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Clinical Outcomes and Quality of Life Following Surgical Treatment for Refractory Epilepsy

A Systematic Review and Meta-Analysis

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Abstract: Surgery for refractory epilepsy is widely used but the efficacy of this treatment for providing a seizure-free outcome and better quality of life remains unclear.

This study aimed to update current evidence and to evaluate the effects of surgery on quality of life in patients with refractory epilepsy.

A systematic review and meta-analysis of the literature were conducted and selected studies included 2 groups of refractory epilepsy patients, surgical and nonsurgical.

The studies were assessed using the Newcastle–Ottawa Scale. The primary outcome was the seizure-free rate. The secondary outcome was quality of life. Adverse events were also reviewed.

After screening, a total of 20 studies were selected: 8 were interventional, including 2 randomized controlled trials, and 12 were observational. All of the studies comprised 1959 patients with refractory epilepsy. The seizure-free rates were significantly higher for patients who received surgery compared with the patients who did not; the combined odds ratio was 19.35 (95% CI = 12.10–30.95, $P < 0.001$). After adjusting for publication bias the combined odds ratio was 10.25 (95% CI = 5.84–18.00). In both the interventional and observational studies, patients treated surgically had a significantly better quality of life compared with the patients not treated surgically. Complications were listed in 3 studies and the rates were similar in surgical and nonsurgical patients.

Our meta-analysis found that for patients with refractory epilepsy, surgical treatment appears to provide a much greater likelihood of seizure-free outcome than nonsurgical treatment, although there is a need for more studies, particularly randomized studies, to confirm this conclusion. Based on more limited data, surgical treatment also appeared to provide a better quality of life and did not seem to increase complications.

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Abbreviations: AED = antiepileptic drug, CI = confidence interval, OR = odds ratio, QOL = quality of life.

INTRODUCTION

It is estimated that 20% to 40% of epilepsy patients have refractory epilepsy.[1] This condition is characterized by frequent recurrent seizures despite treatment with antiepileptic drugs (AEDs).[2] There is no consensus on a specific definition of refractory epilepsy; suggested definitions include the features such as failure to control seizures after 2 or 3 AEDs have been tried and failure to control seizures after a specific time period such as 1 to 2 years. [2] The prevalence of refractory epilepsy is approximately 5 to 8 cases per 1000 population.[3] Approximately 20% to 40% of patients with newly diagnosed epilepsy will become refractory to treatment.[4] The main form of treatment for refractory epilepsy is surgery.[5,6] However, the effectiveness of surgery for providing a seizure-free outcome remains unclear. An important reason for the uncertainty about the effectiveness of surgery is that only a limited number of randomized trials have been carried out to compare patients treated surgically with patients treated nonsurgically.[1,7] Englot and Chang recently reviewed the literature on seizure-free rates after resective epilepsy surgery, in a review that included Class I evidence, meta-analyses, and individual observational case series, and found that such a surgery leads to a seizure-free outcome in about two-thirds of patients with intractable temporal lobe epilepsy.[8]

The goal of surgery for refractory epilepsy is not only to eliminate seizures but to improve the quality of life (QOL) for patients.[9–14] The main determinates of QOL in patients with refractory epilepsy who did not receive surgical treatment have been found to be depression and anxiety, tolerability to AEDs and efficacy of AEDs, seizure frequency, and employment.[15] The effectiveness of surgery for improving QOL in refractory epilepsy is also unclear.

Although only limited randomized trials have been carried out to compare outcome between surgical and nonsurgical refractory epilepsy patients as noted above, a number of observational studies have made such a comparison. While not as reliable as randomized trials, observation studies can be used in meta-analysis if heterogeneity and bias are taken into account.[16]

Meta-analyses have been carried out to assess the long-term outcomes of epilepsy surgery but the majority of the included studies did not have a control group.[17,18] The latest meta-analysis included publications with a control group but only up to the year 2009 for seizure outcome comparison between surgical and nonsurgical refractory epilepsy patients.[16] The aim of this study

was to update previous meta-analyses and include results of randomized controlled trials, and to provide the first, to the best of our knowledge, meta-analytical evaluation of the effects of surgery on QOL in patients with refractory epilepsy.

MATERIALS AND METHODS

Search Strategy

This meta-analysis was conducted in accordance with Preferred Reporting Items of Systematic reviews and Meta-Analyses guidelines.[19] We searched the following databases: Medline, Cochrane Central Register of Controlled Trials, EMBASE, and Google Scholar. Articles published up to December 31, 2013, were included. Reference lists of relevant studies were hand searched. The keywords used for searching were the following: (surgery OR operation OR surgical OR operative) AND (seizure OR epilepsy OR and epileptic). We then used the filters of English, Humans, Clinical trial, and MeSH terms.

Selection Criteria

The inclusion criteria were (1) the patients were diagnosed with refractory epilepsy, intractable epilepsy, or drug-resistant epilepsy; (2) the interventional group received surgical treatment; (3) the control group did not receive surgical treatment and only received AEDs; (4) randomized controlled trial or nonrandomized comparative study.

The exclusion criteria were (1) the study did not have a nonsurgical group as the control group; (2) the study was not published as an original clinical research article, but rather as a letter, comment, editorial, or case report; (3) non-English publication; (4) the study did not report the seizure-free rate after treatment.

Study Selection and Data Extraction

Studies were identified using the search strategy by 2 independent reviewers (BC and SL). When there was uncertainty regarding eligibility, a third reviewer was consulted (HY). Data extraction was also performed by 2 independent reviewers (BC and SL) and a third reviewer (HY) was consulted for any uncertainties. The following information was extracted from studies that met the inclusion criteria: name of the first author, year of publication, study design, demographic data for patients, number of patients, number of patients who were seizure free posttreatment, and results of pre- and posttreatment QOL assessment.

Study Quality Assessment

We used the Newcastle–Ottawa Scale to assess the included studies.[20] The Newcastle–Ottawa Scale is a valid tool for evaluating nonrandomized studies with regard to 3 criteria: patient selection, comparability of study groups, and outcome assessment. Quality assessment was also performed by the independent reviewers and a third reviewer was consulted for any uncertainties.

Outcome Measures

The primary outcome was the seizure-free rate. The secondary outcome was QOL. We also reviewed adverse events.

Statistical Analysis

The primary and secondary outcomes for evaluating efficacy were the seizure-free rate and score for QOL, respectively. The odds ratio (OR) with 95% confidence interval (CI) was calculated for seizure-free rate for patients treated surgically compared with patients who received only nonsurgical treatment. The standardized differences in means (or mean changes after treatment) with 95% CI were calculated for the total score of QOL for the surgical group compared with the nonsurgical group. Heterogeneity among the studies was assessed by calculating the Cochran Q and the I^2 statistic. For the Q statistic, $P < 0.10$ was considered to indicate statistically significant heterogeneity. The I^2 statistic indicates the percentage of the observed between-study variability caused by heterogeneity. Heterogeneity determined using the I^2 statistic was defined as follows: 0% to 40% = no heterogeneity; 30% to 60% = moderate heterogeneity; 50% to 90% = substantial heterogeneity; and 75% to 100% = considerable heterogeneity.[21] If heterogeneity existed between studies (a Q statistic with $P < 0.1$[22] or an I^2 statistic > 50%), we performed the random-effects model (DerSimonian–Laird method).[21,23] Otherwise, the fixed-effects model was recommended (Mantel–Haenszel method). Combined ORs or standardized differences in means were calculated and a 2-sided P value < 0.05 was considered to indicate statistical significance. In addition, subgroup analysis of treatment effectiveness on seizure-free rate was performed according to study type, interventional or observational.

Sensitivity analysis was performed for primary and secondary outcomes based on the leave-one-out approach. Publication bias was assessed by constructing funnel plots for primary outcome and quantitative detection by Egger test.[24] The absence of publication bias is indicated by the data points forming a symmetric funnel-shaped distribution and $P > 0.10$ in Egger test. Moreover, the Duval and Tweedie trim-and-fill method was used to adjust for potential publication bias. The trim-and-fill method formalizes the interpretation of any asymmetry in the funnel plot by imputing suspected missing studies and calculating an adjusted result. The adjusted result is neither intended to actually find the values of missing studies nor to give a better effect size estimate in itself, but can be used as a form of sensitivity analysis to help ascertain the probable effect of publication bias on the meta-analysis.[25–27] All statistical analyses were performed using the Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ).

RESULTS

Literature Search

Initially we identified 253 studies by using the keywords and also found 22 studies by hand searching. A total of 253 studies were left after duplicates were removed and 222 studies were excluded by screening titles and abstracts. Thirty-one studies were left for full text review.

After full text review, 11 more studies were excluded. The reasons for excluding the 11 studies were the following: no nonsurgical control group (n = 2), no numerical data for primary outcome of control group (n = 1), and no interest outcomes (n = 8).

Figure 1 is a flowchart for the selection of studies. The 20 included studies are listed in the References section.[1,6,7,9–14,28–39]

Study Characteristics

The basic characteristics of the studies included in the meta-analysis are summarized in Tables 1 and 2. Among the 20 included studies, there were 8 interventional studies (2 randomized controlled trials [RCTs] and six prospective

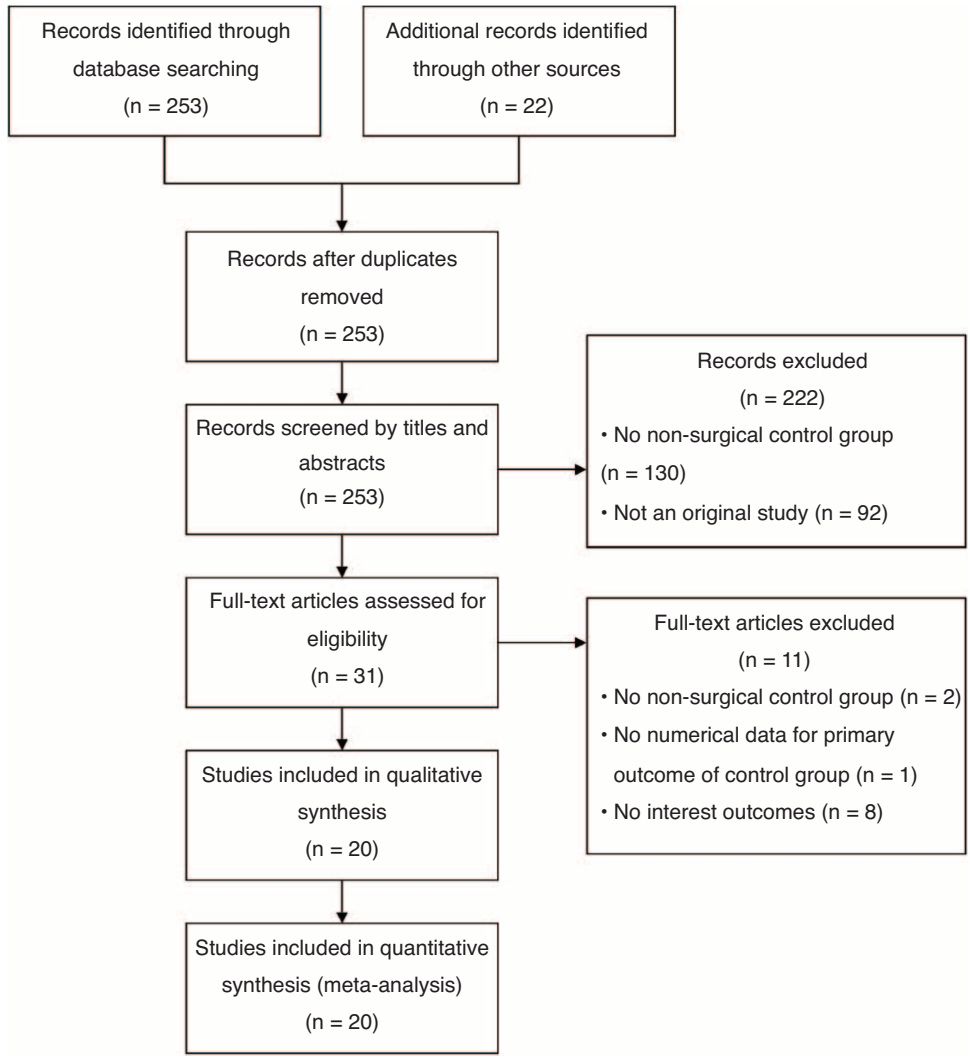

FIGURE 1. Flow chart of study selection.

studies) and 12 observational studies (9 retrospective studies, 2 cross-sectional studies, and 1 cohort study). A total of 1959 patients with refractory epilepsy were enrolled in the 20 studies (657 in the interventional studies and 1302 in the observational studies), and there were 1254 patients treated with surgery (368 in the interventional studies and 886 in the observational studies) and 705 patients who received only nonsurgical treatment with AEDs (289 in the interventional studies and 416 in the observational studies). The indications for surgery and diagnostic imaging/guidance methods are listed in Table 1. The total number of patients in each of the studies ranged from 32 to 248. The brain regions with lesions are listed in Table 1.Seizure-free rates after treatment ranged from 31.2% to 85.7% and 0% to 45.5%, for patients who received surgical treatment and for those who received nonsurgical treatment, respectively. In addition, a total of 7 studies reported the total score for QOL, including 2 studies that used Quality of Life in Epilepsy 89 (QOLIE-89) for assessments,[1,13] 2 that used Quality of Life in Epilepsy-31 Inventory (QOLIE-31),[29,34] and 3 that used Epilepsy Surgery Inventory-55 (ESI-55),[30] Quality of Life in Childhood Epilepsy Questionnaire (QOLCE),[36] and Quality of Life in Epilepsy-10 (QOLIE-10),[6] respectively (Table 2).

Primary Outcome: Seizure-Free Rate

The sample size for evaluating seizure-free rate was less than the number of patients enrolled in 3 studies (Table 2).[12,14,33] For all 20 included studies, moderate heterogeneity among the studies was found after pooling of data ($Q = 35.27$, $df = 19$, $P = 0.013$, $I^2 = 46.13\%$). The combined OR revealed that significantly higher seizure-free rates were observed among patients who received surgical treatment compared to those who received nonsurgical treatment. Among the 20 studies, ORs ranged from 3.33 to 261.9, with the combined OR = 19.35 (95% CI = 12.10–30.95, $P < 0.001$, Figure 2).

Subgroup analysis was conducted according to study types (Figure 2). For the subgroup of 8 interventional studies, large heterogeneity among the studies was found after pooling of data ($Q = 17.88$, $df = 7$, $P = 0.013$, $I^2 = 60.85\%$). The results for the interventional subgroup indicated that patients who received surgical treatment would be more likely to be seizure free

TABLE 1. Characteristics of the Included Studies

First Author (Year)	Study Design	Patients	Region of Lesions (%)	Indication for Surgery	Diagnostic Imaging/ Guidance Methods	Surgical Procedures (%)	NOS Score
Interventional Study							
Engel et al (2012)	RCT	Drug-resistant temporal lobe epilepsy	Mesial temporal lobe (100)	Mesial TLE and disabling seizures that had persisted for no more than two consecutive years following adequate trials of two brand-name AEDs	Inpatient video-EEG monitoring, structural MRI, PET, neuropsychological and neuropsychiatric evaluations	Anteromesial temporal resection	–
Choi-Kwon et al (2008)	Prospective	Intractable epilepsy	Temporal lobe (57.8)	Uncontrolled seizures for more than 2 years despite having received appropriate AED polytherapy for more than 2 years	MRI, PET, ictal SPECT	Anterior temporal lobe resection (69)	8
			Frontal lobe (15.6) Parietal lobe (4.7) Occipital lobe (3.1) Other (18.8)			Neocortical resection (31)	
Elliott et al (2008)	Prospective	Refractory epilepsy	Temporal lobe (55)	Not responded to at least 2 AEDs	NA	Temporal lobe resection (55)	8
			Extratemporal lobe (30) Multilobar (15)*			Extratemporal lobe resection (30) Multilobar resection (15)	
Bien et al (2006)	Prospective	Drug-resistant epilepsy	Temporal lobe (84)	Use of at least 2 AEDs which had not led to seizure freedom or had achieved this aim only at the cost of intolerable side effects	NA	Temporal lobe resection (84)	8
			Frontal lobe (12) Other lobes (4)*			Frontal lobe resection (12) Others lobes resection (4)	
Yasuda et al (2006)	Prospective controlled	Refractory temporal lobe epilepsy	Mesial temporal lobe (100)	Clinical and EEG features of mesial TLE, failure of seizure control with at least 2 AED regimens and seizure frequency at least 1 seizure per month over the year	EEG, MRI, neuropsychological and psychological assessments; patients with unclear origin of ictal discharges were admitted to the hospital for video-EEG and ictal SPECT when necessary before surgery	Transsylvian selective amygdalohippocampectomy (100)	8
Wiebe et al (2001)	RCT	Intractable temporal lobe epilepsy	Temporal lobe (100)	Poorly controlled with medication were examined by epileptologists	EEG, MRI, standardized neuropsychological and psychological assessments	Anterior temporal lobe resection (100)	–

First Author (Year)	Study Design	Patients	Region of Lesions (%)	Indication for Surgery	Diagnostic Imaging/ Guidance Methods	Surgical Procedures (%)	NOS Score
Markand et al (2000)	Prospective	Refractory temporal lobe epilepsy	Temporal lobe (100)	Medically refractory complex partial seizure	Neurologic examination, neuropsychological testing, CT, and/or MRI, prolonged (5–10 days) continuous video-EEG monitoring with sphenoidal electrodes, and/or interictal and ictal SPECT, PET	Anterior temporal lobectomy (100)	8
McLachlan et al (1997)	Prospective	Intractable temporal Lobe Epilepsy	Temporal lobe (100)	Uncontrolled seizures thought to be of temporal lobe origin for at least 3 years despite the use of 3 or more AEDs, and evidence existed that seizures were focal in origin	Continuous EEG with scalp electrodes, and implanted subdural electrodes in selected patients, history and physical examination, neuropsychological assessment, Wada test	Temporal lobectomy (100)	8
Observational Study							
Jones et al (2013)	Retrospective	Intractable temporal Lobe epilepsy	Temporal lobe (100)	Medically intractable complex partial seizures of temporal lobe origin, and at least borderline intelligence (Wechsler Adult Intelligence Scale—revised verbal or performance IQ >69)	Prolonged EEG with scalp, epidural, or subdural elec-trodes, MRI, PET, Wada test, neuropsychological assessment and independent speech and language evaluation	Anterior temporal lobectomy (100)	8
Elliott et al (2012)	Retrospective	Intractable epilepsy	Temporal lobe (62) Extratemporal lobe (38)	NA	NA	Temporal lobe resection (62) Extratemporal lobe resection (38)	7
Smith et al (2011)	Retrospective	Intractable epilepsy	Temporal lobe (61) Extratemporal lobe (39)	NA	NA	Temporal lobe resection (61) Extratemporal lobe resection (39)	7
Skirrow et al (2011)	Retrospective	Drug-resistant temporal lobe epilepsy	Temporal lobe (100)	Preoperative medication-resistant epilepsy, single pathologic diagnosis	Neuropsychologic assessment, ictal and interictal EEG, and MRI	Temporal lobe resection (100)	8
Mikati et al (2010)	Retrospective cohort study	Intractable partial seizures	Temporal lobe (36.8) Extratemporal (36.8) Multilobar (15.8) Other (10.5)*	NA	NA	Temporal lobe resection (36.8) Extratemporal resection (36.8) Multilobar resections (15.8) Hemispherectomy (10.5)	8
Poochikian-Sarkissian et al (2008)	Cross-sectional	Intractable epilepsy	NA	NA	NA	NA	7
Mikati et al (2006)	Retrospective	Intractable temporal lobe epilepsy	Temporal lobe (100)	NA	NA	Temporal lobectomy (100)	8
Mikati et al (2004)	Retrospective	Intractable epilepsy	Temporal lobe (75) Extratemporal lobe (25)	NA	NA	Temporal lobectomy (75) Extratemporal resection (25)	7

First Author (Year)	Study Design	Patients	Region of Lesions (%)	Indication for Surgery	Diagnostic Imaging/ Guidance Methods	Surgical Procedures (%)	NOS Score
Jones et al (2002)	Retrospective	Intractable temporal lobe epilepsy	Temporal lobe (100)	Medical intractable complex partial seizures of temporal lobe origin with or without secondary generalization	Prolonged EEG with scalp, epidural, or subdural electrodes, MRI, PET, Wada test, neuropsychological assessment, and independent speech and language evaluation	Anterior temporal lobectomy (100)	7
Bien et al (2001)	Retrospective	Drug-resistant temporal lobe epilepsy	Temporal lobe (100)	Adequate use of at least 2 standard AEDs in monotherapy had not led to acceptable seizure control	History taking, interictal surface EEG, ictal sur face/sphenoidal EEG, ictal surface/sphenoidal plus depth EEG, neurop sychological testing, MRI, CT, PET, interictal SPECT, ictal SPECT	Temporal lobectomy (46.6) Amygdalohippocampectomy (32.4) Lesionectomy (21.0)	8
Gilliam et al (1999)	Cross-sectional	Refractory epilepsy	Temporal lobe (100)	Medically intractable localization-related epilepsy, with complex partial seizures and a history of secondarily generalized seizures; medical failure determined by trials of at least 3 AEDs incrementally increased to highest tolerable dosages	MRI, interictal and ictal scalp video/EEG with sphenoidal or anterior temporal electrodes, comprehensive neurop sychological testing	Anterior temporal lobectomy (100)	6
Vickrey et al (1995)	Retrospective	Intractable epilepsy	Temporal lobe (87) Extratemporal lobe (11)*	NA	NA	Anterior temporal resection (87) Extratemporal resection (11)	7

AED = antiepileptic drugs, CT = computed tomography, EEG = electroencephalography, MRI = magnetic resonance imaging, NA = not available, NOS = Newcastle–Ottawa Scale, PET = positron emission tomography, RCT = randomized controlled trial, SPECT = single photon emission computed tomography, TLE = temporal lobe epilepsy.

* Data only available for surgical group.

TABLE 2. Outcomes of Included Studies Comparing Surgical Versus Nonsurgical Groups

First Author (Year)	Number of Cases	Mean Age (Year)	Sex (Male %)	Follow-up Time	Seizure-Free Rate (%)	Total Score for QOL*	Questionnaire for QOL
Interventional Study							
Engel et al (2012)	15 vs 23	37.5 vs 30.9	26.7 vs 60.9	All 2 y	73.3 vs 0.0	Treatment effect: 8.5 (−1.0, 18.1)	QOLIE-89
Choi-Kwon et al (2008)	32 vs 32‡	30.6 vs 31.4	59.4 vs 81.3	23.4 vs 19.3 mo	84.0 vs 45.5	–	–
Elliott et al (2008)	20 vs 12	13.7 vs 13.4	40.0 vs 33.3	All 2 y	50.0 vs 0.0	–	–
Bien et al (2006)	131 vs 49	31.1 vs 36.6	53.0 vs 45.0	6.9 vs 6.5 y	51.9 vs 24.5	Treatment effect: 2.6 (−1.6, 6.7)	ESI-55
Yasuda et al (2006)	26 vs 75	36.2 vs 39.5	38.5 vs 35.0	12.7 vs 12.7 mo	73.1 vs 12.0	–	–
Wiebe et al (2001)	40 vs 40	35.5 vs 34.4	42.5 vs 52.5	All 1 y	57.5 vs 7.5	–	–
Markand et al (2000)	53 vs 37	31.0 vs 36.9	62.3 vs 48.6	All 2 y	69.8 vs 0.0	Baseline: 47.2 ± 10.5 vs 42.0 ± 10.1 Final visit: 54.1 ± 12.1 vs 40.1 ± 12.2	QOLIE-89
McLachlan et al (1997)	51 vs 21§	31.9 vs 34.2	57.1 vs 33.3	All 24 mo	42.5 vs 0.0	–	–
Observational Study							
Jones et al (2013)	57 vs 18‖	37.9 vs 37.9	50.9 vs 27.8	17.2 vs 18.2 y	66.7 vs 11.1	–	–
Elliott et al (2012)	69 vs 29	22.5 vs 22.9	44.9 vs 20.7	NA	55.1 vs 0.0	52.5 ± 10.1 vs 45.6 ± 12.2	QOLIE-31
Smith et al (2011)	70 vs 28	22.4 vs 22.9	45.7 vs 28.6	NA	55.7 vs 0.0	–	-
Skirrow C (2011)	42 vs 11	13.3 vs NA	50.0 vs 36.0	All 9 y	85.7 vs 36.4	70.0 ± 15.0 vs 65.0 ± 15.0	QOLIE-31
Mikati et al (2010)	19 vs 19	12.0 vs 11.8	57.9 vs 57.9	3.8 vs 3.4 y	78.9 vs 21.1	74.6 ± 15.6 vs 65.9 ± 18.9	QOLCE
Poochikian-Sarkissian et al (2008)	53 vs 40	40.0 vs 38.2	39.6 vs 52.5	NA	62.3 vs 0.0	19.6 (17.6, 21.6) vs 30.8 (28.5, 33.1)	QOLIE-10†
Mikati et al (2006)	20 vs 17	30.5 vs 31.5	50.0 vs 35.3	All 3 y	85.0 vs 35.3	–	–
Mikati et al (2004)	20 vs 20	32.1 vs 32.2	55.0 vs 55.0	13.45 vs 13.20 mo	85.0 vs 0.0	–	–
Jones et al (2002)	61 vs 23	31.3 vs 34.7	54.0 vs 35.0	5.8 vs 5.7 y	63.9 vs 4.3	–	–
Bien et al (2001)	148 vs 94	31.5 vs 35.5	45.3 vs 46.8	4.8 vs 4.7 y	44.6 vs 4.3	–	–
Gilliam et al (1999)	125 vs 71	31.0 vs 33.0	42.0 vs 48.0	NA	64.8 vs 0.0	–	–
Vickrey et al (1995)	202 vs 46	27.0 vs 26.0	48.0 vs 50.0	5.8 vs 5.7 y	31.2 vs 4.3	–	–

ESI-55 = Epilepsy Surgery Inventory-55, NA = nonavailable, NA = not available, NO = New Castle–Ottawa Scale, QOL = quality of life, QOLCE = Quality of Life in Childhood Epilepsy Questionnaire, QOLIE-10 = Quality of Life in Epilepsy-10, QOLIE-31 = Quality of Life in Epilepsy-31 Inventory, QOLIE-89 = Quality of Life in Epilepsy 89.

* Results are presented as mean ± SD or mean (95% CI).

† High scores indicate poor quality of life.

‡ Patients numbers for evaluating seizure-free rate were 25 and 22, for patients with surgical treatment and those with nonsurgical treatment, respectively.

§ Patients numbers for evaluating seizure-free rate were 40 and 15, for patients with surgical treatment and those with nonsurgical treatment, respectively.

‖ Patients numbers for evaluating seizure-free rate were 42 and 9, for patients with surgical treatment and those with nonsurgical treatment, respectively.

compared to those who received only nonsurgical treatment (combined OR = 14.97, 95% CI = 5.94–37.77, $P < 0.001$, Figure 1). Moreover, for the subgroup of 12 observational studies, no heterogeneity among the studies was found after pooling of data (Q = 11.66, df = 11, $P = 0.390$, $I^2 = 5.63\%$). The results for the observational subgroup also indicated that patients who received surgical treatment would be more likely to be seizure free compared to those who received nonsurgical treatment, but the effect seemed more profound than that for the interventional subgroup (combined OR = 20.67, 95% CI = 12.28–34.80, $P < 0.001$, Figure 2).

Secondary Outcome: Quality of Life

Since the effect measure for the total score of QOL differed by study type, the pooled estimates of meta-analysis are presented for interventional studies and observational studies, respectively (Figure 3).

Regarding interventional studies, only 3 reported the total score of QOL: 2 measured QOL using QOLIE-89,[1,13] and the other one using ESI-55.[30] Large heterogeneity was found when data from the 3 studies were pooled (Q = 4.43, df = 2, $P = 0.109$, $I^2 = 54.9\%$); therefore, a random-effects model of analysis was used (Figure 3A). The results showed that the change in the total score for QOL significantly favored the surgical group over the nonsurgical group (pooled standardized difference in mean changes = 0.49, 95% CI = 0.10–0.88, $P = 0.014$, Figure 3A).

Regarding observational studies, only 4 reported the total score of QOL: 2 measured QOL by using QOLIE-36,[1,34] and the others used QOLCE[36] and QOLIE-10.[6] It should be noted that a higher score indicates poor QOL as measured by QOLIE-10.[6] Extreme heterogeneity was found when data from the 4 studies were pooled (Q = 18.36, df = 3, $P < 0.001$, $I^2 = 83.7\%$); therefore, a random-effects model of analysis was used (Figure 3B). The results indicated that patients who received surgical treatment had significantly better QOL compared with those who received nonsurgical treatment (pooled standardized difference in means = 0.83, 95% CI = 0.16–1.51, $P = 0.016$, Figure 3B).

Adverse Events

In our systematic review, we found that only 3 studies reported details of surgery-related and seizure-related adverse

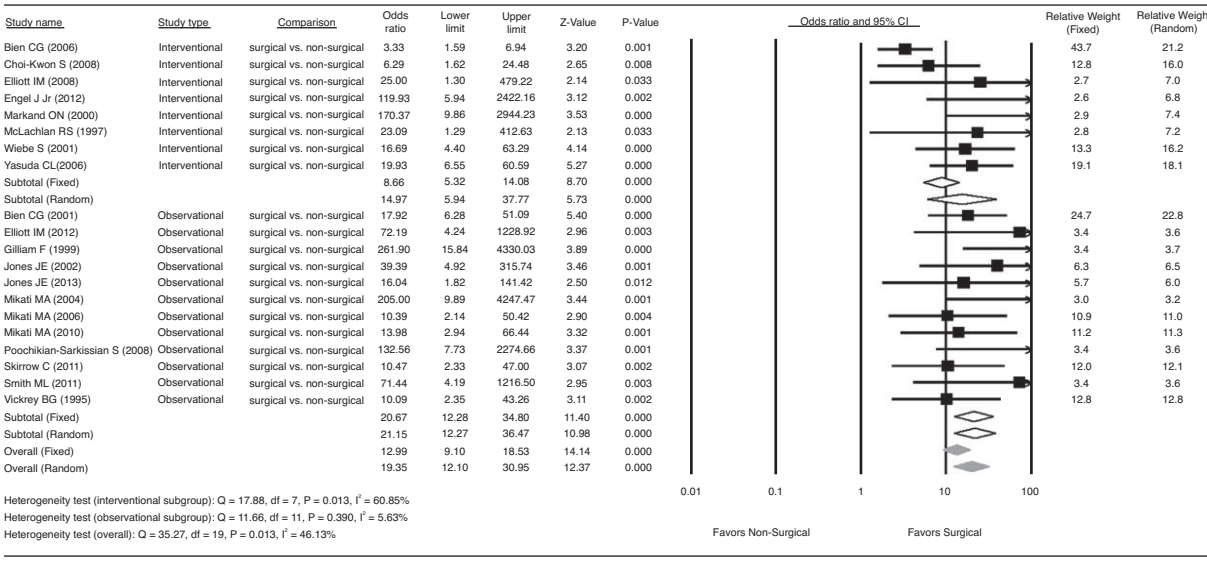

FIGURE 2. Meta-analysis for seizure-free rate of patients with refractory epilepsy compared between surgical and nonsurgical treatments (all studies, interventional, observational).

events.[1,7,31] In the other studies, only the number of deaths was reported, and there was no analysis of the reasons for morbidity or mortality. The results of our systematic review of adverse events are presented in Table 3. Among the most commonly reported adverse events in the surgical group were surgical wound infection, depression, cerebral infarction with clinical symptoms, postoperative vomiting requiring gastrostomy, resection-related bleeding in the subarachnoid space requiring ventriculoperitoneal shunting, shoulder dislocation and fracture due to seizure, transient thrombophlebitis of the right central retinal vein and artery, asymptomatic superior subquadrantic visual field defects, transient mild memory deficit, and decline in verbal memory that interfered with job performance after 1 year, and epidural hematoma requiring surgery.

Quality Assessment

The results of quality assessment are shown in Table 1. The data represent the total score of the Newcastle–Ottawa Scale. The scores ranged from 6 to 8 points, which indicated that all the included studies were considered to be of high quality.

Sensitivity Analysis

The results of the sensitivity analyses, in which the studies were omitted one-by-one, are summarized in Figures 4 and 5 and, for seizure-free rate and QOL, respectively.

Regarding seizure-free rate for all 20 studies (Figure 4A), in the 8 interventional studies (Figure 4B), and the 12 observational studies (Figure 4C), the direction and magnitude of the pooled ORs did not vary substantially with the removal of any study, which indicates good reliability in this meta-analysis.

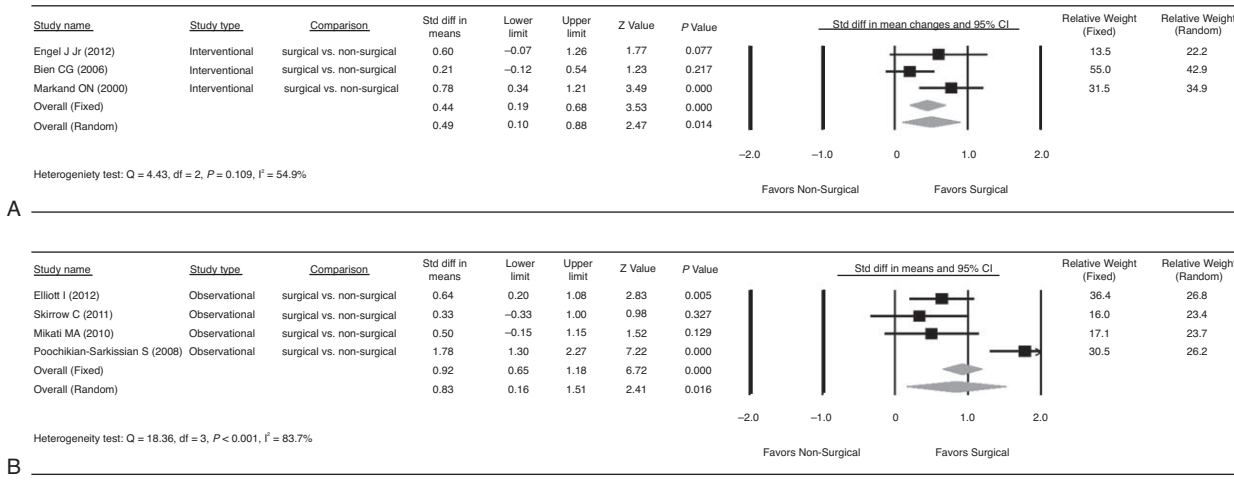

FIGURE 3. Meta-analysis for quality of life of patients with refractory epilepsy compared between surgical and nonsurgical treatments: (A) interventional (B) observational.

TABLE 3. Adverse Events of Included Studies

First Author (Year)	Adverse events, n (%)	
	Surgical Group	**Nonsurgical Group**
Interventional Study		
Engel et al (2012)	Ischemic changes by MRI: 3 (20.0) Cerebral infarction with clinical symptoms:1 (6.7) Surgical procedure related cannot be ruled out: 2 (13.3) Postoperative vomiting (gastrostomy required): 1 (6.7) Resection-related bleeding into the subarachnoid space (ventriculoperitoneal shunt required): 1 (6.7) Shoulder dislocation and fracture due to a seizure: 1 (6.7)	Seizure-related: 5 (21.7) Status epilepticus: 3 (13.0) Seizure-unrelated: 2 (8.7) Tonsillectomy: 1 (4.3) Dehydration related to gastritis: 1 (4.3)
Choi-Kwon et al (2008)	Death: 1 (3.1) Developed schizophrenia: 1 (3.1)	NA
Elliott et al (2008)	NA	NA
Bien et al (2006)	NA	NA
Yasuda et al (2006)	Surgery-related: 4 (15.4) Transient: 2 (7.7) Thrombophlebitis of the right central retinal vein and artery, causing amaurosis in right eye: 1 (3.8) Mild memory deficit without compromising daily life: 1 (3.8) Permanent: 2 (7.7) Epidural hematoma (required operation): 1 (3.8) Surgical wound infection: 1 (3.8) Death: 0	Seizure-related: 7 (9.3) Second- to third-degree burns: 2 (2.7) Falls with head injury: 2 (2.7) Status epilepticus: 3 (4.0) Neurologic deficit: 0 Death: 0
Wiebe et al (2001)	Surgery-related: 4 (10.0) Thalamic infarct, causing sensory abnormalities in left thigh: 1 (2.5) Wound infection: 1 (2.5) Declined verbal memory interfering with the patients' occupations at 1 year: 2 (5.0) Asymptomatic, superior subquadrantic visual-field defects: 22 (55.0) Depression: 7 (17.5) Transient psychosis: 1 (2.5) Death: 1 (2.5)	Neurologic deficit: 0 Depression: 8 (20.0) Transient psychosis: 1 (2.5) Death: 0
Markand et al (2000)	Death: 2 (3.8) Probably cardiac death: 1 (1.9) Committed suicide: 1 (1.9)	Death: 1 (2.7)
McLachlan et al (1997)	NA	NA
Observational Study		
Jones et al (2013)	NA	Death: 1 (5.6)
Elliott et al (2012)	NA	NA
Smith et al (2011)	NA	NA
Skirrow et al (2011)	NA	NA
Mikati et al (2010)	NA	NA
Poochikian-Sarkissian S (2008)	NA	NA
Mikati et al (2006)	NA	NA
Mikati et al (2004)	NA	NA
Jones et al (2002)	NA	NA
Bien et al (2001)	NA	NA
Gilliam et al (1999)	Death (before outcome assessment): 1 (0.8)	NA
Vickrey et al (1995)	Death: 14 (6.9) Death before surgery: 5 (2.5)	Death: 9 (19.6)

MRI = magnetic resonance imaging, NA = not available.

However, regarding QOL among the interventional studies (Figure 5A), the removal of the study by Engel et al[1] or by Markand et al[13] caused the pooled standardized difference in mean changes to become nonsignificant. In addition, regarding QOL among observational studies (Figure 5B), the removal of the study by Elliott et al[28] also caused the pooled standardized difference in means to become nonsignificant. This indicated that the pooled estimates of the meta-analysis on QOL might be influenced by some individual studies.

Publication Bias

The funnel plot for publication bias (standard error by log OR of seizure-free rate) demonstrated evidence of asymmetry,

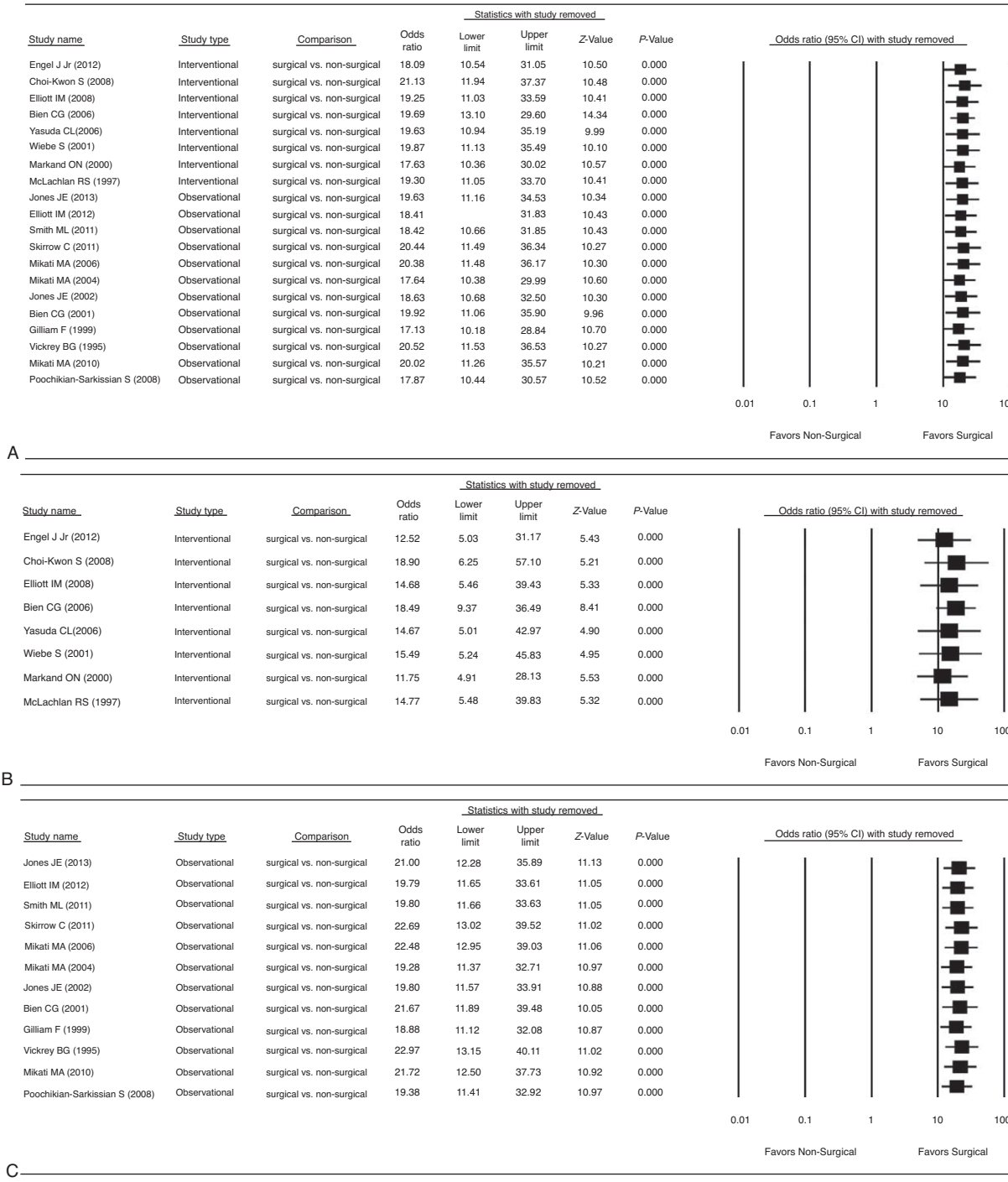

FIGURE 4. Sensitivity analysis for treatment effects on seizure-free rate by leave-one-out approach: (A) all studies, (B) interventional, (C) observational.

indicating evidence of publication bias on the findings in all studies (Figure 6A), interventional studies (Figure 6C), and observational studies (Figure 6E). Using Egger test of intercept, it also indicated that there was significant evidence of publication bias in all studies (Figure 6A, $t = 6.29$, $df = 18$, $P < 0.001$), interventional studies (Figure 6C, $t = 3.26$, $df = 6$, $P = 0.009$), and observational studies (Figure 6E, $t = 4.17$, $df = 10$, $P < 0.001$).

When Duval and Tweedie trim-and-fill method was used to adjust for the effect of publication bias, the theoretically imputed studies are shown in Figure 6B for all studies, Figure 6D for interventional studies, and Figure 6F for

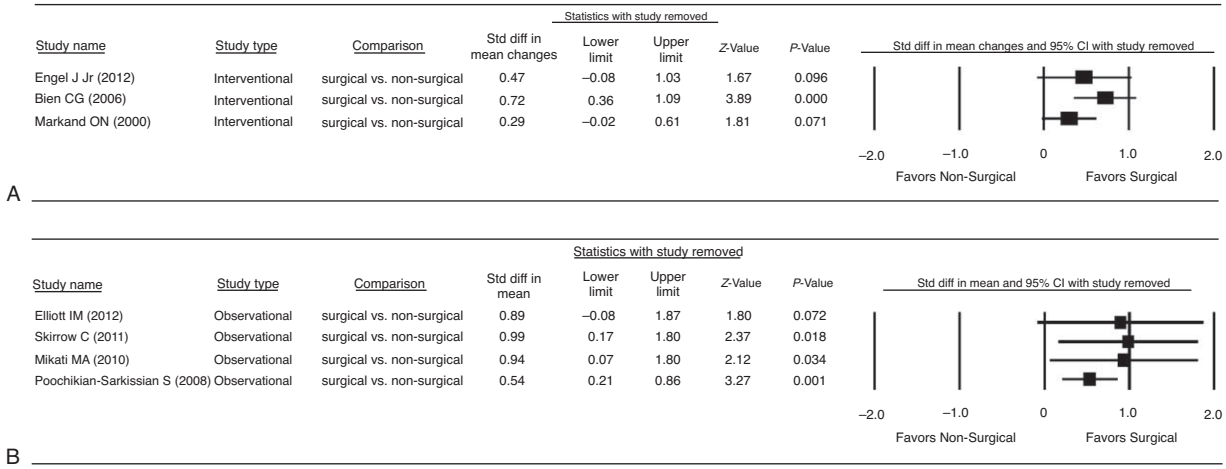

FIGURE 5. Sensitivity analysis for treatment effects on quality of life by leave-one-out approach: (A) interventional, (B) observational.

observational studies. Incorporating these imputed studies, the adjusted point estimates of OR decreased to 10.25 (95% CI = 5.84–18.00, Figure 6B) for all studies, 7.79 (95% CI = 3.19–19.01, Figure 6D) for interventional studies, and 16.25 (95% CI = 9.88–26.71, Figure 6F) for observational studies. Taken together, this suggests that our findings are reliable, but that publication bias may have exaggerated the observed effect size.

Regarding the total score for QOL, due to the small number of selected studies, it was inappropriate to use a funnel plot to assess publication bias. It has been previously shown that 5 or fewer studies are not sufficient to detect funnel plot asymmetry.[26]

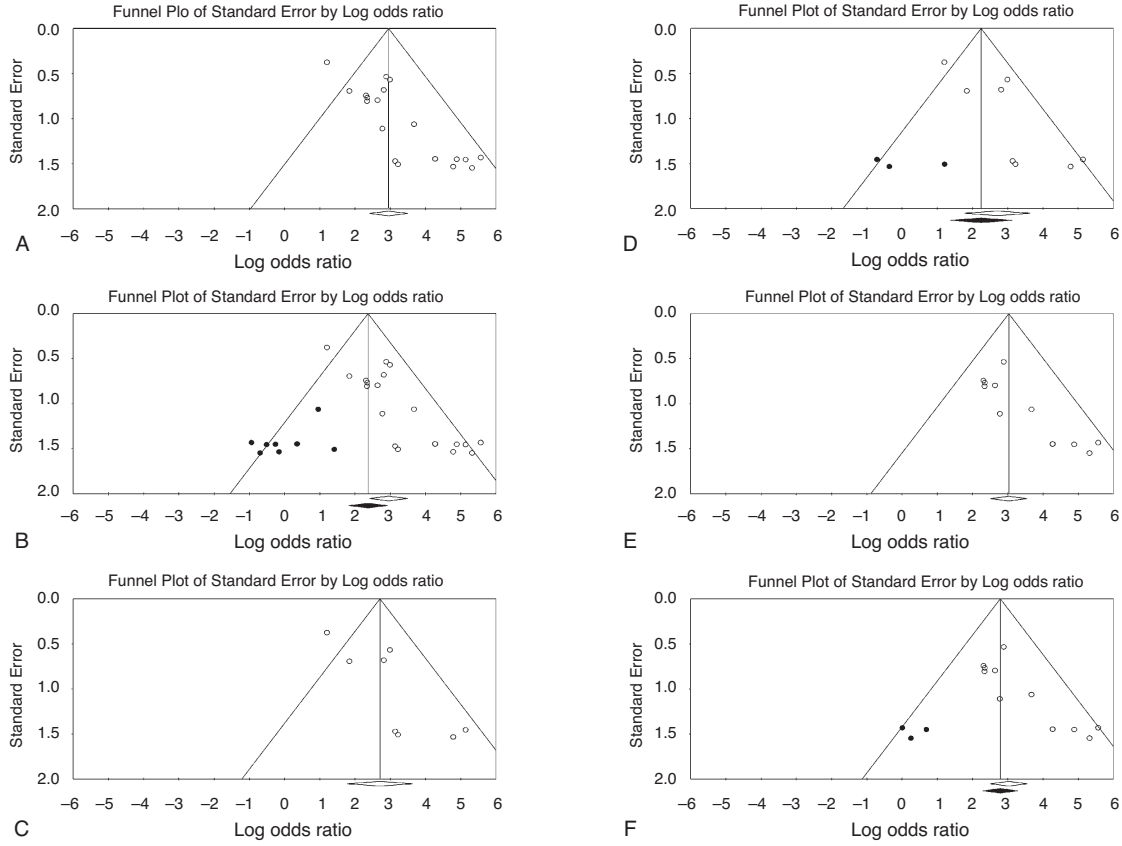

FIGURE 6. Funnel plots for evaluating publication bias regarding seizure-free rate for all studies (A, B), interventional studies (C, D), and observational studies (E, F). White circles represent observed studies, and black circles represent possibly missed studies imputed using Duval and Tweedie trim-and-fill method. White and black rhombuses represent observed and theoretical combined effect size, respectively.

DISCUSSION

The major finding of our meta-analysis of 20 studies comparing refractory epilepsy patients treated surgically with such patients treated nonsurgically and which included a total of 1959 patients was that after adjusting for potential publication bias the surgical patients had 10 times (adjusted pooled OR 10.25) the probability of being seizure free compared with the nonsurgical patients. A secondary finding, which was based on meta-analysis of the 7 studies that reported total score for QOL, was that patients who were treated with surgery had better QOL than patients not treated with surgery.

Our finding that surgical patients with refractory epilepsy were more likely to be seizure free is consistent with the findings of the 2 randomized controlled trials that compared the seizure-free rate between surgical and nonsurgical refractory epilepsy patients.[1,7] Wiebe et al[7] studied 80 temporal lobe epilepsy patients, 40 in each group, and after 1 year of follow-up found that 58% of the patients treated with surgery were seizure free compared with 8% in the group that only received AEDs. Engel et al[1] studied 38 patients, 15 who were treated with surgery and 23 treated only with AEDs The researchers intended to include 200 patients but due to slow accrual the study was terminated early. At the end of 2 years of follow-up, 11 of the 15 patients in the surgical group were seizure free whereas none of the 23 patients in the medical group were seizure free.

We analyzed the studies included in our meta-analysis for publication bias and found that there was evidence of publication bias in all studies. We used a statistical method to correct for publication bias and found that for all studies that the OR for the surgical patients when compared with the nonsurgical patients for being seizure free was reduced from 19.35 to 10.25, which suggested that our initial findings before adjustment for publication bias may have been exaggerated.

Our findings are consistent with those of Schmidt and Stavem[16] who performed a meta-analysis comparing long-term seizure outcome between patients with drug-resistant partial epilepsy who were treated with surgery compared with such patients who did not receive surgery. A total of 20 studies with 2734 patients were included. The main finding was that patients who received surgery with medical treatment were 4 times more likely to be seizure free. We found a greater benefit for surgery which might be due to our analysis not including any studies published before 1995. Only 7 of the studies in our meta-analysis[7,9,12,13,30–32] were included in the meta-analysis by Schmidt and Stavem.

We found 3 studies that reported details about surgery- and seizure-related adverse events.[1,7,31] Adverse events appeared to be similar between the surgical and nonsurgical groups; however, because the number of studies that reported these events was so small it was not feasible to perform quantitative analysis on morbidity or mortality. Although surgery has been shown to be beneficial for patients with intractable seizures, many patients refuse surgery because they fear complications. The findings of our systematic review may allow patients to be more objective about adverse events related to surgery. Our systematic review and meta-analysis show that surgical treatment can not only provide a better chance of being seizure free and having a better QOL compared with nonsurgical treatment, but the complications related to surgery are similar to those related to nonsurgical treatment. The improvements in surgical treatment for refractory epilepsy are to large part due to improvements in technology for diagnostic imaging and guidance during surgery.[39] However, among the studies included in our meta-analysis none used brain mapping, magnetoencephalography, and surgical C-arm to guide surgery.

Studies on recurrent seizures still have not been able to describe the etiology of epilepsy or explain the mechanism of seizure recurrence.[40] Even though our results appear to show that surgery provides a greater likelihood of a seizure-free status than nonsurgical treatment it does not guarantee that the seizure-free state can be maintained completely without using AEDs. It has been reported that ''antiepileptic drug discontinuation is associated with a seizure recurrence in 1 in 3 patients rendered seizure free by epilepsy surgery.'''[41] Since the risk of seizure recurrence is beyond the scope of our meta-analysis, great caution should be used in interpreting our results when providing patients with consultation about postsurgical care.

The most important limitation of our review was that only 2 of the 20 studies were randomized controlled studies. In the nonrandomized studies both groups may not have been completely comparable as there is always some reason why the patients in the control group were not good candidates for surgery. Although all 20 studies included in our analysis reported the seizure-free rate, only 7 reported the total QOL score. Therefore, we had only had a small number of studies to assess the outcomes with regard to QOL and for that reason were not able to analyze publication bias. Moreover, among the 7 studies, 5 different QOL scales were used, and therefore this might contribute to a certain degree of heterogeneity of the included studies. Since QOL is very important with regard to treatment outcome, more attention should be given to assessing QOL. Another limitation was that only 3 studies provided detailed information about adverse events related to surgery and nonsurgical treatment. In addition, we were not able to stratify the results on the basis of lesion location in the brain because the studies in our meta-analysis did not report a sufficient number of outcomes for each anatomical brain region.

CONCLUSION

The results of our meta-analysis showed that for refractory epilepsy patients, surgery appears to provide a much greater likelihood of seizure-free status than nonsurgical treatment (treatment with only AEDs). Our findings also indicate that patients treated surgically appear to be more likely to have a better QOL than patients not treated with surgery, although this conclusion is based on more limited data than the conclusion concerning our primary outcome. In addition, we found that surgical treatment did not appear to result in an increase in rate of complications, although only 3 studies in our meta-analysis provided detailed data on complications. Because our meta-analysis only included 2 randomized studies, more randomized controlled trials comparing surgery and nonsurgery patients are needed to draw firmer conclusions about the benefits of surgery for treatment of patients with refractory epilepsy.

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