Surgical outcomes for medically intractable epilepsy in low- and middle-income countries: a systematic review and meta-analysis

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OBJECTIVE The aim of this study was to describe the current state of epilepsy surgery and establish estimates of seizure outcomes following surgery for medically intractable epilepsy (MIE) in low- and middle-income countries (LMICs).

METHODS The MEDLINE and Embase databases were searched without publication date restriction. This search was supplemented by a manual screen of key epilepsy and neurosurgical journals (January 2005 to December 2016). Studies that reported outcomes for at least 10 patients of any age undergoing surgery for MIE in LMICs over a defined follow-up period were included. A meta-analysis with a random-effects model was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement and MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines. Pooled estimates of seizure freedom and favorable seizure outcomes following anterior temporal lobectomy with or without amygdalohippocampectomy (ATL ± AH) were reported.

RESULTS Twenty studies were selected, of which 16 were from Asian centers. The average age at surgery in all studies was less than 30 years, and the average preoperative duration of epilepsy ranged from 3 to 16.1 years. Mesial temporal sclerosis accounted for 437 of 951 described pathologies, and 1294 of the 1773 procedures were ATL ± AH. Based on 7 studies (646 patients) the pooled seizure freedom estimate following ATL ± AH was 68% (95% CI 55%–82%). Based on 8 studies (1096 patients), the pooled estimate for favorable seizure outcomes was 79% (95% CI 74%–85%).

CONCLUSIONS Surgery for MIE in LMICs shows a high percentage of seizure freedom and favorable outcomes. These findings call for a concerted global effort to improve timely access to surgery for MIE patients in these regions, including investments aimed at refining existing and establishing additional centers.

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KEYWORDS low- and middle-income countries; medically intractable epilepsy; meta-analysis; surgery

ABBREVIATIONS ATL ± AH = anterior temporal lobectomy with or without amygdalohippocampectomy; ECE = epilepsy center of excellence; EEG = electroencephalography; ES = effect size; HIC = high-income country; ILAE = International League Against Epilepsy; LMIC = low- and middle-income country; MIE = medically intractable epilepsy.

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THE burden of epilepsy is disproportionately weighted toward low- and middle-income countries (LMICs), and active epilepsy is associated with higher rates of mortality and biopsychosocial issues.^{6,11,25} Accordingly, the World Health Organization has ranked epilepsy as the second most burdensome neurological ailment.³⁹

Although first-line management is medical therapy, approximately one-third of patients have medically intractable epilepsy (MIE), one-third of whom benefit from surgery.^{44,51,52} For instance, patients with MIE due to temporal lobe epilepsy who have long endured disabling seizures may be afforded seizure freedom following a single operation, anterior temporal lobectomy with or without amygdalohippocampectomy (ATL ± AH).⁶¹ Despite the evidence, access to and use of surgery for MIE is limited in LMICs, which calls for a global effort to promote the procedure's availability.^{14,20,24,26,27,32,60}

The Lancet Commission on Global Surgery has emphasized the need for access to surgical care in LMICs, including a list of high-priority “Bellwether” procedures.³⁷ Absent among these were neurosurgical interventions, including epilepsy surgery.³⁵ This is especially concerning considering the societal impact of MIE.⁴⁸

Given the pressing need to deliver effective and sustainable treatments for epilepsy, the assessment of surgical outcomes in LMICs is increasingly important. We thus conducted a systematic review and meta-analysis of publications pertaining to surgery for MIE in LMICs. We have identified the distribution of surgical programs for MIE in LMICs, the breadth of pathologies treated, the resources leveraged, and the seizure outcomes achieved. Predictors of good seizure outcomes and strategies for better integration of surgical care in the management of patients with MIE in LMICs are explored.

Methods

Search Strategy and Selection Criteria

We performed a systematic review and meta-analysis within the framework of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines focused on studies reporting seizure outcomes following surgical intervention for MIE in LMICs. The MEDLINE (PubMed/Ovid) and Embase electronic databases were searched on July 24, 2017 (English-language literature, no limitations on date or publication type). MeSH terms/keywords related to “epilepsy,” “surgery,” and “low-” or “middle-income countries” were used. Please refer to Appendix 1 for a detailed search strategy. Our search was supplemented by a review of the bibliography of included studies and manually screening the table of contents (January 2005 to December 2016) of *Lancet Neurology*; *Journal of Neurology*; *Neurosurgery*; and *Psychiatry*; *Epilepsia*; *Neurology*; *Journal of Neurosurgery*; and *Neurosurgery*. The search was updated on October 28, 2017, to identify potentially newer publications since our last search.

All identified references and subsequent full-text articles were reviewed for eligibility, independently and in duplicate (A.M. and A.A.). Eligible studies reported seizure outcomes over a defined period of follow-up for at

least 10 patients of any age with MIE undergoing surgery in LMICs. “Low/middle” income status of the home nation in which patients were based was determined according to the classification provided by the World Bank group;⁶³ studies that did not fall under this definition of LMIC but in which the authors considered themselves to be practicing in LMICs were included as such.² In cases of publications potentially based on a duplicate cohort of patients, the study with the largest sample set was selected. This review follows the PRISMA guidelines and MOOSE (Meta-analysis of Observational Studies in Epidemiology) criteria for meta-analyses.⁵³

Outcomes and Data Collection

Surgical procedures were grouped into 2 broad categories. Curative procedures included any surgical intervention that was performed with the aim of achieving seizure freedom, while palliative procedures were surgical procedures performed with the goal of improving seizure control without the intent of cure. Not all demographic statistics were explicitly provided; in these cases, calculations and assumptions were necessary (Table 1).^{8,10,42,54}

The meta-analysis was focused on 2 primary outcomes based on ATL ± AH: 1) seizure freedom (defined as Engel class Ia or International League Against Epilepsy [ILAE] class 1 where reported or as stated by authors), and 2) favorable seizure outcomes (defined as Engel class I or ILAE class 1 or 2).^{18,62} Secondary outcomes included morbidity and mortality.

Given the broad range of possible pathologies and surgical procedures associated with lesionectomy, we focused our quantitative assessment of pooled seizure outcomes exclusively on patients undergoing ATL ± AH in order to minimize heterogeneity.

Risk of Bias and Quality Assessment

Risk of bias was assessed by 2 investigators (A.M. and A.A.) who evaluated 5 criteria. Judgments were based on a guide we developed a priori (Appendix 2). Quality was assessed using the National Institutes of Health Study Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (<https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>). Questions 9, 10, and 11 were omitted as they overlapped significantly with study characteristics already evaluated in our risk of bias assessment. GRADEpro software was used to assess overall quality of evidence.

Statistical Analysis

Studies reporting on our 2 primary outcomes were analyzed separately. The standard error of the seizure freedom rate was calculated based on binominal probabilities. We assessed heterogeneity using I^2 and chi-square tests ($I^2 > 50\%$ and $p < 0.1$ considered significant). In case of heterogeneity, random-effects meta-analysis with residual maximum likelihood estimation was used; otherwise, a fixed-effects meta-analysis was used. Age cohort (pediatric vs adult) was chosen a priori as a potential variable affecting heterogeneity.

For assessing the effect of follow-up duration on sei-

TABLE 1. Summary of studies included in this analysis

Authors & Year	Country	Yrs Pts Enrolled	Study Design	Age at Op (yrs)*	Male Sex	Duration of Epilepsy (yrs)*	No. of Pts Enrolled	No. of Pts at Last FU	Assessment Time Point (mos postop)	Preop Adjuncts Used	International Partnership	Multidisciplinary Discussions
Dwivedi et al., 2017	India	2010–2015	RCT	Median 9.0	60%	Median 4.9	57	57	12	MRI, neuropsych, SPECT, PET, scalp EEG, vEEG, MEG	No	Yes
Pakdaman et al., 2016	Iran	NR	Pro	24.4	71%	14	44	44	60	MRI, neuropsych, scalp EEG, vEEG	No	Yes
Panigrahi et al., 2016	India	NR	Retro	25.3 (TLE) & 17.1 (eTLE)	57%	13.6 (TLE) & 8.8 (eTLE)	697	697	12	MRI, neuropsych, SPECT, PET, scalp EEG, vEEG, depth electrodes, strips/grids	No	No
Aburahma et al., 2015	Jordan	2007–2011	Retro	9.4	57%	6.5	27	27	62.2	NA	No	No
Mandell et al., 2015	Uganda	2005–2008	Retro	15.8	30%	11.3	10	10	17	CT, scalp EEG, vEEG	Yes	No
Alsemari et al., 2014	Saudi Arabia	1998–2012	Retro	NA	59%	NA	502	100	12, 36, & 60	WADA, MRI, neuropsych, SPECT, PET, scalp EEG, vEEG, depth electrodes, strips/grids	No	Yes
Asadi-Pooya et al., 2013	Iran	2009–2012	Retro	9.9	78%	7.7	18	17	22.6	MRI, scalp EEG, vEEG	No	Yes
Ouazzani, 2013	Morocco	2005–2011	Retro	NA†	NA†	NA†	NA†	84	84	MRI, neuropsych, scalp EEG, vEEG	NA†	NA†
Liang et al., 2012	China	2001–2007	Retro	11.3	54%	7.7	206	206	60	MRI, neuropsych, PET, scalp EEG, vEEG, depth electrodes, strips/grids	No	No
Mikati et al., 2012	Lebanon	1996–2006	Retro	23.1	45%	14.1	93	90	Resective op, 58.1; VNS, 26.8	WADA, MRI, neuropsych, SPECT, PET, scalp EEG, vEEG, depth electrodes, strips/grids	No	Yes
Tahir et al., 2012	Pakistan	2006–2008	Retro	22	62%	NA	16	15	18	MRI, scalp EEG, vEEG	Yes	Yes
Dagar et al., 2011	India	2000–2011	Retro	9.8	57%	5.3	118	118	47.3	MRI, neuropsych, SPECT, PET, scalp EEG, vEEG, depth electrodes, strips/grids	No	No
Jayalakshmi et al., 2011	India	2003–2009	Retro	12.1	51%	7.2	87	87	12	MRI, neuropsych, SPECT, PET, scalp EEG, vEEG	No	No
Chemmanam et al., 2009	India	2004–2005	Pro	Median 22†	62%	11.3§	143	115	26.4	MRI, neuropsych, SPECT, scalp EEG, vEEG, depth electrodes, strips/grids	No	Yes
Ramesha et al., 2009	India	1996–2007	Pro	10.2	60%	3	19	18	32.4	MRI, scalp EEG, vEEG	No	Yes
Radhakrishnan et al., 2006	India	1995–2003	Retro	Median 20	74%	Median 9	23	23	48	MRI, neuropsych, scalp EEG, vEEG	No	No
Sylaja et al., 2004	India	1995–2001	Retro	27	76%	15	17	17	12	WADA, MRI, neuropsych, scalp EEG, vEEG	No	Yes
Campos et al., 2000	Chile	1991–1998	Retro	23.8	41%	12	17	17	29.1	MRI, neuropsych, scalp EEG, vEEG, strips/grids	No	No

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TABLE 1. Summary of studies included in this analysis

Authors & Year	Country	Yrs Pts Enrolled	Study Design	Age at Op (yrs)*	Male Sex (%)	Duration of Epilepsy (yrs)*	No. of Pts Enrolled	No. Pts at Last FU	Assessment Time Point (mos postop)	Preop Adjuncts Used	International Partnership	Multidisciplinary Discussions
Rao & Radhakrishnan, 2000	India	1995–1998	Retro	25.6	50%	16.1	119	29	21.8†	WADA, MRI, neuropsych, scalp EEG, vEEG	No	No
Tureczek et al., 2000	Colombia	1989–1995	Retro	NA	NA	NA	NA	NA	NA	WADA, MRI, neuropsych, SPECT, PET, scalp EEG, vEEG, depth electrodes, strips/grids	Yes	No

EEG = electroencephalography; eTLE = extra-TLE; FU = follow-up; MEG = magnetoencephalography; NA = not available; neuropsych = neuropsychological examination; NR = not reported; pro = prospective; pts = patients; RCT = randomized controlled trial; retro = retrospective; TLE = temporal lobe epilepsy; vEEG = video-EEG; VNS = vagus nerve stimulation; WADA = intracarotid sodium amobarbital test.

* Values are means unless otherwise specified.

† Abstract only.

‡ Data pertain to age at start of video-EEG monitoring.

§ Data pertain to the duration of epilepsy before video-EEG monitoring.

¶ Manually calculated based on the number of patients who had 1, 2, and 3 years of follow-up.

zure freedom, all point estimates from the studies were entered separately into the meta-regression model. For all other factors, we combined multiple estimates from the same patients in each study (with assumption of a between time-point correlation of 0.7) before assessing the heterogeneity factors or pooling the data.

Funnel plots and Egger's test were used to evaluate publication bias.¹⁶ All analyses were performed using STATA (version 11, StataCorp), and type I error was considered as 0.05.

Results

Geographic Distribution of Epilepsy Surgery Programs in LMICs

A summary of the screening process is provided in Fig. 1. The majority of studies (16/20) were from Asia. The remaining studies were from Chile, Colombia, Morocco, and Uganda.^{8,30,41,57} One study was randomized.¹⁵ The characteristics of the studies included in the review are summarized in Table 1. The average age at surgery in all studies was less than 30 years, ranging from 9.0 to 27.0 years. Based on studies reporting the preoperative duration of epilepsy, a range of 3.0 to 16.1 years was observed.^{49,50}

One study was based on a mixed population but reported outcomes for adults and pediatrics separately.² One was purely focused on pediatric patients and was randomized.¹⁵ The remaining studies either focused strictly on adults or reported pooled outcomes. The risk of bias was moderate overall, with the exception of the randomized trial by Dwivedi et al., which had low risk of bias.¹⁵ Confidence regarding sample representativeness and treatment standardization were the greatest source of concern (Table S1). The quality of most studies was moderate, again with the exception of the study of Dwivedi et al.¹⁵ Most had limitations in statistical considerations and outcome assessment/adjudication (Table S2). Quality of evidence was moderate for both primary outcomes of interest (seizure freedom and favorable seizure outcome), with risk of bias being the only serious concern in the assessment (Table S3).

Pathologies, Procedures, and Preoperative Adjuncts

The majority of explicitly defined pathologies (437/951; 46.0%) were mesial temporal sclerosis (Table 2), and the majority of surgical procedures (1294/1773; 73.0%) were ATL ± AH (AH not always described). All studies had access to video-electroencephalography (EEG) monitoring, although not all were necessarily dedicated epilepsy monitoring units. Ten centers had invasive EEG monitoring (depth or strip/grid electrodes). Studies using PET and/or SPECT imaging were used in 10 studies; MRI was not performed for preoperative assessment in only one study.³⁰ Sylaja et al. reported outcomes in patients with normal findings on MRI.⁵⁴ Neuropsychological assessment was performed in 15 studies.

Pooled Seizure Outcomes for ATL ± AH

Based on 7 studies (646 patients) reporting an estimate for seizure freedom following ATL ± AH, the pooled estimate was 68% (95% CI 55%–82%; Fig. 2A). A sensitiv-

FIG. 1. PRISMA flow diagram of the screening process.

ity analysis, incorporating 2 studies that were based on patients undergoing ATL $\pm$ AH, yielded a similar estimate for seizure freedom (64%, 95% CI 48%–79%). Based on 8 studies (1096 patients) reporting favorable seizure outcomes, the pooled estimate was 79% (95% CI 74%–85%; Fig. 2B). The GRADE quality of evidence for both of these outcomes was moderate (Table S3).

Due to significant heterogeneity introduced by including the study by Sylaja et al. (with normal findings on MRI), we focused our analysis of pooled outcomes only on studies based on patients with abnormal preoperative imaging findings;⁵⁴ we could not find a publication bias for either seizure freedom ($Z = -0.19$, $p = 0.85$) or favorable seizure outcome ($Z = -0.49$, $p = 0.621$) (Fig. 3A and B).

Two studies included a notable proportion of patients treated with ATL $\pm$ AH, but both reported pooled seizure outcomes that were based on the inclusion of patients with palliative procedures as well.^{29,38} These were not included in the meta-analysis.

Subgroups and Assessment of Heterogeneity

Age Groups

Although a higher percentage of pediatric patients were seizure free (71%, 95% CI 50%–93%; 4 studies, 146 patients) compared with adults (55%, 95% CI 48%–62%; 1 study, 295 patients), this was not statistically significant (effect size [ES] = 0.17, $p = 0.06$) (Fig. 2C). With regard to favorable seizure outcomes, the pooled estimate for adults

(1 study, 295 patients) was 76% (95% CI 69%–82%), while for pediatric patients (4 studies, 156 patients) it was 79% (95% CI 72%–86%); this difference was not statistically significant (ES = 0.03, $p = 0.51$; Fig. 2D).

Follow-Up Duration

Based on a meta-regression model with inclusion of 7 studies (13 observations), an effect of follow-up time on the seizure freedom (ES = -0.0006 , $p = 0.58$; Fig. 4) and favorable seizure outcome estimates (ES = -0.0009 , $p = 0.50$) could not be demonstrated.

Abnormal Preoperative Imaging Findings

Based on a meta-regression model, with inclusion of the preoperative abnormal imaging findings (normal vs abnormal), we showed that normal findings on imaging significantly lower the favorable seizure outcome estimate (ES = -0.38 , $p = 0.02$). The impact on seizure freedom was less profound (ES = -0.34 , $p = 0.07$).

Adverse Events Associated With ATL $\pm$ AH

Morbidity and mortality associated with surgery were not reported in all studies. Among the 467 patients in the study by Panigrahi et al., only 4 (0.9%) experienced major neurological deficits. These included 1 case of monoparesis and dystonia, 2 of hemiparesis, and 1 of memory dysfunction that was not transient.⁴³ Rao and Radhakrishnan reported 1 death of unknown cause, 1 case of persistent

TABLE 2. Characteristics of studies and relevant outcomes reported for surgeries with curative intent

Authors & Year	Pathology Managed	Seizure Freedom Evaluation	Seizure Freedom	Favorable Seizure Outcome	Assessment Time Period (mos)
Dwivedi et al., 2017	Not specified	ILAE	77% (pooled) 100% (temporal lobectomy)		12
Panigrahi et al., 2016	Not specified	Engel		86% (TLE); 65% (eTLE)	12
Mandell et al., 2015	MTS	Engel	60%		17
Alsemari et al., 2014	MTS, tumor, HH, migrational disorder, RE, poststroke/encephalomalacia/gliosis, Sturge-Weber syndrome	ILAE	64% (ATL pooled, 189/295 at 12 mos); 60% (ATL pooled, 118/197 at 36 mos); 56% (ATL pooled, 56/100 at 60 mos); 60% (hemispherect, 38/64 at 12 mos); 72% (ATL pediatric, 50/69 at 12 mos); 67% (ATL pediatric, 29/43 at 36 mos); 71% (ATL pediatric, 15/21 at 60 mos)		12, 36, & 60
Ouazzani, 2013	MTS, tumor, cavernoma, migrational disorder	Engel	60.8% (pooled)	78.4% (pooled)	84
Liang et al., 2012	MTS, tumor, cavernoma, migrational disorder, poststroke/encephalomalacia/gliosis	Engel	67.5% (pooled)		60
Mikati et al., 2012	MTS, tumor, migrational disorder	Engel	75% (pooled)		NA
Tahir et al., 2012	MTS, RE, Sturge-Weber syndrome	Engel	90% (pooled)		18
Dagar et al., 2011	MTS, tumor, cavernoma, migrational disorder, infectious, RE, poststroke/encephalomalacia/gliosis	Engel	68% (lesionectomy); 87% (hemispherot); 76% (ATL); 80% (pooled)		47.3 (lesionectomy)
Jayalakshmi et al., 2011	MTS, tumor, HH, migrational disorder, RE, poststroke/encephalomalacia/gliosis	Engel	48% (extratemporal resection); 72% (ATL); 64% (pooled)		12
Chemmanam et al., 2009	Not specified	NA	78%		NA
Ramesha et al., 2009	RE	Engel	70%		32.4
Radhakrishnan et al., 2006	Tumor	Engel	83%		48
Sylaja et al., 2004	MTS	Other	29%		12
Campos et al., 2000	MTS, tumor, cavernoma, migrational disorder	Engel	88% (pooled)		29.1
Rao & Radhakrishnan, 2000	MTS, tumor, cavernoma	Other	53% (pooled, 62/116 at 12 mos); 68% (pooled, 46/68 at 24 mos); 69% (pooled, 20/29 at 36 mos)		12, 24, & 36
Tureczek et al., 2000	Not specified	Engel	81%		NA

Hemispherect = hemispherectomy; hemispherot = hemispherotomy; HH = hypothalamic hamartoma; MTS = mesial temporal sclerosis; RE = Rasmussen's encephalitis.

hemiplegia, and 3 cases in which the patient required repeat surgery for refractory seizures in their cohort of 164 patients undergoing ATL ± AH; only 29 of 164 patients undergoing surgery were followed to the 3-year mark.⁵⁰ Among the 118 patients with at least 1-year follow-up reported by Dagar et al., 14 (11.8%) experienced either medical or postsurgical complications; there were no deaths.¹² Reporting on adverse events for all patients undergoing surgery, Jayalakshmi et al. observed postsurgical complications in 4 (5.1%) patients; not all of these patients had undergone ATL ± AH.²³ One of 14 patients (7%) in Dwivedi et al.'s randomized trial experienced monoparesis after surgery.¹⁵ One study reported no postoperative complica-

tions.⁴⁵ Adverse events were not reported in the remaining studies.

Description of Surgeries With Palliative Intent

Aburahma et al. observed a > 50% seizure reduction in 59% (16 of 27) of patients undergoing implantation of a vagus nerve stimulator after a 60-month follow-up period. Four patients required repeat surgery for complications.¹ Other studies did not report significant complications.^{23,42} Corpus callosotomy patients had the lowest seizure freedom rates. Asadi-Pooya et al. reported transient complications in 8 patients; one had a major complication and another patient died.⁴ Liang et al. and Mikati et al. did not

FIG. 2. Seizure outcomes for studies reporting results after anterior temporal lobectomy with or without amygdalohippocampectomy (ATL ± AH). **A:** Pooled seizure freedom percentage for studies with pathology detected on preoperative imaging. **B:** Pooled percentage of patients with favorable seizure outcomes among those with pathology detected on preoperative imaging. **C:** Subgroup analysis based on age cohorts for seizure freedom. **D:** Subgroup analysis based on age cohorts for favorable seizure outcomes.

explicitly report seizure outcomes for their palliative cohort (Table 3).^{29,38}

Discussion

The incidence and lifetime prevalence of epilepsy is much higher in LMICs than in high-income countries (HICs).¹⁹ China and India alone account for approximately one-fifth of the global burden of epilepsy.^{46,59} In the current systematic review, we showed that epilepsy surgery is being performed across many LMICs and the range of pathologies managed are broad. Our findings qualitatively and quantitatively reaffirm that surgery for MIE in LMICs is not only feasible but that it can also result in good seizure outcomes and relatively low morbidity, thus supporting the notion that the global community should invest in the optimization of surgical epilepsy care in LMICs.

Seizure Outcomes Following ATL ± AH

With a focus on ATL ± AH procedures, we have demonstrated that at 68% and 79%, the overall pooled percentage of patients who are seizure free or have favorable out-

comes is high, and that this is durable and comparable to most published data from developed nations.^{5,7,17,28,36,56} The duration of follow-up did not significantly affect seizure outcomes, which is in contrast to published literature, and the difference is likely attributable to the small number of studies included.^{7,36}

Regional Trends

The majority of the publications in our review were from Asia. While a publication bias cannot be ruled out, this is also perhaps reflective of the high volume of surgical activity in nations from this continent. Although the majority of the Asian studies were from India, perhaps suggesting improved access to timely surgical care in this nation, the gap between patient needs and access continues to be wide; an estimate from India suggests that only 0.04% of surgical epilepsy candidates receive the intervention.⁴⁶ Over-reliance on traditional healers and a societal stigma regarding epilepsy are contributing factors.³³ Strategies to raise public awareness regarding epilepsy as a medical diagnosis are critical.⁹

A recent epidemiological study based on an HIC popu-

FIG. 3. Funnel plot assessment of publication bias. **A:** Studies reporting seizure freedom. **B:** Studies reporting favorable seizure outcomes.

lation spanning over 2 decades suggested that the incidence of mesial temporal lobe epilepsy has decreased over the past 20 years. This was attributed to both disease-modifying factors and more effective antiepileptic drugs.²¹ While the incidence and prevalence of MIE is currently higher in LMICs than in HICs, it is possible that our current global epidemiological snapshot in LMICs is a representation of the state of epilepsy care in HICs 2 decades ago. Therefore, a systematic assessment of the epidemiology of MIE in LMICs over the coming years would not only be informative for more effective resource allocation but also valuable for the LMIC epilepsy community in learning from the experience already accumulated in HICs. This further emphasizes the need for global partnerships.

Resource Limitations

The burden of epilepsy in LMICs could challenge even the most efficient epilepsy centers in HICs. This is further compounded by the fact that the availability of neurologists is far too low to match the demand from patients in these regions.³ As such, ensuring access to primary physicians who are capable of helping patients navigate treatment options and can monitor their postoperative progress is essential. Successful examples of empowering primary physicians as central players in the management of epilepsy patients have been reported previously.^{13,46}

Dissemination of referral guidelines among primary care physicians will also be critical for efficient use of limited resources. For instance, while in all but one of our studies the authors had access to MRI, a survey in 2006 suggested that just over one-quarter of African countries had an MRI system available.^{22,41} MRI is critical to selecting the ideal surgical candidate and it likely cannot be supplanted by CT. Even among centers that have MRI systems, not all utilize epilepsy-specific imaging protocols, either resulting in inadequate information or necessitating repeat imaging.³ In such settings, primary physicians will play an important role in maintaining the fine balance of referrals for imaging and requesting appropriate imaging in order to avoid overwhelming the system.

Nearly 25% of potential surgical candidates may benefit from invasive EEG monitoring to further delineate seizure focus, and half of these could be surgical candidates.³⁴ Nine of the studies in our review lacked access to invasive EEG, which could indicate that a significant proportion of epilepsy surgery candidates in LMICs are neither identified nor offered the best treatment option. Some authors from LMICs have suggested using a 2-lead EEG with video recording over a truncated monitoring session. To increase sensitivity, additional anterior temporal electrodes are used.^{3,40} Outpatient scalp EEG is also not as widely available as is necessary.⁴⁶ To this point, the exclusion of EEG for the diagnosis of epilepsy in LMICs has been explored as a possibility, although its validity as a means of circumventing this problem is not yet clear.^{31,58}

International Collaboration

One strategy that may be useful on multiple fronts is partnership between centers in LMICs and HICs, which has been proposed as a platform for educational and train-

FIG. 4. Bubble plot showing the relationship between time period of assessment and seizure freedom rate. No effect of follow-up duration on seizure freedom was found.

TABLE 3. Characteristics of studies and relevant outcomes reported for surgeries with palliative intent

Authors & Year		Procedure	Seizure Freedom Evaluation	Seizure Outcome	Assessment Time Period (mos)
Pakdaman et al., 2016	VNS		Other	11% seizure free	60
Aburahma et al., 2015	VNS		Other	50% reduction in 16/27 pts	60
Alsemari et al., 2014	Callosotomy, hemispherot/hemispherect		ILAE	64% seizure free (189/295 at 12 mos, ATL pooled); 60% seizure free (118/197 at 36 mos, ATL pooled); 56% seizure free (56/100 at 60 mos, ATL pooled); 60% seizure free (38/64 at 12 mos, hemispherect); 72% seizure free (50/69 at 12 mos, ATL pediatric); 67% seizure free (29/43 at 36 mos, ATL pediatric); 71% seizure free (15/21 at 60 mos, ATL pediatric)	12, 36, & 60
Asadi-Pooya et al., 2013	Callosotomy		Other	16.6% seizure free (3/18 at 12 mos); 11.1% seizure free (1/9 at 24 mos)	12 & 24
Liang et al., 2012	Callosotomy		Engel	67.5% seizure free (pooled)	60
Mikati et al., 2012	Callosotomy, hemispherot/hemispherect, VNS		Engel	75% seizure free (pooled)	NA
Dagar et al., 2011	Callosotomy, hemispherot/hemispherect, VNS		Engel	79.5% seizure free (pooled)	47.3 (lesion-ectomy)
Jayalakshmi et al., 2011	Callosotomy, hemispherot/hemispherect, VNS		Engel	64.1% seizure free (pooled)	12
Chemmanam et al., 2009	Callosotomy, VNS		NA	78.4% seizure free (pooled)	NA

ing purposes as well.^{31,58} In our review, 2 studies incorporated such collaborations in which teleconferences were used for reviewing surgical candidacy.^{29,41} In the absence of more permanent solutions that allow centers in developing countries to be independent, such partnerships may represent an impactful means of improving access.

Study Limitations

The majority (16/20) of the studies included in our review were retrospective. Only 1 study was randomized,¹⁵ and only 7 had a surgical sample size of more than 100 patients. The overall risk of bias and quality assessments were both moderate, as was the strength of the evidence. Post-operative complication rates were not uniformly reported. Therefore, although the seizure outcomes are encouraging, a more systematic approach to reporting adverse event rates is necessary to build confidence in LMIC surgical centers. Furthermore, given that the majority of reports were from Asia, the generalizability of our findings is also limited. Regardless, our study is the first to systematically assess the status of epilepsy surgery for MIE in LMICs, establish a pooled estimate of seizure freedom and favorable seizure outcomes for the most commonly performed epilepsy procedure with curative intent, and examine areas in need of future development and exploration.

Future Directions

Improving surgical care for epilepsy patients in LMICs requires harmonious global and local efforts. In addition to the measures discussed above, the currently available resources in LMICs can be developed and leveraged in order to maximize output. It may not be possible or even necessary to establish epilepsy surgical centers upfront in every country, as already established, high-performing centers

can potentially serve as regional epilepsy centers of excellence (ECEs). Mikati et al. demonstrated the capacity to treat patients from a number of Middle Eastern and North African countries in Lebanon.³⁸ Ouazzani also reported good outcomes over a prolonged follow-up of patients in Morocco.⁴¹ Centers like these likely have the potential to serve as regional ECEs. Centers not designated primarily as surgical sites could nonetheless serve as a valuable hub for the dissemination of guidelines, transmission of diagnostic data for interpretation, and connection of surgical candidates with regional ECEs.

This vision is already underway in countries such as India.⁴⁸ The feasibility of high-quality research in LMICs has also been demonstrated; this should also be harnessed to better assess outcomes.¹⁵

Challenges Beyond Surgery

International efforts should not stop at selecting the ideal surgical candidates and getting them to surgery. Long-term follow-up is also necessary. Seizure outcome data would need to be paired with health economic studies that assess the long-term impact on society, to facilitate quality assurance and solidify the utility of surgery for major stakeholders. While this approach can be challenging, potential frameworks have been described.^{22,46}

The prevalence of MIE is high in LMICs. Despite resource limitations, surgery for MIE is being performed, and good seizure outcomes are achieved. We strongly believe that surgery for MIE should be considered a necessary surgical procedure for which timely access must be ensured. While this is challenging and a multidisciplinary concerted effort is required, the promise of improving outcomes for patients, families, and the society as a whole make it a worthwhile investment.

Conclusions

Surgical centers in many LMICs have the capacity to perform epilepsy surgery for a variety of pathologies, and our meta-analysis shows that ATL $\pm$ AH is associated with promising outcomes. Despite its potential impact on patients suffering from MIE, epilepsy surgery is widely inaccessible and underutilized in developing countries. Our findings therefore provide quantitative evidence that a global effort to address this problem is justified and should be undertaken urgently to improve access to this vital treatment option.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Conception and design: Ibrahim. Acquisition of data: Ibrahim, Mansouri, Abbasian, Badhiwala, Akbar. Analysis and interpretation of data: Ibrahim, Mansouri, Taslimi, Alotaibi. Drafting the article: Ibrahim, Mansouri. Critically revising the article: Ibrahim, Mansouri, Taslimi, Abbasian, Badhiwala, Akbar, Almenawer, Weil, Fallah, Carmant. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Ibrahim. Statistical analysis: Mansouri. Study supervision: Ibrahim, Mansouri.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

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