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Clinical Paper

Neurological prognostication after cardiac arrest and targeted temperature management 33 °C versus 36 °C: Results from a randomised controlled clinical trial☆

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ABSTRACT

Background: The reliability of some methods of neurological prognostication after out-of-hospital cardiac arrest has been questioned since the introduction of induced hypothermia. The aim of this study was to determine whether different treatment temperatures after resuscitation affected the prognostic accuracy of clinical neurological findings and somatosensory evoked potentials (SSEP) in comatose patients.
Methods: We calculated sensitivity and false positive rate for Glasgow Coma Scale motor score (GCS M), pupillary and corneal reflexes and SSEP to predict poor neurological outcome using prospective data from the Target Temperature Management after Out-of-Hospital Cardiac Arrest Trial which randomised 939 comatose survivors to treatment at either 33 °C or 36 °C. Poor outcome was defined as severe disability, vegetative state or death (Cerebral Performance Category scale 3–5) at six months.
Results: 313 patients (33%) were prognostically assessed; 168 in the 33 °C, and 145 in the 36 °C group. A GCS M ≤2 had a false positive rate of 19.1% to predict poor outcome due to nine false predictions. Bilaterally absent pupillary reflexes had a false positive rate of 2.1% and absent corneal reflexes had a false positive rate of 2.2% due to one false prediction in each group. The false positive rate for bilaterally absent SSEP N20-peaks was 2.6%.
Conclusions: Bilaterally absent pupillary and corneal reflexes and absent SSEP N20-peaks were reliable markers of a poor prognosis after resuscitation from out-of-hospital cardiac arrest but low GCS M score was not. The reliability of the tests was not altered by the treatment temperature.

1. Introduction

Brain injury is the predominant cause of death after resuscitation from out-of-hospital cardiac arrest.[1,2] Induced hypothermia has been reported to improve mortality and long-term neurological function in these circumstances.[3,4] Thus, since 2005 this treatment has been recommended in international post-cardiac arrest guidelines.[5] Several uncontrolled studies suggest existing methods of neurological prognostication for comatose patients after resuscitation from cardiac arrest are affected by hypothermia treatment.[6–12] Consequently, current recommendations suggest

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that prognostic assessment should be multimodal and delayed beyond the previously recommended 72 h after cardiac arrest.[13,14] The field has become even more complex since the Target Temperature Management after Out-of-Hospital Cardiac Arrest (TTM) trial found no differences in mortality or neurological outcome in patients randomised to 33 °C or 36 °C.[15,16] The present study examines whether these treatment temperatures affected the prognostic reliability of clinical findings and somatosensory evoked potentials (SSEP) for comatose patients in the TTM trial.

2. Materials and methods

This study, approved by the TTM trial steering committee before data analysis, is a post hoc analysis of prospectively collected data from 939 adult comatose survivors of out-of-hospital cardiac arrest of primary cardiac origin between November 2010 and January 2013. The TTM trial design, statistical analysis plan, and primary, secondary and tertiary outcomes have previously been published.[15–18] The trial is registered at clinicaltrials.gov NCT01020916. Briefly, a target core temperature of either 33 °C or 36 °C was achieved in patients as soon as possible after randomisation. Patients were then rewarmed to 37 °C 28 h after randomisation at a maximum speed of 0.5 °C per hour.

Sedation was maintained throughout the 36-h intervention period in both groups, but specific regimens were not mandated in the trial.

To reduce outcome bias by premature withdrawal of life-sustaining treatment, a recommendation by an independent physician, blinded to temperature assignment, but with access to all other clinical data, was made to the treating physician for patients still comatose 72 h after rewarming. The independent physician could recommend continuation, no escalation, or withdrawal of life-sustaining treatment based on the patient's Glasgow Coma Scale motor score (GCS M score 1–6), electroencephalogram (EEG), neuroimaging, and, when available, somatosensory evoked potentials (SSEP).[17,19]

This formal prognostication procedure was only performed once for each patient and the information entered into the electronic case report. Based on the recommendation and related information, the treating physician made decisions of whether to continue or withdraw life-sustaining treatment.

Pre-specified predictors of poor neurological outcome and death, allowing withdrawal of life-sustaining treatment were; persistent coma with absent or extensor motor responses to central stimulation (GCS M score ≤ 2) and bilateral absent N20-peaks on SSEP; and persistent coma with GCS M ≤ 2 and treatment-refractory status epilepticus. The definition of status epilepticus and the prevalence of neuroimaging, EEG and SSEP are described in[15] Supplementary Appendix, available at NEJM.org.

Earlier prognostication and, if indicated, withdrawal of life-sustaining treatment was allowable for patients with; brain death diagnosed by national criteria; coma and myoclonic status, defined as continuous myoclonic activity in the face and extremities for at least 30 min in the first 24 h after admission in combination with bilateral absent N20-peaks on SSEP performed after rewarming; and for ethical reasons.[17]

If the above mentioned criteria for prognostication and withdrawal of intensive care were not fulfilled, then intensive care was continued. The patients were examined daily and treatment limitations or withdrawal of intensive care considered if their GCS M score did not improve and central metabolic and pharmacological effects were ruled out.

Neurological outcome by Cerebral Performance Category (CPC) was determined at face-to-face follow up approximately six months after resuscitation.[20] Poor outcome was pre-defined as: severe disability (CPC 3); vegetative state (CPC 4); or death (CPC 5). Good outcome was defined as; good cerebral performance (CPC 1); or moderate cerebral disability (CPC 2).

All electronic case report forms were systematically examined for information regarding the timing and findings of prognostic neurological assessments and withdrawal of life-sustaining treatment. Site investigators were contacted for clarification of incomplete or conflicting data which were corrected accordingly.

2.1. Statistical analysis

Continuous variables are expressed as median (interquartile range) and categorical variables as number of patients (percentages). Mann–Whitney *U* and Chi-squared tests are used to compare continuous and categorical variables respectively. Tests are two-sided and p values < 0.05 are considered statistically significant. The sensitivity and false positive rate (1-specificity) for each examination finding to predict poor outcome are presented with 95% confidence intervals using Wilson's method. Analyses were performed using SPSS software version 22 and R: A Language and Environment for Statistical Computing version 3.0.2.

Groups of patients are categorised by timing of independent prognostic neurological assessment; less than 72; 72–107; 108–144; and more than 145 h after cardiac arrest.

3. Results

3.1. Patients

The baseline characteristics of the intervention groups (Table 1) were similar. Of the 939 included patients, 452 regained consciousness and 139 died before prognostic assessments were performed (Fig. 1). In these 139, presumed causes of death were cerebral injury in 44 (32%); 16 of whom were diagnosed brain dead and five had myoclonic status epilepticus. Sixty-three (45%) died of cardiac or haemodynamic causes and 32 (23%) died of multi-organ failure. Prognostic assessment was not performed in an additional 33 patients, mainly due to transfer to another hospital ($n = 14$) and ongoing sedation ($n = 9$).

3.2. Prognostic neurological assessment

Three hundred and thirteen patients were prognostically assessed, 168 treated at 33 °C and 145 at 36 °C. The groups had similar age, gender, initial rhythm and time to return of spontaneous circulation (Table 2). Median time from cardiac arrest to assessment was 117 (93–137) h, with no difference between groups ($p = 0.71$; Table 2). Assessments were performed before 72 h after cardiac arrest in 38 (12%); between 72 and 107 h in 79 (25%); 108 and 144 h in 131 (42%); and after 145 h in 65 (21%; $p = 0.69$ for differences between temperature groups segregated by assessment period). Of patients being neurologically assessed before 72 h after rewarming (108 h after CA), 62/117 (52%) had a recommendation to withdraw life-sustaining treatment. A neurologist performed the assessment in 142 (45%); an intensivist in 146 (47%) and other physicians in 24 (8%; $p = 0.67$ between temperature groups). Continuation was recommended after 117 assessments (37%), no escalation after 55 (18%) and withdrawal of life-sustaining treatment after 141 (45%; $p = 0.70$ between temperature groups). Of patients receiving prognostication, 138 (83%) in the 33 °C and 128 (88%) in the 36 °C group had poor outcome ($p = 0.15$).

Table 1
Demographic and clinical data.

	All patients	33 °C	33 °C performed prognostication	36 °C	36 °C performed prognostication
Number of patients	939	473 (50%)	168 (36%)	466 (50%)	145 (31%)
Age	65 (56–73)	65 (57–73)	65 (58–72)	65 (56–73)	66 (60–73)
Male	761 (81%)	393 (83%)	144 (86%)	368 (79%)	114 (79%)
Location of CA					
Place of residence	500 (53%)	245 (52%)	104 (62%)	255 (55%)	83 (57%)
Public place	385 (41%)	197 (42%)	57 (34%)	188 (40%)	56 (39%)
Other	53 (6%)	31 (7%)	7 (4%)	22 (5%)	6 (4%)
Initial rhythm[a]					
Shockable rhythm	752 (80%)	375 (79%)	126 (75%)	377 (81%)	103 (71%)
Asystole	113 (12%)	59 (12%)	28 (17%)	54 (12%)	28 (19%)
PEA	65 (7%)	37 (8%)	13 (8%)	28 (6%)	11 (8%)
Unknown	8 (1%)	2(<0.5%)	1(<0.5%)	6 (1%)	3 (2%)
Time to ROSC (min)	25 (17–39)	25 (18–40)	30 (21–45)	25 (16–40)	31 (22–44)
Outcome at 6 month follow-up[b]					
CPC1	378 (41%)	195 (42%)	23 (14%)	183 (39%)	11 (8%)
CPC2	62 (7%)	23 (5%)	7 (4%)	39 (8%)	6 (4%)
CPC3	37 (4%)	17 (4%)	8 (5%)	20 (4%)	3 (2%)
CPC4	9 (1%)	6 (1%)	5 (3%)	3 (1%)	2 (1%)
CPC5	447 (48%)	228 (49%)	125 (74%)	219 (47%)	123 (85%)

Data are numbers of patients and percentages or medians and interquartile range (IQR). CA, cardiac arrest; ROSC, return of spontaneous circulation; PEA, pulseless electric activity; WLST, withdrawal of life-sustaining treatment; CPC, cerebral performance category.

[a] The initial rhythm was missing in one patient who was not neurologically evaluated in 36 °C group.

[b] The outcome at 6 month follow-up was missing in 6 patients (4 in the 33 °C group and 2 in 36 °C) but none belong to the group of patients who underwent neurological prognostication.

3.3. *Effect of targeted temperature on the predictive value of clinical findings and SSEP*

The GCS M score was recorded in 168 (100%) patients in the 33 °C and 144 (99%) in the 36 °C group (Table 3). GCS M ≤2 was found in 119 (71%) in the 33 °C and 108 (75%) in the 36 °C group ($p = 0.45$). Six patients in the 33 °C group had a good outcome despite a poor motor response (GCS M ≤2) compared to 3 patients in the 36 °C group. However, there was no significant difference in sensitivity ($p = 0.87$) or false positive rate ($p = 1.00$) to predict poor outcome by this test between the two temperature groups.

Pupillary light reflexes were recorded in 165 (98%) in the 33 °C and 143 (99%) in the 36 °C group. Bilateral absence was found in 38 (22%) in the 33 °C and 26 (18%) in the 36 °C group ($p = 0.33$). One patient in the 33 °C group had absent pupillary light reflexes and a good outcome. In this patient pupillary light reflexes were tested at 79 h after cardiac arrest and at this time point corneal reflexes were bilaterally present and the GCS M was four. The recommendation

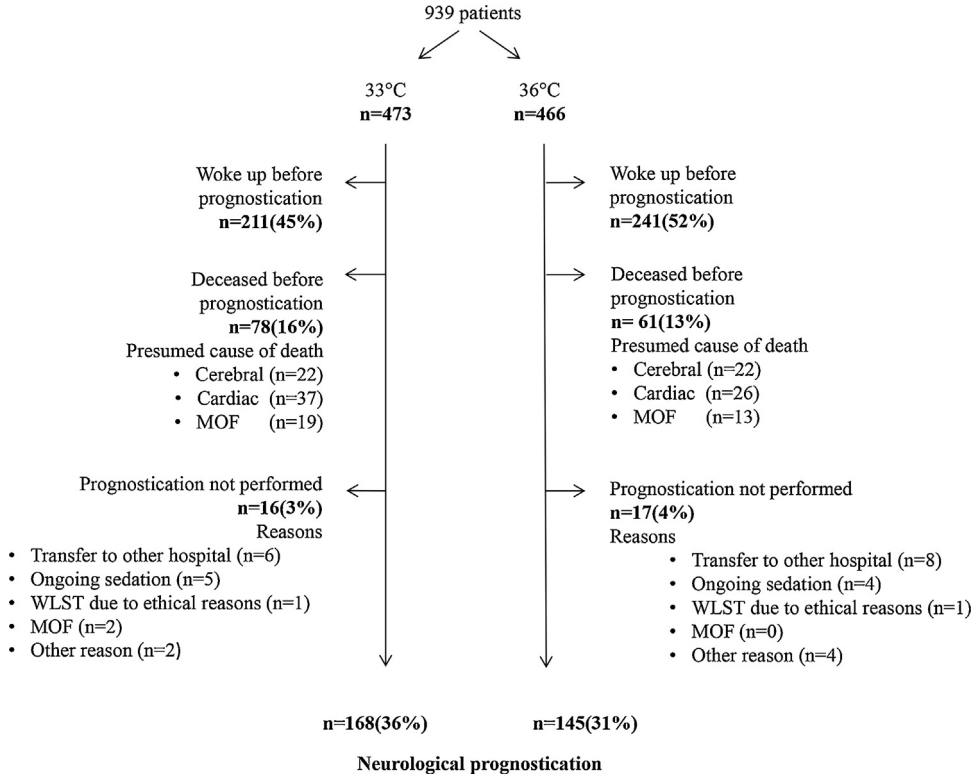

Fig. 1. Study flow chart.

Table 2
Background characteristics of the patients who underwent neurological prognostication.

	33 °C	36 °C	*p*-Value
Number of patients	168	145	
Time from CA to neurological prognostication, hours (IQR)	117 (93–136)	118 (93–140)	0.71
Who performed prognostication[a]			0.67
Neurologist	75 (45%)	67 (47%)	
Intensivist	78 (46%)	68 (47%)	
Other	15 (9%)	9 (6%)	
Recommendation			0.70
Continue active care	65 (39%)	52 (36%)	
Do not escalate	31 (18%)	24 (17%)	
WLST	72 (43%)	69 (48%)	

Data are numbers of patients and percentage or medians and interquartile range. CA, cardiac arrest; IQR, interquartile range; WLST, withdrawal of life-sustaining treatment.
[a] The data regarding who performed the neurological prognostication was missing in one patient in the 36 °C group.

was to continue intensive care and the patient was discharged from ICU on day 15 in CPC 3. At 6 month follow-up the patient had made a good recovery (CPC 1).

Corneal reflexes were recorded in 165 (98%) in the 33 °C and 136 (94%) in the 36 °C group. Bilateral absence was found in 47 (28%) in the 33 °C and 42 (31%) in the 36 °C group ($p = 0.70$). One patient in the 33 °C group had a good outcome. In this patient corneal reflexes were tested at 97 h after cardiac arrest and at the same time point the patient had absent motor response (GCS M = 1) but bilaterally present pupillary light responses. The recommendation was to continue intensive care and the patient was discharged from the ICU on day 27 with CPC 3 but had a good outcome at 6 months (CPC 1).

Among all patients, SSEP were obtained in 110 (23%) in the 33 °C and 94 (20%) in the 36 °C group (Table 5). The median time to SSEP testing after cardiac arrest was 98 (70–120) h in the 33 °C and 86 (69–105) h in the 36 °C group ($p = 0.11$). Bilaterally absent N20-peaks were found in 35 (32%) in the 33 °C and 39 (42%) in the 36 °C group ($p = 0.14$). Of these 74 patients, 58 patients had GCS M = 1–2, two patients had GCS M = 3, one had GCS M = 4, and one had GCS M = 6 at the time of prognostication. Nine patients with absent N20 died before prognostication and information is missing for another three patients. The patient with GCS M = 6 had a good outcome (CPC 2 at ICU discharge and CPC1 at 6 months follow-up) despite lacking N20-responses but interpretation of the SSEP performed at 77 h after cardiac arrest was difficult due to technical artefacts. Two patient with GCS M = 3 died after withdrawal of life-sustaining treatment on day 4 (coma and failing circulation) and day 7 (persisting coma) respectively. The patient with GCS M = 4 had withdrawal of life-sustaining treatment on day 6 because of early myoclonus status and persisting coma in addition to the lacking N20-responses.

3.4. Predictive value of clinical findings and SSEP for patients assessed at different time intervals after cardiac arrest

As the time to assessment after cardiac arrest increased, both the sensitivity and the false positive rate of GCS M ≤2 to predict poor outcome decreased (Table 4). The false positive rate for GCS M ≤2 was 40% (CI 11.7–77.0) when tested within 72 h after cardiac arrest and remained high through the later time intervals (Table 4).

The sensitivity of bilateral absent pupillary or corneal reflexes to predict poor outcome was low and decreased further with time after the end of rewarming (Table 4). A higher false positive rate of 8% (CI 1–33%) in the group assessed between 72 and 107 h after cardiac arrest was due to one patient with absent pupillary light reflexes and another with absent corneal reflexes who had good outcome.

The sensitivity of absent N20-peaks on SSEP to predict poor outcome was moderate (41% in the 33 °C and 50% in the 36 °C group; Table 5). The false positive rate of absent N20-peaks on SSEP was 0% (CI 0.0–13.9) in the 33 °C and 7% (CI 1.1–29.9) in the 36 °C group due to one false prediction.

4. Discussion

Induced hypothermia treatment has made the validity of previously acknowledged prognostic clinical and SSEP findings[6–11,21,22] for comatose patients after cardiac arrest questionable. In this study, using prospectively collected data from 939 patients with out-of-hospital cardiac arrest of primary cardiac origin, we found that different target treatment temperatures of 33 °C and 36 °C had no significant influence on the prognostic value of GCS M score, bilateral absent pupillary or corneal reflexes or N20-peaks on SSEP

Table 3
Prediction of outcome with clinical tests. Comparison between the two interventions groups (33° C versus 36 °C).

	Patients tested *n* (%)	TP *n*	FP *n*	TN *n*	FN *n*	Sensitivity %(95%CI)	*p*-Value	FPR %(95%CI)	*p*-Value
GCS M≤2							0.87		1.00
33 °C	168 (100)	113	6	24	25	81.9 (74.6–87.5)		20.0 (9.5–37.3)	
36 °C	144 (99)	105	3	14	22	82.7 (75.1–88.3)		17.6 (6.1–41.1)	
No pupillary light responses bilaterally							0.25		1.00
33 °C	165 (98)	37	1	29	98	27.4 (20.5–35.5)		3.3 (0.5–16.67)	
36 °C	143 (99)	26	0	17	100	20.6 (14.4–28.6)		0.0 (0.0–18.5)	
No corneal reflexes bilaterally							0.89		1.00
33 °C	165 (98)	46	1	28	90	33.8 (26.4–42.2)		3.4 (0.6–17.17)	
36 °C	136 (94)	42	0	17	77	35.3 (27.2–44.3)		0.0 (0.0–18.5)	

Data are given in numbers and percentages. Sensitivity and false positive rate (FPR) are expressed as percentage with their 95% confidence interval (CI). TP, true positive; FP, false positive; TN, true negative; FN, false negative; GCS M, Glasgow Coma Scale motor score.

Table 4
Prediction of poor outcome at 6 month follow-up in patients who underwent neurological prognostication at different time points.

Test	Time of prognostication (hours (h) after CA)[a]	Patients tested (*n*)	TP *n*	FP *n*	TN *n*	FN *n*	Sensitivity% (CI)	FPR%(CI)
GCS M≤2	<72	38	31	2	3	2	93.9 (80.3–98.4)	40.0 (11.7–77.0)
	72–107	79	59	3	10	7	89.4 (79.6–94.8)	23.1 (8.1–50.3)
	108–144	130	88	3	19	20	81.5 (73.1–87.7)	13.6 (4.7–33.4)
	≥145	65	40	1	6	18	69.0 (56.1–79.4)	14.3 (2.5–51.4)
	All tested	312	218	9	38	47	82.3 (77.2–86.4)	19.1 (10.4–32.6)
No pupillary light responses bilaterally	<72	36	15	0	5	16	48.4 (31.9–65.2)	0.0 (0.0–43.5)
	72–107	78	19	1	12	46	29.2 (19.5–41.2)	7.7 (1.3–33.4)
	108–144	130	25	0	22	83	23.1 (16.1–32.0)	0.0 (0.0–14.9)
	≥145	64	4	0	7	53	7.0 (2.7–16.8)	0.0 (0.0–35.5)
	All tested	308	63	1	46	198	24.1 (19.3–29.7)	2.1 (0.3–11.2)
No corneal reflexes bilaterally	<72	33	18	0	4	11	62.1 (44.0–77.4)	0.0 (0.0–49.0)
	72–107	77	26	1	12	38	40.6 (29.4–52.9)	7.7 (1.3–33.4)
	108–144	127	32	0	22	73	30.5 (22.4–39.8)	0.0 (0.0–14.9)
	≥145	64	12	0	7	45	21.1 (12.4–33.3)	0.0 (0.0–35.5)
	All tested	301	88	1	45	167	34.5 (28.9–40.6)	2.2 (0.3–11.4)

Data are given in numbers and percentages. CA, cardiac arrest; CPC, cerebral performing category; CI, confidence interval; FPR, false positive rate; GCS M, Glasgow Coma Scale motor score; TP, true positive; FP, false positive; TN, true negative; FN, false negative.

[a] The observations were made at different time points in different patients.

at 6 months. Our results also suggest that the clinical expression of the hypoxic-ischaemic brain injury after cardiac arrest of primary cardiac origin is not significantly affected by management at 33 °C or 36 °C when observed in the time frames in this study.

Clinical examination findings constitute the core of neurological prognostication of comatose cardiac arrest victims, with additional information sometimes being obtained from neurophysiology, neuroimaging and biochemical sources.[13,23–25] In this complex process, markers of a poor prognosis are of critical importance since they may lead to withdrawal of supportive care and hence a high likelihood of death.[2,26] Therefore, the false positive rate, the erroneous assignment of a poor prognosis, of an ideal test should be zero. However, since only a minority of patients comatose after resuscitation from cardiac arrest will ultimately recover, any false positive finding will have a major impact on the false positive rate of a test even in a large cohort of patients.

The absence of pupillary light reflexes 72 h after cardiac arrest has been described to be the most accurate clinical predictor of poor neurological outcome[6,9] but in rare cases, bilateral absence of corneal reflexes was consistent with recovery.[9,12] However, absent ocular reflexes are of limited clinical utility because they are less common. Days after the arrest, brain stem functions usually recover in comatose patients since the brain stem seems more resistant to hypoxic-ischaemic injury than the cerebrum.[27] As a consequence, brainstem death is infrequently diagnosed after cardiac arrest.[26,28] A large fraction of comatose cardiac arrest patients may progress to a vegetative state if intensive care is continued.[29] In our study one patient with absent pupillary light reflexes and one patient with absent corneal reflexes made a good recovery. However, none of the patients with the absence of both pupillary light reflexes and corneal reflexes had good outcome.

These findings are consistent with several studies performed before[22,23,25,30,31] and after the introduction of induced hypothermia.[6,8–10,12,21,32]

Importantly our study confirms that a GCS M ≤2 is an unreliable marker of a poor prognosis in comatose patients. Furthermore the false positive rate of these findings remains high beyond 72 h after cardiac arrest. The wide confidence interval for GCS M ≤2 also emphasises the uncertainty of this test and limits its safe use for prognostication.

In our study, bilateral absent N20-peaks on SSEP remained a strong predictor of outcome. Nevertheless false predictions of poor outcome by SSEP have been reported[11] and artefacts which may have caused our single false positive, are a recognised cause of error.[9,12]

Limitations of our study include a possible interaction of sedation, lack of repeated clinical testing, inhomogeneous time-point of prognostication and a risk of "self-fulfilling prophecy" affecting our SSEP-results.

Lingering sedation may affect the reliability of motor responses and corneal reflexes to predict outcome but very limited data exist on the effect of sedation on recovery and prognostication after resuscitation from cardiac arrest.[9] In our study patients with ongoing sedation at the time point of prognostication were excluded but we lack detailed information on the time when sedation was stopped and accumulated doses of sedative agents. Sedatives can alter the EEG[24] but SSEP[33] and pupillary light responses[9] are less affected by these drugs.

Although the TTM trial contains data describing the largest prospectively studied cohort of patients resuscitated after out-of-hospital cardiac arrest, the protocol was not primarily designed to investigate neurological prognostication in these

Table 5
Prognostic accuracy of SSEP at 6 month follow-up.

	Patients tested, *n* (%)	TP *n*	FP *n*	TN *n*	FN *n*	Sensitivity % (95% CI)	*p*-Value	FPR % (CI)	*p*-Value
Bilateral absent SSEP (N20)							0.27		0.38
33 °C	110 (23)	35	0	24	50	41.2 (31.3–51.9)		0.0 (0.0–13.9)	
36 °C	94 (20)	39	1	14	38	50.0 (39.0–61.0)		6.7 (1.1–29.9)	
All tested	204 (22)	74	1	38	88	45.3 (37.8–53.1)		2.6 (0.4–13.2)	

SSEP, somatosensory evoked potentials; TP, true positive; FP, false positive; TN, true negative; FN, false negative; CI, confidence interval; FPR, false positive rate.

circumstances. Serial observations were not recorded. In the present study, the data reported from the different time spans after cardiac arrest are from separate patient cohorts. A selection bias of some patients for early prognostication and, if indicated, subsequent withdrawal of life-sustaining treatment might restrict the generalizability of the results. The TTM trial protocol recommended prognostication not be performed before 72 h after the end of rewarming. Nevertheless some patients were assessed before this time point. The TTM trial protocol acknowledged earlier withdrawal of life-sustaining treatment could be considered in specific circumstances. The earlier performance of prognostic tests might be justifiable in complex clinical situations where relevant findings and results become rapidly available. However, we caution against extrapolating our results to patients comatose less than 72 h after cardiac arrest. Importantly, assessment of prognosis in comatose patients led to a recommendation of withdrawal-of-life sustaining treatment in less than half of the patients. Following previous prognostic evaluations of SSEP[7,8,12] in comatose patients after cardiac arrest, the TTM trial recommended SSEP to support clinical decision making, including withdrawal of life-sustaining treatment. Therefore, the 'self-fulfilling prophecy' is of relevance for our SSEP-results as in most previous studies on this prognostic method[34] but we stress that bilateral absent N20-peaks on SSEP alone were not sufficient to recommend withdrawal of life-sustaining treatment in the TTM trial. Similarly, a GCS M $\leq$2 was only endorsed as supporting a recommendation to withdraw when occurring in combination with a stronger indicator in agreement with recent recommendations.[34] Pupillary and corneal reflexes were not used as prognostic guides.[17,19]

In conclusion we found that bilateral absent pupillary or corneal reflexes or N20-peaks on SSEP were reliable markers of a poor prognosis (severe disability, vegetative state or death at six months) in patients remaining comatose after 36 h of targeted temperature management following out-of-hospital cardiac arrest of primary cardiac origin. The reliability of these findings did not appear altered by temperature and our findings do not support separate guidelines for prognostication for cardiac arrest patients treated at different temperatures of targeted temperature management of either 33 °C or 36 °C.

Authors' contribution

ID and TC designed the study and wrote the first draft of the manuscript. JH and MK contributed to the present study concept and design. MK and JC were principal investigators in the TTM trial. NN was the chief-investigator of the TTM trial and participated in the design and development of the present study. SU was study statistician.

All authors of the manuscript were involved in the analysis and interpretation of the data and reviewed and edited the manuscript.

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Conflict of interest statement

ID, JH, MK, SU, JW, JC, CH, TC have no conflicts of interests to report. HF reports personal fees from Natus Inc, and personal fees from Bard Medical. NN reports personal fees from Bard Medical.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.resuscitation.2015.04.013

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