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Research Article

Candidate Selection for Implantation: Noninvasive Predictors of Seizure Onset Zone Focality and Surgical Outcome in People with Drug-Resistant Epilepsy Evaluated by Intracranial Video-EEG Monitoring—A Retrospective Cohort Study

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Objectives. People with drug-resistant epilepsy are potential candidates for epilepsy surgery, a subset of whom requires intracranial video-EEG monitoring (IVEM) to determine the seizure onset zone (SOZ). The purpose of this study is to investigate noninvasive predictors of SOZ focality and surgical outcome in order to optimise case selection for this procedure. *Materials and Methods*. We performed a retrospective cohort study of patients who underwent IVEM at our centre from January 2006 to July 2021. We applied a multivariate logistic regression model to estimate the effect of potential noninvasive data as influencing factors for both SOZ focality and surgical outcome. A focal SOZ included a sublobar onset on IVEM, and a good surgical outcome was defined as Engel class I. *Results*. A total of 783 underwent a presurgical evaluation, 102 of them with IVEM. Ninety-seven patients were included in the SOZ focality analysis, and 64 were included in the surgical outcome analysis. The presence of focal to bilateral tonic-clonic seizures ($p = 0.03$) and generalised interictal epileptiform discharges (IEDs) during scalp EEG ($p = 0.02$) predicted a nonfocal SOZ. A weekly ($p = 0.01$) or daily seizure frequency ($p < 0.01$), focal to bilateral tonic-clonic seizures ($p = 0.01$), nonlesional MRI ($p < 0.01$), and multifocal ($p = 0.02$) or generalised IEDs ($p < 0.01$) were associated with a poor surgical outcome. *Conclusions*. A high seizure frequency, positive history of focal to bilateral tonic-clonic seizures, nonlesional MRI, and generalised and multifocal IEDs are noninvasive factors that may aid in selecting candidates for IVEM.

1. Introduction

Epilepsy affects approximately 0.5% of the population, which makes it one of the most common neurological diseases [1]. About one-third of all people with epilepsy continue to suffer from epileptic seizures despite adequate pharmacological treatment [2, 3]. Some of them can be treated with epilepsy surgery and become seizure-free after successful intervention [4]. Epilepsy surgery is aimed at improving seizure control by resection of the epileptogenic zone, defined as the area of the cortex that is necessary and sufficient for initiating seizures and whose removal (or disconnection) is necessary for complete abolition of seizures [5]. At the same time, it tries to avoid neurological or neuropsychological deficits preserving essential brain areas [6]. To identify suitable candidates, people with drug-resistant epilepsy (DRE) are usually evaluated in an epilepsy video-EEG monitoring unit [7]. While frequently noninvasive diagnostic methods are sufficient to determine an adequate resection strategy, a subgroup of patients may require intracranial video-EEG monitoring (IVEM) [8]. IVEM

is aimed at localising the seizure onset zone (SOZ), which is defined as the area of the cortex from which clinical seizures are generated, providing an approximation of the epileptogenic zone [9, 10]. In contrast to scalp video-EEG monitoring (SVEM), IVEM is an invasive procedure with all its inherent disadvantages and potential harmful effects. For instance, this procedure implies some risk of infection or intracranial bleeding [11, 12]. In addition, IVEM techniques such as stereoelectroencephalography (SEEG) can be expensive and complex [13]. They require highly trained professionals specialised in epilepsy such as neurosurgeons, neurologists, nurses, or EEG technicians, which are usually only available in a limited number of epilepsy centres in each country [8]. Furthermore, not all patients who undergo IVEM will ultimately benefit from it [14–16]. Different factors may influence the outcome; these include IVEM candidate selection, implantation strategy, subsequent interpretation of the IVEM recordings, and the adequacy of the surgical procedure [17]. For example, in some cases, surgery is not recommended due to a nonfocal SOZ or, conversely, patients are operated on, but seizure control does not improve significantly [14, 16].

Many studies have addressed prognostic factors for postoperative outcome in epilepsy surgery [14, 18, 19]. For example, normal MRI, left hemispheric seizure onset, and use of IVEM have been associated with a poor outcome, while unilateral interictal epileptiform discharges (IEDs) on SVEM and focal lesions on MRI have been associated with a good outcome [19]. Other factors such as generalised IEDs on SVEM data have shown contradictory results [20, 21]. However, few studies have been carried out on predictors for IVEM results based on information from noninvasive presurgical workup [15, 22], and only one study assessed the extent of SOZ [23]. Both postoperative outcome and SOZ focality predictors could be useful in deciding which patients are the best candidates for IVEM. For this reason, we aimed to investigate noninvasive predictive factors for SOZ focality on IVEM and noninvasive prognostic factors of surgical outcome in patients who underwent surgery following IVEM. We focused on factors which are available before an IVEM that previously have been found to be related to a focal SOZ and postsurgical outcome, so they can be used in patient selection. Another aim of this study was to test if these factors coincided and if there was a relationship between SOZ focality and surgical outcome. Finally, we described the clinical features of patients with generalised IEDs to help clarify contradictions in available literature.

2. Material and Methods

2.1. Population and Data Collection. We searched our local database for people with DRE who underwent presurgical evaluation in the refractory epilepsy unit of the University Hospital La Fe in Valencia from January 2006 to July 2021. Data were extracted from the clinical records after chart review. For the statistical analysis, two cohorts were defined, the first of which is the diagnostic cohort which included people with DRE evaluated by SVEM and IVEM. Excluded were all patients with an inconclusive IVEM result in which case no spontaneous typical seizures were recorded and therefore SOZ focality could not be determined. The surgical cohort (the second of the two) was defined as patients who underwent resective surgery following IVEM with a follow-up of at least one year after surgery. The reasons why patients evaluated by IVEM did not undergo surgery and were excluded from the surgical cohort were as follows: (1) a recommendation against a resective surgery due to a nonfocal SOZ (specifically, a large multilobar or bilateral involvement), (2) complete overlapping of eloquent cortex with SOZ (a partial overlap was not a contraindication for resective surgery), (3) clinical improvement after SEEG-guided radiofrequency thermocoagulation treatment only, (4) waiting for a recommended resective surgery, and (5) refusal of a recommended resective surgery after clinical improvement. The study protocol was approved by the local medical ethical committee of the Health Research Institute Hospital La Fe, Valencia; and informed consent was waived because of the retrospective nature of this study. The protocol was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines (see Supporting Information (available here)) [24].

2.2. Electrode Implantation and Intracranial Video-EEG Monitoring. According to the current protocol at the refractory epilepsy unit, IVEM was performed on patients where noninvasive presurgical workup (cerebral MRI, SVEM, neuropsychological tests, fluorodeoxyglucose-positron emission tomography, and subtraction ictal single-photon emission computed tomography coregistered with MRI) had been inconclusive or divergent, to further delimitate the SOZ or if an exploration of the eloquent cortex was needed. Consequently, patients with nonlesional MRI (strictly normal or nonspecific findings) were evaluated for potential implantation. The presence of any finding suggestive of temporal plus epilepsy (distinctive semiological features or bilateral, frontal, or parietotemporal EEG activity) was considered an indication for IVEM [25]. Finally, patients with lesional extratemporal epilepsy underwent IVEM in the subsequent circumstances: multilobar lesions, nonlocalising EEG, or incongruence between MRI and other noninvasive data (especially EEG) [8, 22]. Total length of the IVEM procedure was seven to ten days.

Two types of electrodes were used to perform invasive recording: (1) implantation of subdural electrodes (strip and grid cortical electrodes, Cortac®, PMT Corporation, Chanhassen, USA) or (2) implantation of depth electrodes (Depthalon®, PMT Corporation, Chanhassen, USA, or MICRODEEP®, DIXI medical, Marchaux-Chaudefontaine, France). The implantation strategy was performed on each patient based on semiology and the result of the noninvasive presurgical workup. Subdural electrodes were placed after an open craniotomy for grid electrodes or burr holes for strip electrodes. Depth electrodes under SEEG methodology were implanted guided by the utilization of a stereotactic frame (from 2006 to September 2018) or by a robotic system (neuromate®, Renishaw, Wotton-under-Edge, United Kingdom) (from October 2018). Correct electrode placement was verified by coregistering both cerebral MRI before implantation and cerebral computer tomography after implantation.

2.3. Statistical Analysis and Variable Description. Three statistical analyses were performed. In the first analysis, we applied a multivariate logistic regression model to the diagnostic cohort to assess prognostic factors on SOZ focality (one standing for focal SOZ which was defined as a sublobar onset on IVEM evaluation and zero standing for nonfocal SOZ which included a lobar, multilobar, or bilateral onset on IVEM) [23]. As explanatory variables, we used the following variables: continuous variables being age at IVEM evaluation (years) and epilepsy duration (years) and categorical variables being gender (male or female), baseline seizure frequency (due to highly right-skewed distribution, we divided the baseline seizure frequency into three categories: monthly (one or more seizures per month but less than once a week), weekly (one or more seizures a week but less than once a day), and daily seizure frequency (one or more seizures a day)), history of focal to bilateral tonic-clonic seizures (yes or no response), results of high-resolution MRI (nonlesional, focal lesion (where a sublobar area was affected), or nonfocal lesion (a lobar, multilobar, or bilateral involvement)), IEDs on SVEM (normal/focal only, multifocal only, or generalised), ictal onset on SVEM (focal, multifocal, or nonlocalising), hemispheric lateralisation (left hemisphere, right hemisphere, or unknown), lobar localisation hypothesis (temporal lobe epilepsy or extratemporal lobe epilepsy), and type of IVEM (SEEG or subdural electrodes). Focal ictal onset was defined as all seizures starting in the same EEG region and side, multifocal ictal onset as seizures starting in more than one EEG region or side, and nonlocalising ictal onset as generalised EEG changes (e.g., diffuse suppression) or obscured onset due to a movement artifact. Lateralisation and localisation hypotheses were based on ictal and interictal EEG, MRI findings, localising ictal semiology, and localising neuropsychological deficits. Variable IVEM (SEEG or subdural electrodes) was used as the type of IVEM can be chosen before implantation thus affecting the results.

In the second analysis and using the same explanatory variables as in the first analysis, we applied a multivariate logistic regression model to the surgical cohort to evaluate possible prognostic factors on the outcome of epilepsy surgery following IVEM (one standing for a good outcome and zero standing for a poor outcome). A good outcome was defined as Engel class I, and a poor outcome was defined as Engel class II to IV [19, 26]. Furthermore, follow-up in the good and poor outcome groups was compared using a t-test. Finally, in the third analysis, a univariate logistic regression model was applied to the surgical cohort to investigate if SOZ focality on IVEM correlated with the surgical outcome. Data are given as mean and standard deviation. p values ≤ 0.05 were considered significant. The statistical analysis was performed with R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Diagnostic and Surgical Cohort Description. During the study period, a total of 783 people with DRE underwent a presurgical evaluation, 102 of which fulfilled inclusion criteria and underwent IVEM. Five were excluded as spontaneous typical seizures were not recorded. Ninety-seven were part of the diagnostic cohort (39 with focal SOZ and 58 with nonfocal SOZ) and were included in the first analysis. Twelve patients (12.4%) demonstrated significant clinical improvement after SEEG-guided radiofrequency thermocoagulation and thus did not undergo resective surgery. Following this, sixty-four (66%) were operated on and had at least one year of follow-up, of which 23 had a good outcome and 41 had a poor outcome. These then comprised the surgical cohort and underwent a second and a third analysis (Figure 1). Fifty percent with focal SOZ and 65.9% of nonfocal SOZ cases underwent a bilateral SEEG implantation. Among patients with more than 15 electrodes on SEEG, just one had a focal SOZ, and none achieved a good surgical outcome. Only 13.8% of nonfocal SOZ patients reached an Engel class I outcome versus 38.5% of cases with a focal SOZ. Table 1 summarizes the characteristics of both cohorts.

3.2. Statistical Analysis. In the first analysis ($n = 97$), focal SOZ included those with a sublobar onset on IVEM ($n = 39$), whereas patients with a lobar, multilobar, or bilateral onset were classified as nonfocal SOZ ($n = 58$). In the multivariate analysis adjusted for all variables, a positive history of focal to bilateral tonic-clonic seizures ($p = 0.03$) and generalised IEDs ($p = 0.02$) on SVEM were associated with a decreased OR of having a focal SOZ (Table 2). For the second analysis ($n = 64$), a good outcome was equivalent to Engel class I ($n = 23$), while a poor outcome was defined as Engel class II-IV ($n = 41$). The same variables as the first analysis were statistically significant (presence of focal to bilateral tonic-clonic seizures ($p = 0.01$) and generalised IEDs ($p < 0.01$)), but also weekly ($p = 0.01$) or daily seizures ($p < 0.01$), a nonlesional MRI ($p < 0.01$), and multifocal IEDs ($p = 0.02$) (Table 2). Follow-up was similar ($p = 0.52$), with 6 ± 3.1 years in the good outcome group and 5.5 ± 3.4 years in the poor outcome group. According to the third analysis ($n = 64$), a focal SOZ was associated with a good outcome (OR 5.11, 95% CI [1.7, 15.39], $p < 0.01$).

3.3. Cases with Generalised IEDs. Eighteen of 97 cases presented generalised IEDs (Table 3). The most frequent localisation hypothesis was a frontal lobe epilepsy (FLE) (10 cases). The majority of patients had seizures with a nonlocalising onset (13 cases) and tonic posturing on semiology (12 cases). Twelve had a poor surgical outcome or contraindication for surgery due to a multilobar or bilateral SOZ, and ten of them had generalised paroxysmal fast activity, with or without slow spike-and-wave. From the four patients who had a good surgical outcome or improved after SEEG-guided radiofrequency thermocoagulation, none showed generalised paroxysmal fast activity or slow spike-and-wave, and the IEDs consisted of generalised fast spike-and-wave and/or sporadic spikes. An EEG example of each pattern is represented (Figure 2).

4. Discussion

4.1. Main Results. The present study shows that people with DRE and a positive history of focal to bilateral tonic-clonic

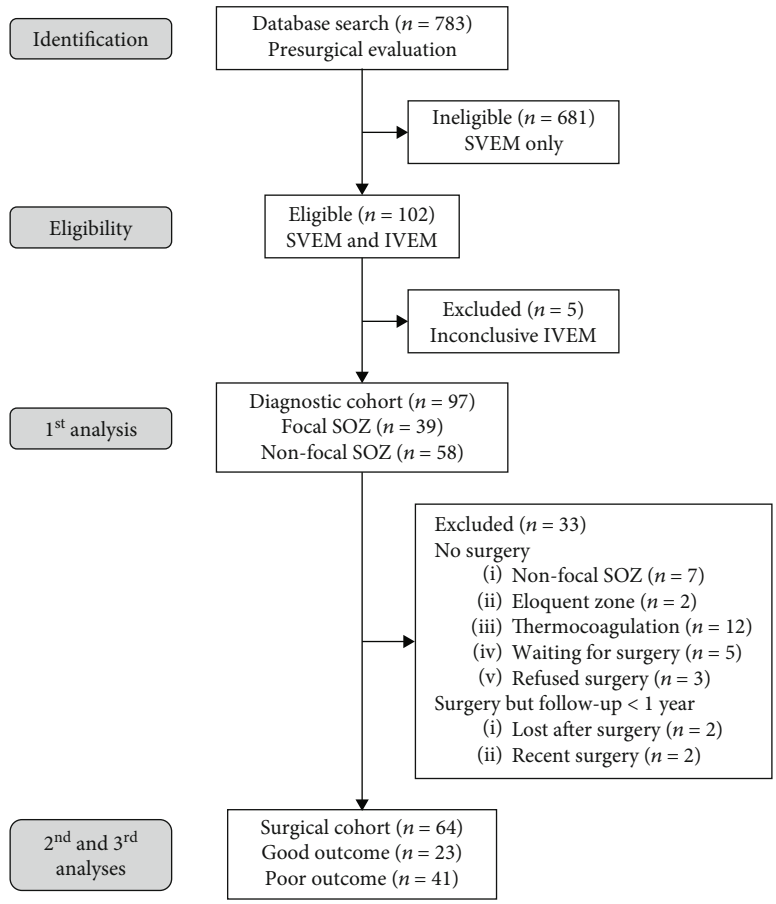

Figure 1: STROBE flow diagram of all people with DRE included in our study. Abbreviations: IVEM: intracranial video-EEG monitoring; DRE: drug-resistant epilepsy; SOZ: seizure onset zone; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology; SVEM: scalp video-EEG monitoring.

seizures or generalised IEDs on SVEM are more likely to have a nonfocal SOZ. These two factors in addition to high seizure frequency (weekly or daily), a nonlesional MRI, and multifocal IEDs on SVEM decrease the chances of a good surgical outcome. This study demonstrated a clear relationship between a focal SOZ and a good prognosis. Moreover, it showed a specific pattern (generalised paroxysmal fast activity) in patients presenting a poor surgical outcome or an extensive SOZ that precluded a resective surgery.

4.2. Surgery Outcome. Engel class I outcome was achieved in 35.9% of our patients, which is in the range of 33% to 62% of previously published studies [17, 27, 28]. This low percentage in comparison could be explained by the relatively high ratio of complex patients with bilateral SEEG implantations (50% focal SOZ and 65.9% nonfocal SOZ), the long mean postoperative follow-up (about 6 years), and the percentage of surgical cases (66%). In our study, only 7 of 58 patients with a nonfocal SOZ were ruled out for surgery. In contrast, other studies with a lower percentage of patients who had undergone surgery could achieve a higher Engel class I outcome ratio, probably due to stricter candidate selection criteria for surgery [16]. The high proportion of bilateral SEEG and the high number of electrodes in some patients (more than 15 electrodes in 5 cases) may also suggest that preimplantation hypotheses were not strong enough for these cases [8, 29]. In addition, 12.4% of the diagnostic cohort did not undergo resective surgery because of substantial clinical improvement or seizure freedom after SEEG-guided radiofrequency thermocoagulation. Some of these patients would probably also have benefited from the surgery.

4.3. Predictive Factors. A positive history of focal to bilateral tonic-clonic seizures was related to both a poor outcome and a nonfocal SOZ in our study. The association with surgical prognosis has also been demonstrated in other studies [30–34]. A focal seizure originating from an extensive SOZ appears more likely to spread to a distant cortex and evolve to a bilateral tonic-clonic seizure. An extensive and highly interconnected SOZ is also more difficult to completely resect, which promotes postoperative seizure recurrence [35].

We also found that generalised IEDs on SVEM were related to a nonfocal SOZ on IVEM, and both multifocal and generalised IEDs decreased the chances of having a good surgical outcome. Consistently, other studies found that unilateral IEDs led to a better outcome [19, 31, 36] and generalised IEDs in FLE did not [20]. The 5-SENSE score study

Table 1: Diagnostic and surgical cohort description.

Variable	Diagnostic cohort[a] ($n = 97$)		Surgical cohort[b] ($n = 64$)	
	Focal SOZ ($n = 39$)	Nonfocal SOZ ($n = 58$)	Good outcome ($n = 23$)	Poor outcome ($n = 41$)
Epilepsy duration (years)	23.6 ± 14.3	23.6 ± 11.8	25.2 ± 15.7	23.5 ± 19.9
Age at evaluation (years)	35.6 ± 11.6	35.3 ± 12.2	34.8 ± 13.2	34.4 ± 10.6
Gender (male)	22 (56.4)	29 (50)	13 (56.5)	21 (51.2)
Seizure frequency				
Daily	7 (17.9)	13 (22.4)	2 (8.7)	11 (26.8)
Weekly	21 (53.8)	35 (60.3)	12 (52.2)	23 (56.1)
Monthly	11 (28.2)	10 (17.2)	9 (39.1)	7 (17.1)
Presence of FBTCS	25 (64.1)	42 (72.4)	15 (65.2)	31 (75.6)
Failed ASMs	8.4 ± 3	10.1 ± 4.3	8.2 ± 3	10.2 ± 4.5
MRI lesion group				
Focal lesion	8 (20.5)	9 (15.5)	6 (26.1)	3 (7.3)
Nonfocal lesion	8 (20.5)	12 (20.7)	6 (26.1)	8 (19.5)
Nonlesional	23 (59)	37 (63.8)	11 (47.8)	30 (73.2)
MRI lesion type				
MTS alone or associated	5 (12.8)	5 (8.6)	6 (26.1)	2 (4.9)
CDM	9 (23.1)	11 (19)	4 (17.4)	7 (17.1)
Others	2 (5.1)	5 (8.6)	2 (8.7)	2 (4.9)
Normal or nonspecific	23 (59)	37 (63.8)	11 (47.8)	30 (73.2)
SVEM IEDs				
Normal or focal only	24 (61.5)	28 (48.3)	15 (65.2)	21 (51.2)
Multifocal only	12 (30.8)	15 (25.9)	6 (26.1)	11 (26.8)
Generalised	3 (7.7)	15 (25.9)	2 (8.7)	9 (22)
SVEM ictal onset				
Focal	23 (59)	27 (46.6)	12 (52.2)	23 (56.1)
Multifocal	2 (5.1)	9 (15.5)	3 (13)	3 (7.3)
Nonlocalising	14 (35.9)	22 (37.9)	8 (34.8)	15 (36.6)
Localisation hypothesis				
TLE	21 (53.8)	31 (53.4)	16 (69.6)	18 (43.9)
FLE	10 (25.6)	17 (29.3)	7 (30.4)	14 (34.1)
PLE or OLE	7 (17.9)	4 (6.9)	0	5 (12.2)
TLE and ETE	1 (2.6)	6 (10.3)	0	4 (9.8)
Lateralisation hypothesis				
Left	20 (51.3)	26 (44.8)	9 (39.1)	21 (51.2)
Right	15 (38.5)	17 (29.3)	10 (43.5)	13 (31.7)
Unknown	4 (10.3)	15 (25.9)	4 (17.4)	7 (17.1)
IVEM type (SEEG/subdural electrodes)	30/9	44/14	17/6	25/16
Bilateral SEEG	15 (50)	29 (65.9)	11 (64.7)	15 (60)
SEEG > 15 electrodes	1 (3.3)	7 (15.9)	0	5 (20)
SOZ focality				
Sublobar	39 (100)	NA	15 (65.2)	11 (26.8)
Lobar	NA	22 (37.9)	5 (21.7)	13 (31.7)
Multilobar	NA	20 (34.5)	2 (8.7)	11 (26.8)
Bilateral	NA	16 (27.6)	1 (4.3)	6 (14.6)

Table 1: Continued.

Variable	Diagnostic cohort[a] ($n = 97$)		Surgical cohort[b] ($n = 64$)	
	Focal SOZ ($n = 39$)	Nonfocal SOZ ($n = 58$)	Good outcome ($n = 23$)	Poor outcome ($n = 41$)
Surgical outcome				
Engel class I	15 (38.5)	8 (13.8)	23 (100)	NA
Engel class II	6 (15.4)	9 (15.5)	NA	15 (36.6)
Engel class III	3 (7.7)	10 (17.2)	NA	13 (31.7)
Engel class IV	2 (5.1)	11 (19)	NA	13 (31.7)
Follow – up < 1 year or no surgery	13 (33.3)	20 (34.5)	NA	NA
Follow-up after surgery (years)	NA	NA	6 ± 3.1	5.5 ± 3.4

Note: data are given in mean ± standard deviation for continuous variables or number (percentage) for categorical variables. Abbreviations: ASMs: antiseizure medications; CDM: cortical development malformation; ETE: extratemporal epilepsy; FBTCS: focal to bilateral tonic-clonic seizures; FLE: frontal lobe epilepsy; IEDs: interictal epileptiform discharges; IVEM: intracranial video-EEG monitoring; MRI: magnetic resonance imaging; MTS: mesial temporal sclerosis; NA: not applicable; OLE: occipital lobe epilepsy; PLE: parietal lobe epilepsy; SEEG: stereoelectroencephalography; SOZ: seizure onset zone; SVEM: scalp video-EEG monitoring; TLE: temporal lobe epilepsy. [a]The diagnostic cohort comprised people with DRE evaluated by IVEM with a conclusive result. Focal SOZ was defined as a sublobar ictal onset identified on IVEM. Nonfocal SOZ included a lobar, multilobar, or bilateral ictal onset on IVEM. [b]The surgical cohort was defined as patients evaluated by IVEM who underwent a surgery and a minimum follow-up of one year. Good outcome was considered as a postoperative outcome of Engel class I. Poor outcome included a postoperative outcome of Engel class II or worse.

Table 2: Diagnostic and surgical cohort analysis.

Variable	Category	Diagnostic cohort ($n = 97$)			Surgical cohort ($n = 64$)		
		OR	[95% CI]	p value	OR	[95% CI]	p value
Epilepsy duration		0.97	[0.92, 1.02]	0.27	1.01	[0.93, 1.11]	0.8
Age at evaluation		1.02	[0.96, 1.08]	0.57	0.91	[0.81, 1.02]	0.09
Gender	Male	1.33	[0.49, 3.6]	0.57	0.47	[0.09, 2.43]	0.37
Seizure frequency	Weekly	0.42	[0.12, 1.48]	0.18	0.05	[<0.01, 0.52]	0.01*
	Daily	0.23	[0.04, 1.47]	0.12	<0.01	[<0.01, 0.15]	<0.01**
Presence of FBTCS	Yes	0.28	[0.09, 0.9]	0.03*	0.07	[<0.01, 0.57]	0.01*
MRI lesion group	Nonfocal	1.06	[0.19, 5.84]	0.95	0.2	[0.01, 3.35]	0.26
	Nonlesional	0.84	[0.21, 3.27]	0.8	0.02	[<0.01, 0.37]	<0.01**
SVEM IEDs	Multifocal only	1.11	[0.34, 3.58]	0.86	0.07	[<0.01, 0.67]	0.02*
	Generalised	0.13	[0.02, 0.68]	0.02*	<0.01	[<0.01, 0.26]	<0.01**
SVEM ictal onset	Multifocal	0.29	[0.03, 2.67]	0.28	0.37	[<0.01, 13.98]	0.59
	Nonlocalising	1.43	[0.42, 4.85]	0.57	1.5	[0.19, 11.65]	0.7
Localisation hypothesis	ETE	1.49	[0.44, 5.08]	0.52	2.48	[0.26, 23.35]	0.43
Lateralisation hypothesis	Right	0.98	[0.34, 2.88]	0.98	1.7	[0.3, 9.66]	0.55
	Unknown	0.33	[0.06, 1.81]	0.2	2.57	[0.19, 34.74]	0.48
IVEM type	SEEG	1.05	[0.35, 3.14]	0.93	1.27	[0.23, 6.91]	0.78

Note: reference categories for the variables are "female" for gender, "monthly" for seizure frequency, "no" for presence of FBTCS, "focal" for MRI lesion group, "normal or focal only" for SVEM IEDs, "focal only" for SVEM ictal onset, "TLE" for localisation hypothesis, "left" for lateralisation hypothesis, and "subdural electrodes" for IVEM type. Abbreviations: CI: confidence interval; ETE: extratemporal epilepsy; FBTCS: focal to bilateral tonic-clonic seizures; IEDs: interictal epileptiform discharges; IVEM: intracranial video-EEG monitoring; MRI: magnetic resonance imaging; OR: odds ratio; SVEM: scalp video-EEG monitoring; TLE: temporal lobe epilepsy. *Statistically significant <0.05. **Statistically significant <0.01.

assessed factors that predicted SOZ focality [23]. Bilateral independent IEDs were the only interictal pattern predictive of a nonfocal SOZ. However, generalised IEDs were not analysed separately, which is in contrast to our methodology. In the same study, a focal ictal SVEM predicted SOZ focality while a hemispheric onset did not, thus also differing from our results. The reason could be that we had to group hemispheric and focal SVEM ictal onset as one variable to limit the number of categories due to a comparatively smaller sample size.

A normal or nonspecific MRI (nonlesional MRI) was related to a poor outcome in our study. In line with this,

Table 3: Cases with generalised IEDs description.

No.	Epilepsy duration (years)	Age at evaluation (years)	Gender	MRI lesion type	SVEM-generalised IEDs					Seizures		Localisation hypothesis	SOZ focality	Surgical outcome
					S	SW	PS	PSW	PFA	SVEM onset	Main semiology			
1	22	25	M	FCD type II	+	+ (2.5 Hz)	+	-	+	NL	Tonic	PLE or OLE	Sublobar	Lost after Sx
2	10	37	F	Gliosis	-	-	-	-	+	NL	Tonic	FLE	Lobar	Engel class IV
3	32	37	M	Sulcation anomaly	+	-	+	-	+	NL	Clonic	PLE or OLE	Sublobar	Engel class IV
4	12	13	M	FCD type I	-	+ (2.5 Hz)	+	+ (2.5 Hz)	+	NL	Tonic	FLE	Lobar	Engel class IV
5	14	18	M	FCD type II	+	-	-	-	-	Focal	Tonic	FLE	Lobar	Engel class I-A
6	26	26	F	FCD type II	+	+ (2 Hz)	+	-	+	NL	Tonic	FLE	Lobar	Engel class IV
7	26	26	F	Nonspecific changes	+	+ (2.5 Hz)	-	-	+	Focal	Automotor	FLE	Multilobar	Engel class III
8	11	23	M	Mild asymmetry	+	+ (2 Hz)	+	-	+	NL	Tonic	FLE	Multilobar	Engel class IV
9	33	45	M	Mild asymmetry	+	-	+	-	+	NL	Tonic	FLE	Lobar	Lost after Sx
10	33	39	M	Nonspecific changes	+	+ (2.5 Hz)	+	+ (2.5 Hz)	+	NL	Tonic	FLE	Bilateral	Engel class III
11	3	11	M	Encephalocele	-	+ (3.5 Hz)	-	+ (3.5 Hz)	-	Focal	Automotor	TLE	Multilobar	Engel class I-B
12	28	30	M	FCD type II	-	-	+	+ (2.5 Hz)	-	NL	Tonic and clonic	TLE	Bilateral	Engel class III
13	41	45	F	Gray-white matter blurring	-	-	-	-	+	NL	Tonic	FLE	Bilateral	No Sx (nonfocal SOZ)
14	30	34	F	Sulcation asymmetry	+	-	-	-	-	NL	Tonic and clonic	FLE	Lobar	Engel class II
15	15	25	M	NPH (NF1)	-	-	+	-	+	NL	Tonic and clonic	TLE and ETE	Bilateral	No Sx (nonfocal SOZ)
16	4	16	M	Sulcation anomaly	+	+ (2.5 Hz)	+	-	+	Multifocal	Automotor	TLE	Multilobar	No Sx (nonfocal SOZ)
17	11	20	F	Porencephalic cyst	+	+ (5 Hz)	-	-	-	NL	Automotor	TLE	Lobar	No Sx (Thermo)
18	10	39	M	Gliosis	-	+ (5 Hz)	-	-	-	Focal	Automotor	TLE	Sublobar	No Sx (Thermo)

Abbreviations: ETE: extratemporal epilepsy; F: female; FCD: focal cortical dysplasia; FLE: frontal lobe epilepsy; Hz: hertz; IEDs: interictal epileptiform discharges; IVEM: intracranial video-EEG monitoring; M: male; MRI: magnetic resonance imaging; NF1: neurofibromatosis type 1; NL: nonlocalising; No.: number; NPH: nodular periventricular heterotopia; OLE: occipital lobe epilepsy; PFA: paroxysmal fast activity; PLE: parietal lobe epilepsy; PS: polyspikes; PSW: polyspike-and-wave; S: spikes; SOZ: seizure onset zone; SVEM: scalp video-EEG monitoring; SW: spike-and-wave; Sx: surgery; Thermo: stereoelectroencephalography-guided radiofrequency thermocoagulation; TLE: temporal lobe epilepsy.

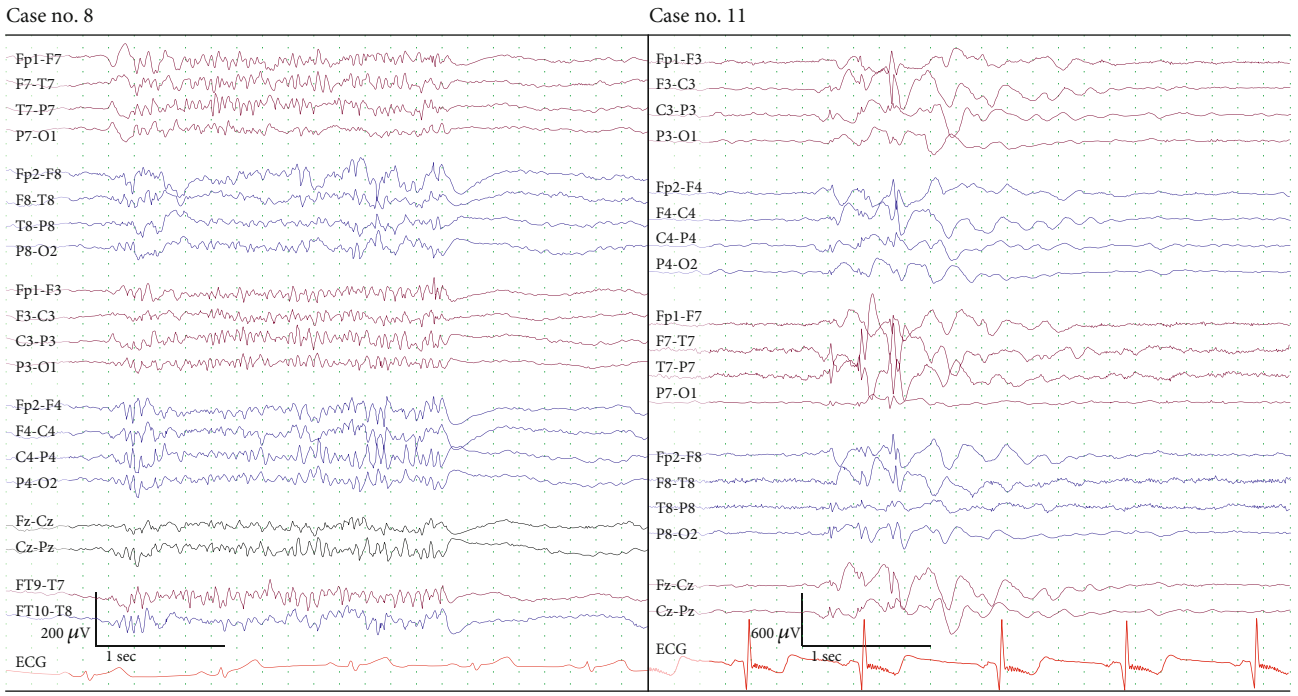

Figure 2: Examples of cases with generalised IEDs. Note: Case No. 8, five-second EEG page showing a generalised paroxysmal fast activity lasting 2.5 seconds. The final outcome was Engel class IV. Case No. 11, five-second EEG epoch showing a 3.5 Hz generalised polyspike-and-wave. The surgery outcome was Engel class I-B. A 1 Hz low frequency filter, 70 Hz high frequency filter, and 50 Hz notch filter were applied to the EEGs. Abbreviations: IEDs: interictal epileptiform discharges; No.: number.

an abnormal (or lesional) MRI and especially the presence of MTS or tumours were associated with a good surgical outcome according to three meta-analyses [18, 19, 37]. Many studies found the same correlation [30, 32, 34, 38], including those with IVEM cohorts [14, 15, 39]. In our study, a nonlesional MRI did not predict a nonfocal SOZ but only a poor surgical outcome, probably because there was no lesion to guide the resection and a focal SOZ could have been partially removed.

In our study, a daily or a weekly seizure frequency increased the risk of a poor surgical outcome. This is consistent with the previous studies, in which more than 20 or 30 seizures per month were associated with a poor outcome [38, 40]. These studies, however, did not present any explanations for the findings. Perhaps, a high baseline seizure frequency could imply a higher predisposition for patients to present epileptic seizures. If epilepsy surgery only decreases the probability of seizure occurrence, it would be very difficult to achieve seizure freedom.

4.4. Generalised IEDs Patterns. Two patterns of generalised IEDs were identified. The first group consisted of patients with paroxysmal fast activity and/or slow spike-and-wave, who had a poor outcome or were not recommended for surgery. This EEG pattern corresponds to focal epilepsy with Lennox-Gastaut features or secondary bilateral synchrony, which is more frequent in FLE [41, 42]. Therefore, these cases could explain why generalised IEDs are associated with a poor outcome in FLE [20]. The second pattern was fast spike-and-wave and/or sporadic spikes, which was found in four patients with good outcome or improvement after SEEG-guided radiofrequency thermocoagulation. These EEG findings are common in idiopathic generalised epilepsy. Indeed, patients with coexisting focal epilepsy and idiopathic generalised epilepsy are known to have a good surgical prognosis and remain drug-responsive [21]. These distinct patterns could justify the discrepancies found in available literature concerning generalised IEDs and surgical outcome.

4.5. SOZ Focality and Surgical Outcome Discrepancies. In our study, a focal SOZ increased the chances of achieving a good surgical outcome, and this is consistent with the previous studies [43, 44]. However, the predictors of SOZ focality and surgical outcome were not the same. A high seizure frequency, a nonlesional MRI, and multifocal IEDs were associated with a poor outcome but not with an extensive SOZ. There are several reasons that may explain this. Firstly, IVEM is limited by sampling bias and can fail to localise the SOZ, especially with subdural electrodes when bilateral or deep targets need to be recorded [8, 45]. This is especially true in nonlesional MRI, in which there is an absence of a structural anomaly with which to guide both implantation and resection. Our study comprised both IVEM with SEEG and subdural electrodes, whereas the 5-SENSE score study only included patients with SEEG [23]. This greater sampling bias in our study could explain why nonlesional MRI was only a predictor for surgical outcome and not for SOZ focality. Secondly, complete resection is not solely dependent on SOZ focality. For example, a focal SOZ that overlaps with the eloquent cortex cannot be completely resected, whereas a larger SOZ that is distant from the eloquent cortex can probably be completely removed [46].

4.6. Limitations. This study has some limitations. As this is a retrospective study, it can be subject to confounding bias; therefore, we used a multivariate analysis to help correct for possible influencing factors. In addition, our diagnostic cohort comprises both SEEG and subdural electrode IVEM, whose different strengths and limitations give rise to patient heterogeneity [8]. To compensate for this, the multivariate analysis included the variable IVEM type. On the other hand, there is a selection bias in the surgical cohort because there are patients who have not been operated on for various reasons and not solely for a nonfocal SOZ. This makes it difficult to interpret noninvasive factors for surgical outcome. Moreover, invasive factors (implantation strategy and IVEM interpretation) and postoperative factors (completeness of resection) were not analysed as the aim of the study was to focus on noninvasive factors that would aid in patient selection for IVEM. Furthermore, the relatively short duration of the minimum follow-up in our study (one year) may have introduced some detection bias. However, this follow-up period was chosen since it is frequently used in epilepsy surgery research and allowed us to gather larger study cohorts [47–49]. Nevertheless, the total sample size in both cohorts was relatively small, which limits the statistical analysis. For example, in our study, the distinct patterns of generalised IEDs were not analysed separately due to the low number of cases of each one. Likewise, the number of variables analysed is high compared to the total number of outcome events in the first and second analyses. This can be a source of false inference, and as a result, we may well have missed a weak to moderate effect of an influencing factor. However, because IVEM is an invasive and complex procedure, it is difficult to recruit patients in a single centre. In the future, multicentric studies could be used to examine a larger population and mitigate these limitations. These studies would also help determine whether one factor or a combination of factors can be considered a contraindication to IVEM.

5. Conclusion

This study shows that noninvasive presurgical assessment could help to optimise patient selection for IVEM. History of focal to bilateral tonic-clonic seizures and generalised IEDs (especially paroxysmal fast activity) are correlated with a nonfocal SOZ on IVEM and a poor surgical outcome. Moreover, high seizure frequency, nonlesional MRI, and multifocal IEDs increase the risk of a poor outcome. This information may also be used to better inform carefully selected patients concerning the chances of subsequent surgery with a good postoperative outcome or even to preclude implantation.

Data Availability

Raw data used for this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

NJP was responsible for the study design, data acquisition, interpretation of the data, writing the manuscript, and drafting the figures. KGH was responsible for the study design, statistical analysis, interpretation of the data, and writing the manuscript. MGS was responsible for the study design, interpretation of the data, and revision of the manuscript for important intellectual content. RCS was responsible for the revision of the manuscript for important intellectual content. AGM was responsible for the revision of the manuscript for important intellectual content. VV was responsible for the study design, interpretation of the data, and revision of the manuscript for important intellectual content. All listed authors have contributed to the manuscript substantially and have agreed to the final submitted version. Nicolas Jannone-Pedro and Kevin G Hampel should be considered as first author as both of them contributed equally to this publication.

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Supplementary Materials

STROBE statement—checklist of items that should be included in reports of cohort studies. *(Supplementary Materials)*

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