Abstract: To estimate children’s long-term seizure outcomes after hemispheric surgery and the associated predictors.

A systematic review of 4 databases and a meta-analysis were performed from January 1, 1995 to August 31, 2015. The databases included PubMed, Embase, Science Direct, and Web of Science; patients were classified into the Engel Class I group and the Engel Class II to IV group, according to their seizure outcomes. Nine potential predictors were then stratified across the groups and estimated using the Wilcoxon rank-sum test for continuous variables and the Chi-squared test for categorical variables.

The search yielded 15 retrospective studies, with a total sample size of 380. Five years after surgery, 268 (0.71, 95% confidence interval [CI]: 0.64–0.78) children were seizure-free; the seizure onset age in the Engel Class I group was significantly higher than that of the Engel Class II to IV group (standardized mean difference [SMD] = 0.26, 95% CI: 0.03–0.49, P = 0.028); specifically, when predicting the positive long-term outcomes, the odds ratio for late onset age (≥3.6 months, median value of the Engel Class II–IV group) versus early onset age was 2.65 (95% CI: 1.454–4.836, z = 3.18, P = 0.001). The abnormal magnetic resonance imaging (MRI) findings were more predictive for positive seizure outcomes than the normal findings (odds ratio [OR] = 4.60, 95% CI: 1.27–16.62, P = 0.02).

Following hemispheric surgery, the long-term prognosis of children with epilepsy was good. Late seizure onset (age ≥3.6 months) and abnormal MRI findings were positive predictors for long-term seizure control in children.

INTRODUCTION

Hemispheric surgery, including anatomic hemispherectomy, traditional functional hemispherectomy, peri-insular hemispherotomy, and so on, has been proven to be an effective treatment for patients with epilepsy arising from varied etiologies, such as Rasmussen encephalitis, Sturge–Weber syndrome, stroke, diffuse hemispheric cortical dysplasia, and tumor.1–5 In the short term, many single or pooled analyses have reported good seizure outcomes in children with epilepsy following hemispheric surgery; the seizure-free rate (Engel Class I) ranges from 43% to 78%.6–12 Some researchers have conducted long-term follow-ups (more than 5 years); however, most evidence is based on a single study.13–28 Hu et al29 have pooled a seizure-free rate of 73% from 1528 patients (56 studies) who underwent hemispheric surgery. However, the subjects in their study covered all age ranges; therefore, their conclusion was not specifically for children. Englot et al30 have conducted a meta-analysis of the predictive indicators for children with epilepsy; however, the participants were restricted to pediatric patients with extra-temporal lobe epilepsy, and the follow-up period was not long term (i.e., >1 year). Teléz-Zenteno et al31 have observed long-term (follow-up time >5 years) seizure outcomes following epilepsy surgery; however, he also included patients of all ages. Considering that surgery results differ substantially between children and adults, no strong long-term evidence concerning seizure outcomes in children, or the factors associated with these outcomes have been reported.

We performed a systematic review and meta-analysis to explore the long-term (a mean/median follow-up time ≥5 years) seizure control outcomes in epileptic children, and we also attempted to identify the predictors of the long-term prognosis of these children.

METHODS

Study Selection

Two reviewers independently identified English-language articles from the PubMed, Embase, Science Direct, and Web of Science databases from January 1, 1995 to August 31, 2015 (a period of at least 20 years). The query was performed using the following search terms alone and in combination: hemispherectomy, hemispherotomy, hemidecortication, hemisphectomy, frontal lobe, parietal lobe, occipital lobe, extra-temporal surgery, disconnection, resection, seizure, epilepsy, pediatric, children, and adolescent. Ethical approval is not required for a meta-analysis.

Inclusion and Exclusion Criteria

The following inclusion criteria were applied: original articles with a sample size of at least 10 patients; the study subjects were children with epilepsy (younger than 19 years of age).
age) undergoing hemispheric surgery; the studies had a minimum mean/median follow-up time of 5 years; the seizure outcome of every included patient was reported; and for each child, the study reported the patient sex, age at onset, age at surgery, seizure type, etiology, seizure duration time, status epilepticus, surgical side, and MRI findings. We excluded duplicate publications (i.e., studies with any overlapping patient populations from the same center); commentaries, reviews, and other types of articles were also excluded.

**Data Extraction**

The following variables were extracted: first author name, publication year, number of patients, patient sex, seizure onset age, seizure duration, seizure type, age at surgery, surgery side, MRI findings, epilepsy continua, etiology, and seizure outcome. Variables 4 to 13 were potential predictors of interest; however, other variables of interest (e.g., seizure frequency, ECG findings, and so on) were not extracted or analyzed because of insufficient data.

**Statistical Analysis**

The Wilcoxon rank-sum test and Chi-squared test were used to perform initial between-group comparisons, according to variable type, and these comparisons were completed in SAS 9.4. The potential predictors of seizure control were then analyzed in a separate meta-analysis. The meta-analysis procedure was conducted in STATA 13.1. The ratio,
SMD and OR were calculated in accordance with the data type. Between-study heterogeneity was assessed using Cochran Q and I\(^2\) tests. A random-effects or fixed-effects model was then selected to estimate the overall effect size. A Z test was performed to continue hypothesis testing of the overall effect size. Finally, publication bias was assessed with a funnel plot and, if necessary, with Egger test.

### RESULTS

For the 15 included studies (Figure 1), the patients ranged in age from 0.25 to 312 months (median, 50 months) at the time of surgery, and the minimum median postoperative follow-up time was 60.28 months.\(^1\)\(^3\)\(^\text{13-24,26-28}\) Each study included 11 to 53 patients, and 5 years after surgery, 268 (71%) of the children were seizure free. Detailed information for each included study is summarized in Table 1.
Long-term Seizure Outcomes

The heterogeneity test results showed an $I^2$ of 53.8% ($\chi^2 = 30.30$, d.f. = 14, $P = 0.007$), indicating that the between-study heterogeneity was large; thus, the random effects model was used to perform the meta-analysis.

The forest plot (Figure 2) showed that the pooled rate of seizure freedom was 0.71 (95% CI: 0.642–0.776, $z = 20.77$, $P < 0.05$), and it was statistically significant.

The sensitivity analysis (Figure 3) showed that after removing study A (Table 1) or study F (Table 1), the overall effect size and its confidence interval changed substantially, indicating that these two studies might be the origin of heterogeneity. Therefore, the forest plot was repeated three additional times after removing study A, study F, and studies A and F; the $I^2$ square results were 47%, 33.7%, and 22.2%, respectively. Therefore, study F contributed most to the heterogeneity.

The funnel plot (Figure 4) showed that the studies were not all symmetrically distributed, and two studies were outside the 95% confidence interval. Therefore, Egger test was performed again to verify the presence of publication bias.

The Egger plot (Figure 4) showed that the 95% confidence interval of the bias included 0 (95% CI: $-4.664$, $0.409$, $P = 0.093$); therefore, publication bias was not found.

Potential Predictors

To explore the potential predictors of long-term seizure control, seizure outcomes were stratified across 10 variables (Table 2), and the Engel Class I patients were compared with the Engel Class II to IV patients. For the categorical variables of gender, seizure type, epilepsy continua, surgery side, and etiology, the Chi-squared test $P$ values were all above 0.05, indicating that distribution of these factors was similar between the two outcome groups. For the MRI findings, the $P$ value was 0.026, which was statistically significant. The seizure free rate in the abnormal MRI group (67/82) was higher than that in the normal MRI group (11/20), and further meta-analysis was performed to calculate the odds ratio. For continuous variables, the age at surgery ($P = 0.426$) and epilepsy duration time ($P = 0.853$) did not differ between the two outcome groups; however, the seizure onset age tended to be younger in the Engel Class II to IV group (median = 3.6 months) compared with the Engel Class I group (median = 8.35 months), with a $P$ value of 0.006. A meta-analysis was performed to calculate the standardized mean difference.
### TABLE 2. Seizure Outcomes Stratified by Factors of Interest

| Factor                          | Engel Class |       |       |       |
|--------------------------------|-------------|-------|-------|-------|
|                                | I           | II–IV | P     |       |
| **Demographic characteristics**|             |       |       |       |
| Gender                         |             |       |       |       |
| Male                           | 93          | 43    | 0.564 |       |
| Female                         | 62          | 33    |       |       |
| Age at onset                   | 8.35 (2.93–50.25) | 3.6 (0.23–34.8) | 0.006 |       |
| Age at surgery                 | 50.5 (12–132) | 48 (12.25–113.1) | 0.426 |       |
| **Epilepsy characteristics**   |             |       |       |       |
| Epilepsy duration              | 23 (6–51.40) | 16.5 (6–51.55) | 0.853 |       |
| Seizure type                   |             |       |       |       |
| Partial                        | 142         | 44    | 0.430 |       |
| Generalized                    | 18          | 8     |       |       |
| Epilepsy continua              |             |       |       |       |
| Yes                            | 53          | 20    | 0.091 |       |
| No                             | 46          | 8     |       |       |
| **Surgery characteristics**    |             |       |       |       |
| Surgery side                   |             |       |       |       |
| Left                           | 59          | 30    | 0.924 |       |
| Right                          | 63          | 33    |       |       |
| **Etiology**                   |             |       |       |       |
| Dysplasia                      | 80          | 33    | 0.729 |       |
| Vascular                       | 33          | 10    |       |       |
| Tuberous sclerosis complex     | 7           | 2     |       |       |
| Tumor                          | 74          | 22    |       |       |
| **MRI findings**               |             |       |       |       |
| Normal                         | 11          | 9     | 0.026 |       |
| Abnormal                       | 67          | 15    |       |       |

Patients were classified into two groups: seizure free (Engel Class I) or continued to have seizures (Engel Class II–IV).

**FIGURE 5.** A forest plot of the age of onset among children with epilepsy.
Age at Seizure Onset

According to the forest plot (Figure 5), the I² result was 40.2%, and the P value of the heterogeneity test was 0.116. Thus, the between-study heterogeneity was relatively small, and a fixed effects model was applied to the meta-analysis. The patients were placed in two groups according to their seizure outcomes, and the age of onset of the patients in the Engel Class I group was significantly older than that of the patients in the Engel Class II to IV group. The SMD was 0.26 (95% CI: 0.03–0.49, z = 2.2, P = 0.028).

The funnel plot (Figure 6) showed a symmetrical distribution of the included articles; however, two studies were outside the 95% confidence interval. Therefore, Egger test was performed again. The Egger plot (Figure 6) showed that all included studies were within the 95% confidence interval, and Egger test showed that the coefficient of bias was 0.741 (95% CI: -2.570–4.053, P = 0.629); thus, publication bias is unlikely.

MRI Findings

Heterogeneity testing of predictor MRI showed an I² result of 12.7%, with a P value of 0.318 (χ² = 2.29, d.f. = 2). Between-study heterogeneity was low, and a fixed effect model was applied to the analysis.

DISCUSSION

Results from 15 retrospective studies showed that 5 years after hemispheric surgery, 71% of all children were seizure free, indicating that the long-term prognosis for seizure control was good, even better than the short-term outcomes (69.3%). This result was similar to the findings of Hamiwka et al in a 10-year follow-up study: children who were seizure free shortly after surgery tended to remain seizure free in the long term. In a prospective population based observational study performed by Reinholdson et al, the long-term follow-up also verified this finding (no difference in seizure control was observed between the 2-year, 5-year, and 10-year follow-ups). However, there was heterogeneity among the 15 included studies. The sensitivity analysis revealed that study A (Table 1) and study F (Table 1) originated the heterogeneity. Considering that the age of onset could significantly affect seizure outcomes, the median age of onset was calculated for each study. The median value of study A was larger (93 months) than that of study F (6 months) as well as the median value of all patients (7.1 months). MRI inspection
was not compared because of the lack of data. This finding aligned with the following age of onset results.

As mentioned above, an early age of onset was a negative predictor of long-term seizure outcomes in children. This result was similar to that of Babini et al., in a long-term study: a young age at seizure onset (in particular, younger than 4 years) was associated with poor seizure outcomes. Marras et al. have also reported a semblable result in cognitive function estimation after hemispheric surgery. In a myoclonic-astatic epilepsy study, Inoue et al. have described a similar finding: the age of onset in patients with refractory seizures was earlier than that patients with favorable prognoses (7–24 months versus 23–38 months). As Inoue et al. have mentioned, early onset exacerbates damage to the central nervous system and, possibly, intellectual disability. In addition, symptoms associated with an early age of onset, such as loss of consciousness or apnoea, can greatly harm brain development and, thus, affect patient prognosis. An early age of onset may also play an important role in widely distributed dysplasia, which is already known to cause poor mental outcomes. The odds ratio (early onset age versus late onset age in predicting negative seizure outcome) was up to 2.65, and early age onset should be treated as a strong predictor for poor seizure control. A more comprehensive evaluation is recommended for children with early onset epilepsy, and surgery should be performed at an early stage.

For the MRI findings, it was quite interesting that a normal MRI finding was associated with relatively poor long-term seizure outcomes (OR = 4.6). This finding was similar to that of Englot et al., who found that among patients with abnormal MRI findings, 216 were Engel Class I versus 146 patients who were Engel Class II to IV, while in the normal MRI group, the numbers were 73 versus 71, respectively. Lazow et al. have also observed that seizure outcomes were favorable in MRI-negative patients. Feng et al. have recommended pre-surgical evaluation of patients with temporal lobe epilepsy, even those with normal MRI findings. In this study, the MRI findings were stratified across onset ages (classified by the median value), and no significant relationship was found. Given that MRI findings are only a type of inspection, there may be no cause-and-effect relationship between MRI findings and seizure outcomes; however, a comprehensive pre-surgical evaluation is still recommended for epileptic children with normal MRI findings.

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