ORIGINAL RESEARCH

The Predictive Power of Intraoperative EEG and Clinical Characteristics for Postoperative Delirium Following Cardiac Surgery

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Introduction: Postoperative delirium is common and associated with poor postoperative outcomes. However, the predictive power of intraoperative electroencephalogram (EEG) features for postoperative delirium has not yet been well studied.

Methods: Intraoperative EEG data from 261 patients who underwent major cardiac surgery were analyzed. Cases were identified using the Confusion Assessment Method. Predictive analytics for delirium outcome were performed using (1) only clinical data, (2) only EEG data, and (3) a combined list of important features from the first two stages.

Results: Eleven percentage of participants experienced postoperative delirium. The patients were generally older and had lower physical and cognitive function. EEG models were found to be highly specific but less sensitive in identifying delirium cases. The combined EEG-clinical model performed comparably to the clinical-only model (AUC = 80%) but outperformed the EEG-only model (AUC = 56%). After adjusting for clinical covariates, only interhemispheric mutual information remained significantly associated with delirium ($OR = 2.29$, $p = 0.03$), with a positive correlation with delirium severity ($\rho = 0.18$, $P \leq 0.01$).

Conclusions: This study enhances our understanding of delirium neurophysiology by emphasizing the role of intraoperative EEG as a marker of brain vulnerability. Although EEG may not constitute a standalone biomarker of delirium, it holds promise for delirium risk stratification.

Key Words: Cardiac surgery, Delirium, Electroencephalography, Machine learning.

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Approximately one-third of elderly patients who undergo cardiac surgery experience postoperative delirium, an acute state of confusion characterized by difficulties in attention and overall cognitive function.[1–3] Postoperative delirium significantly affects postoperative care with notable associations such as long-term cognitive impairment, extended hospital stays, increased likelihood of institutionalization, higher readmission rates, and increased mortality, even up to 10 years after cardiac surgery.[4–7] Given the high incidence and substantial impact of delirium on postoperative care, identifying prognostic markers to predict delirium offers a more promising strategy than relying solely on current subjective diagnostic approaches. This is particularly important because delirium is potentially preventable,[3,8] making early identification and intervention crucial for improving postoperative outcomes.

General anesthesia alters electroencephalogram (EEG) oscillations that depend on the class and dosage of the anesthetic drug.[9] For adults, halogenated ethers such as isoflurane and sevoflurane induce large amplitude slow/delta (0.5–4 Hz), frontal theta (4–8 Hz), and frontal alpha (8–12 Hz) oscillations during general anesthesia.[10,11] At higher doses, these oscillations may transition into burst suppression,[12,13] and patients with low alpha power are more likely to exhibit burst suppression.[14,15] Consistent with this finding, low alpha power[16–19] and burst suppression[19–22] have both been associated with postoperative delirium. Nevertheless, recent findings indicate that the association between low alpha power and postoperative delirium loses significance after adjusting for underlying cognitive function.[23] Therefore, there is a need to identify EEG features that can provide important new information to identify patients at risk of postoperative delirium.

In this study, we investigated the predictive power of EEG features and clinical characteristics of postoperative delirium after major cardiac surgery. We hypothesized that intraoperative EEG features would provide valuable prognostic insights into postoperative delirium beyond what is revealed by clinical risk factors assessed through cognitive and physical health metrics.

METHODS

Study Design and Patient Selection

This is a secondary analysis of EEG data from 262 participants who were enrolled in the Minimizing ICU Neurologic Dysfunction using Dexmedetomidine-induced Sleep trial and had analyzable EEG data without missing delirium

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assessments. Briefly, the Minimizing ICU Neurologic Dysfunction using Dexmedetomidine-induced Sleep trial was a single-center, randomized, placebo-controlled superiority trial conducted at Massachusetts General Hospital between March 2017 and July 2021. The main objective of this study was to examine the delirium-sparing effects of a single sleep-inducing dose of dexmedetomidine in a cohort of nonmechanically ventilated ICU patients who were recovering from cardiac surgery. The study was approved by the Mass General Brigham Institutional Review Board (Protocol 2016P000742) and registered at ClinicalTrials.gov (NCT 02856594). The trial protocol (including exclusion and inclusion criteria) and initial findings have been previously published.[3,24] Patients were excluded if they required total circulatory arrest, were allergic to dexmedetomidine, had renal or liver failure, were admitted to the ICU for more than 2 days in the preceding month, were previously diagnosed with structural or anoxic brain injury, or tested positive for SARS-CoV-2. Patients who were either blind or could not communicate in English were also excluded. All participants provided verbal and written informed consent to participate in the trial.

Delirium cases were identified with twice-daily (AM and PM, with at least 6 hours apart) use of the confusion assessment method (CAM) in the first 3 postoperative days, by trained trial staff.[24] The CAM is an assessment tool designed based on the DSM-IV diagnostic criteria and widely used to identify cases of delirium, with demonstrated sensitivity of 94% to 100% and specificity of 90% to 95%.[25] In addition, the long CAM (CAM-S) score was used to also assess delirium severity as a secondary outcome. Baseline patient characteristics were collected before surgery as part of the preoperative evaluation, typically within 1 month of the scheduled surgery date. These included objective measures such as weight, height, and body mass index, as well as documentation of existing comorbidities. Baseline cognitive function was assessed using the telephonic version of the Montreal Cognitive Assessment tool, a widely used cognitive screening tool, highly sensitive and validated for detecting mild cognitive impairments.[26,27] In addition, patients provided self-reported ratings of their physical and mental health, sleep quality, and pain interference.[28,29]

Electroencephalogram Recording and Processing

Intraoperative EEG data were acquired using SEDLine sensors (Masimo Inc, CA) at a sampling frequency of 250 Hz using a five-electrode montage (Fig. 1A). Assessment of sufficient depth of anesthesia were based on standard institutional practices, typically involving maintenance of end-tidal anesthetic concentration of 0.7 to 1.3 MAC for at least 15 mins after induction of general anesthesia and before initiation of CPB. For each patient, an artifact-free 2-minute segment of EEG was extracted between the induction of anesthesia and initiation of cardiopulmonary bypass (Fig. 1B). Within this 2-minute segment of recordings, signals were segmented into overlapping epochs of 10 seconds with a step size of 4 seconds. Using finite impulse response algorithm for pre-processing, a notch filter was applied to remove the line noise at 60 Hz, and a low-pass filter was applied with an upper cutoff frequency of 30 Hz. The data were then baseline-corrected by subtracting the mean across all the data points, after which the reference channel FPZ was removed from the analysis. The power spectral density was calculated using multitaper spectral estimation with a bandwidth of 1 Hz and for the frequency range of 0.1 to 30 Hz (where delta = 1 to 4 Hz, theta = 4 to 8 Hz, alpha = 8 to 12 Hz, and beta = 12 to 30 Hz). The PSD values were converted into decibels (dB). A total of 29 EEG features (from each channel) were extracted using the (Fitting Oscillations & One Over F) algorithm to decompose the spectral data into periodic and aperiodic components. An arithmetic mean was computed across channels for a given extracted feature. Extracted features nicely fell into the broad categories of power spectral, oscillatory, connectivity and synchronization, entropy, and fractal features (see **Table 1, Supplemental Digital Content 1,** http://links.lww.com/JCNP/A312) using unsupervised algorithms. All data processing and feature extraction were performed using Python (v3.8.5).

Machine Learning and Statistical Analyses

To ascertain the optimal machine learning algorithm for analyzing the baseline clinical and EEG data from our cohort, supervised classification models were trained using four algorithmically distinct methods: Support Vector Machine using a radial kernel, Random Forest, Elastic Net, and extreme Gradient Boosting. For each method, model performance was evaluated by a k-fold cross-validation ($k = 10$), wherein for each of the 10 iterations, the model was trained on 90% of the randomly shuffled dataset (i.e., k-1 folds), and model performance was evaluated on the remaining hold-out fold. Thus, all available datasets were included in the evaluation of the model performance. For each training iteration, the model hyperparameters were fine-tuned by grid optimization, which is a hyperparameter optimization technique that searches for an optimal combination of hyperparameter combinations for the model at hand (see **Table 2, Supplemental Digital Content 1,** http://links.lww.com/JCNP/A313). A final model was then built based on all available data and the average of the hyperparameters from the training iterations of a given algorithm.

Given the relatively higher number of controls than cases (233 vs. 29, respectively), the inverse class and instance weights were used to reduce the misclassification cost. In this article, the minority class (i.e., the set of delirium cases) was assigned higher weights during training, so that the model addressed the class imbalance to optimize the misclassification cost. We used one-hot encoding to transform categorical variables into a numerical representation suitable for machine-learning modeling. Furthermore, we checked for multicollinearity among the extracted features, using various methods (VIF, correlation matrices, Fig. 2B). The performance of each model was assessed using a confusion matrix (for sensitivity and specificity), area under the receiver operator curve (ROC), Cohen's kappa, κ, and no-information rate (NIR). The best-performing model was used to build the final model for feature selection. Statistical analyses were performed in three stages: (1) prediction of delirium cases using EEG features only, (2) prediction of cases using clinical features only, and (3) classification using important features selected from stages I and II. This final subset of important features was based on the relative variable importance of the

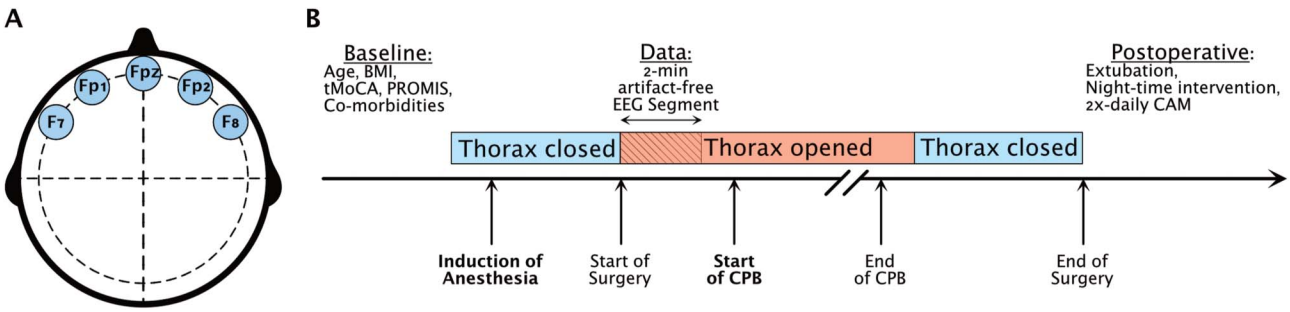

FIG. 1. Study design: **A,** Schematic representation of the five-electrode montage for intraoperative EEG monitoring. The electrodes were positioned at approximately Fp1, Fp2, F7, F8, and approximately 1 cm above Fpz. The ground/reference electrode was Fpz. **B,** A cohort of 262 participants with analyzable EEG data was selected from the parent Minimizing ICU Neurologic Dysfunction using Dexmedetomidine-induced Sleep trial of 394 participants in the modified intention-to-treat cohort. Baseline clinical characteristics were collected before surgery and intraoperatively, using a 2-minutes artifact-free EEG segment between the skin incision and the start of CPB. Postoperatively and following extubation, a night-time interventional dose of either placebo or dexmedetomidine was administered for up to three nights in the cardiac surgical ICU. BMI, body mass index; CAM, confusion assessment method; CPB, cardiopulmonary bypass; EEG, electroencephalogram; PROMIS, patient-reported outcome measurement information system; tMOCA, telephonic-Montreal cognitive assessment tool.

features (i.e., how much each feature contributes to the accuracy of a model's predictions, estimated using Gini or the mean decrease in impurity) using an arbitrary cut-off of at least 50%. Lastly, to eliminate confounding by treatment, a *post hoc* analysis stratified by treatment was also performed. In this article, treatment was handled as an effect modifier, given the significant results of the primary trial results.[3] Statistical tests used include the Student *t*-test for univariate analyses and logistic regression for multivariable analyses. All statistical analyses were performed using the *R* environment for statistical computing (version 4.2.2) at a significance level, $\alpha \leq 0.05$.[30]

RESULTS

Baseline Profile of Participants

A subset of 302 participants from the original cohort of 394 had analyzable EEG data. Among these participants, 262 were evaluated for delirium, while 40 were excluded from follow-up assessment based on predetermined criteria. On average, the delirium group was older (73 vs. 69 years for controls, $p = 0.002$) and exhibited lower baseline neurocognitive scores (telephonic version of the Montreal Cognitive Assessment tool score of 18 vs. 19 for controls, $P = 0.030$). The data are summarized in Table 1.

Analyses of Clinical Variables

Using clinical characteristics outlined in Table 1, we trained the data with four different algorithms to classify participants according to delirium outcome. Based on the model performance metrics reported in **Supplemental Digital Content 1** (see **Tables 3 and 4,** http://links.lww.com/JCNP/A314 and, http://links.lww.com/JCNP/A315) the Random Forest model demonstrated the best predictive performance on the hold-out testing sets, with an area under the ROC curve of 72% (95% confidence interval [CI]: 62%–81%), Cohen kappa of 97%, and specificity of 98% (96%–100%). However, the model sensitivity was low, at 10% (7%–15%) (Fig. 2A and see **Figure 1A, Supplemental Digital Content 1,** http://links.lww.com/JCNP/A320). Age, body mass index, physical function, and subjective and objective cognitive functions were the most important baseline clinical predictors of postoperative delirium (see **Figure 1B, Supplemental Digital Content 1,** http://links.lww.com/JCNP/A320).

Analyses of Electroencephalogram Features

In a univariate analysis comparing the each of the 29 EEG features with delirium outcome (see **Table 5, Supplemental Digital Content 1,** http://links.lww.com/JCNP/A316), we found that 11 features met the threshold for statistical significance (alpha power, beta power, total power, periodic-aperiodic offset, periodic-aperiodic error, Lempel–Ziv complexity, permutation entropy, Hjorth mobility, Hjorth complexity, number of zero crossings, inter-hemispheric mutual information (IHMI), unadjusted $P < 0.05$). The mean values of these features were lower in the delirium group, except for the Hjorth mobility, number of zero crossings, and IHMI. For variables such as IHMI, alpha, and beta power, which showed significant differences between cases and controls, kernel density plots revealed a bimodal distribution (see **Figure 1C, Supplemental Digital Content 1,** http://links.lww.com/JCNP/A320). Electroencephalogram-only models were highly specific but lacked sensitivity in identifying delirium cases (see **Tables 3 and 4, Supplemental Digital Content 1,** http://links.lww.com/JCNP/A314 and http://links.lww.com/JCNP/A315). Furthermore, the predictive power of the EEG features was not different from that of a random classifier (area under ROC = 56%, 95% CI: 36%–64%, Fig. 2A and see **Table 3, Supplemental Digital Content 1,** http://links.lww.com/JCNP/A314).

Combined Analyses of Clinical and Electroencephalogram Features

In a combined model that included the important clinical and EEG features from the preceding analyses, model performance

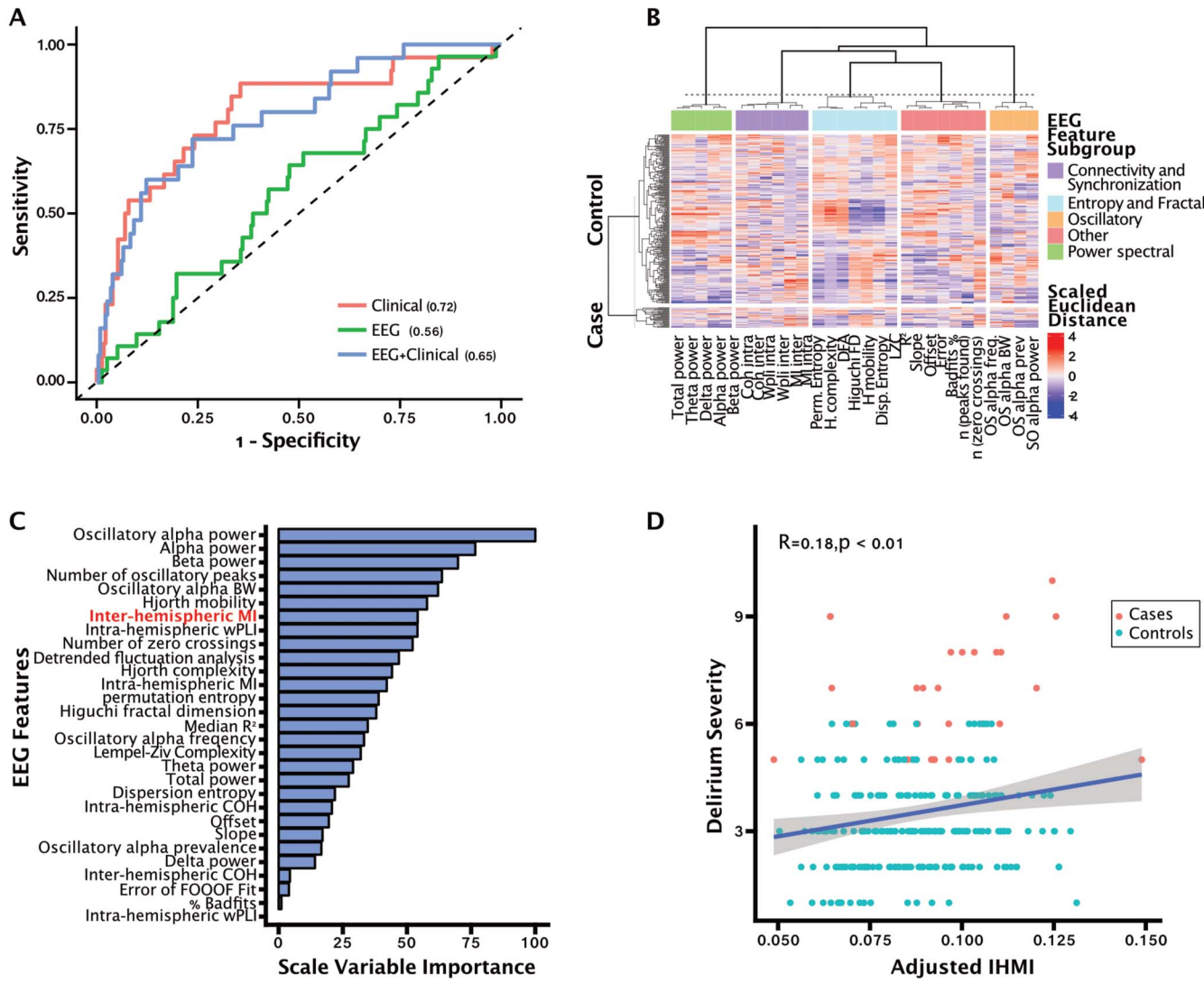

FIG. 2. Machine Learning Analyses: **A,** Receiver operator curve analyses of the binary classifier were performed using (1) only baseline clinical data (in red), (2) only EEG data (in green), and (3) a combined clinical-EEG feature set (in blue). **B,** Unsupervised clustering with dendrography showed five major groups of the 29 total EEG features, without a clear visual pattern for discriminating delirium cases from nondelirium controls. **C,** A bar chart of EEG features ranked in decreasing order of importance for delirium outcome prediction based on GINI (mean decrease in impurity) from the best-performing machine learning method, Random Forest. **D,** Bivariate analyses of delirium severity and adjusted IHMI (adjusted for the clinical characteristics). %Bad fits, percentage of epochs with a bad fit; COH, coherence; EEG, electroencephalogram; FOOOF, fitting oscillations & one over F; MI, mutual information; R^2, coefficient of determination of the FOOOF fit; wPLI, weighted phase lag index; IHMI, inter-hemispheric mutual information; R, Pearson's correlation coefficient.

was on par with that of the clinical-only model across all metrics, with AUC = 65% (95% CI: 60%–70%, Fig. 2A and see **Table 3, Supplemental Digital Content 1,** http://links.lww.com/JCNP/A314). In addition, unsupervised clustering of EEG features did not yield discernible visual patterns that could effectively differentiate between cases and controls (Fig. 2B). To ascertain the statistical associations with delirium outcomes, a multivariable analysis of the EEG features was performed, which involved adjustment for clinical covariates. In this article, we observed that, among the most important EEG features (Fig. 2C), only IHMI remained statistically significant (see **Table 6, Supplemental Digital Content 1,** http://links.lww.com/JCNP/A317). Given this observation between IHMI and the occurrence of delirium, a subsequent correlational analysis further suggested a significant linear dependency between IHMI and delirium severity (rho = 0.18, $P < 0.01$, Fig. 2D). To eliminate the possibility of confounding by treatment, we conducted a sensitivity analysis focusing only on participants in the parent trial who were randomized only to the placebo group. The proportion of study subjects with postoperative delirium (see **Table 7, Supplemental Digital Content 1,** http://links.lww.com/JCNP/A318) and results of machine learning analyses (ML data not

TABLE 1. Table of Clinical Characteristics of Study Participants

Category	Characteristic	Case ($N = 29$) (%)	Control ($N = 233$) (%)	*P*
Baseline characteristics	Age (years)	73 (±6.4)	69 (±6.1)	0.002*
	Biological sex			0.013*
	Female	13 (45)	51 (22)	
	Male	16 (55)	182 (78)	
	Body mass index (kg/m^2)	28 (±5.0)	28 (±5.2)	0.926
	Telephonic MoCA	18 (±3.0)	19 (±2.1)	0.030*
Self-reported health metrics (PROMIS)	Global mental health†			0.130
	Fair	2 (7)	10 (4)	
	Good	7 (24)	27 (12)	
	Very good	12 (41)	88 (38)	
	Excellent	8 (28)	108 (46)	
	Global physical health			0.044*
	Poor	5 (17)	16 (7)	
	Fair	5 (17)	19 (8)	
	Good	8 (28)	63 (27)	
	Very good	10 (34)	88 (38)	
	Excellent	1 (3)	47 (20)	
	Physical function			0.015*
	Severe	0 (0)	3 (1)	
	Moderate	13 (45)	46 (20)	
	Mild	13 (45)	124 (53)	
	Normal	3 (10)	60 (26)	
	Pain interference			0.363
	Moderate	3 (10)	19 (8)	
	Mild	6 (21)	28 (12)	
	Normal	20 (69)	186 (80)	
	Applied cognition			0.024*
	Severe	1 (3)	5 (2)	
	Moderate	5 (17)	9 (4)	
	Mild	3 (10)	29 (12)	
	Normal	20 (69)	190 (82)	
	Sleep disturbance‡			0.453
	Moderate	0 (0)	13 (6)	
	Mild	5 (17)	44 (19)	
	Normal	21 (72)	171 (73)	

Continuous variables are reported as mean (±SD), and categorical variables as frequency (%). Continuous variables were compared between cases and controls using the Student *t*-test (or Kruskal–Wallis test, where appropriate). Categorical variables, on the other hand, were compared using the χ^2 test (or, where appropriate, Fisher exact test).

*Statistically significant difference at alpha ≤0.05.

†No study subjects reported "poor" for PROMIS global mental health.

‡Approximately 10% ($n = 3$) of delirium cases and 2% ($n = 5$) controls had missing entries for sleep disturbance (PROMIS).

MoCA, Montreal cognitive assessment test; PROMIS, Patient-Reported Outcomes Measurement Information System.

shown) in this placebo-only group mirrored findings in the overall cohort, and the IHMI findings were preserved (see **Table 8, Supplemental Digital Content 1,** http://links.lww.com/JCNP/A319 *cf* see **Table 5, Supplemental Digital Content 1,** http://links.lww.com/JCNP/A316).

DISCUSSION

Our study investigated the predictive capacity of intraoperative EEG and clinical characteristics for postoperative delirium after major cardiac surgery. The results revealed a nuanced picture of delirium prediction. Electroencephalogram-based models demonstrated high specificity but lower sensitivity in differentiating delirium cases from controls. Interestingly, an integrated model combining EEG and clinical variables exhibited comparable discriminatory power to a model based solely on clinical factors. After adjusting for clinical covariates, we identified a significant association between IHMI and the occurrence of postoperative delirium. These findings underscore the multifaceted nature of delirium and highlight the challenges in its prediction. While our study reinforces the relationship between EEG parameters (particularly IHMI) and delirium, it also emphasizes that reliance on a single risk marker is often insufficient for accurate prediction. This complexity necessitates a comprehensive approach to delirium assessment and prevention in cardiac surgical patients.

The IHMI represents the statistical dependence between two brain hemispheres.[31–33] A high IHMI value suggests strong statistical dependence, indicating effective information sharing between the hemispheres. Conversely, lower IHMI values suggest less effective information sharing. However, the

disruption of normal neural circuit functioning during general anesthesia complicates the interpretation of IHMI as defined.[34] For instance, bivariate coherence of frontal alpha oscillations has been well characterized during general anesthesia.[11] Coherence can also be conceptualized as a measure of statistical dependence between two brain hemispheres.[11,35,36] However, biophysical models suggest that increased coherence during general anesthesia indicates impaired information processing due to the entrainment of thalamocortical communication.[37–39] Consequently, further research is necessary to fully understand the significance of IHMI during general anesthesia, and in particular, for subjects at risk of postoperative delirium.

The association between alpha power and postoperative delirium is consistent with previously reported findings.[16–18] Similar to Khalifa et al.'s findings,[23] the statistical significance of our alpha power association with delirium diminished considerably after accounting for the clinical covariates. This finding strengthens the robustness of the IHMI as a putative marker of delirium. While clinical covariates collected through questionnaires demonstrated superior predictive power for postoperative delirium compared with EEG features alone, practical hurdles in implementing these questionnaires in routine clinical settings, and their subjective nature as a possible limitation for preoperative risk assessment, must be acknowledged. To balance accuracy with clinical practicality while acknowledging the limitations of relying solely on clinical diagnoses, we propose a dual strategy for delirium diagnosis. This strategy combines clinical diagnostics, such as the CAM, with a carefully chosen set of questionnaires supplemented by intraoperative EEG data when available. As demonstrated in our study, this approach has the potential to enhance the precision and practicality of delirium prediction in the clinical setting.

While this study has strengths, including a relatively large sample size and characterization of a diverse set of EEG features, certain limitations warrant consideration. Utilization of a 2-minute EEG segment spanning the period between anesthesia induction and the onset of cardiopulmonary bypass may limit other novel insights that may have been associated with other EEG segments, such as during cardiopulmonary bypass. Moreover, although reflective of recently published literature, the incidence of POD in our cohort led to an imbalance in the case-to-control ratio. To address this, we used inverse class weighting in our machine learning model. Finally, some of the baseline characteristics in our study relied on self-reported data. Nevertheless, it is essential to emphasize that the questionnaires used in our study were specifically validated for this purpose.[40,41]

In conclusion, this study contributes significantly to our understanding of the intraoperative EEG features associated with postoperative delirium. Although EEG features analyzed in our study did not constitute a sufficient standalone panel of delirium biomarkers, they offer additional insights when interpreted in concert with clinical variables and may potentially improve risk stratification for patients at most risk of postoperative delirium.

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