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Authors: Rossetti AO, Tovar Quiroga DF, Juan E, Novy J, White RD, Ben-Hamouda N, Britton JW, Oddo M, Rabinstein AA

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EEG predicts poor and good outcome after cardiac arrest: a two center study

Running title: Predictors of good and poor prognosis after CA

Andrea O. Rossetti[1], MD; Diego F. Tovar Quiroga[2]; Elsa Juan[1], PhD; Jan Novy[1], MD PhD; Roger D. White,[3] MD PhD; Nawfel Ben-Hamouda[4], MD; Jeffrey W. Britton[2], MD; Mauro Oddo[4], MD; Alejandro A. Rabinstein[2], MD.

[1]Department of Clinical Neurosciences, [4]Department of Intensive Care Medicine, Centre Hospitalier Universitaire Vaudois (CHUV) and Université de Lausanne (UNIL), Lausanne, Switzerland.

[2]Department of Neurology, [3]Department of Anesthesiology, Mayo Clinic, Rochester (MN), USA.

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Address for correspondence:

Dr Andrea Rossetti

Service de Neurologie

CHUV, BH07

Rue du Bugnon 44

CH-1011-Lausanne

Email: andrea.rossetti@chuv.ch

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The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

Authors' contributions:

Conception and design of the study: AOR, AAR.

Acquisition and analysis of data: AOR (including statistics), DFTQ, EJ, JN, JWB, AAR.

Drafting a significant portion of the manuscript or figures: AOR, JN, JWB, AAR.

Revising the manuscript for important intellectual content: all authors.

Abstract

Objective: The prognostic role of EEG during and after targeted temperature management (TTM) in post-cardiac-arrest patients, relatively to other predictors, is incompletely known. We assessed performances of EEG during and after TTM towards good and poor outcome, along with other recognized predictors.

Design: Cohort study (April 2009 - March 2016).

Setting: Two academic hospitals (CHUV, Lausanne, Switzerland; Mayo Clinic, Rochester, MN).

Patients: Consecutive comatose adults admitted after cardiac arrest, identified through prospective registries.

Interventions: All patients were managed with TTM, receiving pre-specified standardized clinical, neurophysiological (particularly, EEG during and after TTM), and biochemical evaluations.

Measurements and Main Results: We assessed EEG variables (reactivity, continuity, epileptiform features, and pre-specified "benign" or "highly malignant" patterns based on the ACNS nomenclature), and other clinical, neurophysiological (SSEP) and biochemical prognosticators. Good outcome (Cerebral Performance Categories 1 and 2) and mortality predictions at three months were calculated. Among 357 patients, early EEG reactivity and continuity, and flexor or better motor reaction had >70% positive predictive value for good outcome; reactivity (80.4%, 95%CI: 75.9-84.4%) and motor response (80.1%, 95%CI: 75.6-84.1%) had highest accuracy. Early "benign" EEG heralded good outcome in 86.2 % (95% CI: 79.8%-91.1%). False-positive rates (FPR) for mortality were <5% for epileptiform or nonreactive early EEG, nonreactive late EEG, absent SSEP, absent pupillary or corneal reflexes, presence of myoclonus, and NSE >75 µg/l; accuracy was highest for early EEG reactivity (86.6%, 95%CI: 82.6-90.0). Early "highly malignant" EEG had an FPR of 1.5 % with accuracy of 85.7% (95% CI: 81.7%-89.2%).

Conclusions: This study provides Class III evidence that EEG reactivity predicts both poor and good outcome, and motor reaction good outcome after cardiac arrest. EEG reactivity seems to be the best discriminator between good and poor outcomes. Standardized EEG interpretation seems to predict both conditions during and after TTM.

Clinicians are increasingly confronted with expectations to provide early, reliable risk stratification of outcome in comatose patients after cardiac arrest (CA). Current recommendations emphasize the need of a multimodal approach [1-3], where available prognosticators target identification of poor outcome patients [4]. There is therefore an important need to learn about the value of readily available tools orienting towards good outcome.

Electroencephalography (EEG) represents one of the most frequently used prognosticators [5]. Several groups have repetitively highlighted its value for prediction of poor prognosis [6-15]. In addition, some studies have highlighted that background continuity [6, 16, 17] and reactivity [18] can identify patients with good outcome. However, these analyses did not systematically examine the role of early versus late (after return to normothermia and off sedation) features, nor the place of EEG in comparison with other predictors.

We aimed to explore the role of specific EEG features for good and poor outcome prognostication, and to compare it to the performance of other predictors, considering both early and later assessments. Furthermore, we intended to validate a recently proposed EEG scoring system [14], based on the American Clinical neurophysiology Society (ACNS) EEG nomenclature [19].

Methods

Design, patients, and settings

This cohort study includes consecutive adults (>18 years) receiving TTM in the ICU for hypoxic-ischemic encephalopathy following CA, with both early (during targeted temperature management, TTM) and late (after return to normothermia and off sedation, 48-72 hours after admission) EEG, and functional outcome at three months. Only subjects with missing EEG data were not included. Patients were identified through existing, prospective registries of the CHUV, Lausanne Switzerland, between April 2009 and March 2016, and the Mayo Clinic, Rochester, MN, between November 2009 and March 2014, approved by their IRB; consents were waived (no intervention).

Procedures and variables

All patients received 24 hours TTM: mild hypothermia to 33-34°C [20], or controlled normothermia at 36°C [21], under standard sedation. At the CHUV, midazolam (0.1 mg/kg/h) or propofol (less frequently; 2-3 mg/kg/h), and fentanyl (1.5 µg/kg/h) infusions were given during the first 24-36 hours; curare was administered for shivering. At the Mayo Clinic, the protocol comprised midazolam infusions (0.015 mg/kg/h) or alternatively, propofol (1-2 mg/kg/h). Fentanyl was perfused up to 1 µg/kg/h. Curare was given as needed. Patients with myoclonus or EEG seizures were treated with nonsedating anticonvulsants (valproate, levetiracetam).

Video-EEGs (CHUV: Viasys, Madison, WI; Mayo clinic: XLTEK, Pleasanton, CA) using 21 electrodes according to the 10–20 system were performed continuously for 24-48 hours, starting as soon as possible after CA, or over 20-30 minutes during the first 9-30 hours and thereafter, within 72 hours after return to normothermia and off sedation. In both approaches, scoring was performed during and after TTM and sedation weaning, at the times of reactivity assessment, tested by applying repetitive auditory, visual, and nociceptive stimuli (finger compression, bilateral nipple pinching if no reactivity seen before) [12, 15]. EEG were categorized by certified interpreters (AOR, DFTQ, JN, JWB) for the presence/absence of 3 dichotomous features: reactivity (recognizable background with reproducible changes in amplitude or frequency within 1-2 seconds of any stimulation, excluding SIRPIDs [22, 23], and muscle artifacts); spontaneous discontinuous pattern (suppressions of at least 10% of the recording [19]); repetitive epileptiform activity (periodic or rhythmic spikes, sharp waves, or spike-waves [9, 24] occurring at least over 10% of the record). Scoring, blinded to outcome, was prospective at the CHUV and retrospective at the Mayo Clinic. For this study, recordings performed before 2013 were rescored to comply with the ACNS nomenclature [19] (that was used since then), using registries' data and analysis of raw traces in unclear situations (<5%, especially for continuity). A distinction between burst-suppression and discontinuity was not definitely retrievable in all cases without epileptiform components, but suppression <10 µV was identified as "flat recording", and reactivity scoring did not change across time.

Within 96 hours from CA, at normothermia and off sedation, patients were serially examined; best results were considered for this analysis. Pupillary and corneal reflexes were categorized as present vs. bilaterally absent; response to pain as flexion or better vs. extension or none [3].

Early myoclonus was considered if appearing within 24 hours after sedation discontinuation. After TTM, cortical responses of somatosensory evoked potentials (SSEP) were categorized as present vs. bilaterally absent. Serum neuron-specific enolase (NSE) was measured within the first 72 hours, and assessed through automated immunofluorescent assays (Thermo Scientific Brahms NSE Kryptor®, Hennigsdorf, Germany); results of peak values were categorized using a threshold of 75 µg/l [15].

Decision to withdraw ICU support was made by interdisciplinary consensus within 10 days after CA, according to a pre-specified multimodal approach [9]. Importantly, early EEG scoring was not used for this decision.

Data collection and outcome assessment

Demographic and clinical variables were collected prospectively using Utstein's recommendations [25]; CA etiology was dichotomized as cardiac vs. non-cardiac, and initial heart rhythm as ventricular fibrillation or tachycardia vs. asystole or pulseless activity. At the CHUV, time to return of spontaneous circulation was estimated on patient's admission. Best neurological outcome within 3 months was assessed blinded to clinical results: at the CHUV prospectively through a telephone interview, at the Mayo Clinic through charts review (patients were routinely seen at 3 months), using Cerebral Performance Categories (CPC) [26]; CPC 1-2 defined good recovery [4].

Statistics

Contingency tables were tested through Fisher exact or chi square tests, and normally distributed variables with two-tailed t-tests, as needed. Two outcomes were considered: good functional outcome (CPC 1-2) and mortality. Sensitivity and positive predictive values (PPV) were calculated for good outcome, and sensitivity and false positive rates (FPR, 1-specificity) for mortality [4]. Accuracies (true negatives and positives / all patients) were calculated for variables with positive PPV of >70% for good outcome and FPR < 5% for mortality, with 95% confidence intervals (binomial distribution). We tested separately PPV for good outcomes considering "benign EEG patterns" (continuous, not suppressed background with reactivity, without epileptiform discharges), and FPR for mortality considering "highly malignant patterns" (suppression or burst-suppression, with or without periodic discharges), as recently defined [14]

using the ACNS nomenclature [19]. Backward stepwise logistic regression analyses were conducted using variables with PPV of >70% for a good outcome, or FPR < 5% for mortality, adjusted for treating centers; calibration was assessed with a Hosmer-Lemeshow test. Calculations were performed using STATA software, version 12 (College Station, TX, USA).

Results

We studied 260 patients at the CHUV (134 overlapping with [15]) and 97 at the Mayo Clinic (62 overlapping with [27]); at 3 months, 180 (50.4%; 88.2% of survivors) had a good outcome, 24 (6.7%) with CPC 3, and 153 (42.9%) died; nobody had a CPC 4. Included patients represent about 80% of those treated with TTM in the study period. **Table 1** illustrates their characteristics. Patients at the Mayo Clinic tended to present more frequently with shockable rhythms; all had continuous EEG (institutional protocol). A CHUV subgroup was treated targeting 36°C, while all other patients received hypothermia to 33°C. CHUV patients had more often nonreactive and discontinuous EEGs, while early epileptiform features were more frequent at the Mayo Clinic. Although outcomes did not differ statistically, they had a tendency to be better at the Mayo Clinic; accordingly, absent pupillary reflexes or motor reactions to pain were more frequent at the CHUV. Time to return of spontaneous circulation at the CHUV was 23.8 ± 19.0 min; the first EEG including reactivity assessment was performed 17.9 ± 6.2 hours after CA (in 236 patients, 91%, within 24 hrs).

Table 2 summarizes predictive performances for good outcome (CPC 1-2). Three variables showed a PPV >70%: early EEG reactivity and continuity, and flexor or better motor response. All features had sensitivities >80%; EEG reactivity and motor reaction showed the highest accuracy. The multivariable logistic regression confirmed that the three were independently related to favorable prognosis (**Table 3a**). Early and late “benign” EEG had also high PPV.

Table 4 shows mortality prediction (**suppl. Tables:** stratification between previously published and new patients). Several variables had an FPR <5%; while sensitivity was below 50% for nearly all, EEG reactivity stood out (especially early EEG, displaying the highest accuracy). Early and late “highly malignant EEG” also showed very low FPR. Multivariable analysis identified early EEG reactivity and epileptiform discharges, and late EEG reactivity, as

independently related to mortality (**Table 3b**). **Figure 1** illustrates the predictive performance of the principal variables towards the two main outcomes.

Discussion

Several studies evaluated predictors of poor prognosis after CA, but our analysis is one of the few also assessing indicators of good outcome, and explores prognosticators during and after TTM in relation to both outcomes. It shows that EEG reactivity during TTM and sedation has the highest accuracy for both good and poor outcome. It also highlights the prognostic value for good outcome when the motor response to pain is flexion or better. Furthermore, a predefined "benign" EEG background [14] has a high PPV for good outcome, while a "highly malignant" pattern [14] has a very low FPR for mortality, both during and after TTM.

EEG reactivity

During TTM, reactivity seems the most robust discriminator between good and poor outcome, and is independently related to them. Reactivity during TTM correlates with neuronal injury reflected by NSE [12]. While mild therapeutic hypothermia should not exert a major impact on EEG [28], pharmacological sedation may influence background continuity [6, 15, 16]. Epileptiform features, which indeed do not significantly correlate with neuronal injury markers [12], showed lower sensitivity for mortality as compared to reactivity, and lower specificity for good outcome. We recognize that reactivity has an imperfect interrater reliability [29, 30], with a heterogeneous prevalence at our two centers, even if both are familiar with the stimulus type (nipples pinching) that seems to be most sensitive [31].

Timing of EEG assessment

EEG has been traditionally used after TTM and off sedation [9, 10, 32]: lack of reactivity forecasts unfavourable prognosis [9, 10], similarly to low voltage (<20 μV), suppressed or burst-suppressed background [6, 14], or burst-suppression with identical bursts [8]. Epileptiform features were also related to poor outcome [9]. These features are found in current prognostic recommendations [1].

Recently, increasing attention was directed towards EEG recorded during TTM and sedation [24]: suppressed or low-voltage background shows higher correlation with poor outcome [6, 16, 33, 34], similarly to lack of reactivity [11, 15], and epileptiform features [12, 13, 34]. Additionally, and innovatively [4], EEG has been reported to herald good outcome if a continuous background and normal voltage are seen at 12-24 hours [6, 16], or showing reproducible reactivity [18]. It is possible that recordings performed early after CA and standardized conditions may be exposed to less confounders (co-morbidities such as infections, vigilance, and co-medications).

This study validates recent findings of the TTM-trial EEG analysis [14] on pre-defined "benign" and "highly malignant patterns", confirming the robustness of prediction for poor and good outcome after return of normothermia, albeit with slightly higher FPR, probably reflecting a less standardized reading and the considerably greater number of patients, better corresponding to real clinical practice. Additionally, we expanded the usefulness of this approach into recordings obtained during TTM and sedation.

Comparison with previous studies on clinical EEG

The CHUV reactivity analyses [11, 18] were single-center, including 90 patients, with only few other predictors. The Mayo Clinic study [17], including 54 patients, did not evaluate other variables, and assigned EEG into one of three predefined categories, preventing more granular analyses. The Yale series [6] included 100 patients, and did not consider biochemical markers or SSEP. The Belgian assessment [33] involved 92 patients, also used a composite EEG scoring, and did not analyze in detail EEG after sedation, nor other prognosticators. A study from Pittsburgh on EEG counterparts of myoclonus included 65 patients; it did not report on a multimodal approach [34]. The Dutch 2-centers cohort was large (277 patients); however, EEG scorings were also composite, and EEG reactivity, corneal reflexes, or NSE were not addressed. Finally, the TTM trial analysis [14], with 103 subjects from European hospitals, was limited to normothermia, not confirming the value of low voltage [6, 16]; other prognosticators were not addressed. Quantitative EEG receives growing interest [29, 35], but this approach is still limited by generalizability [4].

While our study appears in line with these previous findings, it adds new information. It includes the largest number of patients, from two relatively heterogeneous cohorts in terms of EEG recordings, CA types, sedation, TTM, and neurophysiological, clinical and biochemical features (**Table 1**), in distinct locations with different practical approaches. This should reinforce generalizability of the findings. It validates outside a rigid study setting not only a recently proposed EEG scoring following the ACNS nomenclature [14, 30, 36], but it also analyzes core EEG features (reactivity, continuity and epileptiform transients), allowing detailed understanding of the prognostic role of each for both poor and, importantly, good outcome. Both sites used a pre-defined protocol for discontinuation of ICU measures, rendering identification of items potentially biased by the self-fulfilling prophecy more straightforward [4].

Motor reaction

The remarkable prognostication performance of responses better than extension for identification of good prognosis may appear somewhat surprising. Extension or lack of movements was found to forecast poor prognosis before the hypothermia era [3], but was strongly questioned after convergent reports of unacceptable high FPRs in patients undergoing TTM (and sedation) [9, 37-39]: it is thus not mentioned in current recommendations [1], and false positivity is high (15.2%) in this study. Our results indicate that a flexor or better reaction shortly after TTM independently heralds favourable outcome in a significant proportion of patients, confirming a previous observation [6]. This may represent a revival of this clinical sign to specifically detect favourable recovery, in a context where nearly all prognosticators are directed towards identification of poor prognosis.

Limitations

First, EEG scoring occurred prospectively at the CHUV but retrospectively -albeit blinded- at the Mayo Clinic; this may explain some heterogeneity of findings. Second, we included both continuous and routine EEG recordings. Some groups advocate continuous EEG [6, 16] as electrical activity evolves and seizures may be detected [7]. This technique is however not likely to be widely available, and routine EEGs, including stimulations for reactivity, seem to offer comparable information [40], at lower costs [27]. Third, EEG assessment times were not strictly uniform, and prevalence of EEG reactivity and continuity, brainstem reflexes, and motor

reaction, differed across centers. Although heterogeneous data ascertainment is possible, this reflects the observational design with different sedation policies (higher doses at CHUV), and patients' profile (somewhat worse outcome at CHUV). Our findings may thus be generalizable to other settings. Moreover, multivariable models were adjusted for centers; patients at CHUV had worse outcomes on the raw data, but had higher chance of good outcome in the analysis adjusted for poor prognostic features. Reasons for this discrepancy are unclear, and may in part reflect the subjectivity of the CPC, which nevertheless is validated. Importantly, the difference between centres was significant but almost marginal (CI approaching 1), and mortality was not different. Fourth, several EEG items related to the ACNS-nomenclature were inferred retrospectively for records preceding 2013; due to this, low voltage >10µV was not systematically considered as incompatible with "benign", as opposed to [14]; "highly malignant" or "benign" patterns were also scored retrospectively, but blinded from the outcome. It is possible that this generated some errors, but it seems unlikely that these were systematic. Fifth, we did not analyze brain imaging, used unsystematically. Sixth, outcome assessment was not uniform, and occurred at three (but not six) months, reflecting the centers' practices in those years. Finally, although cause of death and decisions to withdraw life support were not specifically recorded, the latter were always discussed after clinical examinations off sedation, and EEG scoring occurred blindly towards outcome; therefore, despite having being available to clinicians, early EEG is unlikely to have been affected by the self-fulfilling prophecy.

Conclusion

It is of outmost importance to always formulate a prognosis after carefully evaluating all available information from different sources, in order to minimize risks of false poor prediction [1, 2, 4]. While current guidelines still rely on relatively late EEG [1, 3], early EEG represents a valuable tool to identify patients both with good and poor prognosis. Thus, information provided by EEG has important practical implications, but should never be used alone for prognostication.

Table 1: Clinical characteristics of the two cohorts (if no denominator is given, all patients were tested).

Table 2: Predictors of good outcome in the whole cohort.

Table 3. **A**: multiple logistic regression of predictors of good outcome with PPV >70%, and **B**: of predictors of mortality with FPR <5%, controlling for treating center.

Table 4: Predictors of mortality in the whole cohort.

Suppl. Table: Subset of mortality predictors according to previously and newly published patients.

Figure 1: Accuracy towards good outcome (grey bars) and mortality (black bars) of predictors with a positive predictive value >70% for good outcome and false positive rate <5% for mortality.

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Accuracy of the predictors
100
95
90
85
80
75
70
65
60
55
50
Good outcome
Mortality
Early EEG reactive
Early EEG continuous
Early EEG epileptiform
Late EEG not reactive
Motor GCS ≥3
SSEP bilaterally absent
Pupillary reflex bilaterally absent
Corneal reflex bilaterally absent
Early Myoclonus
Serum NSE ≥75 µg/l

Table 1: Clinical characteristics of the two cohorts (if no denominator is given, all patients were tested).

Variable	**CHUV 260 pts**	**Mayo 97 pts**	**P (test)**
Age, years, mean (±SD)	61.8 (±14.5)	61.2 (±11.3)	0.710 (t)
Male gender (%)	187 (71.9%)	68 (70%)	0.735 (χ^2)
Non-cardiac cause (%)	61 (22.5%)	14 (14.4%)	0.062 (χ^2)
Asystole or pulseless electrical activity (%)	94 (36.1%)	13 (13.4%)	**<0.001** (χ^2)
TTM with 36°C target (all others: 33°C)	27 (10.4%)	0 (0%)	**0.001** (Fisher)
Continuous EEG monitoring	41 (15.8%)	97 (100%)	**<0.001** (χ^2)
Early EEG not reactive	93 (35.8%)	18 (18.6%)	**0.002** (χ^2)
Early EEG not continuous	139 (53.5%)	22 (22.7%)	**<0.001** (χ^2)
Early EEG epileptiform	45 (17.3%)	36 (37.1%)	**<0.001** (χ^2)
Early EEG "benign"	105 (40.3%)	54 (55.7%)	**0.010** (χ^2)
Early EEG "highly malignant"	89 (34.2%)	19 (19.6%)	**0.007** (χ^2)
Late EEG not reactive	82 (31.5%)	15 (15.5%)	**0.002** (χ^2)
Late EEG not continuous	97 (37.3%)	9 (9.3%)	**<0.001** (χ^2)
Late EEG epileptiform	67 (25.8%)	30 (30.9%)	0.330 (χ^2)
Late EEG "benign"	132 (50.8%)	62 (63.9%)	**0.027** (χ^2)
Late EEG "highly malignant"	84 (32.3%)	15 (15.5%)	**0.002** (χ^2)
Bilaterally absent SSEP	55/244 (22.5%)	6/16 (37.5%)	0.171 (χ^2)
Bilaterally absent pupillary reflex	48/258 (18.6%)	6/97 (6.2%)	**0.004** (χ^2)
Motor GCS <3	125 (48.1%)	33 (34.0%)	**0.017** (χ^2)
NSE ≥75µg/l	48/233 (20.6%)	13/96 (13.5%)	0.134 (χ^2)
Good CPC at 3 months (1-2) (%)	124 (47.7%)	56 (57.7%)	0.091 (χ^2)
Mortality (%)	118 (45.4%)	35 (36.1%)	0.114 (χ^2)

CPC= cerebral performance category; NSE = neuron specific enolase; SSEP = somatosensory evoked potentials; TTM= targeted temperature management. For "benign" and "highly malignant" EEG definitions, please see text.

Table 2: Predictors of good outcome in the whole cohort.

		Distribution				Good Outcome (CPC 1-2)				Accuracy	
Variable	**Tested patients**	**TP**	**FP**	**FN**	**TN**	**Sensitivity (%)**	**95% CI (%)**	**PPV (%)**	**95% CI (%)**	**Point Est.**	**95% CI (%)**
Age < 65	357	118	75	62	102	65.6	58.1-72.5	61.1	53.9-68.1		
Cardiac etiology	357	152	130	27	48	84.9	78.8-89.8	53.9	47.9-59.8		
Shockable rhythm	357	150	100	30	77	83.3	77.1-88.5	60.0	53.6-66.1		
Early EEG reactive	357	178	68	2	109	98.9	96.0-99.9	72.4	66.3-77.9	80.4	75.9-84.4
Early EEG continuous	357	144	42	36	135	80.0	73.4-85.6	77.4	70.7-83.2	78.2	73.5-82.3
Early EEG not epileptiform	357	175	101	5	76	97.2	93.6-99.1	63.4	57.4-69.1		
Early EEG “benign”	357	137	22	43	155	76.1	69.2-82.1	86.2	79.8-91.1	81.8	77.4-85.7
Late EEG reactive	357	179	81	1	96	99.4	96.9-99.9	68.9	62.8-74.4		
Late EEG continuous	357	168	83	12	94	93.3	88.6-96.5	66.9	60.7-72-7		
Late EEG not epileptiform	357	173	87	7	90	96.1	92.2-98.4	66.5	60.4-72.3		
Late EEG “Benign”	357	163	31	17	146	90.6	85.3-94.4	84.0	78.1-88.9	86.5	82.6-89.9
SSEP present	260	119	80	0	61	100	97.0-100	59.8	52.6-66.7		
Pupillary normal	355	177	124	3	51	98.3	95.2-99.7	58.8	53.0-64.4		
Corneal normal	354	175	104	5	70	97.2	93.6-99.1	52.7	56.8-68.4		
Motor GCS ≥3	357	151	42	29	135	83.9	77.7-88.9	78.2	71.7-83.8	80.1	75.6-84.1
No early myoclonus	357	176	113	4	74	97.8	94.4-99.4	60.9	55.0-66.6		
NSE <75 µg/l	329	169	99	0	61	100	97.8-100	63.1	57.0-68.9		

TP= true positive, FP= false positive, FN= false negative, TN= true negative. CPC= cerebral performance category; SSEP= somatosensory evoked potentials; GCS= Glasgow Coma Score; NSE= neuron specific enolase. Accuracies were only calculated for items with PPV >70%.

Table 3. **A**: multiple logistic regression of predictors of good outcome with PPV >70%, and **B**: of predictors of mortality with FPR <5%, controlling for treating center.

A	OR	95% CI	P
Early EEG reactive	39.68	9.01-175.43	<0.001
Early EEG continuous	3.80	1.5877.75	<0.001
Motor GCS ≥3	4.69	2.47-9.04	<0.001
Center CHUV	2.13	1.04-4.35	0.038
B	OR	95% CI	P
Early EEG not reactive	21.97	5.74-84.08	<0.001
Early EEG epileptiform	15.07	4.62-49.2	<0.001
Late EEG non reactive	41.37	4.94-346.36	0.001
Center CHUV	1.79	0.66-4.89	0.254

A: Hosmer-Lemeshow P= 0.777; **B**: Hosmer-Lemeshow P= 0.994. GCS= Glasgow Coma Score.

Table 4: Predictors of mortality in the whole cohort.

		Distribution				Mortality (CPC 5)				Accuracy	
Variable	**Tested patients**	**TP**	**FP**	**FN**	**TN**	**Sensitivity (%)**	**95% CI (%)**	**FPR (%)**	**95% CI (%)**	**Pojnt Est.**	**95% CI (%)**
Male gender	357	105	150	48	54	68.6	60.6-75.9	73.5	66.9-79.5		
Age > 64	357	84	75	69	129	54.9	46.7-63.0	36.8	30.1-43.8		
Noncardiac etiology	357	41	34	112	170	26.8	20.0-34.6	16.7	11.8-22.5		
Nonshockable rhyhtm	357	66	41	87	163	43.1	35.2-51.4	20.1	14.8-26.3		
Early EEG not reactive	357	108	3	45	201	70.6	62.7-77.7	1.5	0.3-4.2	86.6	82.6-90.0
Early EEG not continuous	357	123	48	30	156	80.4	73.2-86.4	23.5	17.9-30.0		
Early EEG epileptiform	357	74	7	79	197	48.3	40.2-56.6	3.4	1.4-6.9	75.9	71.1-80.2
Early EEG « Highly malignant »	357	105	3	48	201	68.3	60.6-75.9	1.5	0.3-4.2	85.7	81.7-89.2
Late EEG not reactive	357	96	1	57	203	62.8	54.6-70.4	0.5	0.0-2.7	83.8	79.5-87.4
Late EEG not continuous	357	88	18	65	186	57.5	49.2-65.5	8.8	0.5-13.6		
Late EEG epileptiform	357	85	12	68	192	55.6	47.3-63.3	5.9	3.1-10-5		
Late EEG « Highly malignant »	357	96	3	57	201	62.8	54.6-70.4	1.5	0.3-4.2	83.2	78.9-86.9
SSEP bilaterally absent	260	60	1	63	136	48.8	39.7-58.0	0.7	0.0-4.0	75.4	69.7-80.1
Pupillary bilaterally abnormal	355	50	4	103	198	32.7	25.3-40.7	2.0	0.5-5.0	69.9	64.8-74.6
Corneal bilaterally abnormal	354	69	6	84	195	45.1	37.1-53.3	3.0	1.1-6.4	74.6	69.7-79.0
Motor GCS <3	357	127	31	26	173	83.0	76.1-88.6	15.2	10.6-20.9		
Early Myoclonus	357	63	5	90	199	41.2	33.3-49.4	2.5	0.8-5.6	73.4	68.5-77.9
NSE ≥75 µg/l	329	60	1	77	191	43.8	35.3-52.5	0.5	0.0-2.9	76.3	71.3-80.8

TP= true positive, FP= false positive, FN= false negative, TN= true negative. CPC= cerebral performance category; SSEP= somatosensory evoked potentials; GCS= Glasgow Coma Score; NSE= neuron specific enolase. Accuracies were only calculated for items with FPR <5%.

Supplementary Table1: Subset of good outcome predictors according to previously and newly published patients.

Previously published patients (196)		**Distribution**				**Good outcome (CPC 1-2)**	
Variable	**Tested patients**	**TP**	**FP**	**FN**	**TN**	**PPV (%)**	**95% CI (%)**
Early EEG reactive	196	96	40	1	59	70.6	62.2 – 78.1
Early EEG continuous	196	85	21	12	78	80.2	71.3 – 87.3
Early EEG not epileptiform	196	92	55	5	44	62.6	54.2 – 70.4
Early EEG « Benign »	196	73	12	24	87	85.9	76.6 – 92.5
Late EEG reactive	196	97	42	0	57	70.8	62.4 – 78.3
Late EEG continuous	196	85	21	12	78	80.2	71.3 – 87.3
Late EEG not epileptiform	196	92	50	5	49	63.4	54.9 – 71.3
SSEP present	134	59	40	0	35	59.6	49.3 – 69.3
Pupillary normal	194	95	70	2	27	57.6	49.7 – 65.2
Motor GCS ≥3	196	80	26	17	73	82.4	73.4 – 89.4
No early Myoclonus	196	94	67	3	32	58.4	50.4 – 66.1
NSE <75 µg/l	183	92	57	0	34	61.7	53.4 – 69.6
Newly published patients (161)		**Distribution**				**Good outcome (CPC 1-2)**	
Variable	**Tested patients**	**TP**	**FP**	**FN**	**TN**	**PPV (%)**	**95% CI (%)**
Early EEG reactive	161	82	28	1	50	74.5	65.4 – 82.4
Early EEG continuous	161	59	21	24	57	73.8	62.7 – 83.0
Early EEG not epileptiform	161	80	45	3	33	64.0	54.9 – 72.4
Early EEG « Benign »	161	64	10	19	68	86.5	76.5 – 93.3
Late EEG reactive	161	82	39	1	39	67.7	58.7 – 76.0
Late EEG continuous	161	75	37	8	41	67.0	57.4 – 75.6
Late EEG not epileptiform	161	81	37	2	41	68.6	59.5 – 76.9
SSEP present	126	60	40	0	26	60.0	49.7 – 69.7
Pupillary normal	161	82	54	1	24	60.3	51.6 – 68.6
Motor GCS ≥3	161	71	16	12	62	81.6	71.9 – 89.1
No early Myoclonus	161	82	46	1	32	64.1	55.1 – 72.3
NSE <75 µg/l	146	77	42	0	27	64.7	55.4 – 73.2

Supplementary Table2: Subset of mortality predictors according to previously and newly published patients.

Previously published patients (196)		**Distribution**				**Mortality (CPC 5)**	
Variable	**Tested patients**	**TP**	**FP**	**FN**	**TN**	**FPR (%)**	**95% CI (%)**
Early EEG not reactive	196	59	1	23	113	0.9	0.0 - 4.8
Early EEG not continuous	196	69	21	13	93	18.4	11.8 -26.8
Early EEG epileptiform	196	42	5	40	109	4.4	1.4 – 9.9
Early EEG « Highly malignant »	196	53	2	29	112	1.2	0.2 – 6.2
Late EEG not reactive	196	57	0	25	114	0.0	0.0 - 3.2
Late EEG not continuous	196	47	10	35	104	8.8	4.3 – 15.5
Late EEG epileptiform	196	45	9	37	105	7.9	3.7 – 14.5
SSEP bilaterally absent	134	34	1	27	72	1.3	0.0 – 7.4
Pupillary bilaterally absent	194	30	2	60	110	1.8	0.2 – 6.3
Motor GCS <3	196	67	17	15	97	14.9	8.9 - 22.8
Early Myoclonus	196	31	4	51	110	3.5	1.0 – 8.7
NSE ≥75 µg/l	183	34	0	41	108	0.0	0.0 - 3.4
Newly published patients (161)		**Distribution**				**Mortality (CPC 5)**	
Variable	**Tested patients**	**TP**	**FP**	**FN**	**TN**	**FPR (%)**	**95% CI (%)**
Early EEG not reactive	161	49	2	22	88	2.2	0.2 - 7.8
Early EEG not continuous	161	54	27	17	63	30.0	20.8 – 40.6
Early EEG epileptiform	161	32	2	39	88	2.2	0.2 – 7.8
Early EEG « highly malignant »	161	52	1	19	89	1.1	0.0 – 6.0
Late EEG not reactive	161	39	1	32	89	1.1	0.0 – 6.0
Late EEG not continuous	161	41	8	30	82	8.9	3.9 -16.8
Late EEG epileptiform	161	40	3	31	87	3.3	0.7 – 9.4
SSEP bilaterally absent	126	26	0	36	64	0.0	0.0 - 5.6
Pupillary bilaterally absent	161	20	2	43	88	2.2	0.2 – 7.8
Motor GCS <3	161	60	14	11	76	15.5	8.8 24.7
Early Myoclonus	161	32	1	39	89	1.1	0.0 – 6.0
NSE ≥75 µg/l	146	26	1	36	83	1.2	0.0 – 6.5

TP= true positive, FP= false positive, FN= false negative, TN= true negative. CPC= cerebral performance category; SSEP= somatosensory evoked potentials; GCS= Glasgow Coma Score; NSE= neuron specific enolase.