

Neurological Prognostications for the Therapeutic Hypothermia among Comatose Survivors of Cardiac Arrest

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Abstract

Background: Currently, there are limited data of prognostic clues for neurological recovery in comatose survivors undergoing therapeutic hypothermia (TH). We aimed to evaluate clinical signs and findings that could predict neurological outcomes, and determine the optimal time for the prognostication. **Materials and Methods:** We retrospectively reviewed database of postarrest survivors treated with TH in our hospital from 2006 to 2014. Cerebral performance category (CPC), neurological signs and findings in electroencephalography (EEG) and brain computed tomography (CT) were evaluated. In addition, the optimal time to evaluate neurological status was analyzed. **Results:** TH was performed in 51 postarrest patients. Approximately 53% of TH patients survived at discharge and 33% of the hospital survivors had favorable outcome (CPC1-2). The prognostic clues for unfavorable outcome (CPC3-5) at discharge were lack of pupillary light response (PLR) and/or gag reflex after rewarming, and the absence of at least one of the brainstem reflexes, no eye-opening, or abnormal motor response on the 7th day. Myoclonus and seizure could not be used to indicate poor prognosis. In addition, prognostic values of EEG and CT findings were inconclusive. **Conclusions:** Our study showed the simple neurological signs helped predict short-term neurological prognosis. The most reliable sign determining unfavorable outcome was the lack of PLR. The optimal time to assess prognosis was either at 48–72 h or 7 days after return of spontaneous circulation.

Keywords: Comatose survivor, neurological prognostication, therapeutic hypothermia

INTRODUCTION

It is difficult to manage postcardiac arrest survivors because when treated with therapeutic hypothermia (TH), they commonly remain comatose after rewarming. In addition, previous studies conducted in patients who have undergone TH showed an increase in false-positive prediction for poor neurological outcome.^[1] On the other hand, survivors without hypothermia have to be continuously sedated so the neurological prognostications for these survivors cannot be made accurately.^[2] As a result of this, it is difficult to make a decision whether to withhold or withdraw life-sustaining treatment to unawake patients which the former choice can incur costly investigations and result in futile treatment, especially for those patients with irreversible conditions. In addition, there are limited data on the optimal time for neurological prognostication. Some recommendations, including those from the American Heart Association, suggest that physicians should delay the assessment beyond 72 h

after the return of spontaneous circulation (ROSC).^[3,4] Other guidelines recommend the prognostic assessment at 72 h after completing rewarming.^[5]

Thus, this study was conducted to evaluate the neurological predictive factors and the appropriate time for prognostication. The hypothesis was that the neurological symptoms, (viz., myoclonus and seizure), simple neurological signs at two different time points, and neurological investigations including electroencephalography (EEG), computed tomography of the brain (brain CT), may be able to predict the neurological outcomes in the survivors treated with hypothermia.

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MATERIALS AND METHODS

Patients

We retrospectively reviewed our database for postcardiac arrest survivors who had TH from 2006 to 2014 at the 2 medical Intensive Care Units (ICUs) and 1 CCU at the King Chulalongkorn Memorial Hospital. The patients were identified from the hospital database using “ICD 10 code I 460-cardiac arrest with successful resuscitation” and “ICD9 code 9961-TH” for the diagnosis of postcardiac arrest survivor and intervention of TH, respectively.

Hypothermia protocol

All comatose survivors from cardiac arrest with Glasgow Coma Score (GCS) ≤ 8 after ROSC were evaluated for TH. In the condition of CCU or ICU-bed availability, all patients who were eligible for TH were cooled to 32°C–34°C for 24 h by external cooling methods with or without internal cooling methods, followed by rewarming. All patients were sedated. Shiverings were treated with extra sedation and neuromuscular blockades. The sedative drugs and neuromuscular blockades were interrupted after completing the rewarming process. In addition, during the 1st week of a postrewarming period, a controlled normothermia protocol was implemented. The patients with postrewarming pyrexia (core temperature $>38^\circ\text{C}$) were decreased their temperature by conventional cooling blankets (for keeping the temperature of 37°C) and treated with acetaminophen if no contraindication. Hemodynamic and respiratory parameters were continuously monitored, and vasopressors or inotropic drugs were administered to maintain hemodynamic stability. Antiepileptic drugs were prescribed if the patients developed clinical or electrical signs of seizure.

Data collection

Baseline characteristics, cooling practice, symptoms, signs, and clinical outcomes were collected from the patients’ medical charts and flow sheets. All data were recorded by ICU staff, including primary physicians, intensivists, neurologists, and critical care nurses. The simple neurological signs at two different time points, immediately after rewarming (48–72 h) and on the 7th day, were evaluated from the recorded data. These signs consisted of (1) GCS: eye-opening, motor response and verbal response, and (2) brainstem reflexes: pupillary light response (PLR), gag reflex, corneal reflex, and Doll’s eye reflex. The neurological symptoms, namely seizure and myoclonus, were obtained from the clinical data, EEG, and brain CT images.

Outcome measurements

Glasgow–Pittsburgh cerebral performance category (CPC) at discharge was used to evaluate the neurological outcomes. The outcomes were dichotomized as follows: (1a) favorable outcome: CPC1 = good cerebral performance and CPC2 = moderate disability, and (2a) unfavorable outcome: CPC3 = severe disability, CPC4 = vegetative state and CPC5 = brain death or (1b) regained consciousness: CPC1–3 and (2b) unconsciousness: CPC 4–5.

Data analysis

The patients’ baseline characteristics were described according to the types of variables and the normality of their distributions. Continuous variables were reported as mean (standard deviation) or median (interquartile range). Categorical variables were reported as numbers or percentages. The factors associated with clinical outcomes were analyzed. Unpaired-*t*-test or Mann–Whitney U-test was used to compare between two groups with continuous variables. Chi-square or Fisher’s exact test was used to analyze the association between the two groups with categorical variables. We used a two-sided test, and $P < 0.05$ was considered statistically significant. In addition, sensitivity, specificity, false positive rate, positive predictive value, negative predictive value, likelihood ratio, and accuracy were analyzed.

The study was approved by the Institutional Review Board, Faculty of Medicine, Chulalongkorn University (IRB No. 219/58).

RESULTS

Patients

All 51 postcardiac arrest survivors treated with TH in the two medical ICUs and CCU during the 8-year period were included in the analysis to assess the neurological prognostic factors. The baseline characteristics and clinical data of the patients are shown in Table 1.

There were 40 (78%) survivors from out-of-hospital cardiac arrest and 11 (21.6%) survivors from in-hospital cardiac arrest. The majority of primary cardiac rhythms was nonshockable rhythm (78.4%). Cardiovascular events including myocardial infarction and arrhythmia were the main causes of cardiac arrest [Table 1]. Approximately, 57% of the survivors were males and the median age was 59 years. The median time from collapse to ROSC, the median time from ROSC to hypothermia induction and the median time from hypothermia initiation to targeted temperature were 26 min, 5 h, and 4 h, respectively. About 65% of the patients achieved targeted temperature within 6 h after inducing the cooling process, but 15.7% of all patients did not attain the targeted temperature. Seventeen patients developed myoclonus whereas eight patients developed seizures. Overall, 52.9% (27/51) survived and discharged from the hospital with a median LOS of 13 days. Nine of 27 hospital survivors had good neurological recovery (six patients with CPC1 and three patients with CPC2). Eight of the hospital survivors had a severe disability (CPC3) and the others (10) were in vegetative state (CPC4).

A short duration from the time of collapse to ROSC was associated with favorable outcome ($P = 0.044$). The absence of vasopressor use was clinically independent predictor for good neurological recovery (CPC1–2, $P = 0.024$), ability to regain consciousness (CPC1–3, $P = 0.01$), and survival ($P < 0.001$). Survival improved when the temperature was achieved in < 6 h from ROSC ($P = 0.038$) and protocol was completed ($P = 0.027$). Cardiac rhythm, location of arrest, target temperature attainment, rebound hyperthermia, and age were not associated with any clinical outcomes.

Table 1: Baseline characteristics of the postcardiac arrest survivors

	All	Unfavorable outcome			Unconsciousness			Survival		
		UF	F	P	U	C	P	Death	Alive	P
n (%)	51	42 (82.4)	9 (17.6)	NS	34 (66.7)	17 (33.3)	NS	24 (47.1)	27 (52.9)	NS
Age, years old, median (IQR)	59	60 (24)	44 (34)	NS	60.5 (21)	49 (29)	NS	59 (22)	59 (32)	NS
Sex, n (%)				NS			0.046			0.039
Male	29 (56.9)	22 (52.4)	7 (77.8)		16 (47.1)	13 (76.5)		10 (41.7)	19 (70.4)	
Female	22 (43.1)	20 (47.6)	2 (22.2)		18 (52.9)	4 (23.5)		14 (58.3)	8 (29.6)	
Location of cardiac arrest, n (%)										
Out-of-hospital	40 (78.4)	32 (76.2)	8 (88.9)	NS	25 (73.5)	15 (88.2)	NS	17 (70.8)	23 (85.2)	NS
In hospital	11 (21.6)	10 (23.8)	1 (11.1)		9 (26.5)	2 (11.8)		7 (29.2)	4 (14.8)	
Primary cause of cardiac arrest rhythm, n (%)				NS			NS			NS
Shockable	11 (21.6)	7 (16.7)	4 (44.4)		6 (17.6)	5 (29.4)		5 (20.8)	6 (22.2)	
Nonshockable	40 (78.4)	35 (83.3)	5 (55.6)		28 (82.4)	12 (70.6)		19 (79.2)	21 (77.8)	
Cause of cardiac arrest										
Arrhythmia	9	9	0		7	2		3	6	
MI	16	13	3		9	7		7	9	
Electrical injury	2	0	2		0	2		0	2	
Brugada	5	4	1		3	2		1	4	
Others	19	16	3		15	4		13	6	
Delayed CPR, minutes, median (IQR)	10 (15)	10 (15.75)	9 (7)	NS	10 (16.5)	10 (8.5)	NS	10 (17.25)	10 (13)	NS
CPR duration, minutes, median (IQR)	15 (10)	16.5 (17)	10 (8.5)	NS	18 (21.75)	14 (9.5)	NS	15.5 (25.5)	15 (10)	NS
CPR number, median (IQR)	1 (0)	1 (0)	1 (0)	NS	1 (0)	1 (0)	NS	1 (1)	1 (0)	NS
Time from collapse to ROSC, minutes, median (IQR)	26 (18)	28.5 (22)	21 (8)	0.044	29.5 (26)	24 (8)	NS	30.5 (29.3)	24 (10)	NS
ROSC to initiate TH, h, median (IQR)	5 (3)	5 (5.5)	5 (2.25)	NS	4.17 (5.63)	5 (2.34)	NS	4.67 (5.38)	5 (3)	NS
Time from TH induction to achieved target, h, median (IQR)	4 (3)	4 (5)	4 (3.13)	NS	3.75 (3.38)	4 (4)	NS	4 (6)	4 (3)	NS
ROSC to achieve targeted temperature, h, median (IQR)	10.5 (6)	10.25 (6)	10.5 (6)	NS	9.5 (5.88)	11 (5)	NS	10.5 (7)	9.75 (5.75)	NS
Targeted temperature achievement, n (%)	43 (84.3)	34 (81)	9 (100)	NS	28 (82.4)	15 (88.2)	NS	19 (88.9)	24 (79.2)	NS
ROSC to targeted temperature <6 h, n (%)	4	4 (12.1)	0 (0)	NS	4 (14.8)	0 (0)	NS	4 (21.1)	0 (0)	F=0.038
Need of vasopressor, n (%)	25 (46)	24 (57.1)	1 (11.1)	F=0.024	21 (61.8)	4 (23.5)	0.01	20 (83.3)	5 (18.5)	<0.001
Shivering, n (%)	11 (21.6)	7 (16.7)	4 (44.4)	NS	3 (8.8)	8 (47.1)	0.002	3 (12.5)	8 (29.6)	NS
Myoclonus, n (%)	17 (33.3)	15 (35.7)	2 (22.2)	NS	12 (35.3)	5 (29.4)	NS	10 (25.9)	7 (41.7)	NS
Seizure, n (%)	8 (15.7)	7 (16.7)	1 (11.1)	NS	4 (11.8)	4 (23.5)	NS	3 (18.5)	5 (12.5)	NS
Number of patients with CT brain, n (%)	22 (43.1)	18 (42.9)	4 (44.4)	NS	11 (32.4)	11 (64.7)	0.028	8 (33.3)	14 (51.9)	NS
Number of patients with EEG, n (%)	15 (29.4)	13 (31)	2 (22.2)		10 (29.4)	5 (29.4)		8 (33.3)	7 (25.9)	
EEG pattern, n (%)										
No electrical activity	1 (6.7)	0	1		0	1		0	1	
No epileptiform	6 (40)	6	0		4	2		4	2	
Status epilepticus	3 (20)	2	1		2	1		1	2	
Burst suppression	2 (13.3)	2	0		2	0		2	0	
Slow-wave pattern	2 (13.3)	2	0		2	0		1	1	
Localized abnormality	1 (6.7)	1	0		0	1		0	1	
Protocol completion, n (%)	36 (70.6)	30 (64.3)	9 (100)	NS	23 (61.8)	16 (88.2)	0.036	15 (58.3)	24 (81.5)	0.027
Postrewarm pyrexia, n (%)	20 (39.2)	17 (40.5)	3 (33.3)	NS	14 (41.2)	6 (35.3)	NS	10 (41.7)	10 (37)	NS
LOS, days, median (IQR)	13 (20)	14 (22.25)	11 (13)	NS	9.5 (21)	13 (19.5)	NS	6 (19.25)	20 (22)	NS

UF: Unfavorable outcome; F: Favorable outcome; U: Unconsciousness; C: Consciousness; LOS: Length of stay; NS: Not significant; IQR: Interquartile range; CPR: Cardiopulmonary resuscitation; EEG: Electroencephalography; CT: Computed tomography; ROSC: Return of spontaneous circulation; TH: Therapeutic hypothermia

Neurological prognostications

Neurological symptoms and signs

According to the data in Table 1, myoclonus and seizure were not exclusively poor prognostic symptoms. One patient with myoclonus and one patient with both seizure and myoclonus

had favorable neurological outcomes post-TH. The clinical data of these patients are shown in Table 2.

Tables 3 and 4 present the results of the simple neurological signs used as the prognostic tools to evaluate the neurological outcomes post-TH. In the early period of treatment (48–72 h),

the absence of PLR and gag reflex were the only two reliable signs predicting the unfavorable neurological outcomes

Table 2: Clinical data of the two patients who had myoclonus with or without the epilepticus status with favorable outcomes

Clinical data	Patient 1 Epilepticus with myoclonus status	Patient 2 Myoclonus
Age (years old)	39	44
Sex	Female	Male
Location of cardiac arrest	In hospital	Out-of-hospital
Primary cause of cardiac arrest rhythm	PEA	Asystole
Cause of cardiac arrest	Massive hemoptysis	Brugada
EEG findings	Status epilepticus	No electrical activity
CT brain	Not done	Not done
Time from collapse to ROSC	4 min	27 min
ROSC to achieve targeted temperature	7 h	27 h
Need of vasopressor	No	No
Protocol completion	Yes	Yes
Postwarm pyrexia	No	Yes
CPC upon hospital discharge	1	2

PEA: Pulseless electrical arrest; EEG: Electroencephalography; CT: Computed tomography; CPC: Cerebral performance category; ROSC: Return of spontaneous circulation

False-positive rate (FPR 0%), but the sensitivities of these signs were low. Noticeably, most of the patients with absent pupillary response (8/9 patients) had dilated nonreactive pupils. There was only one patient with pinpoint pupils who became vegetative at hospital discharge. In addition, any lack of the following responses on the 7th day can be used to precisely (FPR 0%) prognoses unfavorable outcomes: brainstem reflexes, motor response worse than withdraws from pain ($M \leq 3$), and no spontaneous opening of the eyes. Similarly, the accurate predictive signs for unawakening were the absence of PLR and gag responses after rewarming (FPR 0% and 5.9%, respectively), and the absence of any brainstem reflexes on the 7th day (all FPR 0%). However, all of these predictors had a large 95% confidence interval (CI) due to the small sample size.

Neurological investigations

Electroencephalography

EEG data were not available for all patients who had TH because of limited resources. EEG monitorings were temporarily performed on patients suspected with or had status epilepticus or patients who had abnormal movements with uncertain diagnoses. Only 15 patients had EEG data. The results of the EEG yielded six patterns: (1) no electrical activity, (2) no epileptiform, (3) status epilepticus, (4) burst suppression, (5) slow-wave pattern, and (6) localized abnormal pattern. The patients from each EEG finding are shown in Table 1. Due to the small number of patients with EEG

Table 3: Sensitivity, false positive rate, positive predictive value, negative predictive value, likelihood ratio, and accuracy of the simple neurological signs immediately after rewarming to predict the outcomes of the patients

Variables investigated	Sensitivity (%)	95% CI	FPR (%) (1-specificity)	95% CI	P	OR	95% CI	P
After rewarming								
Predictors for unconsciousness on hospital discharge: CPC 1-3 versus CPC 4-5								
No eye opening	97.1	84.67-99.93	41.18	18.44-67.08	$\chi^2 < 0.001$	47.14	5.163-430.41	<0.001
$M \leq 3$	91.2	76.32-98.14	41.18	18.44-67.08	$\chi^2 < 0.001$	14.76	3.2-68.096	<0.001
$V \leq 3$					Could not be evaluated			
Lack of PLR*	26.47	12.88-44.36	0	0-19.51	$\chi^2: 0.019$	13.04	0.71-238.93	0.08
Lack of Gag reflex	32.4	17.39 to 50.53	5.9	0.15-28.69	$\chi^2: 0.036$	7.65	0.9-65.319	0.06
Lack of Corneal	32.4	17.39-50.53	23.5	6.81-49.9	Fisher's test: 0.746	1.55	0.411-5.884	0.51
Lack of Doll's eye	32.35	17.39-50.53	17.8	1.46-36.44	Fisher's test: 0.175	3.59	0.7-18.512	0.13
Myoclonus	35.29	19.75-53.51	29.41	10.31-55.96	Fisher's test: 0.760	1.31	0.372-4.607	0.67
Seizure	11.76	3.3-27.45	23.5	6.81-49.9	Fisher's test: 0.416	0.43	0.094-2.003	0.28
Predictors for unfavorable outcome on hospital discharge: CPC 1-2 versus CPC 3-5								
No eye opening	90.48	77.38-97.34	22.22	2.81-60.01	$\chi^2 < 0.001$	33.25	5.078-217.713	<0.001
$M \leq 3$	85.71	71.46-94.51	22.22	2.81-60.01	$\chi^2 < 0.001$	21	3.494-126.217	<0.001
$V \leq 3$					Could not be evaluated			
Lack of PLR*	21.43	10.3-36.81	0	0-33.63	Fisher's test: 0.332	5.39	0.286-101.28	0.26
Lack of gag reflex	28.57	15.72-44.58	0	0-33.63	Fisher's test: 0.094	7.79	0.42-144.24	0.17
Lack of corneal	33.33	19.57 to 49.55	11.1	0.28-48.25	Fisher's test: 0.251	4	0.454-35.231	0.21
Lack of doll's eye	28.57	15.72-44.58	11.1	0.28-48.25	Fisher's test: 0.417	3.2	0.36-28.423	0.29
Myoclonus	35.71	21.55 to 51.97	22.2	2.81-60.01	Fisher's test: 0.699	1.94	0.357-10.575	0.44
Seizure	16.67	6.97-31.36	11.11	0.28-48.25	Fisher's test: 1.000	1.6	0.172-14.905	0.68

*Only one patient with lack of PLR had pinpoint pupils, but the others had dilated nonreactive pupils. FPR: False positive rate; M: Motor response (GCS); $M \leq 3$: Flaccid response, decerebration, and decortication; V: Verbal response (GCS); $V \leq 3$: No verbal response; incomprehensible sound and inappropriate words; PLR: Pupillary light response; CI: Confidence interval; OR: Odds ratio; GCS: Glasgow Coma Score; CPC: Cerebral performance category

Table 4: Sensitivity, false-positive rate, positive predictive value, negative predictive value, likelihood ratio, and accuracy of the simple neurological signs on the seventh day for predicting the outcome of the patients after therapeutic hypothermia postcardiac arrest

Variable investigated	Sensitivity (%)	95% CI	FPR (%) (1-specificity)	95% CI	P	OR	95% CI	P
On the 7th day								
Predictors for unconsciousness upon hospital discharge: CPC 1-3 versus CPC 4-5								
No eye opening	97.06	84.67-99.93	23.53	6.81-49.9	$\chi^2 < 0.001$	107.25	10.93-1015.12	<0001
M \leq 3	97.06	84.67-99.93	23.53	6.81-49.9	$\chi^2 < 0.001$	107.25	10.93-1052.12	<0.001
V \leq 3	100	0-10.28	64.7	38.33-85.79	Fisher's test 0.001	39	2.035-747.3	0.015
Lack of PLR*	44.12	27.19-62.11	0	0-19.51	$\chi^2 < 0.001$	27.82	1.547-500.191	0.024
Lack of gag reflex	66.7	48.17-82.04	0	0-19.51	$\chi^2 < 0.001$	68.48	3.77-1243.99	0.0043
Lack of corneal	51.52	33.54-69.2	0	0-19.51	$\chi^2 < 0.001$	37.12	2.06-668.276	0.014
Lack of doll's eye	57.58	39.22-74.52	0	0-19.51	$\chi^2 < 0.001$	47.07	2.61-848.77	0.009
Predictors for unfavorable outcomes on hospital discharge: CPC 1-2 versus CPC 3-5								
No eye opening	88.1	74.37-96.02	0	0-33.63	$\chi^2 < 0.001$	129.55	6.57-2553.93	0.0014
M \leq 3	88.1	74.37-96.02	0	0-33.63	$\chi^2 < 0.001$	129.55	6.57-2553.93	0.0014
V \leq 3	100	91.59-100	33.3	7.49-70.07	Fisher's test <0.001	157.86	7.284-3421.25	0.0013
Lack of PLR*	35.71	21.55-51.97	0	0-33.63	$\chi^2 0.033$	10.71	0.58-196.82	0.11
Lack of gag reflex	53.66	37.42-69.34	0	0-33.63	$\chi^2 0.011$	21.92	1.2-401.55	0.037
Lack of corneal	41.46	26.32-57.89	0	0-40.96	$\chi^2 0.051$	13.57	0.74-248.95	0.078
Lack of doll's eye	46.34	30.66-62.58	0	0-33.63	$\chi^2 0.029$	16.47	0.9-301.61	0.059

*All patients with lack of PLR had dilated nonreactive pupils. FPR: False-positive rate; M: Motor response (GCS), M \leq 3: Flaccid response, decerebration, and decortication; V: Verbal response (GCS), V \leq 3: No verbal response, incomprehensible sound and inappropriate words; PLR: Pupillary light response; CI: Confidence interval; OR: Odds ratio; GCS: Glasgow Coma Score; CPC: Cerebral performance category

investigations, we could not evaluate the prognostic value of EEG. However, interestingly enough, we noticed that one of three patients with status epilepticus, confirmed by EEG, subsequently recovered completely as shown in Table 2.

Brain computed tomography images

Twenty-two patients were investigated for the primary causes of cardiac arrest, seizure, or new localizing neurological signs by brain CT. The findings of the brain CT images were as follows: (1) normal, (2) old cerebral infarction, (3) brain atrophy, (4) brain swelling, (5) subarachnoid hemorrhage, and (6) posterior reversible encephalopathy syndrome (PRES). The findings of the brain swelling and PRES may indicate prognostic signs of poor outcomes because all of the three patients with brain swelling had unfavorable outcomes on hospital discharge and one patient with PRES died. However, the predictive value of the brain CT findings was inconclusive because for each brain CT finding, there were few patients. In addition, the brain CT investigations were performed at different time points for purposes not related to TH.

DISCUSSION

TH improves neurological recovery and survival among postcardiac arrest patients. The mechanisms of the neuroprotective effect are avoidance of hyperthermia, reduction in metabolic demand, and reduction in ischemic-reperfusion injury.^[6] The prevention of fever reduces cerebral metabolic rate and oxygen consumption, which preserves energy stores and improves brain glucose utilization.^[6,7] Besides, TH also

prevents fever-related tissue injury. In addition, it is known that ischemia-reperfusion triggers further neuroinflammation, resulting from effects of excitotoxicity, free radical production, blood-brain barrier disruption, blood vessel leakage, and cerebral thermopooling. TH improves cerebral perfusion and decreases hyperemia following reperfusion, which prevents the secondary brain injury and reduces intracranial pressure.^[7-11]

The patients undergoing TH have low-metabolic rate and usually receive sedatives and muscle relaxant agents during the first 48 h after ROSC, which interferes the neurological prognostication.^[2] The majority of evidence concerning prognostication after cardiac arrest was based on studies conducted in patients not treated with TH. Our study demonstrated the prognostic factors for the unfavorable neurological outcome at hospital discharge in the postcardiac arrest patients undergoing TH. The absence of PLR and/or Gag reflex were the reliable predictors after rewarming, while the absence of at least one of the brainstem reflexes, no eye-opening, or abnormal motor response were the reliable predictors on the 7th day. Nevertheless, myoclonus and seizure were the weak indicators for the unfavorable outcome. In addition, there were inconclusive prognostic values of EEG and CT findings.

According to the good predictive values of the simple signs in the patients treated with TH, physicians could use these signs for early neurological prognostication to avoid unnecessary life-supporting treatment. Our study demonstrated the absence of PLR was the most reliable predictor for unconsciousness and unfavorable outcome which is consistent with other studies

Table 5: Neurological findings to predict the unfavorable outcomes (cerebral performance category 3-5) after therapeutic hypothermia following cardiac arrest

Study designs	Our study		Rossetti et al. ^[12]		Bisschops et al. ^[13]		Okada et al. ^[14]		Bouwes et al. ^[15]		Legri et al. ^[16]		Dragancea et al. ^[17]	
	Retrospective Single center	Prospective Single center	Retrospective Single center	Prospective Single center	Retrospective Single center	Prospective Single center	Retrospective Single center	Prospective Multicenter	Retrospective Single center	Prospective Multicenter	Retrospective Single center	Prospective Multicenter	Retrospective Single center	Prospective Multicenter
Year	2018	2010	2011	2010	2012	2011	2012	2012	2013	2015	2013	2015	2013	2015
n	51	109	103	103	66	103	66	M≤2 (n=284) PLR (n=196) Corneal (n=130)	106	313	106	313	106	313
Time for evaluation	1. Immediately after rewarming (48-72 h) 2. On 7 th day	36-72 h	1. At 72 h 2. On 7 th day	1. At 72 h 2. On 7 th day	On admission	1. At 72 h 2. On 7 th day	On admission	At 72 h	<72 h	1. <72 h 2. 72-107 h 3. 108-144 h 4. ≥145 h	<72 h	1. <72 h 2. 72-107 h 3. 108-144 h 4. ≥145 h	<72 h	1. <72 h 2. 72-107 h 3. 108-144 h 4. ≥145 h
Time of outcome	Upon hospital discharge	At 3-6 months	After 3 months	After 3 months	On hospital discharge	After 3 months	On hospital discharge	After 6 months	At 1 year	6 months	At 1 year	6 months	At 1 year	6 months
Predictors, 95% CI (%)														
Timing	Sensitivity 48-72 h	FP NA	Sensitivity 36-72 h	FP NA	Sensitivity On admission	FP NA	Sensitivity On admission	FP NA	Sensitivity <72 h	FP NA	Sensitivity <72 h	FP NA	Sensitivity <72 h	FP NA
No eye opening	90.48 (77.38-97.34)	22.22 (2.81-60.01)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Motor response	M≤3	M≤3	M≤2	M≤2	M≤2	M≤2	M≤2	M≤2	M≤2	M≤2	M≤2	M≤2	M≤2	M≤2
Verbal response	85.71 (71.46-94.51)	22.22 (2.81-60.01)	76.2 (66.1-84)	16 (6.4-34.7)	34.3 (24.1-46.3)	11.1 (4.4-25.3)	92.3 (75.9-97.9)	52.5 (37.5-67.1)	74 (66-81)	10 (6-16)	NA	NA	93.9 (80.3-98.4)	40 (11.7-77)
Lack of PLR	21.43 (10.3-36.81)	0 (0-33.63)	NA	NA	76.9 (57.9-89)	30 (18.1-45.4)	NA	NA	NA	NA	NA	NA	48.4 (31.9-65.2)	0 (0-43.5)
Lack of gag reflex	28.57 (15.72-44.58)	0 (0-33.63)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lack of corneal reflex	33.33 (19.57-49.55)	11.1 (0.28-48.25)	NA	NA	NA	NA	NA	NA	NA	26 (18-37)	4 (1-13)	NA	62.1 (44-77.4)	0 (0-49)
Lack of doll's reflex	28.57 (15.72-44.58)	11.1 (0.28-48.25)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Myoclonus	35.71 (21.55-51.97)	22.2 (2.81-60.01)	41.7 (31.7-52.3)	4 (0.7-19.5)	53.7 (41.9-65.1)	11.1 (4.4-25.3)	NA	18 (12-26)	1 (0-7)	62.7 (51.4-72.7)	12.9 (5.1-28.9)	NA	NA	NA
Seizure	16.67 (6.97-31.36)	11.1 (0.28-48.25)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Timing	On 7 th day	On 7 th day	On 7 th day	On 7 th day	On 7 th day	On 7 th day	On 7 th day	On 7 th day	On 7 th day	On 7 th day	On 7 th day	On 7 th day	On 7 th day	On 7 th day
No eye opening	88.1 (74.37-96.02)	0 (0-33.63)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Motor response	M≤3	M≤3	M≤2	M≤2	M≤2	M≤2	M≤2	M≤2	M≤2	M≤2	M≤2	M≤2	M≤2	M≤2
Motor response	88.1 (74.37-96.02)	0 (0-33.63)	10.4 (5.2-20)	2.8 (0.5-14.2)	NA	NA	NA	NA	NA	69 (56.1-79.4)	14.3 (2.5-51.1)	NA	69 (56.1-79.4)	14.3 (2.5-51.1)

Contd...

Table 5: Contd...

	Predictors, 95% CI (%)											
	Sensitivity	FP	Sensitivity	FP	Sensitivity	FP	Sensitivity	FP	Sensitivity	FP	Sensitivity	FP
Verbal response	V \leq 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	100	33.3	NA	NA								
	(91.59-100)	(7.49-70.07)										
Lack of PLR	35.71	0	NA	NA	NA	NA	NA	NA	NA	NA	7	0
	(21.55-51.97)	(0-33.63)									(2.7-16.8)	(0-35.5)
Lack of gag reflex	53.66	0	NA	NA								
	(37.42-69.34)	(0-33.63)										
Lack of corneal reflex	41.46	0	NA	NA	NA	NA	NA	NA	NA	NA	21.1	0
	(26.32-57.89)	(0-40.96)									(12.4-33.3)	(0-35.5)
Lack of doll's reflex	46.34	0	NA	NA								
	(30.66-62.58)	(0-33.63)										

Percentage FP: Percentage false positive; E: Eye opening (GCS); M: Motor response (GCS); V: Verbal response (GCS); PLR: Pupillary light response; NA: Data not available; GCS: Glasgow Coma Score; CI: Confidence interval

shown in Tables 5 and 6. Gag reflex was the second-most reliable sign because it has a little higher FPR. The delayed time of neurological recovery from hypothermia induced low central nervous system metabolism and unpredictable clearance of the sedative drugs can result in high FPR of Doll's eye, corneal reflex, eye-opening, and motor response after rewarming.^[19-22] For example, 25% of the patients with M2-extensor posturing after rewarming regained consciousness later and one of them fully recovered. In addition, 1 of 12 patients with M1-absent motor response after rewarming was awake with minimal disability. Aside from the PLR, other signs such as the eye opening, motor response, and brainstem signs can be used to assess the outcome of TH 7 days after ROSC which is the most appropriate time to conduct the prognostications. Moreover, we observed that CPC scores upon hospital discharge were better than the CPC scores at day 7 by 1 scale in some patients. Therefore, time to reach maximal neurological recovery may take a little longer than 1 week. Furthermore, the patients who regained consciousness after TH protocol completion had good outcomes. None of the patients with CPC1 and 2 after rewarming deteriorated to unfavorable outcome.

As for other symptoms and signs such as myoclonus with or without status, epilepticus cannot be used to indicate poor prognosis. Our study showed a few patients with myoclonus with or without status epilepticus were able to achieve complete or nearly complete recovery. Thus, both myoclonus and status epilepticus were less accurate signs to predict unfavorable prognosis. This finding contradicts some of the data from previous studies, which showed myoclonus was associated with neocortical damage and poor outcome.^[23,24] However, recent small studies showed variable FPR of myoclonus in predicting poor outcomes.^[25-27] Hence, we conclude myoclonus is not an absolute predictor of unfavorable outcome.

Another poor predictor that can be used is the findings from the EEG. However, in this study, approximately 30% of all patients had EEG. It is unfortunate that the EEG was not utilized to its full potential to predict poor prognosis. We observed two patients with burst-suppression pattern that later died which is consistent with the suggestions from experts that burst suppression EEG pattern was associated with poor outcome.^[28,29] However, some experts disagreed with this because one study showed that burst-suppression can temporarily appear after inducing hypothermia.^[13,30] For this reason, burst-suppression pattern cannot be used as a single predictor for poor outcome. Moreover, continuous EEG monitoring is recommended to detect subtle seizure which is common among comatose survivors.^[31,32] One study showed nonconvulsive status epilepticus (NCSE) in 12% of the survivors undergoing TH and the presence of seizure was associated with poor outcome.^[33] In our study, more than half of the persistent comatose patients were not monitored with EEG, so we did not know whether NCSE occurred or not. This information may affect the presence or absence of certain neurological signs and clinical outcome.

Table 6: Neurological findings for predicting the patients' unconsciousness or death (cerebral performance category 4-5) after therapeutic hypothermia following cardiac arrest

	Our study		Al Thenayan <i>et al.</i> ^[18]		Samaniego <i>et al.</i> ^[2]	
Study designs	Retrospective Single center		Retrospective Single center		Prospective Single center	
Year	2018		2008		2011	
<i>n</i>	51		37		53	
Time for evaluation	1. Immediately after rewarming (48-72 h) 2. On 7 th day		At 72 h		At 72 h Data from 44 survivors with TH and under sedation	
Time of outcome	On hospital discharge		6 days after ROSC		3 months	
Predictors	Sensitivity (95% CI) (%)	FP (95% CI) (%)	Sensitivity (95% CI) (%)	FP (95% CI) (%)	Sensitivity (95% CI) (%)	FP (95% CI) (%)
Timing	48-72 h		At 72 h		At 72 h	
No eye opening	97.1 (84.67-99.93)	41.18 (18.44-67.08)	NA		NA	
Motor response	M _{≤3}		M _{≤2}		M _{≤2}	
	91.2 (76.32-98.14)	41.18 (18.44-67.08)	14 test positive cases/NA	14 (3-44)	88 (68-97)	11 (2-35)
Verbal response	NA		NA		NA	
Lack of PLR	26.47 (12.88-44.36)	0 (0-19.51)	6 test positive cases/NA	0 (0-48)	17 (5-38)	0 (0-21)
Lack of gag reflex	32.4 (17.39-50.53)	5.9 (0.15-28.69)	NA		NA	
Lack of corneal reflex	32.4 (17.39-50.53)	23.5 (6.81-49.9)	6 test positive cases/NA	0 (0-48)	32 (16-54)	5 (0-28)
Lack of doll's reflex	32.35 (17.39-50.53)	17.8 (1.46-36.44)	NA		NA	
Myoclonus	35.29 (19.75-53.51)	29.41 (10.31-55.96)	8 test positive cases/NA	0 (0-40)	8 (1-27)	0 (0-21)
Seizure	11.76 (3.3-27.45)	23.5 (6.81-49.9)			NA	
Timing	On 7 th day					
No eye opening	97.06 (84.67-99.93)	23.53 (6.81-49.9)	NA		NA	
Motor response	M _{≤3}					
	97.06 (84.67-99.93)	23.53 (6.81-49.9)	NA		NA	
Verbal response	V _{≤3}					
	100 (0-10.28)	64.7 (38.33-85.79)	NA		NA	
Lack of PLR	44.12 (27.19-62.11)	0 (0-19.51)	NA		NA	
Lack of gag reflex	66.7 (48.17-82.04)	0 (0-19.51)	NA		NA	
Lack of corneal reflex	51.52 (33.54-69.2)	0 (0-19.51)	NA		NA	
Lack of doll's reflex	57.58 (39.22-74.52)	0 (0-19.51)	NA		NA	

Percentage FP: Percentage false positive; E: Eye opening (GCS); M: Motor response (GCS); V: Verbal response (GCS); PLR: Pupillary light response; NA: Data not available; CI: Confidence interval; GCS: Glasgow Coma Score; TH: Therapeutic hypothermia; CPC: Cerebral performance category; ROSC: Return of spontaneous circulation

Other tools that can be used are the brain CT images. For example, loss of gray-white matter differentiation was an early sign of brain edema. Some authors proposed that the attenuations in the grey matter to those in gray-white matter ratio at the basal ganglia and cerebrum in the brain CT within an hour after ROSC of <1.14 can predict unfavorable neurological outcome with FPR of 0% (95% CI 0%–16.1%).^[34-37] In our study, all patients with obvious brain swelling had unfavorable outcome.

Notably, there were quite a high percentage of patients with unfavorable outcomes in our study. The reason for this is because TH was administered to patients with a high probability to develop poor outcomes such as those patients with relative contraindication for TH (e.g., sepsis), patients with prolonged time from collapse to ROSC (more than 30 min) and in-hospital patients who had poor

cardiopulmonary reserve.^[38] Another explanation for high unfavorable outcomes is that the time from ROSC to cooling induction took a long time to accomplish because there were insufficient number of ICU beds and the primary physicians lacked knowledge of TH. The other explanation is that we included patients with nonshockable rhythm, especially those patients who may have had prolonged time from collapse to CPR initiation or had irreversible diseases.^[39] It is also possible that lack of absolute criteria for treatment withdrawal may have resulted in unintentional termination of treatment among patients with reversible conditions. However, due to the high proportion of the patients with the poor outcome, we could demonstrate the reliable prognostic factors for the unfavorable neurological outcome.

Our study had several limitations. It is possible that the retrospective design of the study could have affected the

results of the study. Certain data were not available to us because the EEG was selectively performed on patients with clinically suspected seizure. Therefore, it is possible that we may have underdiagnosed patients with nonconvulsive seizure which may affected the prognostic results. Second, there were limited data on serial neurological signs between 3 and 7 days after ROSC. Furthermore, the neurological data obtained from the medical records were collected and interpreted by various staff with different skills, which may be less precise. Third, the study had a small sample size so the power was not enough to detect any significant differences or occurrences. Furthermore, the findings from the brain CT finding is not enough to ascertain the significance of the outcome, especially for the loss of the gray-white matter differentiation. In addition, we did not know to what extent the sedative drugs or neuromuscular blockades would affect the presence of the neurological signs, especially during the early assessment. Last, this study demonstrated only the predictive signs for short-term outcomes in terms of physical disability. Hence, these results cannot predict long-term neurological outcome and functional ability, including cognitive function and quality of life.

CONCLUSIONS

Our analysis showed that the simple neurological signs can help predict the short-term neurological prognosis of comatose survivors undergoing TH. The most reliable sign which determined unconsciousness and unfavorable outcome was the lack of PLR. The optimal time to assess prognosis was either 48–72 h or 7 days after ROSC. Physicians can use these neurological signs to predict the outcomes post-TH. Myoclonus and status epilepticus cannot be used to predict absolutely poor outcomes. However, there were limited data of EEG and brain CT findings in predicting the outcome post-TH.

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Conflicts of interest

There are no conflicts of interest.

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