REVIEW ARTICLE

Assessing Prognosis Following Cardiopulmonary Resuscitation and Therapeutic Hypothermia—A Critical Discussion of Recent Studies

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SUMMARY

Background: The prognosis of patients who are comatose after cardiopulmonary resuscitation (CPR) is poor but can be improved by mild therapeutic hypothermia. We studied the question whether the known, reliable indicators of a poor prognosis after CPR are also valid for patients treated with CPR and hypothermia.

Methods: This review is based on a selective search of the PubMed database for recent articles on the assessment of prognosis in persons who are comatose after CPR and therapeutic hypothermia.

Results: On the basis of 21 clinical trials, 4 of which yielded level I evidence, 9 level II evidence, and 8 level III evidence, the following were identified as reliable indicators of a poor prognosis: generalized myoclonus, bilateral absence of the pupillary light response or of the corneal reflex, bilateral absence of the cortical components of median nerve somatosensory evoked potentials, a burst-suppression or isoelectric EEG, continuous generalized epileptiform discharges, and an elevated serum concentration of neuron-specific enolase (with a higher cutoff value than for normothermic patients).

Conclusion: If the prognosis is poor, this should be thoroughly discussed with the patient's family, and the nature and extent of further intensive treatment should be reconsidered. The patient's wishes, if known, are paramount. Any decision to withhold care should be taken only if there are multiple concurrent indicators of a poor prognosis. If only one such indicator is present, or if the findings are inconsistent, such decisions should be postponed.

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The exact number of resuscitations in Germany is unknown. Probably some 30 000 to 40 000 patients are resuscitated outside hospital each year, only 5% to 10% of whom survive to hospital discharge (1, 2). The number of resuscitations within hospitals has been stated as one to five per 1000 admissions or 0.175 per hospital bed per year (3). The OPS code 8–77 (resuscitation measures) was assigned over 82 000 times in Germany in the year 2011 (4) (OPS = Classification of Operations and Procedures [*Operationen- und Prozedurenschlüssel*], the German modification of the International Classification of Procedures in Medicine). It is unclear, however, in how many of these cases resuscitation measures were initiated before hospital admission. Around 80% of patients resuscitated outside hospital reach the hospital in a comatose state. They usually have an extremely unfavorable outcome, i.e., they either die or survive with irreversible severe brain damage (5, 6).

Ten years ago it was shown that 24 hours of hypothermia (body temperature around 33°C) after cardiopulmonary resuscitation may improve the prognosis of resuscitated patients, at least in those who meet the following criteria:

- Age 18 to 75 years
- Confirmed cardiac arrest or ventricular fibrillation
- Time to commencement of resuscitation 5 to 15 minutes
- No extended period of hypotension (less than 30 minutes under 60 mm Hg on average) or hypoxemia (less than 15 minutes under 85%) after return of spontaneous circulation (7).

Survival was significantly higher in hypothermic patients (81 of 137 versus 62 of 138; 59% versus 45%; $p = 0.02$), particularly in those without or with only slight neurological deficits (75 of 136 versus 54 of 136; 55% versus 39%; $p = 0.009$) (7). Therapeutic hypothermia was thus swiftly added to the guidelines for resuscitation (8) and is now standard in many intensive care units. The question arises of whether the previous parameters for assessing the prognosis of resuscitated patients (9–13) are also reliable after therapeutic

BOX

Indicators of unfavorable prognosis in normothermic patients

- **Generalized early myoclonus** within the first 24 hours after resuscitation
- **Absence of pupillary reaction to light** on the 3rd day after resuscitation
- **Absence of corneal reflex** on the 3rd day after resuscitation
- **Absence of motor reaction to pain** on the 3rd day after resuscitation
- **Absence of cortical SEP components (N20)** after stimulation of the median nerve within the first 3 days after resuscitation (SEP, somatosensory evoked potentials)
- **Burst-suppression EEG** within the first 3 days after resuscitation
- **Isoelectric EEG** within the first 3 days after resuscitation
- **Continuous generalized epileptiform discharges** within the first 3 days after resuscitation
- **Elevated neuron-specific enolase in serum** within the first 3 days after resuscitation (for threshold values see text and *Table 2*)

hypothermia. A large number of studies on this topic have been published in the past few years (14–36). In this article I undertake a critical appraisal of these publications, including a recent prospective class 1 study (14) with 391 patients, more than in all previous class 1 studies put together.

Method

I carried out a selective literature search of the Medline database (PubMed) with the search terms “resuscitation” and “hypothermia” in connection with “prognosis,” EEG,” “electroencephalography,” “SEP,” “somatosensory evoked potentials,” and “neuron-specific enolase.” A total of 21 relevant studies were identified: four class 1 studies (14–17), nine class 2 studies (18–26), and eight class 3 studies (27–34) (classified according to [11]) (*Table e1*).

Indicators of unfavorable prognosis

In normothermic patients

A number of clinical, electrophysiological, and biochemical parameters are—in the absence of sedative substances—reliable indicators of poor prognosis in normothermic patients (9–13) (*Box*). They are based on studies of variable quality with variable numbers of patients, and include only one prospective class 1 study (12). All of these indicators display high specificity but only low sensitivity (9–13); in other words, the absence of prognostically unfavorable parameters does not necessarily mean that the prognosis is favorable.

In therapeutic hypothermia

For hypothermic patients—as for normothermic patients—there is no completely uniform definition of

what constitutes a poor prognosis. In most cases death, persistent vegetative state, and severe disability with permanent dependence on care are viewed as unfavorable outcomes, corresponding to Cerebral Performance Category (CPC) 3–5 or Glasgow Outcome Scale (GOS) 1–3. A few publications define only death and persistent vegetative state as unfavorable (CPC 4–5, GOS 1–2).

Absence of the effects of sedative medications is also a basic precondition for assessing the prognosis in patients who have been treated with hypothermia, above all with regard to the clinical findings (18). In the first few days it is therefore advisable to use sedative substances with a short half-life (e.g., propofol) and discontinue them in good time before the examination. It must be remembered that analgesic and sedative substances (e.g., propofol, midazolam, fentanyl, sufentanyl) are metabolized more slowly during therapeutic hypothermia, so that their half-lives are longer than in normothermic patients. However, there have been no systematic studies of large groups of patients. Preliminary findings indicate that hypothermia has no effect on how long it takes patients with a good prognosis to become conscious. Normothermic and hypothermic patients with a favorable prognosis predominantly regain consciousness within 3 days (37).

Clinical indicators

It can be expected that the known clinical indicators of a poor prognosis will also be reliable after therapeutic hypothermia, because these parameters have general validity independent of the reason for the coma. This expectation is essentially confirmed by the studies carried out to date (*Table 1*). The pupillary reaction to light, the corneal reflex, and the motor reaction to pain are simple to test and evaluate. In contrast, differentiation of generalized myoclonus from epileptic seizures is not always easy, and multifocal action myoclonus has sometimes been misinterpreted as postanoxic early myoclonus (38). Postanoxic early myoclonus occurs within the first 1 or 2 days after resuscitation. The myoclonus can be suppressed by relaxation or deep sedation during hypothermia, thus becoming apparent only after the patient’s restoration to normal body temperature and cessation of relaxation and sedation. It comprises irregular brief convulsions of individual muscles or muscle groups, both spontaneously and in response to external stimuli (touching the patient, aspiration, acoustic stimuli), typically increasing in intensity; sometimes it is evoked only by external stimuli. Predominantly the muscles of the face, upper arm, and shoulder are affected, but all muscle groups can potentially be involved.

In the absence of a motor reaction to pain or of the accompanying extension response, however, far more false-positive results are reported in hypothermic than in normothermic patients on the 3rd day after resuscitation (14, 15, 18, 27, 32). This may be because during the therapeutic hypothermia the patients have to be treated with analgesic and sedating substances,

TABLE 1

Clinical indicators of unfavorable prognosis in large groups of resuscitated patients treated with mild therapeutic hypothermia following resuscitation

	n	Early myoclonus	Bilateral absence of pupillary reaction to light	Bilateral absence of corneal reflex	Lack of pain reaction or extensor response
Al Thenayan et al. 2008 (27)	37	n = 8 all died	n = 6 all died	n = 6 all died	n = 14 ● 12 died ● 2 conscious 2 of 14 false positive → FPR = 0.14
Fugate et al. 2010 (15)	103	n = 9 all died	n = 8 all died	n = 9 all died	n = 17 ● 15 died ● 2 survivors 2 of 17 false positive → FPR = 0.12
Rossetti et al. 2010 (16)	111	n = 36 ● 35 unfavorable course ● 1 favorable course 1 of 36 false positive → FPR = 0.03	n = 47 at least one of the reflexes absent ● 45 unfavorable course ● 2 favorable course 2 of 47 false positive → FPR = 0.04		n = 36 ● 35 unfavorable course ● 1 favorable course 1 of 36 false positive → FPR = 0.03
Bisschops et al. (2011) (26)	162	n = 40 ● 36 unfavorable course ● 4 favorable course 4 of 40 false positive → FPR = 0.10	n = 58 absence of one of these parameters ● 54 unfavorable course ● 4 favorable course 4 of 58 false positive → FPR = 0.07 n = 10 absence of all of these parameters ● 10, all unfavorable course		
Cronberg et al. 2011 (17)	111	n = 15 all died	n = 5 all died	n = 5 all died	n = 28 all died
Samaniego et al. 2011 (18)	44	n = 9 all died or persistent vegetative state	n = 15 all died or persistent vegetative state	n = 22 ● 20 died or persistent vegetative state ● 2 conscious 2 of 22 false positive → FPR = 0.09	n = 47 ● 43 died or persistent vegetative state ● 4 conscious 4 of 47 false positive → FPR = 0.09
Bouwes et al. 2012 (14)	391	no data	n = 22 ● 21 unfavorable course ● 1 favorable course 1 of 21 false positive → FPR = 0.05	n = 23 ● 21 unfavorable course ● 2 favorable course 2 of 23 false positive → FPR = 0.09	n = 112 ● 96 unfavorable course ● 16 favorable course 16 of 112 false positive → FPR = 0.14
Daubin et al. 2011 (e16)	97	n = 26 all died or persistent vegetative state	n = 18 all died or persistent vegetative state	n = 31 all died or persistent vegetative state	n = 61 ● 51 unfavorable course* ● 10 favorable course* 10 of 61 false positive → FPR = 0.16

With the exception of Daubin et al. (e16), unfavorable course = death, persistent vegetative state, or severe deficit with constant dependence on care; favorable course = no or only moderate disability. Classification according to Cerebral Performance Category (CPC) or Glasgow Outcome Scale (GOS). Daubin et al. (e16) rated severe deficit with constant dependence on care as favorable course; therapeutic hypothermia was carried out in only 65 of the 97 patients. FPR, false-positive rate

sometimes need to be given relaxants, and on average receive higher doses of analgesic and sedating substances (propofol, midazolam, fentanyl, sufentanyl) than normothermic patients. Furthermore, these substances are metabolized more slowly in the hypothermic state, so that at the end of hypothermia patients show higher drug levels and thus more prolonged medicinal attenuation of protective reflexes than normothermic patients at the same point in time. For this reason, the absence of a pupillary reaction to light and the corneal reflex should not be evaluated as prognostic

factors until the 3rd day after resuscitation and at least 24 hours after the last dose of analgesic medication (18). The absence of reaction to painful stimuli has no prognostic value at this time.

Electrophysiological indicators

After the end of therapeutic hypothermia—and according to recent findings also during hypothermia in patients receiving analgesic and sedating substances (such as fentanyl and midazolam)—missing cortical components of the median nerve somatosensory

TABLE 2

Comparison of NSE threshold values as indicators of unfavorable prognosis in large groups of resuscitated patients who received no hypothermia versus mild therapeutic hypothermia after resuscitation

24 hours					
Normothermia	n	Threshold value	Hypothermia	n	Threshold value
Roine et al. 1989 (e10)	70	21 (GOS 1–2)	Tiainen et al. 2003 (33)	34	31 (GOS 1–3)
Martens et al. 1998 (e4)	64	50 (GOS 1–2)	Oksanen et al. 2009 (23)	90	41 (GOS 1–3)
Zandbergen et al. 2006 (12)	272	33 (GOS 1–2)	Rundgren et al. 2009 (25)	97	38 (GOS 1–3)
48 hours					
Normothermia	n	Threshold value	Hypothermia	n	Threshold value
Rosén et al. 2001 (e11)	66	24 (GOS 1–2)	Cronberg et al. 2011 (17)	111	33 (GOS 1)
Zingler et al. 2003 (e5)	27	43 (GOS 1–2)	Bouwes et al. 2012 (14)	310	● 58 (GOS 1–3) 93% specificity ● 82 (GOS 1–3) 100% specificity
Zandbergen et al. 2006 (12)	241	33 (GOS 1–2)			
Meynaar et al. 2003 (e12)	110	25 (GOS 1–3)			
72 hours					
Normothermia	n	Threshold value	Hypothermia	n	Threshold value
Prange et al. 1995 (e6)	69	120 (GOS 1–2) 69 (GOS 1–3)	Rundgren et al. 2009 (25)	102	27 (GOS 1–3)
Fogel et al. 1997 (e7)	43	24 (GOS1–2)	Steffen et al. 2010 (24)	97	79 (GOS 1–3)
Martens et al. 1998 (e4)	64	50 (GOS 1)	Storm et al. 2012 (34)	35	57 (GOS 1–3)
Schoerhuber et al. 1999 (e8)	56	40 (GOS 1–3)			
Pfeifer et al. 2005 (e9)	97	65 (GOS 1–2)			
Zandbergen et al. 2006 (12)	209	33 (GOS 1–2)			
Meynaar et al. 2003 (e12)	110	25 (GOS 1–2)			
Steffen et al. 2010 (24)	133	27 (GOS 1–3)			
72 hours in mixed groups (normothermic und hypothermic patients)					
		n normothermic/hypothermic			
	Reisinger et al. 2007 (e15)	177 157/20	80 (CPC 4)		
	Daubin et al. 2011 (e16)	97 32/65	97 (CPC 4–5)		

CPC, Cerebral Performance Category; NSE, neuron-specific enolase; GOS, Glasgow Outcome Scale; GOS 1–2, death or persistent vegetative state; GOS 1–3, death, persistent vegetative state, severe deficit with constant care

evoked potential (SEP) reliably indicate a poor prognosis (14–16, 18, 32). A favorable course has been reported only very occasionally in hypothermic patients with bilateral loss of the cortical components (32) and is also rare in normothermic patients (39). Since there are no confirmed concentration–effect relationships for centrally attenuating substances that may affect electrophysiological parameters, and findings in brain-healthy patients cannot simply be extrapolated to patients with acute diffuse cerebral hypoxia, only findings after

discontinuation of analgesic and sedating substances should be used to determine the prognosis.

With regard to EEG, the unfortunate lack of uniform definition of certain patterns has hampered the comparison of findings in the past. Burst-suppression EEG is usually thought to be a certain sign of poor prognosis in normothermic patients (11, 13, 38). This seemed to be relativized by a recent investigation that reported a favorable course in 2 of 28 hypothermic patients (20). However, rather than employing the conventional

definitions of this EEG pattern, for example from professional societies (e1) or standard textbooks (e2), the authors classified interruption of all EEG activity in the form of flat segments as burst-suppression pattern (20). The use of such a broad definition led to this pattern being diagnosed in an unusually large proportion of patients (28 of 108, 25.9%), far higher than in earlier studies (e.g., 8 of 276 patients = 2.9% in the prospective class 1 study by Zandbergen et al. [12]). Moreover, all EEG recordings were made while the patients were taking midazolam and fentanyl, so these drugs may have affected the results (20). Using the conventional definitions of a burst-suppression pattern (e1, e2), I know of no case of a favorable course, either in the literature or in my own experience of more than 40 hypothermic patients.

Another publication by the same group seems to relativize the poor prognosis of patients with convulsive or nonconvulsive status epilepticus, given that 4 of 63 hypothermic patients had a favorable course (21). However, the authors based their definition of status epilepticus on very broad EEG criteria and included EEG patterns that do not necessarily point to an epileptic event (such as periodic lateralized epileptiform discharges [21, e3]). It should be emphasized that all patients with a favorable course on EEG still showed background activity and EEG responses to external stimuli (21). Neither from the literature nor from the past 10 years of personal experience do I know of a favorable outcome in any patient with continual generalized peaks or sharp waves but no background activity or reactions to external stimuli.

The past few years have seen the publication of the first studies of automated EEG monitoring (28–30), in which the so-called bispectral index is recorded from only one or two channels (instead of the usual 8 to 18 channels). A score of 0 corresponds to an isoelectric EEG, 100 to a normal finding. To date a bispectral index of 0 has always indicated a poor prognosis and a bispectral index over 0 has not permitted a safe prediction of the outcome. Known prognostically unfavorable patterns such as burst-suppression EEG or generalized epileptiform discharges and aspects such as presence/absence of background activity or preserved/lost reactivity to external stimuli cannot be reliably registered with the bispectral index. In the next years this will still only be possible with 8-channel or, better, 16-channel recordings evaluated by physicians familiar with this method.

Neuron-specific enolase in serum

The greatest differences between hypothermic and normothermic patients reported to date relate to neuron-specific enolase (NSE) in serum. The widely adopted threshold value of 33 µg/L within the first 3 days for normothermic patients is based on the only prospective class 1 study, where all patients with a serum NSE concentration over 33 µg/L either died or had not yet regained consciousness by 4 weeks after resuscitation (12). NSE exceeded 33 µg/L in 42 of 272 patients at 24 hours, in 52 of 241 patients at 48 hours,

and in 46 of 209 patients at 72 hours, which clearly shows low sensitivity despite its high specificity. However, this value was not found in all studies: In isolated cases threshold values over 60 µg/L have been reported (Table 2) (e4–e9). Some studies on the prognostic relevance of NSE after hypothermia fail to mention this, arousing the impression that 33 µg/L was the absolute limit in normothermic patients.

Overall, the threshold values reported after therapeutic hypothermia lie in the range known for normothermic patients (Table 2). However, special attention should be paid to studies which compare the prognostically unfavorable threshold values of serum NSE before and after the introduction of therapeutic hypothermia at a single center under identical laboratory conditions. Thus Fugate et al. (15) reported a favorable course in 2 of 28 normothermic patients with an NSE concentration exceeding 33 µg/L, corresponding to a false-positive rate (FPR) of 0.07. In therapeutic hypothermia, on the other hand, 12 of 31 patients with serum NSE over 33 µg/L experienced a favorable course, corresponding to an FPR of 0.39 (15). Other groups have also observed unacceptably high FPRs when using an NSE threshold value of 33 µg/L as indicator of a poor prognosis (0.10, 10 of 99 patients [14]; 0.15, 3 of 20 patients [20]). Finally, Steffen et al. reported threshold values of 26.9 µg/L for normothermic patients and 78.9 µg/L for therapeutic hypothermia (24). The highest NSE concentration reported to date for a hypothermic patient with a favorable course was 91.7 µg/L (e16).

Consequences

A predictably poor outcome—death, vegetative state, or in the best case severe neurological deficits necessitating constant care and assistance—has wide-reaching consequences. In such cases the nature and extent of intensive treatment should be reconsidered and discussed with the patient's relatives and with the team on the intensive care unit (11, 13, 40, e13, e14). The patient's own wishes are decisive. The Third Act Amending Guardianship Legislation (*Drittes Gesetz zur Änderung des Betreuungsrechts*) of 29 July 2009 stipulates that, in the presence of an advance patient directive, “the care provider must respect the will of the care recipient” if the corresponding treatment situation arises (e17). If there is no advance directive (e17), “the care provider must determine the treatment wishes or putative will of the care recipient and decide on this basis whether the care recipient agrees to a medical procedure according to paragraph 1” (§1901a). If it seems clear that the patient would prefer palliative care to therapeutic measures in the case of irreversible loss of consciousness or permanent massive brain damage, this wish must be respected and treatment restricted accordingly. Administration of morphine and benzodiazepines is justified—and welcomed by relatives—to avoid any chance that the patient will suffer despite the presence of massive brain damage excluding conscious perception of pain.

Such wide-reaching decisions cannot be taken on the basis of one single parameter. The certainty of the prognosis is increased if two or more parameters agree in indicating an unfavorable outcome (16, 35, 36, e16). In practice this means that at least one unfavorable clinical sign should be accompanied by at least one unfavorable electrophysiological parameter or a significantly elevated serum NSE concentration, or better still both. Only then can the poor prognosis be regarded as confirmed.

The following clinical indicators of an unfavorable prognosis are just as reliable and well documented in patients who have been treated with hypothermia as they are in normothermic patients:

- Generalized early myoclonus within the first 24 to 48 hours
- Bilateral absence of pupillary reaction to light on the 3rd day after resuscitation
- Bilateral absence of corneal reflex on the 3rd day after resuscitation.

The reliable electrophysiological indicators of an unfavorable prognosis after therapeutic hypothermia are:

- Bilateral absence of cortical SEP components after stimulation of the median nerve
- Isoelectric EEG (at amplification of 2 μ V/mm)
- Burst-suppression EEG according to the standard definition (see above)
- Generalized epileptiform discharges without background activity and lack of reactivity to external stimuli.

An elevated serum NSE concentration is also a reliable indicator of a poor prognosis following therapeutic hypothermia; however, the threshold values are higher than in normothermic patients. According to current data, an unfavorable prognosis can be assumed with 100% certainty only if the threshold value is set at 97 μ g/L.

Conflict of interest statement

The author declares that no conflict of interest exists.

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KEY MESSAGES

- A 24-hour period of hypothermia (around 33°C) is currently recommended in the guidelines for the treatment of patients who have undergone cardiopulmonary resuscitation.
- On the basis of a number of studies carried out in recent years, the prognosis of these patients can be assessed just as reliably as for normothermic patients.
- Generalized myoclonus within the first 24 hours and bilateral absence of pupillary reaction to light and/or the corneal reflex are reliable clinical indicators of an unfavorable prognosis, i.e., death, permanent coma, persistent vegetative state, or severe deficits necessitating constant care.
- Bilateral absence of cortical potentials on median nerve SEP, burst-suppression EEG, and generalized epileptiform discharges with no reactivity to external stimuli and no discernible background activity are reliable electrophysiological indicators of a poor prognosis.
- Elevated serum concentrations of neuron-specific enolase have to be above 97 μ g/L to serve as a safe indicator of an unfavorable prognosis.

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REVIEW ARTICLE

Assessing Prognosis Following Cardiopulmonary Resuscitation and Therapeutic Hypothermia—a Critical Discussion of Recent Studies

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eTABLE 1

Studies of large groups of resuscitated patients in whom mild therapeutic hypothermia was carried out, with the prognostic parameters investigated

	n	Type of study			Clinical parameters				Electrophysiology		NSE
		Pro-spective	Retro-spective	Evi-dence level	Early myo-clonus	Pupillary reaction to light	Corneal reflex	Pain reaction	EEG	SEP	
Bouwes et al. 2012 (14)	391	X		I	X	X	X	X		X	X
Fugate et al. 2010 (15)	103	X		I	X	X	X	X	X	X	
Rossetti et al. 2010 (16)	111	X		I	X		X	X	X		
Cronberg et al. 2011 (17)	111	X		I	X	X	X	X	X	X	X
Samaniego et al. 2011 (18)	44	X		II	X	X	X	X	X	X	
Rundgren et al. 2010 (19)	95	X		II					X		
Rossetti et al. 2012 (20)	61	X		II					X		
Rossetti et al. 2009 (21)	137	X	X	II					X		
Rittenberger et al. 2012 (22)	101	X		II					X		
Oksanen et al. 2009 (23)	90	X		II							X
Steffen et al. 2010 (24)	97	X		II							X
Rundgren et al. 2009 (25)	102	X		II							X
Bisschops et al. 2011 (26)	162		X	II	X	X	X	X	X		
Al Thenayan et al. 2008 (27)	37		X	III	X	X	X	X			X
Stammet et al. 2009 (28)	45	X		III					X (only BIS)		
Leary et al. 2010 (29)	62	X		III					X (only BIS)		
Seder et al. 2010 (30)	97	X		III					X (only BIS)		
Mani et al. 2012 (31)	38		X	III					X		
Leithner et al. 2010 (32)	112		X	III						X	
Tiainen et al. 2003 (33)	34	X		III							X
Storm et al. 2012 (34)	35	X		III							X

SEP, somatosensory evoked potentials; NSE, neuron-specific enolase; BIS, bispectral index

eTABLE 2

Electrophysiological indicators of unfavorable prognosis in large groups of resuscitated patients in whom mild therapeutic hypothermia was carried out after resuscitation

	n	EEG					SEP
		Isoelectric EEG	Burst-suppression EEG	Epileptiform discharges	Flat EEG (under 20 μ V)	Nonreactive	Bilateral absence of N20
Rundgren et al. 2009 (25)	95		n = 38 with one of these patterns, all died				
Fugate et al. 2010 (15)	103		n = 1 died	n = 4 all died	n = 3 all died	n = 9 all died	
Stammet et al. 2009 (28)	45	n = 14* ¹ all unfavorable course (CPC 3–5)					
Leary et al. 2010 (29)	62	n = 16* ¹ all unfavorable course (CPC 3–5)					
Seder et al. 2010 (30)	97	n = 9* ¹ all unfavorable course (CPC 3–5)					
Samaniego et al. 2011 (18)	85		without false positives				n = 14 (CPC 4–5)
Bisschops et al. 2011 (26)	103		n = 2 all unfavorable course (GOS 4–5)		n = 10 • 9 unfavorable course (CPC 3–5) • 1 favorable course 1 of 10 false positive → fpr = 0.10	n = 15 all unfavorable course (CPC 3–5)	
Cronberg et al. 2011 (17)	111		n = 16 all died	n = 22 • 21 died • 1 dependent on care (CPC 3)	n = 3 all died		n = 14 all died
Rossetti et al. 2012 (20)	61		n = 28* ^{2,3} • 26 unfavorable course (CPC 3–5) • 2 favorable course 2 of 28 false positive → FPR = 0.07	n = 10* ³ all unfavorable course (CPC 3–5)			
Rossetti et al. 2009 (21)	137			n = 63 (status)* ⁴ • 59 unfavorable course (CPC 3–5) • 4 favorable course 4 of 63 false positive → FPR = 0.06			
Rossetti et al. 2010 (16)	111			n = 39/first EEG* ³ • 35 died • 4 survivors 4 of 39 false positive → FPR = 0.10		n = 56/first EEG* ³ • 53 died • 3 survivors 3 of 56 false positive → FPR = 0.05	n = 33 all died
Rittenberger et al. 2012 (22)	101			n = 12 (status) all unfavorable course (CPC 3–5)			
Mani et al. 2012 (31)	38			n = 17 • 16 unfavorable course (CPC 3–5) • 1 favorable course 1 of 17 false positive → FPR = 0.06			

	n	EEG					SEP
		Isoelectric EEG	Burst-suppression EEG	Epileptiform discharges	Flat EEG (under 20 µV)	Nonreactive	Bilateral absence of N20
Leithner et al. 2010 (32)	112						n = 36 • 35 unfavorable course (CPC 3–5) • 1 good improvement 1 of 36 false positive → FPR = 0.03
Bouwes et al. 2012 (14)	391						n = 42 all unfavorable course (CPC 3–5)
Daubin et al. 2011 (e16)	95 ^{*5}	n = 32 with one of these patterns, all died or persistent vegetative state					n = 33 all died

CPC, Cerebral Performance Category; CPC 3–5, death, persistent vegetative state, severe deficit with constant care; CPC 4–5, death or persistent vegetative state; GOS, Glasgow Outcome Scale

^{*1} Isoelectric EEG assumed on basis of bispectral index (BIS) of 0

^{*2} Definition of burst-suppression pattern deviated from other studies (see text for detail)

^{*3} EEG recordings during therapeutic hypothermia under midazolam 0.1 mg/kg BW/h plus fentanyl 1.5 µg/kg BW/h

^{*4} Influence of midazolam and/or fentanyl at the time of EEG recordings cannot be excluded

^{*5} Therapeutic hypothermia carried out in only 65 of 97 patients

FPR, false-positive rate; N20, cortical components of median nerve SEP (SEP, somatosensory evoked potentials) (see Box)