Background Frequency Patterns in Standard Electroencephalography During Targeted Temperature Management as an Early Prognostic Tool in Out-of-Hospital Cardiac Arrest Survivors: a retrospective cohort study

Youn-Jung Kim
Asan Medical Center
Min-jee Kim
Eulji University Hospital
Yong Seo Koo
Asan Medical Center
Won Young Kim (wonpia73@naver.com)
Department of Emergency Medicine, University of Ulsan College of Medicine, Asan Medical Center
https://orcid.org/0000-0002-6904-5966

Research

Keywords: Out-of-hospital cardiac arrest, Electroencephalography, Anoxic brain injury, Prognostication

Posted Date: January 8th, 2020

DOI: https://doi.org/10.21203/rs.2.20295/v1

Abstract

Background

Electroencephalography is a widely used tool for detecting epileptiform and assessing neurological outcomes after cardiac arrest. We investigated the prognostic value of standard electroencephalography during early post-cardiac arrest period and evaluated the performance of electroencephalography findings combined with other clinical features for predicting good outcome.

Methods

This observational registry-based study was conducted at tertiary care hospital in Korea. Data of all consecutive adult comatose out-of-hospital cardiac arrest survivors who underwent electroencephalography during targeted temperature management between 2010 and 2018 were extracted. Electroencephalography findings, classified according to the American Clinical Neurophysiological Society critical care electroencephalography terminology, and good neurologic outcome-related clinical features were identified via multivariable logistic analysis.

Results

Good outcomes were observed in 36.5% of 170 patients. Median electroencephalography time was 22.0 hours. Electroencephalography background, voltage and other findings (burst suppression, reactivity to pain stimuli) significantly differed between good and poor outcome groups. Electroencephalography background with dominant alpha and theta waves had the highest odds ratio of 9.8 (95% confidence interval 3.9-24.9) in multivariable logistic analysis. Electroencephalography background frequency enabled identification of a good neurologic outcome (sensitivity, 83.87%; specificity, 75.93%). Combination of other clinical features (age<65 years, initial shockable rhythm, resuscitation duration<20 min) with electroencephalography findings increased predictive performance for good neurologic outcomes (sensitivity, 95.2%; specificity, 100%).

Conclusions

Background frequency patterns of standard electroencephalography during targeted temperature management may play a role as an early prognostic tool in out-of-hospital cardiac arrest patients.

Introduction

Hypoxic–ischaemic brain injury is common after resuscitation from cardiac arrest (CA). Most out-of-hospital cardiac arrest (OHCA) survivors are initially unconscious at hospital admission [1, 2], and they undergo intensive post-resuscitation care including targeted temperature management (TTM) [3]. Despite substantial allocations of medical resources, the overall outcomes of OHCA remain dismal, with only 8.3% survivors with a good neurological outcome and eligible for discharge [4]; furthermore, withdrawal of life-sustaining therapy (WSLT) owing to perceived poor neurological prognosis is a leading cause of death [5–7]. Multimodal approach and delayed timing (after > 72 h) of prognostication has been recommended to minimise the possibility of inaccurate WSLT for patients who demonstrate a change in neurological recovery [3]. However, one of the most pressing issues for relatives and healthcare workers is to rapidly obtain reliable information regarding the probability of achieving favourable neurological outcomes. Although numerous studies have focused on discovering factors for poor neurologic outcome, it is essential to develop strategies for predicting good neurologic outcomes among OHCA survivors in order to appropriately tailor medical therapies for each patient.

Electroencephalography (EEG) in post-CA patients has been used for dual purposes: detection of seizure activity in the early stage of TTM and prognostication of neurological outcomes. The current guideline describes the prognostic role of standard EEG at ≥ 72 hours after CA [3]. However, recent studies have reported the feasibility of using EEG as an early prognostic tool for OHCA survivors [5, 8, 9]. Continuous EEG monitoring provides more real-time information than standard intermittent EEG; however, its requirement for an extensive amount of medical resources and timely unavailability are major limitations in clinical practice [9, 10]. Moreover, its prognostication value has not yet reached a consensus because the reliability of EEG has been limited by varying classification systems and inter-rater variability. Thus, American Clinical Neurophysiology Society (ACNS) recently proposed a standardised EEG terminology that can be suitably used for critically ill patients after CA [11].

Here, the objective was to investigate the prognostic value of standard intermittent EEG during early post-CA period based on the standardised ACNS terminology [11] and evaluate the performance of EEG findings combined with other clinical features for predicting good outcome.

Methods

Study design and patients

This retrospective, observational, registry-based cohort study was conducted at the emergency intensive care unit (ICU) of a tertiary care university-affiliated teaching hospital in Korea. Data were extracted from OHCA registry containing prospectively collected data of consecutive adult patients (≥ 18 years) with OHCA since January 2010 [12]. The Institutional Review Board of the University of Ulsan College of Medicine reviewed and approved the study protocol (No. 2019 – 1883), and informed consent was waived because of the retrospective nature of the study.

We included comatose patients with successfully resuscitated non-traumatic OHCA who were subjected to TTM between January 2010 and December 2018 and underwent routine EEG during TTM period [within 72 h after return of spontaneous circulation (ROSC)]. We excluded patients who could not undergo EEG assessment within 72 h after ROSC or who showed poor-quality EEG data. All patients were followed up for 1 month after experiencing CA and were also subjected to neurologic assessment according to Cerebral Performance Category (CPC) score.

Management and data collection

All patients were treated according to the then-current advanced cardiac life support guidelines.[3, 13] TTM was performed for all unconscious patients using Arctic Sun Energy Transfer Pad (Medivance Corp., Louisville, CO, USA), and the target temperature (33°C or 36°C) was maintained for 24 h. After 24 h, patients were rewarmed at a rate of 0.25°C/h following the maintenance of normothermia for 72 h after ROSC. The temperature was monitored using an oesophageal temperature probe. A combination of midazolam, propofol and remifentanil was used for sedation and analgesia. If necessary, a neuromuscular blocking agent was administered to control shivering. Patients with seizure activity observed on electroencephalograms were treated with valproate or levetiracetam. Standard EEG examination was performed as soon as possible after ICU admission, but it was delayed whenever the patient was admitted to ICU on weekends or after daytime between 8 AM and 6 PM on weekdays owing to practical issues. A 30-min scalp EEG was performed by the Stellate EEG system in which 21 electrodes placed according to the international 10–20 electrode system (Fp1-2, F7-8, T7-8, P7-8, F3-4, C3-4, P3-4, O1-2, Fz, Cz, Pz), with a sampling rate of 200 Hz and a 0.1-Hz high-pass filter. All patients received standard intensive care according to institutional protocol. WSLT was legally prohibited in South Korea during the study period.

Demographic and clinical data, including age, sex, previous medical history, resuscitation profiles such as the presence of a witness during collapse, initially documented rhythm, resuscitation duration and interventions performed in Emergency Department, were obtained. Two board-certified epileptologists (M.K., Y.S.K) reviewed and interpreted EEG recordings, blinded to the outcome. Background EEG were categorised according to the predominant frequency (alpha, theta, delta waves; Fig. 1), voltage (attenuation or suppressed, < 10 uV; low voltage, 10–20 uV; normal; >20 uV), others (reactivity, stage II sleep transients, burst suppression or burst attenuation) and superimposed findings such as sporadic epileptiform were also assessed according to ACNS guidelines [11]. Discontinuous background (10–49% periods of suppression/attenuation or 50–99% periods of suppression or attenuation with burst suppression/attenuation) with attenuated/suppressed voltage or burst suppression/attenuation categorized to undetermined frequency. All discordant EEG findings were discussed until a consensus was reached. The primary endpoint was a good neurological outcome at 1 month defined as a Cerebral Performance Category score of 1 (no significant impairment) or 2 (moderate impairment but able to complete activities of daily living).

Statistical analysis

Because of a non-normal distribution, continuous variables are presented as median values with interquartile ranges (IQRs) using Kolmogorov–Smirnov test. Categorical variables are expressed as an absolute number and percentage. The patients were categorised into two groups based on their CPC scores at 1 month: a good neurologic outcome group (CPC 1 and 2) and a poor neurologic outcome group (CPC 3–5). Comparisons of demographic and clinical characteristics between the good and poor neurologic outcome groups were performed using Mann–Whitney U-test for continuous variables and Chi-square test for categorical variables. Clinical features and EEG findings of potential prognostic value were first examined at baseline using univariate logistic analysis, with a cut-off p value of < 0.05. We selected significant variables on the basis of clinical judgment. Age of < 65 years, resuscitation duration of < 20 min, initial shockable rhythm, predominant background EEG frequency (alpha and theta waves vs. delta and undetermined waves), suppressed voltage (all activity, < 10 μV), burst suppression or burst attenuation and reactivity to pain stimuli were candidates for the multivariable model, and these variables were assessed using multiple logistic regression analysis.[11, 14] The results of the multivariate logistic regression analyses were summarised by estimating the odds ratios (ORs) and 95% confidence intervals (CI). The Hosmer–Lemeshow test for logistic regression model was performed. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for good neurological outcome at 1 month were calculated. Two-tailed p values of < 0.05 were considered to be statistically significant. All statistical analyses were performed using IBM SPSS for Windows, version 21.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 172 non-traumatic comatose OHCA survivors who underwent standard intermittent EEG during TTM were admitted during the study period; of them, 2 were excluded because of poor-quality ECG data (Fig. 2). Thus, 170 patients were ultimately included in the study. Patients were categorised into the good (n = 62, 36.5%) and poor (n = 108, 63.5%) neurological outcome groups, respectively.

The demographic and clinical characteristics of the patients are summarised in Table 1. The median patient age was 60.0 years, and two-thirds of them were males (66.5%). Median EEG time after ROSC was 22.0 [12.8–40.3] h. The patients in the good neurologic outcome group were younger (median, 54.5 vs. 62.0 years; p = 0.002) and had a higher rate of initial shockable rhythm (69.4% vs. 21.3%; p < 0.001) as well as a higher likelihood of having a witnessed CA (85.5% vs. 68.5%; p = 0.014). Flow time did not differ statistically between the two groups (median, 0.0 vs. 0.0 min, p = 0.617), but resuscitation duration was shorter in the good neurologic outcome group (median, 12.0 vs. 27.0 min, p < 0.001). Among continuous or nearly continuous background pattern (54.7%), alpha and theta waves were more prevalent in the good neurologic outcome group in contrast to the delta wave. Undetermined background activity was predominant in the poor neurologic outcome group (Table 2; p < 0.001). Majority of patients in the good neurologic outcome group had normal voltage (83.9%). Burst suppression/burst attenuation and reactivity to pain stimuli were detected in < 20% of the total study patients (12.9% and 16.5%, respectively), but there were significant differences between the good and poor neurologic groups (4.8% vs. 17.6%; p = 0.017 for burst suppression/burst attenuation; 27.4% vs. 10.2%; p = 0.004 for reactivity to pain stimuli).

Table 1
Demographic and clinical characteristics of out-of-hospital cardiac arrest patients subjected to targeted temperature management according to neurologic outcome at 1 month.

Characteristics	**Total (n = 170)**	**Good neurologic outcome (n = 62)**	**Poor neurologic outcome (n = 108)**	**p value**
Age, years	60.0 (45.8–71.0)	54.5 (39.0–64.3)	62.0 (49.0–73.0)	0.002
Age < 65 years	107 (62.9%)	47 (75.8%)	60 (55.6%)	0.008
Male	113 (66.5%)	44 (71.0%)	69 (63.9%)	0.347
Previous medical history				
Hypertension	58 (34.1%)	15 (24.2%)	43 (39.8%)	0.039
Diabetes mellitus	43 (25.3%)	9 (14.5%)	34 (31.5%)	0.014
Acute myocardial infarction	8 (4.7%)	2 (3.2%)	6 (5.6%)	0.712
Congestive heart failure	12 (7.1%)	7 (11.3%)	5 (4.6%)	0.125
Chronic kidney disease	20 (11.8%)	4 (6.5%)	16 (14.8%)	0.103
Malignancy	13 (7.6%)	3 (4.8%)	10 (9.3%)	0.379
Arrest characteristics				
Presence of a witness	127 (74.7%)	53 (85.5%)	74 (68.5%)	0.014
Bystander CPR	120 (70.6%)	44 (71.0%)	76 (70.4%)	0.934
Initial shockable rhythm	66 (38.8%)	43 (69.4%)	23 (21.3%)	< 0.001
No flow time, min	0.0 (0.0–3.0)	0.0 (0.0–3.0)	0.0 (0.0–3.8)	0.617
Resuscitation duration, min	22.0 (10.0–35.3)	12.0 (6.8–23.0)	27.0 (16.0–40.0)	< 0.001

Values are expressed as median (interquartile ranges) or n (%) as appropriate.
CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; EEG, electroencephalography.

Characteristics	Total (n = 170)	Good neurologic outcome (n = 62)	Poor neurologic outcome (n = 108)	p value
Time from ROSC to target temperature, hours	5.4 (3.9–7.4)	5.8 (4.8–7.3)	5.1 (3.8–7.5)	0.134
Time from ROSC to EEG, hours	22.0 (12.8–40.3)	20.0 (10.8–34.5)	23.0 (14.3–49.3)	0.145
Values are expressed as median (interquartile ranges) or n (%) as appropriate.				
CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; EEG, electroencephalography.				

Table 2
Standard intermittent electroencephalography findings based on the standardised terminology of the American Clinical Neurophysiology Society

EEG findings	Total (n = 170)	Good neurologic outcome (n = 62)	Poor neurologic outcome (n = 108)	p value
Background frequency				< 0.001
Dominant alpha waves	61 (35.9%)	37 (59.7%)	24 (22.2%)	
Dominant theta waves	17 (10.0%)	15 (24.2%)	2 (1.9%)	
Dominant delta waves	15 (8.8%)	2 (3.2%)	13 (12.0%)	
Undetermined	77 (45.3%)	8 (12.9%)	69 (63.9%)	
Background voltage				< 0.001
Attenuation or suppressed (< 10 uV)	64 (37.6%)	5 (8.1%)	59 (54.6%)	
Low voltage (10–20 uV)	13 (7.6%)	5 (8.1%)	8 (7.4%)	
Normal (> 20 uV)	93 (54.7%)	52 (83.9%)	41 (38.0%)	
Other background findings				
Burst suppression/burst attenuation	22 (12.9%)	3 (4.8%)	19 (17.6%)	0.017
Reactivity to pain stimuli	28 (16.5%)	17 (27.4%)	11 (10.2%)	0.004
Stage II Sleep transients	9 (5.3%)	6 (9.7%)	3 (2.8%)	0.075
Sporadic epileptiform discharge	14 (8.2%)	4 (6.5%)	10 (9.3%)	0.522
Values are expressed as n (%).				
EEG, electroencephalography.				

In univariate analysis, age, initial shockable CA rhythm, presence of a witness during CA, resuscitation duration and EEG findings, such as predominant background EEG frequency and voltage, burst suppression or burst attenuation and reactivity to pain stimulus, were associated with good neurologic outcome. After multivariate logistic regression analysis, age of < 65 years (adjusted OR, 2.930; 95% CI, 1.131–7590; p = 0.027), initial shockable CA rhythm (adjusted OR, 9.698; 95% CI, 3.683–25.537; p < 0.001), < 20-min resuscitation duration (adjusted OR, 4.087; 95% CI, 1.528–10.931; $p = 0.005$) and EEG background with dominant alpha and theta waves (adjusted OR, 9.800; 95% CI, 3.851–24.941; $p < 0.001$) were associated with good neurologic outcome at 1 month (Table 3).

Table 3
Multivariate logistic regression analysis for predicting good neurologic outcome.

Characteristics	Adjusted odds ratio	95% CI	p value
Age < 65 years	2.930	1.131–7.590	0.027
Initial shockable rhythm	9.698	3.683–25.537	< 0.001
Resuscitation duration < 20 min	4.087	1.528–10.931	0.005
EEG background of dominant alpha and theta waves	9.800	3.851–24.941	< 0.001
Other covariables: suppressed voltage (all activity < 10 μV), burst suppression/burst attenuation, and reactivity to pain stimuli.			
CI, confidence interval; EEG, electroencephalography.			

The presence of EEG background with dominant alpha and theta waves predicted good neurologic outcomes with a sensitivity of 83.87%, a specificity of 75.93%, a positive predictive value of 66.67% and a negative predictive value of 89.13% (Table 4). The performance of EEG findings in combination with other clinical features for the prediction of good outcomes was summarised in Table 4. The dominant presence of alpha and theta waves observed on EEG within 72 h of ROSC or OHCA along with an initial shockable CA rhythm predicted good neurologic outcomes with a sensitivity of 95.16% and a specificity of 62.04%. The presence of all the four criteria predicted good neurologic outcomes with a specificity of 100.0% and a positive predictive value of 100.0%.

Table 4
Predictive value of clinical and electroencephalography findings for good neurologic outcome.

	Good neurologic outcome (n = 62)	Poor neurologic outcome (n = 108)	Sensitivity	Specificity	PPV	NPV	Accuracy
EEG pattern	52	26	83.87%	75.93%	66.67%	89.13%	78.82%
EEG pattern or initial rhythm	59	41	95.16%	62.04%	59.00%	95.71%	74.12%
EEG pattern and initial rhythm	36	8	58.06%	92.59%	81.82%	79.37%	80.00%
EEG pattern and initial rhythm and age	27	4	43.55%	96.30%	87.10%	74.82%	77.06%
EEG pattern and initial rhythm and resuscitation duration	21	4	33.87%	96.30%	84.00%	71.72%	73.53%
EEG pattern and initial rhythm and age and resuscitation duration	17	0	27.42%	100.00%	100.00%	70.59%	73.53%

EEG pattern: background frequency with dominant alpha and theta waves; initial rhythm: initial shockable rhythm; age: age of < 65 years; resuscitation duration: resuscitation duration of < 20 min.

PPV, positive predictive value; NPV, negative predictive value, EEG, electroencephalography.

Discussion

The present study adds to the current understanding regarding the use of EEG as an early prognostic tool after OHCA. Standard EEG examination revealed that 45.9% (78/170) of the non-traumatic OHCA survivors had dominant alpha and theta waves, and the presence of these EEG findings indicated a good neurologic outcome with a sensitivity of 83.87% and a negative predictive value of 89.13% during the early period. Furthermore, EEG findings combined with other clinical features, including age, shockable rhythm and resuscitation duration, led to an increase in predictive performance for good neurologic outcomes, with a sensitivity of 95.2% and a specificity of 100%.

EEG is very sensitive for detecting hypoxic and ischemic brain injury, widely available, non-invasive and has a robust body of evidence supporting its utility for prognostic purposes [14, 15]. EEG findings in post-CA patients, such as burst suppression, low voltage (< 20 μV), lack of reactivity and sporadic epileptiform features, have been suggested to be prognostic tools [16–21]. Recently, literatures have suggested that in certain carefully selected patient subsets, aggressive invasive management may improve outcomes. Thus, it is essential to develop a technique for identifying patients who may have a chance of neurological recovery after experiencing OHCA. However, previous observational studies have focused on the identification of EEG findings, such as myoclonic jerks and burst suppression, for poor neurologic outcome with a low false positive rate and have given rise to concerns of confirmation bias, also known as self-fulfilling prophecy [3]. This is particularly important since WLST is a leading cause of death in post-CA patients. In this registry-based study, we included all consecutive comatose OHCA survivors who underwent EEG during TTM from areas where WSLT was legally prohibited.

We determined that EEG findings of predominant alpha and theta waves, absence of a low voltage, non-existence of burst suppression and reactivity to pain stimulus showed a significant association with good neurologic outcome in univariable logistic regression analysis [19]. However, after adjusting for other clinical prognostic features including age, initial CA rhythm and resuscitation duration, only the detection of dominant alpha and theta waves on a standard electroencephalogram was a significant prognostic finding for good neurologic outcome (adjusted OR, 9.800; 95% CI, 3.851–24.941; $p < 0.001$).

Although EEG is a commonly used ancillary test for neurological prognosis after CA, the use of different classification systems and inter-rater variability, including reproducibility and reliability, serve as limitations [22]. Thus, the standardised classification of EEG findings as either highly malignant, malignant or benign patterns based on the ACNS terminology appears to improve EEG prognostic accuracy [19]. However, published data focusing on the background EEG frequency of early standard EEG in an era of early TTM is limited. The background of EEG is suppressed at a cerebral blood flow rate of < 10 mL/100 g of brain tissue/min [23]. The ongoing brain oscillatory activities occurring during the resting state represent dynamic changes in the brain, while the integrity of corticothalamic circuits reflects the degree of brain damage [23]. Here, our strategy for evaluating the predominant background EEG frequency, categorised into generalised delta activity of 1–3 cycles per second (Hz), theta activity of 4–7 Hz and alpha activity of 8–12 Hz, was simple and relatively objective. The dominant alpha and theta waves showed a good neurologic outcome with a sensitivity of 83.87% and a negative predictive value of 89.13% in the early period. It has been proposed that a single theta (5–7 Hz) wave is produced when a low level of afferent input to neocortical neurons gives rise to spontaneous oscillations of Layer V pyramidal cells at this frequency, thereby indicating an initial stage of improvement in corticothalamic integrity [24, 25]. Alpha (8–12 Hz) is linked to normal, tonic firing mode of the thalamus, which represents normal integrity of the corticothalamic circuit. Our results are consistent with the reports of previous EEG spectral analysis-based studies on CA survivors, which revealed that the patients who showed the presence of alpha and theta frequency bands while undergoing continuous EEG monitoring after CA had favourable outcome as opposed to the patients with a lower frequency band [26, 27]. In line with these studies, we identified three clinical factors, namely age of < 65 years (adjusted OR, 2.930; 95% CI, 1.131–7590), initial shockable rhythm (adjusted OR, 9.698; 95% CI, 3.683–25.537) and resuscitation duration of < 20 min (adjusted OR, 4.087; 95% CI, 1.528–10.931), that were associated with good neurologic outcomes at 1 month. Patients with EEG findings or shockable initial rhythm are predicted to have a good neurologic outcome with a sensitivity of 95.2%, whereas those with EEG findings as well as the three above-mentioned clinical factors are predicted to have a good neurologic outcome with a specificity of 100%. Our findings suggested that a combination of findings of early standard EEG during TTM and the three clinical features could have practical implications in the identification of comatose OHCA survivors with good neurologic outcomes.

Limitations

The results of our study should be interpreted in the context of the following limitations. First, the timing of standard EEG examination could affect the outcome. Although at our centre, standard EEG is usually performed as soon as possible after ICU admission, the median EEG examination period was 22 h because of its unavailability on a 24/7 basis. Nevertheless, our heterogeneous EEG timing during TTM reflected the real-world situation and can be generalizable to other settings. Second, although sedation policies and treating physicians remained unchanged, the likelihood of clinically important EEG findings and transitions or different effects of drugs, including sedative agents and antiepileptic drugs, should be considered. Third, the long study period between 2010 and 2018 accompanied by changes in treatment guidelines might affect the outcome of OHCA survivors. Fourth, this study was based on data from a single institution and had an observational study design, which limited generalisation and gave rise to an unmeasurable confounding bias. Finally, despite our sample size being relative larger than that of previous studies, there was an inevitably high potential of random effect generation resulting from a small sample.

Conclusion

This study demonstrated that standard intermittent EEG findings of predominant background frequency during the early post-CA period could be an early prognostic tool to identify patients with good neurologic outcomes. Furthermore, a combination of EEG findings and three other clinical features (age < 65 years, initial shockable rhythm and resuscitation duration of < 20 min) has practical implications for early prognostication of good neurologic outcome. Further prospective multi-centre studies are warranted to validate the predictive value of early standard intermittent EEG findings proposed in this study.

Abbreviations

ACNS
American Clinical Neurophysiology Society
CA
cardiac arrest
CI
confidence interval
CPC
Cerebral Performance Category

EEG
electroencephalography
ICU
intensive care unit
IQR
interquartile ranges
NPV
negative predictive value
OHCA
out-of-hospital cardiac arrest
OR
odds ratio
PPV
positive predictive value
TTM
targeted temperature management
WSLT
withdrawal of life-sustaining therapy

Declarations

Ethics approval and consent to participate

The Institutional Review Board of the University of Ulsan College of Medicine reviewed and approved the study protocol (No. 2019-1883), and informed consent was waived because of the retrospective nature of the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

None of the authors have potential conflicts of interest to be disclosed.

Funding: None

Authors' contributions

YJK, and WYK designed the study; YJK, MK, YSK and WYK collected the data; YJK, MK and WYK analyzed the data; YJK, MK, YSK and WYK interpreted the data; YJK, MK and WYK wrote the paper; and all authors reviewed and approved the final manuscript.

Acknowledgement: None

References

1. Coppler PJ, Elmer J, Calderon L, Sabedra A, Doshi AA, Callaway CW, Rittenberger JC, Dezfulian C: **Validation of the Pittsburgh Cardiac Arrest Category illness severity score**. *Resuscitation* 2015, **89**:86-92.
2. Rittenberger JC, Tisherman SA, Holm MB, Guyette FX, Callaway CW: **An early, novel illness severity score to predict outcome after cardiac arrest**. *Resuscitation* 2011, **82**(11):1399-1404.
3. Callaway CW, Donnino MW, Fink EL, Geocadin RG, Golan E, Kern KB, Leary M, Meurer WJ, Peberdy MA, Thompson TM: **Part 8: post–cardiac arrest care: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care**. *Circulation* 2015, **132**(18_suppl_2):S465-S482.
4. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, De Ferranti S, Després J-P, Fullerton HJ, Howard VJ: **Executive summary: heart disease and stroke statistics—2015 update: a report from the American Heart Association**. *Circulation* 2015, **131**(4):434-441.
5. Taccone FS, Baar I, De Deyne C, Druwe P, Legros B, Meyfroidt G, Ossemann M, Gaspard N: **Neuroprognostication after adult cardiac arrest treated with targeted temperature management: task force for Belgian recommendations**. *Acta neurologica belgica* 2017, **117**(1):3-15.
6. Lemiale V, Dumas F, Mongardon N, Giovanetti O, Charpentier J, Chiche J-D, Carli P, Mira J-P, Nolan J, Cariou A: **Intensive care unit mortality after cardiac arrest: the relative contribution of shock and brain injury in a large cohort**. *Intensive care medicine* 2013, **39**(11):1972-1980.
7. Elmer J, Torres C, Aufderheide TP, Austin MA, Callaway CW, Golan E, Herren H, Jasti J, Kudenchuk PJ, Scales DC: **Association of early withdrawal of life-sustaining therapy for perceived neurological prognosis with mortality after cardiac arrest**. *Resuscitation* 2016, **102**:127-135.
8. Rossetti AO, Tovar Quiroga DF, Juan E, Novy J, White RD, Ben-Hamouda N, Britton JW, Oddo M, Rabinstein AA: **Electroencephalography predicts poor and good outcomes after cardiac arrest: a two-center study**. *Critical care medicine* 2017, **45**(7):e674-e682.
9. Monteiro ML, Taccone FS, Depondt C, Lamanna I, Gaspard N, Ligot N, Mavroudakis N, Naeije G, Vincent J-L, Legros B: **The prognostic value of 48-h continuous EEG during therapeutic hypothermia after cardiac arrest**. *Neurocritical care* 2016, **24**(2):153-162.
10. Rittenberger JC, Weissman A, Baldwin M, Flickinger K, Repine MJ, Guyette FX, Doshi AA, Dezfulian C, Callaway CW, Elmer J: **Preliminary experience with point-of-care EEG in post-cardiac arrest patients**. *Resuscitation* 2019, **135**:98-102.
11. Hirsch L, LaRoche S, Gaspard N, Gerard E, Svoronos A, Herman S, Mani R, Arif H, Jette N, Minazad Y: **American clinical neurophysiology society's standardized critical care EEG terminology: 2012 version**.

Journal of clinical neurophysiology 2013, **30**(1):1-27.

12. Yoon JC, Kim Y-J, Lee Y-J, Ryoo SM, Sohn CH, Seo D-W, Lee Y-S, Lee JH, Lim KS, Kim WY: **Serial evaluation of SOFA and APACHE II scores to predict neurologic outcomes of out-of-hospital cardiac arrest survivors with targeted temperature management**. *PloS one* 2018, **13**(4):e0195628.
13. Peberdy MA, Callaway CW, Neumar RW, Geocadin RG, Zimmerman JL, Donnino M, Gabrielli A, Silvers SM, Zaritsky AL, Merchant R: **Part 9: post–cardiac arrest care: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care**. *Circulation* 2010, **122**(18_suppl_3):S768-S786.
14. Muhlhofer W, Szaflarski JP: **Prognostic value of EEG in patients after cardiac arrest—an updated review**. *Current neurology neuroscience reports* 2018, **18**(4):16.
15. Friberg H, Cronberg T, Dünser MW, Duranteau J, Horn J, Oddo M: **Survey on current practices for neurological prognostication after cardiac arrest**. *Resuscitation* 2015, **90**:158-162.
16. Sandroni C, Cariou A, Cavallaro F, Cronberg T, Friberg H, Hoedemaekers C, Horn J, Nolan JP, Rossetti AO, Soar J: **Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine**. *Intensive care medicine* 2014, **40**(12):1816-1831.
17. Sivaraju A, Gilmore EJ, Wira CR, Stevens A, Rampal N, Moeller JJ, Greer DM, Hirsch LJ, Gaspard N: **Prognostication of post-cardiac arrest coma: early clinical and electroencephalographic predictors of outcome**. *Intensive care medicine* 2015, **41**(7):1264-1272.
18. Hofmeijer J, Tjepkema-Cloostermans MC, van Putten MJ: **Burst-suppression with identical bursts: a distinct EEG pattern with poor outcome in postanoxic coma**. *Clinical neurophysiology* 2014, **125**(5):947-954.
19. Westhall E, Rossetti AO, van Rootselaar A-F, Kjaer TW, Horn J, Ullén S, Friberg H, Nielsen N, Rosén I, Åneman A: **Standardized EEG interpretation accurately predicts prognosis after cardiac arrest**. *Neurology* 2016, **86**(16):1482-1490.
20. Oddo M, Rossetti AO: **Early multimodal outcome prediction after cardiac arrest in patients treated with hypothermia**. *Critical care medicine* 2014, **42**(6):1340-1347.
21. Ruijter BJ, van Putten MJ, Hofmeijer J: **Generalized epileptiform discharges in postanoxic encephalopathy: quantitative characterization in relation to outcome**. *Epilepsia* 2015, **56**(11):1845-1854.
22. Westhall E, Rosén I, Rossetti AO, van Rootselaar A-F, Kjaer TW, Friberg H, Horn J, Nielsen N, Ullén S, Cronberg T: **Interrater variability of EEG interpretation in comatose cardiac arrest patients**. *Clinical Neurophysiology* 2015, **126**(12):2397-2404.
23. Jordan KG: **Emergency EEG and continuous EEG monitoring in acute ischemic stroke**. *Journal of Clinical Neurophysiology* 2004, **21**(5):341-352.
24. Silva LR, Amitai Y, Connors BW: **Intrinsic oscillations of neocortex generated by layer 5 pyramidal neurons**. *Science* 1991, **251**(4992):432-435.

25. Schiff ND: **Mesocircuit mechanisms underlying recovery of consciousness following severe brain injuries: model and predictions**. In: *Brain Function and Responsiveness in Disorders of Consciousness.* Springer; 2016: 195-204.
26. Forgacs PB, Frey HP, Velazquez A, Thompson S, Brodie D, Moitra V, Rabani L, Park S, Agarwal S, Falo MC: **Dynamic regimes of neocortical activity linked to corticothalamic integrity correlate with outcomes in acute anoxic brain injury after cardiac arrest**. *Annals of clinical translational neurology* 2017, **4**(2):119-129.
27. Kustermann T, Nguissi NAN, Pfeiffer C, Haenggi M, Kurmann R, Zubler F, Oddo M, Rossetti AO, De Lucia M: **Electroencephalography-based power spectra allow coma outcome prediction within 24 h of cardiac arrest**. *Resuscitation* 2019.

Figures

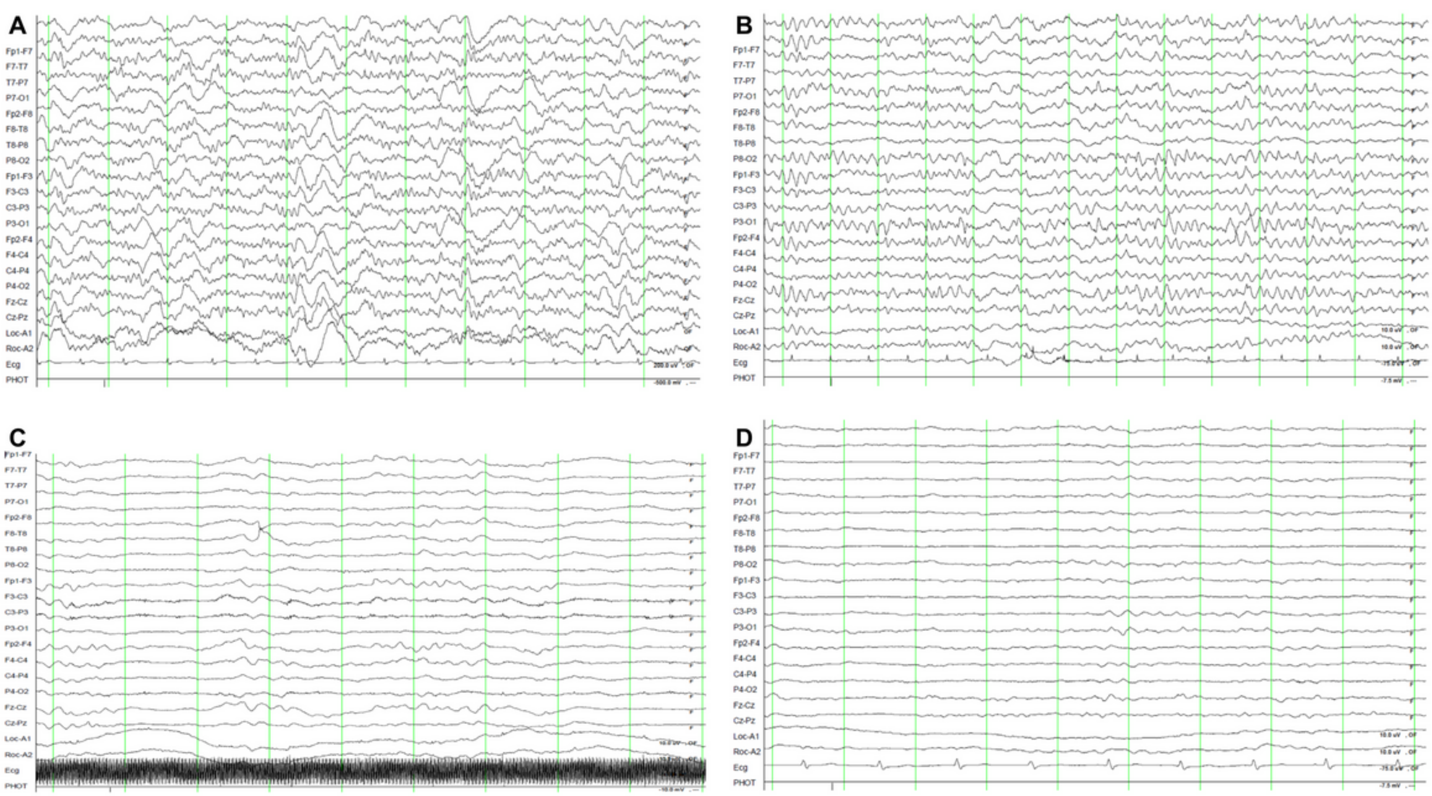

Figure 1

Example of predominant background electroencephalography frequency in out-of-hospital cardiac arrest survivors subjected to targeted temperature management. (A) predominant alpha waves, (B) predominant theta waves, (C) predominant delta waves, (D) undetermined background electroencephalography.

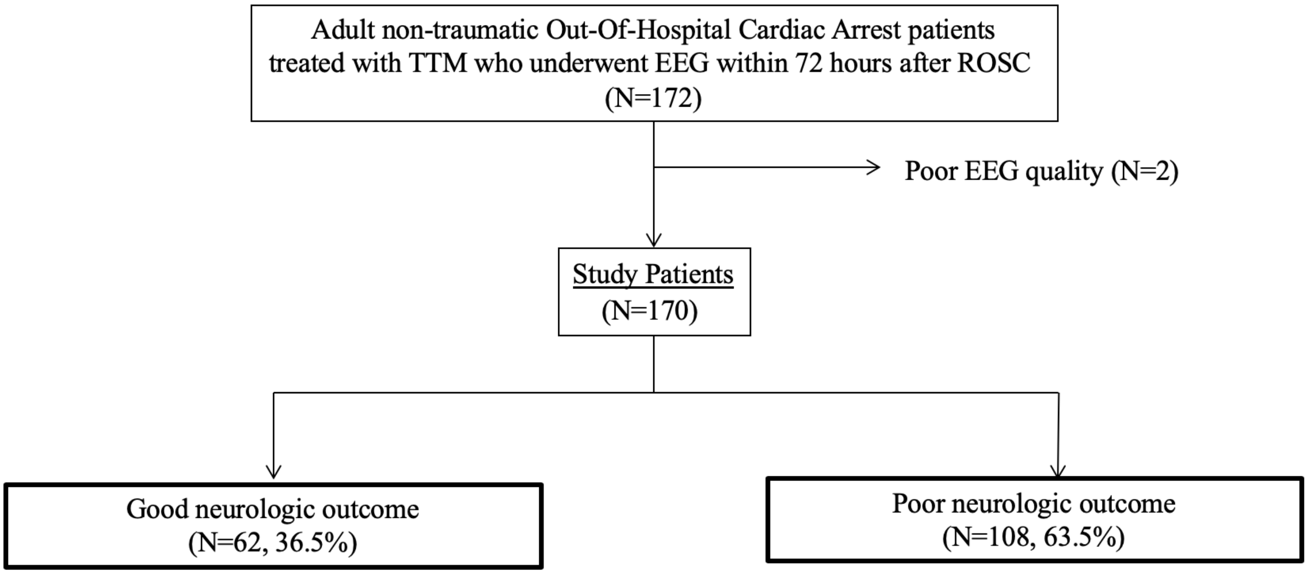

Figure 2

Patient flow diagram. Abbreviations: TTM, targeted temperature management; EEG, electroencephalography; ROSC, return of spontaneous circulation.