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REVIEW

Identification of common predictors of surgical outcomes for epilepsy surgery

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Abstract: Although epilepsy surgery is an effective treatment for patients with drug-resistant epilepsy, surgical outcomes vary across patient groups and studies. Identification of reliable prognostic factors for surgical outcome is important for outcome research. In this study, recent systematic reviews and meta-analyses on prediction of seizure outcome have been analyzed, and common predictors of seizure outcome or unrelated factors for temporal lobe epilepsy (TLE), lesional extratemporal lobe epilepsy (ETLE), and tuberous sclerosis complex have been identified. Clinical factors such as lesional epilepsy, abnormal magnetic resonance imaging, partial seizures, and complete resection were found to be common positive predictors, and factors such as nonlesional epilepsy, poorly defined and localized epileptic focus, generalized seizures, and incomplete resection are common negative predictors, while factors such as age at surgery and side of surgery are unrelated to seizure outcome for TLE and lesional ETLE. In addition, diagnostic neuroimaging and resection are among the most important predictors of seizure outcome. However, common predictors of seizure outcome could not be identified in nonlesional ETLE because no predictors were found to be significant in adult patients (by meta-analysis), and outcome prediction is difficult in this case. Meta-analysis of other outcomes, such as neuropsychologic outcomes, is rare due to lack of evaluation standards. Further studies on identification of reliable predictors of surgical outcomes are needed.

Keywords: neuroimaging, epilepsy surgery, outcome prediction, common predictors

Introduction

Around one third of patients with focal seizures are resistant to antiepileptic drugs. For these patients, epilepsy surgery brings the hope of a seizure-free outcome and improved quality of life. Epilepsy surgery can achieve a 60%–90% likelihood of seizure-free outcome in patients with temporal lobe epilepsy (TLE) and 40%–60% in extratemporal lobe epilepsy (ETLE).[1] However, there are still uncertainties in surgical candidates, and it is important to estimate possible risks, identify factors related or unrelated to outcomes, and predict postoperative outcomes prior to surgery.

The predictive value of neuroimaging for epilepsy surgical outcome has been reported by a number of studies. For example, Lerner et al,[2] Cossu et al,[3] Widdess-Walsh et al,[4] and Jeha et al[5] have shown that complete resection of the abnormality detected by preoperative magnetic resonance imaging (MRI) is the most important predictor of a favorable postoperative outcome. Functional neuroimaging modalities, such as magnetoencephalography (MEG)/magnetic source imaging (MSI), positron emission tomography (PET), and ictal single-photon emission computed tomography (SPECT) also have clinical value in predicting seizure-free outcome.[6] In addition, Kuzniecky et al,[7] Eberhardt et al,[8] and Stefan et al[9] have

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demonstrated that bilateral magnetic resonance spectroscopy (MRS) metabolite alterations in TLE with hippocampal sclerosis (HS) have a predictive value for surgical outcome.

In addition to neuroimaging, other predictors and risk factors for seizure outcome have also been identified. The presence of radiographic mesial temporal sclerosis (MTS) is considered to be a factor predictive of a favorable seizure outcome after surgical intervention.[10] The surgical option of localized frontal resection versus more extensive lobectomy with/without an extrafrontal component has been found to be predictive of outcome after frontal lobectomy,[11] while bilateral temporal onset,[12] frequent secondary generalized seizures,[13,14] and head trauma[15] have been identified as poor predictors of seizure control.

In general, reasons for failure of epilepsy surgery are multifactorial,[16,17] and outcome predictors are hard to identify, especially in nonlesional TLE or ETLE cases.[18–20] On the other hand, patients with unilateral radiographic mesial temporal sclerosis are considered to be the "ideal" candidates for epilepsy surgery. Recently, Feis et al[21] studied patients with left TLE (n=49, 89.8% or 44/49 with hippocampal sclerosis) who underwent selective amygdalohippocampectomy, and found that surgical outcome could be predicted in males (94% balanced accuracy) and in females (96% balanced accuracy) using presurgical structural MRI.

However, the above study findings triggered the following questions. How applicable is such high-accuracy outcome prediction? In addition to predicting outcome in unilateral lesional TLE, what about outcome prediction in bilateral TLE, nonlesional TLE, or ETLE cases? What is the full and real picture of surgical outcome prediction? Is seizure outcome in general predictable? How are the presurgical findings related to surgical outcomes? Is it possible to use presurgical neuroimaging and/or other factors to predict surgical outcomes? How reliable are the predictors? Since the findings vary among studies, is it possible to identify common predictors based on the findings of systematic reviews and meta-analyses? Further, what is the role of presurgical neuroimaging in predicting seizure outcome? Moreover, in addition to seizure outcome, how good is the prediction of other outcomes? To address the above questions, recent systematic reviews and meta-analyses on epilepsy surgical outcome prediction were reviewed and their findings were analyzed.

Methods

Paper selection and classification

A Medline query was performed via PubMed using the keywords "epilepsy", "surgical outcome", and "predictor" for papers published since 2000. The articles were filtered for reviews and meta-analyses. Ten meta-analyses and three comprehensive reviews on seizure outcome prediction were indentified. The articles were classified according to epilepsy substrates as lesional or nonlesional TLE, ETLE, or tuberous sclerosis complex (TSC). In addition, to understand predictors of other outcomes and the role of other factors (such as type of surgery), further Medline queries were undertaken. Four related articles (two reviews and two meta-analyses) on other outcomes and four meta-analyses on surgical options or other interventions were identified.

Table 1 gives an overview of the literature studied in this paper. The literature was classified as lesional or nonlesional TLE or ETLE subgroups. Lesion in this paper refers to mesial temporal sclerosis or hippocampal sclerosis, gliotic tissue, tumors, and other circumscribed anomalies, including malformations of cortical development and focal cortical dysplasia.[22] In addition, tubers in tuberous sclerosis complex were considered to be special lesions, and meta-analyses on outcome prediction in tuberous sclerosis complex were classified as a separate subgroup. Further, given that the majority of epilepsy cases in Tonini et al[23] and Téllez-Zenteno et al[1] were TLE, these two articles were counted as those addressing seizure outcome in TLE. Moreover, since the majority of epilepsy cases in Téllez-Zenteno et al[22] were lesional, this paper was classified into lesional epilepsy subgroups.

Extraction of findings

To summarize the findings of the meta-analyses and reviews, outcome predictors (both positive and negative) and unrelated factors were extracted from the results of the papers. To overcome the variations between studies, common predictors of seizure outcome were extracted from the findings of the meta-analyses and reviews.

Common predictors or factors unrelated to surgical outcome in the literature were identified by counting the frequency of appearance of a predictor/unrelated factor in every literature subgroup (such as lesional or nonlesional TLE). If the papers in a literature subgroup had overlap (eg, for adults with lesional TLE), and the frequency of a predictor/unrelated factor was ≥ 2, the predictor/unrelated factor was considered to be as a common predictor/unrelated factor. On the other hand, if the papers in a literature subgroup had no overlap (eg, one for children and the other for adult patients), then the predictors/factors found by meta-analysis were still considered.

Table 1 Overview of literature on predictors of seizure outcome after surgery for epilepsy

	TLE	ETLE
Lesional	McIntosh et al (review)[41] Tonini et al[23] Téllez-Zenteno et al[1] Téllez-Zenteno et al[22] Rowland et al[26] (FCD) Englot et al[42] (children) Najm et al[25] (review)	Téllez-Zenteno et al[22] Rowland et al[26] (FCD) Englot et al[11] (FLE) Englot et al[43] (children)
Nonlesional	McIntosh et al (review)[41] Tonini et al[23] Téllez-Zenteno et al[1] Téllez-Zenteno et al[22] Rowland et al[26] (FCD) Englot et al[42] (children) Najm et al[25] (review)	Ansari et al[20,44] (adults and children) Englot et al[11] (FLE) Englot et al[43] (children)
TSC	Jansen et al[27] (review) Zhang et al[45] Fallah et al[46]	

Other outcomes	Surgical options and other interventions
Vaz[35]	Spencer et al[39]
Schmidt et al[32] (review)	Schmidt and Stavem[38]
Téllez-Zenteno et al[33]	Englot et al[40]
Ives-Deliperi and Butler[37] (review)	Josephson et al[34]

Note: Papers marked as review are review papers, otherwise are meta-analyses.
Abbreviations: FLE, frontal lobe epilepsy; FCD, focal cortical dysplasia; ETLE, extratemporal lobe epilepsy; TLE, temporal lobe epilepsy; TSC, tuberous sclerosis complex.

Results

Prediction of seizure outcome

The outcome predictors and factors unrelated to seizure outcome in patients with lesional or nonlesional TLE extracted from the literature are listed in Table 2. For patients with lesional or nonlesional ETLE, predictors and unrelated factors are listed in Table 3 (lesional ETLE) and Table 4 (nonlesional ETLE). Predictors and unrelated factors in patients with tuberous sclerosis complex are shown in Table 5.

The predictors and factors unrelated to seizure outcome identified by the reviews and meta-analyses varied between patient groups and studies. In patients who underwent temporal lobectomy, seizure outcome was associated with a number of predictors, including diagnostic neuroimaging, lesional versus nonlesional epilepsy, and complete versus incomplete resection. However, in challenging epilepsy cases such as nonlesional ETLE, surgical outcome predictors were hard to identify, especially in adult patients. A meta-analysis by Ansari et al found that none of the factors (age at surgery, age at seizure onset, duration of epilepsy, seizure semiology, abnormality on MRI, lateralization of seizures) were significantly associated with seizure outcome, indicating that shortening the duration of epilepsy or pursuing surgery early does not improve outcomes in this case.[20]

Common predictors and factors unrelated to seizure outcome in the findings of the meta-analyses for lesional and nonlesional TLE, lesional ETLE, and tuberous sclerosis complex were identified and the results are shown in Table 6. Because no predictors of seizure outcome for adult nonlesional ETLE patients were found by the meta-analysis of Ansari et al,[20] common predictors could not be extracted from the findings of the reviews or meta-analysis in nonlesional ETLE.

Other outcomes and interventions

The main findings of reviews or meta-analyses on other outcomes such as discontinuation of antiepileptic drugs (AEDs) and neuropsychologic outcomes are summarized in Table 7. Further, the main findings of the meta-analyses on epilepsy surgical options or other interventions are summarized in Table 8.

Discussion

Identification of reliable prognostic factors or predictors of outcomes of epilepsy surgery is critical to reduce uncertainties for both surgical candidates and surgical teams. This study gathered together recent reviews and meta-analyses in this area, classified them into lesional or nonlesional TLE, ETLE, or tuberous sclerosis complex subgroups, summarized the findings, and made an effort to identify common predictors in order to obtain more reliable prognostic factors.

Common predictors of seizure outcome

Early research found that predictors of early recurrence include diffuse and poorly localized epilepsy, need for invasive electroencephalographic (EEG) recordings, and presence of interictal epileptiform abnormalities on postoperative EEG,[24] while more recent research found that a predictor of late failure was pathology consistent with focal cortical dysplasia type 1.[25] On the other hand, clinical factors, such as seizure frequency, duration of epilepsy, sex, age of onset, and laterality of seizure focus have not been shown to be risk factors for seizure recurrence.[18,19] The results of this study indicate that lesional epilepsy (with a focal and identifiable lesion), an abnormal MRI, partial seizures, and complete resection are common positive predictors of seizure outcome in patients who undergo surgery for lesional or nonlesional TLE or lesional ETLE. On the other hand, indicators such as nonlesional epilepsy, a poorly defined and localized

Table 2 Predictors of seizure outcome for lesional and nonlesional TLE

	Surgery type/literature scope/ pooled seizure freedom rate	Positive predictors	Negative predictors	Unrelated factors/trend
McIntosh et al[41] (review)	Patients with TLE surgery; 126 papers since 1991; 33%–93%, median 70%	HS on MRI; unilateral anterior temporal interictal and ictal EEG abnormalities; ictal hyperperfusion SPECT; temporal lobe abnormality on PET; extent of mesial resection (with mesial foci); absence of seizures in the first postoperative week	Head trauma; preoperative convulsive seizures; epileptiform abnormal EEG post-surgery; HS + FCD on MRI; acute postoperative seizures	Age at onset; sex; duration of epilepsy; EEG depth electrodes versus scalp only; preoperative seizure frequency; tumor versus nontumor on MRI; preresection to postresection ECoG change; side of surgery; extent of lateral resection; length of follow-up
Tonini et al[23] (meta-analysis)	Patients with temporal and extratemporal resection; 47 (29 TLE; 18 ETLE-related) papers since 1984; 35%–80%	Extensive surgical resection (OR 0.24, 0.16–0.36); abnormal MRI (0.44, 0.29–0.65); mesial temporal sclerosis (0.47, 0.35–0.64); history of febrile seizures (0.48, 0.27–0.83); EEG/MRI concordance (0.52, 0.32–0.83); tumors (0.58, 0.42–0.80)	Need for intracranial monitoring (OR 2.72, 1.60–4.60); presence of postoperative discharges (OR 2.41, 1.37–4.27)	Neuromigrational defects (OR 1.51, 0.96–2.37); CNS infections (OR 1.37, 0.54–3.46); vascular lesions (OR 1.51, 0.68–3.34); interictal spikes (OR 0.55, 0.25–1.16); side of resection (OR 1.7, 0.74–1.84)
Téllez-Zenteno et al[1] (meta-analysis)	Patients underwent epilepsy surgery; 76 papers/83 studies; 66% TLE, 27% FLE, 46% OLE, 46% parietal resections, 61% hemispherectomy, 34% ETLE resections	In TLE: surgery after 1980; seizure outcome using Engel's class I system (improvement in patient selection, identification of seizure focus, and surgical techniques improve outcomes)	Surgery before 1980 Seizure outcome using other system	<40 or >40 patients Follow-up of 5–10 years or >10 years
Téllez-Zenteno et al[22] (meta-analyses)	Patients with lesional or nonlesional epilepsy; 40 papers (35 TLE and ETLE, 20 TLE, 13 ETLE), 2,860 lesional/ 697 nonlesional patients	Presence of a lesion on histopathology or MRI	Nonlesional	
Rowland et al[26] (meta-analyses)	Patient with FCD; 37 papers included 2,014 patients; 55.8%±16.2%	Milder semiology; partial (or generalized) seizures (1.46); a temporal location (1.35); abnormal MRI (1.67); FCD type II (versus type I) histologic classification (1.38); complete resection (3.91)	Generalized seizures; nontemporal location; normal MRI; FCD type I; incomplete resection	Age at surgery; EEG localization of ictal onset
Englot et al[42] (meta-analyses)	Children with TLE; 36 studies since 1993 included 1,318 pediatric patients; 76%	Lesional epilepsy etiology (1.08, 1.02–1.15); abnormal MRI (1.27, 1.16–1.4); partial (lack of generalized) seizures (1.36, 1.2–1.56). (gross-total lesionectomy; ATL; daily seizures)	Nonlesional epilepsy; normal MRI; generalized seizures; subtotal resection	Age at surgery; sex; duration of epilepsy; ictal EEG; ECoG; side of surgery
Najm et al[25] (review)	Patients underwent epilepsy surgery	Well localized EEG; unilateral focal lesion on MRI; complete resection; no FCD type I pathology	Early recurrence: poorly localized EEG; bilateral/multifocal lesions on MRI; need for ictal EEG, and interictal abnormal postoperative EEG; incomplete resection; late recurrence: FCD type I pathology (lack of pathologic changes)	

Abbreviations: TLE, temporal lobe epilepsy; OR, odds ratio; ATL, anterior temporal lobectomy; ECoG, electrocorticography; EEG, electroencephalography; MRI, magnetic resonance imaging; PET, positron emission tomography; FLE, frontal lobe epilepsy; OLE, occipital lobe epilepsy; FCD, focal cortical dysplasia; ETLE, extratemporal lobe epilepsy; HS, hippocampal sclerosis; SPECT, single-photon emission computed tomography; CNS, central nervous system.

Table 3 Predictors of seizure outcome for lesional ETLE

	Surgery type/literature scope/ pooled seizure freedom rate	Positive predictors	Negative predictors	Unrelated factors/trend
Téllez-Zenteno et al[22] (meta-analyses)	Patients with lesional or nonlesional epilepsy; 35 studies 2,860 patients	Presence of a lesion on histopathology or MRI	Nonlesional	
Rowland et al[26] (meta-analyses)	Patient with FCD; 37 papers included 2,014 patients; 55.8%±16.2%	Partial seizures (1.46); a temporal location (1.35); abnormal MRI (1.67); FCD type II histologic classification (1.38); complete resection (3.91)	Generalized seizures (1.46); extratemporal location (1.35); FCD type I histologic classification (1.38); incomplete resection (3.91)	Age at surgery; EEG localization of ictal onset
Englot et al[11] (meta-analyses)	Patient with frontal lobe epilepsy; 1,199 patients in 21 studies; 45.1%	Lesional epilepsy origin (1.67); abnormal preoperative MRI (1.64); extensive lobectomy (1.71)	More poorly defined epileptic focus; nonlesional epilepsy origin (1.67); normal preoperative MRI (1.64); localized frontal resection (1.71)	Presurgical PET; EEG; ictal EEG; epilepsy duration; seizure frequency; surgery side; intraoperative interictal EEG
Englot et al[43] (meta-analyses)	Children with ETLE; 36 studies included 1,259 pediatric patients; 56%	Shorter epilepsy duration (≤7 years, 1.52, 1.07–2.14); lesional epilepsy (1.34, 1.19–1.49); absence of generalized seizures (1.61,1.18–2.35); localizing ictal EEG findings (1.55, 1.24–1.93)	>7-year epilepsy history; nonlesional epilepsy; generalized seizures; nonlocalizing EEG	Sex; surgery lobe and side; ECoG; age at surgery; daily seizures; abnormal MRI; lateralizing interictal EEG

Abbreviations: ECoG, electrocorticography; EEG, electroencephalography; MRI, magnetic resonance imaging; PET, positron emission tomography; FCD, focal cortical dysplasia; ETLE, extratemporal lobe epilepsy.

Table 4 Predictors of seizure outcome for nonlesional ETLE

	Surgery type/literature scope/ pooled seizure freedom rate	Positive predictors	Negative predictors	Unrelated factors/trend
Ansari et al[20] (meta-analysis)	Adult patients underwent surgery for nonlesional ETLE; 131 patients since 1990			Age at surgery; age of seizure onset; duration of epilepsy; seizure semiology; abnormality on MRI; lateralization of the seizures; need for intracranial monitoring; pathologic findings; type and location of surgery
Ansari et al[44] (meta-analysis)	Children underwent surgery for nonlesional ETLE; 17 studies; 95 patients	Seizure type (partial versus generalized, *P*=0.025); pathologic findings (*P*=0.039, cortical dysplasia versus other)	Diffuse nature of the pathology involved in ETLE; difficulty in localizing seizure focus; involvement of "eloquent" nonresectable cortex in epileptogenesis	Lateralization of the seizures (*P*=0.976); abnormal MRI findings (*P*=0.902); use of intracranial monitoring (*P*=0.124); duration of epilepsy; age at surgery (*P*=0.073); surgery type (*P*=0.059), and cerebral resection site (*P*=0.059)
Englot et al[11] (meta-analyses)	Patient with frontal lobe epilepsy; 1,199 patients in 21 studies; 45.1%	Lesional epilepsy origin (1.67); abnormal preoperative MRI (1.64); localized frontal resection versus more extensive lobectomy with/without an extrafrontal component (1.71)	More poorly defined epileptic focus	Presurgical PET; EEG; interictal EEG; epilepsy duration; seizure frequency; surgery side; intraoperative interictal EEG
Englot et al[43] (meta-analyses)	Children with ETLE; 36 studies included 1,259 pediatric patients; 56%	Shorter epilepsy duration, ie, ≤7 years (1.52, 1.07–2.14); lesional epilepsy (1.34, 1.19–1.49); an absence of generalized seizures (1.61,1.18–2.35); localizing ictal EEG findings (1.55, 1.24–1.93)	>7-year epilepsy history; nonlesional epilepsy; generalized seizures; nonlocalizing EEG	Sex; surgery lobe and side; ECoG; marginal/insignificant predictors: age at surgery; daily seizures; abnormal MRI; lateralizing interictal EEG

Abbreviations: ECoG, electrocorticography; EEG, electroencephalography; MRI, magnetic resonance imaging; PET, positron emission tomography; FCD, focal cortical dysplasia; ETLE, extratemporal lobe epilepsy.

Table 5 Predictors of seizure outcome for TSC

	Surgery type/literature scope/ pooled seizure freedom rate	Positive predictors	Negative predictors	Unrelated factors/trend
Jansen et al[27] (review)	Patients with TSC; 25 papers (177 patients) since 1960; 57%	No or mild intellectual disability (RR 4.8; 1.4–15.8); resective surgery (RR 2.5; 2.1–3.0)	Presence of tonic seizures (RR 1.7; 1.2–2.4); moderate or severe intellectual disability (IQ <70, RR 1.8; 1.2–2.8); multifocal SPECT findings; corpus callosotomy (RR 2.5; 2.1–3.0)	Age at onset; duration of epilepsy; age at surgery; seizure types; interictal EEG; ictal EEG; invasive EEG recording; MRI and PET findings
Zhang et al[45] (meta-analyses)	Patients with TSC; 229 patients in 13 studies since 1990; 59%	Seizure onset later than one year of age; unifocality in interictal or ictal EEG; extent of resection: lobectomy	Onset age under one year; bilateral focality; tuberectomy	Age at surgery; sex; seizure type; a history of infant spasm; mental retardation; number of cortical tubers; intracranial EEG monitoring
Fallah et al[46] (meta-analyses)	Children with TSC; 20 papers on 181 patients; 56%	Absence of generalized seizure semiology (3.1); No or mild developmental delay (7.3); unifocal ictal scalp EEG abnormality (3.2); EEG/MRI concordance (4.9)	Generalized seizure semiology; severe developmental delay; bilateral ictal EEG; EEG/MRI discordance	Sex; age at seizure onset; age at surgery; seizure frequency; lack of infantile spasms; IQ; no or unifocal interictal scalp EEG abnormality; less tuber burden; PET; SPECT; MEG.

Abbreviations: EEG, electroencephalography; MRI, magnetic resonance imaging; PET, positron emission tomography; ETLE, extratemporal lobe epilepsy; RR, risk ratio; MEG, magnetoencephalography; IQ, intelligence quotient; SPECT, single-photon emission computed tomography; TSC, tuberous sclerosis complex.

epileptic focus (with normal MRI, bilateral/multifocal lesion on MRI, or nonlocalizing EEG), generalized seizures, and incomplete resection are common negative predictors, while clinical factors such as age at surgery and side of surgery are consistently unrelated to surgical outcome following surgery for patients with TLE or lesional ETLE.

The common predictors/unrelated factors provide a very rough picture on what clinical factors are associated/unassociated with seizure outcome and how they are related or unrelated to outcome. For example, abnormal preoperative MRI has been frequently identified as a strong positive predictor of postoperative outcome (with a wide odds ratio of 0.44–1.67), while a normal MRI and a nonlocalizing EEG have been frequently regarded as strong negative predictors, whereas duration of epilepsy and seizure frequency have been frequently identified as factors unrelated to seizure outcome. However, because no predictors were found for adult patients with nonlesional ETLE[20] and there is no other meta-analysis on seizure outcome prediction in this case, common prognostic factors/predictors could not be identified for nonlesional ETLE in adults. More studies are needed to identify possible predictors/risk factors of seizure outcome in challenging cases such as nonlesional ETLE.

Neuroimaging as an outcome predictor

Mild lesions, such as mild hippocampal sclerosis and focal cortical dysplasia, are hard to identify on regular MRI. They may be missed by MRI, misinterpreted as nonlesional, and even excluded from presurgical evaluation. Therefore, there are controversies regarding the utility of neuroimaging in predicting surgical outcome.[26] Given that neuroimaging modalities such as PET, SPECT, and MEG are less frequently used than MRI in presurgical evaluation,[27] and usually do not reach the significance threshold in multivariate analysis as does MRI,[11] they are less frequently identified as predictors of surgical outcome by meta-analyses. In addition, meta-analyses such as the one reported by Téllez-Zenteno et al[22] tend to emphasize the presence of a lesion as a predictor regardless of what neuroimaging is used to identify the lesion. However, advances in neuroimaging have increased the diagnostic yield by revealing dysplastic lesions that previously eluded visual inspection,[28] and the predictive value of neuroimaging with regard to outcome has been increasingly identified.[2–5,7–9] In addition to MRI, MEG/MSI, PET, and ictal SPECT also have a positive predictive value in predicting seizure outcome.[6] Further, it was found that focal unilateral MRS metabolite alterations that are in agreement with the EEG

Table 6 Common predictors of seizure outcome for lesional or nonlesional TLE, lesional ETLE, and TSC

	Lesional or nonlesional TLE	Lesional ETLE	TSC
Positive predictors	Lesional epilepsy; abnormal MRI; partial seizures; complete resection	Focal and identifiable lesion; abnormal MRI; partial epilepsy; complete resection	No or mild developmental delay; unifocal ictal EEG abnormality; extensive resection (lobectomy)
Negative predictors	Nonlesional epilepsy; poorly localized EEG; bilateral/multifocal lesions on MRI or normal MRI; generalized seizures; FCD type I; need for ictal EEG; incomplete resection; abnormal postoperative EEG	Nonlesional epilepsy; poorly defined and localized epileptic focus; generalized seizures	Severe developmental delay; bilateral or multifocal focality; corpus callosotomy or tuberectomy
Unrelated factors	Age at surgery; sex; duration of epilepsy; ictal EEG; side of surgery	Age at surgery; seizure frequency; EEG; surgery side	Age at surgery; sex; a history of infantile spasm; seizure types; invasive EEG recording; PET findings; tuber burden

Abbreviations: EEG, electroencephalography; MRI, magnetic resonance imaging; ETLE, extratemporal lobe epilepsy; TLE, temporal lobe epilepsy; FCD, focal cortical dysplasia; TSC, tuberous sclerosis complex; PET, positron emission tomography.

focus are associated with a good outcome, while contralateral or bilateral metabolite abnormalities are associated with a poor outcome.[29] Therefore, diagnostic imaging and resection have been regarded as the most important factors in prediction of seizure outcome following surgery for focal cortical dysplasia.[26] The results of this study tend to support this, in that diagnostic imaging and resection were the most important factors in seizure outcome prediction, not only for focal cortical dysplasia, but also for other lesional or nonlesional TLE and ETLE.[16,23]

Further, the utility of neuroimaging predictors of seizure outcome has been explored. Because patients with unilateral radiographic mesial temporal sclerosis are considered "ideal" candidates for epilepsy surgery, research on outcome prediction has been done in this group of patients as a priority, and high prediction/classification accuracy has been obtained. Using a multivariable analysis model, Berg et al found that mesial temporal sclerosis (relative risk 1.47–1.49) coupled with documented etiology (1.32) and partial seizures (1.17–1.24) could identify patients (n=133 and n=81, respectively) with a nearly 100% seizure-free outcome.[30] Focke et al applied automatic support vector machine classification to MRI and diffusion tensor images for left or right hippocampal sclerosis in TLE, and achieved a 90%–100% classification accuracy.[31] In addition, Feis et al found that surgical outcome could be predicted in male (94% balanced accuracy) and female (96% balanced accuracy) patients using presurgical structural MRI.[21] These results are encouraging, but are not applicable to other cases. For example, in patients with nonlesional or bilateral/multifocal

Table 7 Main literature findings on other outcomes including discontinuation of AEDs and neuropsychologic outcomes

	Subjects/literature scope	Main findings
Vaz[35] (meta-analysis)	Patients with RATL; 13 studies, 324 patients	Inconsistent results: 14/22 variables indicated declined nonverbal memory; 8/22 demonstrated improved nonverbal memory
Schmidt et al[32] (review)	Patients after temporal lobe surgery; 13 retrospective and five prospective studies since 1980, 1,658 patients	Rate of surgical cure: ~25% adult and ~31% children or adolescents were seizure-free for 5 years without AEDs. Positive predictor of surgical cure: children versus adults with HS, and patients with typical versus atypical Ammon's horn sclerosis or tumor
Téllez-Zenteno et al[33] (meta-analysis)	Patients underwent epilepsy surgery; 1991–2005; 35 papers; 20% of the patients achieved long-term AED discontinuation	AED discontinuation: children achieved better AED outcomes than adults; longer follow-up associated with lower rates of AED discontinuation Cognitive outcomes: memory decline after left temporal resections; intelligence not significantly changed; long-term memory outcomes associated with seizure freedom and side of temporal lobe resection; negative predictors of cognitive outcome were early onset, long duration, and poor seizure control. Unconfirmed long-term outcomes: improved long-term psychosocial outcomes reported by noncontrolled studies were less clear in controlled studies
Ives-Deliperi and Butler[37] (review)	Patient underwent ATL; 21 papers	Naming decline following ATL: declines in visual naming are common in the dominant hemisphere; no reports of deficits in auditory naming Strong predictors of naming decline: absence of structural hippocampal pathology and late-onset epilepsy

Abbreviations: AEDs, antiepileptic drugs; ATL, anterior temporal lobectomy; RATL, right anterior temporal lobectomy; HS, hippocampal sclerosis.

Table 8 Main literature findings on surgical options or other interventions

	Subjects/literature scope	Main findings
Spencer et al[39] (meta-analysis)	Patients underwent MST with/without resection; 211 patients at six centers	Rates of excellent outcome (>95% seizure reduction): for patients who underwent MST alone, 62%–63% (partial seizure), 71% (generalized seizure); for patients who underwent MST + cortical resection, 68% (partial seizure), 87% (generalized seizure) Neurologic deficits: in 23% patients with MST + resection versus 19% MST alone; hemiparesis, memory decline, and visual field compromise (but not language and sensory deficits) were found in those with MST alone Insignificant predictors of outcome: EEG localization, age at epilepsy onset, duration of epilepsy, and location of MST
Schmidt and Stavem[38] (meta-analysis)	Patients with TLE surgery versus no surgery; 29 studies, 1,621 patients	Rate of seizure freedom: 44% patients with TLE surgery versus 12% nonoperated controls Pooled risk difference in favor of surgery: 42% (95% CI 32%–51%) Benefit of surgery: surgery + medical treatment is four times as likely as medical treatment alone to achieve seizure freedom
Englot et al[40] (meta-analysis)	Patient underwent VNS; 74 studies with 3,321 patients	Benefit of VNS: patients with generalized epilepsy and children benefited significantly from VNS, seizure reduced by about 50% in approximately 50% of patients Positive predictors: post-traumatic epilepsy and tuberous sclerosis; VNS predicted a ≥50% reduction in seizures Role of VNS: an adjunctive therapy in patients not amenable to resection
Josephson et al[34] (meta-analysis)	Patient underwent ATL or SAH; 11 studies include 1,203 patients	Seizure outcome of ATL versus SAH: patients were statistically more likely to be seizure-free after ATL than after SAH Role of SAH: less operative risk; SAH is needed if neuropsychologic outcomes are substantially different.

Abbreviations: CI, confidence interval; SAH, selective amygdalohippocampectomy; MST, multiple subpial transection; TLE, temporal lobe epilepsy; VNS, vagus nerve stimulation; ATL, anterior temporal lobectomy; EEG, electroencephalography.

TLE, because the odds ratios of the predictors (eg, abnormal MRI for focal cortical dysplasia with an odds ratio of 1.67 or probability of 0.63[26]) are relatively low, the predictive power of these common predictors is limited, and the prediction accuracy is low. Thus, the overall prediction accuracy for surgical outcome is not high, especially in challenging epilepsy cases such as nonlesional ETLE, and more research is needed to improve it.

Other outcome prediction

Discontinuation of AEDs is an important outcome of surgical treatment for epilepsy, and a surgical cure for drug-resistant epilepsy is regarded as both seizure freedom and discontinuation of AEDs.[32] Téllez-Zenteno et al reported that children achieved better AED discontinuation than adults and longer follow-up was associated with less AED discontinuation.[33] Schmidt et al found that better cure rates were achieved in children with hippocampal sclerosis and those with typical Ammon's horn sclerosis or tumors.[32] These findings indicate that young age is associated with a better chance of AED discontinuation.

Meta-analysis of neuropsychologic outcomes is difficult and rare due to a lack of standardized testing and reporting between studies.[34] For example, Vaz found that the current research cannot provide consistent evidence regarding nonverbal memory outcome following right anterior temporal lobectomy,[35] and the improved long-term psychosocial outcomes consistently reported by uncontrolled studies were less clear in controlled studies.[33] However, a meta-analysis covering 35 papers (from 1991 to 2005) found that memory decline occurred in patients after left temporal resections but that intelligence was not significantly changed by surgery.[33] Further, presurgical functional MRI is useful in predicting verbal memory decline following left anterior temporal lobectomy,[36] but neuroimaging is not regarded as a predictor of cognitive outcomes by meta-analysis.[33] Other factors seemed to be more significant. For example, long-term memory outcomes were associated with seizure freedom and side of temporal lobe resection,[33] while decline in naming was associated with the absence of structural hippocampal pathology and late-onset epilepsy.[37] In general, poor cognitive outcome is associated with early onset, long duration of epilepsy, and poor seizure control.[33]

Impact of interventional options on outcomes

Finally, treatment options and types of surgery play a critical role in determining surgical outcomes. Schmidt and Stavem reported that surgery and medical treatment is four times as likely as medical treatment alone to achieve seizure freedom.[38] In epilepsy surgery, anterior temporal lobectomy is more likely to achieve seizure freedom than

selective amygdalohippocampectomy, while selective amygdalohippocampectomy may have improved neuropsychologic outcomes.[34] As adjunctive therapies, multiple subpial transection and vagus nerve stimulation could reduce (but not cure) seizures, and preserve some neuropsychologic functions.[39,40]

Limitations

This study is limited by the available reviews and meta-analyses identified in the literature. In addition, the simple method used in this study to identify common predictors might be biased due to the few meta-analyses available and the variable findings of the meta-analyses in each subgroup (lesional, nonlesional TLE, or ETLE). Therefore, the common predictors extracted might not reflect true outcome predictors. Ideally, a comprehensive meta-analysis could include and analyze all the related studies in the literature in each subgroup of children or adult patients, thereby providing a clearer picture of the truly reliable predictors of seizure outcome, and largely reduce the variations in the findings of different meta-analyses in each subgroup. Better methods for exploring outcome prediction and identifying reliable predictors of seizure outcome after epilepsy surgery are needed.

Conclusion

In summary, common predictors/factors for TLE, lesional ETLE, and tuberous sclerosis complex were identified in this study. Clinical factors such as lesional epilepsy, abnormal MRI, partial seizures, and complete resection are common positive predictors, and indicators such as nonlesional epilepsy, poorly defined and localized epileptic focus (with normal MRI or bilateral/multifocal lesion on MRI, or nonlocalizing EEG), generalized seizures, and incomplete resection are common negative predictors, while factors such as age at surgery and side of surgery are unrelated to seizure outcome after surgery for TLE and lesional ETLE. Diagnostic neuroimaging and resection are among the most important predictors of seizure outcome in TLE and lesional ETLE. However, no common predictors of seizure outcome were identified in nonlesional ETLE. In addition, meta-analysis of other outcomes, such as neuropsychologic outcomes, has been rare due to lack of evaluation standards. Further studies on the identification of reliable prognostic factors for surgical outcomes are needed.

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Disclosure

The authors report no conflicts of interest in this work.

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