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Review

Long-term outcomes of pediatric epilepsy surgery: Individual participant data and study level meta-analyses☆

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ABSTRACT

Objective: Long-term seizure outcomes of pediatric epilepsy surgery are understudied. A systematic review and independent patient data meta-analysis was performed to study seizure outcomes ≥ 10 years following pediatric resective epilepsy surgery.

Methods: Electronic literature searches of PubMed, Web of Science, and CINAHL were conducted for relevant articles from inception to April 2020. The following search terms were used in various combinations: "pediatric", "child", "adolescent", "epilepsy", "resective", "surgery", "long-term", "longitudinal", "10 year". Two reviewers (W.B.H., T.B.C.) performed title, abstract, and full-text screening. All relevant perioperative factors reported that may be associated with long-term seizure outcomes were recorded at a study or individual participant level. The primary outcome was long-term (≥ 10 year) seizure freedom measured by the Engel Classification scale, and available data on functional outcomes were also reviewed.

Results: Twenty-five articles met criteria for inclusion in the study, which were analyzed for proportions of 10-year seizure freedom ranging from 57.6% at the study level to 64.8% at the individual patient level. At the study level, the proportion of patients remaining seizure free at least 10 years postoperatively (61.2%; 95% CI 52.5–69.3) was significantly less than at 1 year (74.2%; 95% CI 69.3–78.6; $p = 0.008$) but not at 2 years (67.9%; 95% CI 58.6–76.0) or 5 years (63.7%; 95% CI 55.4–71.2). No differences in long-term seizure freedom were detected by etiology or surgery type. At the individual patient level, univariate logistic regression analyses of all variables putatively associated with seizure freedom demonstrated that lobectomy (OR 0.280, 95% CI 0.117–0.651, $p = 0.003$) was associated with decreased long-term seizure freedom (41.9%) compared to lesionectomy (75.7%) and hemispherectomy (69.4%), which achieved similar results.

Conclusion: Resective surgery is a durable and potentially curative treatment option for select pediatric patients with refractory epilepsy. On a group level, two-thirds of children have long-term seizure freedom ≥ 10 years after resective epilepsy surgery. Given the greatest rate of change occurs in the first 2 years, this may serve as the best short-term follow-up period to predict long-term outcome. Although lobectomy appears to be a strong predictor for lower likelihood of long-term seizure freedom, long-term prognostication on an individual patient level is still not possible. Uniform data reporting and prospective, multicenter studies collecting high quality, stratified (e.g., by etiology, surgery type) data over an extended postoperative interval are recommended to further examine the durability of resective surgery as a treatment for pediatric epilepsy.

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1. Introduction

Epilepsy is one of the most common pediatric neurologic disorders, affecting up to 0.5% of children [1]. For the third of pediatric epilepsy patients that are refractory to medical therapy and are deemed surgical candidates following a multidisciplinary pre-operative workup [2,3], surgery is a safe and effective intervention to prevent the irreversible physiologic sequelae associated with recurrent seizures [4–6]. A recent large meta-analysis [7] and a randomized controlled trial [8] each showed that for children with drug-resistant epilepsy, surgery achieved a significantly higher proportion of seizure freedom compared to medical therapy in the short term.

For pediatric patients undergoing resective epilepsy surgery, general predictors of seizure freedom include greater extent of resection, neoplastic etiology, lesional epilepsy, and complete resection of epileptiform foci [7,9,10]. The majority of the outcomes based studies in pediatric epilepsy surgery focuses on 1 or 2 year seizure outcomes while long-term outcomes are less well defined due to the small number of surgical patients with adequate follow-up.

To date, there remains a paucity of literature that documents long-term seizure outcomes $\geq$ 10 years post-operatively. Based on the well documented gradual decline of seizure freedom over time, we hypothesize that seizure freedom in the long-term will be significantly less than earlier interval follow-up. In addition to understanding the durability of resective surgery as a therapeutic intervention for pediatric epilepsy, comparisons of long-term follow-up with discrete shorter interval follow-up periods may provide insight on the minimal follow-up duration necessary for prediction of long-term seizure outcomes. This information would help to define the appropriate follow-up approach for this patient population while providing important information to guide preoperative counseling, patient follow-up, and postoperative expectations.

2. Literature review

Pooled estimates of short-term seizure outcomes after pediatric epilepsy surgery demonstrate seizure freedom rates ranging from 50 to 67% depending on the pathology and type of resection [11]. Long-term seizure freedom and its steady decline over time has primarily been studied in adult populations [12,13]. A catch-all systematic review and meta-analysis from 2005 evaluated the long-term rates of seizure freedom defined by median follow-up of at least 5 years [14] which found proportions of seizure freedom to range from 66% for patients undergoing temporal resections to 34% for patients from grouped extratemporal surgical series.

The first systematic review and meta-analysis including long-term seizure outcomes for a pediatric population was recently published in 2020 [7]. In this robust analysis that included 258 studies, follow-up was stratified by 1, 2, 5, and 10 years after surgery. They showed the rate of seizure freedom following surgery to decline longitudinally from 65% at one year to 40% at 10 years postoperatively. However, as is the case for the rest of the literature, their study design did not intend to identify patients with 10-year follow-up specifically and therefore only 2 studies representing a limited number of patients were included for this follow-up.

There are relatively few published series that systematically document long-term seizure and functional outcomes of pediatric epilepsy surgery for $\geq$ 10 years. Because pediatric epilepsy surgery encompasses different proportions of underlying etiologies and interventions compared with adults, such long-term surgical outcomes in this particular population warrants investigation. Here, we present a systematic review and meta-analysis on the seizure outcomes of pediatric epilepsy surgery from studies explicitly reporting long-term outcomes $\geq$ 10 years postoperatively.

3. Methods

3.1. Protocol and registration

A review protocol was registered a priori through PROSPERO (CRD42021218334).

3.2. Eligibility criteria

Inclusion criteria were: case control, cohort, or randomized controlled trial methodology, at least 90% have undergone $\geq$ 1 resective epilepsy surgery (i.e. surgery where tissue was resected or disconnected with curative intent, such as hemispherectomy/hemispherotomy, lobectomy, and lesionectomy), seizure outcomes reported. For study-level (SL) analysis, at least 90% of participants $\leq$ 18 years old at time of surgery with mean follow-up $\geq$ 10 years. Studies were also included that reported individual patient data (IPD) for at least 5 participants $\leq$ 18 years old at surgery with $\geq$ 10-year follow-up. When a specific length of follow-up or age group was not reported in the title or abstract for epilepsy surgery outcomes, a full-text review was performed to determine if the article met eligibility criteria. Exclusion criteria were: reviews, single case studies, mixed adult and pediatric studies that do not stratify by age or duration of follow-up, studies that report positive outcomes only, participants that have undergone palliative surgical procedures (e.g. corpus callosotomy, VNS, etc.) or with most recent surgery $<$ 10 years from follow-up.

3.3. Search strategy

We performed a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. Electronic search records for relevant articles from inception to April 2020 were performed through three medical databases: PubMed, Web of Science, and Cumulative Index to Nursing and Allied Health Literature (CINAHL). The following search terms, with relevant iterations, were applied in various combinations: “pediatric,” “epilepsy,” “surgery,” “resection,” “outcome,” “long-term”, “follow-up”. The search was limited to humans but did not restrict by language (non-English articles were translated through the publisher’s website, by the authors, or Google translator). To ensure the inclusion of all relevant articles, both reviewers (W.B.H., T.B.C.) performed manual bibliography searches of the included studies and utilized the “related articles” feature of PubMed, and another reviewer with content expertise (A.F.) manually searched for articles. Any disagreements in title/abstract screening and full-text screening were resolved through discussion.

3.4. Selection and coding of data

Our primary outcome measure was seizure freedom $\geq$ 10 years after surgery. This outcome was dichotomized to “seizure freedom” (Engel classification scale class I) and “seizure recurrence” (Engel class II, III, IV) to account for heterogeneity in outcome reporting between studies (other scales were converted to Engel classification when possible). All perioperative factors plausibly associated with seizure outcome were recorded at the SL and IPD when possible: sex, age at seizure onset, age at surgery, duration of seizures, types of seizures, seizure frequency, antiseizure medication (ASM) used, laboratory examination (MRI, EEG, ECoG), etiology (tumor or non-tumor), side affected, resective surgery type (hemispheric/mutilobar, lobar, focal), extent of resection, complications, and seizure freedom at shorter follow-up intervals (1, 2, 5 years). For SL data, continuous variables were reported as means and range, and categorical variables were reported as number of individuals within each category.

Independently abstracted data were managed on Microsoft Excel Spreadsheet (version 2016; Microsoft, Redmond, WA, USA).

3.5. Assessment of risk of bias and agreement

The risk of bias for each study was evaluated by 1 reviewer (W.B.H.) and verified by a second reviewer (T.B.C.) using the Quality in Prognosis Studies (QUIPS) tool (Hayden 2013). Using the QUIPS tool, each study was assigned low, moderate, or high risk of bias for each of six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. Mean risk scores for each domain were calculated by associating level of risk with numbers (low = 1, moderate = 2, high = 3).

We calculated Cohen's kappa score to determine the strength of agreement for title and abstract, as well as full-text screening using the Covidence web application (www.covidence.org, Veritas Health Innovation Ltd, Melbourne, Australia) 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 >0.81 as almost perfect agreement.

3.6. Assessment of publication bias and heterogeneity

For studies including study-level data, we assessed publication bias through visual assessment for symmetry of funnel plots for seizure freedom event rates at ≥ 10 years of follow-up. Because the study primarily aimed to include only papers reporting stratified data for patients with ≥ 10 years of follow-up, earlier interval funnel plots were not performed.

Heterogeneity of the data was assessed using the I^2 statistic. I^2 levels of 0–30%, 30–60%, 60–90%, and 90–100% were deemed low, moderate, substantial, and considerable, respectively.

3.7. Statistical methods

3.7.1. Individual patient data meta-analysis

Seizure outcomes were reported as Engel class at last available follow-up, which we coded as a dichotomous value (seizure freedom vs seizure recurrence). Given the wide range of last available follow-ups ≥ 10 years, we were able to perform a logistic regression for seizure freedom depending on follow-up length ≥ 10 years to determine whether seizure freedom changed significantly after 10 years.

Data permitting, we planned to perform time-to-event and survival analyses. Alternatively, univariate logistic regression was performed for variables *a priori* associated with long term seizure outcomes to identify clinical features statistically significantly associated with seizure freedom at ≥ 10 years of follow-up. However, variables representing fewer than 25 patients (20% of our IPD group) were not included in our analyses. We subsequently considered all variables with $p < 0.2$ on univariate analysis for inclusion in a multivariate analysis. The number of included variables was to be limited by the number of non-events within our cohort, with the usual 10:1 ratio. Odds ratios (ORs) and their 95% confidence intervals (CI) were determined for every variable, and statistical significance was set at $p < 0.05$ (two-tailed). When possible, missing data was accounted for by Rubin's multiple imputation procedure and Ender's full information maximum likelihood estimation, but no significant changes were observed in either model.

Statistical analyses at the individual patient level were conducted using RStudio (Version 1.2.5033, RStudio, Inc.).

3.7.2. Study-level meta-analysis

Studies reporting SL data reported the proportion of patients with seizure freedom and recurrence at various predetermined follow-up periods (e.g., 1, 2, 5, and 10+ years). Using a random-effects model to account for heterogeneity, we created forest plots to visualize the pooled seizure freedom event rate with 95% CI at each of these follow-up periods.

Potential influences on seizure freedom event rate estimates were investigated through time point and subgroup analyses, as well as meta-regression. When studies allowed, we descriptively compared event rate estimates by etiology, surgery type, and follow-up duration, both for the entire cohort and each identified etiology type. Etiology was dichotomized to *tumor* vs *non-tumor* (perinatal cerebral infarction, intracranial hemorrhage, hemiconvulsion-hemiplegia-epilepsy syndrome, sequelae of brain trauma and infection, cortical dysplasia, hemimegalencephaly, and neuronal migration disorders, etc.), because of distinct operative and clinical considerations of tumors. Additionally, too few studies reported progressive etiologies to further categorize etiology as congenital, acquired, and progressive. We assessed the influence of these SL variables on estimates by running 6 meta-regression models including these covariates. Meta-regression was based on method of moments and used a mixed methods approach. Statistical significance was set at $p < 0.05$ (two-tailed).

Statistical analyses at the study level were conducted using the Comprehensive Meta-Analysis software suite (version 3; Biostat, Englewood, NJ, USA).

4. Results

4.1. Individual study and overall estimates

A total of 1707 citations, with duplicates removed, were identified from our electronic database search of PubMed, Web of Science, and CINAHL, as well as hand searching of references and "related articles" on PubMed. Title and abstract screening among our two reviewers showed a moderate agreement ($k = 0.54$) and led to full-text screening of 302 articles, which showed excellent agreement ($k = 0.92$). Overall, 25 articles met criteria and were used in the study (Fig. 1).

Pertaining only to participants with data for at least 10 years of postoperative follow-up, 12 of the studies reported IPD [15–25] for a total of 122 participants with a mean duration of postoperative follow-up of 14.6 years (Range = 10–38 years) and long-term seizure freedom observed in 79 participants (64.8%). Thirteen of the studies reported SL data only [26–38] for a total of 719 participants with a stratified follow-up of up to 21 years and long-term seizure freedom observed in 414 participants (57.6%) (Table 1).

4.2. Descriptive information of each study

The studies included in the IPD and SL analyses were published between 1984 and 2020, and had wide geographic representation including four continents (i.e., North America, South America, Europe, Asia). Recorded perioperative variables, etiology, and type of surgery varied considerably across all studies. The included IPD studies reported 5–21 participants with long-term (i.e., ≥ 10 years) postoperative follow-up and a wide range of seizure freedom (20.0–87.5%) at last follow-up. SL studies reported 7–130 participants with long-term follow-up and a wide range of seizure freedom (39.5–85.7%) (Table 1).

4.3. Assessment of quality of studies

The studies overall had a low mean risk of bias with respect to study participation, study attrition, outcome measure, study confounding, and statistical analysis and reporting. There was moderate risk of bias with respect to prognostic factor measurement (Fig. 2).

4.4. Publication bias

Publication bias was assessed by funnel plots obtained for studies reporting SL data. Visual examination revealed mild asymmetry in seizure freedom event rates at 10 years (Fig. 3), suggesting a relative absence of studies reporting low seizure freedom rates at this time point.

4.5. Statistically significant variables associated with outcome

All dichotomous (Table 2) and continuous (Table 3) variables

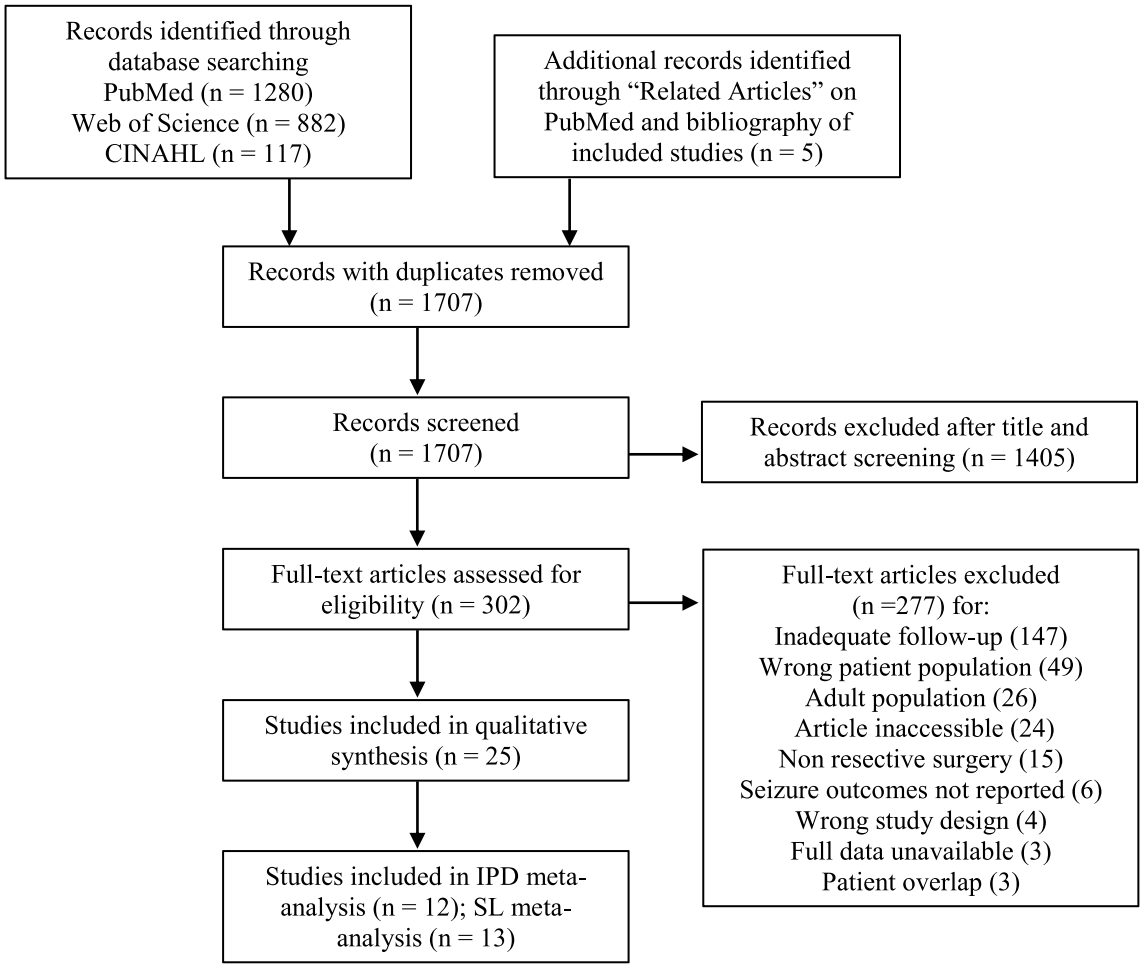

Fig. 1. PRISMA 2009 Flow Diagram for screening strategy.

putatively associated with seizure freedom, as well as length of post-operative follow-up (Table 3) were recorded.

4.5.1. *Individual patient data meta-analysis*

We first verified with univariate logistic regression that length of follow-up beyond 10 years was not associated with a further decrease of seizure freedom compared with 10 years (OR 1.067, 95% CI 0.992–1.168, $p = 0.114$), justifying our decision to group all follow-up periods of 10 years and above as $\geq$ 10 years of follow-up (Table 4).

Studies reporting individual patient data typically did not report seizure outcomes at shorter follow-up intervals. Therefore, seizure outcomes at 10 years and beyond could not be compared with short-term outcomes in this population.

Because time to seizure recurrence was not recorded, a meaningful survival analysis could not be performed. Instead, univariate logistic regression analyses of all variables putatively associated with seizure freedom (Table 4) demonstrated that lobectomy (OR 0.280, 95% CI 0.117–0.651, $p = 0.003$) was associated with decreased long-term seizure freedom (41.9%) compared to lesionectomy (75.7%) and hemispherectomy (69.4%), which achieved similar results (respectively OR 2.184, 95% CI 0.938–5.458, $p = 0.079$, and OR 1.493, 95% CI 0.691–3.299, $p = 0.313$). Other clinically relevant variables approached but did not reach statistical significance. Evolution to bilateral tonic-clonic (OR 0.486, 95% CI 0.161–1.454, $p = 0.194$) and repeat resective surgery (OR 0.178, 95% CI 0.022–0.974, $p = 0.062$) showed a trend towards decreased seizure freedom at $\geq$ 10 years of follow-up. None of the other analyzed variables showed an association with long term seizure outcomes.

Because of the heterogeneity of data and considerable missing data, the sample of patients reporting more than one of the individual variables reaching the threshold for inclusion in the multivariate analysis was too low to make any meaningful statistical comparisons by multivariate analysis.

4.5.2. *Study-level meta-analysis*

Studies reporting SL data also reported seizure outcomes at discretely shorter follow-up intervals. Therefore, we compared seizure outcomes at 10 years and beyond with short-term outcomes in this population.

The overall random-effects pooled event rates of seizure freedom were 74.2% (95% CI 69.3–78.6; Supp Fig. 1A) at 1 year, 67.9% (95% CI 58.6–76.0; Supp Fig. 1B) at 2 years, 63.7% (95% CI 55.4–71.2; Supp Fig. 1C) at 5 years, and 61.2% (95% CI 52.5–69.3; Fig. 4) $\geq$ 10 years of follow-up (Table 5). On meta-regression, the pooled event rate of seizure freedom at $\geq$ 10 years was only statistically significantly lower than at 1 year of follow-up ($p = 0.008$) (Fig. 5; Table 6). When pooled seizure freedom event rates at $\geq$ 10 years were compared with 1-, 2-, and 5-year intervals for congenital, acquired, and tumor etiologies, such statistically significant differences were not observed despite a trend towards significance between $\geq$ 10 and 1 year for congenital etiologies (Supp Tables 1 and 2; Supp Fig. 2A, B, C, respectively). This was likely due to the considerably smaller number of studies included in these subgroup analyses (Supp Table 2).

Etiology subgroup analysis found that random-effects pooled event rate of seizure freedom at $\geq$ 10 years was 62.0% (95% CI 55.2–68.3) for non-tumor etiologies, and 73.9% (95% CI 61.6–83.3) for tumors

Table 1
Characteristics of included studies.

First author (year)	N*	Mean age at surgery (range)	Study location	Perioperative variables reported †	Etiology of seizures ‡	Extent of Surgery	Mean follow-up duration (range)	Seizure outcome scale	Seizure freedom ≥ 10-year follow-up
IPD Studies									
Babini (2013)	8	12.9 (5–18)	Italy	a, b, c, d, e, f, g, t	Tumor	Lesionectomy	13.8 (11–17)	Engel	7/8 (87.5%)
Davies (1993)	10	11.1 (3–16)	USA	a, b, c, d, e, g, h, s, t, v	Various	Hemispheric	29 (19–38)	Qualitative	7/10 (70,0%)
Di Rocco (2006)	11	N/A	Italy	b, s	HME	Hemispheric	14.3 (10–17)	Engel	9/11 (81.8)
Ehrsted (2018)	18	12.4 (1–18)	Sweden	a, b, c, e, f, g, h, q, r, t	Tumor	Lesionectomy	14.1 (10–19)	Engel	12/18 (66,7%)
Granata (2014)	8	10.5 (6.3–15)	Italy	a, b, c, d, e, n, o, p, q, s	RE	Hemispheric	14.8 (11–15.4)	Qualitative	7/8 (87.5%)
Lindsay (1984)	5	12.6 (10–16)	England	b	Various	Lesionectomy, Hemispheric	14.2 (10–19)	Qualitative	4/5 (80,0%)
Sinclair (2003)	21	7.4 (1.3–16)	Canada	a, b, c, d, f, i, j, k, l, m	Various	Lesionectomy, Hemispheric	10.9 (10–12)	Engel	11/21 (52.4%)
Terra-Bustamante (2009)	5	9.8 (4–12)	Brazil	a, b, c, d, f, e, i, n, o, p, q	RE	Hemispheric	11.4 (10.2–12.8)	Engel	1/5 (20%)
Viggedal (2012)	13	11.0 (3.8–16.9)	Sweden	b, d, e, n, o, q, r,	Various	Lesionectomy, Hemispheric	10 (10–10)	Engel	5/13 (38.5%)
Villemure (1993)	5	7.6 (3–15)	Canada	a, b, c, d, e, n	Various	Hemispheric	14.2 (12–17)	Rasmussen's	4/5 (80,0%)
von der Brelie (2014)	11	13.5 (6–18)	Germany	a, b, c, d, e, h, i, k, l, m, n, p, r	CM	Lesionectomy	16.6 (10.9–21.7)	ILAE	9/11 (81.8%)
Wang (2014)	7	N/A	USA	a, e, f, p	HME, RE	Hemispheric	15.3 (11–26)	Engel	3/7 (42.9)
Total	**122**	9.9 (1–18)					14.6 (10–38)		**79/122 (64.8%)**
SL Studies							Stratification of follow-up (years)		
Liu (2020)	71	10.35 (0.5–47)	China	a, b, c, g, i, m, o, t	TSC	Lesionectomy	1, 4, 10	ILAE	44/71 (62.0%)
Reinholdson (2020)	127	13.6 (0.2–18.9)	Sweden	a, b, c, d, g, h, n, v	Not reported	Lesionectomy, Hemispheric	5, 10, 15, 20	ILAE	63/127 (49.6%)
Martinez-Lizana (2018)	13	10.3 (0–18)	Germany	a, b, c, d, k, m, t	MCD	Lesionectomy, Lobar, Hemispheric	1, 2, 5, 7, 10	Engel	10/13 (76.9%)
Hosoyama (2017)	85	9.78	Japan	a, b, c, d, e, r, u, v, w, x	Various	Lesionectomy, Lobar, Hemispheric	All 10–30 non-stratified	Engel	65/85 (76.5%)
Fallah (2015)	84	8.7 (0.5–21.6)	USA	a, b, c, i, m, s, t	Tumor	Lesionectomy	1, 2, 5, 10	Engel	47/84 (56%)
Hallbook (2013)	30	(0.5–18.2)	Sweden	a, b, c, d, e, n, o, p, q, s	Various	Lesionectomy, Lobar, Hemispheric	5–9, 10–14, 15–21	Engel	17/30 (56.7%)
Lopez-Gonzalez (2012)	130	12.3	USA	b, d, e, h, k, m, s	Various	Lesionectomy	1, 2, 5, 12	Engel	53/130 (40.8%)
Hamiwka (2005)	38	9.6 (0.5–18)	USA	a, f, k, m, s, t	Tumor, MCD	Lobar, Hemispheric	2, 5, 10	Engel	15/38 (39.5%)
Jarrar (2002)	32	14.4 (7–18)	USA	a, b, c, e, g, v, u	Tumor, MTS	Lobar	1, 5, 15	Engel	17/32 (53.1%)
Benifla (2008)	42	12.5[a] (0.7–18.8)	Canada	a, b, c, e, f, m, u, v, x	Various	Lesionectomy, Lobar	0.5, 1, 5, 10+	Engel	28/42 (66.7%)
Mathern (1999)	12	(0–37)	USA	d, e, s	Various	Lobar, Hemispheric	0.5, 1, 2, 5, 10	Custom	9/12 (75%)
Muhlebner (2014)	7	8 (0–20)	Austria	a, b, c, f, m, s	MCD	Lesionectomy, Hemispheric	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 14	ILAE	6/7 (85.7%)
Wessling (2015)	48	11.5 (1.6–17.7)	Germany	a, b, c, d, e, h, m, s, v	Tumor	Lesionectomy, Lobar	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14	ILAE	40/48 (84%)
Total	**719**								**414/719 (57.6%)**

*For individual patient data (IPD) studies, the subsequent metrics correspond with only participants with ≥ 10 year follow up.
† Perioperative variables reported: a) Age at seizure onset; b) Age at surgery; c) Duration seizure onset to surgery; d) Sex; e) Side affected; f) Preop seizure type; g) Preop seizure frequency; h) Preop # of AEDs; i) Preop EEG; j) CT; k) MRI; l) SPECT; m) ECoG; n) Preop neuro status; o) Preop cognitive status; p) Postop neuro status; q) Postop cognitive status; r) Postop # of AEDs s) Complications; t) Completeness of resection; u) Driving; v) Employment/school w) Marriage, x) Satisfaction.
‡ Various represents ≥ 3 different etiologies.
[a] Median.

(Table 5). Meta-regression showed no statistically significant differences between tumor and non-tumor etiologies; however, there was a trend towards a statistically significant increase in seizure long-term freedom for tumor etiologies (tumor: coefficient = 0.442, $p = 0.163$; Table 6; Supp Fig. 2D). Surgery subgroup analysis revealed that random-effects pooled event rate of seizure freedom at ≥ 10 years was 45.0% (95% CI 20.6–72.1) for focal (lesionectomy), 60.8% (95% CI 48.0–72.2) for lobar (lobectomy), and 54.1% (95% CI 45.6–62.3) for multilobar or hemispheric surgery (Table 5). Meta-regression showed neither statistically significant differences nor trends between focal, lobar, and hemispheric/multilobar surgery (lobar: coefficient = 0.594, $p = 0.236$; hemispheric/multilobar: coefficient = 0.282, $p = 0.606$; Table 6; Supp

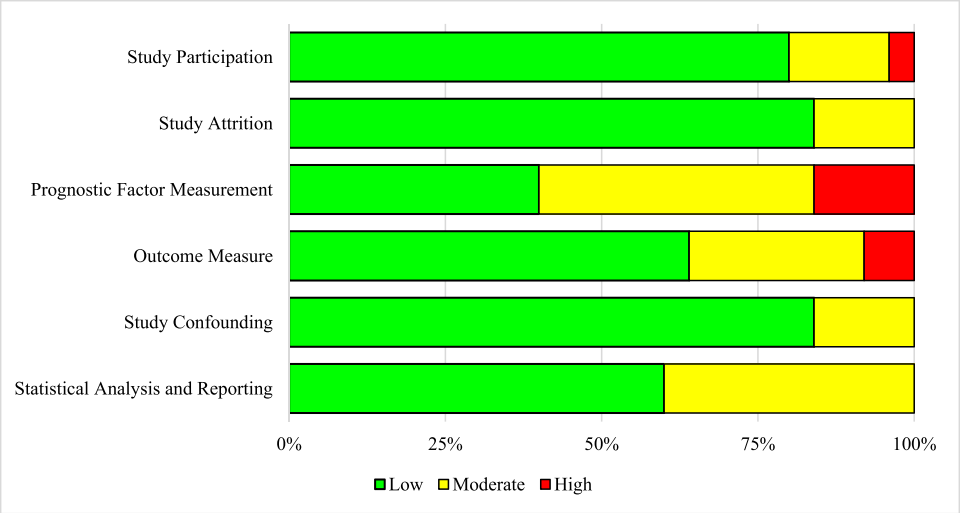

Fig. 2. Summary risk of bias assessment overall using the QUIPS tool. Prognostic factor measurement across studies had moderate risk of bias. All remaining factors had low overall risk of bias.

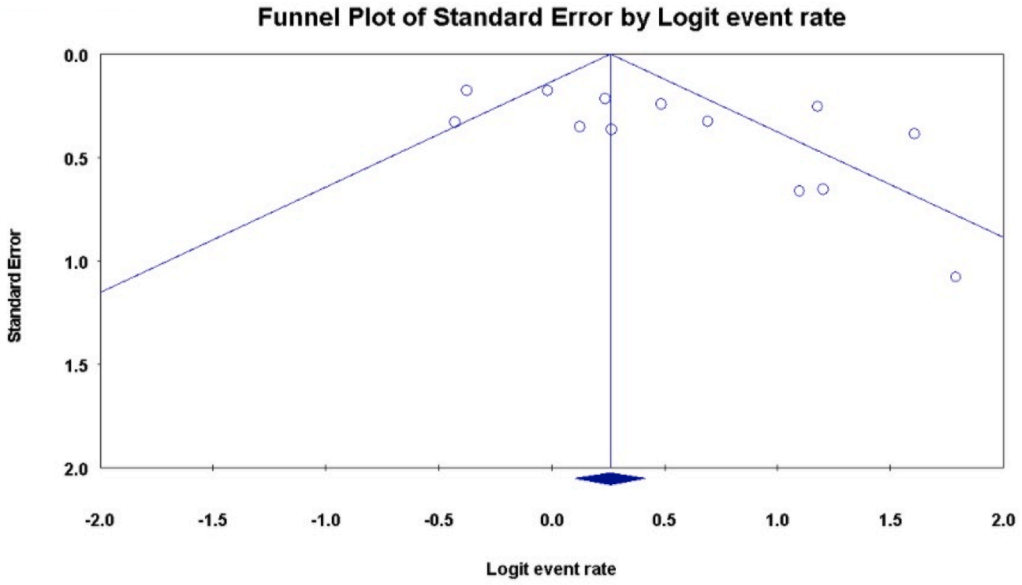

Fig. 3. Funnel plot of SL seizure freedom event rate at least 10 years postoperatively. The mild asymmetry suggests a relative paucity of studies reporting low seizure freedom rates at this time point.

Fig. 2E).

5. Discussion

Long term seizure outcomes and impact on clinical follow-up

This study, aimed to systematically analyze the long-term seizure outcomes of pediatric patients undergoing resective epilepsy surgery with at least 10 years of follow-up, demonstrates that between half and two-thirds of patients are seizure free at this follow-up period. Moreover, our finding that seizure outcomes at least 10 years postoperatively only differ significantly from 1-year, but not 2-, and 5-year follow-up periods suggests that the proportion of pediatric patients that remains seizure free declines abruptly in the first 2 years post-operatively then plateaus until 10 years post-operatively and beyond. This highlights the curative potential of resective epilepsy surgery for select patients.

Our results are consistent with those of a previous mixed pediatric and adult meta-analysis pooling data at least five years postoperatively, which concluded that the benefits of epilepsy surgery were durable during that period [14]. In contrast, a recent comprehensive meta-analysis on pediatric epilepsy surgery found a steady decline over time followed by a sharp decline at 10 years postoperatively [7]. The discrepancy between our results and those of the latter study can be explained by differences in our methodologies: our search strategy was designed specifically to identify studies reporting seizure outcome at 10 or more years of follow-up, which lead to identification of a larger number of studies at this time point. This approach means our analysis uniquely complements other analyses pooling data predominantly from the shorter term.

Seizure freedom 2 years postoperatively and beyond was associated with long-term seizure freedom in our large cohort, suggesting that this postoperative interval may serve as the most appropriate short-term follow-up period for predicting long-term seizure outcomes. This information can be used by epilepsy teams to anticipate long-term outcomes, manage patient follow-up visits, and provide appropriate expectations to patients and their families. For example, patients and families may reasonably hope for a curative resection (i.e., expectations of sustained

Table 2
IPD meta-analysis summary tables (frequencies and percentages) of preoperative and operative categorical variables.

Independent variable	Number	%
Sex		
Male	54	61.4
Female	34	38.6
Preop seizure freq		
Daily seizures	14	38.9
Weekly seizures	7	19.4
Monthly seizures or less	15	41.7
Evolution to bilateral tonic-clonic	18	25.7
Etiology		
Congenital	32	28.8
Progressive	20	18.0
Acquired	59	53.2
Tumor etiology	35	31.5
Localization		
Extratemporal	17	27.9
Temporal	44	72.1
Surgery type		
Lesionectomy	37	31.7
Lobectomy	31	26.5
Hemispherectomy	49	41.9
Reoperation	8	25.8

Table 3
IPD meta-analysis summary tables (mean, median, interquartile range, and range) of preoperative continuous variables and length of postoperative follow-up.

Independent variable	n	Mean	Median	IQR	Range
Age seizure onset	85	6.11	6.00	1.50–10.00	0.00–17.00
Age surgery	115	9.94	10.50	6.00–14.00	0.58–18.00
Seizure duration	78	5.35	4.00	2.00–9.00	0.00–17.00
#AEDs preop	29	1.97	2.00	1.00–2.00	0.00–6.00
Length FU ≥ 10 years	122	14.56	12.00	10.82–17.00	10.00–38.00

FU: Follow-up. ASM: Antiseizure medication.

Table 4
IPD meta-analysis univariate analysis odds ratios, confidence intervals, and p-values of variables associated with long-term seizure freedom.

Independent variable	**OR**	**Lower 95% CI**	**Higher 95% CI**	**p-value**
Female	0.687	0.284	1.660	0.403
Age seizure onset	1.035	0.941	1.143	0.489
Age surgery	1.024	0.948	1.107	0.549
Seizure duration	1.004	0.903	1.122	0.946
Weekly seizures	1.000	0.138	9.041	1.000
Monthly seizures or less	1.100	0.208	5.832	0.909
Evolution to bilateral tonic-clonic	0.486	0.161	1.454	0.194*
Congenital	1.482	0.619	3.774	0.389
Progressive	0.572	0.213	1.561	0.266
Acquired	1.032	0.468	2.268	0.937
Tumor	1.202	0.518	2.897	0.673
Temporal	0.929	0.324	2.589	0.888
#AEDs preop	0.816	0.447	1.502	0,490
Lesionectomy	2.184	0.938	5.458	0.079*
Lobectomy	0.280	0.117	0.651	0.003**
Hemispherectomy	1.493	0.691	3.299	0.313
Reoperation	0.178	0.022	0.974	0.062*
Length FU ≥ 10 years	1.067	0.992	1.168	0.114

*Variables with $p < 0.2$ considered as trending towards statistical significance. ** Variables with $p < 0.05$ considered statistically significant. ASM: Antiseizure medication. FU: Follow-up.

seizure freedom). However, they must keep in mind that a significant subset of patients initially seizure-free within one year postoperatively may have seizure recurrence in the long term, which becomes significantly less likely if seizure freedom is sustained two years postoperatively according to our findings. Carefully conveying this information to patients will help to ensure adequate follow-up and facilitate early identification of candidacy for reoperation when appropriate.

5.1. Lack of independent predictors of seizure outcomes

We sought to identify predictors of long-term seizure outcomes by performing IPD and SL-meta-analyses using clinically relevant variables typically associated with short-term seizure freedom. Overall, the only variable associated with long-term seizure outcomes was surgery type, with lobectomy correlating with decreased seizure freedom relative to focal and hemispheric surgeries. We attribute this finding to the general success of these smaller and larger surgeries in the pediatric cohort. Indeed, lesionectomy is consistently associated with good seizure outcomes due to the success of this intervention on pediatric tumor patients [39]. This contrasts our SL finding that lesionectomy was associated with a lower pooled seizure freedom event rate. However, the latter was non statistically significant and based on data from only 4 studies. Furthermore, though tumor etiology only showed a trend towards increased seizure freedom in our SL analysis and no significant association in our IPD analysis, this discrepancy may be due to our inclusion of many non-tumor etiologies highly amenable to lesionectomy, including cerebral cavernous malformations [25]. Hemispherectomy has also been associated with long-term seizure freedom in a meta-analysis of pediatric epilepsy surgery outcomes that showed strong associations with short-term seizure freedom [7].

Regarding etiology, patients undergoing resective epilepsy surgery for tumors trended toward better long-term seizure outcomes compared with non-tumor etiologies. Of the two major tumor series included in this analysis, one reported durable rates of seizure freedom up to 14 years after surgery [38], whereas the other reported a drop-off at 10 years compared to 1, 2, and 5-year follow-up [31]. This former study corroborates our finding that tumor patients had durable seizure freedom through long term follow-up. Our IPD association of lesionectomy (the typical surgery for tumorigenic epilepsy), with long-term seizure freedom supports the favorable seizure outcomes of tumorigenic epilepsy seen in our pooled estimates and in the literature. A fairly consistent property across tumorigenic epilepsies is that they represent anatomically self-limited seizure onset zones [40,41] that are highly amenable to surgical resection. This contrasts with non-tumor etiologies, which are more likely to be associated with wide-spread network disorder epilepsies [42] (e.g., malformations of cortical development) less amenable to surgical resection. A multivariate analysis to further characterize the relationship between lesionectomy and tumor vs non-tumor etiology was performed but yielded no meaningful results due to inadequate sample size at 10-year follow-up.

Importantly, most relevant clinical variables analyzed showed no association with long-term seizure freedom. One such example is the lack of association between temporal resection and long-term seizure outcome. Given the literature on short-term seizures outcomes, temporal resection is expected to lead to higher seizure freedom rates than extra-temporal resection [7], however we did not find any such relationship in the long term. This can be explained by the small number of patients with data regarding temporal vs extra-temporal resection (44 and 23, respectively) which likely did not provide the power to confirm meaningful associations, as well as extra-temporal resection patients performing unexpectedly well in this small subgroup (60.9% seizure freedom vs 59.1% seizure freedom in the temporal resection subgroup).

5.2. Generalizability of data

Our findings suggest that when counseling pediatric epilepsy patients and their families, treating physicians may reasonably expect patients who are seizure-free at two-year follow-up to remain seizure free in the long-term, warranting less frequent follow-up intervals. Patients with tumor-related epilepsy who are seizure free at this interval

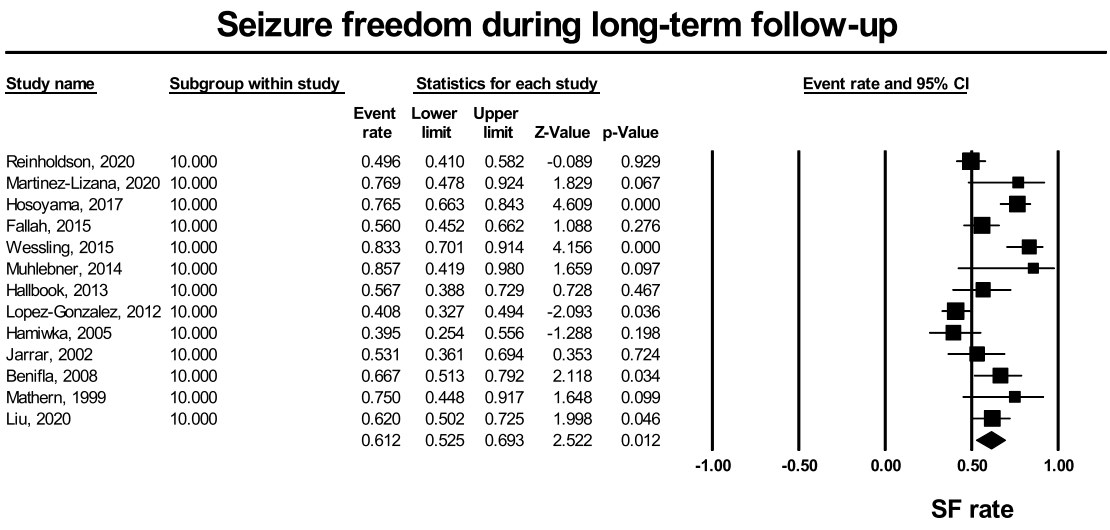

Fig. 4. SL pooled estimates and forest plots of seizure freedom event rates at least 10 years postoperatively. SF: Seizure freedom.

Table 5
Study-level (SL) meta-analysis pooled seizure freedom event rates.

Follow-up	Number of studies	SF event rate	Lower limit	Upper limit
10 yrs	13	0.612	0.525	0.693
5 yrs	11	0.637	0.554	0.712
2 yrs	6	0.679	0.586	0.760
1 yr	8	0.742	0.693	0.786
Etiology				
Non tumor	7	0.620	0.552	0.683
Tumor	6	0.739	0.616	0.833
Surgery type				
Focal	4	0.450	0.206	0.721
Lobar	7	0.608	0.480	0.722
Hemispheric/ multilobar	4	0.541	0.456	0.623

SF: Seizure freedom.

may be more likely to have durable outcomes relative to other etiologies. Given that pediatric epilepsy surgery represents a diverse group of interventions used to treat a variety of epileptogenic pathologies, the utility of generalizing this data to a specific patient with a specific disease and surgery is limited. These analyses are the result of population level data and are therefore not suited to predict outcomes for individual patients.

5.3. Call for uniform data reporting

The purported associations, and lack thereof, identified in our study highlight the need for uniform longitudinal data collection to enable robust stratified analyses that can accurately be extrapolated to individual patients. Guidelines, such as the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [43], have been developed to support standard reporting practices; however, none of the included studies utilized such tools. In fact, as a result of non-uniform reporting of data, we were only able to perform a high-quality meta--analysis on the rates of seizure freedom over time, leaving the stability of seizure freedom for specific etiologies and interventions largely unknown. The lack of statistically significant associations detected among relevant clinical variables may be secondary to the low number of studies reporting stratified data, low number of patients, as well as heterogeneous data reporting between studies, consistent with our large confidence intervals (Table 2; multivariate analysis) and possibly resulting in a type II statistical error. For studies which report more than one etiology or surgery type, the stratified perioperative and outcome data specific to each of these groups must be reported. To understand the durability of these outcomes in assessing resective epilepsy surgery as a curative intervention, this data must be collected systematically over time at predetermined intervals of follow-up.

5.4. Strengths and limitations

This review presented notable strengths. We performed a comprehensive search not limited by language or date of publication. Missing data was requested and received for inclusion in the analysis by at least one author, as well as accounted for with multiple imputations. We utilized the available data by performing IPD and SL analyses, which proved complementary. Of note, seizure freedom rates at $\geq$10 years were similar between patients in the IPD and SL analyses. Given the heterogeneity of reported data across studies, this was a robust solution to addressing the same research question with multiple statistical approaches.

There were also several important limitations, which need to be considered. Despite the rigorous search strategy developed, some eligible studies may have been missed as a result of screening errors or inappropriate indexing (e.g., title and abstract screening resulted in moderate inter-rater reliability). Heterogeneous reporting limits the validity of appropriate data abstraction and assessment of risk of bias. Differences in criteria for postoperative follow-up may have covaried with duration and interval of follow-up (e.g., patients with seizure freedom were more or less likely to follow-up than patients with seizure recurrence). Similarly, attrition by nature of very long-term follow-up increases risk of selection bias. The latter two statements may explain the observed mild publication bias in favor of studies reporting higher long-term seizure freedom rates (Fig. 3). Other patient important outcomes (e.g., quality of life, working capacity) were unable to be evaluated. The generalizability of outcome durability to individual patients is limited in the SL analysis due to reporting interval outcomes between participants rather than within participants longitudinally. This could potentially be resolved by an IPD meta-analysis, but only most recent follow-up was uniformly reported in included IPD studies which precludes a survival analysis. Furthermore, despite our rigorous search strategy, few patients could be included in our IPD meta-analysis, possibly resulting in a type II statistical error. Therefore, long-term

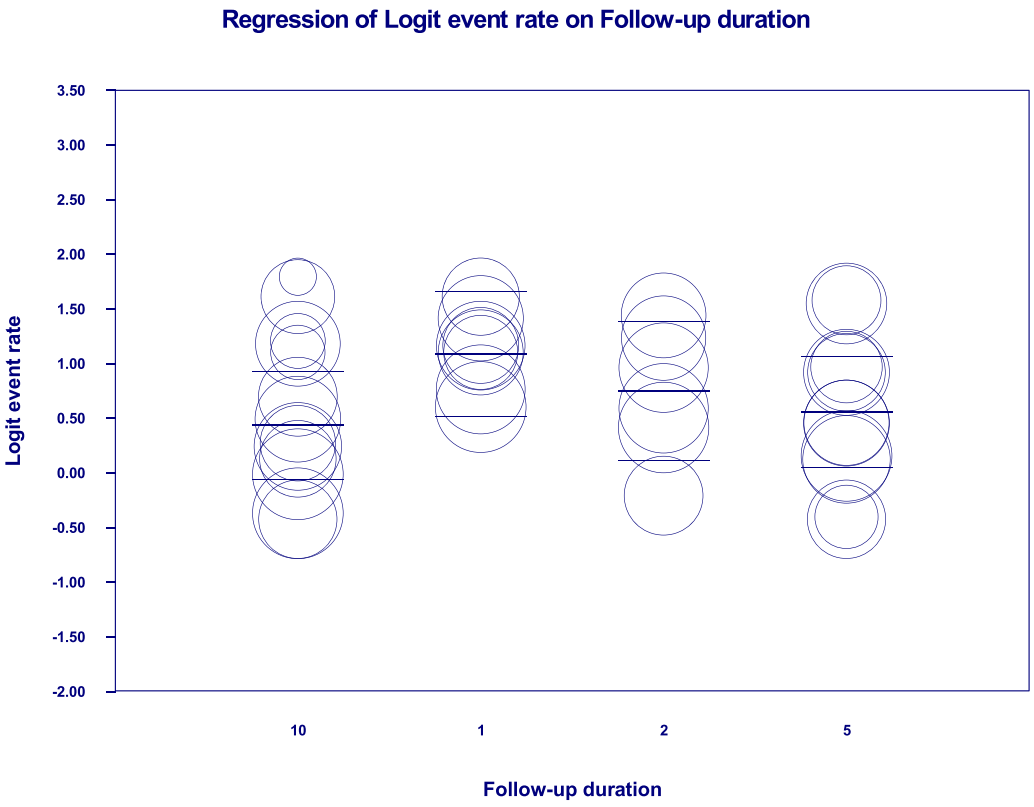

Fig. 5. SL meta-regression scatter plot showing pooled estimates of seizure freedom event rates with 95% confidence intervals for entire study population at 10 vs 1, 2, and 5 years of follow-up. Circles represent seizure freedom event rate for each study at a particular length of follow-up. The size of the circle indicates the study's relative weight. For each length of follow-up, the middle horizontal line represents the weighted overall seizure freedom event rate, whereas the upper and lower horizontal lines represent the upper and lower limit of the 95% confidence interval, respectively.

Table 6
SL meta-analysis meta-regressions.

Follow-up (Ref 10 yrs)	Number of studies	Coefficient	Lower 95% CI	Higher 95% CI	P-value
5 yrs	11	0.123	−0.328	0.574	0.593
2 yrs	6	0.314	−0.200	0.828	0.231
1 yr	8	0.652	0.171	1.133	0.008**
Etiology (Ref non tumor)					
Tumor	6	0.442	−0.177	1.062	0.163
Surgery type (Ref focal)					
Lobar	7	0.594	−0.389	1.576	0.236
Hemispheric/ multilobar	4	0.282	−0.791	1.354	0.606

** Variables with $p < 0.05$ considered statistically significant. ref: Reference.

seizure outcomes still cannot be predicted on an individual patient level. This would ideally require prospective, multicenter studies collecting high quality, stratified (e.g., by etiology, surgery type) data over an extended postoperative interval, possibly with a control group consisting of patients with medically refractory epilepsy who are not candidates for surgery, matched according to individual characteristics, to distinguish between the effects of surgery and the natural history of the disease.

Importantly, our study pooled the best available data exclusively on studies reporting seizure outcomes at 10 or more years of follow-up, and comparisons to earlier interval follow-ups reported within these studies were made when possible. This leaves numerous studies reporting shorter interval follow-up (e.g., 1, 2, or 5 years) only that were not included in our analysis. Therefore, the estimates of proportions of seizure freedom must be interpreted only in the context of studies reporting long-term follow-up. An ideal search strategy may include studies reporting any length of follow-up; however, a recent comprehensive meta-analysis by Widjaja utilizing this approach compiled only two studies reporting follow-up at 10 years [7]. While our proportions of seizure freedom at 1, 2, and 5 years are comparable, albeit slightly higher, than theirs (74.2% vs 64.8%, 67.9% vs 62.9%, 63.7% vs 60.3%, Harris vs Widjaja, respectively) the proportion at 10 years is discrepant (57.6% vs. 39.7) which highlights the utility of our specific and distinct research question. Further studies on long-term outcomes must consider "resolved" epilepsy, defined by 10 years of seizure freedom with no seizure medicines for the last 5 years [44]. Variable seizure outcome scales without true duration of seizure freedom reported (Table 1) and vague reporting of ASMs in the current literature unfortunately did not allow for such an analysis in the present study. Future studies should emphasize "resolved" epilepsy as an appropriate metric of long-term outcome.

6. Conclusions

Resective surgery is a durable and potentially curative treatment option for select pediatric patients with refractory epilepsy. The rate of seizure freedom declines abruptly following surgery then stabilizes for at least a decade postoperatively. Given the greatest decrease occurs in the first 2 years, this may be an important milestone to predict long-term outcome. Although lobectomy appears to be a strong predictor for lower likelihood of long-term seizure freedom, long-term prognostication on an individual level is still not possible. Uniform data reporting and prospective, multicenter studies collecting high quality, stratified (e.g., by etiology, surgery type) data over an extended postoperative interval are recommended to further examine the durability of resective surgery as a treatment for pediatric epilepsy.

Compliance with ethical standards

All authors had access to the study data and reviewed and approved the final manuscript. The authors have no conflicts of interest to declare. No funding was received.

Declaration of Competing Interest

None of the authors has any conflict of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2022.08.010.

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