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Intraoperative neuromonitoring as an independent predictor for postoperative delirium in ICU following aneurysm clipping

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A R T I C L E I N F O

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A B S T R A C T

Objectives: This study aims to evaluate the diagnostic accuracy of significant intraoperative neurophysiological monitoring (IONM) changes as an independent predictor of postoperative delirium (POD) in patients undergoing aneurysm clipping.

Methods: IONM and clinical data from 273 patients who underwent craniotomy for aneurysm clipping from 2019 until 2021 were retrospectively reviewed. Significant IONM changes and POD were respectively evaluated based on visual review of data and clinical documentation. POD was assessed multiple times in the ICU using the Intensive Care Delirium Screening Checklist (ICDSC).

Results: Of the 273 patients undergoing craniotomy with IONM, 83 had POD (30.4 %). Significant IONM changes were noted in 42 patients, of which 19 patients had POD (45.2 %). In contrast, 231 patients had no IONM changes during surgery, of which 64 (27.7 %) patients had POD. Multivariable analysis showed that significant IONM changes were associated with POD, OR: 2.09 (95 % CI 1.01–4.43, *p*-value: 0.046). Additionally, somatosensory evoked potentials (SSEP) changes were significantly associated with POD (p-value: 0.044).

Conclusion: Significant IONM changes are associated with an increased risk of POD in patients undergoing craniotomy for aneurysm clipping. Our findings offer a strong basis for future research and analysis of EEG and SSEP monitoring to detect and possibly prevent POD.

1. Introduction

Postoperative delirium (POD) is a serious complication in surgical patients, increasing morbidity, mortality, and health care expenditure [1–5]. Incidence rates vary depending on the type of surgery, with rates ranging from 15 % to 42.2 % in craniotomy patients, especially those requiring neurosurgery intensive care unit (NICU) stays [6,7].

The clinical picture of POD is heterogenous, with multiple predisposing and precipitating factors, but few modifiable factors that can serve as opportunities for interventions [8]. Intraoperative hypotension is one of these modifiable precipitating factors [9,10]. However, the numerical criteria to define intraoperative hypotension are highly variable, and depending on the chosen criteria for hypotension, the incidence of post-operative complications varies considerably [11]. Thus, neither clinical trials to evaluate delirium from all causes, nor management of intraoperative hypotension management to reduce

Abbreviation: AUC, Area Under the Curve; CBF, Cerebral Blood Flow; CI, Confidence Interval; DOR, Diagnostic Odds Ratio; EEG, Electroencephalography; IONM, Intraoperative Neurophysiological monitoring; IRB, Institutional Review Board; OR, Odds Ratio; ROC, Receiver Operating Characteristic; SSEP, Somatosensory Evoked Potentials; ASA, American Society of Anesthesiologists; POD, Postoperative Delirium; ICDSC, Intensive Care Delirium Screening Checklist; MAP, mean arterial pressure; PPV, positive predictive value; NPV, negative predictive value..

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complications based on a specific criterion have been successful [12,13]. Transient regional cerebral alterations can be associated with hypoperfusion during placement of temporary or permanent clip for cranial aneurysms, even in the absence of general intraoperative hypotension [14–17].

Studies on cerebral blood flow (CBF) during surgeries like carotid endarterectomy (CEA) and cardiac surgeries have highlighted utilization of intraoperative neuromonitoring (IONM), such as somatosensory evoked potentials (SSEP) and electroencephalography (EEG), in assessing CBF changes [18–23]. We aim to demonstrate the association between IONM changes and POD in patient underwent clipping for aneurysm, leveraging its dynamic nature as a continuous intraoperative signal rather than a postoperative diagnostic tool. Previous research suggests that IONM may predict POD in cardiovascular and CEA surgeries and even postoperative neurological deficits during endovascular management of brain aneurysms [24–27].

Our study evaluates whether IONM changes are associated with POD in patients undergoing craniotomy for aneurysm clipping. We believe that the identification of such an association can establish IONM changes as a modifiable independent predictor for POD, guiding intraoperative management strategies to mitigate the risk of POD.

2. Methods

2.1. Study design

The study was approved by the Institutional Review Board (IRB) at the University of Pittsburgh (IRB#:18120055) and had a retrospective cohort design. We included patients who underwent craniotomy for aneurysm clipping with SSEP and EEG monitoring at the University of Pittsburgh Medical Center (UPMC) Health Systems from January 1, 2019 until December 31, 2021. We included all patients who had complete medical records including Intensive Care Delirium Screening Checklist (ICDSC) scores in this study.

2.2. Confounders

In addition to traditional demographic information (age, gender, etc.), confounding factors that could contribute to POD were also extracted from the medical record including preexisting medical conditions, surgery characteristics, and preoperative medication use. Preexisting conditions include diabetes, depression, hypertension, smoking status, history of alcohol use, history of drug use, and history of schizoaffective disorders, which were determined using the ICDE-9/10 diagnostic codes from diagnoses recorded within the UPMC hospital network prior to surgery. Surgery details including admission type, elective status, length, and more were also extracted from these records. Furthermore, American Society of Anesthesiologists (ASA) class status was obtained from Anesthesia Preoperative Documentation. Finally, any mean arterial pressure (MAP) value less than 55 mmHg in the operating room was considered as intraoperative hypotension. The MAP values were obtained through arterial line monitoring if available, or non-invasive blood pressure cuff if an arterial line was not placed. If both arterial and non-invasive values were recorded at a single timestamp, the arterial value was used.

2.3. Delirium assessment

The presence of delirium during the duration of patient's ICU stay was the primary outcome of this study. Using the ICDSC, delirium was assessed 2 times daily during the patient's stay in the ICU; the ICDSC utilizes a scoring system from 0 to 8 in order to assess delirium. The ICDSC score is computed from the registered bedside nurse's observations of the patient's status and behavior across a 12-h shift. Any patient with a single ICDSC score greater than or equal to 4 is considered to have POD [28,29].

2.4. Intraoperative neurophysiologic monitoring

Patients who underwent IONM had both SSEP and EEG monitoring during surgery as previously described monitored by a clinical neurophysiologist throughout the procedure. Any changes are communicated directly to the surgical team to allow timely intervention and prevent prolonged interruptions. Changes communicated to the surgical team are significant, according to the criteria set by the American Clinical Neurophysiology Society (ACNS) [23,30]. EEGs were obtained by placing electrodes on the scalp according to the International 10–20 system. In total, eight channels were recorded starting after intubation, but before incision: F3-P3, P3-O1, F3-T3, T3-O1, F4-P4, P4-O2, F4-T4, and T4-O2. Based on a visual analysis of the EEG waves and spectral data, a significant EEG change is defined as a more than 50 % increase in theta or delta activity, or at least a 50 % decrease in fast frequency amplitude [31] (Fig. 1).

SSEPs were obtained through stimulating either the median or ulnar nerves in the upper limbs, and the tibial or peroneal nerves within the lower limbs. Using subdermal needle electrodes (Rhythm Link ® SC USA), a continuous current stimulation up to 75 mA was applied at intensities that consistently produced a supramaximal SSEP response. Scalp electrodes, placed according to the international 10–20 system, were utilized to record the SSEPs, including both the P4/Fz and P3/Fz. By utilizing electrodes placed at the bilateral Erb's point, peripheral potentials produced within the brachial plexus were captured. Furthermore, averages for each recorded SSEP set used at least 128 trials per calculation. Based on visual review, a significant change in SSEP consists of a sustained and consistent 50 % decrease in cortical SSEP amplitude [32] (Fig. 2).

2.5. Statistical analysis

First, patients were divided into two groups, those who had POD and those who did not. Then, sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) were calculated, and we created receiver operating characteristic (ROC) curves for changes in SSEP alone, EEG alone, both, and either SSEP or EEG. Diagnostic accuracy was predicted using the area under the ROC curve (AUC).

True positives were defined as: significant IONM change (either EEG or/and SSEP) that is accompanied by POD. True negatives were defined as: lack of both IONM change and POD. False positives were defined as: significant IONM change in the absence of POD. False negatives were defined as: lack of IONM change despite POD.

To address the secondary aim, chi-square and fisher's exact test for categorical data and independent t-tests for continuous data were utilized to compare the baseline patient and operative characteristics. On multivariable binary logistic regression analysis, all variables with $P < 0.1$ in the univariate analyses were included in the initial regression model to determine the independent predictors of POD utilizing stepwise approach. We checked for possibility of collinearity utilizing variance inflation factor (VIF) and utilizing pseudo R squared and Akaike Information Criterion (AIC) for appropriateness and fitness of the prediction model… R software version 4.2.2 was used for all statistical analysis and a p-value <0.05 was considered statistically significant.

3. Results

3.1. Overall patient demographics

We reviewed the medical records of 273 patients who underwent craniotomy for aneurysm clipping between 2019 and 2021 with IONM utilizing SSEP and EEG. Patients were divided into 2 groups, one group with POD ($n = 83$, 30.4 %) and one group without POD ($n = 190$, 69.6 %). The mean age for patients with POD and without POD was 58.1 and 53.8, respectively. Other characteristics of the patients are summarized in Table 1, along with association with POD and their associated

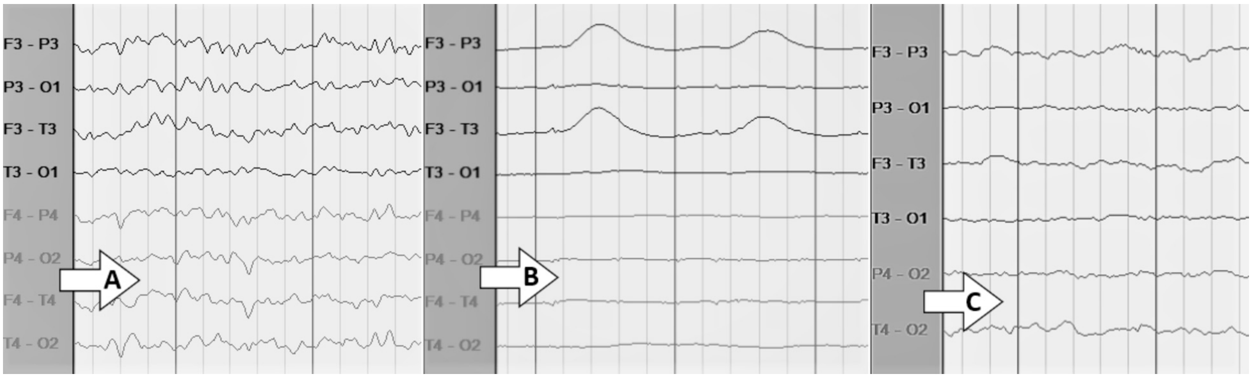

Fig. 1. EEG of the same case in Fig. 2 A. Baseline before intervention. B. During, Burst suppression-flat EEG. C. After intervention, start of EEG return.

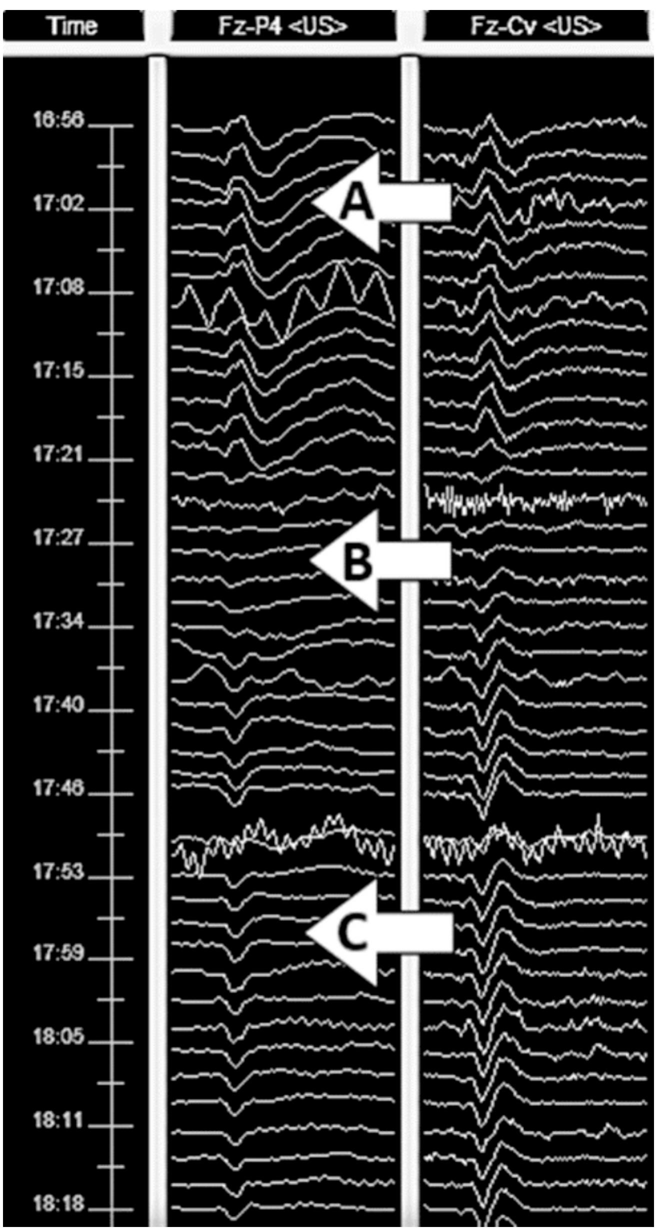

Fig. 2. A. Cortical SSEP from left ulnar nerve. B. Significant decrease in cortical SSEP amplitude. C. Return of SSEP signal after intervention.

Table 1
Baseline characteristics and univariable analysis

Variable	Patients without POD n = 190 (69.6 %)	Patients with POD *n* = 83 (30.4 %)	*p-value*
Age (years)(SD)*	53.8 (11.8)	58.1 (10.3)	0.003
Gender	145 (76.3 %)	61 (73.5 %)	0.730
Body mass index(kg/ m^2)(SD)*	28.4 (7.1)	28.9 (11.0)	0.702
Priority of procedure (Elective)	155 (81.6 %)	51 (61.4 %)	<0.001
Duration of procedure (min) (SD)*	292.4 (101.9)	300.8 (122.6)	0.587
Hypertension	116 (61.1 %)	58 (69.9 %)	0.208
Diabetes Mellitus	17 (8.9 %)	12 (14.5 %)	0.252
Intraoperative hypotension	159 (83.7 %)	74 (89.2 %)	0.321
Smoking	64 (33.7 %)	42 (50.6 %)	0.012
Depression	44 (23.2 %)	20 (24.1 %)	0.990
History of alcohol use	14 (7.4 %)	15 (18.1 %)	0.015
History of drug use	7 (3.7 %)	10 (12.0 %)	0.018
Schizoaffective disorders	10 (5.3 %)	8 (9.6 %)	0.282
ASA class			
1	2 (1 %)	0 (0 %)	NA
2	27 (14.2 %)	3 (3.6 %)	0.010
3	133 (70 %)	40(48.2 %)	0.001
4	28 (14.7 %)	39 (47.0 %)	<0.001
5	0 (0 %)	1 (12.0 %)	NA
SSEP changes	20 (10.5 %)	18 (21.7 %)	0.024
EEG changes	10 (5.3 %)	5 (6.0 %)	0.779
IONM changes	23 (12.1 %)	19 (22.9 %)	0.037

POD: postoperative delirium, SSEP: somatosensory evoked potential, EEG: electroencephalogram, IONM: intraoperative neurophysiological monitoring, ASA: American Society of Anesthesiologists.
* Mean. SD: Standard Deviation.

significance.

3.2. *Diagnostic accuracy of IONM to predict POD*

Table 1 divides the study population according to the presence or absence of POD and presents the characteristics by subgroup. Of the full sample of 273 patients who underwent craniotomy for aneurysm clipping, 42/273 (15.4 %) had significant IONM changes in either EEG, SSEP, or both. The overall incidence of POD was 83/273 (30.4 %). Of the 42 patients with significant IONM changes, 19 (45.2 %) experienced delirium postoperatively. Comparatively, of the 231 patients who did not have IONM changes, 64 (27.7 %) had delirium.

When analyzing each IONM modality separately, 18 (60 %) out of 38 patients who had significant SSEP changes experienced POD, and 5 (33.3 %) out of the 15 patients with significant EEG changes experienced POD. Among the 235 patients who did not have SSEP changes, 65(27.7 %) had delirium; 78(30.2 %) of the 258 patients who did not have EEG

Table 2
Summary of the Effectiveness of Different Intraoperative Neurophysiological monitoring (IONM) Modalities, Both Independently and in Combination, in Predicting Occurrence of Postoperative Delirium (POD).

	SSEP changes	EEG changes	SSEP and EEG changes	SSEP or EEG changes
Number of patients	38	15	11	42
Patients with Delirium	18	5	4	19
Sensitivity (95 % CI)	0.22 (0.13, 0.32)	0.06 (0.02, 0.14)	0.05 (0.01, 0.12)	0.23 (0.14, 0.33)
Specificity (95 % CI)	0.90 (0.84, 0.94)	0.95 (0.91, 0.97)	0.96 (0.93, 0.99)	0.88 (0.82, 0.92)
PPV (95 % CI)	0.47 (0.31, 0.64)	0.33 (0.12, 0.62)	0.36 (0.11, 0.69)	0.45 (0.30, 0.61)
NPV (95 % CI)	0.72 (0.66, 0.78)	0.70 (0.64, 0.75)	0.70 (0.64, 0.75)	0.72 (0.66, 0.78)
AUC (95 % CI)	0.56 (0.51, 0.61)	0.50 (0.47–0.53)	0.51 (0.48, 0.53)	0.55 (0.50, 0.61)
DOR (95 % CI)	2.35 (1.17, 4.73)	1.15 (0.38, 3.49)	1.32 (0.38, 4.65)	2.16 (1.10, 4.22

DOR: Diagnostic Odd Ratio, CI: confidence interval, AUC: area under curve, PPV: positive predictive value, NPV: negative predictive value, SSEP: somatosensory evoked potential, EEG: Electroencephalogram

changes also experienced delirium.

Table 2 also includes the calculated sensitivities, specificities, PPV, and NPV, along with DOR and AUC for EEG and SSEP changes, both independently and combined, to be able to predict POD occurrence. Highest specificity and NPV (96 % and 70 %, respectively) were found when changes occurred in both SSEP and EEG, while highest sensitivity and PPV (23 % and 45 %, respectively) were found when changes occurred in either SSEP or EEG.

3.3. Association between different IONM modalities and POD

Upon univariable analysis, SSEP changes during surgery and IONM changes (either EEG changes, SSEP changes, or both) (Figs. 1 and 2) during surgery were both associated with POD (*p*-value: 0.024 and 0.037, respectively). Upon multivariable analysis (Table 3) while adjusting for age, gender, body mass index, procedure priority, procedure length, hypertension, diabetes mellitus, intraoperative hypotension, smoking, depression, history of alcohol or drug use, schizophrenic disorders, and ASA class, both IONM changes (OR: 2.09, CI: 1.01–4.32) and SSEP changes (OR: 2.17, CI: 1.01–4.62) still showed significant association with POD (p-value: 0.046 and 0.044, respectively).

3.4. Associations between confounding variables and POD

The univariate analysis (Table 1) showed significant associations between several different variables and delirium. Being older, having a non-elective procedure, being a smoker, having a history of alcohol use, having a history of drug use, and ASA class (2, 3, or 4) status were all significantly associated with POD. The results showed no association between the presence of delirium and gender, body mass index, length of procedure, hypertension, diabetes mellitus, intraoperative hypotension, history of depression, or schizophrenic disorders. Upon multivariable analysis using the IONM model, age, non-elective surgeries, being a smoker, and history of drug use were significantly associated with delirium (*p*-values: 0.003, 0.001, 0.014, and 0.021, respectively) (Table 3).

Table 3
Multivariable binary logistic regression prediction model for postoperative delirium.

Predictors	aOR*	95 % Confidence Interval		*p-value*
IONM Changes	2.09	1.01	4.32	0.046
Age	1.04	1.01	1.07	0.003
Non-Elective	2.70	1.47	5.00	0.001
Smoking	2.06	1.16	3.67	0.014
History of Drug Use	3.55	1.22	10.79	0.021

IONM: Intraoperative neurophysiological monitoring, aOR: adjusted odd ratio.
* Adjusting for age, priority of procedure (elective vs non-elective), smoking, history of drug use, ASA class, history of alcohol, and IONM changes.

4. Discussion

The study aims to evaluate IONM as an independent predictor for POD which may be associated with alterations in brain perfusion. Alterations in brain perfusion during aneurysms clipping manifest as changes in SSEP and EEG, enabling the surgical team to intervene and maintain adequate cerebral perfusion and reduce perioperative stroke. The current study provides evidence that this approach may help reduce adverse outcomes related to POD among neurosurgical patients [33–35]. We believe that our study will contribute to the limited literature on the association between significant IONM changes and POD during clipping of brain aneurysm clipping, offering a potentially modifiable risk factor for POD.

Changes in IONM changes (SSEP or EEG) during surgery indicate decreased cerebral perfusion, which, if prolonged may lead to stroke. Our group has previously demonstrated that patients who experience perioperative strokes following cardiac, vascular and endovascular coiling of brain aneurysms surgeries are more likely to exhibit significant changes in SSEP and/or EEG during surgery [24,27,36–41]. Importantly, patients who do not exhibit significant IONM changes are less likely to experience a stroke. [42,43] In a longitudinal cohort study, patients with covert strokes (new infarctions on post operative imaging, and no clinical symptoms of stroke) had an increased risk of delirium [44]. Furthermore, prior studies have shown that periprocedural hemodynamic depression (bradycardia or hypotension) increases the likelihood of covert strokes [45]. In a small, randomized trial, patients who underwent cardiac surgery showed an increased incidence of POD in patients who were assigned to a group with MAP 60–70 mmHg vs MAP of 80–90 mmHg [46]. In a large multicenter retrospective study of patients undergoing non cardiac surgery under general anesthesia POD was noted in patients with a MAP <55 mg Hg [47]. It has been suggested that hypotension during surgery leads to a critical decrease in CBF in patients undergoing cardiovascular surgeries, which in turn contributes to the development of delirium. Our previous research has demonstrated an association between IONM changes and intraoperative hypotension with POD in patients undergoing cardiovascular surgeries. [25,26,48,49] Therefore, we hypothesize that IONM changes in patients experiencing intraoperative hypotension could serve as a critical predictor for POD. We believe that this hypothesis could also apply to patients undergoing brain aneurysm clipping. During this procedure, temporary interruption of blood flow occurs, resulting in hypoperfusion to the aneurysm-specific area. Consequently, this alteration in blood flow may contribute to the development of POD.

We identified an independent association between IONM changes and POD (*p*-value 0.046). However, we did not observe a significant correlation between overt intraoperative hypotension and POD (p-value 0.3). Despite this, we believe that our hypothesis remains relevant in our study population. Patients undergoing clipping may experience levels of hypotension or hypoperfusion at a cellular level that are challenging to assess directly. This hypothesis is supported by the observation that EEG alone was not associated with POD (p-value 0.78). EEG primarily reflects overall cerebral perfusion, which may not capture localized changes in cerebral prefusion that occur during clipping procedures. In contrast, SSEP changes reflect cortical somatosensory areas more specifically and may provide a localized reflection of hypoperfusion during clipping. Given the nature of the clipping procedure, which involves more localized alterations in cerebral blood flow, SSEP may be more sensitive to changes in cerebral perfusion compared to EEG [50]. By leveraging both modalities, clinicians can obtain a more nuanced understanding of cerebral hemodynamics and potentially mitigate the risk of adverse postoperative outcomes [51–53].

In our study when evaluating the diagnostic accuracy of IONM changes to identify POD, we observed low sensitivity but high specificity. The AUC analysis indicated that IONM changes (0.55) has limited discrimination for identifying patients with POD. while the highest sensitivity was observed when either change in IONM modalities (SSEP or EEG) was exhibited, with a sensitivity of 23 % and an intraoperative diagnostic odds ratio of 2.16. However, the dynamic and real-time nature of IONM, wherein most detected abnormalities are immediately communicated to the surgical team which leads to interventions, may inadvertently lead to an increase in false positive cases, consequently reducing the AUC and sensitivity. Hence, IONM changes can serve as a neurophysiological real-time intraoperative independent predictor for timely identification of conditions leading to POD with an opportunity for revaluating interventions.

In our study patients who underwent non-elective surgery were independently twice more likely to experience POD (*p*-value 0.001). Patients presenting as emergencies for aneurysms often have subarachnoid hemorrhage, which generally results in poorer outcomes compared to those who present electively. This difference in presentation can significantly impact postoperative recovery and increase the risk POD in this group of patients [54,55]. Previous studies have noted that patients undergoing emergency non cardiac surgery are up to three times more likely to experience POD compared to those undergoing elective surgery [56]. Another study in patients over 65 years of age and undergoing colorectal surgery found high incidence of delirium in both acute and elective surgery [57]. In our study, age emerged as one of the independent predictors for POD with mean age of 58.1 years (*p*-value 0.003). Additionally, the results revealed that smoking and a history of drug use were independently associated with POD (p-value 0.014 and 0.021, respectively) confirming findings from existing literature. [58,59]

It is important to note that research and clinical management should not only prioritize the identification and treatment of POD but also on understanding and identifying the pathophysiology contributing to its development, potentially reducing its incidence. Moreover, it is worth considering whether POD could serve as an initial indicator for other conditions, such as cognitive impairment or strokes. Prolonged unconsciousness may hinder a comprehensive neurological examination, potentially obscuring the detection of new postprocedural neurological deficits that warrant further investigation and intervention [60]. Therefore, future research should focus on evaluating the effectiveness of managing hypoperfusion in specific patient populations who may benefit from maintaining optimal cerebral perfusion during brain aneurysm clipping. This approach could provide valuable insights into the postoperative prognosis of patients, particularly before they awaken from sedation. This is especially pertinent for patients who remain unconscious for extended periods following prolonged surgery.

4.1. Limitation

This study is not without limitations as well. First, the study utilized data from a surgical population restricted to intracranial aneurysm surgeries. Second, the data is exclusively from a single tertiary center, which could affect the generalizability of these results due to the complexity of our patient population. Third, the study is retrospective in nature and thus may suffer from selection bias and inability to separate exact causation such as the preexisting dementia. Finally, ICDSC was only obtained in patients admitted to the intensive care unit, which probably increases the overall incidence of POD.

5. Conclusion

This study aims to provide insights into modifiable intraoperative factors influencing POD in patients undergoing brain aneurysm clipping. Our findings indicate that IONM can serve as an independent predictor of POD in this patient population.

CRediT authorship contribution statement

Abdullah M. Al-Qudah: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Pooja S. Tallapaneni:** Writing – review & editing, Writing – original draft. **Donald J. Crammond:** Writing – original draft. **Jeffrey Balzer:** Writing – review & editing. **Katherine M. Anetakis:** Writing – review & editing. **Varun Shandal:** Writing – review & editing. **Jingyuan Biaesch:** Writing – original draft. **Malik Ghannam:** Writing – review & editing. **Neelesh Nadkarni:** Writing – review & editing. **Bradley A. Groos:** Writing – review & editing. **Michael Lang:** Writing – review & editing. **Kathirvel Subramanium:** Writing – review & editing. **Senthilkumar Sadhasivam:** Writing – review & editing. **Parthasarathy D. Thirumala:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization.

Declaration of competing interest

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