



ORIGINAL ARTICLE

Distribution of postictal slowing has an additional yield to interictal epileptiform discharge in predicting surgical outcomes in temporal lobe epilepsy

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Funding information

The Ministry of Higher Education of the Arab Republic of Egypt.

Abstract

Objective: To investigate whether the slowing of bilateral postictal scalp electroencephalography (EEG) after focal impaired awareness seizures is associated with poor seizure outcomes after temporal lobe epilepsy (TLE) surgery.

Methods: This retrospective cohort study was conducted in the Department of Epileptology, Tohoku University Hospital from 2010 to 2020. The study included 42 patients with TLE who underwent a detailed presurgical evaluation and sequential resective surgery for the unilateral probable epileptogenic temporal lobe with 1 year or more of follow-up. We reviewed the interictal epileptiform distribution and those of the ictal and postictal epochs of the first focal impaired awareness seizure recorded in presurgical scalp EEG. We classified patients either with postoperative seizure-free status (Engel I) as group A or those with seizure persistence (Engel II-IV) as group B.

Results: Of 42 patients, 29 (69%) were classified into group A. Compared with group B, group A had a lower number of bilateral postictal polymorphic delta activity (PPDA) (10.3%: 61.5%) and bilateral interictal epileptiform discharges (IEDs) (13.8%: 69.2%) ($P = 0.003$, $P = 0.001$, respectively). A combined analysis of bilateral PPDA and IEDs per individual patient showed significantly more frequent seizure persistence after surgery ($P < 0.0001$) than a single analysis of bilateral IEDs or PPDA alone ($P = 0.001$). The regression analysis revealed that bilaterally distributed PPDA or IEDs had 13.50 or 13.72 times higher odds of persisting seizures within 1 year of surgery (95% confidence interval: 1.90–95.88; 2.12–88.87, respectively) ($P = 0.009$, 0.006).

Significance: The results of this study revealed that the bilateral distribution of PPDA was associated with poor postoperative seizure outcomes in patients with TLE, as well as bilateral IEDs. Additionally, the concomitant bilateral distribution of interictal and postictal changes is a strong indicator of poor surgical outcomes.

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KEYWORDS

interictal epileptiform discharges, postictal polymorphic delta activity, spatial distribution, surgical outcomes, temporal lobe epilepsy

1 | INTRODUCTION

Temporal lobe epilepsy (TLE) is the most common cause of focal drug-resistant epilepsy in adults.¹ Nearly two-thirds of surgical procedures for intractable epilepsy are performed on the temporal lobe after proper presurgical localization of the epileptogenic zone (EZ). Despite careful selection of candidates for TLE surgery, seizures persist after surgery in 30%–40% of patients.² Earlier studies on epileptogenic zone (EZ) localization and postoperative seizure prediction have focused on analyzing EEG activity in ictal and interictal intervals.^{3,4} In other words, postictal activity has not been extensively examined.⁵ Postictal EEG delta activity is present in 57%–81% of patients with TLE and may be unilateral or bilateral.

The findings of prior intracranial EEG studies suggest that patients with widespread postictal slowing may be less likely to benefit from targeted resections.^{6–8} In this study, we aimed to clarify our hypothesis that the bilateral distribution of postictal slow activity relates to the poor outcome of epilepsy surgery in adult patients with TLE, which has not yet been investigated.

2 | METHODS

2.1 | Patient data

This study was a retrospective cohort study conducted in the epilepsy monitoring unit of the Department of Epileptology, Tohoku University Hospital from 2010 to 2020. The inclusion criteria were as follows: (a) patients aged 15 years or above with (b) drug-resistant unilateral temporal lobe epilepsy; (c) confirmed with comprehensive epilepsy evaluation including video EEG and imaging study of brain MRI, which had lesions evaluated from a histopathological standpoint; (d) no history of prior brain surgery or any medical comorbidity; (e) resective surgery for the unilateral probable epileptogenic temporal lobe, based on the comprehensive evaluation, had been conducted; and (f) no clear postoperative events (g) with at least 1-year follow-up.⁹ Patients less than 15 years of age were excluded to avoid potential confounding effects of age-related differences in EEG patterns and neuroplasticity. This study was approved by the institutional review board (IRB) of Tohoku University, Graduate School of Medicine (2021-1-1119).

Clinical data were collected from the patients' medical charts. Selected patients were categorized into one of two

Key Points

- Bilateral postictal polymorphic delta activity (PPDA) distribution associated with poor postoperative seizure outcomes in temporal lobe epilepsy.
- Bilateral interictal epileptiform discharges also associated with poor postoperative seizure outcomes in temporal lobe epilepsy.
- The concomitant bilateral distribution of interictal and postictal changes is a strong indicator of poor surgical outcomes.

surgical outcome groups: group A was defined as seizure-free or substantially improved (auras only), corresponding to Engel I, while group B had persistent seizures corresponding to Engel II–IV.¹⁰

2.2 | Scalp Electroencephalography analysis

Electroencephalography recordings with 21 channels according to the international 10-20 system and subtemporal electrodes (T1/T2) were performed using a long-term video EEG system (Neurofax EEG-1200; Nihon Kohden). The EEG evaluation was conducted by board-certified epileptologists. We studied ictal EEG recordings of the first focal impaired awareness seizure (FIAS) for each patient, to avoid bias from patients who had many seizures. We also excluded seizures that occurred during sleep, to avoid sleep-related slow waves interfering with the postictal slowing.

Ictal EEG recordings were divided into three segments: (a) preictal, (b) ictal, and (c) postictal. A preictal EEG state (a) was evaluated from a sample of 20 seconds obtained from the EEG 60 seconds preceding the onset of any EEG change that initiated the seizure. An ictal EEG segment (b) was defined as the earliest identifiable EEG ictal change (seizure onset) that continued until the cessation of repetitive epileptiform potentials or rhythmic waves (seizure offset). Each ictal EEG pattern at onset (PAO) and the late significant pattern (LSP) were defined based on previously published protocols as follows: PAO is the first sustained (at least 3 seconds in duration)

evidence of electroencephalographic seizure that was distinguished from background EEG activity, while the LSP was the dominant ictal EEG pattern after the first 10 seconds of seizure onset.¹¹ Ictal duration was defined as the time from seizure onset to offset of the ictal rhythm. A postictal EEG segment (c) was defined either with (a) beginning at the end of the ictal segment and continuing until the EEG returned to the preictal state or (b) 300 seconds elapsed, whichever occurred first. The postictal segment was reviewed to detect postictal polymorphic delta activity (PPDA). PPDA was defined as a newly appearing polymorphic delta activity or one with an amplitude >50% compared with activities in the preictal EEG segment.¹²

The aforementioned ictal patterns (PAO and LSP) were categorized as bilateral or lateralized. PPDA was assigned to one of the following three categories: (a) lateralized (defined as delta with voltage more than twice the voltage of delta present contralaterally), (b) bilateral, or (c) no PPDA. Representative EEGs of bilateral or lateralized PPDA are shown in Figure 1.

Concerning interictal EEG recordings, we identified the distribution of interictal rhythmic slow activity (IRSA) and interictal epileptiform discharges (IEDs), such as spikes or sharp waves, as follows: (a) lateralized, (b) bilateral, or (c) none.^{13,14}

2.3 | Statistical analysis

Statistical analyses were performed using SPSS version 26 (IBM Corp.). Categorical data are presented as numbers and percentages. Categorical data were compared using Fisher's exact test or the chi-square test for independence when Fisher's exact test was inappropriate. When appropriate, data were presented as median (interquartile range [IQR]) and compared using the Mann-Whitney test or Kruskal-Wallis H test when there were more than two groups. Statistical significance was set at $P < 0.05$. Preoperative predictors of seizure persistence were correlated with surgical outcomes using binomial logistic regression. Predictors without significant correlation were excluded from the multiple regression analysis until only significant predictors were included.

3 | RESULTS

3.1 | Patient demographic and clinical characteristics

This study recruited 42 patients who met the inclusion criteria, 22 of whom were female and 23 underwent resective surgery of the left temporal lobe. Of the 42 patients, 29

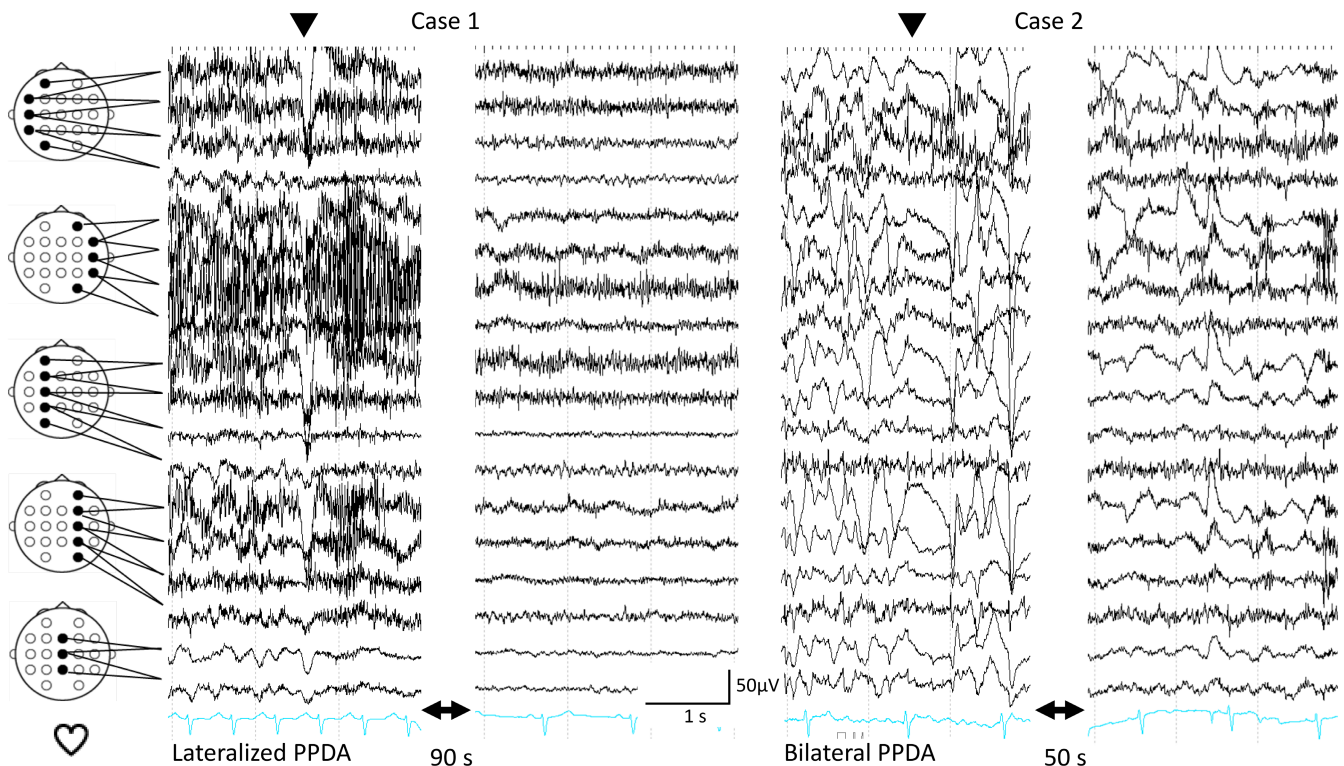


FIGURE 1 Representative electroencephalograms of ictal offsets, indicated with arrowheads, and postictal segments of two patients diagnosed with right temporal lobe epilepsy. Patient 1 (left) has right-hemispheric postictal polymorphic delta activity (PPDA), or lateralized PPDA, and patient 2 (right) has bilateral PPDA

(69%) patients were seizure-free (group A) and 13 (31%) patients continued to have persistent seizures (group B). Sex and side of surgery did not statistically differ between the groups ($P = 0.59, 0.21$, respectively). The median ages (with IQR) at seizure onset, surgery, and epilepsy duration also showed no statistically significant differences between the groups (Table 1). No statistically significant correlation was observed between the standard anterior temporal lobectomy (ATL) and selective amygdalohippocampectomy (SAH) in group A vs. group B ($P = 0.19$). From a pathological standpoint, hippocampal sclerosis (HS) was found in 19 patients (45.2%), tumors in 11 (26.2%), vascular malformations in five (11.9%), cortical atrophy in four (9.5%), cortical dysplasia in two (4.8%), and dual pathology of HS and vascular malformation in one (2.4%). There were no statistically significant differences between prognosis and the five pathological entities ($P = 0.43, 0.27, 1.00, 0.50, \text{ and } 1.00$, respectively).

3.2 | Relationship between postoperative seizure outcome and electroencephalography parameters (ictal duration, lateralization of ictal, postictal, and interictal electroencephalography findings)

The median and IQR of the ictal duration of groups A and B were 60 (48-92.5) for group A and 67 (57-137.5) for group B, respectively. No statistically significant differences were observed between the groups ($P = 0.18$).

Comparisons of the distributions of EEG parameters between the two groups are shown in Table 2. In all analyzed ictal EEG, the pattern at onset (PAO) lateralized to the affected temporal lobe. In contrast, the ictal latent significant pattern (LSP) presented a variety of distributions. Specifically, most subjects showed bilateral ictal LSPs, with 79.3% and 92.3%, respectively, in groups A and B, without a statistically significant difference ($P = 0.41$).

TABLE 1 Comparisons of quantitative characteristics between the two groups

Characteristic	Group A	Group B	Median difference ^a	P value
	(n = 29)	(n = 13)		
	Median (IQR)	Median (IQR)		
Age at seizure onset (y)	15 (9–22)	17 (8–23.5)	1 (–7 to 7)	0.87
Age at surgery (y)	34 (24.5–50)	31 (21.5–43.5)	–4 (–13 to 6)	0.36
Epilepsy duration (y)	17 (8–25)	16 (8.5–22)	–1 (–9 to 5)	0.73

^aThe median difference (95% confidence interval) was calculated using the Hodges-Lehmann estimator.

TABLE 2 Comparisons of EEG parameter distributions between the two groups

EEG parameters	Group A (n = 29) (Seizure free for 1y after surgery)	Group B (n = 13) (Seizure persistent after surgery)	P value (FET)
Ictal LSP			0.41
Lateralized	6 (20.7%)	1 (7.7%)	
Bilateral	23 (79.3%)	12 (92.3%)	
PPDA			0.003
No	4 (13.8%)	1 (7.7%)	
Lateralized	22 (75.9%)	4 (30.8%)	
Bilateral	3 (10.3%)	8 (61.5%)	
IEDs			0.001
No	2 (6.9%)	0 (0.0%)	
Lateralized	23 (79.3%)	4 (30.8%)	
Bilateral	4 (13.8%)	9 (69.2%)	
IRSA			0.52
No	6 (20.7%)	2 (15.4%)	
Lateralized	19 (65.5%)	7 (53.8%)	
Bilateral	4 (13.8%)	4 (30.8%)	

Abbreviations: FET, Fisher's exact test; IEDs, Interictal epileptiform discharges; IRSA, Interictal rhythmic slow activity; LSP, late significant pattern; PPDA, Postictal polymorphic delta activity.

Regarding the distribution of postictal results, we found a statistically significant difference between the groups. In detail, group A had a higher number of no PPDA (13.8%: 7.7%) and lateralized PPDA (75.9%: 30.8%) and a lower number of bilateral PPDA (10.3%: 61.5%), compared with group B ($P = 0.003$). We found a statistically significant difference in the distribution of IEDs between the groups. Notably, compared with group B, group A had a higher number of no IEDs (6.9%: 0%) and lateralized IEDs (79.3%: 30.8%) and a lower number of bilateral IEDs (13.8%: 69.2%) ($P = 0.001$). In the distribution of the IRSA, we did not find a statistically significant difference between the groups ($P = 0.52$). Moreover, no statistically significant correlation was found for spatial distributions between PPDA and IRSA ($P = 0.21$).

With regard to individual patient results, the combined analyses of either the absence or lateralized distribution of both IEDs and PPDA showed significantly more frequent seizure freedom outcomes (75.9%: 15.4%) (Table 3). Interestingly, the combined analysis of both bilateral PPDA and IEDs revealed significantly more frequent seizure persistence after surgery ($P < 0.0001$), as illustrated in Table 4.

Table 5 shows predictors of the likelihood of persistent seizures. Regression analysis was performed for identifying potential preoperative predictors of seizure persistence since the bilateral nature of EEG parameters (ictal LSP, PPDA, IEDs, and IRSA), sex, history of GTCs, and side of temporal lobe were affected. The predictors without significant correlation were excluded from the multiple regression analysis and only significant predictors were included. The logistic regression model was statistically

significant ($\chi^2 [2] = 20.65, P < 0.001$). The model correctly classified 83.3% of patients, with 46.2% sensitivity and 100% specificity. Thus, bilateral PPDA and IEDs were identified as statistically significant independent predictors. Patients with bilaterally distributed PPDA or IEDs had 13.50- or 13.72- times, respectively, higher odds of persisted seizures within 1 year of surgery.

4 | DISCUSSION

This study revealed that the bilateral distribution of postictal delta activity was associated with poor postoperative seizure outcomes in patients with TLE. In addition, we found that the combined analysis of both IEDs and PPDA provided better biomarkers for surgical outcomes in patients with TLE. To date, few studies have addressed the role of postictal delta activity in the presurgical evaluation of intractable epilepsy. Our study sheds light on the clinical role of postictal slow activity as a biomarker for predicting surgical outcomes for TLE.

Our findings align with those of a previous postictal scalp EEG study, in which TLE used the same criteria for PPDA localization.¹² They discovered that lateralized PPDA occurred in 70% of FIAS of temporal lobe origin with a lateralization value of approximately 90% when present. Nonetheless, the investigators did not discuss the significance of the role of bilateral PPDA in their study. They only focused on the lateralized PPDA value and did not investigate its relation with postoperative seizure outcome.¹² Our results are also supported by an earlier intracranial study of postictal slow focus (PISF) in FIAS

TABLE 3 Conflicts and concordance between IEDs and PPDA regarding their spatial distribution per individual patient for both group A and group B

IEDs	Group A (n = 29) (Seizure free after surgery)		Group B (n = 13) (Seizure persistent after surgery)	
	PPDA		PPDA	
	Lateralized/not	Bilateral	Lateralized/not	Bilateral
Lateralized / not	22 (75.9%)	3 (10.3%)	2 (15.4%)	2 (15.4%)
Bilateral	4 (13.8%)	0 (0%)	3 (23.1%)	6 (46.1%)

Abbreviations: IEDs, Interictal epileptiform discharges; PPDA, postictal polymorphic delta activity.

TABLE 4 Group comparison for single versus combined analysis of IED and PPDA bilaterality

Modality	Group A (n = 29) (Seizure free for 1 year after surgery)	Group B (n = 13) (Seizure persistent after surgery)	P value (FET)
Bilateral PPDA	3 (10.3%)	8 (61.5%)	0.001
Bilateral IEDs	4 (13.8%)	9 (69.2%)	0.001
Combined analysis of Bilateral IEDs and Bilateral PPDA	0 (0.0%)	6 (46.2%)	<0.0001

Abbreviations: Fisher's exact test (FET); PPDA, Postictal polymorphic delta activity (PPDA); IEDs, Interictal epileptiform discharges (IEDs).

TABLE 5 Predictors of the likelihood of persistent seizure within 1 year after surgery

Predictor	Multivariable regression analysis		
	P value	AOR	95% CI
PPDA	0.009		
Lateralized or not		r (1)	r (1)
Bilateral		13.50	1.90–95.88
IEDs	0.006		
Lateralized or not		r (1)	r (1)
Bilateral		13.72	2.12–88.87

Abbreviations: AOR; Adjusted odds ratio; r (1), Reference category; 95% CI, confidence interval; PPDA, postictal polymorphic delta activity; IEDs, Interictal epileptiform discharges.

electrocorticograms of 64 patients with intractable focal epilepsy. The researchers found that 75% of the patients presented PISF more frequently in seizures of temporal lobe origin. Furthermore, they found a strong correlation between the occurrence of lateralized PISF and favorable seizure outcomes following temporal lobe surgery.⁶ Considering these past reports and this study, we stress the importance of evaluating the postictal EEG features when determining whether a candidate should be offered surgery.

Poor surgical prognosis in bilateral PPDA may be explained by the “involved distributed propagation network” theory, which was clarified by intracranial EEG studies of postictal EEG delta activity.^{7,8} These studies revealed that seizures that engage distributed propagation networks (distributed-network, DN) exhibited a more significant postictal increase in delta power and broadband connectivity than those with the focal network (FN). The network mechanisms driving widespread postictal EEG changes are poorly understood, but a leading hypothesis is that following seizure termination, deactivated subcortical relay nuclei can serve as hubs or “gateways” to facilitate widespread seizure propagation.^{7,8} We speculate that some characteristic seizure propagation mechanisms, with which bilateral PPDA appears, might be associated with epileptogenesis, although clarifying their causality is challenging.¹⁵ We did not detect any relationship between seizure outcomes and essential characteristics, such as age at seizure onset, age at surgery, epilepsy duration, and ictal duration. However, our data are consistent with those of other studies and support that neither long epilepsy duration nor prolonged seizure activity plays a role in the development of a widespread epileptic network.^{14,16} Notably, a previous study analyzed scalp ictal EEG patterns, including ictal LSP, which refers to ictal propagation to the [contralateral](#) side. The investigators found no significant correlation between the ictal

LSP pattern and postsurgical seizure outcomes, which is in line with our results.¹¹

Our IRSA distribution findings are consistent with those of Koutroumanidis et al. They correlated the lateralization of presurgical interictal temporal delta activity in TLE with the pathology and outcome after temporal lobe resection. They reported lateralized slow activity in 66% of 141 patients, showing no statistically significant difference between the favorable and unfavorable outcomes in the lesional epilepsy group.¹³ Meanwhile, Wu et al. and Tatum et al. considered IRSA as a significant indicator of poor surgical outcomes in their studies.^{17,18} Their contradictory findings may be explained by applying different treatment strategies, namely, laser ablation in their study and surgical resection in our study, in addition to the different distributions of possible EZ. Laser ablation is a less invasive treatment option for temporal lobe epilepsy. However, as the procedure is not an “actual” resection, it may fail to sacrifice EZ completely, with a lower chance of achieving an Engel-I outcome for intractable TLE relative to conventional surgical procedures (ATL and SAH).¹⁹ Moreover, Tatum et al. found that the postoperative development of temporal intermittent rhythmic delta activity, or TIRDA (de novo), in 10 patients post-laser interstitial thermal therapy (LITT), serves as a biomarker for predicting unsuccessful seizure outcomes following LITT. It is an early indicator for ATL, while no statistically significant relationship was observed between the presence of preoperative TIRDA in four patients and seizure recurrence post LITT.¹⁷

Our IED distribution results are consistent with previous literature, where bilateral interictal abnormalities were identified to frequently present in temporal plus epilepsies and associate with poor surgical outcomes in TLE.^{20,21} This finding is also compatible with a recent multicenter cohort study that highlighted the importance of the distribution of interictal epileptiform discharges in predicting epilepsy surgery outcomes.⁴

An individual case analysis of favorable outcomes found four (13.8%) patients who presented with bilateral IEDs only, without bilateral PPDA, and three (10.3%) patients with bilateral PPDA only without bilateral IEDs. This observation implies that a single analysis of IED and PPDA may only limit the identification of appropriate surgical candidates for TLE. In contrast, there was no concordance between the bilateral distributions of IEDs and PPDA per patient among postoperative seizure-free patients (group A). Thus, a combined analysis of both IEDs and PPDA may be key for epilepsy surgery in TLE.

Our study had some limitations. First, it included a small number of patients, which makes it difficult to assess the statistical significance of some variable associations. Second, this study had inherent limitations related

to its retrospective design. Consequently, a prospective large cohort study is needed to investigate the spatial distribution of preoperative scalp EEG parameters, especially PPDA, and to evaluate their predictive value for favorable postoperative seizure outcomes.

In conclusion, our analysis of postictal delta activity during presurgical evaluation may allow us to predict the prognosis of postoperative seizure status in TLE. Moreover, the combined analysis of PPDA and IEDs during routine presurgical scalp EEG evaluations may facilitate clinical decision-making and enable more precise predictions of surgical outcomes.

AUTHOR CONTRIBUTIONS

S. Shaaban contributed to the acquisition and analysis of the data and drafted the manuscript. Y. Kakisaka contributed to the acquisition and analysis of data and writing of the manuscript. T. Belal designed the study and contributed to the writing of the manuscript; I. Elmenshawi conceived and designed the study; N. Nakasato contributed to the conception and design of the study; and all authors reviewed and approved of the final manuscript.

ACKNOWLEDGMENTS

The researcher (S. Shaaban) received a joint supervision scholarship from the Ministry of Higher Education of the Arab Republic of Egypt. All authors thank the members of the Department of Epileptology of Tohoku University Hospital for their efforts and contribution to this study.

CONFLICT OF INTEREST

None of the authors have any conflicts of interest to disclose. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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How to cite this article: Shaaban S, Kakisaka Y, Belal T, Jin K, Osawa S-i, Tominaga T, et al. Distribution of postictal slowing has an additional yield to interictal epileptiform discharge in predicting surgical outcomes in temporal lobe epilepsy. *Epilepsia Open*. 2022;7:802–809. <https://doi.org/10.1002/epi4.12660>