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**Prognostic value of Electroencephalographic paroxysms in post-anoxic coma: a new regularity EEG-based score**

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**Running title:** EEG score for the prognosis of post-anoxic coma

**Abstract**

*Objectives.*- Several electroencephalographic (EEG) features —mainly the reactivity of background activity—have been suggested as reliable predictors of outcome for patients with post-anoxic coma (PAC). However, EEG in PAC often contains abundant EEG paroxysms (EP) that may hinder the detection of background EEG activity. We aimed to identify the features, among the different paroxysmal and non-paroxysmal EEG patterns, that may predict the outcome of patients with PAC.

*Methods.*- We retrospectively reviewed the clinical and EEG characteristics of 67 patients with PAC and selected those with abundant EP. We classified EP according to several features and assessed their prognostic value for survival at 15 days. We calculated a global regularity score, as the sum of the value (1 if regular, 0 if not) attributed to each of 4 features of EP (duration, morphology, amplitude, and frequency).

*Results.*- The 35 patient-group with abundant EP showed a higher mortality than the group without abundant EP. Among 12 features of EP, three regularity features (regularity of EP duration, morphology, amplitude) had a poor prognostic value. A global regularity score  $\geq 3$  showed a positive predictive value of 100 % for a poor outcome and a negative predictive value of 54 %, with good interrater consistency (Cohen's kappa = .63).

*Conclusions.* –The presence of EP and their regularity features in PAC patients are strongly associated with poor outcome. We propose a global regularity score, easily derived from visual EEG inspection, that may be a reliable prognostic tool for these patients. Prospective and larger studies are needed to confirm these findings.

**Keywords:** EEG, Outcome, Paroxysms, Post-anoxic coma, Prognosis, Regularity, Score.

## **Introduction**

Clinical, electrophysiological, biological and imaging markers all contribute to define the prognosis for survival of patients in a coma after cardiac arrest [2,3,13]. Several features of electroencephalography (EEG) are predictive of poor outcome, such as ‘malignant’ EEG-patterns including suppressed background activity, with or without periodic discharges and burst-suppression [9]. These patterns must be studied after the end of hypothermia and after sedation has been cleared [9]. Nonreactive background activity after 24 hours is predictive of poor outcome, but with low specificity [13,14,9]. In addition, the background EEG activity can be difficult to analyse when the amplitude of this activity is low, or in the presence of abundant paroxysmal events [19]. ‘Malignant’ EEG patterns such as burst-suppression and ‘epileptiform’ activities including both non-epileptic and epileptic paroxysms may indicate a poor prognosis [15,18]. Post-anoxic status epilepticus (SE) predicts a poor outcome [11], although patients with preserved EEG reactivity may have a favourable outcome [12].

Rather than ‘epileptiform’ EEG abnormalities or ‘electrographic post-anoxic SE’, the term electroencephalographic paroxysms (EP) may better depict the various EEG patterns seen in patients with post-anoxic coma (PAC). These patterns presumably reflect different underlying causes with different prognostic values. Both interictal epileptiform activity [9] and non epileptiform EP, such as generalized periodic discharges (GPDs)[4,5], can be seen in PAC, and the influence they have on the prognosis of PAC remains unclear. We aimed to further explore if specific features of these EP may have a prognostic value in patients with PAC.

## **Methods**

### **Patients**

We retrospectively collected 90 patients suffering from PAC (Glasgow coma scale < 8), treated in intensive care units at the Pitié-Salpêtrière hospital, over a period of five years.

From the patients for whom EEGs were routinely recorded for the assessment of coma, we identified 67 patients in whom the recordings were made within the first 10 days after cardiac arrest (mean delay  $2.8 \pm 2.1$  days) without sedation or therapeutic hypothermia at the time of the recording.

Clinical data were collected from medical charts. Survival at 15 days was chosen for evaluating outcome, as for patients with EP, the mortality during whole hospitalisation was too high (91%) to be discriminatory.

Signed consent was not requested as EEGs were performed in clinical care purposes. The study was approved by the ethical committee of our hospital (Comité de protection des personnes).

### **EEG recordings and analysis**

EEG recordings were made at the bedside with 8 electrodes for 20 minutes. EEG results were reviewed by two electroencephalographers (YN and VN), blind to the outcome of the patients.

Background activity was defined as baseline oscillatory EEG activity, excluding any EP. In some patients, background activity could not be detected due to abundant EP or suppression-bursts. Reactivity of the background EEG was defined as any change in the frequency or amplitude of background rhythm after auditory (n=5, during a 20-min EEG) or nociceptive stimulation (n=8; right and left sides). The interval between each stimulation was more than 15 secs.

EP were defined by waves with abrupt onset, rapid attainment of a maximum amplitude, and sudden termination [8]. EP were defined as repetitive if they occur periodically or rhythmically during some part of the recording. Repetitive EP were then considered as abundant if the number of 20-sec duration epochs containing repetitive EP represented at least

50% of the total epochs of the record [5]. Sporadic EP (nonperiodic and nonrhythmic) were defined as abundant if they occurred  $\geq 1$  per 10 sec [5].

These EP were then classified as follows (Figure S1): 1) spike, 2) polyspikes, 3) spike and wave or polyspikes and wave, 4) sharp wave [7], 5) Lateralized periodic discharges (LPDs) and GPDs [4,5], 6) triphasic waves, including negative-positive-negative complexes [7] and positive-negative-positive complexes, 7) high-amplitude waves during burst-suppression. The EP 1-4 were termed 'epileptic', EP 5-7 'non epileptic', and unclassified.

We performed 12 objective quantitative or qualitative measures of the EEG paroxysms, which were visually analysed (Table 2). They consisted of mean duration, amplitude, frequency of EP, their rhythmic, sporadic, or burst-suppression organisation, their reactivity to noxious stimuli, and 5 regularity measures of EP (based on duration, amplitude, morphology, frequency, and a global regularity score; see below for calculation). In addition, we evaluated the presence of background activity and its reactivity (Table 2).

The regularity features of EP were analysed on selected 40-second sessions of EEG recording which contained the most abundant EP. We examined the duration, amplitude, frequency and morphology of EP. We then calculated the ratio between highest and lowest values of each variable. The regularity criterion of each variable was a ratio  $< 1.5$  for duration,  $< 2$  for amplitude,  $< 1.5$  for frequency, and unchanged number and polarity of phases for morphology. We excluded the extreme values by rejecting the 10% of EEG records which contained the least regular EP from analysis. Figure 1 shows examples of different EP features classified as regular or not.

We then calculated a global regularity score (GRS). A value (1 if regular, 0 if not) was attributed to each of the 4 regularity features. GRS (ranging from 0 to 4) was the sum of these values. We finally classified EP as regular if they had a  $GRS \geq 3$  (i.e. presence of at least three regularity features), or not regular if they had a  $GRS < 3$ . The consistency of scoring was

tested by comparing ratings of two other EEG experts (PL, VHNM) who independently scored all EEGs. The reliability between raters to identify regular EP (with GRS  $\geq 3$ ) was good (Cohen's kappa = 0.63).

### **Statistical analysis**

Continuous variables were compared by using Mann Whitney test and qualitative variables were compared by using Chi 2 or the exact test of Fischer when appropriate. Kaplan Meier analysis generated survival curves for patients with low versus high regularity score for EP. Survival in the two populations was compared by using a Log rank test. Differences were considered significant at  $P$  values  $< 0.05$  (two-sided). Statview software (SAS institute, version 5.0) was used for statistical analyses.

### **Results**

#### **Global group (n=67)**

Among the total of 67 patients with PAC, 35 had abundant EP on EEG. The remaining 32 patients showed delta, theta or alpha waves, or suppressed (i.e.  $<10 \mu\text{V}$ ) or disorganized background activity. The prevalence of EP was not significantly different between out- and in-hospital cardiac arrest (49 vs. 62%), or between patients treated or not with therapeutic hypothermia (46 vs. 26%). Patients with EP were older (60.6 vs. 47.6 years,  $P=0.006$ ), had more frequently convulsive generalised seizures (38 vs. 13%,  $P=0.02$ ) or myoclonus (45 vs. 7%,  $P=0.0005$ ) and had a higher rate of mortality during hospitalisation (91 vs 69%,  $P=0.002$ ) than those without EP (Table 1).

#### **Group with EEG paroxysms (n=35)**

Background EEG activity was detectable in 19/35 (54%) patients with EP. Reactivity was observed only in 4/19 (21%). In addition, the presence of background activity and its reactivity did not provide any prognostic value for survival after 15 days (Table 2).

We then examined the EP, which consisted of spikes (n=2), polyspikes (n=6), spikes or polyspikes and waves (n=8), sharp waves (n=4), LPDs/GPDs (n=7), triphasic waves (n=4), burst waves (n=3), and wave of unclassified morphology (n=1). These EP were classified as epileptic (n=20) and non-epileptic (n=15) (Table 3). Patients with epileptic EP had a higher rate of myoclonus than those with non-epileptic EP (63 vs. 21%;  $P=0.017$ ). Other parameters including mortality rate, survival at 15 days after cardiac arrest, and occurrence of convulsive seizures were not different between the epileptic and non-epileptic EP groups (Table 3).

We therefore examined 12 objective features of EP, because the classification of EP as epileptic or not, failed to predict outcome. Of the 12 features of EP, only 4, all linked to regularity, provided a reliable prognosis of a poor outcome (Table 2). They were the regularity of EP duration ( $P=0.016$ ), amplitude ( $P=0.049$ ), morphology ( $P=0.024$ ), and the  $GRS \geq 3$  (i.e. presence of at least three regularity features) ( $P=0.005$ ). The GRS showed 100% positive predictive value (PPV) and 54 % negative predictive value (NPV) (Table S1 in Supplementary data).

Figure 2 shows the EEG of 9 patients with  $GRS \geq 3$ . While this EP regularity is present, the EEG patterns may differ and be classified as epileptic abnormalities, GPDs or triphasic waves. Figure 3 shows the EEG of additional 9 patients, with  $GRS \leq 2$ . We compared Kaplan Meier curves between patients with  $GRS \geq 3$  and  $\leq 2$  and found a much lower survival for patients with  $GRS \geq 3$  ( $P=0.0003$ ) (Figure 4).

Six patients from the whole PAC cohort were taking at least one anti-epileptic drug (clobazam, levetiracetam, sodium valproate and phenytoin) at the time of EEG, which showed EPs for all those patients. Of the 35 patients with PAC and presence of EP on the EEG, only

two had electrical seizures with temporally and spatially organized rhythmic discharges, as illustrated in Figure S2.

## **Discussion**

This study shows that repetitive EP are present in EEG recordings from about half of our PAC patients and that their presence is associated with a higher rate of mortality. Whether EP are classified as epileptic or not has no additional predictive value for survival. Only regularity features of EP—4 of 12 features evaluated—provide useful prognostic information about short-term outcome.

In contrast to some studies [13,14], we found that background reactivity had no prognostic value in our patients. This conflicting finding can be explained by the presence of abundant EP on EEG of our patients. Consequently, background EEG activity was rarely detectable. However, we showed even in this situation, our regularity score was able to predict the outcome.

The novelty of our study is to highlight the value of different regularity features of EP to predict the outcome of patient with PAC and to define a new and simple score. We found a good consistency of the global regularity score between different raters. The  $GRS \geq 3$  predicts survival of less than 15 days with 100% PPV and 54% NPV. The GRS does not depend on EEG patterns (epileptic or not), nor on complex EEG classification [10].

Previous studies have reported the prognostic value of regular post-anoxic EEG features. Monotonous, very regular EEG activities, like alpha coma [17], usually reflect severe brain damage where sub-cortical networks have little effect on cortical EEG. Interburst intervals in burst-suppression are more regular in the EEG of patients with PAC, compared with those of patients receiving phenobarbital [2]. Burst-suppression with identical bursts was invariably associated with poor outcome [6]. A regular signal amplitude has been used to formulate a

mathematical index for recovery in patients with PAC [16]. Quantitative measurement of several GPD features showed that the regularity of periods was associated with a poor prognosis [1]. The GRS for EP we described here, based on visual reading of multichannel EEG, may be more easily used by physicians and is also applicable for all patterns of EEG paroxysmal activities.

Antiepileptic drugs should be administered only if clinical seizures (tonic or clonic seizure, myoclonus) or electrographic seizures (rhythmic activities, with specific features [5]) are detected.

A previous study has shown that status epilepticus can be an independent outcome predictor after cerebral anoxia [9]. In our study, epileptic EP were not associated with a worse prognosis compared to non-epileptic EP (survival at day 15; 45 vs. 33%;  $P=0.73$ ).

Our study has some limitations. The work was based on 20-minute routine EEG records, thus might not cover all EEG fluctuations and miss epileptic seizures. Nevertheless, we showed that analysis of routine EEGs could predict poor outcome with a PPV of 100% (for EP with a regularity score  $\geq 3$ ). In addition, the sample of patients is small and monocentric. We evaluated our score on early mortality. Prospective studies are needed to confirm the prognostic value of GRS, on long term neurological evaluation, in combination with other clinical, biological and neurophysiological markers, in patients with PAC and EP.

In conclusion, our study suggests that EP, detected during early routine EEG procedures after cardiac arrest, are associated with a poor outcome. Furthermore, regularity features of EP in patients with PAC were strongly associated with a poor outcome while other EP features had no prognostic value. We propose a *global regularity score* as a reliable, suitable and rapid tool to make an early prognosis for PAC patients with abundant EP and poor background activity.

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**Conflict of interest:** Yann Nadjar, Pierre Levy, Vi-Huong Nguyen-Michel and Louis Puybasset declare that they have no conflict of interest. Charles-Edouard Luyt received speaker honoraria from ThermoFisher Brahms and MSD companies. Vincent Navarro received honoraria from UCB, Eisai, outside the topics of the study.

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**Table 1**

Demographic and clinical characteristics of patients according to presence of EEG paroxysms (EP+) or not (EP-) in the first EEG recording after cardiac arrest without anaesthetic drug sedation nor hypothermia.

EP: electroencephalographic paroxysms. Mean $\pm$  standard deviation or n/total (%) are given.

**Table 2**

Prognostic value of background activity and 12 EP features including the global regularity score on the survival after 15 days in patients with PAC who presented EP on their first EEG after cardiac arrest.

EP: electroencephalographic paroxysms. PAC: post anoxic coma. Mean $\pm$  standard deviation or n/total (%) are given.

**Table 3**

Comparison of outcome and clinical measures between patients with epileptic EP (epileptic EP+) or without (epileptic EP-).

EP: electroencephalographic paroxysms. LPDs: lateralized periodic discharges. GPDs: generalized periodic discharges.

**Table S1**

Predictive values of the global regularity score  $\geq 3$  for survival  $< 15$  days.

PPV: positive predictive value. NPV: negative predictive value (NPV). Se: sensitivity. Spe: specificity. CI: confidence intervals.

## Figure 1

### Examples of different EP features classified as regular or not regular

Samples of EEG records classified as « regular » or « not regular » for each of the four regularity features: frequency, morphology, amplitude and duration. In part A1, EP frequency does not change, staying around 1.2 Hz, whereas, in part A2, frequency is not regular, changing from 0.5 Hz to 1 Hz. In part B1, the morphology of the EP is very regular, consisting of the same successions of similarly oriented phases (negative, positive, negative), however frequency and amplitude are not regular. In part B2, the morphology of the EP is clearly changing over time; the first appearing EP in the sample has four phases whereas the two following only have two. In part C1, the EP amplitude is very regular, whereas in part C2 the same EP recognizable to its morphology changes from low to high voltage. In part D1, duration of the EP is the same for each occurrence, whereas in part D2, duration of EPs can be short or long over the sample.

EP: electroencephalographic paroxysms.

## Figure 2

### EEG of 9 patients with a global regularity score $\geq 3$

EEG samples, in a bipolar longitudinal montage, from 9 patients with post-anoxic coma, showing EP with a global regularity score  $\geq 3$ . Close to each EEG samples, a visual cue indicates how the EEG was scored according to the four regularity features (D for duration of the EP, M for morphology, F for frequency, and A for amplitude, as detailed for EEG n°1). If the cue is white, this means that the feature was scored as not regular, if black the feature was scored as regular. None of these patients survived longer than 15 days after cardiac arrest. Morphological classifications of the EP are heterogeneous (epileptic figures for n°1, 2, 3, 4, 5, 7; triphasic waves for n°6 and 8; GPDs for n°9).

EP: electroencephalographic paroxysms. GPDs: generalized periodic discharges.

### **Figure 3**

#### **EEG of 9 patients with a global regularity score $\leq 2$**

EEG samples, in a bipolar longitudinal montage, from 9 patients with post-anoxic coma showing EP with a global regularity index  $\leq 2$ . Close to each EEG samples, a visual cue indicates how the EEG was scored according to the four regularity features (D for duration of the EP, M for morphology, F for frequency, and A for amplitude, as detailed for EEG n°1). If the cue is white, this means that the feature was scored as not regular, if black the feature was scored as regular. EP are heterogeneous based on morphological classifications (epileptic figures for n°2, 3, 5, 6, 7, 8; triphasic waves for n°1 and 9; GPDs for n°4).

EP: electroencephalographic paroxysms. GPDs: generalized periodic discharges.

### **Figure 4**

#### **Kaplan Meier survival curves for patients who presented EP at first EEG, with low or high global regularity scores.**

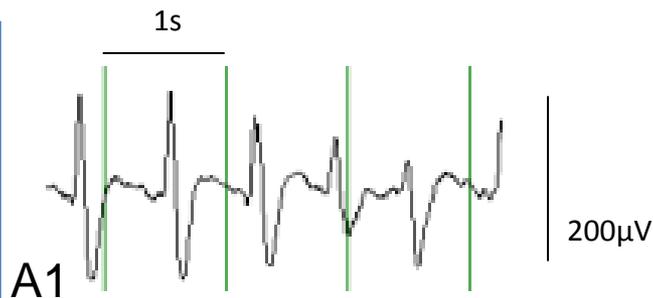
The two curves were compared by using Log rank test.

EP: electroencephalographic paroxysms.

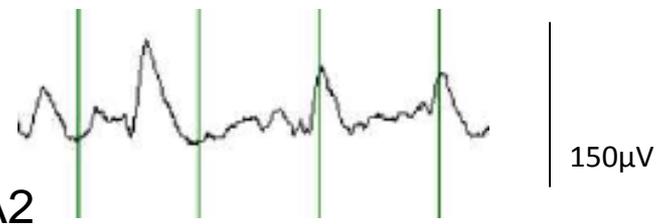
Regular

Not regular

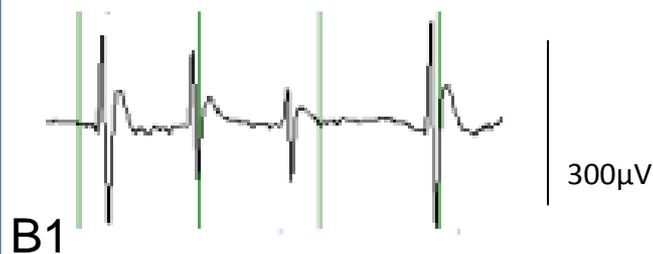
EP frequency



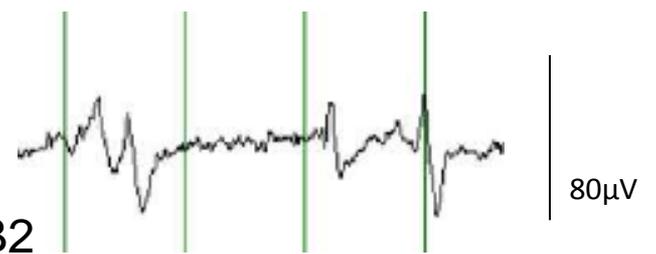
A2



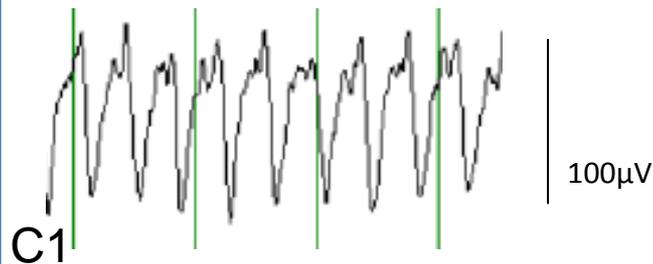
EP morphology



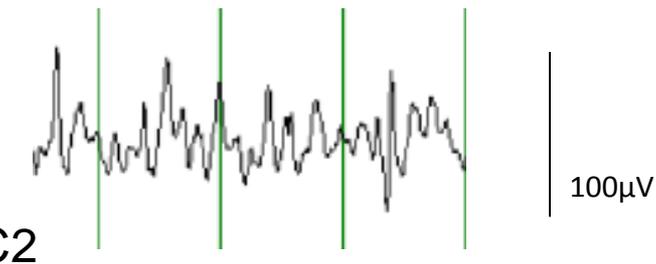
B2



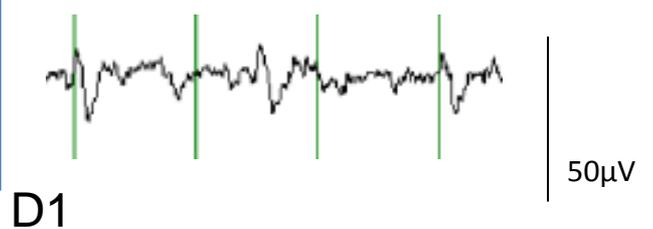
EP amplitude



C2



EP duration



D2

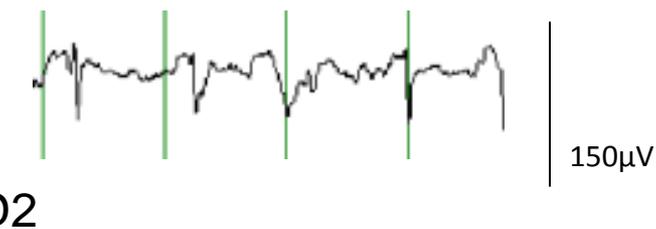
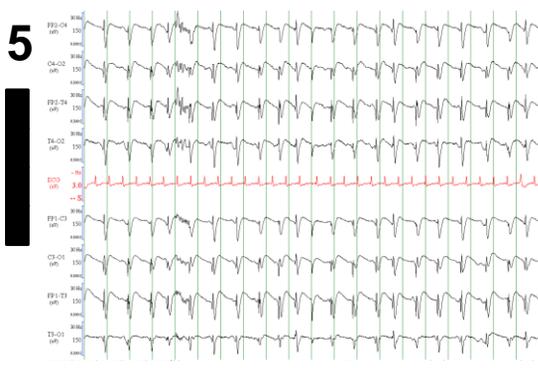
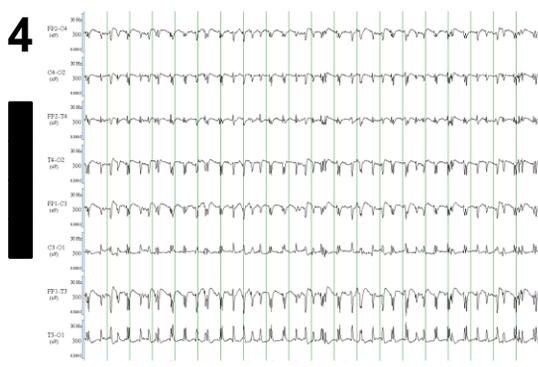
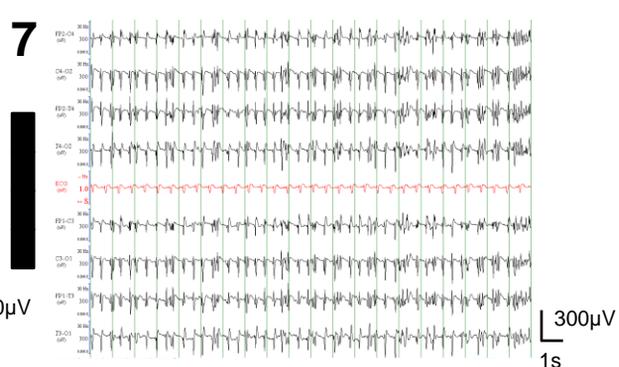
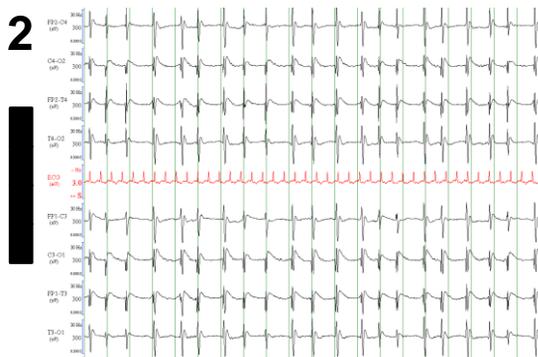
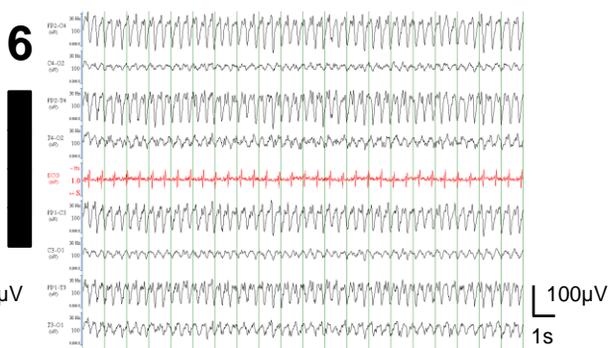
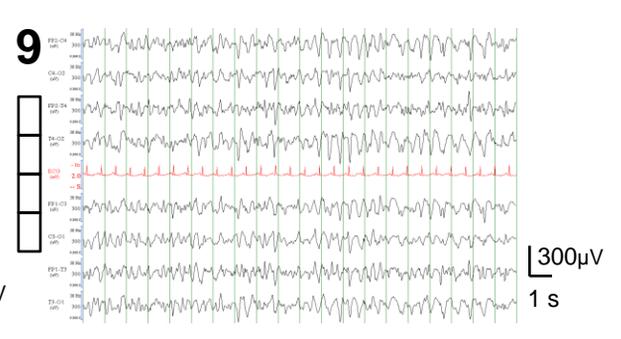
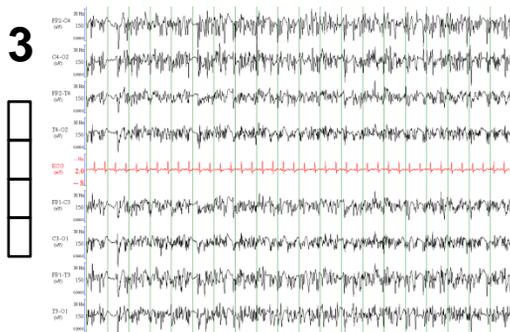
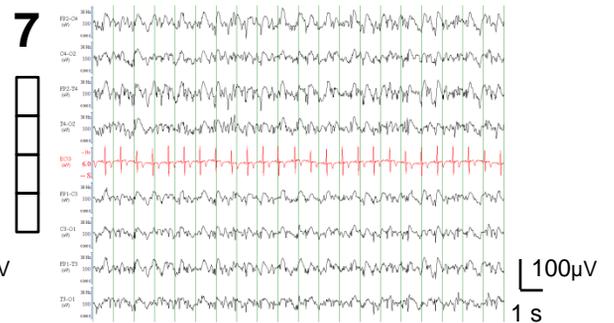
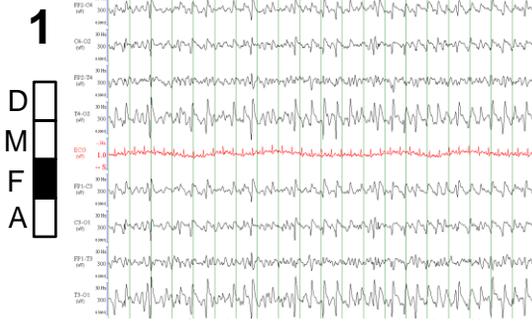
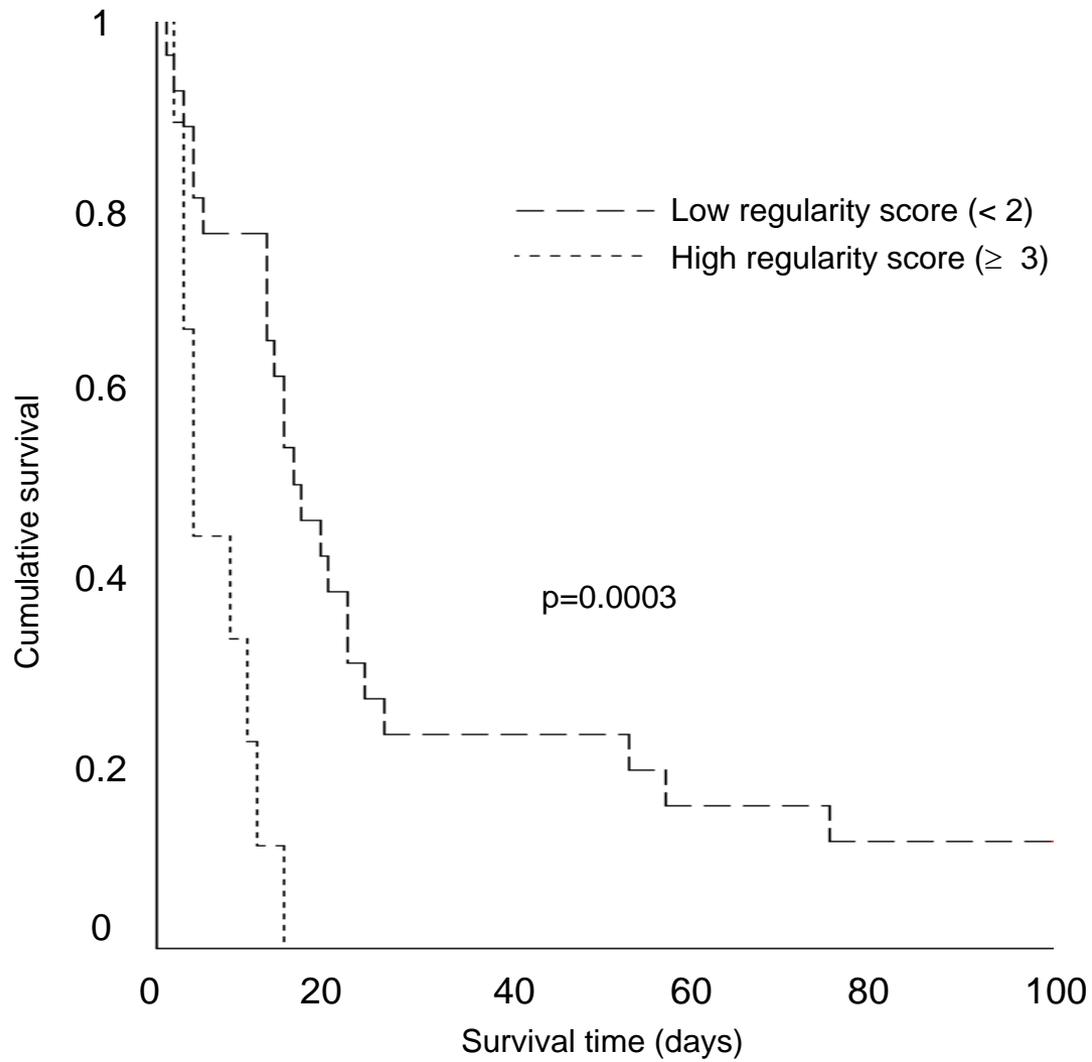


Figure 1.







**Table 1** Demographic and clinical characteristics of patients

Variables	EP- ( <i>n</i> =32)	EP+ ( <i>n</i> =35)	<i>P</i> value	Total ( <i>n</i> =67)
<i>Age (years)</i>	47.6 ± 18.3	60.6 ± 17.6	0.006	54.72 ± 19
<i>Males</i>	19/32 (59)	27/35 (77)	0.117	46/67
<i>Mortality</i>	19/32 (69)	32/35 (91)	0.002	52/67 (77)
<i>Clinical generalized seizure</i>	4/31 (13)	13/34 (38)	0.02	17/66 (26)
<i>Myoclonus</i>	2/30 (7)	15/33 (45)	0.0005	17/64 (26)

Demographic and clinical characteristics of patients according to presence of EEG paroxysms (EP+) or not (EP-) in the first EEG recording after cardiac arrest without anaesthetic drug sedation nor hypothermia.

EP: Electroencephalographic paroxysms

Mean± standard deviation or n/total (%) are given

**Table 2** Prognostic value of background activity, 12 EP features, including the global regularity score in PAC patients

Variables	Survival < day 15 (n=21)	Survival > day 15 (n=14)	P value
<b>Background activity</b>			
<i>Presence</i>	11/21 (52)	8/14 (57)	1
<i>Reactivity</i>	2/11 (18)	2/8 (25)	1
<b>12 EP features</b>			
<i>EP Duration (ms)</i>	397 ± 180	352 ± 289	0.6
<i>EP Amplitude (µV)</i>	144 ± 74	118 ± 103	0.38
<i>EP Frequency (Hz)</i>	2.99 ± 3.56	4.83 ± 4.86	0.38
<i>Rhythmic EP</i>	8/19 (42)	6/13 (46)	1
<i>Sporadic EP</i>	6/21 (28)	6/14 (43)	1
<i>Burst suppression pattern</i>	5/21 (24)	3/14 (21)	1
<i>EP reactivity to noxious stimuli</i>	3/20 (15)	5/14 (36)	0.22
<i>EP duration regularity</i>	11/18 (61)	2/12 (17)	0.016
<i>EP amplitude regularity</i>	9/20 (45)	1/13 (8)	0.049
<i>EP morphology regularity</i>	9/19 (47)	1/13 (8)	0.024
<i>EP frequency regularity</i>	10/19 (53)	3/13 (23)	0.09
<i>Global regularity score ≥ 3</i>	9/21 (43)	0/14 (0)	0.005

Prognostic value of background activity and 12 EP features (morphology, organisation, reactivity) including the global regularity score on the survival after 15 days in patients with PAC who presented EP on their first EEG after cardiac arrest.

EP: Electroencephalographic paroxysms; PAC: post anoxic coma

Mean± standard deviation or n/total (%) are given

**Table 3** Comparison of outcome and clinical measures between patients with epileptic EP (epileptic EP+) and without (epileptic EP-)

		Mortality	Survival ≥ day 15	Clinical generalised seizure	Myoclonus	Awakeness
<i>Epileptic EP+</i>	Spikes ( <i>n</i> =2)	2/2	1/2	1/2	2/2	
	Polyspikes ( <i>n</i> =6)	6/6	4/6	2/6	3/6	
	Spikes and waves and polyspikes and waves ( <i>n</i> =8)	8/8	2/8	4/7	5/7	
	Sharp waves ( <i>n</i> =4)	3/4	2/4	1/4	2/4	
<i>Total (%)</i>	20 (100)	19 (95)	9 (45)	8/19 (42)	12/19 (63)	4 (20)
<i>Epileptic EP-</i>	LPDs / GPDs ( <i>n</i> =7)	7/7	3/7	2/7	1/6	
	Triphasic waves ( <i>n</i> =4)	3/4	1/4	2/4	0/4	
	Burst waves during burst-suppression ( <i>n</i> =3)	2/3	1/3	1/3	1/3	
	Unclassified EP ( <i>n</i> =1)	1/1	0/1	0/1	1/1	
<i>Total (%)</i>	15 (100)	13 (87)	5 (33)	5 (33)	3/14 (21)	1(7)
<i>P value</i>		0.56	0.73	0.72	0.017	0.36

Comparison of outcome and clinical measures between patients with epileptic EP (epileptic EP+) or without (epileptic EP-)

EP: Electroencephalographic paroxysms; LPDs: Lateralized periodic discharges; GPDs:

Generalized periodic discharges