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Neurological outcome of postanoxic refractory status epilepticus after aggressive treatment

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ABSTRACT

Refractory status epilepticus (RSE) occurs in up to 30% of patients following resuscitation after cardiac arrest. The impact of aggressive treatment of postanoxic RSE on long-term neurological outcome remains uncertain. We investigated neurological outcome of cardiac arrest patients with RSE treated with a standardized aggressive protocol with antiepileptic drugs and anesthetics, compared with patients with other electroencephalographic (EEG) patterns. A prospective cohort of 166 consecutive patients with cardiac arrest in coma was stratified according to four independent EEG patterns (benign; RSE; generalized periodic discharges (GPDs); malignant nonepileptiform) and multimodal prognostic indicators. Primary outcomes were survival and cerebral performance category (CPC) at 6 months. Refractory status epilepticus occurred in 36 patients (21.7%) and was treated with an aggressive standardized protocol as long as multimodal prognostic indicators were not unfavorable. Refractory status epilepticus started after 3 ± 2.3 days after cardiac arrest and lasted 4.7 ± 4.3 days. A benign electroencephalographic patterns was recorded in 76 patients (45.8%), a periodic pattern (GPDs) in 13 patients (7.8%), and a malignant nonepileptiform EEG pattern in 41 patients (24.7%). The four EEG patterns were highly associated with different prognostic indicators (low flow time, clinical motor seizures, N20 responses, neuron-specific enolase (NSE), neuroimaging). Survival and good neurological outcome (CPC 1 or 2) at 6 months were 72.4% and 71.1% for benign EEG pattern, 54.3% and 44.4% for RSE, 15.4% and 0% for GPDs, and 2.4% and 0% for malignant nonepileptiform EEG pattern, respectively. Aggressive and prolonged treatment of RSE may be justified in cardiac arrest patients with favorable multimodal prognostic indicators.

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1. Introduction

Prognostication of neurological outcome in patients in coma after cardiac arrest requires a multimodal diagnostic approach to assess the severity of postanoxic encephalopathy, which includes clinical examination, EEG pattern, somatosensory evoked potentials, neuron-specific enolase (NSE), and neuroimaging [1].

Refractory status epilepticus (RSE) has been reported in up to 30% of comatose patients after cardiac arrest using continuous EEG (cEEG) [2], is frequently associated with clinical motor seizures (myoclonic, clonic, or tonic–clonic) [3], and is typically resistant to moderate intensity, unstandardized treatment [4].

The standardized American Clinical Neurophysiology Society (ACNS) terminology of critical care EEG [5] and the Salzburg criteria for nonconvulsive status epilepticus (NCSE) [6] allow a clear distinction of two EEG patterns, which are frequently reported under the same term "status epilepticus" (SE). Sharply contoured generalized periodic discharges (GPDs, GPDs+; previously termed generalized periodic epileptic discharges (GPEDs)) have been consistently reported as a highly malignant pattern associated with a poor neurological prognosis [7]. Refractory status epilepticus without periodic discharges has also been associated with poor prognosis [8], but a subset of these patients might achieve a good functional recovery [9].

Both the intensity and duration of treatment of RSE in postanoxic patients are controversial and raise ethical issues of therapeutic obstinacy versus premature withdrawal of life support [10,11].

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In the present study, we investigated survival and long-term neurological outcome in consecutive postanoxic patients with RSE without periodic discharges treated with an aggressive standardized protocol, compared with patients with a benign EEG pattern, a nonepileptiform malignant EEG pattern, and GPDs.

2. Materials and methods

2.1. Study design

This is a prospective cohort study exploring survival and long-term neurological outcome of postanoxic patients with RSE after aggressive standardized treatment. This study was approved by the Ethics Committee of San Gerardo Hospital, Monza, Italy. Consecutive patients in coma after cardiac arrest admitted between January 2011 and May 2016 in the hospital's Cardiac Intensive Care Unit (ICU) were included in the study.

To be included in the cohort, patients had to be in coma for >24 h after cardiac arrest. Patients who regained consciousness or died <24 h after cardiac arrest were excluded.

Data collection was performed by review of medical records for demographics and clinical data, including clinical motor seizures, brainstem reflexes, NSE, somatosensory evoked potentials, and neuroimaging. Electroencephalographic patterns within the first 5 days from cardiac arrest were independently reviewed and categorized by three neurophysiologists (see below). Neurological outcome was assessed at 6 months after cardiac arrest by telephone contact (see below).

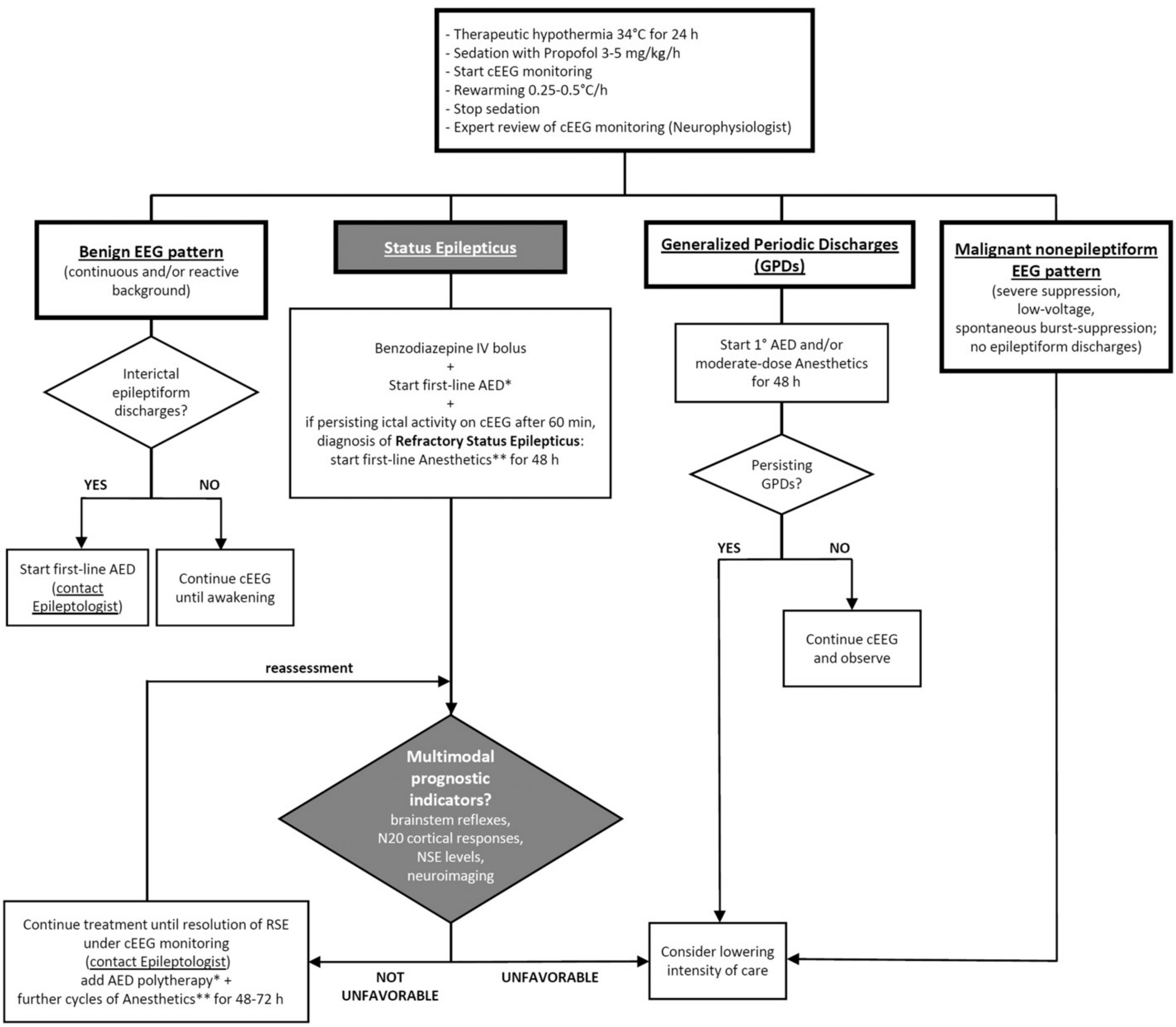

Fig. 1. Standardized protocol for treatment of hypoxic–ischemic encephalopathy in ICU. *Antiepileptic drugs (loading dose). First-line: valproate 30 mg/kg iv bolus; levetiracetam 40 mg/kg iv bolus; phenytoin (if contraindication to valproate/levetiracetam AND absent cardiac risks) 20 mg/kg iv bolus. Second-line: lacosamide 400 mg iv bolus; topiramate 300–500 mg oral loading; perampanel 6–12 mg oral loading. Maintenance daily doses according to usual schedules for each AED. **Anesthetics. First-line: propofol 1–2 mg/kg iv bolus + 2–6 mg/kg/h iv maintenance, target burst-suppression guided by cEEG (60–70% BSR) ± midazolam. Second-line: thiopental 5–15 mg/kg iv bolus + 0.5–10 mg/kg/h iv maintenance, target burst-suppression guided by cEEG (60–70% BSR); ketamine 1.5–3 mg/kg iv bolus + 1–5 mg/kg/h iv maintenance, target typical ketamine pattern, no epileptiform discharges ± midazolam. BSR = burst suppression rate (% of time the waveform is isoelectric over the previous 60 s). iv = intravenous.

2.2. Aggressive standardized treatment of postanoxic status epilepticus

Patients were treated according to the local institutional protocol for reducing brain damage after cardiac arrest (Fig. 1). This includes targeted temperature management at 34 °C for 24 h, simplified 4-channel cEEG monitoring applied within 24 h from cardiac arrest, and on-call neurological consultations with an epilepsy specialist.

A multimodal prognostic approach was applied in all cases, i.e., an unfavorable profile was considered when most indicators converged indicating a poor prognosis, while a not unfavorable (i.e., potentially favorable) profile was considered when most indicators converged against a poor prognosis. Brainstem reflexes (pupillary, corneal) were performed within 24 h and, if bilaterally absent, were considered indicators of poor prognosis. Neuron-specific enolase levels were performed at 48 h, and we adopted the cutoff >68 ng/mL as indicator of poor prognosis [12]. Median nerve somatosensory evoked potentials were performed at 72 h, if patients remained in coma, and, if bilaterally absent, they were considered indicators of poor prognosis. Neuroimaging (computer tomography (CT) or magnetic resonance imaging (MRI)) was performed if clinically indicated and feasible; if moderate–severe anoxic brain injury was present (see below), it was considered an indicator of poor prognosis.

Our protocol for aggressive standardized treatment of SE was guided by cEEG and available prognostic indicators (Fig. 1) and was developed from previous expert opinions on this topic [13,14]. Early identification of prognostic EEG patterns (see below) was performed by on-call epilepsy specialists within the first 5 days after cardiac arrest, with multiple consultations as needed.

2.3. Study definitions

Status epilepticus was defined according to the International League Against Epilepsy (ILAE) classification [15]. In accordance with the Salzburg EEG criteria [6], a frequency of epileptiform discharges (sharp waves and spikes) >2.5 Hz was applied for the diagnosis of NCSE. A minimum duration of 30 min of electrographic seizure activity was used for the diagnosis of an episode of NCSE. No patients included in this study had previous epileptic encephalopathy.

Status epilepticus was defined as refractory (RSE) after failure of benzodiazepines and a first intravenous antiepileptic drug (AED) and super-refractory after failure of a first cycle (48 h or more) of anesthetics-induced burst-suppression pattern (burst suppression rate >70%).

Motor seizures were defined as any observable myoclonic, clonic, or tonic–clonic manifestation that occurred during the entire stay in the ICU.

Status myoclonus was defined as continuous and generalized myoclonic jerks with duration >30 min within the first 5 days after cardiac arrest.

Generalized periodic discharges were defined as sharply contoured, sharp, or spiky discharges showing a periodic pattern with a frequency <2.5 Hz. A minimum duration of 30 min of continuous periodic discharges was used for the diagnosis of an episode of GPDs. Periodic discharges with a frequency >2.5 Hz were considered SE.

EEG background activity was categorized as continuous (<10% periods of attenuation or suppression) or discontinuous (>10% periods of attenuation or suppression, including spontaneous burst–suppression and suppression).

EEG background reactivity was defined as any response elicited by auditory or noxious stimuli, excluding stimulus-induced rhythmic periodic or ictal discharges (SIRPIDs).

Magnetic resonance imaging evidence of anoxic brain injury was dichotomized as mild or moderate–severe according to diffusion weighted images (DWI) and/or fluid attenuated inversion recovery (FLAIR) abnormalities in the cortical gray matter and deep basal ganglia [16].

Computer tomography evidence of anoxic brain injury was dichotomized as mild or moderate–severe according to gray matter to white matter ratio and diffuse cerebral edema [17].

2.4. Prognostic EEG pattern

Four mutually exclusive EEG patterns, within the first 5 days after cardiac arrest, were defined as follows:

- *Benign EEG pattern*: continuous or reactive (or both) EEG background activity at any time point, with no episodes of SE or GPDs.
- *RSE pattern*: one or more episodes of RSE at any time point, with no episodes of GPDs <2.5 Hz at any time, independently of EEG background activity.
- *GPD pattern*: one or more episodes of GPDs <2.5 Hz at any time point, independently of EEG background activity or RSE.
- *Malignant nonepileptiform EEG pattern*: consistently discontinuous and unreactive EEG background activity, with no episodes of SE or GPDs at any time.

Examples of the four prognostic EEG patterns are illustrated in Fig. 2. Three neurophysiologists independently reviewed the EEGs of different patients and categorized them in the four EEG patterns.

2.5. Study outcomes

Primary outcomes were survival and neurological disability, assessed using the cerebral performance category (CPC), at 6 months after cardiac arrest [18]. All patients or caregivers were contacted by phone call, no patient was lost to follow-up. The CPC ranges from 1 to 5, with 1 representing intact function and 5 representing brain death. The CPC was dichotomized as follows: patients with a CPC of 1 or 2 were classified as good neurological outcome, and patients with a CPC of 3 or greater were classified as poor neurological outcome.

2.6. Statistical analysis

Descriptive statistics were performed in the study population for the main demographic and clinical variables. Data are reported as frequencies and percentages for categorical variables, or as medians and interquartile ranges (IQRs) for continuous variables. Selected prognostic indicators (clinical motor seizures, low flow time, N20, NSE, neuroimaging) were described separately for each EEG pattern and compared using the chi-square or the Wilcoxon–Mann–Whitney test. Clinical characteristics of RSE (onset, duration, response to treatment) were described using mean, standard deviations, ranges, frequencies, percentages, and cumulative incidence functions. The effect of demographic and clinical variables on study outcomes was evaluated using univariable logistic regression models. Results are reported as odds ratios (ORs) with 95% confidence intervals (95% CIs). The significance level was set at 0.05. Statistical analyses were performed with the Statistical Analysis System (SAS) statistical package (version 9.4; SAS Institute, Cary, NC, USA).

3. Results

3.1. Study population

The initial cohort consisted of 206 consecutive cardiac arrest patients, 40 patients were excluded because they died within the first 24 h and were not EEG-monitored. All the remaining 166 patients survived the first 24 h, had continuous EEG monitoring, and were included in the analysis.

Therapeutic hypothermia (34 °C) for 24 h, followed by gradual rewarming over the next 12 h, was applied in 148 patients (89.1%).

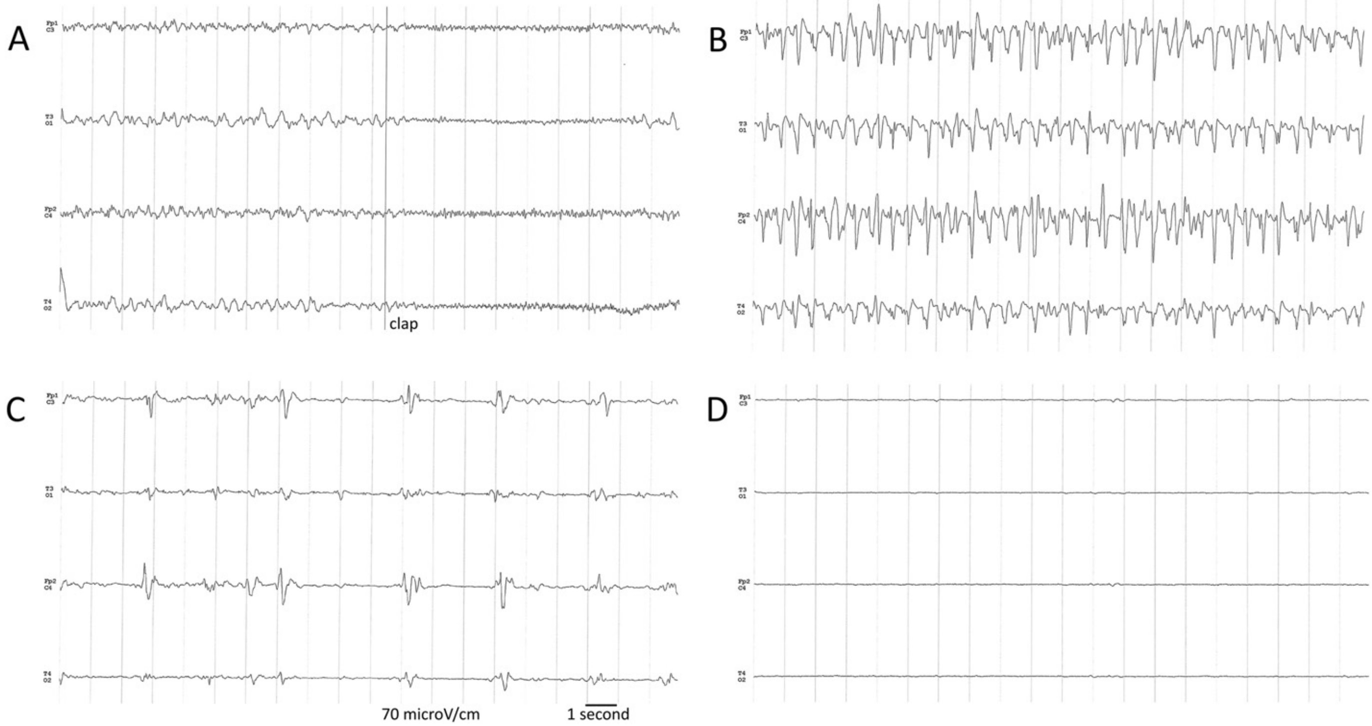

Fig. 2. Prognostic EEG patterns in postcardiac arrest patients. Representative epochs from 4-channel continuous EEG monitoring of patients with benign EEG pattern (A), RSE pattern (B), GPDs pattern (C), and malignant nonepileptiform EEG pattern (D).

Demographic and clinical characteristics of the study population are shown in Table 1. Median age was 61 years (IQR: 51–71). Most patients had preserved brainstem reflexes (pupillary: 84.1%, corneal: 70.1%) and bilaterally present cortical N20 responses (82.5%). Early brain imaging with MRI or CT (within 7 days) was performed in 87 patients (52.4%) and showed moderate–severe anoxic brain injury in 33 patients (37.9%).

Table 1
Clinical characteristics of the study population.

	Unit	Median or n (%)	IQR
Age	Years	61.0	51.0–71.0
Days in ICU	Days	7.5	4.0–15.0
Sex	Male (%)/female (%)	120 (72.7)/46 (27.7)	
No flow time	Minutes	1.0	1.0–7.5
Low flow time	Minutes	28.0	14.5–53.0
Out of hospital cardiac arrest	n (%)	112 (67.5)	
ECMO	n (%)	84 (50.6)	
Hypothermia	n (%)	148 (89.1)	
Pupillary reflex[a]	Bilaterally present (%)	127 (84.1)	
Corneal reflex[a]	Bilaterally present (%)	103 (70.19)	
NSE	μg/L	48.0	31.6–98.7
Cortical N20 response[b]	Bilaterally absent (%)	20 (17.5)	
MRI or CT (within 7 days)	Performed in n (%)	87 (52.4)	

n = number. IQR = interquartile range. ICU = Intensive Care Unit. ECMO = extracorporeal membrane oxygenation. NSE = neuron specific enolase. MRI = magnetic resonance imaging. CT = computerized tomography.
[a] Missing data in 9.0% for pupillary reflex and 11.4% for corneal reflex, respectively.
[b] Missing data in 31.3% for cortical N20 responses (patients either awakened or died before performing median nerve somatosensory evoked potentials at 72 h).

3.2. Prognostic EEG patterns

Continuous EEG monitoring was used to categorize patients in the four distinct, mutually exclusive, EEG patterns within the first 5 days of recording: 76 patients (45.8%) had a benign EEG pattern, 36 patients (21.7%) had RSE, 13 patients (7.8%) had GPDs, and 41 patients (24.7%) had a malignant nonepileptiform EEG pattern (Table 2).

The four EEG patterns were highly associated with different prognostic indicators (clinical motor seizures $p < 0.0001$; low flow time $p < 0.0001$; N20 $p < 0.0001$; NSE $p < 0.0001$; neuroimaging $p = 0.0003$). Refractory status epilepticus displayed similarities with the benign EEG pattern while GPDs displayed similarities with the malignant nonepileptiform EEG pattern for low flow time ($p < 0.0001$), N20 ($p < 0.0001$), NSE ($p < 0.0001$), and neuroimaging ($p < 0.0001$) but not for clinical motor seizures ($p = 0.8673$), as shown in Table 2.

3.3. Characteristics and treatment of RSE

Status epilepticus occurred in 43 (25.9%) patients and met the criteria for RSE pattern in 36 (21.7%) patients while in 7 (4.2%), patients evolved from a RSE to GPDs within the first 5 days. These latter patients were considered as GPDs, together with other 6 (3.6%) patients that exhibited exclusively GPDs.

Clinical motor seizures (myoclonic, clonic, or tonic–clonic) during the ICU stay were more prevalent in patients with GPDs (61.5%) compared with RSE (44.4%), as shown in Table 2. Status myoclonus was the most common type of clinical seizure manifestation in GPDs (62.5%) while it was infrequent in RSE (18.7%). All patients with status myoclonus had poor neurological outcome.

Timing of RSE is shown in Fig. 3. The mean onset of RSE was 3 ± 2.3 days after cardiac arrest. The mean duration of RSE was 4.7 ± 4.3 days after onset. Treatment was successful in terminating RSE in 35 (81.4%) patients while 8 (18.6%) patients died during RSE.

Table 2
EEG patterns, clinical seizures and selected prognostic indicators.

EEG pattern (day 0 to 5)	n (%)	Clinical motor seizures n (% of pattern)	Status myoclonus n (% of motor seizures)	Low flow time, min (median)	NSE, μg/L (median)	Absent[a] N20 n (% of pattern)	MRI–CT anoxic injury[b] (n, % of subset)
Benign EEG pattern	76 (45.8)	6 (7.8)	0 (0)	20	36	3 (4.5)	7 (19.4)
RSE pattern	36 (21.7)	16 (44.4)	3 (18.7)	26	47	4 (16.7)	4 (22.2)
GPDs pattern	13 (7.8)	8 (61.5)	5 (62.5)	40	99	6 (54.6)	5 (62.5)
Malignant nonepileptiform EEG pattern	41 (24.7)	4 (9.8)	3 (75.0)	56	248	7 (58.3)	17 (68.5)
Total	166 (100)	34 (20.5)	11 (32.3)	28	48	20	33 (37.9)

n = number. NSE = neuron specific enolase.
[a] Bilaterally absent cortical N20 responses, missing data in 31.3% for cortical N20 responses (patients either awakened or died before performing somatosensory median nerve evoked potentials at 72 h).
[b] Moderate–severe degree of anoxic brain injury based on MRI or CT imaging <7 days (this examination was performed in a subset of 87 patients).

Status epilepticus was refractory in all cases and super-refractory in 21 (58.3%) cases, requiring treatment with anesthetics and multiple AEDs.

3.4. Long-term neurological outcome and survival

Considering the entire cohort, survival was achieved in 77 patients (46.4%) and good neurological outcome (CPC: 1–2) in 70 patients (42.2%) at 6 months (Table 3). EEG pattern in the first 5 days after cardiac arrest was highly associated with both survival ($p = 0.0001$) and neurological outcome ($p < 0.0001$).

Patients with a benign EEG pattern had the highest chance of both survival (72.4%) and good neurological outcome (71.1%) and were chosen as a reference to compare patients with other EEG patterns. Patients with a RSE pattern had a moderate reduction in survival (52.8%; OR: 0.43, 95% CI: 0.19–0.97) and good neurological outcome (44.4%; OR: 0.33; 95% CI: 0.13–0.80). Patients with GPDs have a dramatic reduction in survival (15.4%; OR: 0.07; 95% CI: 0.01–0.34) and good neurological outcome (0%; OR: 0.02; 95% CI: 0.00–0.12). An even more dramatic reduction was observed for patients with malignant nonepileptiform EEG pattern for both survival (2.4%; OR: 0.01; 95% CI: 0.00–0.07) and good neurological outcome (0%; OR: 0.01; 95% CI: 0.00–0.04).

4. Discussion

The intensity and duration of treatment of postanoxic RSE are a highly controversial issue [19,20]. No evidence is currently available on whether a more aggressive treatment would substantially affect the final neurological outcome in refractory postanoxic SE.

Aggressive and prolonged treatment carries the risk of futility [21] while a low-intensity and short-lasting treatment carries the risk of self-fulfilling prophecies, i.e., negative outcome being the consequence of withdrawal of care due to (sometimes erroneous) prognostication of a negative outcome [22]. This latter risk might be particularly high if prognostication relies on a single negative indicator, such as refractory epileptiform EEG activity.

In the present study, we reported survival and long-term neurological outcome of a prospective cohort of postcardiac arrest patients in coma >24 h, who received a standardized aggressive treatment with AEDs and anesthetics if RSE was detected by cEEG monitoring. Intensity and duration of treatment were guided not only by EEG but also by multimodal prognostic indicators.

We adopted a strict definition of RSE, according to the ILAE definition, ACNS terminology, and Salzburg criteria. In particular, we made a clear distinction between low frequency (<2.5 Hz) periodic discharges (GPDs) and RSE without periodic discharges, which were considered

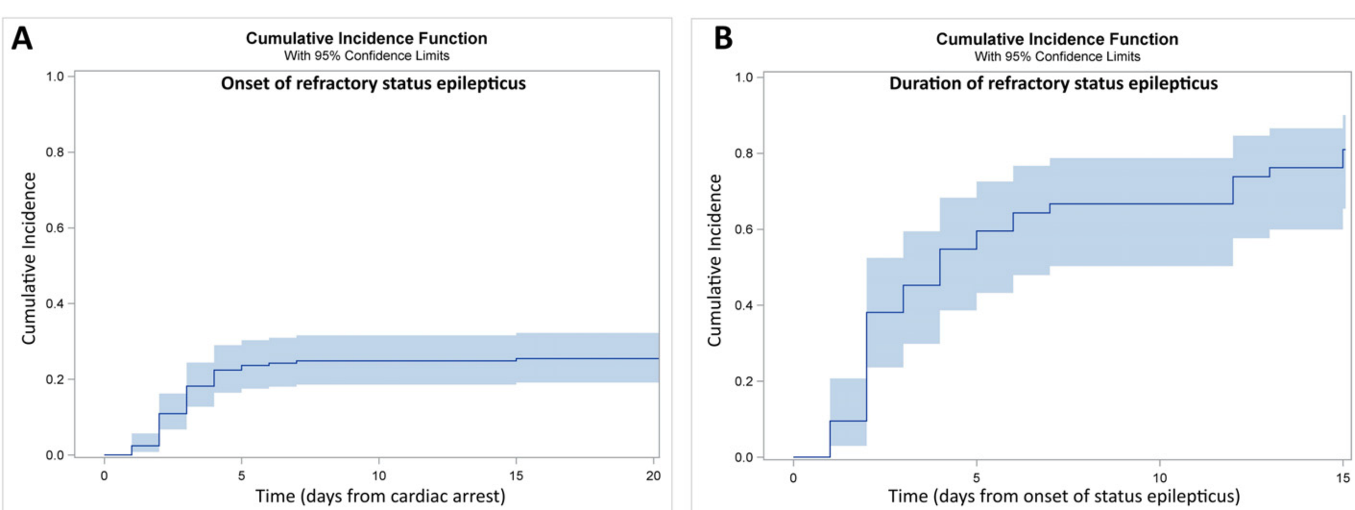

Fig. 3. Time course of refractory status epilepticus in postcardiac arrest patients. Cumulative incidence with 95% confidence limits is shown for onset (A) and duration (B) of refractory status epilepticus.

Table 3
Effect of EEG patterns on neurological outcome and survival at 6 months.

EEG pattern (day 0 to 5)	Survival n (%)	OR (95% CI)	p	CPC 1–2 n (%)	OR (95% CI)	p
Benign EEG pattern	55/76 (72.4)	1.00 (ref)		54/76 (71.0)	1.00 (ref)	
RSE pattern	19/36 (52.8)	0.43 (0.19–0.97)	0.0431	16/36 (44.4)	0.33 (0.13–0.80)	0.0127
GPDs pattern	2/13 (15.4)	0.07 (0.01–0.34)	0.0010	0/13 (0.0)	0.02 (0.00–0.12)	<0.0001
Malignant nonepileptiform EEG pattern	1/41 (2.4)	0.01 (0.00–0.07)	<0.0001	0/41 (0.0)	0.01 (0.00–0.04)	<0.0001
Main effect of EEG patterns			0.0001			<0.0001

n = number; OR = odds ratio; CI = confidence interval; ref = reference category. CPC = cerebral performance category.

as two mutually exclusive EEG patterns. In case of evolution from RSE to GPDs, patients were considered as GPDs. Besides RSE and GPDs, we identified two other nonepileptiform EEG patterns based on background activity and reactivity, which were termed benign and malignant according to previous studies [23,24]. These four mutually exclusive EEG patterns were easily and unequivocally identified in the first 5 days after cardiac arrest using cEEG monitoring and allowed a prognostic analysis.

Our results showed that patients with RSE represent a distinct population in terms of indicators of severity of anoxic brain injury and may present a good neurological prognosis in over 40% with a standardized, aggressive, and prolonged treatment. Our results are remarkably different from recent observational studies without aggressive standardized treatment, which reported <10% of good neurological outcome in postanoxic patients with RSE defined according to the ACNS terminology [25,26].

Compared with patients with GPDs, patients with RSE displayed lower low flow time and NSE levels and were less likely to show clinical motor seizures, absent N20 responses, and severe anoxic brain injury on neuroimaging. The four EEG patterns delineate a range of severity of anoxic brain injury and were strongly associated with long-term survival and neurological prognosis, with patients with RSE appearing more similar to patients with a benign EEG pattern, while patients with GPDs appearing more similar to patients with a malignant nonepileptiform EEG pattern.

Notably, no predefined limit of duration of treatment was applied. Onset of RSE was variable with a mean of 3 days after cardiac arrest, which could be potentially explained by the combined effect of hypothermia and sedation in the first 24–48 h. In more than 50% of cases, RSE lasted more than 72 h, and in approximately 30% of cases, RSE lasted more than 7 days.

5. Conclusions

Our findings suggest that prolonged treatment is necessary and beneficial in selected cases of postanoxic RSE and warn against early outcome prediction (and early decisions of withdrawal of care) in case of RSE. Our findings revealed some important issues, in terms of patient selection, intensity, and duration of treatment, which could inspire the design of future randomized controlled trials comparing aggressive versus conservative treatment of postanoxic SE.

Declaration of Competing Interest

None.

Acknowledgments

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