence interval (95% CI) was calculated for each regression coefficient.

In our study, some predictive variables showed significant correlations (e.g. the correlation between total power at the delta band with anxiety and depression, as shown in Figure 2b). During the MLR modelling, predictors were selected based on the principle of independence. Specifically, if Predictor A was significantly correlated with Predictor B, we performed separate modelling for each predictor and selected only one of them for inclusion in the final model. Among the different candidate models, we chose the one with the highest coefficient of

determination (R^2) to ensure the best performance of the model.

Leave-One-Out Cross-Validation (LOOCV) was used in data analysis (Duda et al., 2001). Specifically, the dataset of all patients (N) was divided into N-1 training datasets and one test dataset, and this process was repeated N times to ensure that each dataset was used as the test dataset once. During each iteration, the linear regression model was applied to the training dataset to explore the relationship between predictors and postoperative pain ratings. Predictive values were then calculated using the test dataset. Subsequently, correlations between the predictive values and the corresponding real values were calculated to evaluate the predictive performance of models.

To tap into the issue of multiple hypothesis testing, we conducted the False Discovery Rate (FDR) correction to the P values in correlation and MLR analyses (Benjamini & Hochberg, 1995). All statistical analyses were carried out in SPSS 25.0 (SPSS Inc., New York, USA), and the statistical significance level was set at 0.05.

3 | RESULTS

3.1 | Demographic and behavioural results

All included patients completed follow-up sessions. Table 1 summarized the general demographic data, surgical data, preoperative anxiety and depression scores and preoperative and postoperative pain ratings (NRS) of all enrolled patients. The majority of the enrolled patients were female (64%), and most of them had fair

general status (ASA II 81.3%). Moreover, all patients had low HADS scores (lower than 6 points for each subscale) for preoperative stress or anxiety. Notably, 56% of patients reported pain ratings over 3 on POD3 (indicating postoperative acute pain) and 34.7% of patients reported pain ratings over 3 at POW12 (indicating postoperative chronic pain). Nevertheless, surgical treatment significantly relieved the patient's low back pain, as the patient's postoperative pain ratings gradually decreased after surgery and the averaged ratings were less than 3 at POW4. There was no significant difference in the dosage of analgesics used during hospitalization between patients with postoperative acute pain and those without postoperative acute pain.

3.2 | Power spectral density

As presented in Figure 2a, grand averaged power spectra distribution showed a strong alpha peak (around 10 Hz) and a secondary beta peak (around about 18 Hz). Scalp topographies within the canonical frequency range of delta (1–4 Hz), theta (4–7 Hz), alpha (7–14 Hz), beta (14–30 Hz) and gamma (30–45 Hz) oscillations were also displayed in Figure 2a. Notably, alpha oscillations were maximal at bi-lateral occipital regions.

Whereas no significant correlations were observed between total powers and postoperative pain ratings (see Table S1), correlation analyses revealed significant negative correlations between the total power at delta band (recorded at Cz) and anxiety ($\rho = -0.35$, $P_{FDR} = 0.002$) and depression scores ($\rho = -0.32$, $P_{FDR} = 0.003$; Figure 2b). No other significant correlations were found ($P_s > 0.05$).

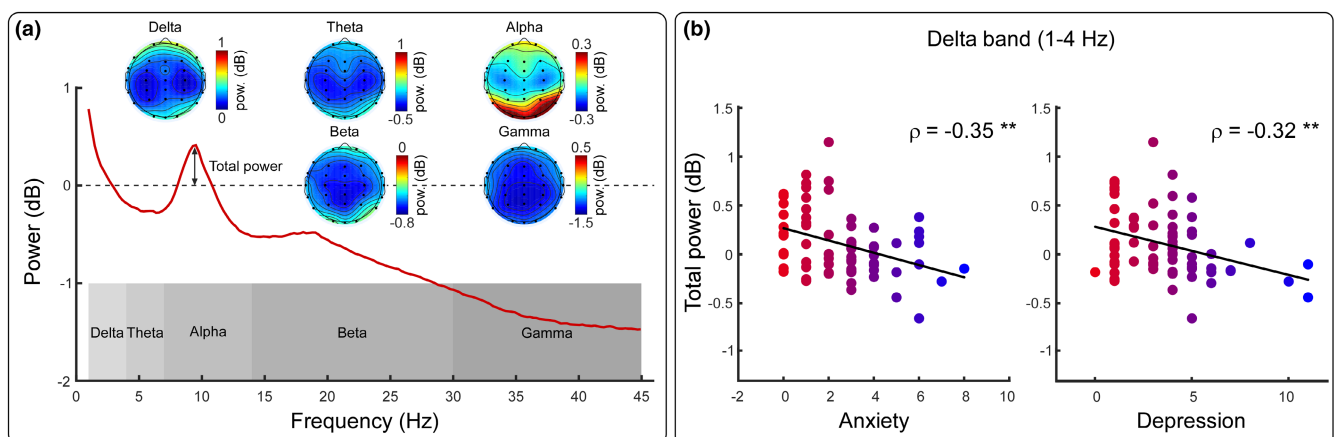


FIGURE 2 Grand average power spectrum and correlations between EEG total powers and anxiety and depression scores. (a) Grand average power spectrum (red line; Cz-avg) and scalp topographies of total powers at delta (1–4 Hz), theta (4–7 Hz), alpha (7–14 Hz), beta (14–30 Hz) and gamma bands (30–45 Hz). A canonical peak around 10 Hz (alpha band) was accompanied by a secondary peak around 18 Hz (beta band). (b) Scatter plots showed the negative correlations between delta-band total power (1–4 Hz) and preoperative anxiety (left) and depression (right) scores (**: $P_{FDR} < 0.01$).

3.3 | Periodic and aperiodic components

The periodic and aperiodic components were extracted from PSD for each patient, including the peak frequency, bandwidth and relative power of alpha oscillations, as well as the aperiodic exponent and offset of aperiodic signals (Figure 3a). For periodic signals, a significant negative correlation was observed between the peak alpha frequency (PAF) and the postoperative pain on POD2 (Figure 3b, $\rho = -0.28$, $P_{\text{FDR}} = 0.02$). Moreover, a significant negative correlation was observed between the relative power of alpha oscillations and POD2 ratings (Figure 3b, $\rho = -0.25$, $P_{\text{FDR}} = 0.04$). The inset in Figure 3c provided a schematic illustration of the relationship between the PAF and POD2 ratings. Randomly selecting data from 7 patients with different POD2 ratings ranging from 2 to 8 (Figure 3c) and dividing all patients into three POD2 levels (i.e. $\text{POD2} < 4$, $4 \leq \text{POD2} \leq 5$ and $\text{POD2} > 5$; Figure 3d), we intuitively illustrated the patients with higher frequency of alpha oscillations (i.e. faster oscillations) reported lower pain ratings on POD2. No significant correlations between other periodic features and POD2 ratings, as well as between all periodic features and postoperative pain ratings collected at other time points, were observed ($P_s > 0.05$).

Aperiodic offsets were significantly and negatively correlated with postoperative pain ratings on POD7 (Figure 4b; $\rho = -0.28$, $P_{\text{FDR}} = 0.03$). However, no significant correlation was found between the aperiodic exponents and postoperative pain ratings on POD7 (Figure 4; $\rho = -0.16$, $P_{\text{FDR}} = 0.19$). To demonstrate the relationship between aperiodic components and postoperative pain ratings on POD7, we divided all patients into three POD7 levels (i.e. $\text{POD7} < 4$, $4 \leq \text{POD7} \leq 5$ and $\text{POD7} > 5$; Figure 4) and intuitively illustrated the patients with a higher offset of aperiodic component (translated the frequency axis into the log space) reported lower pain ratings on POD7. No significant correlations between both aperiodic features and postoperative pain ratings collected at other time points were observed ($P_s > 0.05$).

3.4 | Multiple linear regression results

Table 2 summarized significant MLR results to predict postoperative pain using demographic information, preoperative pain and EEG features. Specifically, postoperative pain on POD2 could be predicted by the PAF and preoperative pain ($F = 5.66$, $P_{\text{FDR}} = 0.006$; adjusted $R^2 = 0.13$) with the following model: $\text{POD2} = -0.55 \times \text{PAF} - 0.16 \times \text{preoperative pain} + 10.43$. Postoperative pain on POD3 could be also predicted by the PAF and preoperative pain ($F = 7.14$, $P_{\text{FDR}} = 0.002$; adjusted $R^2 = 0.16$) with

the following model: $\text{POD3} = -0.23 \times \text{preoperative pain} - 0.51 \times \text{PAF} + 10.04$. Postoperative pain on POD5 could be also predicted by the PAF ($F = 5.26$, $P_{\text{FDR}} = 0.025$; adjusted $R^2 = 0.06$) with the following model: $\text{POD5} = -0.44 \times \text{PAF} + 7.88$. Postoperative pain on POD7 could be predicted by the total power of delta oscillations ($F = 6.11$, $P_{\text{FDR}} = 0.016$; adjusted $R^2 = 0.08$) with the following model: $\text{POD7} = -1.21 \times \text{total power of delta} + 4.16$. Postoperative pain at POW10 could be predicted by the age of patients ($F = 5.03$, $P_{\text{FDR}} = 0.028$; adjusted $R^2 = 0.06$) with the following model: $\text{POW10} = 0.06 \times \text{age} - 1.87$. Postoperative pain at POW12 could also be predicted by the age of patients ($F = 4.93$, $P_{\text{FDR}} = 0.03$; adjusted $R^2 = 0.059$) with the following model: $\text{POW12} = 0.08 \times \text{age} - 3.8$.

To validate the effectiveness of these models, we performed LOOCV. The results showed that model-predicted values were positively correlated with postoperative pain on POD2 ($\rho = 0.27$, $P_{\text{FDR}} = 0.04$) and on POD3 ($\rho = 0.33$, $P_{\text{FDR}} = 0.014$; Figure 5). However, the correlation coefficients between the predicted values and the actual pain ratings for the models of POD5, POD7, POW10 and POW12 were not significant ($P_{\text{FDR}} > 0.2$).

4 | DISCUSSION

The diagnoses and treatments of lumbar stenosis and spondylolisthesis have become increasingly required in the elderly population (Berardino et al., 2021). Lumbar spinal surgery is one of the commonly used procedures for back and leg pain management, especially for patients aged 60 or older with lumbar spinal stenosis (Ulrich et al., 2022). Chronic pain is a common complication following lumbar spinal surgery, affecting more than 20% of patients (Thomson, 2013; Weir et al., 2017). To identify predictors of postoperative pain, we performed a longitudinal study, with preoperative pain ratings, resting-state EEG activities, anxiety and depression scores and demographic information collected before surgery, and postoperative pain ratings collected ten times after surgery, ranging from Day 1 to Week 12. We observed a high incidence of acute and chronic postoperative pain in older patients (i.e. pain ratings > 3 ; POD3: 56.0%; POW12: 34.7%). Moreover, we found that preoperative pain and resting-state EEG features, that is the PAF, were the primary predictors of acute postoperative pain. While age was a significant predictor of chronic postoperative pain in MLR models, the predictive performance for chronic postoperative pain based on age is poor when applying LOOCV. Our study suggests the potential for predicting acute and chronic postoperative pain by utilizing preoperative measurements. This discovery holds significant implications for pain assessment,

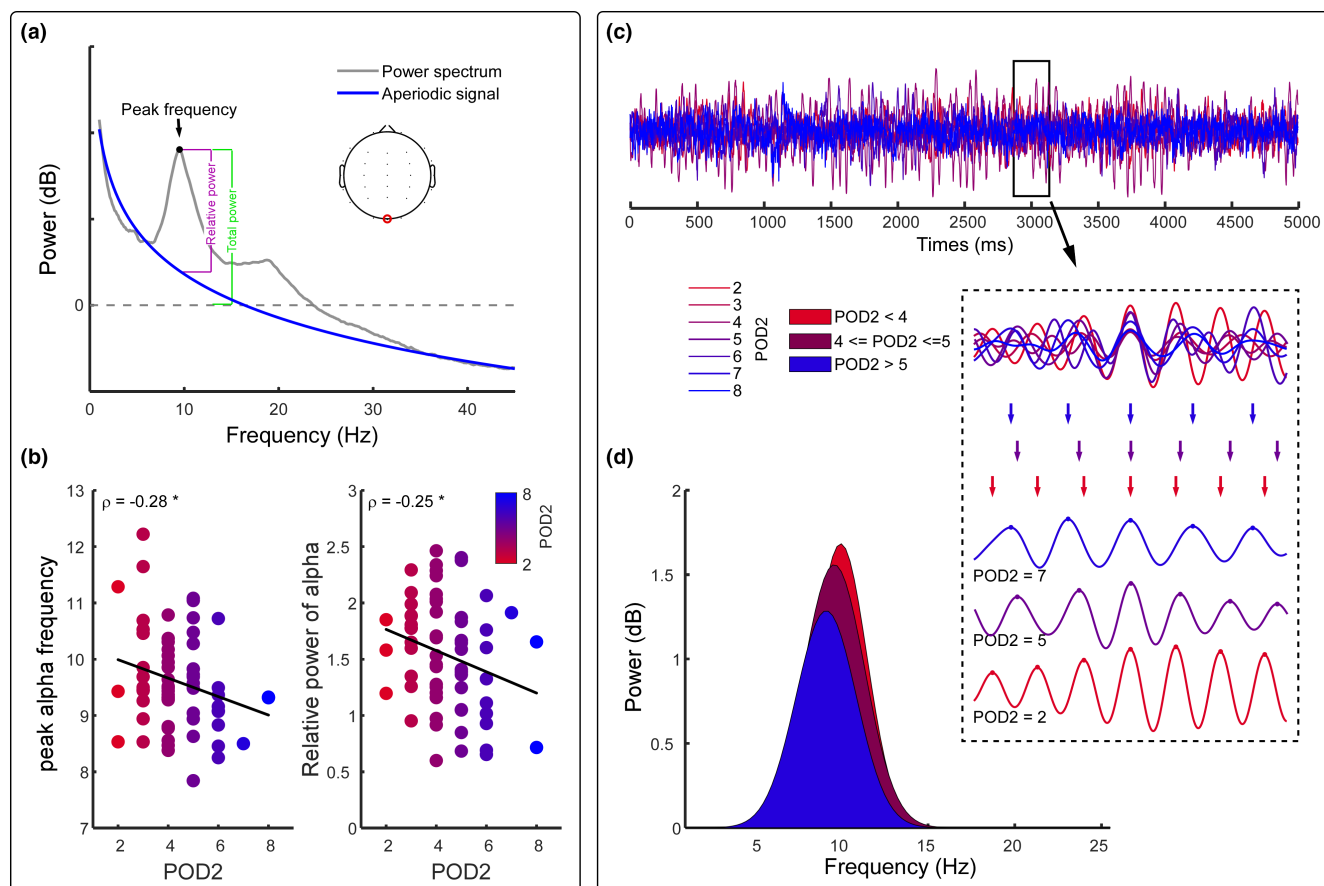


FIGURE 3 The extraction of periodic and aperiodic components from power spectra and the correlation between pain ratings on postoperative Day 2 (POD2) and the peak alpha frequency (PAF). (a) Power spectrum (grey line; Oz-avg) and its aperiodic signal (blue line) were illustrated with labels of total power, relative power and PAF. (b) Scatter plots showed that POD2 ratings were negatively correlated with the PAF and with the relative power of alpha oscillations ($*P_{FDR} < 0.05$). (c) Raw signals were recorded from several representative patients with line colours encoded POD2 ratings. Enlarged waveforms displayed bandpass filtered signals (7–14 Hz). The subfigure showed three alpha waves corresponding to different POD2 levels (POD2=2, 5, and 7). Peaks of the alpha waves were marked by coloured arrows, indicating that patients with different POD2 ratings may exhibit varying peak frequencies. (d) After removing the aperiodic components, the power spectrum of periodic signals was reconstructed using the peak frequency, relative power and bandwidth of alpha oscillations. Patients with larger POD2 ratings tended to have a lower peak frequency and a reduced relative power of alpha oscillations.

as it could pave the way for the development of tailored and highly effective treatment strategies in the future. By identifying individuals who are at a higher risk for experiencing postoperative pain, healthcare professionals can intervene early and provide targeted interventions to mitigate their postoperative pain experience.

Previous studies have shown that the PAF is lower in chronic pain patients than healthy subjects (Furman et al., 2020; Sarnthein et al., 2006), which suggested that PAF may serve as a reliable biomarker for prolonged pain sensitivity (Furman et al., 2020). In our study, we observed a significant correlation between the PAF and pain ratings on POD2, with patients exhibiting higher PAF before surgery experiencing lower pain on POD2. This observation was consistent with another study, which revealed that the preoperative PAF was negatively related to postoperative pain (within 72 hours after surgery) in lung cancer patients

(Millard et al., 2022). Moreover, MLR analysis revealed that PAF and preoperative pain were predictors of postoperative pain on POD2 and POD3. We also observed a significant correlation between the relative power of alpha oscillations and pain ratings on POD2, with patients exhibiting higher alpha relative power before surgery experiencing lower pain on POD2. Notably, the PAF and the total power of alpha oscillations calculated using the conventional spectral analysis were not significantly correlated with postoperative pain ($P_s > 0.05$). These contradictory findings may suggest that controlling aperiodic activity using the FOOOF algorithm could improve the accuracy of quantifying neural oscillations in resting-state EEG data (Donoghue et al., 2020; Donoghue & Watrous, 2023). In other words, separating periodic and aperiodic components is crucial for clarifying the putative functional roles of neural oscillations (Donoghue & Watrous, 2023).

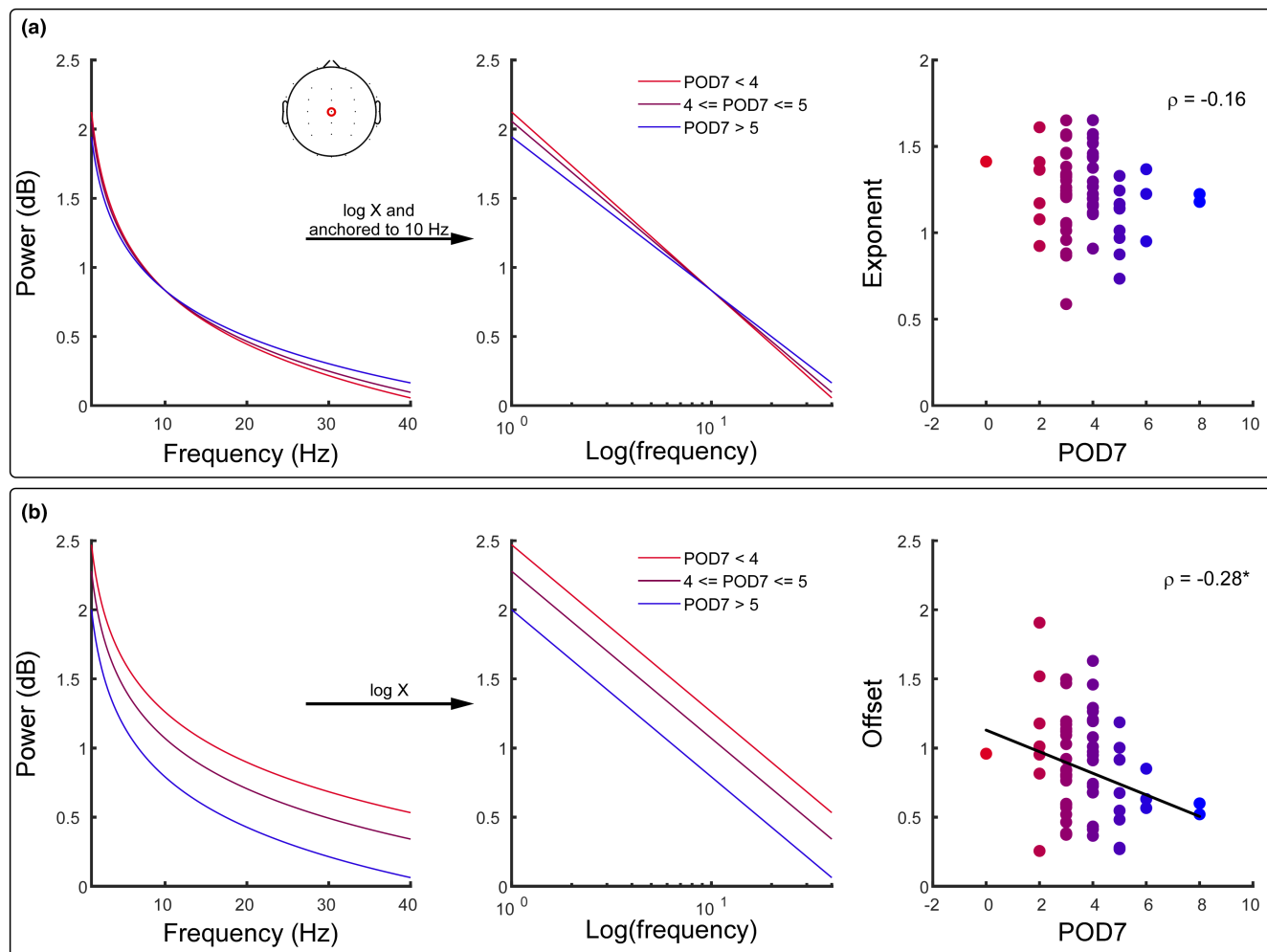


FIGURE 4 Correlation between aperiodic features and pain ratings on postoperative Day 7 (POD7). (a) There was no significant correlation between POD7 ratings and aperiodic exponents. To highlight the distinctions in aperiodic exponents among various grouped curves, we initially fixed the original curves at a specific frequency (10 Hz) and subsequently controlled the aperiodic offsets of the curves to a fixed value. (b) A significant negative correlation was also observed between POD7 ratings and aperiodic offsets, and patients with larger POD7 ratings showed a lower offset of aperiodic components (* $P_{FDR} < 0.05$). To highlight the distinctions in aperiodic offsets among various grouped curves, we controlled the aperiodic exponents of the curves to a fixed value.

TABLE 2 Multiple linear regression of postoperative pain using preoperative features.

Y	X	β	SE	P_{FDR} value
POD2	PAF	-0.55	0.19	0.006
	Preoperative pain	-0.16	0.07	0.032
POD3	Preoperative pain	-0.23	0.08	0.003
	PAF	-0.51	0.20	0.013
POD5	PAF	-0.44	0.19	0.025
POD7	Delta total power	-1.21	0.50	0.016
POW10	Age	0.06	0.03	0.028
POW12	Age	0.08	0.04	0.030

Abbreviations: FDR, false discovery rate; PAF, peak alpha frequency; POD, postoperative day; POW, postoperative week; SE, standard error.

Recently, interests in aperiodic components of EEG signals have grown due to their connection to various neurological and psychiatric conditions (Ladas et al., 2023; Lendner et al., 2020; Ostlund et al., 2021). It has been suggested that aperiodic activity might be influenced by conscious and perceptual states and reflect overall neural excitability levels (Ladas et al., 2023; Lendner et al., 2020; Waschke et al., 2021). Although the involvement of aperiodic components of EEG signals in pain processing remains not fully understood, the present study found significant correlations between aperiodic offsets and postoperative pain on POD7. This finding suggests that aperiodic activity might be a potential indicator of disruptions in excitatory-inhibitory balance associated with pain (Ahmad et al., 2022; Chini et al., 2022; Gao et al., 2017). Notably, postoperative pain on POD7 can be predicted

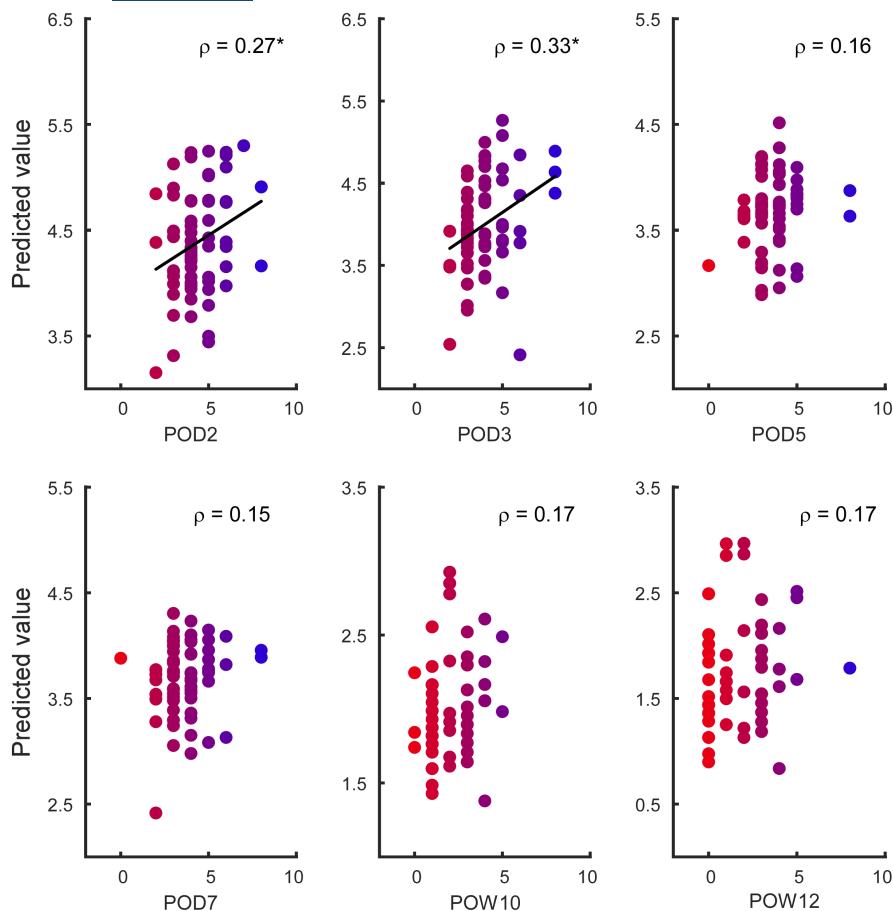


FIGURE 5 Correlations between predicted values and postoperative pain ratings after surgery. After performing LOOCV, significant correlations were observed between POD2 and POD3 ratings and their respective predicted values (* $P_{FDR} < 0.05$). The correlations between the predicted values and the ratings of POD5, POD7, POW10 and POW12 were not significant.

by the total power of theta oscillations. This observation would be reasonable, considering that the aperiodic offset is closely associated with the power of EEG signals at low frequencies, including theta oscillations.

The postoperative pain at the later stage (i.e. pain ratings at POW10 and POW12) was significantly predicted by the age of the patients. However, when applying the LOOCV method in MLR analysis, our results indicated that the predictive performance of chronic pain models based on age was not significant. This poor predictive performance of these models may be attributed to several factors: the decreasing reliability of pain rating methods over time, the small sample size of the study. Additionally, during postoperative recovery, chronic pain ratings tend to concentrate within a smaller range of values, resulting in a lower degree of variance explained by the model. However, evidence from rodent studies suggests that there was a notable increase in action potential firing response to mechanical stimuli in age mice compared to their counterparts in the control group. The firing rates in the aged mice exhibited less reduction when exposed to sustained or repeated stimuli, suggesting that they may have greater difficulty adapting or desensitizing to painful stimuli (Weyer et al., 2016). There seems to be a decrease in the

efficiency of inhibitory systems in older individuals, making them more susceptible to experiencing severe pain if they are repeatedly exposed to stimuli (Tinnirello et al., 2021). These findings potentially provide an explanation for the heightened levels of pain sensitivity observed in elderly individuals. Combining the findings from these studies, our results suggest that older patients might require more targeted pain management strategies to prevent or manage chronic postoperative pain.

It is important to acknowledge several limitations in the present study. First, the clinical experimental design used in this study may potentially be confounded by other unwanted factors. Although a standardized operative procedure was adopted for all patients, the surgery process itself may vary, including the duration of the surgery, surgery complexity and the attitude of patients towards analgesics, which might affect the perception of postoperative pain. Future research should consider the impact of these factors and attempt to control them. Second, the sample size of the present study is relatively small, and there is variation in the age and education levels among the patients. These factors might affect the results and limit the generalizability of our findings. In future research, it would be necessary to expand the sample size

and minimize the influence of irrelevant variables to increase the reliability and validity of our results. Moreover, our study utilized the NRS to assess postoperative pain only once a day. However, future research could consider increasing the frequency of pain assessments. This would provide a more comprehensive understanding of the temporal changes in postoperative pain, allowing for a more accurate evaluation of pain development trends and influencing factors. By increasing the frequency of assessments, we could observe the onset, peak and duration of postoperative pain more finely, aiding in a deeper understanding of its characteristics and evolution. Additionally, more frequent assessments would enhance data stability and reliability, facilitating more effective analysis and interpretation of pain-related factors.

AUTHOR CONTRIBUTIONS

QH was responsible for study design, patient recruitment, data collection and provided assistance with data analysis and manuscript drafting. HW conducted data analysis and drafted the manuscript. YL participated in patient recruitment and data collection. XL, YG and XZ contributed to manuscript drafting and editing. YF contributed to study design, study monitoring and supervision. LH contributed to study design, data analysis, manuscript writing and supervision.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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