PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Clinical predictors of two-year outcome of resective epilepsy surgery in adults with refractory epilepsy: a cohort study
AUTHORS	Kanchanatawan, Buranee; Limothai, Chusak; Srikijvilaikul, Teeradej; Maes, Michael

VERSION 1 - REVIEW

REVIEWER	Gonzalo Alarcon Reader and Honorary Consultant in Clinical Neurophysiology Department of Clinical Neurophysiology
REVIEW RETURNED	20-Feb-2014

GENERAL COMMENTS	Only that the term "secondarily generalised" is applicable to seizures and discharges, not epilepsies. They should use focal epilepsy, or focal epilepsy with secondarily generalised discharges or seizures.

REVIEWER	Carmen Barba Children's Meyer Hospital, Florence, Italy
REVIEW RETURNED	01-Mar-2014

GENERAL COMMENTS	The authors responded to most of my previous comments and the paper is much improved in readability and methodology However there are two major points that have not been satisfyingly addressed a) The authors should determine in what percentage of patients who disclosed a better outcome at 24 months, it was necessary to increase or keep unchanged the drug intake. b) The authors should describe in more details the group of patients in whom the outcome improved and analyse the role of etiology and family history in the different figures at 24 months compared to 6 months follow-up c) The short follow-up remains the major limitation. This point should be better addressed in introduction and discussion

REVIEWER	Georgia Ramantani, MD, PhD, senior consultant for pediatric neurology, epileptology Epilepsy Center, University Hospital Freiburg, Germany
REVIEW RETURNED	08-Mar-2014

GENERAL COMMENTS	The subject matter of the study is important, since epilepsy surgery constitutes an option for an increased number of drug-resistant

	epilepsy patients. The authors have apparently made several modifications to the original manuscript, in order to address reviewers´ comments. However, a number of important issues remain unresolved: 1. Although this study includes a large number of patients with a fairly long follow-up, there is some confusion regarding the objective that unfortunately persists throughout the manuscript (abstract, introduction, methods, results, conclusion). In my opinion, it would make more sense to restrict the goals of this study to the clinical predictors of seizure freedom and potentially develop a scoring system helping clinicians to screen potential surgical candidates OR assess pre- postsurgical AED use OR focus on neuropsychiatric factors influencing surgical outcomes. 2. The results of this study clearly concern (almost) exclusively (predominantly) mesial temporal lobe epilepsy in adults with the vast majority of patients presenting with hippocampal sclerosis or other MRI-visible lesion. This evidently results into a relevant bias regarding the full cohort of potential epilepsy surgery candidates that may be MRI-negative or have extratemporal epilepsy or diverse epilepsy substrates. Furthermore, statistics are hard to interpret, since some factors are underrepresented (MRI-negative, seizure recurrence, secondary generalized seizures). In my opinion, it would make more sense to focus on long-term (mesial) temporal lobe epilepsy surgery outcomes in adults with MRI-visible lesions and exclude the rest of the cohort rather than attempt to compare this series with more inclusive and thus diverse cohorts from other epilepsy surgery programs. 3. Although the authors have used quite elaborate statistics, it is still unclear how possible confounders such as age at epilepsy onset, duration of epilepsy and age at surgery have been disentangled, especially since older age at surgery is surprisingly linked to superior surgical outcomes. 4. The surprising main finding of the study i.e. that outcomes improve considerably with time in epilepsy surgery should be discussed in further detail, since it is in contradiction with several previous large studies. The limitations of the study should be addressed also in the sense of a possible bias in patient selection, since outcomes are indeed much better than generally reported.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name Gonzalo Alarcon
Institution and Country Reader and Honorary Consultant in Clinical Neurophysiology
Department of Clinical Neurophysiology
United Kingdom
Please state any competing interests or state 'None declared': None

Only that the term "secondarily generalised" is applicable to seizures and discharges, not epilepsies. They should use focal epilepsy, or focal epilepsy with secondarily generalised discharges or seizures.

Answer: In the Results section and Table 2 we have now used focal epilepsy with secondarily generalised seizures

Reviewer: 2
Reviewer Name Carmen Barba
Institution and Country Children's Meyer Hospital, Florence, Italy

Please state any competing interests or state 'None declared': None declared

The authors responded to most of my previous comments and the paper is much improved in readability and methodology
However there are two major points that have not been satisfyingly addressed
a) The authors should determine in what percentage of patients who disclosed a better outcome at 24 months, it was necessary to increase or keep unchanged the drug intake.

Answer: We now show results of RM design ANOVAs and logistic regression analyses which show that there may be a weak association with one AED:
In order to examine possible associations between the improvement in Engel class classification and use of AEDs, we have performed RM design ANOVAs with dosage of AEDs at 6 and 24 months as time factor and improvement in Engel class I classification as factor. We found a significant time X group interaction only for levetiracetam dosage ($F=5.47$, $df=1/187$, $p=0.02$). Logistic regression analysis with use of AEDs (and other variables listed in Table 2) showed that only dosage of levetiracetam was a significant explanatory variable (Wald=10.99, df=1, p=0.001, Nagelkerke=0.110). In the subgroup of patients who had improved at 24 months, the use of levetiracetam showed 1 negative rank, 5 positive ranks and 17 ties, while in those who did not improve there were 16 negative ranks, 5 positive ranks and 166 ties.

b) The authors should describe in more details the group of patients in whom the outcome improved and analyse the role of etiology and family history in the different figures at 24 months compared to 6 months follow-up

Answer: in the first version we already mentioned that there are no significant associations and we now show some of these negative results with respect to role of etiology and family history:
For example, there were no significant associations between improvement in Engel class classification and family history of epilepsy ($\chi 2=1.16$, $df=1$, $p=0.281$), temporal versus extratemporal lobe epilepsy ($p=0.415$ by Fisher's exact probability test) and type of epilepsy ($p=0.599$ by Fisher's exact probability test).

c) The short follow-up remains the major limitation. This point should be better addressed in introduction and discussion

Answer:
In the Discussion we now state:
Limitations of this study are the shorter follow-up period (24 months) and the lower number of subjects not allocated to Engel class I as a result of the unexpected high success rate of epilepsy surgery in this cohort.
It was already addressed in "Strengths and limitations of the study" that: The shorter follow-up period (24 months) is a limitation of the study.

Reviewer: 3
Reviewer Name Georgia Ramantani, MD, PhD, senior consultant for pediatric neurology, epileptology
Institution and Country Epilepsy Center, University Hospital Freiburg, Germany
Please state any competing interests or state 'None declared': None declared.

The subject matter of the study is important, since epilepsy surgery constitutes an option for an increased number of drug-resistant epilepsy patients. The authors have apparently made several modifications to the original manuscript, in order to address reviewers´ comments. However, a number of important issues remain unresolved:

1. Although this study includes a large number of patients with a fairly long follow-up, there is some confusion regarding the objective that unfortunately persists throughout the manuscript (abstract, introduction, methods, results, conclusion). In my opinion, it would make more sense to restrict the goals of this study to the clinical predictors of seizure freedom and potentially develop a scoring system helping clinicians to screen potential surgical candidates OR assess pre- postsurgical AED use OR focus on neuropsychiatric factors influencing surgical outcomes.

Answer: In our opinion, the two aims of the study are very clear and adequate and the Results and Discussion are structured around these two aims, i.e. as stated in the Abstract:
This study was carried out to delineate a) possible differences in the success rate of resective epilepsy surgery 6 and 24 months after surgery; and b) the clinical predictors of a good response to surgery.
Therefore, we will not change the aims of the study.

2. The results of this study clearly concern (almost) exclusively (predominantly) mesial temporal lobe epilepsy in adults with the vast majority of patients presenting with hippocampal sclerosis or other MRI-visible lesion. This evidently results into a relevant bias regarding the full cohort of potential epilepsy surgery candidates that may be MRI-negative or have extratemporal epilepsy or diverse epilepsy substrates. Furthermore, statistics are hard to interpret, since some factors are underrepresented (MRI-negative, seizure recurrence, secondary generalized seizures). In my opinion, it would make more sense to focus on long-term (mesial) temporal lobe epilepsy surgery outcomes in adults with MRI-visible lesions and exclude the rest of the cohort rather than attempt to compare this series with more inclusive and thus diverse cohorts from other epilepsy surgery programs.

Answer: This is a cohort of consecutively admitted patients in one of the only two refractory surgery units in Thailand (at the time of the study). So, there is clearly no bias, but since we used selection criteria the results could be more difficult to extrapolate. However, here I would like to add that the associations of Engel class I with the significant predictors were not affected after considering the effects of these epilepsy types or etiologies in the analyses. So from and a statistical point of view our results should hold in related cohorts of more heterogeneous epilepsy patients. This is now addressed in the Discussion as:
Nevertheless, the associations of Engel class outcome with the significant predictors (discussed in detail below) were not affected after adjusting for the effects of epilepsy type or etiology in the multivariate analyses.

3. Although the authors have used quite elaborate statistics, it is still unclear how possible confounders such as age at epilepsy onset, duration of epilepsy and age at surgery have been disentangled, especially since older age at surgery is surprisingly linked to superior surgical outcomes.

Answer: Yes, the logistic regression analysis shows a small effect of age at surgery, but not age at epilepsy onset or duration of epilepsy. I do not understand how this could be disentangled. There are simply no associations with age at epilepsy onset and duration of epilepsy.
Therefore our statement in the first version is accurate: “Therefore, further research should delineate whether age at surgery significantly contributes to Engel class outcome”.

4. The surprising main finding of the study i.e. that outcomes improve considerably with time in epilepsy surgery should be discussed in further detail, since it is in contradiction with several previous large studies.

We have discussed this in further detail based on the remarks of referee 2, i.e.
We have performed post-hoc analyses to predict membership to the group of patients who had

improved at 24 months. We found that there was only one significant, although weak, predictor, i.e. use of levetiracetam. Thus, in a few patients the increased use of levetiracetam post-surgery may be associated with a better outcome at 24 months.

The limitations of the study should be addressed also in the sense of a possible bias in patient selection, since outcomes are indeed much better than generally reported.

Answer: there is no bias in patient selection as all patients were included based on selection criteria. It was already discussed that: Limitations of this study are the shorter follow-up period (24 months) and the lower number of subjects not allocated to Engel class I as a result of the unexpected high success rate of epilepsy surgery in this cohort. As such the results should be interpreted with caution. Future research should validate the predictors delineated in our study.