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CRITICAL REVIEW

Predictors of outcomes after surgery for medically intractable insular epilepsy: A systematic review and individual participant data meta-analysis

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Abstract

Insular epilepsy (IE) is an increasingly recognized cause of drug-resistant epilepsy amenable to surgery. However, concerns of suboptimal seizure control and permanent neurological morbidity hamper widespread adoption of surgery for IE. We performed a systematic review and individual participant data meta-analysis to determine the efficacy and safety profile of surgery for IE and identify predictors of outcomes. Of 2483 unique citations, 24 retrospective studies reporting on 312 participants were eligible for inclusion. The median follow-up duration was 2.58 years (range, 0-17 years), and 206 (66.7%) patients were seizure-free at last follow-up. Younger age at surgery (≤18 years; HR = 1.70, 95% CI = 1.09-2.66, $P = .022$) and invasive EEG monitoring (HR = 1.97, 95% CI = 1.04-3.74, $P = .039$) were significantly associated with shorter time to seizure recurrence. Performing MR-guided laser ablation or radiofrequency ablation instead of open resection (OR = 2.05, 95% CI = 1.08-3.89, $P = .028$) was independently associated with suboptimal or poor seizure outcome (Engel II-IV) at last follow-up. Postoperative neurological complications occurred in 42.5% of patients, most commonly motor deficits (29.9%). Permanent neurological complications occurred in 7.8% of surgeries, including 5% and 1.4% rate of permanent motor deficits and dysphasia, respectively. Resection of the frontal operculum was independently associated with greater odds of motor deficits (OR = 2.75, 95% CI = 1.46-5.15, $P = .002$). Dominant-hemisphere resections were independently associated with dysphasia (OR = 13.09, 95% CI = 2.22-77.14, $P = .005$) albeit none of the observed language deficits were permanent. Surgery for IE is associated with a good efficacy/safety profile. Most patients experience seizure freedom, and neurological deficits are predominantly transient. Pediatric patients and those requiring invasive monitoring or undergoing stereotactic ablation procedures experience lower rates of seizure freedom. Transgression of the frontal operculum should be avoided if it is not deemed part of the epileptogenic zone. Well-selected candidates undergoing dominant-hemisphere resection are more likely to exhibit transient language deficits; however, the risk of permanent deficit is very low.

KEYWORDS
epilepsy, epilepsy surgery, insula, insular epilepsy, insulectomy, surgical outcome

1 | INTRODUCTION

Insular epilepsy (IE) is a rare form of drug-resistant epilepsy (DRE), comprising under 3% of cases investigated at tertiary epilepsy centers.[1] However, recognition of IE as a significant cause of DRE has increased since its contemporary definition in 2004.[2–4] Increased safety of both open[5–8] and stereotactic electroencephalography (SEEG) electrode placement in the insula and peri-Sylvian region[2,7,9–20] has led to increased detection of IE in many centers around the world.[2,6,11,16,21–32] Over the last 15 years, several institutions have reported their experience with resective surgery for IE.[6,16,21–27,29–33] These studies have shown IE surgery to be feasible, albeit with variable seizure freedom rates and a non-negligible neurological morbidity profile. Consequently, widespread adoption of IE surgery has been hampered, primarily due to concerns of its efficacy[16] and safety[34] profile and perceived "unfavorable risk-to-benefit ratio".[34–36]

Safety concerns for IE surgery are related to the complex and eloquent cortical anatomy of the insular-peri-Sylvian region. The insula harbors diverse functions and is draped by functional opercular cortices and Sylvian arteries,[33] making resections in the operculoinsular region both technically challenging and associated with non-negligible neurological risks. Motor and language

deficits may arise directly from microsurgical resection, transgression, or retraction of functional peri-Sylvian cortical regions or indirectly from cortical or subcortical middle cerebral artery (MCA)-territory ischemic stroke.[37–39] While major technological advances have made microsurgical resection for IE safer, permanent neurological impairment (eg, hemiplegia) rates exceed 20% in some contemporary series.[32,40]

Characterizing the rate of transient and permanent deficits and their predictors may address concerns for the safety of surgery for IE and facilitate patient counseling. The identification of patient or operative variables associated with postoperative neurological deficits has the potential to refine surgical indications or modify the surgical technique, respectively. Due to the perceived unfavorable risk-to-benefit ratio,[34] in particular concerns for language complications in dominant-hemisphere IE,[36] some centers have advocated for safer palliative neuromodulation approaches such as responsive neurostimulation (RNS) instead of resective surgery in some patients with IE deemed "unresectable".[34–36,41,42] Whether potentially curative resective surgery should be replaced by safer but less effective neuromodulation procedures remains disputable.

While there is relatively good evidence that IE surgery has good efficacy compared with extra-temporal epilepsy (ETE),[16,43,44] the success rate is highly variable. Perceived poor efficacy, in particular for some specific groups such as those with non-lesional IE, has led some groups to perform resective surgeries of the insular area for circumscribed structural lesions exclusively.[30,34] Finally, the landscape of "resective" epilepsy surgery has changed over the last decade, with the application of minimally invasive approaches, such as MR-guided laser thermal ablation (MRgLA)[25,45,46] and radiofrequency ablation (RFA).[47] These techniques lend themselves favorably to a "minimally invasive paradigm" for IE surgery, especially when combined with SEEG.[48] While these stereotactic ablation procedures are indeed less invasive, their outcome profile compared with open resective surgery for IE has yet to be systematically studied.

Due to the rarity of IE, the current available evidence regarding seizure outcome and safety arises mainly from single-center retrospective studies with small number of patients and heterogeneous patient populations—limiting the ability to draw firm conclusions and identify predictors of outcome. Herein, we present an individual participant data (IPD) meta-analysis (IPDMA) of post-operative outcomes in patients undergoing IE surgery.

The objectives of our study were twofold: (a) to describe the efficacy of the surgical treatment of IE and identify predictors of seizure recurrence and (b) to quantify the incidence of neurological complications associated with the surgical treatment of IE and identify factors that predict these complications.

Key Points

- Most patients undergoing surgery for insular epilepsy (IE) experience postoperative seizure freedom (66.3%), and only a minority (<8%) develop permanent neurological deficits.
- Pediatric age and invasive EEG monitoring are associated with shorter time to seizure recurrence.
- Stereotactic ablation (MRgLA/RFA) is associated with a greater likelihood of seizure recurrence compared with open resection.
- While neurological complications are frequent (42.5%), the vast majority are transient, and most recover within 3 months of surgery.
- Patients undergoing frontal operculum resection are at greater risk of motor impairment, including hemiparesis.
- Surgery of language-dominant IE in well-selected candidate is associated with a low rate of postoperative dysphasia, which was transient in all cases in this study.

2 | METHODS

2.1 | Search strategy

To select eligible articles, we conducted a systematic review of the literature in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[49] The search strategy was developed a priori but was not published and used permutations of the following search terms and their variations: "epilepsy" and "insulectomy." To identify potentially eligible studies, we conducted an electronic literature search using 11 databases: Africa-Wide Information [Ebsco], AMED [Ovid] (Allied and Complementary Medicine Database), BIOSIS [Ovid], CINAHL [Ebsco] (Nursing and Allied Health Literature), Cochrane [Wiley], Embase [Ovid], Global Health [Ovid], LILACS (Latin American and Caribbean Health Sciences), Medline [Ovid], PubMed [NLM], and Web of Science [Thomson Reuters] for relevant articles from database inception to January 19th, 2020, (performed by a librarian, E.G.). The search was restricted to humans but with no language limitations.

The results were entered into Endnote X7 (Thomson Reuters) for systematic and manual removal of duplicates. Following the selection of eligible studies, two reviewers (S.O., W.S.) manually searched the bibliographic references of our included studies for additional relevant articles. The complete search strategy and results are available in Appendix S1.

2.2 | Eligibility criteria

In order to be included in this IPDMA, studies were required to meet the following inclusion criteria: (a) case–control, cohort, or randomized controlled trial methodology, (b) consecutive participants (IPD series with a minimum of two participants), (c) at least 80% of patients underwent an insulectomy (± extrainsular corticectomy) for epilepsy due to non-neoplastic lesions or grade 1 neoplasms, and (d) seizure outcome was reported for individual participants. Exclusion criteria for the studies were the following: (a) single case reports, (b) reviews, (c) participants undergoing insular surgery for Grade II (e.g. low grade gliomas), III and IV neoplasms, (d) participants for whom the insula was not at least partly resected (eg, pure operculectomy were excluded), (e) participants undergoing neuromodulation (eg, RNS, deep brain stimulation, vagus nerve stimulation), (f) participants undergoing invasive investigation (eg, SEEG or open sampling) without resection, (g) IPD not available, and (h) non-human subjects.

2.3 | Data extraction

For individual participants in studies that met the inclusion criteria, we extracted the following information: sex, age at epilepsy onset, age at surgery, epilepsy duration, epilepsy etiology (dysplastic lesion or other), history of previous epilepsy surgery, preoperative seizure frequency (daily, weekly, or monthly), seizure semiology, preoperative imaging findings and concordance, scalp EEG findings, use of intracranial electrodes or intraoperative electrocorticography for invasive EEG monitoring, use of MRgLA or RFA, side of handedness and hemispheric dominance, side of surgery (left, right and whether performed on the dominant side), type of operculoinsular surgery, extent of insular, opercular, and extraopercular resection, Engel class outcome, seizure freedom, seizure recurrence, and time to first recurrent seizure and/or last follow-up. For the etiology of epilepsy, both focal cortical dysplasia and tuberous sclerosis were combined and included into "dysplastic lesions." Other etiologies included cavernomas, gliosis, hippocampal sclerosis, Rasmussen's encephalitis, and tumors.

Postoperative neurological deficits were also recorded and classified as transient or permanent. Complications were categorized as permanent if deficits were still present at last follow-up. Deficits consisted of a variety of motor and sensory deficits, dysarthria, dysphagia, and dysphasia. Motor complications included facial or upper extremity motor dysfunction and hemiparesis while sensory complications included auditory dysfunction, neglect syndrome, olfactogustatory dysfunction, general somatosensory changes, and visual field deficits.

The incidence of auras (e. pain or laryngeal constriction during seizure), side of hemispheric dominance, and postoperative dysphasia were reported both for the entire cohort and excluding preschool age children (<6 years) as this subgroup is inherently different and is generally unable to report subjective manifestations,[32,50,51] has higher likelihood of atypical language representation (eg, right-side or bilateral), and harbors neuroplasticity with greater potential for postoperative language recovery, respectively.[52–55]

Title and abstract screening was performed by two independent screeners with content expertise (S.O., W.S.), and full-text review of screened studies was performed independently. A list of all articles screened was compiled. Relevant studies were included in our final analysis if they respected our eligibility criteria.

One reviewer (S.O.) performed data abstraction, verified by a second reviewer (A.W.). Authors removed duplicate participants. In cases of identical cohorts described in many articles, we considered only the most recent article. Corresponding authors of all included studies were systematically contacted, and additional data were used when supplied by the authors.

2.4 | Data classification

We performed data collection and categorization into specific variables (Tables 1–3) according to predefined definitions. Although most variables are self-descriptive and encompass easily categorizable data, some required the elaboration of specific definitions/inclusion criteria to standardize data classification across studies.

In clinical characteristics (Table 1), "early/initial motor semiology" was defined as motor signs exhibited at onset of seizures or immediately following auras. We defined "≥ two concordant studies" as two or more noninvasive imaging studies (MRI, PET, SPECT, and/or MEG) that overlapped with the epileptogenic zone (EZ) or the resection cavity.

TABLE 1 Clinical characteristics of study population.

Variable	Value	No. of patients[a]
Total no. of patients	312	
General		
Sex (female)	133 (50.0%)	266
Age at epilepsy onset (y)	8.8 ± 8.7 (0–48)	261
Age at epilepsy onset (≤18 y)	227 (87.0%)	261
Age at surgery (y)	20.8 ± 12.8 (0.5–59)	306
Age at surgery (≤18 y)	177 (57.8%)	306
Age at surgery (≤6 y)	31 (10.1%)	306
Epilepsy duration (y)	12.0 ± 9.9 (0–55)	256
Epilepsy etiology (dysplastic lesion)	149 (73.4%)	203
Previous stereotactic ablative or resective surgery	74 (28.5%)	260
Epilepsy characteristics		
Preoperative seizure frequency (daily)	93 (68.9%)	135
Generalized seizures	32 (13.1%)	245
Early/initial motor semiology	147 (60.0%)	245
Laryngeal constriction during seizure	23 (14.4%)	160
Laryngeal constriction during seizure (excluding preschool children)	18 (13.0%)	138
Pain during seizure	19 (11.9%)	159
Pain during seizure excluding (excluding preschool children)	18 (13.1%)	137
Scalp EEG		
Ictal lateralizing ictal discharges	175 (72.6%)	241
Interictal lateralizing interictal discharges	115 (74.7%)	154
Preoperative imaging		
MRI lesion	155 (52.4%)	296
MRI insular/opercular lesion	117 (42.9%)	273
MEG insular spike cluster	94 (60.6%)	155
MEG concordant to the SEEG EZ or resection cavity	116 (73.4%)	158
PET insular hypometabolism	78 (44.8%)	174
PET concordant to the SEEG EZ or resection cavity	100 (52.4%)	191
Ictal SPECT insular activation	60 (52.6%)	114
SPECT concordant to the SEEG EZ or resection cavity	69 (61.1%)	113
≥2 Concordant imaging studies	107 (42.8%)	250

Note: Values are presented as number of surgeries (%), mean ± SD (range).

Abbreviations: EEG, electroencephalogram; EZ, epileptogenic zone; MEG, magnetoencephalography; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single photon emission computed tomography.

[a]Number of patients for whom the information was available.

In operative characteristics and post-operative outcomes (Table 2), the side of dominance was recorded if (a) it was clearly stated in the article, (b) the result of an fMRI or a WADA test was available, or (c) a patient was right-handed (in which case dominance was set as left-sided). The variable "entire epileptogenic zone removed" was defined as any surgery that incorporated the intracranial EEG-proven EZ or the MRI-evident epileptogenic

TABLE 2 Operative characteristics and post-operative outcomes of study population.

Variable	Value	No. of patients[a]
Total no. of patients	312	
Surgery		
Side (Right)	176 (58.9%)	299
Dominant side (Yes)	53 (38.4%)	138
MRgLA or RFA	70 (22.4%)	312
Entire epileptogenic zone removed	160 (76.6%)	209
Invasive EEG monitoring		
Intracranial electrodes	264 (84.6%)	312
Intraoperative ECoG	29 (13.7%)	212
Type of operculoinsular surgery (resection of ablation)		
Pure insulectomy	73 (27.1%)	269
Pure operculoinsulectomy	95 (36.1%)	263
Operculoinsulectomy plus	95 (36.1%)	263
Extent of insular surgery (resection or ablation)		
Complete insulectomy	67 (30.7%)	218
Posterior insulectomy	135 (64.9%)	208
Extent of opercular surgery (resection or ablation)		
Frontal	110 (43.3%)	254
Parietal	59 (23.0%)	257
Temporal	46 (19.2%)	240
Extent of operculoinsular plus surgery (resection or ablation)		
Frontal lobectomy	58 (22.1%)	263
Temporal lobectomy or SAH	47 (17.9%)	263
Orbitofrontal corticectomy	20 (7.9%)	252
Duration of follow-up (y)	3.3 ± 2.5 (0.1–17)	308
Postoperative seizure control outcome		
Seizure recurrence	116 (37.5%)	309
Time to seizure recurrence (y)	1.3 ± 1.3 (0–7)	307
Engel Class I	206 (66.7%)	309
Engel Class IA	81 (75.0%)	108
Engel Class IB	17 (15.7%)	108
Engel Class IC	8 (7.4%)	108
Engel Class ID	2 (1.9%)	108

Note: Values are presented as number of surgeries (%), mean ± SD (range).

Abbreviations: ECoG, electrocorticography; MRgLA, MR-guided laser ablation; RFA, radiofrequency ablation; SAH, selective amygdalohippocampectomy.

[a]Number of patients for whom the information was available.

lesion entirely. "Pure insulectomy" was defined as an open resective or ablative procedure (ie, MRgLA or RFA) that was restricted to the insula, "pure operculoinsulectomy" involved ablation or resection of the insula and any portion of the operculum, while "operculoinsulectomy plus" was defined as surgery that included but extended beyond the operculo-insular region. Within the "extent of opercular resection" category, an orbitofrontal surgery was not considered a frontal operculum surgery unless it was evident that the fronto-opercular region was included or the surgery involved removal of a lesion extending from the insula to the frontal lobe. In addition, we did not consider a temporal, frontal, and/or parietal lobectomy to include the operculum unless it was clearly stated or illustrated. An operation was categorized as "operculoinsulectomy plus" if (a) it was clearly stated that the surgery included but extended beyond the operculum, (b) a lesionectomy was performed and included a lesion that encompassed but extended beyond the operculo-insular region, or (c) a frontal lobectomy, temporal lobectomy, or an orbitofrontal resection was carried out in addition to an operculo-insular region resection. All cases of orbitofrontal resections that were not considered frontal opercular resections were included in the "operculoinsulectomy plus" group.

With respect to postoperative complications (Table 3), we defined "hemiparesis" as a contralateral motor deficit of the upper extremity and lower extremity (required the impairment of both extremities) with or without facial weakness. "Isolated facial and/or upper extremity motor dysfunction" was defined as lower extremity-sparing weakness involving the contralateral upper extremity and/or face. "Somatosensory changes" encompassed paresthesias, pain, and/or total or partial loss of sensation.

Ambiguous cases had no data collected, and we deemed the information unavailable. We assumed that a specific test (eg, noninvasive imaging and electrophysiological investigations) was *not* performed only if it was clearly mentioned. Otherwise, we judged the information unavailable. Therefore, we only considered an investigation *normal* if the article explicitly stated that the test was conducted and the results revealed no abnormal findings.

2.5 | Outcomes

The two outcomes of interest for each participant were (a) seizure outcome and (b) postoperative neurological deficits. Seizure outcome was assessed using the Engel classification at last follow-up and by measuring the time to seizure recurrence. Seizure outcome at last follow-up was categorized as good (Engel I) or suboptimal/poor (Engel II-IV). We defined seizure recurrence as the occurrence of any seizure excluding auras during the follow-up period (ie, Engel IB were not classified as recurrences). Time to first recurrent seizure for patients with seizure recurrence and time to last follow-up for patients who did not experience recurrence were also recorded to perform a time-to-event analysis. We estimated time to first recurrent

TABLE 3 Complication profile of the study population.

Neurological complication	Value	No. of patients[a]
Total no. of patients with complication profile	221	
No. of patients with postoperative complications	94 (42.5%)	221
Transient	74 (33.9%)	218
Permanent	17 (7.8%)	218
Transient duration <1 wk	5 (2.5%)	204
Transient duration 1 wk to 3 mo	46 (22.5%)	204
Transient duration >3 mo	9 (4.4%)	204
Motor complications	68 (30.8%)	221
Transient	57 (26.1%)	218
Permanent	11 (5.0%)	218
Hemiparesis	46 (20.8%)	221
Isolated facial and/or UE motor dysfunction	22 (10.0%)	221
Sensory complications	23 (10.4%)	221
Somatosensory changes	9 (4.1%)	221
Visual field deficits	8 (3.6%)	221
Olfactogustatory changes	5 (2.3%)	221
Auditory dysfunction	2 (0.9%)	221
Neglect	1 (0.5%)	221
Dysphasia	17 (7.7%)	221
Transient	14 (6.4%)	218
Permanent	3 (1.4%)	218
Dysphasia (excluding preschool children)	16 (8.3%)	192
Transient	13 (6.9%)	189
Permanent	3 (1.6%)	189
Dysphasia in dominant-hemisphere surgeries	8 (16.3%)	49
Transient	8 (16.3%)	49
Permanent	0 (0%)	49
Dysphasia in dominant-hemisphere surgeries (excluding preschool children)	8 (17.4%)	46
Transient	8 (17.4%)	46
Permanent	0 (0%)	46
Dysarthria	6 (2.7%)	221
Dysphagia	1 (0.5%)	221

Note: Values are presented as number of surgeries (%).

Abbreviation: UE, upper extremity.

[a]Number of patients for whom the information was available.

seizure to be half of the entire follow-up duration if not explicitly mentioned in the included article.[56]

2.6 | Evidence grading

Two reviewers (N.A.S, A.S.) critically appraised included studies for quality and risk of bias, and disagreements were reconciled via discussion. The quality of studies was assessed using the GRADE framework (Table S1).[57] The ROBINS-I tool was used to denote the risk of bias for each included study (Table S1).[58] The risk of bias for this meta-analysis was determined upon consideration of the risk of bias of all included studies in aggregate.

2.7 | Statistical analysis

We calculated Cohen's Kappa score to evaluate the strength of agreement for full-text review using a computer software with the following thresholds for interpretation: <0.20 as slight, 0.21-0.40 as fair, 0.41-0.60 as

moderate, 0.61-0.80 as substantial, and 0.0.81 as almost perfect agreement.[59]

Demographic, perioperative, and outcome characteristics of the included patients were summarized using descriptive statistics. Continuous variables were reported using mean, standard deviation, and total range. Categorical variables were reported using frequency and proportion. Age at epilepsy onset and surgery was dichotomized into two categories ("≤18 years", ">18 years") and reported accordingly. Missing data were handled by the multiple imputation by chained equations method.[60] Only variables with <40% of the data missing were included in the imputation.[61] Ten complete datasets were imputed for each regression analysis, and parameters and standard errors from the analysis were pooled according to Rubin's rules.[62]

To account for the variability in follow-up among included patients and heterogeneity between studies, a mixed-effects Cox proportional hazards model was constructed, with the study that the patient originated from acting as the random-effects variable, to perform a time-to-event analysis of seizure recurrence. Time-to-event analyses are advantageous for the evaluation of seizure outcomes because it accounts for both the dynamic nature of postoperative seizures and variability in follow-up across patients by placing an increasingly positive value on a longer delay to seizure recurrence or follow-up duration that is entirely seizure-free, and vice versa. This allows for all patients to be included in time-to-event analyses regardless of follow-up duration; thus, all patients were included in the Cox regression analysis of time-to-seizure recurrence.[63] Mixed-effects logistic regression modeling, with the same random-effects variable, was also performed to identify independent predictors of seizure freedom at last follow-up and postoperative complications. Only patients who had at least 1 year of follow-up were included in the logistic regression analysis of seizure freedom. Cox regression and logistic regression of time-to-seizure recurrence and seizure freedom were performed for two patient cohorts: (a) the entire cohort, and (b) the cohort of patients who underwent surgery confined to the insula.

For both mixed-effects Cox and logistic regression analysis, univariate regression analysis was first performed to identify putative predictors of the outcome. Covariates with *P*-value <.20 were included in a subsequent multivariate regression analysis to identify independent predictors. During multivariate analysis, backward stepwise selection of variables using Akaike information criterion (AIC) followed by inclusion of variables that were selected in a majority of the 10 imputed models was done in order to create the most optimal model with the strongest predictors.[64] Hazard ratios (HR), odds ratios (OR), *P*-values, and 95% confidence intervals (CI) were computed and reported for putative and independent predictors. Kaplan–Meier curves with the entire cohort of patients stratified by independent predictors identified in the time-to-event analysis were also generated to validate the difference in time-to-seizure recurrence. A two-sided *P*-value <.05 was used as the threshold for statistical significance. All statistical analyses were performed in RStudio (RStudio Inc., Version 1.2.1335).

3 | RESULTS

3.1 | Study selection and risk of bias

Using the search strategy detailed above, 4567 citations were initially identified. After exclusion of duplicates, 2483 citations remained, of which 191 were reviewed in full text following title and abstract screening (unweighted $\kappa = 0.746$). Twenty-four articles reporting IPD on 293 patients were included at first (Figure S1).[6,11,21–32,45,47,65–72] Contacting the corresponding authors leads to complementary data in 145 of the 293 participants and supplied 19 additional patients.[16,37] Ultimately, 312 participants were included in the final analysis. Twenty-two articles were retrospective case series, while two were retrospective case–control studies. The evaluation of quality and risk of bias of all included studies is detailed in Table S1. Table S2 provides characteristics of all included studies.

3.2 | Cohort characteristics

Baseline and clinical characteristics of the entire participant cohort are displayed in Table 1. Over half of the patients were 18 years or younger at time of surgery (57.8%) and exhibited a lesion on MRI (52.4%). A dysplastic lesion was found on histopathological analysis in most patients (73.4%).

Operative characteristics and seizure outcomes of all participants are summarized in Table 2. About one-third of patients (38.4%) underwent surgery of the dominant hemisphere. An intracranial study was performed in most cases (84.6%). While surgical technique involved open microsurgical resection in most patients, several (22.4%) underwent stereotactic ablation procedures (eg, MRgLA or RFA). Despite the commonly reported risk of motor deficits when operating within that region,[24,37] the posterior insula was targeted in almost two-third of patients (64.9%).

Participants were followed for 3.3 ± 2.5 years on average. During the follow-up period, 116 (37.5%) patients

experienced seizure recurrence. The average time to seizure recurrence was 1.3 ± 1.3 years, and a Kaplan–Meier curve depicting the seizure freedom function of the cohort is displayed in Figure 1. Overall, the probability of seizure freedom after surgery for IE at 1-, 5-, and 10-year follow-up was 79.1% (95% CI = 74.0%-83.3%), 55.3% (95% CI = 47.7%-62.3%), and 47% (95% CI = 36.8%-56.6%). At last follow-up, 206 (66.7%) patients exhibited an Engel I seizure outcome.

Postoperative neurological complications of the entire cohort are detailed in Table 3. Overall, 94 patients (42.5%) experienced a postoperative neurological complication. The majority of complications were transient (78.7% of complications) and resolved within 3 months of follow-up (68.9% of complications). Sixty-eight patients (30.8%) experienced motor complications making up the majority of the postoperative adverse events, with the most common motor deficit being hemiparesis (61.7% of motor complications). A permanent motor deficit was observed in 5% of surgeries. Patients for whom a posterior insulectomy, frontal operculectomy, or parietal operculectomy was included in the surgery exhibited a similar rate of permanent motor deficits (7.3%, 7.4% and 7.1%, respectively). In addition, of all the patients who underwent a pure insulectomy exclusively, only one patient (1.6%) developed a permanent hemiparesis. Furthermore, 1.4% of patients developed a permanent postoperative dysphasia. Interestingly, only eight of the 49 patients (16.3%) who underwent surgery on the dominant side developed dysphasia, of which none were permanent.

3.3 | Predictors of efficacy

Results of the univariate and multivariate mixed-effects Cox regression analysis are reported in Table 4. For the entire cohort, younger age at surgery, specifically 18 years or younger, (HR = 1.70, 95% CI = 1.09-2.66, P = .022), and invasive EEG monitoring with intracranial electrodes (HR = 1.97, 95% CI = 1.04-3.74, P = .039) were significantly and independently associated with earlier seizure recurrence. In the subgroup that only underwent a pure insulectomy, the use of MRgLA or RFA instead of open resection (HR = 3.45, 95% CI = 1.18-10.06, P = .033) was independently associated with shorter duration of seizure freedom. Kaplan–Meier curves with patients stratified by these variables are presented in Figure 2.

Table 5 reports the results of the mixed-effects logistic regression analysis of seizure freedom at last follow-up. Performing MRgLA or RFA instead of an open resection was the only independent predictor of suboptimal/poor seizure outcome (Engel II-IV) at last follow-up for both the entire cohort (OR = 2.05, 95% CI = 1.08-3.89, P = .028) and the subgroup that underwent a pure insulectomy (OR = 4.40, 95% CI = 1.24-15.54, P = .025).

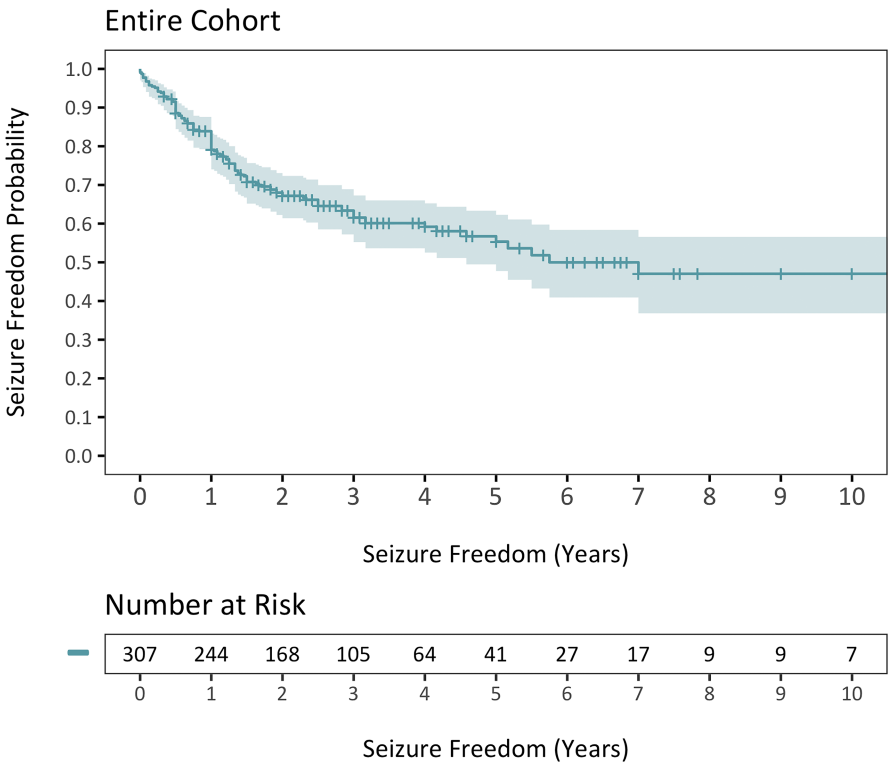

FIGURE 1 Kaplan–Meier curve of the seizure freedom function following insular epilepsy surgery.

TABLE 4 Mixed-effects Cox regression with stepwise variable selection and MICE for predictors of shorter time to seizure recurrence for entire study cohort and pure insulectomy patients.

Covariate	HR[a]	95% CI	*P*-value
Univariate Cox regression for entire cohort			
Age at surgery (≤18 y)	1.72	1.09–2.72	.021*
No insular or opercular lesion on MRI	1.42	0.89–2.25	.143
Previous stereotactic ablative or resective surgery	1.39	0.90–2.15	.140
Intracranial EEG electrodes	1.98	1.04–3.77	.039*
MRgLA or RFA	1.69	0.95–2.99	.077
Multivariate Cox regression for entire cohort			
Age at surgery (≤18 y)	1.70	1.09–2.66	.022*
Intracranial EEG electrodes	1.97	1.04–3.74	.039*
Univariate Cox regression for patients with pure insulectomy			
<2 Concordant imaging studies	2.13	0.74–6.09	.175
Previous stereotactic ablative or resective surgery	1.98	0.90–4.37	.102
MRgLA or RFA	3.10	1.07–8.98	.047*
Posterior insula not resected	2.07	0.78–5.49	.160
Multivariate Cox regression for patients with pure insulectomy			
MRgLA or RFA	3.45	1.18–10.06	.033*

Abbreviations: EEG, electroencephalogram; HR, hazard ratio; MICE, multiple imputation by chained equations; MRgLA, MR-guided laser ablation; MRI, magnetic resonance imaging; RFA, radiofrequency ablation.

[a]HR >1 indicates a shorter time to seizure recurrence.

*$P < .05$.

3.4 | Predictors of neurological complications

Findings from the mixed-effects logistic regression analysis of postoperative neurological complications are shown in Table 6. While resection of the posterior insula was associated with higher incidence of postoperative neurological complications on univariate analysis, no independent predictors were identified following multivariate analysis. However, when examining only postoperative motor complications, resection of the frontal operculum (OR = 2.75, 95% CI = 1.46-5.15, $P = .002$) was a significant and independent predictor associated with increased odds. Furthermore, resection of the posterior insula trended toward an association with hemiparesis on univariate analysis but did not reach significance. The only independent predictor of hemiparesis identified was resection of the frontal operculum (OR = 2.41, 95% CI = 1.18-4.90, $P = .016$). Finally, surgery on the patient's dominant hemisphere was the only variable significantly associated with dysphasia on multivariate analysis (OR = 13.09, 95% CI = 2.22-77.14, $P = .005$) while open resection and temporal operculum resections were only trending toward significance on univariate analysis.

3.5 | Trade-off between likelihood of seizure freedom and risk of neurological deficits

A two-by-two contingency table comparing the prevalence of seizure freedom and permanent postoperative deficit outcomes is shown in Table 7. Of the patients with both seizure outcome and neurological complication data available, the majority (58.6%) experienced seizure freedom at last follow-up and had no permanent neurological deficits. Patients who continued to experience seizures and had permanent postoperative neurological deficits following IE surgery (i.e. the poorest outcome) were in the minority and least represented, constituting 0.9% of the cohort.

4 | DISCUSSION

We performed a systematic review of the literature and meta-analysis with IPD on the surgical treatment of drug-resistant IE. This review included 312 participants from 24 studies. Compared with the surgical treatment of temporal

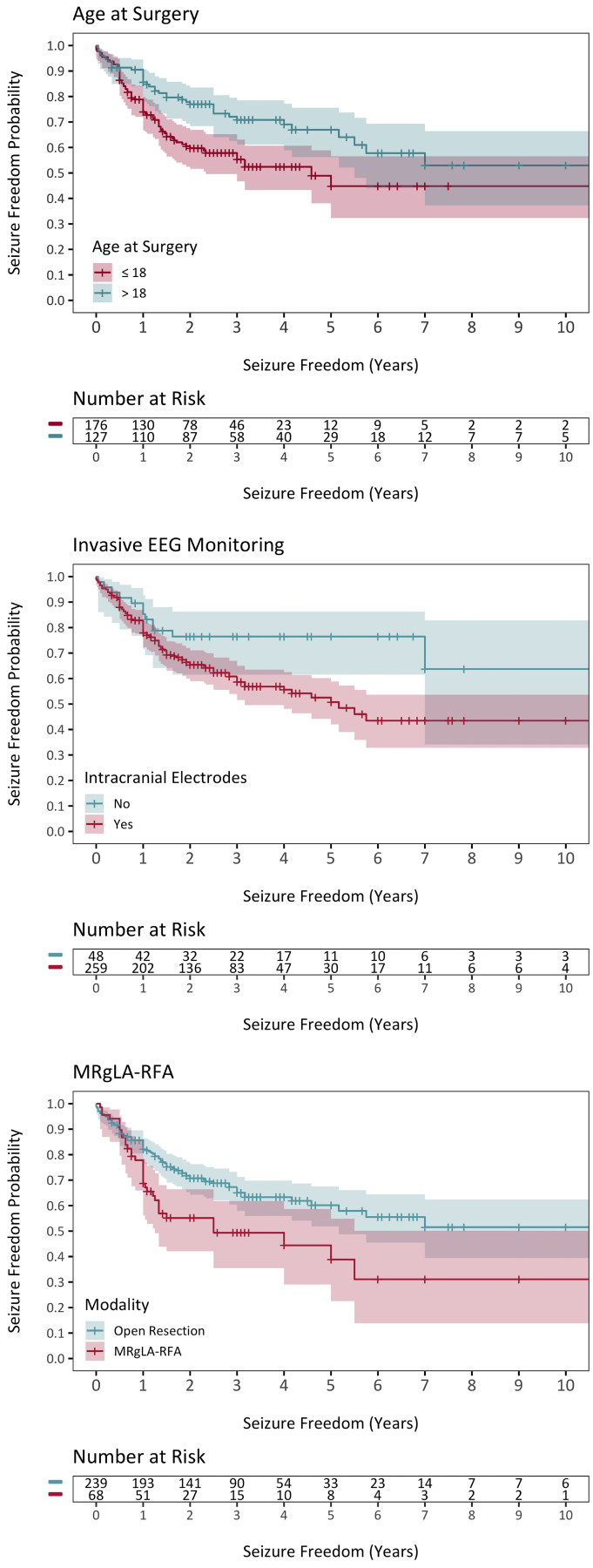

FIGURE 2 Kaplan–Meier curve of the seizure freedom function following insular epilepsy surgery with patients stratified by: (A) age at surgery, (B) intracranial monitoring, (C) MRgLA-RFA.

TABLE 5 Mixed-effects logistic regression with stepwise variable selection and MICE for predictors of seizure recurrence for entire study cohort and pure insulectomy patients with at least 1 year of follow-up.

Covariate	OR[a]	95% CI	*P*-value
Univariate logistic regression for entire cohort with at least 1-year follow-up			
Age at surgery (≤18 y)	1.49	0.83–2.69	.184
Previous stereotactic ablative or resective surgery	1.54	0.84–2.81	.165
MRgLA or RFA	2.12	1.07–4.21	.031*
Multivariate logistic regression for entire cohort with at least 1-year follow-up			
MRgLA or RFA	2.05	1.08–3.89	.028*
Univariate logistic regression for patients with pure insulectomy and at least 1-year follow-up			
Previous stereotactic ablative or resective surgery	3.14	0.82–12.04	.099
Intraoperative ECoG not utilized	3.77	0.74–19.12	.119
MRgLA or RFA	4.16	1.22–14.18	.026*
Posterior insula not resected	2.46	0.74–8.25	.149
Multivariate logistic regression for patients with pure insulectomy and at least 1-year follow-up			
MRgLA or RFA	4.40	1.24–15.54	.025*

Abbreviations: ECoG, electrocorticography; EEG, electroencephalogram; MICE, multiple imputation by chained equations; MRgLA, MR-guided laser ablation; MRI, magnetic resonance imaging; OR, odds ratio; RFA, radiofrequency ablation.

[a]OR >1 indicates greater odds of suboptimal/poor seizure outcome (Engel II, III, IV) at last follow-up.

*$P < .05$.

and other ETE, which have been carried out in epilepsy centers worldwide for over half a century, widespread surgery for IE is relatively new, and data regarding its safety and efficacy are limited. While many meta-analyses have systematically studied the clinical outcomes and predictors in temporal lobe epilepsy (TLE) and other forms of ETE (eg, frontal, parietal, and occipital lobe epilepsies), only one such study exists for IE.[73–80] In this regard, Kerezoudis et al performed a recent meta-analysis of patients undergoing surgery for insular epilepsy that revealed rates of overall seizure freedom (64.3%) and postoperative neurological deficits (43.2%, most of which were transient) comparable to our study. While their assessment is valuable, the overall findings are limited by the fact that the heterogeneity between studies was not accounted for, multivariate analyses were not performed, missing data were not imputed, and predictors of postoperative neurological complications were not evaluated.[80] In addition, no independent predictors of seizure freedom were identified.[80]

There are several main findings in the current study: (a) The surgical treatment of drug-resistant IE results in very good seizure freedom rates that are comparable to those obtained with surgery for ETE[43,44,73,78,79,81]; similar seizure recurrence patterns are also seen, including 79% and 55% postoperative seizure freedom rates at 1 and 5 years respectively; (b) the efficacy-to-permanent deficit profile is favorable, with <1% of patients harboring poor outcome (seizure recurrence and permanent deficit); (c) independent patient-related predictors of seizure recurrence include younger (pediatric) age and cases requiring invasive EEG monitoring; (d) the seizure-free rate following stereotactic ablation procedures (MRgLA or RFA) was significantly lower than following open resective surgery; (e) surgical treatment of IE is associated with a significant rate of neurological complications in just under half of cases (42.5%)—however, the vast majority are transient and <8% of all surgically treated patients exhibit permanent neurological deficits; (f) the most common neurological complication was motor deficit (30.8%); (g) there was no independent predictor of overall neurological deficits, although posterior insulectomy and opercular resection trended toward significance; (h) frontal operculectomy was independently associated with postoperative motor impairment and hemiparesis, and (i) although dominant-hemisphere surgery was independently associated with a higher likelihood of postoperative language impairment, none of the patients who underwent surgery on the dominant side exhibited permanent dysphasia.

4.1 | Efficacy of insular epilepsy surgery

This study demonstrates that IE surgery is effective in the majority of patients and comparable in efficacy to other

TABLE 6 Mixed-effects logistic regression with stepwise variable selection and MICE for predictors of postoperative neurological complications, motor deficits, hemiparesis, and dysphasia in the entire study population.

Covariate	OR[a]	95% CI	*P*-value
Univariate logistic regression of risk factors for neurological complication			
Any region of the operculum resected	1.87	0.87–4.03	.112
Posterior insula resected	2.09	1.03–4.22	.042*
Multivariate logistic regression of predictors for neurological complication			
No independent predictors			
Univariate logistic regression of risk factors for motor deficits			
Frontal operculum resected	2.09	1.04–4.22	.001*
Parietal operculum resected	1.76	0.83–3.71	.140
Multivariate logistic regression of predictors for motor deficits			
Frontal operculum resected	2.75	1.46–5.15	.002*
Univariate logistic regression of risk factors for hemiparesis			
Frontal operculum resected	2.25	1.114.56	.026*
Posterior insula resected	1.82	0.83–3.97	.134
Multivariate logistic regression of predictors for hemiparesis			
Frontal operculum resected	2.41	1.18–4.90	.016*
Univariate logistic regression of risk factors for dysphasia			
Surgery on dominant side	10.03	1.86–54.03	.008*
Open resection	5.88	0.62–55.46	.123
Temporal operculum resected	2.22	0.71–6.92	.172
Multivariate logistic regression of predictors for dysphasia			
Surgery on dominant side	13.09	2.22–77.14	.005*

Abbreviations: MICE, multiple imputation by chained equations; OR, odds ratio.

[a]OR >1 indicates greater odds of experiencing neurological complications, motor deficits, hemiparesis or dysphasia.

*$P < .05$.

TABLE 7 Evaluation of the trade-off between likelihood of seizure freedom and risk of permanent neurological deficit after insular epilepsy surgery.

	Seizure freedom	Seizure recurrence	Total
No permanent deficits	126 (58.6%)	72 (33.5%)	198 (92.1%)
Permanent deficits	15 (7.0%)	2 (0.9%)	17 (7.9%)
Total	141 (65.6%)	74 (34.4%)	215

Note: Values are presented as number of surgeries (% of total surgeries with available data).

forms of ETE.[43,44,73,78,79,81] While 1-year outcome shows very high proportion of seizure freedom, the rate declines over time to 47% at 10-year follow-up, which compares favorably to long-term outcome for resective epilepsy surgery.[73,82–84]

In our study, we observed a higher rate of seizure recurrence following stereotactic ablation procedures. Although we acknowledge that stereotactic interventions may have been performed for noncurative purposes in some patients, which may render the comparison of open vs minimally approaches partly biased, the use of MRgLA or RFA was the strongest predictor of seizure recurrence (pure insulectomy cohort) and suboptimal/poor seizure outcome (whole cohort and pure insulectomy cohort). Over the last decade, minimally invasive stereotactic ablation treatments have gained in popularity.[46–48] The widespread adoption of SEEG for investigation of refractory epilepsy, in particular of insular or peri-sylvian origin, has made these minimally invasive ablation treatment alternates appealing.[25] Radiofrequency ablation, in which electrodes are used to ablate epileptic foci, has been used for half a century for several types of focal epilepsy,[48] and more recently, MRgLA has emerged as another minimally invasive alternative for DRE.[46] In the last few years, both these technologies have been increasingly utilized to treat IE.[25,45,47] In our study, the limited number of patients fitting our inclusion criteria prompted the pooling of MRgLA and RFA procedures (both SEEG-guided and volume-based thermocoagulation) into one category. While we recognize that these stereotactic procedures

are not equivalent and may exhibit dissimilar efficacies, combining minimally invasive approaches together allowed us to perform a sufficiently powered analysis. Despite these drawbacks, our findings suggest that, although very useful in well-selected cases, these treatment modalities may be less effective than open microsurgical resection. IE is rarely limited to the insula and usually involves an extensive epileptogenic network encompassing peri-sylvian regions and/or more distant cortical area. This is supported by a recent study revealing structural abnormalities (eg, reduced cortical thickness) extending far beyond the operculo-insular region.[85,86] However, MRgLA and RFA can only target small volumes of brain and are limited by the vector direction of the probe.[46,87] This may result in incomplete ablation of the EZ and explain seizure recurrence or persistence. Furthermore, our analysis revealed that, even in cases of more limited EZs for which an operculum-sparing pure insular resection was performed, stereotactic procedures were less likely to control seizures, suggesting that the extent of the EZ may not be the sole contributor to the higher rate of seizure recurrence. Two recent studies, both included in our analysis, are consistent with our findings. In a report of 26 pediatric patients undergoing IE surgery, those who underwent MRgLA had 43% seizure freedom compared with 50% seizure freedom in the open resection cohort.[45] A more recent study reporting on 19 patients showed that RFA is associated with seizure freedom in 53% of cases.[47] It is interesting to note that despite the minimally invasive nature of these approaches, the latter study reported a significant proportion of patients with transient neurological deficits (42%) following RFA.[47] Further confirming this finding, open surgery was not associated with greater likelihood of neurological morbidity compared with stereotactic ablation procedures in our study. While MRgLA and RFA allow for smaller incision, avoidance of ICU stay, less postoperative pain, and reduced narcotic use, and shorter hospitalization, they do not necessarily reduce neurological morbidity, which is most often transient even for open surgical resections.[27,46] These procedures can be associated with significant peri-ablation edema, which may explain the similar rate of postoperative deficits compared with open procedures.[88] Although stereotactic ablation procedures have an overall lower likelihood of seizure freedom without clearly reducing the risk of neurological impairment, many patients become seizure-free, and both MRgLA and RFA will therefore likely have a significant role in the surgical treatment of IE going forward. These procedures remain an excellent option in cases with higher likelihood of success (eg, small lesional epileptogenic foci), when conventional surgery is contra-indicated or risky, or when patients prefer a minimally invasive alternative.[48] In addition, they can be used to predict the outcome of a subsequent open resective surgery, may be employed for palliative purposes, and can often be repeated safely.[25,48]

Pediatric patients exhibited earlier seizure recurrence than their adult counterparts in our study, which contrasts several studies regarding resective epilepsy surgery in which younger age at surgery was either not significantly associated with seizure outcome[89–91] or predicted better seizure control.[92,93] It is well established that incomplete resection of the EZ is one of strongest predictors of seizure recurrence.[89,94,95] The fact that children often harbor challenging DRE with a higher proportion of malformations of cortical development and extensive multi-lobar EZs that are difficult to localize, map, and completely resect could explain the poorer seizure control observed in our study.[89,94,95] In addition, the description of auras may often be imprecise in younger children,[50,51] which may render the identification of the EZ more challenging and result in suboptimal postoperative seizure control.

Finally, we found that the use of intracranial monitoring predicted shorter time to seizure recurrence. This observation, which is concordant with prior studies on IE,[16] is likely related to the challenging nature of these invasively monitored patients who typically exhibit non-lesional epilepsy and/or discordant preoperative imaging.[16,43,44,73] Moreover, invasive localization of the operculo-insular EZ constitutes a challenging task for which accurate targeting and dense monitoring of the peri-Sylvian region (including both the insula and all three opercula) is often required.[11,67] It is therefore conceivable that, in some of the included cases, sparse sampling of the operculo-insular area or anatomical misplacement of electrodes may have resulted in suboptimal identification of the EZ, ultimately contributing to imprecise surgical targeting and unsatisfactory seizure control.

4.2 | Safety of insular epilepsy surgery

The current study provides the landscape of neurological risks associated with the surgical treatment of IE. Despite historical high morbidity rates associated with surgery for IE,[39] modern reports demonstrate that IE surgery can be carried out with moderate permanent morbidity.[16,27] Overall, 42% of patients undergoing surgery for IE experienced neurological deficits in our study, but only a reasonably small fraction of these complications were permanent (7.8% of all surgically treated patients). Additionally, the vast majority of patients who exhibited transient deficits recovered rapidly (68.9% within 3 months). The risk profile

seems to be specific to the neuroanatomical structures in the insular peri-sylvian region, including a predominance of motor impairment (30.8%), followed by language (7.7%, or 16.3% of dominant hemisphere operations), somatosensory changes (4.1%), and visual field deficits (3.6%).

Even though the rate of neurological impairment following surgery for IE is acceptable, it remains non-negligible. The identification of underlying patient risk factors or modifiable surgical techniques to reduce the postoperative morbidity is therefore essential. Our study pinpointed independent predictors of postoperative motor deficits, which occurred in almost one-third of the cohort. While previous stimulation and lesional studies have linked the insula to motor control,[96,97] our study included only patients who underwent an insulectomy (no control group) and was therefore not designed to examine whether motor impairment can result from insular cortex resection itself. Rather, we found that resection of the frontal operculum independently predicted both motor deficits (a category encompassing upper extremity, lower extremity, and/or facial weakness) as well as hemiparesis specifically. In addition, parietal operculum and posterior insular resections trended toward an association with postoperative motor impairment and hemiparesis, respectively. In this regard, the vascularization pattern overlying the frontoparietal operculum and the posterior insula may explain motor deficits following surgery within the operculo-insular region.[33,98–100] Penetrating vessels arising from posterior M2 and M3 MCA branches supply portions of the corticospinal tract.[33,98–100] More specifically, long insular arteries (LIA) arising from M2 branches over the posterior–superior insula[33,98–100] and the long medullary arteries (LMA) originating from M3 branches covering the frontal and parietal opercula supply the corona radiata.[33,98–100] These branches (LIA, LMA) do not harbor anastomoses, and their sacrifice during insular or opercular resection can result in subcortical ischemia.[101] Moreover, injury to LIAs arising from M2 branches overlying the posterior insula specifically has been identified as a risk factor for corona radiata strokes and postoperative motor deficits in epilepsy[37,38] and glioma surgery.[100] Resections sparing this region have been shown to avoid motor deficits, albeit at the expense of incomplete EZ removal and reduced seizure freedom.[24] It is therefore conceivable that the high incidence of motor deficits observed in our study may be related to ischemic lesions to the corona radiata, and this is further supported by a recent study revealing a 60% rate of corona radiata strokes following insular surgeries for refractory epilepsy.[37,38] The strongest predictor of motor deficit identified in our study was resection of the frontal operculum, which is consistent with the largest series of surgery for IE.[37] The fact that extensive resections of opercular gliomas and removal of insular gliomas in the vicinity of the frontal operculum (Sanai-Berger zone I) have been correlated with permanent motor deficits further supports our findings.[100,102–105] While cumulative evidence suggests that postoperative motor dysfunction following frontal opercular resection can indeed result from subcortical strokes,[90] direct injury to the opercular portion of the primary motor cortex may also cause motor impairment but typically results in more isolated deficits consisting of transient facial weakness.[102–105] Considering the significant association observed in our study between frontal operculum resection and hemiparesis (involving both upper and lower extremity), vascular injury of the LMAs supplying the densely packed corona radiata is a plausible major etiology for postoperative weakness. In addition, direct insult to the primary motor cortex may have contributed to the brachiofacial weakness observed in some patients. Some authors have recommended transopercular transgression during insulectomy for IE, even in cases in which the opercula are non-epileptogenic.[29] The findings from our study suggest that this approach could result in a higher rate of neurological impairment, especially when the frontal operculum is incorporated in the resection. Although most of these motor complications were transient, 5% of patients undergoing surgery for IE have permanent motor impairment. For that reason, we advocate an operculum-sparing approach in cases of pure IE. Furthermore, it is worth mentioning that although the frontal operculum is at increased motor risk and should be approached cautiously, the risk of permanent weakness is relatively low (~7%). When involved in the EZ, surgery of the frontal operculum may be considered in well-selected cases if the benefit-to-risk ratio is favorable. Finally, despite the commonly reported risk of ischemia-related hemiparesis and the trend observed in our analysis,[24,37,38] surgery within the parietal opercular or posterior insular regions was not identified as independent predictor of motor deficits. For that reason, although surgery within these regions should be carried out carefully, our study suggests that it should not be necessarily prohibited.

Language impairment is a major concern when considering surgery for dominant-hemisphere IE.[34] In this IPDMA, dominant side surgeries was associated with the occurrence of dysphasia on multivariate analysis. Responsive neurostimulation (RNS) has been advocated as an alternative to microsurgical resection, particularly to avoid the language complications in dominant-hemisphere IE.[34,36] While data are limited, a single center study showed similar seizure reduction following IE surgery to large-scale, multi-center trials of RNS for eloquent neocortical epilepsy.[34–36,42] This alternative

may be an option in patients with higher risk of deficits (eg, nonlesional language-dominant hemisphere IE involving frontal and temporal opercula) and lower likelihood of seizure freedom following resective surgery.[34,36] In our study, the overall rate of transient and permanent dysphasia was 6.4% and 1.4% respectively, most likely resulting from surgeries on the language-dominant hemisphere (not always specified in the included studies). Furthermore, when analyzing only dominant-side surgeries, the rate of dysphasia was surprisingly low (16.3%) and, interestingly, none of these patients (0/49) were permanently impaired. We also performed an analysis in a subpopulation in which preschool children were excluded. Young children have an increase likelihood of epilepsy-driven relocalization of language regions, may display a bilateral distribution of language areas prior to surgery, and can exhibit a greater postoperative functional recovery,[53,55,106] all of which may predispose to a lower rate of transient and/or permanent dysphasia. This low risk of language deficit was corroborated by our study in which only one preschool child (1/31) exhibited a transient dysphasia and none were permanently disabled. Excluding preschool children from the analysis led to a comparable low rate of transient (6.4%) and permanent dysphasia (1.6%), further reinforcing the safety of insular surgery for IE in older children and adults. The low incidence observed in our study may be related to the fact that patients operated on the dominant insula often undergo invasive functional mapping at first and only patients in whom at least a portion of the EZ does not exhibit language function are typically considered for a subsequent surgery. In these cases, surgical removal may be typically restricted to the nonfunctional portion of the EZ or the whole extent of a language-sparing EZ. Nevertheless, our findings suggest that properly investigated and well-selected patients can likely undergo resection of the dominant insula without significant risks for permanent language deficits.

4.3 | Strengths and limitations

Strengths of this review include: (a) We performed a comprehensive search; (b) we did not exclude studies based on language of publication; (c) we obtained IPD to perform our meta-analysis; and (d) corresponding authors of all included studies were contacted for additional data. This is a very robust and rigorous method for conducting meta-analyses especially given that the majority of studies are small with a fair amount of heterogeneity; (e) we accounted for heterogeneity in clinical practices and patient populations across institutions through mixed-effects modeling; and (f) we adjusted for the length of follow-up, which eliminated biases that would have resulted if putative predictive variables were associated with length of follow-up.

The review also has limitations: (a) Although an exhaustive search strategy was utilized, it is possible that some studies were not identified due to inappropriate indexing or errors in screening; (b) non-standardized reporting affects the validity of data abstraction and assessment of risk of bias; (c) there is a lack of recognized criteria for assessment of bias in prognostic cohort studies. This required us to develop and utilize our own methodology, which has not been validated; (d) neuropsychological and quality of life outcomes following surgery for IE are other important outcome measures but were not evaluated; (e) surgical experience (years of experience) was not investigated but may influence the safety of surgery for IE.[37] The favorable results of the current study should not preclude the necessity of sufficient surgical experience prior to performing surgery within the operculo-insular region; and (f) the rarity of IE led to the inclusion of studies with a high risk of bias. Given the nature of surgery for IE, selection bias is likely since patients who underwent this procedure were inherently thought to be good candidates from the standpoint of achieving seizure freedom with acceptable neurological risks. While this study is not able to account for the factors that went into determining surgical candidacy, these findings are from the largest cohort of IE patients to date, which provides a robust sample size to increase confidence and generalizability.

5 | CONCLUSION

We performed the largest meta-analysis studying predictors of outcome and first assessing predictors of neurological complications following surgery for IE. Through this IPDMA, the surgical treatment of IE was recognized as an effective and safe therapeutic option in experienced centers. Our analysis revealed that most patients experience postoperative seizure freedom and only a minority develop permanent neurological deficits. We were also able to identify specific predictors of both seizure outcome and neurological complications. Pediatric patients and those requiring invasive EEG monitoring exhibited a lower rate of seizure freedom. Patients undergoing stereotactic ablation procedures were more likely to have seizure recurrence than those undergoing open microsurgical resection. Resection of the frontal operculum was a strong predictor of the most observed complication, namely motor impairment. Finally, although postoperative dysphasia following dominant-side insular surgeries is not uncommon even in well-selected patients, it is very frequently transient.

Despite the inherent biases of IPDMA, results of the current study suggest that (a) since the minimally invasive benefits of stereotactic procedures may be offset by a reduced seizure freedom rate, their role should be further refined towards patients most likely to benefit from this approach for various reasons (eg, diagnostic, curative, and palliative purposes), (b) transgression of the frontal operculum should be avoided if it is not deemed part of the EZ, and (c) dominant-hemisphere IE should not be considered a contraindication for insular surgery. Further research involving standardized multicenter studies with prospective follow-ups is necessary to provide external validation of efficacy and safety of insular surgery for IE, identify the optimal surgical candidates, and guide the choice of surgical approach.

CONFLICT OF INTEREST

A.G.W. is a consultant for Monteris Medical inc. None of the other authors has any conflict of interest to disclose for the current study. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ETHICAL APPROVAL

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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REFERENCES

1. Singh R, Principe A, Tadel F, Hoffmann D, Chabardes S, Minotti L, et al. Mapping the insula with stereo-electroencephalography: the emergence of semiology in insula lobe seizures. Ann Neurol. 2020;88:477–88.
2. Isnard J, Guénot M, Sindou M, Mauguière F. Clinical manifestations of insular lobe seizures: a stereo-electroencephalographic study. Epilepsia. 2004;45:1079–90.
3. Obaid S, Zerouali Y, Nguyen DK. Insular epilepsy: semiology and noninvasive investigations. J Clin Neurophysiol. 2017;34:315–23.
4. Zerouali Y, Ghaziri J, Nguyen DK. Multimodal investigation of epileptic networks: the case of insular cortex epilepsy. Prog Brain Res. 2016;226:1–33.
5. Weil AG, Fallah A, Lewis EC, Bhatia S. Medically resistant pediatric insular-opercular/perisylvian epilepsy part 1: invasive monitoring using the parasagittal transinsular apex depth electrode. J Neurosurg Pediatr. 2016;18:511–22.
6. Park YS, Lee YH, Shim KW, Lee YJ, Kim HD, Lee JS, et al. Insular epilepsy surgery under neuronavigation guidance using depth electrode. Child Nerv Syst. 2009;25:591–7.
7. Surbeck W, Bouthillier A, Weil AG, Crevier L, Carmant L, Lortie A, et al. The combination of subdural and depth electrodes for intracranial EEG investigation of suspected insular (perisylvian) epilepsy. Epilepsia. 2011;52:458–66.
8. Bouthillier A, Surbeck W, Weil AG, Tayah T, Nguyen DK. The hybrid operculo-insular electrode: a new electrode for intracranial investigation of perisylvian/insular refractory epilepsy. Neurosurgery. 2012;70:1574–80; discussion 1580.
9. Robles SG, Gelisse P, El Fertit H, Tancu C, Duffau H, Crespel A, et al. Parasagittal transinsular electrodes for stereo-EEG in temporal and insular lobe epilepsies. Stereotact Funct Neurosurg. 2009;87:368–78.
10. Afif A, Chabardes S, Minotti L, Kahane P, Hoffmann D. Safety and usefulness of insular depth electrodes implanted via an oblique approach in patients with epilepsy. Neurosurgery. 2008;62:ONS471–9; discussion 479–80.
11. Alomar S, Mullin JP, Smithason S, Gonzalez-Martinez J. Indications, technique, and safety profile of insular stereo-electroencephalography electrode implantation in medically intractable epilepsy. J Neurosurg. 2018;128:1147–57.
12. Cardinale F, Rizzi M, Vignati E, Cossu M, Castana L, d'Orio P, et al. Stereoelectroencephalography: retrospective analysis of 742 procedures in a single centre. Brain. 2019;142:2688–704.
13. Bourdillon P, Châtillon CE, Moles A, Rheims S, Catenoix H, Montavont A, et al. Effective accuracy of stereoelectroencephalography: robotic 3D versus Talairach orthogonal approaches. J Neurosurg. 2018;131:1938–46.
14. Chassoux F, Navarro V, Catenoix H, Valton L, Vignal JP. Planning and management of SEEG. Neurophysiol Clin. 2018;48:25–37.
15. Ryvlin P, Kahane P. The hidden causes of surgery-resistant temporal lobe epilepsy: extratemporal or temporal plus? Curr Opin Neurol. 2005;18:125–7.
16. Bouthillier A, Weil AG, Martineau L, Letourneau-Guillon L, Nguyen DK. Operculoinsular cortectomy for refractory epilepsy. Part 1: is it effective? J Neurosurg. 2019;133:1–10.
17. Tomycz LD, Hale AT, Haider AS, Clarke DF, Lee MR. Invasive insular sampling in pediatric epilepsy: a single-institution experience. Oper Neurosurg (Hagerstown). 2018;15:310–7.
18. Isnard J, Taussig D, Bartolomei F, Bourdillon P, Catenoix H, Chassoux F, et al. French guidelines on stereoelectroencephalography (SEEG). Neurophysiol Clin. 2018;48:5–13.
19. Tandon N, Tong BA, Friedman ER, Johnson JA, Von Allmen G, Thomas MS, et al. Analysis of morbidity and outcomes associated

with use of subdural grids vs Stereoelectroencephalography in patients with intractable epilepsy. JAMA Neurol. 2019;76:672–81.
20. Yan H, Katz JS, Anderson M, Mansouri A, Remick M, Ibrahim GM, et al. Method of invasive monitoring in epilepsy surgery and seizure freedom and morbidity: a systematic review. Epilepsia. 2019;60:1960–72.
21. Ding H, Zhou J, Guan Y, Zhai F, Wang M, Wang J, et al. Bipolar electro-coagulation with cortextomy in the treatment of insular and insulo-opercular epilepsy explored by stereoelectroencephalography. Epilepsy Res. 2018;145:18–26.
22. Ahmed R, Otsubo H, Snead C 3rd, Donner E, Widjaja E, Ochi A, et al. Diagnostic evaluation and surgical management of pediatric insular epilepsy utilizing magnetoencephalography and invasive EEG monitoring. Epilepsy Res. 2018;140:72–81.
23. Hagiwara K, Jung J, Bouet R, Abdallah C, Guenot M, Garcia-Larrea L, et al. How can we explain the frontal presentation of insular lobe epilepsy? The impact of non-linear analysis of insular seizures. Clin Neurophysiol. 2017;128:780–91.
24. Ikegaya N, Takahashi A, Kaido T, Kaneko Y, Iwasaki M, Kawahara N, et al. Surgical strategy to avoid ischemic complications of the pyramidal tract in resective epilepsy surgery of the insula: technical case report. J Neurosurg. 2018;128:1173–7.
25. Perry MS, Donahue DJ, Malik SI, Keator CG, Hernandez A, Reddy RK, et al. Magnetic resonance imaging-guided laser interstitial thermal therapy as treatment for intractable insular epilepsy in children. J Neurosurg Pediatr. 2017;20:575–82.
26. Freri E, Matricardi S, Gozzo F, Cossu M, Granata T, Tassi L. Perisylvian, including insular, childhood epilepsy: presurgical workup and surgical outcome. Epilepsia. 2017;58:1360–9.
27. Weil AG, Le NMD, Jayakar P, Resnick T, Miller I, Fallah A, et al. Medically resistant pediatric insular-opercular/perisylvian epilepsy. Part 2: outcome following resective surgery. J Neurosurg Pediatr. 2016;18:523–35.
28. Proserpio P, Cossu M, Francione S, Tassi L, Mai R, Didato G, et al. Insular-opercular seizures manifesting with sleep-related paroxysmal motor behaviors: a stereo-EEG study. Epilepsia. 2011;52:1781–91.
29. Gras-Combe G, Minotti L, Hoffmann D, Krainik A, Kahane P, Chabardes S. Surgery for nontumoral insular epilepsy explored by stereoelectroencephalography. Neurosurgery. 2016;79:578–88.
30. von Lehe M, Wellmer J, Urbach H, Schramm J, Elger CE, Clusmann H. Insular lesionectomy for refractory epilepsy: management and outcome. Brain. 2009;132:1048–56.
31. Heers M, Rampp S, Stefan H, Urbach H, Elger CE, von Lehe M, et al. MEG-based identification of the epileptogenic zone in occult peri-insular epilepsy. Seizure. 2012;21:128–33.
32. Dylgjeri S, Taussig D, Chipaux M, Lebas A, Fohlen M, Bulteau C, et al. Insular and insulo-opercular epilepsy in childhood: an SEEG study. Seizure. 2014;23:300–8.
33. Türe U, Yaşargil MG, Al-Mefty O, Yaşargil DC. Arteries of the insula. J Neurosurg. 2000;92:676–87.
34. Chen H, Dugan P, Chong DJ, Liu A, Doyle W, Friedman D. Application of RNS in refractory epilepsy: targeting insula. Epilepsia Open. 2017;2:345–9.
35. Jobst BC, Gonzalez-Martinez J, Isnard J, Kahane P, Lacuey N, Lahtoo SD, et al. The insula and its epilepsies. Epilepsy Curr. 2019;19:11–21.
36. Smith JR, Fountas KN, Murro AM, Park YD, Jenkins PD, Morrell M, et al. Closed-loop stimulation in the control of focal epilepsy of insular origin. Stereotact Funct Neurosurg. 2010;88:281–7.
37. Bouthillier A, Weil AG, Martineau L, Letourneau-Guillon L, Nguyen DK. Operculoinsular cortectomy for refractory epilepsy. Part 2: is it safe? J Neurosurg. 2019;133:960–70.
38. Finet P, Nguyen DK, Bouthillier A. Vascular consequences of operculoinsular corticectomy for refractory epilepsy. J Neurosurg. 2015;122:1293–8.
39. Silfvenius H, Gloor P, Rasmussen T. Evaluation of insular ablation IN surgical treatment of temporal lobe epilepsy. Epilepsia. 1964;5:307–20.
40. Ikegaya N, Iwasaki M, Kaneko Y, Kaido T, Kimura Y, Yamamoto T, et al. Cognitive and developmental outcomes after pediatric insular epilepsy surgery for focal cortical dysplasia. J Neurosurg Pediatr. 2020;26:543–51.
41. Nair DR, Laxer KD, Weber PB, Murro AM, Park YD, Barkley GL, et al. Nine-year prospective efficacy and safety of brain-responsive neurostimulation for focal epilepsy. Neurology. 2020;95:e1244–56.
42. Heck CN, King-Stephens D, Massey AD, Nair DR, Jobst BC, Barkley GL, et al. Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: final results of the RNS system pivotal trial. Epilepsia. 2014;55:432–41.
43. Ansari SF, Maher CO, Tubbs RS, Terry CL, Cohen-Gadol AA. Surgery for extratemporal nonlesional epilepsy in children: a meta-analysis. Childs Nerv Syst. 2010;26:945–51.
44. Ansari SF, Tubbs RS, Terry CL, Cohen-Gadol AA. Surgery for extratemporal nonlesional epilepsy in adults: an outcome meta-analysis. Acta Neurochir (Wien). 2010;152:1299–305.
45. Hale AT, Sen S, Haider AS, Perkins FF, Clarke DF, Lee MR, et al. Open resection versus laser interstitial thermal therapy for the treatment of pediatric insular epilepsy. Neurosurgery. 2019;85:E730–6.
46. Lewis EC, Weil AG, Duchowny M, Bhatia S, Ragheb J, Miller I. MR-guided laser interstitial thermal therapy for pediatric drug-resistant lesional epilepsy. Epilepsia. 2015;56:1590–8.
47. Mullatti N, Landre E, Mellerio C, Oliveira AJ, Laurent A, Turak B, et al. Stereotactic thermocoagulation for insular epilepsy: lessons from successes and failures. Epilepsia. 2019;60:1565–79.
48. Catenoix H, Bourdillon P, Guénot M, Isnard J. The combination of stereo-EEG and radiofrequency ablation. Epilepsy Res. 2018;142:117–20.
49. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med. 2009;151:W65–94.
50. Fohlen M, Taussig D, Ferrand-Sorbets S, Chipaux M, Dorfmuller G. Clinical semiology of temporal lobe seizures in preschool children: contribution of invasive recording to anatomical classification. Epileptic Disord. 2021;23:590–610.
51. Park JT, Fernandez-Baca Vaca G. Epileptic seizure semiology in infants and children. Seizure. 2020;77:3–6.
52. Weiss-Croft LJ, Baldeweg T. Maturation of language networks in children: a systematic review of 22years of functional MRI. Neuroimage. 2015;123:269–81.

53. Karami M, Nilipour R, Barekatain M, Gaillard WD. Language representation and presurgical language mapping in pediatric epilepsy: a narrative review Iran J child neurol. Summer. 2020;14:7–18.
54. Gaillard WD, Berl MM, Moore EN, Ritzl EK, Rosenberger LR, Weinstein SL, et al. Atypical language in lesional and nonlesional complex partial epilepsy. Neurology. 2007;69:1761–71.
55. Barba C, Montanaro D, Grisotto L, Frijia F, Pellacani S, Cavalli A, et al. Patterns and predictors of language representation and the influence of epilepsy surgery on language reorganization in children and young adults with focal lesional epilepsy. PLoS One. 2020;15:e0238389.
56. McIntosh AM, Kalnins RM, Mitchell LA, Fabinyi GC, Briellmann RS, Berkovic SF. Temporal lobectomy: long-term seizure outcome, late recurrence and risks for seizure recurrence. Brain. 2004;127:2018–30.
57. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924–6.
58. Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.
59. Cyr L, Francis K. Measures of clinical agreement for nominal and categorical data: the kappa coefficient. Comput Biol Med. 1992;22:239–46.
60. van Buuren S, Groothuis-Oudshoorn K. mice: multivariate imputation by chained equations in R. J Stat Softw. 2011;45:1–67.
61. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials – a practical guide with flowcharts. BMC Med Res Methodol. 2017;17:1–10.
62. Rubin DB. Multiple imputation for nonresponse in surveys. New York: Wiley; 1987.
63. Fallah A. Time to rethink how to measure postoperative seizure outcomes for potentially curative resective epilepsy surgery. Epilepsy Behav. 2014;41:53–4.
64. Brand JPL. Development, implementation, and evaluation of multiple imputation strategies for the statistical analysis of incomplete data sets. Rotterdam: Erasmus University; 1999.
65. Yin C, Zhang X, Xiang J, Chen Z, Li X, Wu S, et al. Altered effective connectivity network in patients with insular epilepsy: a high-frequency oscillations magnetoencephalography study. Clin Neurophysiol. 2020;131:377–84.
66. Yu T, Ni D, Zhang X, Wang X, Qiao L, Zhou X, et al. The role of magnetoencephalography in the presurgical evaluation of patients with MRI-negative operculo-insular epilepsy. Seizure. 2018;61:104–10.
67. Wang X, Hu W, McGonigal A, Zhang C, Sang L, Zhao B, et al. Electroclinical features of insulo-opercular epilepsy: an SEEG and PET study. Ann Clin Transl Neurol. 2019;6:1165–77.
68. Wang S, Tang Y, Aung T, Chen C, Katagiri M, Jones SE, et al. Multimodal noninvasive evaluation in MRI-negative operculoinsular epilepsy. J Neurosurg. 2019;132:1334–44.
69. Alexander H, Cobourn K, Fayed I, Depositario-Cabacar D, Keating RF, Gaillard WD, et al. Magnetic resonance-guided laser interstitial thermal therapy for the treatment of nonlesional insular epilepsy in pediatric patients: thermal dynamic and volumetric factors influencing seizure outcomes. Childs Nerv Syst. 2019;35:453–61.
70. Blustajn J, Krystal S, Taussig D, Ferrand-Sorbets S, Dorfmuller G, Fohlen M. Optimizing the detection of subtle insular lesions on MRI when insular epilepsy is suspected. Am J Neuroradiol. 2019;40:1581–5.
71. Sala-Padro J, Fong M, Rahman Z, Bartley M, Gill D, Dexter M, et al. A study of perfusion changes with Insula Epilepsy using SPECT. Seizure. 2019;69:44–50.
72. Bouthillier A, Nguyen DK. Epilepsy surgeries requiring an operculoinsular cortectomy: operative technique and results. Neurosurgery. 2017;81:602–12.
73. Téllez-Zenteno JF, Dhar R, Wiebe S. Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. Brain. 2005 May;128:1188–98.
74. Kuang Y, Yang T, Gu J, Kong B, Cheng L. Comparison of therapeutic effects between selective amygdalohippocampectomy and anterior temporal lobectomy for the treatment of temporal lobe epilepsy: a meta-analysis. Br J Neurosurg. 2014;28:374–7.
75. Jain P, Tomlinson G, Snead C, Sander B, Widjaja E. Systematic review and network meta-analysis of resective surgery for mesial temporal lobe epilepsy. J Neurol Neurosurg Psychiatry. 2018;89:1138–44.
76. Lee AT, Burke JF, Chunduru P, Molinaro AM, Knowlton R, Chang EF. A historical cohort of temporal lobe surgery for medically refractory epilepsy: a systematic review and meta-analysis to guide future nonrandomized controlled trial studies. J Neurosurg. 2019;133:71–8.
77. Josephson CB, Dykeman J, Fiest KM, Liu X, Sadler RM, Jette N, et al. Systematic review and meta-analysis of standard vs selective temporal lobe epilepsy surgery. Neurology. 2013;80:1669–76.
78. Harward SC, Chen WC, Rolston JD, Haglund MM, Englot DJ. Seizure outcomes in occipital lobe and posterior quadrant epilepsy surgery: a systematic review and meta-analysis. Neurosurgery. 2018;82:350–8.
79. Englot DJ, Wang DD, Rolston JD, Shih TT, Chang EF. Rates and predictors of long-term seizure freedom after frontal lobe epilepsy surgery: a systematic review and meta-analysis. J Neurosurg. 2012;116:1042–8.
80. Kerezoudis P, Singh R, Goyal A, Worrell GA, Marsh WR, Van Gompel JJ, et al. Insular epilepsy surgery: lessons learned from institutional review and patient-level meta-analysis. J Neurosurg. 2021;136:523–35.
81. Englot DJ, Breshears JD, Sun PP, Chang EF, Auguste KI. Seizure outcomes after resective surgery for extra-temporal lobe epilepsy in pediatric patients. J Neurosurg Pediatr. 2013;12:126–33.
82. Dwivedi R, Ramanujam B, Chandra PS, Sapra S, Gulati S, Kalaivani M, et al. Surgery for drug-resistant epilepsy in children. N Engl J Med. 2017;377:1639–47.
83. Wiebe S, Blume WT, Girvin JP, Eliasziw M. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med. 2001;345:311–8.
84. Mohan M, Keller S, Nicolson A, Biswas S, Smith D, Osman Farah J, et al. The long-term outcomes of epilepsy surgery. PLoS One. 2018;13:e0196274.
85. Obaid S, Tucholka A, Ghaziri J, Jodoin PM, Morency F, Descoteaux M, et al. Cortical thickness analysis in operculoinsular epilepsy. Neuroimage Clin. 2018;19:727–33.
86. Obaid S, Rheault F, Edde M, Guberman GI, St-Onge E, Sidhu J, et al. Structural connectivity alterations in operculo-insular epilepsy. Brain Sci. 2021;11:1041.

87. Curry DJ, Gowda A, McNichols RJ, Wilfong AA. MR-guided stereotactic laser ablation of epileptogenic foci in children. Epilepsy Behav. 2012;24:408–14.
88. Tandon V, Lang M, Chandra PS, Sharan A, Garg A, Tripathi M. Is edema a matter of concern after laser ablation of epileptogenic focus? World Neurosurg. 2018;113:366–72.e363.
89. Rowland NC, Englot DJ, Cage TA, Sughrue ME, Barbaro NM, Chang EF. A meta-analysis of predictors of seizure freedom in the surgical management of focal cortical dysplasia. J Neurosurg. 2012;116:1035–41.
90. Lerner JT, Salamon N, Hauptman JS, Velasco TR, Hemb M, Wu JY, et al. Assessment and surgical outcomes for mild type I and severe type II cortical dysplasia: a critical review and the UCLA experience. Epilepsia. 2009;50:1310–35.
91. Zhang J, Liu W, Chen H, Xia H, Zhou Z, Mei S, et al. Identification of common predictors of surgical outcomes for epilepsy surgery. Neuropsychiatr Dis Treat. 2013;9:1673–82.
92. Fountas KN, King DW, Meador KJ, Lee GP, Smith JR. Epilepsy in cortical dysplasia: factors affecting surgical outcome. Stereotact Funct Neurosurg. 2004;82:26–30.
93. Barba C, Cossu M, Guerrini R, Di Gennaro G, Villani F, De Palma L, et al. Temporal lobe epilepsy surgery in children and adults: a multicenter study. Epilepsia. 2021;62:128–42.
94. Englot DJ, Han SJ, Rolston JD, Ivan ME, Kuperman RA, Chang EF, et al. Epilepsy surgery failure in children: a quantitative and qualitative analysis. J Neurosurg Pediatr. 2014;14:386–95.
95. Oluigbo CO, Wang J, Whitehead MT, Magge S, Myseros JS, Yaun A, et al. The influence of lesion volume, perilesion resection volume, and completeness of resection on seizure outcome after resective epilepsy surgery for cortical dysplasia in children. J Neurosurg Pediatr. 2015;15:644–50.
96. Afif A, Minotti L, Kahane P, Hoffmann D. Anatomofunctional organization of the insular cortex: a study using intracerebral electrical stimulation in epileptic patients. Epilepsia. 2010;51:2305–15.
97. Nguyen DK, Nguyen DB, Malak R, Leroux JM, Carmant L, Saint-Hilaire JM, et al. Revisiting the role of the insula in refractory partial epilepsy. Epilepsia. 2009;50:510–20.
98. Tanriover N, Rhoton AL Jr, Kawashima M, Ulm AJ, Yasuda A. Microsurgical anatomy of the insula and the sylvian fissure. J Neurosurg. 2004;100:891–922.
99. Shibahara I, Sato S, Hide T, Saito R, Kanamori M, Sonoda Y, et al. Postcentral gyrus resection of opercular gliomas is a risk factor for motor deficits caused by damaging the radiologically invisible arteries supplying the descending motor pathway. Acta Neurochir (Wien). 2021;163:1269–78.
100. Kumabe T, Higano S, Takahashi S, Tominaga T. Ischemic complications associated with resection of opercular glioma. J Neurosurg. 2007;106:263–9.
101. Phan TG, Donnan GA, Wright PM, Reutens DC. A digital map of middle cerebral artery infarcts associated with middle cerebral artery trunk and branch occlusion. Stroke. 2005;36:986–91.
102. Sanai N, Polley MY, Berger MS. Insular glioma resection: assessment of patient morbidity, survival, and tumor progression. J Neurosurg. 2010;112:1–9.
103. Hervey-Jumper SL, Li J, Osorio JA, Lau D, Molinaro AM, Benet A, et al. Surgical assessment of the insula. Part 2: validation of the Berger-Sanai zone classification system for predicting extent of glioma resection. J Neurosurg. 2016;124:482–8.
104. Hervey-Jumper SL, Berger MS. Insular glioma surgery: an evolution of thought and practice. J Neurosurg. 2019;130:9–16.
105. Magill ST, Han SJ, Li J, Berger MS. Resection of primary motor cortex tumors: feasibility and surgical outcomes. J Neurosurg. 2018;129:961–72.
106. Chou N, Serafini S, Muh CR. Cortical language areas and plasticity in pediatric patients with epilepsy: a review. Pediatr Neurol. 2018;78:3–12.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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