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Clinical paper

EEG for good outcome prediction after cardiac arrest: A multicentre cohort study

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Abstract

Aim: Assess the prognostic ability of a non-highly malignant *and* reactive EEG to predict good outcome after cardiac arrest (CA).

Methods: Prospective observational multicentre substudy of the "Targeted Hypothermia versus Targeted Normothermia after Out-of-hospital Cardiac Arrest Trial", also known as the TTM2-trial. Presence or absence of highly malignant EEG patterns and EEG reactivity to external stimuli were prospectively assessed and reported by the trial sites. Highly malignant patterns were defined as burst-suppression or suppression with or without superimposed periodic discharges. Multimodal prognostication was performed 96 h after CA. Good outcome at 6 months was defined as a modified Rankin Scale score of 0–3.

Abbreviations: ACNS, American Clinical Neurophysiology Society, CA, Cardiac Arrest, CI, Confidence Intervals, eCRF, electronic Case Report Form, EEG, Electroencephalography, IQR, Interquartile Range, mRS, modified Rankin Scale, TTM, Targeted Temperature Management, WLST, Withdrawal of Life-Sustaining Therapy

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Results: 873 comatose patients at 59 sites had an EEG assessment during the hospital stay. Of these, 283 (32%) had good outcome. EEG was recorded at a median of 69 h (IQR 47–91) after CA. Absence of highly malignant EEG patterns was seen in 543 patients of whom 255 (29% of the cohort) had preserved EEG reactivity. A non-highly malignant *and* reactive EEG had 56% (CI 50–61) sensitivity and 83% (CI 80–86) specificity to predict good outcome. Presence of EEG reactivity contributed ($p < 0.001$) to the specificity of EEG to predict good outcome compared to only assessing background pattern without taking reactivity into account.

Conclusion: Nearly one-third of comatose patients resuscitated after CA had a non-highly malignant *and* reactive EEG that was associated with a good long-term outcome. Reactivity testing should be routinely performed since preserved EEG reactivity contributed to prognostic performance.

Keywords: EEG, Reactivity, Prognosis, Coma, Cardiac arrest, Outcome

Introduction

Prognostication of comatose patients following cardiac arrest (CA) is an important task. The multimodal prognostic algorithm of the 2021 ERC-ESICM guidelines for post resuscitation care includes highly malignant EEG patterns beyond 24 h, i.e. burst-suppression or suppression with or without superimposed periodic discharges[1]. The algorithm is primarily designed to predict poor outcome, leaving approximately half of patients with indeterminate predictions[2–4]. In this context, it is important to identify predictors of good outcome; understanding these predictors can contribute to improving patient care by facilitating timely interventions and optimizing resources to support recovery and rehabilitation efforts.

Electroencephalography (EEG) is a tool capable of predicting both good and poor outcomes. Guidelines recommend using the standardized EEG terminology by the American Clinical Neurophysiology Society (ACNS)[5] to improve prognostic accuracy and inter-rater reliability. However, consensus on what constitutes a favourable EEG is lacking. Some definitions include continuous normal-voltage EEG background patterns[6–8], while others allow low-voltage patterns[9–10] or discontinuous patterns[11–13]. Many studies include preserved EEG reactivity to external stimuli in the definition of a favourable EEG[14–18] but the optimal combination of favourable EEG features for predicting good outcomes after CA remains unclear[19].

Another knowledge gap is the role of EEG reactivity in enhancing specificity in good outcome predictions compared to assessing only the EEG background pattern. A recent Dutch study indicated that presence of reactivity may have an additional value for prediction of good outcome[20]. Similar trends have been reported in other small cohort studies[7,15,21] but these results need to be validated in a larger cohort.

We recently evaluated the EEG recommendations of the ERC-ESICM guidelines regarding poor outcome prediction with highly malignant EEG patterns in the international TTM2-trial[22]. The present study aims to assess the prognostic accuracy of a non-highly malignant *and* reactive EEG in comatose resuscitated patients to predict good outcome within this large multicentre cohort. Additionally, we investigate whether preserved EEG reactivity enhances specificity in predicting good outcomes compared to solely considering the background pattern. Finally, we investigate whether the timing of EEG recording impacts the prognostic ability.

Methods

This is a substudy of the international "Targeted Hypothermia versus Targeted Normothermia after Out-of-hospital Cardiac Arrest. A Randomised Clinical Trial," also known as the TTM2-trial. In this trial, adult comatose patients resuscitated after out-of-hospital CA of presumed cardiac cause were randomly assigned to temperature control at 33 °C versus early treatment of fever (≥37.8 °C) (ClinicalTrials.gov NCT02908308)[23]. The trial protocol was approved by the ethics committees in participating countries. Consent was obtained from each patient regaining mental capacity, a legal representative, or waived according to local legislation[24]. The trial randomised 1900 patients between November 2017 and January 2020.

According to the TTM2 protocol, EEG was mandatory in patients who remained unconscious between 48 and 96 h after CA. At this time interval patients were normothermic and sedation was stopped or kept as low as possible. EEG assessments could also be performed outside of this time interval according to local routines or clinical indications. The first EEG assessment 0–14 days after CA was used in the main analyses of the present study. Instructions for performing and interpreting EEG were specified in the TTM2 protocol (Suppl EEG instructions). Local EEG reviewers assessed the EEG recordings and results were prospectively reported in the electronic case report form (eCRF) by the investigator team. The EEG reviewers were not blinded to clinical data in the EEG referral. The presence or absence of highly malignant EEG patterns and EEG reactivity were reported. Sites were instructed to use the EEG definitions according to the American Clinical Neurophysiology Society (ACNS)[25]. Highly malignant EEG patterns were defined as burst-suppression background with suppression periods (<10 μV) constituting ≥50% of the recording or suppressed background (<10 μV the entirety of the record) with or without superimposed periodic discharges.

A non-highly malignant EEG encompasses a broad spectrum of EEG patterns: continuous, nearly continuous, discontinuous, normal-voltage or low-voltage background activity with or without superimposed discharges. EEG reactivity to external stimuli was defined as a change in the EEG background frequency or amplitude after sound stimuli or painful stimuli[25]. Appearance of muscle activity or eye blink artefacts or SIRPIDs (Stimuli induced Rhythmic, Periodic or Ictal Discharges) do not qualify as a reactive EEG. The recommendations to the sites were to repeat the sound stimuli (call the patient's name and clap hands) and pain stimuli (distal and proximal) at least twice respectively and with >20 s delay between stimuli.

At 96 h or later, a physician blinded to the target temperature intervention conducted multimodal prognostication in patients that were still alive and comatose. The trial protocol criteria for predicting a poor prognosis were met if at least two of the following indicators were present: bilateral absence of pupillary and corneal reflexes, myoclonic status, unreactive highly malignant EEG, brain CT or MRI showing signs of global ischemic injury, elevated NSE levels, and bilaterally absent cortical SSEP N20 responses. Details are reported in the trial protocol[24]. Follow-up was conducted face-to-

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face or by telephone interview 180 days after CA. A good outcome was defined as a modified Rankin Scale (mRS) score of 0–3 (no symptoms, no significant disability, slight disability or moderate disability).

For statistical analyses, we used SPSS version 28. We included the first EEG performed within 14 days after CA. We calculated the ability of EEG to predict a good outcome (specificity, sensitivity, positive predictive value and negative predictive value). To evaluate the added value of EEG reactivity compared to a non-highly malignant EEG background in isolation, we used the McNemar test. For the primary analysis, a *p*-value <0.05 was considered statistically significant. We assessed the prognostic ability of EEG across different time intervals by conducting comparisons between adjacent time windows (0–24 h, 24–48 h, 48–72 h, 72–96 h, 96–120 h, and beyond 120 h) and between early EEGs (<24 h) vs later EEGs (>24 h). Both types of comparisons were conducted within the same individuals at multiple time points and among different individuals. We employed McNemar's and Fisher's tests: the choice of test was dependent on whether a patient had an EEG within one or both compared time windows. Fisher's method was applied to combine the p-values from the two methods. We approximated 95% confidence intervals (CI) according to Wilson's method.

Results

Patients

Out of the 1900 patients enrolled in the TTM2-trial, 1029 were still comatose during the prognostication period (≥96 h), making them eligible for an EEG as per protocol. However, 110 of these patients did not undergo EEG testing. During the hospital stay, 919 patients performed an EEG within 14 days after CA. Among these patients, 14 were excluded due to missing EEG results in the eCRF, and an additional 32 patients were excluded because reactivity testing was not conducted. Hence, the primary analysis included 873 patients (697 [80%] males; mean age 65 years) from 59 trial sites. The flow chart of inclusion in the study is presented in Fig. 1. Baseline characteristics are presented in Table 1.

EEG recordings were conducted at a median of 69 h after CA (IQR 47–91). Prognostication was carried out in 616 (71%) still comatose patients and 417 (48%) patients underwent withdrawal of life-sustaining therapy (WLST). At six-month follow-up, 283 (32%) patients had good neurological outcome.

Predictive value of non-highly malignant EEG (regardless of reactivity)

Out of the 873 patients studied, 543 (62%) patients had absence of highly malignant patterns, of whom 259 had a good outcome (Fig. 2). This pattern showed 92% sensitivity, 52% specificity, 48% positive predictive value (PPV) and 93% negative predictive value (NPV) to predict good outcome (Table 2).

Predictive value of non-highly malignant and reactive EEG

255 (29%) patients exhibited absence of highly malignant patterns *and* preserved reactivity, of whom 157 had a good outcome. The sensitivity was 56%, the specificity 83%, the PPV 62% and the NPV 80% to predict good outcome.

Added value of reactivity testing

A non-highly malignant *and* reactive EEG demonstrated significantly higher specificity to predict good outcome compared to a non-highly malignant EEG without considering reactivity (83% vs 52%; $p < 0.001$).

Time point of EEG

The first available EEG within each time interval (0–24 h, 24–48 h, 48–72 h, 72–96 h, 96–120 h, and beyond 120 h) was used to assess prognostic ability (Suppl Table E1). Among the 873 patients, 298 (34%) underwent a second EEG, and 128 (15%) underwent a third EEG, resulting in a total of 1299 EEGs. For this analysis, one EEG per patient per time interval was included, yielding a total of 1206 EEGs analysed. During the first 24 h after CA a non-highly malignant *and* reactive EEG predicted good outcome with sensitivity 49%, specificity 92%, PPV 83%, and NPV 70%. The prognostic ability beyond 24 h (until 14 days) after CA showed sensitivity 57%, specificity 83%, PPV 61% and NPV 81%. We could not detect any statistically significant difference in sensitivity or specificity across the various time points.

Unfavourable multimodal prognostication and favourable EEG

Of 616 patients who underwent multimodal prognostication, poor prognosis was predicted in 241 patients (Table 1), of whom 235 (98%) had a poor outcome. Among the 241 patients with a likely poor prognosis, 22 had a non-highly malignant *and* reactive EEG, of whom 4 (18%) patients had a good outcome.

Discussion

We aimed to assess the ability of EEG to predict good outcome in comatose resuscitated patients, within the context of a large multicentre cohort. We found that a non-highly malignant *and* reactive EEG predicted a good long-term neurological outcome, with a specificity of 83% and a sensitivity of 56%. To our knowledge this study is the largest investigation of the value of preserved EEG reactivity, involving 59 trial sites in Europe, USA, Australia and New Zealand.

The ability of a non-highly malignant *and* reactive EEG to predict good outcome is comparable to previous studies which used various EEG definitions to define favourable EEG patterns[9,13–14,17,26]. Our definition of a favourable EEG was proposed considering the previous literature and the EEG criteria used in the European post resuscitation care guidelines[1]. The guidelines regarding prediction of poor outcome recommends using highly malignant EEG patterns combined with at least one other concordant predictor in the prognostic algorithm. Conversely, for good outcome prediction, the definition of a non-highly malignant *and* reactive EEG appears easy to understand by treating teams that are familiar with the present European guidelines.

This study shows that preserved EEG reactivity significantly contributes to the prognostic performance, even if the background patterns include a broad spectrum of favourable and less favourable EEG patterns. Our findings validate results from previous smaller cohort studies that investigated reactivity testing in good outcome prediction[14–16,20]. This is despite the fact that visual assessment of

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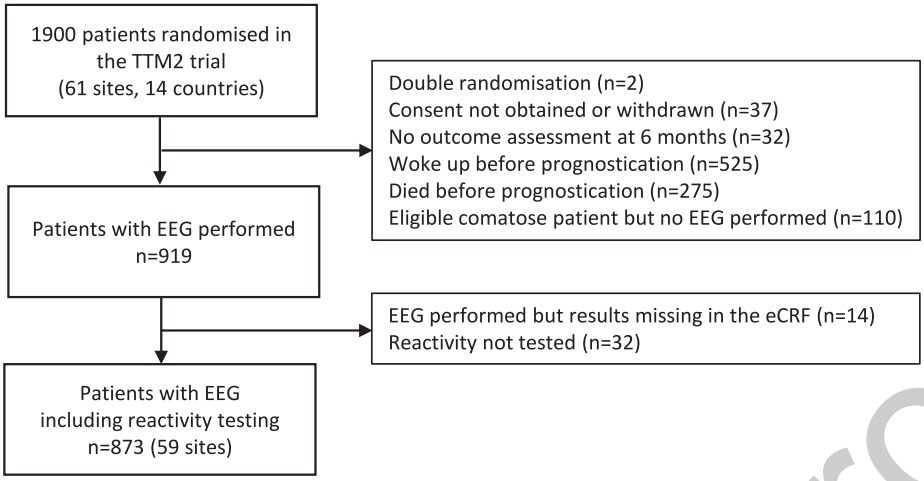

Fig. 1 – Flow chart of inclusion and exclusion.

Table 1 – Patients characteristics.

	Study cohort *n* = 873	Non-highly malignant *and* reactive EEG *n* = 255
Age–years (mean ± std dev)	64.9 ± 12.9	61.8 ± 14.1
Male gender – no. (%)	697(79.8)	211 (82.7)
CA related variables		
Bystander witnessed CA – no. (%)	692 (79.3)	202 (79.2)
Shockable[a] first rhythm – no. (%)	605 (69.3)	201 (78.8)
Time to ROSC[b] –minutes, median (IQR)	27 (19–41)	25 (16–34)
ICU related variables		
TTM 33 °C – no. (%)	457 (52.3)	132 (51.8)
Time to EEG from CA – hours, median (IQR)	69 (47–91)	67 (46–91)
Reactive EEG background	287 (32.9)	255 (100)
Clinical seizures/motor events[c] – no. (%)	339 (38.8)	52 (20)
Propofol in the first 72 h – no. (%)	754 (86.4)	213 (83.5)
Propofol cumulative dose up to 72 h – mg, median (IQR)	9215 (4617–14370)	10,308 (5095–16000)
Midazolam in the first 72 h – no. (%)	392 (44.9)	128 (50.2)
Midazolam cumulative dose up to 72 h – mg, median (IQR)	150 (26–343)	185 (26–408)
Prognostication performed – no. (%)	616 (70.6)	183 (71.8)
Poor prognosis likely at the time of prognostication[d] – no. (%)	241/616 (39.1)	22/183 (12)
WLST performed – no. (%)	417 (47.8)	41 (16)
WLST due to neurological reason – no. (%)	303 (34.7)	23 (9)
Outcome		
Good neurological outcome mRS 0–3 – no. (%)	283 (32.4)	157 (61.6)
mRS 0 – no. (%)	93 (10.7)	56 (22)
mRS 1 – no. (%)	44 (5)	22 (8.6)
mRS 2 – no. (%)	97 (11.1)	54 (21.2)
mRS 3 – no. (%)	25 (2.9)	15 (5.9)
mRS 4 – no. (%)	23 (2.6)	14 (5.5)
mRS 5 – no. (%)	20 (2.3)	7 (2.7)
mRS 6 – no. (%)	534 (61.6)	71 (27.8)
mRS missing – no.(%)	37 (4.2)	16 (6.3)

Abbreviations: CA cardiac arrest; mRS modified Rankin scale; ROSC return of spontaneous circulation; TTM target temperature management; WLST withdrawal of life-sustaining therapy.

[a] Ventricular fibrillation, pulseless ventricular tachycardia or unknown rhythm responsive to shock.

[b] For unwitnessed arrests, time intervals were calculated from the emergency call to ROSC.

[c] Myoclonic seizures or tonic/clonic seizures.

[d] Presence of at least two concordant predictors of poor outcome at the time-point of prognostication (96 h): Both pupillary and corneal reflexes absent at 96 h after CA or later, an early (within 48 h) status myoclonus, an unreactive highly malignant EEG pattern, brain CT with signs of global ischemic injury, serial levels of NSE consistently higher than locally established levels, N20 SSEP wave bilaterally absent more than 48 h after CA, in patients without confounding factors and motor response or with a stereotypic extensor response to painful stimulation at ≥96 h after CA.

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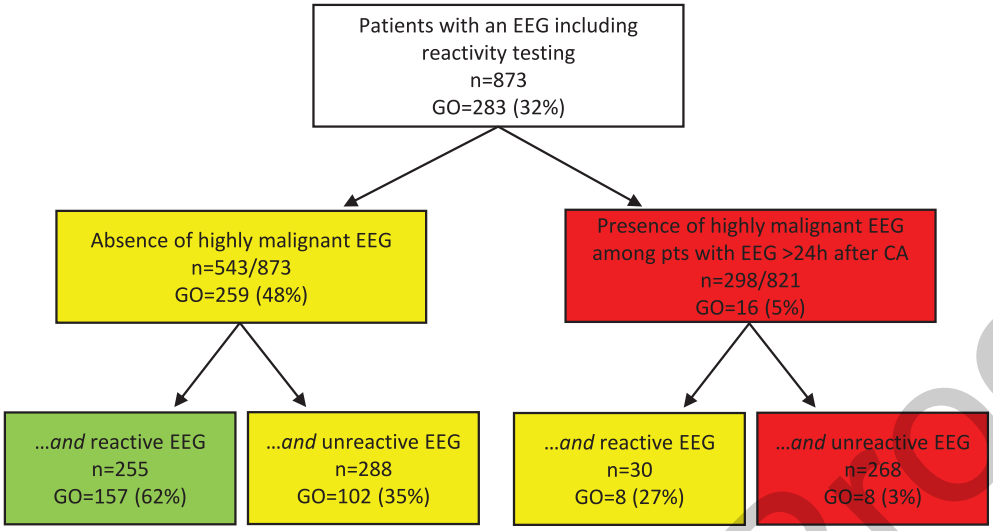

Fig. 2 – EEG-cohort of the TTM2-trial. The EEG-cohort of the TTM2-trial. Observe that only EEGs with reactivity testing are presented. 873 patients had an EEG 0–14 days after CA of whom 821 patients had an EEG beyond 24 h after CA. The distribution of EEG patterns and proportion of patients with good outcome (GO) for the respective pattern is shown. A highly malignant EEG is defined using the standardized EEG terminology by the American Clinical Neurophysiology Society as: Burst-suppression (amplitude < 10 μV, ≥50% of the recording) with or without discharges; Suppressed background (amplitude < 10 μV the entirety of the record) with or without periodic discharges. Green represents patterns associated with good outcome. Yellow represents patterns with no certain prognostic value. Red represents pattern associated with poor outcome. This supplementary figure summarises the results of the present study (good outcome prediction) and previously published results (poor outcome prediction).[22] (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2 – Prognostic ability of EEG to predict good outcome.

EEG patterns	Cohort *n*=	Pattern prevalence *n*=(%)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	TP *n*=	FP *n*=	TN *n*=	FN *n*=
Non-highly malignant *and* reactive EEG[a]	873	255(29.2)	55.5 (49.7–61.2)	83.4 (80.2–86.2)	61.6 (55.5–67.4)	79.6 (76.3–82.6)	157	98	492	126
Non-highly malignant EEG[b] (regardless of reactivity)	873	543(62.2)	91.5 (87.8–94.3)	51.9 (47.8–55.9)	47.7 (43.5–51.9)	92.7 (89.5–95.2)	259	284	306	24

Abbreviations: CI confidence interval; NPV negative predictive value; PPV positive predictive value; TP true positives; FP false positives; TN true negatives; FN false negatives.

[a] Defined as absence of highly malignant patterns, i.e. burst-suppression or suppression with or without superimposed periodic discharges and presence of EEG reactivity to external stimuli.

[b] Defined as absence of highly malignant patterns, i.e. burst-suppression or suppression with or without superimposed periodic discharges (regardless of reactivity).

reactivity has a large inter-rater variability among experts[27]. Importantly, for the local EEG review the sites were instructed to use the standardised ACNS EEG terminology 2012 version[25] to define EEG reactivity, burst-suppression and suppression, and the definitions for these patterns are the same in the recent 2021 version of the ACNS terminology[5].

In recent years various quantitative EEG techniques to assess reactivity have been proposed[28–31], but there is no consensus on the best quantitative methodology and in the present study reactivity was assessed visually according to the definitions of the ACNS.

We previously reported that one third of patients in the EEG-cohort of the TTM2-trial who had an EEG beyond 24 h exhibited an unreactive highly malignant EEG, which strongly predicted poor outcome[22]. The present study shows that nearly one third of patients displayed a non-highly malignant *and* reactive EEG, that was associated with good outcomes. Notably, another one third of patients did not fall into either of these categories; instead, they exhibited an EEG pattern without clear prognostic implications, such as a non-highly malignant EEG but without reactivity to stimuli (Fig. 2).

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Additionally, our study examined the impact of the timing of EEG recordings on prognostic accuracy. We hypothesized that a non-highly malignant *and* reactive EEG during the first day after CA would more strongly predict a good outcome, but we could not detect a statistically significant difference in sensitivity or specificity across different time intervals. This suggests that EEG may indicate good prognosis regardless of the timing of the recording. We note that the positive predictive value for a non-highly malignant *and* reactive EEG to predict good outcome is higher early after the arrest, but this finding should be interpreted cautiously as the cohort gradually changed over time, for instance due to awakenings and deaths.

Following the return of spontaneous circulation after CA the EEG background is initially suppressed and subsequently the EEG activity typically return during the following hours to days. A continuous normal-voltage background activity appearing very early after CA, i.e. within 12–24 h, strongly predicts a good outcome[10,32–37]. To assess the time point of this transition towards a continuous normal-voltage background, cEEG-monitoring is the most plausible method of choice, but also more resource consuming compared to a 20-minute intermittent routine EEG. However, the present study shows that when considering EEG reactivity in an intermittent EEG performed it can provide useful prognostic information.

If there are discordant signs in the multimodal prognostication caution is recommended in the recent European guidelines and the potential of EEG, biomarkers in blood and MRI to predict recovery is discussed. In our EEG-cohort multimodal prognostication according to the trial protocol suggested a likely poor prognosis in 241 patients of whom only 2% had a good outcome. Among the small minority of patients who had discordant multimodal prognostication findings with a non-highly malignant *and* reactive EEG, 18% had a good outcome, but since absolute number are low this interesting finding must be validated in future studies.

Strengths of the study includes the international multicentre setting involving 59 sites in several continents and a conservative trial protocol regarding withdrawal of care. This study also has limitations. Firstly, although instructions regarding the EEG review and testing of reactivity (sound- and pain stimuli) were sent to each site and included in the protocol we cannot confirm that all local EEG reviewers followed these instructions and exactly which stimulation protocol that was used for testing reactivity. Secondly, the local EEG reviewers were blinded to the long-term outcome of the comatose patients but were not blinded to clinical data in the EEG referral. Thirdly, EEG results were available during prognostication, and since EEG was part of the multimodal prognostication protocol, self-fulfilling prophecies may have biased our results. However, it is important to note that an unreactive EEG by itself was not included in the trial protocol as a predictor of poor outcome. Fourthly, our definition of a non-highly malignant *and* reactive EEG includes various background patterns, for instance continuous, discontinuous, normal-voltage or low-voltage, and the specific distribution of these subtypes remain unknown due to how the data was prospectively reported in the eCRF. Finally, this study focuses solely on predicting good outcomes through EEG, without considering other predictors of good outcomes.

Conclusions

We conclude that a non-highly malignant *and* reactive EEG in a comatose patient resuscitated after CA is associated with a good long-term outcome. Reactivity testing should be routinely performed since preserved EEG reactivity contributed to prognostic performance.

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Statistical analysis

Susann Ullén, PhD and Kaja Doupana Stigsson PhD, statisticians within our academic institution (Clinical Studies Sweden – Forum South, Skane University Hospital, Lund, Sweden) supervised the statistical analysis.

CRediT authorship contribution statement

S. Turella: Writing – review & editing, Writing – original draft, Formal analysis. **J. Dankiewicz:** Writing – review & editing, Resources, Project administration, Funding acquisition, Data curation. **N. Ben-Hamouda:** Writing – review & editing, Data curation. **K. Bernhard Nilsen:** Writing – review & editing, Data curation. **J. Düring:** Writing – review & editing, Data curation. **C. Endisch:** Writing – review & editing, Data curation. **M. Engstrøm:** Writing – review & editing, Data curation. **D. Flügel:** Writing – review & editing, Data curation. **N. Gaspard:** Writing – review & editing, Data curation. **A.M. Grejs:** Writing – review & editing, Data curation. **M. Haenggi:** Writing – review & editing, Data curation. **S. Haffey:** Writing – review & editing, Data curation. **L. Imbach:** Writing – review & editing, Data curation. **B. Johnsen:** Writing – review & editing, Data curation. **D. Kemlink:** Writing – review & editing, Data curation. **C. Leithner:** Writing – review & editing, Data curation. **S. Legriel:** Writing – review & editing, Data curation. **H. Lindehammar:** Writing – review & editing, Data curation. **G. Mazzon:** Writing – review & editing, Data curation. **N. Nielsen:** Writing – review & editing, Resources, Project administration, Funding acquisition, Data curation. **A. Peyre:** Writing – review & editing, Data curation. **B. Ribalta Stanford:** Writing – review & editing, Data curation. **E. Roman-Pognuz:** Writing – review & editing, Data curation. **A.O. Rossetti:** Writing – review & editing, Data curation. **C. Schrag:** Writing – review & editing, Data curation. **A. Valeriánová:** Writing – review & editing, Data curation. **P. Wendel-Garcia:** Writing – review & editing, Data curation. **F. Zubler:** Writing – review & editing, Data curation. **T. Cronberg:** Writing – review & editing, Resources, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization. **E. Westhall:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Data curation, Conceptualization.

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Data availability

The data set of the present study could be available from the corresponding author on a reasonable request to the TTM2-trial steering group.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: 'Tobias Cronberg is member of the editorial board of Resuscitation. None of the authors report any disclosures relevant to this manuscript.'.

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Appendix A. Supplementary material

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