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External validation of the Epilepsy Surgery Grading Scale in a Japanese cohort of patients with epilepsy

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ABSTRACT

Objective. The Epilepsy Surgery Grading Scale (ESGS) is a simple method to predict the likelihood of a patient with epilepsy proceeding to surgery and achieving seizure freedom. Usefulness of the ESGS has been confirmed in established epilepsy centres in the United States and Belgium for adult patients with drug-resistant focal epilepsy undergoing presurgical evaluation. However, the applicability of the ESGS has not yet been evaluated in a wider range of epilepsy patients that may reflect the general spectrum of epilepsy. The present study validated the ESGS in a Japanese epilepsy centre in which admission-based comprehensive epilepsy studies were indicated beyond presurgical evaluation.

Methods. This single-centre retrospective study included adult patients with epilepsy admitted to the Epilepsy Monitoring Unit from 2010 to June 2019. Patients were classified as ESGS Grade 1 (most favorable), Grade 2 (intermediate), and Grade 3 (least favourable). Patients were grouped into three cohorts: all patients, patients with drug-resistant focal epilepsy, and patients who underwent resective epilepsy surgery. We assessed progression to surgery and seizure freedom at one year after surgery.

Results. Of the 1,158 total admissions, 670 patients met the inclusion criteria and formed the total cohort. Of these, 435 (64.9%) had drug-resistant focal epilepsy and 78 (11.6%) proceeded to resective surgery. Overall, progression to surgery was observed in 41.3%, 16.6%, and 4.8% of patients with Grade 1, 2, and 3, respectively. In the surgical cohort, seizure freedom was observed in 85.2%, 65.2%, and 31.3% of patients with Grade 1, 2, and 3, respectively.

Significance. Our results indicate that the ESGS is effective in predicting whether a patient proceeds to epilepsy surgery and achieves seizure freedom even in the general population of epilepsy patients, regardless of type or resistance to antiepileptic drugs.

Key words: epilepsy surgery, grading scale, validation study

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Epilepsy surgery has been established as an effective treatment option for patients with drug-resistant epilepsy with an average 64% rate of seizure freedom [1]. Careful patient selection based on various diagnostic evaluation methods may improve outcome. In recent years, several preoperative prognostic factors have been identified that may influence surgical outcome [1]. Unfortunately, epilepsy surgery continues to be underutilized in both developed and developing countries [2-4], partly because of gaps in knowledge about surgical

indications and identification of the patients most likely to benefit from surgery [5-7]. Currently, no standard method or procedure is generally adopted for the selection of the best candidates for surgery or for predicting seizure outcomes after surgery, at least as an initial evaluation method suitable for general neurologists. Such standard protocols would be valuable in the initial systematic and objective decision-making process for patients with drug-resistant epilepsy who are likely to benefit from epilepsy surgery.

The Epilepsy Surgery Grading Scale (ESGS), published in 2017, has the potential to identify the patients who are likely to become seizure-free after epilepsy surgery [8]. This numerical scale is based on five diagnostic parameters which together provide a total score that is used to classify a patient into three distinct grades, with Grade 1 indicating the greatest likelihood of favourable surgical outcome. Initial validation of the scale in 407 patients in New York showed that the ESGS effectively stratified patients into these three clinical categories and so could predict the likelihood of seizure freedom after surgery. However, only one validation study has been performed in an independent population with drug-resistant focal epilepsy in Belgium [9]. Results from this study confirm the usefulness of the ESGS in predicting surgical outcomes. Any newly developed predictive model requires extensive external validation studies to allow universal acceptance and adoption in clinical use. Consistent observation of findings, when performed in different cohorts by different investigators, can strongly support the utility of this scale [10]. Furthermore, the applicability of the ESGS in a broad range of epilepsy patients, similar to that seen in a general neurology clinic, has not yet been studied. The present study was an external validation of the ESGS in a Japanese cohort with epilepsy treated in a comprehensive epilepsy centre in Japan. This study included a wider range of epilepsy patients, other than drug-resistant focal epilepsy patients, to reflect the characteristics of a more general population.

Methods

This retrospective electronic chart review identified patients aged 18 years old and above with epilepsy who were admitted for the first time to the Epilepsy Monitoring Unit (EMU) of the Department of Epileptology, Tohoku University Hospital, for comprehensive evaluation, since the establishment of the EMU in 2010 up to June 2019. Indications for admission included epilepsy diagnosis, classification of seizure type, and presurgical evaluation, which led to a wider coverage of patients than previous studies [2, 3]. Our patients usually undergo a two-week admission for long-term video electroencephalography (EEG) monitoring and neuropsychological evaluation during the first week, followed by 3-T magnetic resonance (MR) imaging, fluorodeoxyglucose-positron emission tomography (FDGPET), and magnetoencephalography (MEG) studies during the second week. Patients with non-epileptic seizures, previous brain surgery, and neurodegenerative or progressive medical disease were excluded. Patients with incomplete data sets (*e.g.* no MRI) were also excluded.

Patients were grouped into three cohorts. The first cohort included all epilepsy patients admitted to the EMU regardless of epilepsy classification (focal or generalized) and antiepileptic drug (AED) use. The second cohort included patients with drug-resistant focal epilepsy. Drug-resistant epilepsy was defined as failure of at least two AEDs [11]. Unlike previous studies, we did not have a presurgical cohort since all admissions were discussed in a weekly multidisciplinary conference. The third cohort was the surgical cohort including patients who underwent surgery and completed at least a one-year follow-up period.

All patients were classified according to the ESGS score, which was calculated as the sum of the scores obtained from five parameters: Intelligence Quotient (IQ), seizure semiology, MRI, EEG, and concordance between MRI and EEG [8]. The individual components of the parameters are listed in *table 1*. Based on the total score, patients were classified into three categories: Grade 1 with a score of ≥7.5, Grade 2 with a score of >4 to <7.5, and Grade 3 with a score of ≤4 [8]. Outcome measures were rate of progression to surgery and rate of seizure freedom, defined as ≥12 months based on the Engel classification [12], as assessed during the most recent follow-up visit.

Data were analysed using SPSS Statistics v22.0. Statistical significance was set at $p<0.05$. Student's t-test and Pearson's chi-square test were used for analysis of continuous and categorical variables, respectively. Bonferroni correction was performed for post-hoc analysis of multiple comparisons to check for family-wise error rate.

Results

A total of 1,158 patients were admitted to the EMU. Of these, 488 patients were excluded, with 670 patients remaining to form the broadest cohort (Cohort 1). Mean age at admission was 33.9 years and mean age at epilepsy onset was 18.7 years (*table 1*). Mean number of AED trials was four. Based on epilepsy classification, 524 (78.2%) patients had focal epilepsy, 123 (18.4%) had generalized epilepsy, and 23 (3.4%) had unknown epilepsy.

A total of 78 patients proceeded to resective epilepsy surgery (*table 1*). Patients who underwent surgery tended to have tried a significantly higher number of AEDs compared to those who did not undergo surgery ($p < 0.001$). However, age at admission, sex, and age at

▼ **Table 1.** Baseline characteristics of patients included in the study.

Parameters	All patients (*n* = 670)	Drug-resistant focal epilepsy (*n* = 435)		*p* value	Surgical cohort (*n* = 66)**		
		Proceeding to surgery (*n* = 78)*	No surgery (*n* = 357)		Total (*n* = 66)	Seizure-free (*n* = 43)	Not seizure-free (*n* = 23)
Age at admission, mean ± SD, years	33.9 ± 12.9	33 ± 12.1	35.7 ± 12.5	0.078			
Male sex	320 (47.8%)	37 (47.4%)	161 (45.1%)	0.707			
Age at epilepsy onset, mean ± SD, years	18.7 ± 14.6	15 ±11.5	18.1 ± 14.3	0.071			
Number of AED trials, mean ± SD	3.98 ± 2.6	5.4 ± 2.2	4.5 ± 2.0	0.001			
Parameters of the ESGS							
IQ							
IQ <70	163 (24.3%)	20 (25.6%)	101 (28.3%)		17	8	9
IQ ≥70	367 (54.8%)	55 (70.5%)	194 (54.3%)		46	33	13
Unknown	140 (20.9%)	3 (3.8%)	62 (17.4%)		3	2	1
Semiology							
Unilateral focal motor	29 (4.3%)	1 (1.3%)	22 (6.2%)		0	0	0
Other	640 (95.5%)	77 (98.7%)	334 (93.6%)		66	43	23
Unknown	1 (0.1%)	0	1 (0.3%)		0	0	0
MRI							
Normal	417 (62.2%)	23 (29.5%)	195 (54.6%)		20	10	10
Unilateral mesial temporal sclerosis	64 (9.6%)	24 (30.8%)	36 (10.1%)		23	19	4
Other temporal lesion	50 (7.5%)	17 (21.8%)	26 (7.3%)		14	10	4
Extratemporal lesion	75 (11.2%)	11 (14.1%)	49 (13.7%)		8	4	4
≥2 pot entially epileptogenic lesions	64 (9.6%)	3 (3.8%)	51 (14.3%)		1	0	1
EEG							
Normal	151 (22.5%)	6 (7.7%)	90 (25.2%)		4	3	1
Unifocal temporal	204 (30.4%)	46 (59.0%)	126 (35.3%)		42	32	10
Unifocal extratemporal	65 (9.7%)	10 (12.8%)	46 (12.9%)		7	2	5
Bilateral independent or multifocal	113 (16.9%)	16 (20.5%)	71 (19.9%)		13	6	7
Bisynchronous or generalized	137 (20.4%)	0	24 (6.7%)		0	0	0

▼ **Table 1.** Baseline characteristics of patients included in the study (Continued).

Parameters	All patients (n = 670)	Drug-resistant focal epilepsy (n = 435) Proceeding to surgery (n = 78)*	Drug-resistant focal epilepsy (n = 435) No surgery (n = 357)	p value	Surgical cohort (n = 66)** Total (n = 66)	Surgical cohort (n = 66)** Seizure-free (n = 43)	Surgical cohort (n = 66)** Not seizure-free (n = 23)
Concordance between MRI and EEG							
Concordant	90 (13.4%)	36 (46.2%)	50 (14.0%)		32	24	8
Partially concordant	104 (15.5%)	13 (16.7%)	73 (20.4%)		10	6	4
Not concordant	476 (71.0%)	29 (37.2%)	234 (65.5%)		24	13	11
ESGS							
Grade 1	75 (11.2%)	31 (39.7%)	41 (11.5%)				
Grade 2	157 (23.4%)	26 (33.3%)	95 (26.6%)				
Grade 3	438 (65.4%)	21 (26.9%)	221 (61.9%)				

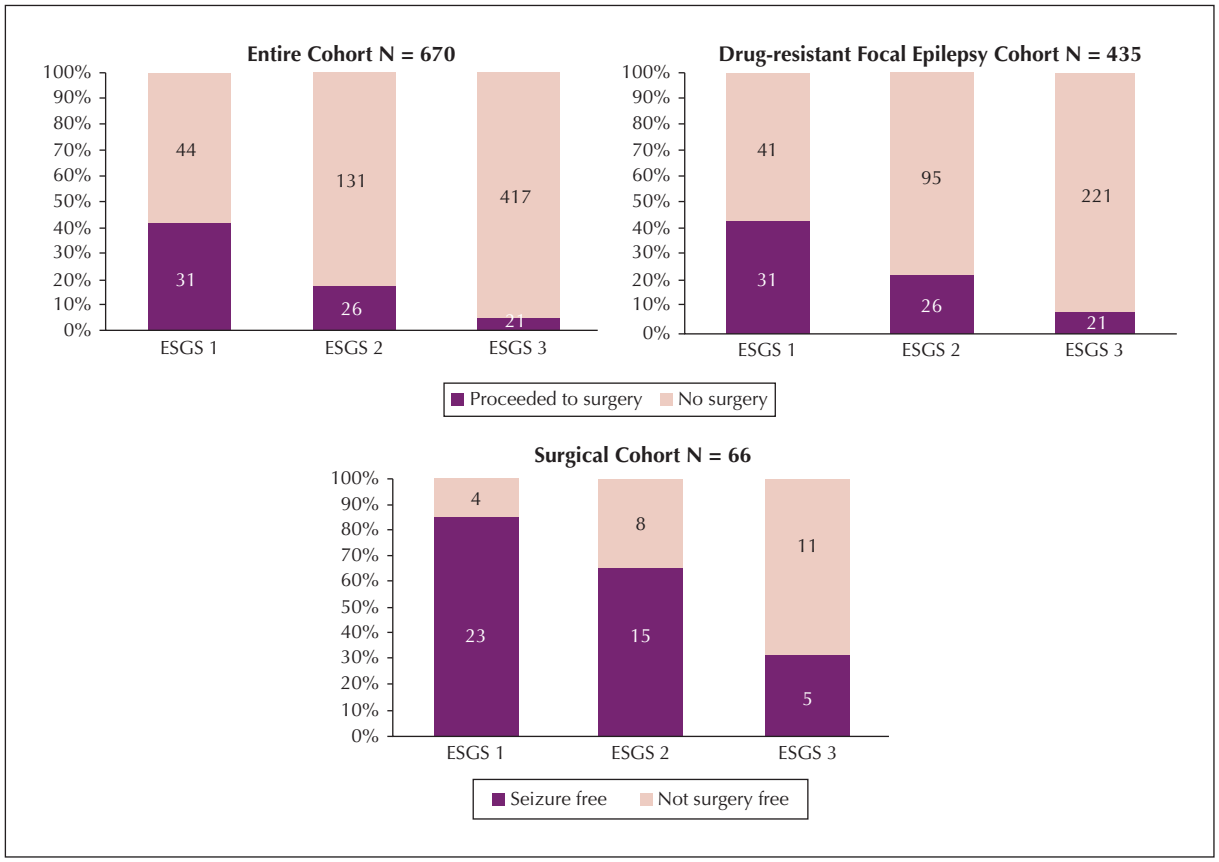
AEDs: antiepileptic drugs.
*12 patients were included who had follow-up durations of less than one year.
**Actual number of patients who completed at least one year of follow-up (surgical cohort).

onset of epilepsy showed no significant differences. Of these, 66 patients completed at least one year of follow-up (surgical cohort). The other 12 patients had follow-up durations of less than a year. None of the patients with generalized epilepsy and with fewer than two AEDs proceeded to surgery.

The rates of proceeding to surgery among all patients were 41.3% (31/75), 16.6% (26/157), and 4.8% (21/438) for Grades 1, 2, and 3, respectively, as shown in *figure 1*, with significant differences between all groups (Grades 1 and 2, $p < 0.001$; Grades 1 and 3, $p<0.001$; Grades 2 and 3, $p < 0.001$). Rates of proceeding to surgery among drug-resistant epilepsy patients were 43.1% (31/72), 21.5% (26/121), and 8.7% (21/242) for Grades 1, 2, and 3, respectively, with significant differences between all groups (Grades 1 and 2, $p=0.002$; Grades 1 and 3, $p < 0.001$; Grades 2 and 3, $p < 0.001$). Overall rate of one-year seizure freedom was 65.2% (43/66) in the surgical cohort: 85.2% (23/27) in Grade 1 patients, 65.2% (15/23) in Grade 2 patients, and 31.3% (5/16) in Grade 3 patients, with no significant difference between Grades 1 and 2 (p = 0.10), but significant differences between Grades 2 and 3 (p = 0.04) and Grades 1 and 3 ($p < 0.001$). Using Bonferroni correction, adjusting the statistical significance to $p < 0.017$, the difference between Grades 2 and 3 was not significant.

In our study, most patients were Grade 3, followed by Grade 2, and lastly Grade 1, as opposed to the two previous studies in which most patients were Grade 2 (*table 2*). Across all studies, Grade 1 patients had the highest rate of proceeding to surgery and achieving seizure freedom, followed by Grade 2, then Grade 3. In addition, the rates of seizure freedom in our study and the preliminary study [8] are very similar to those of the validation study [9].

Based on examination of the individual parameters, MRI, EEG, and concordance between the two, higher ESGS scores were also more frequent in the surgical cohort, except for MRI findings (*table 1*). Among all patients who proceeded to surgery, those with normal MRI findings and unilateral mesial temporal sclerosis represented a similar proportion, of 29.5 % and 30.8%, respectively. Half of the patients with normal MRI achieved seizure freedom. In total, 76% (32/42) patients with unifocal temporal interictal epileptiform discharges on EEG became seizure-free and patients with unifocal extratemporal interictal discharges demonstrated a slightly lower rate of seizure freedom. For patients with bilateral independent or multifocal discharges, the number of patients who were not seizure-free or who became seizure-free was almost the same. Moreover, three quarters of surgical patients with concordant MRI and EEG findings became seizure-free (24/32). However, more than 50% of patients with partially and non-concordant findings also became seizure-free. Most patients in both the



■ **Figure 1.** Outcomes according to Epilepsy Surgery Grading Scale (ESGS) grade. Numbers in bars represent numbers of patients in each category.

▼ **Table 2.** Outcome comparison between the validation studies.

ESGS	Rate of proceeding to surgery		
	Present study (*n* = 435)*	Dugan *et al.* [8] (*n* = 407)	Conte *et al.* [9] (*n* = 238)
Grade 1	31/72 (43.1%)	32/52 (61.5%)	67/78 (85.9%)
Grade 2	26/121(21.5%)	66/253 (26.1%)	52/93 (55.9%)
Grade 3	21/242 (8.7%)	15/102 (14.7%)	21/67 (31.3%)
ESGS	**Rate of seizure freedom**		
	Present study (*n* = 66)**	**Dugan *et al.* [8] (*n* = 113)**	**Conte *et al.* [9] (*n* = 140)**
Grade 1	23/27 (85.2%)	27/32 (84.4%)	44/67 (65.7%)
Grade 2	15/23 (65.2%)	47/66 (71.2%)	26/52 (50.0%)
Grade 3	5/16 (31.3%)	5/15 (33.3%)	6/21 (28.6%)

*Drug-resistant focal epilepsy patients.
**Surgical cohort excluding 12 patients due to follow-up duration of less than one year.

surgical and non-surgical cohorts had IQ ≥70. Only one patient with unilateral focal motor seizures proceeded to surgery.

Discussion

The present findings support the potential of the ESGS in predicting the likelihood of seizure-free status after surgery in patients with epilepsy. The present cohort had different characteristics from the two previous studies [8, 9], but our results confirm applicability of the ESGS to geographically independent populations of patients with epilepsy. The present study, in which the participants reflected those in a general neurology clinic setting, emphasizes that the ESGS has the potential to be adapted worldwide.

For both the total and drug-resistant focal epilepsy cohorts, Grade 1 patients had the highest rate of proceeding to surgery followed by Grade 2, then Grade 3. The surgical cohort showed the same trend for seizure

freedom, one year after surgery. These results are similar to those of the two prior studies, suggesting that the ESGS may be used to effectively classify patients according to the likelihood of proceeding to surgery and becoming seizure-free. The concordance of findings across three independent cohorts strongly supports the relationship between the ESGS and clinical outcome [10].

Our cohort was unique regarding the inclusion of all patients with epilepsy, regardless of epilepsy classification and number of AED trials. This cohort therefore resembles the usual population of epilepsy patients in a general neurology setting, for which the ESGS was designed. In addition, all patients with generalized epilepsy obtained ESGS Grade 3, which further indicates the accuracy of the scoring system to correctly classify patients. This classification may have led to lower rates of progression to surgery compared to the previous studies, but the ESGS is still effective even for patients with undetermined epilepsy and for newly diagnosed patients. In Asia, a substantial number of epilepsy patients are still managed by primary care physicians, especially in remote areas [13], therefore the ESGS may be an important clinical tool to identify good surgical candidates and facilitate referral to specialized epilepsy centres. Based on public health policy, patients with ESGS Grade 1 may have higher priority to undergo comprehensive EMU study, especially in resource-limited countries.

Our cohort also contained a majority of patients with Grade 3, whereas the majority in the two previous studies were classified as Grade 2. This difference persisted even after excluding patients with generalized epilepsy and focal epilepsy who were not drug resistant. Possible explanations for this finding are differences in the aetiology of epilepsy, indications for EMU admission, and epilepsy care model between countries. For example, our EMU admits patients not only for presurgical evaluation but also for epilepsy diagnosis and/or classification. In Japan, as in many other countries, even tertiary epilepsy centres must accept non-epilepsy cases. Nevertheless, earlier referral to more specialised epilepsy centres is the key to develop better epilepsy care systems, not only for surgery but also for pharmacological treatment and psychosocial care [14]. Our present findings indicate the practical potential of the ESGS to effectively select patients admitted to the EMU, especially in resource-poor countries with a limited number of epilepsy centres.

The rates of seizure freedom in our surgical cohort are comparable to those of the preliminary study [8]. In our surgical cohort, the majority of patients with Grade 2 had either normal, extratemporal, or other temporal MRI findings, and only one had unilateral mesial temporal sclerosis. Most patients also had non-concordant or partially concordant EEG and MRI findings. These patients are most likely to benefit from additional diagnostic studies to localize the seizure focus. Use of further diagnostic studies, such as MEG, FDG-PET, ictal single-photon emission computed tomography, Wada test, and intracranial EEG placement, especially for the extratemporal lobe or MRI-negative focal epilepsies, could account for the seizure freedom rates particularly among Grade 2 patients.

Assessment of the individual prognostic factors in the ESGS showed that MRI findings, interictal discharges, and concordance between MRI and EEG, which together make up the total score, generally correlated with the predicted likelihood for surgery and seizure freedom. Our observations of the MRI findings are interesting. A systematic review reported that 55% of patients with normal MRI and 67% of patients with abnormal MRI achieved good surgical outcomes, comparable to our findings. Likewise, our findings of good surgical outcome in more than 50% of patients with partially or non-concordant MRI and EEG was also similar [1]. The subtractive effects of IQ <70 and unilateral focal motor seizures were not apparent in our findings, which may be due to the small proportions of such patients in the entire cohort.

Our study has a number of limitations. First, the study was retrospective. Second, long-term video-EEG monitoring may have resulted in more effective identification of interictal abnormality, therefore increasing the ESGS scores of the patients [15]. Use of 3 T MRI may also yield different results compared to 1.5 T MRI which is more commonly available [16, 17]. Therefore, prospective studies in a general neurology clinic setting are needed to assess the feasibility and applicability of the ESGS in an actual clinical setting. Third, the surgical cohort had a small sample size which could have resulted in statistically insignificant findings. The significant difference seen between Grades 2 and 3 in the surgical cohort prior to the Bonferroni correction may have been due to chance. A larger sample size or a longer duration of the study, to increase patient recruitment, may be employed in future studies. Nevertheless, the concordant results in all three validation studies, along with the simplicity and ease of use of the ESGS based on our experience, demonstrates the potential of the ESGS as a cost-effective tool for the preliminary evaluation of epilepsy patients. ■

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

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TEST YOURSELF

(1) Which of the following is correct regarding the findings of this study?

A. The ESGS was effective in predicting whether a patient proceeds to surgery.
B. The ESGS was effective in predicting whether a patient attains seizure freedom after resective surgery.
C. A & B
D. None of the above

(2) Which ESGS grade is most associated with the likelihood of proceeding to surgery and becoming seizure-free?

A. Grade 1
B. Grade 2
C. Grade 3
D. Grade 4

(3) True or False. ESGS is useful in predicting surgery and becoming seizure-free, even in a general cohort of epilepsy patients.

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section ``The EpiCentre''.