

# Independent risk factors for seizures in critically ill patients on continuous EEG

Pedro V.F. Naves, Luis O. Caboclo

Department of Clinical  
Neurophysiology, Hospital Israelita  
Albert Einstein, São Paulo, Brazil

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## ABSTRACT

**Objective.** The objective of this study was to characterize the independent risk factors for seizures in critically ill patients monitored with continuous EEG (cEEG).

**Methods.** We retrospectively investigated variables associated with cEEG seizures, first in the entire cohort of 156 patients and, subsequently, in the subgroup without seizures in the first 30 minutes of monitoring.

**Results.** Seizures were observed in 19.2% of recordings, and in 50% of these, seizures occurred in the first 30 minutes. In the entire cohort, epilepsy, acute seizures prior to cEEG, interictal epileptiform discharges (IEDs), lateralized periodic discharges (LPDs), and brief potentially ictal rhythmic discharges (BIRDs) were associated with a higher incidence of cEEG seizures, whereas coma, intravenous anaesthetic drugs, and generalized periodic discharges (GPDs) were associated with a lower incidence of seizures. On multivariate analysis, this association was maintained for acute seizures before cEEG (OR: 5.92) and IEDs (OR: 6.81). Excluding patients with seizures at the beginning of monitoring, acute seizures before cEEG, IEDs, LPDs, and BIRDs were associated with an increased risk of seizures. The presence of IEDs or LPDs in the first 30 minutes was associated with a 4.14-fold greater chance of seizures on cEEG. On multivariate analysis, acute seizures prior to recording (OR 7.29) and LPDs (OR: 5.38) remained associated with seizures on cEEG. Due to the sample size, BIRDs were not included in multivariate models.

**Significance.** Acute seizures prior to monitoring, IEDs, LPDs and BIRDs are important risk factors for cEEG seizures in critically ill patients.

**Key words:** continuous EEG, seizure, ictal-interictal continuum

Seizures are common in critically ill patients [1-3], being recorded in approximately 10% to 30% of those monitored with continuous EEG (cEEG) [2-5]. In this setting, most seizures do not exhibit prominent motor signs (so-called non-convulsive seizures) [2, 5, 6] and can only be reliably detected with EEG monitoring.

Several studies have found an association between seizures or status epilepticus (SE) and worse clinical outcome, even after adjusting for other variables related to prognosis [5-8]. The possibility of additional neurological injury second-

ary to epileptic activity increases the importance of investigating risk factors for seizures in critically ill patients.

The ictal-interictal continuum (IIC) represents a dynamic and unstable pathophysiological state, mainly characterized by periodic and rhythmic electroencephalographic patterns distributed between clearly defined interictal patterns, on one side, and definitely ictal patterns, on the other [9, 10]. Despite the growing body of studies with cEEG monitoring, the clinical significance of IIC patterns has not yet been adequately clarified. Investigation of the ictogenicity

## Correspondence:

Pedro VF Naves  
Department of Clinical  
Neurophysiology,  
Hospital Israelita Albert  
Einstein,  
Av. Albert Einstein, 627 – bloco  
B, 4º andar,  
São Paulo, SP, Brazil  
<pvfnaves@yahoo.com.br>

associated with electroencephalographic abnormalities found in critically ill patients may contribute to a better characterization of the risk of seizures and to the management of these patients.

The aim of this study was to analyse the independent seizure risk associated with electroencephalographic and non-electroencephalographic variables in critically ill patients monitored with cEEG.

## Methods

### Subjects

We retrospectively included all patients  $\geq 18$  years with an acute alteration in level of consciousness who underwent cEEG monitoring for at least 20 hours at the Hospital Israelita Albert Einstein, São Paulo, Brazil, between January 1<sup>st</sup>, 2017 and September 30<sup>th</sup>, 2018. All cEEGs were requested and terminated at the discretion of the patient's treating physicians. For patients with more than one cEEG recording during a hospitalization, only the first recording was analysed. The study was approved by the local ethics committee.

### Clinical, demographic, and radiographic variables

The following data were retrospectively collected from medical charts: age, sex, history of epilepsy, level of consciousness at the time cEEG was initiated (categorized as awake, lethargy, stupor, or coma), use of intravenous anaesthetic drugs (IVADs) (propofol, midazolam or thiopental), and the presence of acute seizures prior to cEEG (electrographic seizures recorded on previous EEG or witnessed clinical seizures) during the current hospitalization. Neuroimaging reports (CT, MRI) were reviewed and classified according to the presence of acute structural injury.

### cEEG recordings

cEEG was recorded using the Nihon Kohden<sup>®</sup> digital video-EEG system with 21 electrodes, positioned according to the international 10-20 system. The entire raw cEEG recordings were reviewed, page by page, by a clinical neurophysiologist certified by the Brazilian Clinical Neurophysiology Society (PVFN); disagreements between this review and the previous monitoring report were analysed by a second certified clinical neurophysiologist (LOC).

### cEEG variables

We identified the presence and time of emergence (from onset of cEEG) of interictal epileptiform

discharges (IEDs; non-periodic and non-rhythmic), lateralized periodic discharges (LPDs), bilateral independent periodic discharges (BIPDs), generalized periodic discharges (GPDs), lateralized rhythmic delta activity (LRDA), generalized rhythmic delta activity (GRDA), brief potentially ictal rhythmic discharges (BIRDs) and seizures (electrographic seizure or SE). Periodic and rhythmic patterns were defined according to the American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology [11]. BIRDs were defined as very brief ( $<10$  seconds) lateralized runs of rhythmic activity  $>4$  Hz, with or without evolution [12]. Electrographic seizures were defined based on the modified Young criteria [13]. Patterns lasting  $<10$  seconds and clearly associated with clinical manifestations, compatible with epileptic seizures, were also characterized as electrographic seizures. Electrographic SE was defined as patterns lasting  $\geq 10$  minutes that met the Salzburg consensus criteria [14].

### Statistical analysis

Data were analysed using IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY). Bivariate analysis was performed to identify variables associated with seizures on cEEG in the entire cohort and after excluding patients with seizures in the first 30 minutes of monitoring. Student's *t*-test or Mann-Whitney test was used for quantitative variables, according to the normal distribution of data, and Chi-square or Fisher's exact test for qualitative variables. In the group of patients without seizures in the first 30 minutes, after identifying electroencephalographic variables associated with cEEG seizures, we also analysed whether the presence of these abnormalities in the initial 30 minutes was associated with subsequent seizures on cEEG. Odds ratios (OR), with 95% confidence intervals (CI), were estimated using unadjusted logistic regression. Variables with  $p < 0.1$  on bivariate analysis were then included in multiple logistic regression models (full model; data reported as OR and 95% CI) to identify independent associations. A  $p$  value  $< 0.05$  was considered statistically significant.

## Results

### Study cohort

A total of 156 patients were included (22-96 years; mean:  $68.5 \pm 18.6$ ); 53.8% ( $n=84$ ) female. At the time monitoring was initiated, 51 (32.7%) patients were comatose and 105 (67.3%) lethargic or stuporous, with a higher prevalence of IVADs in comatose patients (76.5% vs. 24.8%;  $p < 0.001$ ).

## Seizures on cEEG

cEEG duration ranged from 20 to 186 hours (mean:  $50.3 \pm 29.8$ ). Seizures were recorded in 19.2% ( $n=30$ ) of recordings, and SE was defined in 36.7% (11/30). Among patients with cEEG seizures, the first seizure was detected in the first 30 minutes in 50% (15/30), in the first hour in 56.7% (17/30), and in the first nine hours in 93.3% (28/30). In 6.7% (2/30), the first seizure was observed only after 36 hours of recording.

## Variables associated with seizures on cEEG

In the entire cohort, IEDs, LPDs, BIRDs, history of epilepsy and acute seizures prior to monitoring were associated with a higher incidence of seizures on cEEG, whereas GPDs, use of IVADs and coma at the beginning of the recording were associated with a lower incidence of cEEG seizures (*table 1*). On multivariate analysis, IEDs (OR=6.81; 95% CI: 1.95-23.79;  $p=0.003$ ) and acute seizures prior to monitoring (OR=5.92; 95% CI: 2.06-17.03;  $p=0.001$ ) were the only variables independently associated with seizures on cEEG.

After excluding patients with seizures in the first 30 minutes of the recording, IEDs, LPDs, BIRDs and acute seizures prior to monitoring were associated with a higher incidence of seizures on cEEG; other variables, including GPDs, history of epilepsy, IVADs and coma at the beginning of the recording, were not associated with cEEG seizures. Patients with IEDs or LPDs during the first 30 minutes of monitoring were more likely to have subsequent seizures on cEEG, when compared to those without any of these patterns at the beginning of the recording (OR=4.14; 95% CI: 1.36-12.6;  $p=0.015$ ) (*table 2*) (there were no patients with BIRDs in the first 30 minutes). On multivariate analysis, LPDs (OR=5.38; 95% CI: 1.34-21.57;  $p=0.018$ ) and acute seizures prior to monitoring (OR=7.29; 95% CI: 1.84-28.92;  $p=0.005$ ) remained associated with cEEG seizures, and IEDs (OR=5.38; 95% CI: 0.98-29.45;  $p=0.052$ ) showed a trend towards an association with increased risk of seizures on monitoring, close to significance.

Due to the small sample size, BIRDs were not included in both multivariate models.

## Discussion

In this retrospective study of 156 critically ill adult patients monitored by cEEG, seizures were detected in 19.2%. In half of the recordings with seizures, the first seizure was observed within the first 30 minutes,

and in 56.7%, within the first hour of cEEG. These findings were similar to those previously reported [2, 4, 15].

While acute seizures prior to monitoring were associated with cEEG seizures in both multivariate models, a history of epilepsy failed to show an independent association with seizures in our study. In the study by Claassen *et al.* [2], both epilepsy and acute seizures prior to cEEG were independent predictors of seizures on monitoring. In the study by Struck *et al.* [3], although epilepsy and acute seizures prior to monitoring were associated with electrographic seizures, the individual significance of these variables was not analysed in the multivariate model. Westover *et al.* [4] did not find an association between epilepsy and electrographic seizures in 625 critically ill patients monitored by cEEG. Our findings suggest that it is the acute decrease in epileptic threshold, in patients with or without epilepsy, that represents an independent risk factor for subsequent seizures on cEEG.

In contrast to previous series [2-4], coma was associated with a lower incidence of seizures in the entire cohort of this study, although this association was not maintained neither in the multivariate model, nor after excluding patients with seizures in the first 30 minutes of monitoring. Coma was associated with a higher incidence of cEEG seizures in some studies [2, 3], but this finding was not observed by other authors [16, 17]. Struck *et al.* [17] did not find an association between coma and seizures in a recent multicentre study with 2,111 patients on cEEG. In our study, IVADs were also associated with a lower incidence of seizures in the entire cohort, as well as with coma. The significantly higher prevalence of IVADs among comatose patients may have contributed to our results, in view of the antiseizure effect of propofol, midazolam and thiopental.

In line with previous studies [2-4, 15, 18], IEDs, LPDs and BIRDs were associated with an increased risk of seizures on cEEG. Although BIRDs were not included in multivariate models, all patients with this abnormality had seizures, concordant with the high ictogenicity reported by other authors, who detected seizures in 75% to 78% of patients with BIRDs [3, 12].

Of note, the presence of an EEG risk pattern on initial monitoring was a significant predictor of seizures. Patients with IEDs or LPDs within the first 30 minutes had a 4.14-fold greater chance of seizures, compared to those without any of these patterns at the beginning of monitoring, with subsequent seizures in 24.1% and 7.1%, respectively. Our findings corroborate previous results, which revealed subsequent seizures in 22% to 26% of

▼ **Table 1.** Variables associated with seizures on cEEG: the entire cohort.

Variable	Seizures on cEEG		OR	95% CI		p
	No	Yes				
<b>Sex, n (%)</b>						0.730
Female	67 (79.8)	17 (20.2)	1.00			
Male	59 (81.9)	13 (18.1)	0.87	0.39	1.94	
<b>Age (years)</b>			0.99	0.97	1.01	0.529**
Mean $\pm$ SD	69 $\pm$ 19.1	66.6 $\pm$ 17				
Median (min; max)	73 (22; 96)	67.5 (24; 93)				
<b>Epilepsy, n (%)</b>						<b>0.001</b>
No	104 (86.7)	16 (13.3)	1.00			
Yes	22 (61.1)	14 (38.9)	4.14	1.76	9.70	
<b>Acute seizures prior to cEEG, n (%)</b>						<b>&lt;0.001</b>
No	90 (91.8)	8 (8.2)	1.00			
Yes	36 (62.1)	22 (37.9)	6.88	2.80	16.86	
<b>Coma, n (%)</b>						<b>0.037</b>
No	80 (76.2)	25 (23.8)	1.00			
Yes	46 (90.2)	5 (9.8)	0.35	0.13	0.97	
<b>IVAD, n (%)</b>						<b>0.007</b>
No	67 (73.6)	24 (26.4)	1.00			
Yes	59 (90.8)	6 (9.2)	0.028	0.11	0.74	
<b>Acute structural injury (neuroimaging), n (%)</b>						0.176
No	64 (77.1)	19 (22.9)	1.00			
Yes	60 (85.7)	10 (14.3)	0.56	0.24	1.30	
<b>IEDs, n (%)</b>						<b>&lt;0.001</b>
No	83 (95.4)	4 (4.6)	1.00			
Yes	43 (62.3)	26 (37.7)	12.55	4.11	38.27	
<b>LPDs, n (%)</b>						<b>0.002*</b>
No	112 (85.5)	19 (14.5)	1.00			
Yes	14 (56)	11 (44)	4.63	1.83	11.71	
<b>BIPDs, n (%)</b>						0.192*
No	126 (81.3)	29 (18.7)	1.00			
Yes	0 (0)	1 (100)	&			
<b>GPDs, n (%)</b>						<b>0.029</b>
No	101 (77.7)	29 (22.3)	1.00			
Yes	25 (96.2)	1 (3.8)	0.14	0.02	1.07	
<b>LRDA, n (%)</b>						0.464*
No	115 (79.9)	29 (20.1)	1.00			
Yes	11 (91.7)	1 (8.3)	0.36	0.05	2.91	

▼ **Table 1.** Variables associated with seizures on cEEG: the entire cohort (*continued*).

Variable	Seizures on cEEG		OR	95% CI		p
	No	Yes				
<b>GRDA, n (%)</b>						0.767*
No	108 (80)	27 (20)	1.00			
Yes	18 (85.7)	3 (14.3)	0.67	0.18	2.43	
<b>BIRDs, n (%)</b>						<b>0.007*</b>
No	126 (82.4)	27 (17.6)	1.00			
Yes	0 (0)	3 (100)	&			

SD: standard deviation; cEEG: continuous EEG; IVAD: intravenous anesthetic drug; IEDs: interictal epileptiform discharges; LPDs: lateralized periodic discharges; BIPDs: bilateral independent periodic discharges; GPDs: generalized periodic discharges; LRDA: lateralized rhythmic delta activity; GRDA: generalized rhythmic delta activity; BIRDs: brief potentially ictal rhythmic discharges; OR: odds ratio; CI: confidence interval. Chi-square; \* Fisher's exact; \*\* Student's t; & not possible to estimate.

▼ **Table 2.** Variables associated with seizures on cEEG: patients without seizures in the first 30 minutes.

Variable	Seizures on cEEG		OR	95% CI		p
	No	Yes				
<b>Sex, n (%)</b>						0.991
Female	67 (89.3)	8 (10.7)	1.00			
Male	59 (89.4)	7 (10.6)	0.99	0.34	2.91	
<b>Age (years)</b>			1.00	0.97	1.03	0.906**
Mean $\pm$ SD	69 $\pm$ 19.1	69.6 $\pm$ 16.3				
Median (min; max)	73 (22; 96)	73 (34; 93)				
<b>Epilepsy, n (%)</b>						0.079*
No	104 (92)	9 (8)	1.00			
Yes	22 (78.6)	6 (21.4)	3.15	0.96	10.31	
<b>Acute seizures prior to cEEG, n (%)</b>						<b>0.001</b>
No	90 (95.7)	4 (4.3)	1.00			
Yes	36 (76.6)	11 (23.4)	6.88	2.05	23.01	
<b>Coma, n (%)</b>						0.451
No	80 (87.9)	11 (12.1)	1.00			
Yes	46 (92)	4 (8)	0.63	0.19	2.10	
<b>IVAD, n (%)</b>						0.321
No	67 (87)	10 (13)	1.00			
Yes	59 (92.2)	5 (7.8)	0.57	0.18	1.76	

▼ **Table 2.** Variables associated with seizures on cEEG: patients without seizures in the first 30 minutes (*continued*).

Variable	Seizures on cEEG		OR	95% CI		p
	No	Yes				
<b>Acute structural injury (neuroimaging), n (%)</b>						0.695
No	64 (88.9)	8 (11.1)	1.00			
Yes	60 (90.9)	6 (9.1)	0.80	0.26	2.44	
<b>IEDs, n (%)</b>						<0.001
No	83 (97.6)	2 (2.4)	1.00			
Yes	43 (76.8)	13 (23.2)	12.55	2.71	58.15	
<b>LPDs, n (%)</b>						<0.001*
No	112 (94.1)	7 (5.9)	1.00			
Yes	14 (63.6)	8 (36.4)	9.14	2.88	29.07	
<b>BIPDs, n (%)</b>						0.106*
No	126 (90)	14 (10)	1.00			
Yes	0 (0)	1 (100)	&			
<b>GPDs, n (%)</b>						0.305*
No	101 (87.8)	14 (12.2)	1.00			
Yes	25 (96.2)	1 (3.8)	0.29	0.04	2.30	
<b>LRDA, n (%)</b>						>0.999*
No	115 (89.1)	14 (10.9)	1.00			
Yes	11 (91.7)	1 (8.3)	0.75	0.09	6.23	
<b>GRDA, n (%)</b>						0.693*
No	108 (88.5)	14 (11.5)	1.00			
Yes	18 (94.7)	1 (5.3)	0.43	0.05	3.46	
<b>BIRDs, n (%)</b>						0.011*
No	126 (90.6)	13 (9.4)	1.00			
Yes	0 (0)	2 (100)	&			
<b>IEDs or LPDs &lt; 30 minutes, n (%)</b>						0.015*
No	104 (92.9)	8 (7.1)	1.00			
Yes	22 (75.9)	7 (24.1)	4.14	1.36	12.60	

SD: standard deviation; cEEG: continuous EEG; IVAD: intravenous anesthetic drug; IEDs: interictal epileptiform discharges; LPDs: lateralized periodic discharges; BIPDs: bilateral independent periodic discharges; GPDs: generalized periodic discharges; LRDA: lateralized rhythmic delta activity; GRDA: generalized rhythmic delta activity; BIRDs: brief potentially ictal rhythmic discharges; OR: odds ratio; CI: confidence interval. Chi-square; \* Fisher's exact; \*\* Student's t; & not possible to estimate.

patients with early epileptiform discharges and in 3% to 8% of those without epileptiform abnormalities on initial recording [4, 15].

BIPDs were recorded in a single patient in our cohort; thus, although this patient had seizure on cEEG, it was

not statistically significant. A similar limitation was observed by other authors [3, 19].

In our study, LRDA was not associated with seizures on cEEG. LRDA was previously associated with an increased risk of seizures [3, 19, 20], but modifiers



such as frequency and *Plus* modifiers (superimposed fast, rhythmic, or sharp activity) appear to affect this association [19]. In the study by Rodriguez-Ruiz *et al.* [19], only LRDA at frequencies  $\geq 1.5$  Hz was associated with cEEG seizures, and a *Plus* modifier increased the LRDA seizure risk. We did not analyse the effect of periodic and rhythmic pattern modifiers on seizure risk; the influence of these specific features may have contributed to our results.

Consistent with previous studies [2, 3, 19], GRDA was not associated with seizures in our patients. GPDs were associated with a lower incidence of cEEG seizures in the entire cohort; this association, however, did not remain significant either on multivariate analysis or after excluding patients with early seizures. The association between GPDs and seizures was diversely characterized in studies with critically ill patients monitored by cEEG. GPDs were associated with non-convulsive seizures in the case-control study by Foreman *et al.* [21]. In the studies by Jette *et al.* [22] and Struck *et al.* [3], GPDs were not associated with seizures. In two other studies, GPDs without triphasic morphology were associated with seizures during cEEG, while GPDs with triphasic morphology were not [2, 18]. GPDs at  $<1.5$  Hz and without a *Plus* modifier were not associated with seizures in the study by Rodriguez-Ruiz *et al.* [19].

## Conclusion

Among risk factors for electrographic seizures or SE in critically ill patients, acute seizures prior to monitoring stand out as a major and independent predictor. Different electroencephalographic abnormalities recorded on cEEG in these patients represent distinct positions along a spectrum of ictogenicity, with IEDs, LPDs and BIRDs consistently associated with an increased risk of seizures and GRDA clearly not associated with seizures. Further studies investigating the effect of modifiers are required to better characterize the seizure risk associated with these abnormalities, especially regarding GPDs and LRDA. Additionally, based on our results, we may hypothesise that the intrinsic risk of seizures associated with periodic and rhythmic patterns is higher within a context of previous epileptic activity among patients without seizures at the commencement of cEEG. ■

## Supplementary material.

Summary slides accompanying the manuscript are available at [www.epilepticdisorders.com](http://www.epilepticdisorders.com).

## Disclosures.

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.

## Key points

- Variables associated with cEEG seizures were retrospectively investigated in 156 critically ill patients.
- Seizures were observed in 19.2% of recordings.
- Acute seizures prior to monitoring, IEDs, LPDs and BIRDs were consistently associated with cEEG seizures.
- Among patients without seizures on initial cEEG, early IEDs or LPDs were associated with a 4.14-fold increased chance of cEEG seizures.

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## TEST YOURSELF

(1) What variables were consistently associated with cEEG seizures?

(2) Which variable was 100% associated with cEEG seizures?

(3) Was the presence of an EEG risk pattern on initial monitoring a significant predictor of seizures on cEEG?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, [www.epilepticdisorders.com](http://www.epilepticdisorders.com).