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Timing of neuroprognostication in postcardiac arrest therapeutic hypothermia*

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Abstract

Objective—Early assessment of neurologic recovery is often challenging in survivors of cardiac arrest. Further, little is known about when to assess neurologic status in comatose, postarrest patients receiving therapeutic hypothermia. We sought to evaluate timing of prognostication in cardiac arrest survivors who received therapeutic hypothermia.

Design—A retrospective chart review of consecutive postarrest patients receiving therapeutic hypothermia (protocol: 24-hr maintenance at target temperature followed by rewarming over 8 hrs). Data were abstracted from the medical chart, including documentation during the first 96 hrs post arrest of “poor” prognosis, diagnostic tests for neuroprognostication, consultations used for determination of prognosis, and outcome at discharge.

Setting—Two academic urban emergency departments.

Patients—A total of 55 consecutive patients who underwent therapeutic hypothermia were reviewed between September 2005 and April 2009.

Intervention—None.

Results—Of our cohort of comatose postarrest patients, 59% (29 of 49) were male, and the mean age was 56 ± 16 yrs. Chart documentation of “poor” or “grave” prognosis occurred “early”: during induction, maintenance of cooling, rewarming, or within 15 hrs after normothermia in 57% (28 of 49) of cases. Of patients with early documentation of poor prognosis, 25% (seven of 28) had care withdrawn within 72 hrs post arrest, and 21% (six of 28) survived to discharge with favorable neurologic recovery. In the first 96 hrs post arrest: 88% (43 of 49) of patients received a head computed tomography, 90% (44 of 49) received electroencephalography, 2% (one of 49) received somatosensory evoked potential testing, and 71% (35 of 49) received neurology consultation.

Conclusions—Documentation of “poor prognosis” occurred during therapeutic hypothermia in more than half of patients in our cohort. Premature documentation of poor prognosis may

*See also p. 979.

contribute to early decisions to withdraw care. Future guidelines should address when to best prognosticate in postarrest patients receiving therapeutic hypothermia.

Keywords

cardiac arrest; cardiopulmonary resuscitation; do not resuscitate; mild therapeutic hypothermia; prognosis; resuscitation

Approximately 300,000 out-of-hospital cardiopulmonary arrests occur annually in the United States (1), and increases by 200,000 events to include in-hospital cardiac arrests (2). Currently, the median survival to discharge is poor, with only 6.4% of patients surviving an out-of-hospital event vs. 17% of patients who survive an inpatient event (3, 4). To date, therapeutic hypothermia (TH) is the only treatment shown to improve both survival and neurologic outcomes in comatose survivors of cardiac arrest (5, 6). Decisions about the level of care provided for postcardiac arrest patients often rely on the potential for these patients to have meaningful neurologic recovery. Currently lacking are guidelines to inform clinicians about the optimal timeframe for assessing neurologic recovery and determining prognosis in patients treated with TH.

Prior studies have identified physical exam findings at 3 days status post arrest that can assist in predicting neurologic outcome, however, patients who have undergone TH have been excluded from these studies (7, 8). No publication to date provides definitive evidence regarding the optimal timing for post TH. Extrapolating the parameters set forth by Levy et al (7) and Wijdicks et al (8) to patients who have received TH may not be valid and may lead to premature withdrawal of care (9). As TH is more widely adopted in postarrest care, the timing of neurologic prognostication, and diagnostic modalities required for this assessment, will need to be further elucidated. The American Heart Association and International Liaison Committee on Resuscitation 2010 guidelines favor that prognostication should be delayed in patients receiving TH (10).

Since appropriate timing for when to prognosticate in postarrest TH is unclear, we conducted a retrospective study of medical records for postarrest patients who underwent TH to determine whether there is variability in when practitioners designate that a patient has a "poor" prognosis for neurologic recovery. Specifically, we analyzed chart documentation during the first 96 hrs post arrest to determine when the phrasing "poor," "grave," or "grim" was documented by the primary critical care attending or neurology consult attending in the medical chart. We also analyzed which diagnostic tools and consultations occurred during TH implementation, maintenance, rewarming, and soon after rewarming.

MATERIALS AND METHODS

Study Design/Setting

This was a retrospective chart review of data from two academic hospitals with TH protocols. All charts of consecutive postcardiac arrest patients who received TH from September 2005, when the protocol was first initiated, until April 2009, were reviewed. Data collection was limited to April 2009 because at that time a resuscitation consulting service was created to make recommendations to the primary admitting team regarding postarrest care of patients undergoing TH.

Patient Population

Subjects were included in the cohort if they were >18 yrs of age, had a cardiac arrest with return of spontaneous circulation, and received postarrest TH in either the medical or cardiac

intensive care unit (ICU). Cardiac arrest patients were excluded from our analysis if they were initiated on the TH protocol, but were later determined to meet exclusion criteria. Therefore, these patients did not receive hypothermia treatment but did continue to receive standard postcardiac arrest care.

TH Protocol

The TH protocol included several elements. Patients were eligible to receive TH if they had a Glasgow Coma motor score of <6 after resuscitation. Exclusion criteria included absence of a pulse for >60 mins elapsed time from collapse to return of spontaneous circulation, significant active bleeding, the presence of a “do-not-attempt-resuscitation” (DNAR) status, presentation >12 hrs from time of arrest, or any finding of intracranial bleed. TH was initiated with intravenous infusion of 2 L cold normal saline and external cooling body wraps (Meditherm III, Gaymar Industries, Orchard Park, NY). Core body temperature was measured using a bladder or esophageal probe. TH was maintained for 24 hrs after goal temperature of $32\text{--}34^{\circ}\text{C}$ was reached. Both sedating and paralyzing agents were used for the duration of the TH protocol. Controlled, active rewarming was undertaken with a goal rate of $0.25\text{--}0.5^{\circ}\text{C}$ per hour. Once the patient achieved normothermia, the paralytic was discontinued (11). The protocol does not clearly define when and if Neurology should become involved in the care and prognostication of the TH patient; this is left to the discretion of the primary care team. The use of a head computed tomography scan initially to rule out intracranial hemorrhage or other such insults as the cause of the initial cardiac arrest is recommended. The TH protocol also recommends continuous electroencephalogram monitoring while patients are sedated and/or paralyzed. Additional details about the TH protocol are detailed elsewhere (11).

Prognostication Definition, Timing, and Measures

Electronic medical charts were reviewed to determine patient characteristics (demographics, initial rhythm, past medical history) and cooling characteristics (time to target temperature, duration of maintenance, rewarming phases).

Documentation of Prognostication

We reviewed progress notes (primarily written or endorsed by the attending intensivist providing care for the patient) and consultation notes (primarily written or endorsed by the attending neurologist) for documentation of “poor” prognosis (defined as use of the words “poor,” “grim,” or “grave”), and timing of documentation. In cases where both the neurologist and intensivist documented a “poor,” “grim,” or “grave” prognosis, for our analysis, the physician who made the initial statement in the chart was characterized as making the primary notation of “poor” prognosis.

Timing of Prognostication

We recorded at what stage in the TH protocol individuals were assigned a “poor” prognosis. TH stages were categorized as: 1) induction ($>34^{\circ}\text{C}$), 2) maintenance ($32\text{--}34^{\circ}\text{C}$), 3) rewarming ($>34^{\circ}\text{C}$), and 4) subsequent normothermia ($>37^{\circ}$). Prognostication documented in the medical record during the delivery of TH or within 15 hrs of completing the protocol was considered in our analysis to be characterized as “intra-TH prognosis.”

Potential Tools of Prognostication

Additional medical chart data abstracted from the first 96 hrs of postcardiac arrest care included: computed tomography scan of head neuron-specific enolase (NSE), Somatosensory Evoked Potential (SSEP), electroencephalogram, and timing of neurology consultation.

Outcomes

We collected data regarding patient disposition, categorized as: 1) DNAR with withdrawal of care, 2) rearrest without return of spontaneous circulation, or 3) survival to discharge from the hospital. Surviving patients were additionally subclassified by cerebral performance category (CPC) with respect to their neurologic recovery upon discharge from the hospital. The CPC scale corresponds with the following categories: 1) good cerebral performance (full function of activities of daily living), 2) moderate cerebral disability (disabled but independent), 3) severe cerebral disability (conscious but disabled and dependent), 4) coma/vegetative state (unconscious), and 5) brain death or death (12, 13).

Analysis

The cohort was divided into two groups: patients who received an “intra-TH” poor prognosis and patients who did not receive a poor prognosis during TH and were thus titled “post-TH” prognosis (i.e., no documentation of prognosis was recorded during the TH protocol). These groups were compared with respect to demographics, prearrest comorbidities, arrest location, and postarrest intensive care location using a chi-square test ($p < .05$ was considered significant). In instances of small cell frequencies, exact p values are reported. The use of neurology consultation and the use of potential neuroprognostication (i.e., computed tomography, SSEP, NSE) modalities were also compared.

As a retrospective chart review, this study was approved with a waiver of informed consent by the University of Pennsylvania Institutional Review Board.

RESULTS

We reviewed medical charts from 55 patients who had the postcardiac arrest TH protocol initiated. Of this group, 11% (six of 55) of patients were excluded before analysis because these patients met exclusion criteria for the TH protocol, who had TH initiated but promptly discontinued. These individuals had an intracranial hemorrhage ($n = 2$), surgical complication ($n = 1$), admission to a surgical unit ($n = 1$), or advance directive indicating care was not desired ($n = 2$), which excluded them from receiving TH and resulted in their exclusion from our cohort. Of the cohort of 49 patients, 59% (29 of 49) were male and the mean age of patients was 56 ± 16 yrs.

Of this cohort, 57% (28 of 49) had documentation of “intra-TH” poor prognosis in the medical chart. Patients with “intra-TH” poor prognosis were more often female (57%), but otherwise had similar background characteristics when compared with patients who did not have a documented “intra-TH” poor prognosis (Table 1).

Timing of Poor Prognosis

In patients who received documentation of “poor” prognosis, there was variability in when this determination occurred (Fig. 1). Subjects who received a prognosis later (>96 hrs after arrest) in their ICU course, or who received a favorable prognosis, were classified as “post-TH” prognosis and not included in the timeline. Specifically, 18% (five of 28) of patients received a “poor” prognosis at the initiation of TH, before achieving goal temperature of $<34^{\circ}\text{C}$. Several, 29% (eight of 28), were assigned a poor prognosis while they were at target temperature, which is the longest phase in the TH protocol (24 hrs), and 18% (five of 28) received a diagnosis of poor prognosis during the rewarming phase. Finally, 36% (ten of 28) were assigned a poor prognosis shortly (<15 hrs) after arrival at normothermia. In total, 64% (18 of 28) patients who were assigned a “poor” prognosis during the formal TH protocol were still receiving sedation and paralytic drugs.

Temporal Trends in Early Poor Prognosis

To evaluate temporal trends in the determination of early “poor” prognosis (i.e., was there a volume-outcome relationship), we identified the number of patients with documentation of “intra-TH” prognosis by year. We found that in 2005, 50% (two of four) of patients who underwent TH were assigned an intra-TH “poor” prognosis. In the years 2006–2009, 40% (two of five), 33% (two of six), 63% (12 of 19), and 67% (ten of 15), respectively, were assigned a “poor” prognosis intra-TH (Fig. 1).

Medical Service Documenting Prognosis

The primary medical service (either the admitting team under the medical intensivist or the cardiac intensivist) assigned “poor” prognosis to postarrest patients receiving TH in 75% (21 of 28) of cases, while the neurology consultant documented this prognosis in the remaining 25% (seven of 28) of patients (Table 2).

Postcardiac Arrest Care and Consultation

The Neurology Service was consulted in 75% (21 of 28) of patients with “intra-TH” prognosis. Most (24 of 28) received a head computed tomography (in the first 72 hrs post arrest), while only 4% (one of 24) received a SSEP (5 days status post normothermia), and no patient had an NSE (Table 3). In 43% (15 of 35) of all neurology consultations, the neurology physician documented a need to wait until sedation and paralytic had been weaned before comment on prognosis. Of patients with an intra-TH poor prognosis, 57% (16 of 28) received TH in the medical ICU while 43% (12 of 28) received TH in the cardiac ICU, with the majority of patients being receiving a prognosis by the primary critical care team (Table 2).

Code Status

In patients with documentation of “intra-TH” poor prognosis, palliative care was instituted in 25% (seven of 28) who did not have a prior advanced directive (i.e., DNAR C). Of these seven patients, two had documentation of poor prognosis and advancement to DNAR C within the same time-stamped note in the chart, two patients had code status advanced between 20–90 mins after poor prognosis, and three patients had code status advanced under 24 hrs after poor prognosis was mentioned (Fig. 1). Furthermore, six patients who were determined to have an “intra-TH” poor prognosis had a DNAR order implemented within 24–48 hrs after prognosis.

Outcomes

Of patients documented as “intra-TH” poor prognosis, 21% (six of 28) had a CPC of 1 or 2 (good outcome) at hospital discharge, and 7% (two of 28) of patients had a CPC of 3 or 4 (poor outcome). In total, 20 out of 28 “intra-TH” poor prognosis patients did not survive to discharge. Of these eight surviving patients, one survivor with a CPC 1 had received a prognosis during the induction phase of hypothermia, while three other patients with a CPC 1 and one individual with a CPC of 3 were given a poor prognosis while in the maintenance phase of cooling. Two survivors had documentation of poor prognosis during the rewarming phase at 35.5°C (CPC 1) and 36.5°C (CPC 4), respectively. CPC classifications were documented for all patients who underwent TH during the study time period (Table 4). A significant number of patients (20) assigned a “poor” intra-TH prognosis died, while a significant number of patients (14) who were not early prognosticated were discharged with a CPC of 1.

Etiology for Declaration of “Poor Prognosis”

Without clear documentation in the medical chart, it is impossible to determine the “reasoning” behind the declaration of “poor prognosis.” As a means of identifying the medical differences between the two groups, the incidence of shock in postcardiac arrest care and the presenting rhythm were compared (Table 1). In patients who were in the post-TH prognosis group, 19% (four of 21) had some element of shock requiring vasopressor support while in the group that did receive an intra-TH prognosis, 54% (15 of 28) required vasopressors during their ICU course. We found that presenting rhythms varied in that the early prognosis group had a higher rate of pulseless electrical activity arrest (50% vs. 29%) and a lower rate of ventricular fibrillation/ventricular tachycardia arrest (39% vs. 57%), however, neither of these findings were statistically significant.

DISCUSSION

“Poor” prognosis was assigned during the TH protocol to more than half of the comatose postcardiac arrest patients in our cohort. Significant variation was noted in the tools implemented for neuroprognostication, as well as the timing of when patients were given a “poor” prognosis. This is important since prognostication may affect family and physician decisions about level of treatment and determinations of DNAR status or withdrawal of care.

Several studies have addressed the timing of postarrest prognostication (in the absence of TH). The neurologic exam has been identified as a useful aide in predicting outcome 24 to 72 hrs after return of spontaneous circulation. Edgren et al (14) reported that the lack of motor response, eye opening, and absence of pupil response on day 3 was 100% predictive of poor outcome. In a meta-analysis (representing data from approximately 2,000 patients), Booth et al (15) identified that patients who lack pupillary and corneal reflexes at 24 hrs, and motor response at 72 hrs, have an “extremely small” chance for meaningful neurologic recovery (likelihood ratio, 10.2; 95% confidence interval 1.8–48.6 and 9.2; 95% confidence interval 2.1–49.4, respectively). Similarly, Levy et al (7) reported that those lacking a pupil/corneal response at 24 hrs and motor response at 72 hrs had poor neurologic recovery. The American Academy of Neurology guidelines also support that absent pupil reflex, corneal reflexes, and motor response on day 3 as predictive of poor outcome, with a false-positive rate of 0% (95% confidence interval: 0 to 3) (8). As in the other studies cited, these neurologic findings were noted in postarrest patients not receiving TH (8, 15). In our study, several patients had documentation of “poor” prognosis, citing lack of motor response and pupillary reactivity, of concern in many cases was that the exam was performed while patients were still hypothermic and receiving sedative and paralytic drugs.

Studies that have addressed prognostication in postcardiac arrest survivors have traditionally excluded hypothermic patients, since hypothermia is thought to alter the normal physiology of multiple organ systems (16). An important consideration regarding neurologic assessments is that drug clearance is markedly reduced when core body temperature drops below 35°C (16). Opiates, sedatives, and paralytics may accumulate in the context of receiving TH. Although medications may be limited or discontinued before neurologic evaluation, their altered pharmacodynamics in the setting of hypothermia make the validity of clinical neurologic assessment questionable during and shortly after completion of TH (16).

There is a paucity of data to inform the optimal timing of neuroprognostication in survivors of cardiac arrest who have undergone TH. Al Thenayan et al (17) identified that absent pupillary and corneal reflexes on day 3 were consistent with poor outcome, while use of the motor response on day 3 was unreliable and should be delayed until 6 days post arrest. Yannopoulos et al (18) suggest clinical prediction of outcome should be reserved until 72

hrs post arrest, a scenario that Friberg and Rundgren (19) further support, stating that bedside neurologic exam should not be performed until 72 hrs after normothermia and should be supplemented by at least one other prognostic tool (SSEP, NSE, electroencephalogram). Rittenberger et al (20) conducted a retrospective study of patients who underwent TH to evaluate the prognostic capability of the clinical examination, and found that absence of papillary or corneal reflex at 72 hrs excludes survival. In the absence of data documenting optimal procedure for neuroprognostication, clinicians have minimal guidance on how and when to best assign prognosis in this setting (10). In addition, we found that trends in intra-TH prognosis did not decrease over time. This suggests that education and exposure to TH protocols over time did not specifically affect outcomes.

Several reports have explored other modalities for assisting in the task of prognostication. Tiainen et al (21) initially described that patients undergoing hypothermia had lower levels of NSE than those who remained normothermic. Rundgren et al (22) investigated the utility of NSE in predicting neurologic recovery post TH. Patients enrolled in this study received full supportive care for 72 hrs post normothermia. The authors arrived at a cutoff value that was useful at 48 hrs after arrest and reported that a rise of $>2 \mu\text{g/L}$ between 24 and 48 hrs after arrest was an indicator of poor neurologic outcome. Another modality being investigated for its utility in the prognostication of patients undergoing TH is SSEP. Tiainen et al (23) in 2005 found that median nerve short-latency SSEP remains a good tool for neuroprognostication despite hypothermic temperatures. Several studies have indicated that short-latency SSEP or N20 responses accurately predict permanent coma (24, 25). However, Leithner et al (26) suggest that SSEP may not be reliable in hypothermic patients. Of note, in our study of 49 individuals, none had an NSE level measured and only one individual had an SSEP performed. Despite the infrequent use of these modalities at our study institutions in this postarrest TH population, their role in the literature is still being elucidated.

The question of when to neuroprognosticate TH patients remains a challenge to both the neurology consultant and the intensivist primarily caring for the patient. Our review showed that Neurology was consulted in 75% of individuals in the “intra-TH” prognosis cohort, with the question posed to project neurologic outcome. In 43% (15 of 35) of all neurology consultations, the neurology physician documented a need to wait until sedation and paralytic had been weaned before comment on prognosis. However, there were scenarios where prognosis was determined based on neurologic criteria while patients were paralyzed and sedated, which raises the ethical question of whether neurologic prognostication and discussion of withdrawal of care should be addressed during the TH protocol.

This study has several limitations. First, it was a retrospective chart review, relying on physician documentation. Although we used the documentation available in the chart to assess decisions made with respect to withdrawal of care, we acknowledge that this may be an over-simplification since the complete thought process of the clinician is often not clearly delineated in the medical record. We also recognize that evaluation of patients and their prognosis is not a static process and some notes may have been completed at times different from what was indicated directly within the chart. Patient, family, physician, and interpersonal factors also play significant roles in decisions about continuing or withdrawing care, and these are often incompletely represented in chart notes expressing only general sentiments, leaving out much of the complexity of the discussions. We also recognize a possible bias in formally obtaining neurology consultation and at which day after initiation of TH that this should occur. Again, without written documentation of the medical decision-making process, the rationale for when to obtain neurologic consultation could not be further analyzed. Although we collected data from two sites, the small sample size limits generalizability to all postarrest patients receiving TH.

In conclusion, our study found that patients who received postarrest TH were often assigned a poor prognosis before completion of the TH protocol. In addition, our study demonstrated large variation in the timing of prognostic assessments, as well as a discrepancy in the outcomes of patients assigned a poor prognosis before completion of TH. Further research is needed to establish guidelines for timing of prognostic assessments and to validate tools used to assess neurologic recovery in patients who have undergone postcardiac arrest TH.

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Figure 1.

Timeline of documentation of poor prognosis in relation to the phase within therapeutic hypothermia. The y-axis represents year of patient arrest and subsequent hypothermia. The x-axis represents phase within the hypothermia protocol. Each *box* represents an individual patient. The *arrow* indicates when patients had care withdrawn, if this occurred. The *star* indicates patients who had “poor” prognosis but survived to discharge. The number of patients who underwent therapeutic hypothermia is documented below each designated year.

Table 1

Demographics, presenting rhythms, and relevant past medical history for all subjects

Patient Characteristics	Intra-Therapeutic Hypothermia Prognosis ^a (n = 28)	Post-Therapeutic Hypothermia Prognosis ^b (n = 21)	All (n = 49)	p
Demographics				
Age (years)	57.8 ± 13.7	54.8 ± 18.6	56.0 ± 15.9	.65
Female	57% (16)	19% (4)	41% (20)	.01
Initial rhythm ^c				
Ventricular tachycardia/ventricular fibrillation	39% (11)	60% (12)	47% (23)	.34
Pulseless electrical activity	50% (14)	30% (6)	41% (20)	
Asystole	11% (3)	10% (2)	10% (5)	
Comorbid conditions				
Myocardial infarction	14% (4)	24% (5)	18% (9)	.47
Coronary artery disease	46% (13)	43% (9)	45% (22)	.80
Hypertension	57% (16)	43% (9)	51% (25)	.32
Dysrhythmia	21% (6)	14% (3)	18% (9)	.52
Congestive heart failure	39% (11)	19% (4)	31% (15)	.13
Cerebrovascular attack	18% (5)	5% (1)	12% (6)	.22
Dementia	7% (2)	0 (0)	4% (2)	.50
Diabetes	36% (10)	33% (7)	35% (17)	.86
Cancer	7% (2)	19% (4)	12% (6)	.38
Liver	4% (1)	5% (1)	4% (2)	1.00
End-stage renal disease	25% (7)	5% (1)	16% (8)	.06
Intensive care unit course				
Shock (vasopressor use)	54% (15)	19% (4)	39% (19)	.02

^aEarly prognosis is defined as “grave,” “grim,” or “poor” prognosis recorded during the therapeutic hypothermia (TH) protocol or within 15 hrs of becoming normothermic;

^bpost-TH prognosis is defined as subjects who did not receive a prognosis of “grave,” “grim,” or “poor” during the TH protocol but had their prognosis (either good or bad) withheld until 15 hrs after completion of TH;

^cone patient in the post-TH group had an unknown initial rhythm and was excluded from this analysis.

Table 2

Location of postarrest care and service responsible for determination of intratherapeutic hypothermia prognosis

Location of Postarrest Care	Intratherapeutic Hypothermia Prognosis (n = 28)	Post-Therapeutic Hypothermia Prognosis (n = 21)	All Patients (n = 49)
Service providing prognosis			
Medical intensive care unit	57% (16)	43% (9)	51% (25)
Critical care team	69% (11)		
Neurology	31% (5)		
Cardiac care unit	43% (12)	57% (12)	49% (24)
Critical care team	83% (10)		
Neurology	17% (2)		

Table 3

Timing of neurology consultation and modalities implemented

Consultation/Modality	Intra-TH Prognosis (n = 28)	Post-TH Prognosis (n = 21)	Total TH (n = 49)
Neurology consult	75% (21)	67% (14)	71% (35)
Day 1	25% (7)	29% (6)	37% (13)
Day 2	18% (5)	10% (2)	14% (7)
Day 3	21% (6)	14% (3)	18% (9)
>Day 3	11% (3)	14% (3)	12% (6)
Electroencephalogram	86% (24)	95% (20)	90% (44)
Head computed tomography	86% (24)	91% (19)	88% (43)
Sustained somatosensory evoked potential	4% (1)	0 (0)	2% (1)
Neuron-specific enolase	0 (0)	0 (0)	0 (0)

TH, therapeutic hypothermia.

Table 4

Cerebral performance category for all patients

CPC Category	Intratherapeutic Hypothermia (n = 28)	Post-Therapeutic Hypothermia (n = 21) ^a
CPC 1	5	14
CPC 2	1	0
CPC 3	1	0
CPC 4	1	0
CPC 5	20	6

CPC, cerebral performance category.

^aOne patient in the post-therapeutic hypothermia group had an unknown CPC and was excluded from this analysis.