Neurologic Prognostication: Neurologic Examination and Current Guidelines

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Abstract

Clinical examination is paramount for prognostication in patients who are comatose after resuscitation from cardiac arrest. At 72 hours from recovery of spontaneous circulation (ROSC), an absent or extensor motor response to pain (M $\leq$ 2) is a very sensitive, but not specific predictor of poor neurologic outcome. Bilaterally absent pupillary or corneal reflexes are less sensitive, but highly specific predictors. Besides the clinical examination, investigations such as somatosensory evoked potentials (SSEPs), electroencephalography (EEG), blood levels of neuron-specific enolase (NSE), or imaging studies can be used for neuroprognostication. In patients who have not been treated using targeted temperature management (TTM), the 2006 Practice Parameter of the American Academy of Neurology suggested a unimodal approach for prognostication within 72 hours from ROSC, based on status myoclonus (SM) within 24 hours, SSEP, or NSE at 24 to 72 hours and ocular reflexes or M $\leq$ 2 at 72 hours. The 2015 guidelines from the European Resuscitation Council and the European Society of Intensive Care Medicine suggest a multimodal prognostication algorithm, to be used in both TTM-treated and non-TTM-treated patients with M $\leq$ 2 at $\geq$ 72 hours from ROSC. Ocular reflexes (pupillary and corneal) and SSEPs should be used first, followed by a combination of other predictors (SM, EEG, NSE, imaging) if results of the first predictors are normal.

Keywords

- cardiac arrest
- prognostication
- clinical examination

Clinical examination has been used for neurologic prognostication after cardiac arrest (CA) since the beginning of postresuscitation practice. In 1974 and 1977, two seminal studies conducted in comatose CA survivors showed that on initial clinical examination both an absent, extensor, or decorticate response to pain[1] and a bilaterally absent pupillary light response (PLR),[2] respectively, were associated with a significantly higher rate of poor neurologic outcome, defined as a persistent vegetative state or severe neurologic disability. In 1985, in their first large multicenter study on neuroprognostication in anoxic-ischemic coma, Levy et al[3] conducted neurologic examinations on the day of admission, on day 3, on day 4 to day 7 and on day 8 to day 14 in 210 resuscitated comatose patients. Results showed that an absent PLR on initial clinical examination (52 patients), a decorticate or worse motor response on day 2 to 3 (70 patients), or the combination of an absent response to verbal commands *plus* the absence of spontaneous eye movements and eye opening (38 patients) was associated with a 0% rate of clinical recovery at 1 year (95% confidence intervals [CIs] from 0–5% to 0–20%).

In the 20 years following Levy's study, evidence accumulated on other outcome predictors,[4] such as short-latency somatosensory evoked potentials (SSEPs) or biomarkers like neuron-specific enolase (NSE), which could usefully complement the neurologic examination.[5,6] However, no specific guidelines were formulated for a systematic approach to neuroprognostication in postanoxic coma.

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The American Academy of Neurology 2006 Practice Parameter

In 2006, a group of experts from the Quality Standards Subcommittee of the American Academy of Neurology (AAN) performed a systematic review[6] of the available evidence with the purpose of providing practical recommendations for early prognostication in comatose survivors of CA.

The study group assessed the predictive value of seven variables: circumstances surrounding cardiopulmonary resuscitation (CPR), elevated body temperature, neurologic examination, electrophysiological studies, biochemical markers, monitoring of brain function, and neuroimaging studies. A literature review was performed on studies of comatose adults ($\geq$ 17 years) resuscitated from CA, and it was restricted to predictors of poor neurologic outcome, defined either as (1) death or persisting unconsciousness after 1 month; or (2) death, persisting unconsciousness, or severe disability requiring full nursing care after 6 months. The study group reviewed 391 studies (1996–2006); 48 studies were included in the final review.

The conclusions of the expert group were the following:

1. The circumstances surrounding CPR, such as anoxia time, duration of CPR, and cause of CA, are related to poor outcome, but cannot discriminate accurately between patients with poor outcomes and those with favorable outcomes. The same applies to body temperature.
2. One or more of the following predict poor outcome accurately (false-positive rate [FPR] 0% [0–3]):
   (a) Presence of myoclonus status epilepticus (defined as spontaneous, repetitive, unrelenting, generalized multifocal myoclonus involving the face, limbs, and axial musculature in comatose patients) within the first 24 hours after recovery of spontaneous circulation (ROSC) in patients with primary circulatory arrest
   (b) Absence of PLR within days 1 to 3 after ROSC
   (c) Absent corneal reflexes (CRs) within days 1 to 3
   (d) Absent or extensor motor responses after 3 days
3. In relation to EEG patterns, the generalized suppression to $\leq$ 20 μV, burst-suppression with generalized epileptiform activity, or generalized periodic complexes on a flat background, are strongly, but not invariably associated with poor outcome; the bilateral absence of the N20 SSEP wave with median nerve stimulation recorded on days 1 to 3 or later after ROSC accurately predicts a poor outcome.
4. Serum NSE levels $\geq$ 33 μg/L at days 1 to 3 after ROSC accurately predict poor outcome (FPR 0% [0–3]).
5. There are inadequate data to support or refute the prognostic value of monitoring of brain oxygenation and intracranial pressure (ICP), and of neuroimaging studies like computed tomography (CT) or magnetic resonance imaging (MRI) of the brain.

Before starting the prognostication process, the AAN recommended excluding major confounding factors. These factors include acute renal or liver failure, major metabolic derangements, circulatory shock, the use of sedatives or neurologic blocking agents, and induced hypothermia.

The AAN 2006 guidelines represented the first systematic approach to early neuroprognostication in comatose survivors of CA; their included algorithm (►**Fig. 1**) was both simple and practical. However, these guidelines also had important limitations:

1. The AAN 2006 review was based on studies conducted before the advent of targeted temperature management (TTM) for postresuscitation care.[7] Because both TTM itself and sedatives or neuromuscular blocking drugs used to maintain it might potentially interfere with prognostication indices, especially clinical examination,[3] the predictive value of those indices had to be reassessed in TTM-treated patients.
2. The definitions of a false-positive rate (FPR) among included studies were heterogeneous. In most studies, the standard FPR definition was used: the ratio between the number of false-positives and the number of patients with good outcome. However, in other studies the FPR was defined as the ratio between the number of false-positives and the number of patients with a positive test result, which caused an underestimation of the FPR of the predictors with highest sensitivity, like the motor score. Some of the studies adopting a nonstandard FPR definition, like the PROPAC (Prognosis in Postanoxic Coma) study,[8] had a large sample size; when their data were pooled together in the AAN review this resulted in a heavy distortive weight toward an overestimation of the overall test performance, especially as far as clinical predictors were concerned.[9]
3. Studies published both before[10] and after[11,12] the AAN review showed that the thresholds recommended by the AAN for outcome prediction in non-TTM-treated patients using biomarkers were inconsistent.[9]
4. New evidence concerning the prognostic value of EEG and imaging studies accumulated after the publication of the AAN 2006 guidelines.
5. The AAN 2006 review did not adequately address some important limitations of prognostication studies, such as the risk of "self-fulfilling prophecy," which is a bias occurring when the treating physicians are not blinded to the results of the outcome predictor and use it to make a decision to withdraw life-sustaining treatment (WLST).[13] Although the presence of self-fulfilling prophecy in prognostication studies was acknowledged in the AAN document, this bias was not adequately weighted in terms of quality of evidence, which was often rated as high even in the absence of adequate blinding.
6. Finally, in most of the studies included in the AAN review, prognostication was made within 72 hours, with the consequent risk of a too early WLST, which may have biased the results. Recent evidence showed that a WLST before 72 hours from ROSC is potentially associated with an increased risk of mortality.[14,15]

The 2012 Swedish Resuscitation Council Guidelines

In the years following the publication of the AAN 2006 guidelines, TTM became a standard component of

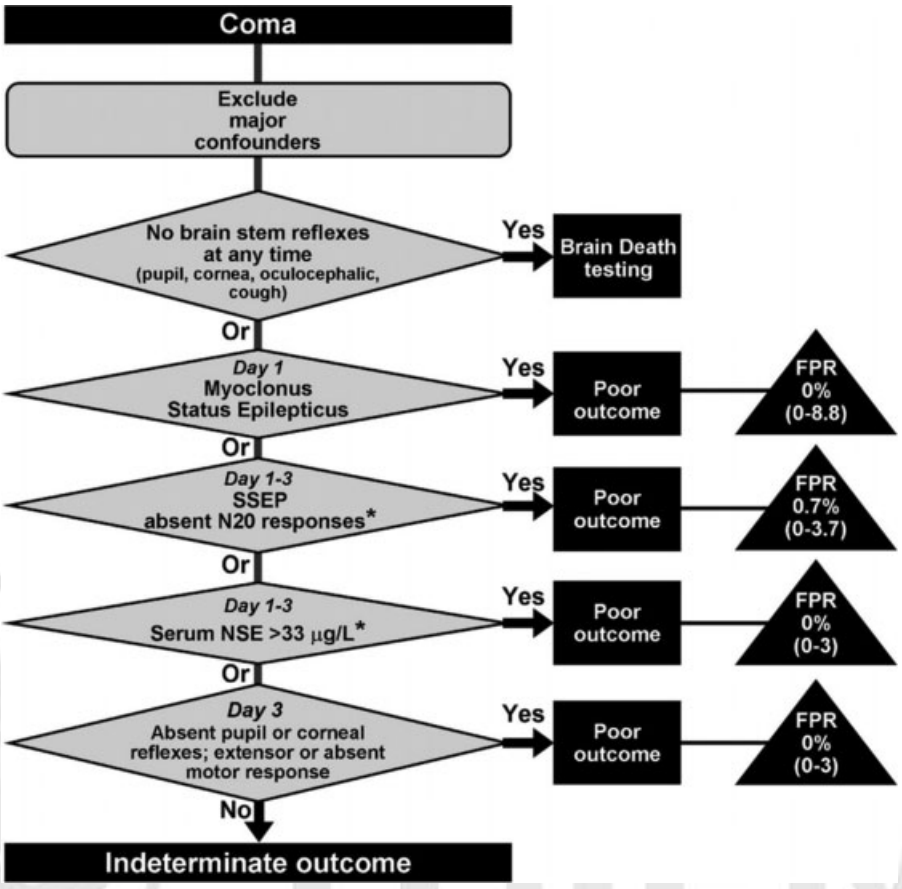

Fig. 1 The American Academy of Neurology 2006 prognostication algorithm. If there are no brainstem reflexes at any time, brain death testing should be considered. Myoclonus status epilepticus at day 1, absent N20 somatosensory evoked potential (SSEP) waves or serum neuron-specific enolase (NSE) $>$ 33 μg/L at days 1–3, and the absence of both pupillary and corneal reflexes or an absent or extensor motor response on day 3 predict a poor neurologic outcome with $\approx$ 0% false-positive rate (FPR) and narrow confidence intervals. If none of these criteria are met, the outcome is indeterminate. (Reproduced from Wijdicks et al[6].)

postresuscitation care worldwide. In 2012, the Swedish Resuscitation Council commissioned its task force on postresuscitation care to develop national recommendations for neuroprognostication after CA to be used in both TTM-treated and non-TTM-treated patients.[16] Members of the task force, together with an expert panel, performed a nonsystematic literature review and formulated final recommendations based on expert consensus. These recommendations included several innovative points[17]:

1. Given the interference of TTM on clinical neurologic examination,[18] the document suggested postponing the final assessment of TTM-treated patients to $\geq$ 72 hours after normothermia is achieved: ~4.5 days after the arrest.
2. A bilaterally absent N20 SSEP wave was confirmed as an accurate predictor of poor outcome after CA, especially when recorded after restoration of normal body temperature.[19]
3. As far the EEG was concerned, the Swedish guidelines highlighted an unreactive background[20] or a spontaneous burst suppression[21] as predictors of poor outcome.
4. For biochemical markers, the guidelines suggested caution, given the lack of standardization and the presence of confounders (especially hemolysis for NSE), and recommended that at least two samples had to be analyzed to reduce the risk of error and evaluate the trend.
5. Finally, the Swedish guidelines suggested using imaging studies, such as computed tomography (CT) and magnetic resonance imaging (MRI) of the brain, as supplemental tools for prognostication in combination with other predictors.

The 2014 ERC-ESICM Advisory Statement and Algorithm

The 2013 Swedish recommendations were aimed for a national audience. The following year, a group of experts of the European Resuscitation Council (ERC) and the Trauma and Emergency Medicine (TEM) Section of the European Society of Intensive Care Medicine (ESICM) planned an advisory statement on neurologic prognostication in adult comatose survivors of CA.[22] Their aims were to

1. Update and summarize the available evidence, including that on TTM-treated patients
2. Provide practical recommendations on the most reliable prognostication strategies, based on a robust analysis of

the evidence, in anticipation of the 2015 ERC Guidelines on Resuscitation
3. Identify knowledge gaps and suggest directions for future research

Results from three recent systematic reviews[9,23,24] on prognostication after CA (total 39 studies including 5392 patients) were used as a data source. A Cerebral Performance Category (CPC) of 3 to 5 (severe neurologic disability, persistent vegetative state, or death) as opposed to CPC 1–2 (absent, mild, or moderate neurologic disability) was adopted as a definition of poor outcome, based on preferences from the majority of clinicians[25] and investigators.[26] Grading was made according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria.[27,28] Given the importance of the risk of self-fulfilling prophecy, limitations were graded as serious when the treating team was not blinded to the results of the predictor of poor outcome that was being studied, and very serious when the investigated predictor was used as a criterion for WLST. According to GRADE, recommendations were stated as either strong ("recommendation") or weak ("suggestion").[27,28] Recommendations from the ERC-ESCIM Advisory Statement and the relevant prognostication algorithm have been incorporated into the current (2015) ERC-ESICM guidelines for post-resuscitation care.[29]

Evidence Concerning Clinical Examination

Pupillary Light Reflex

The 2014 evidence review showed that at 72 hours from ROSC, an absent PLR predicts poor outcome with 0% FPR, both in TTM-treated and in non-TTM-treated patients (95% CIs 0–2 and 0–8, respectively).[8,18,19,30–34] However, its sensitivity is low (24% and 18%, respectively).

Corneal Reflex

A bilaterally absent CR has a similar performance to the PLR, but it is slightly less specific, probably because of its higher sensitivity to the interference from residual effects of sedatives or neuromuscular blocking drugs[18] and to its inconsistent testing methods. At 72 hours from ROSC, the FPR of CR was 5% (0–25) in one study[8] in non-TTM-treated patients, and 4% (1–7) in 7 studies[18,19,30–33] in TTM-treated patients; sensitivities were 29% and 34%, respectively.

Motor Response to Pain

In non-TTM-treated patients,[8] an absent or extensor motor response to pain, corresponding to a motor score (M) = 1 or 2 of the Glasgow Coma Scale (M $\leq$ 2) at 72 hours from ROSC has a high (74% [68–79]) sensitivity for prediction of poor outcome, but the FPR is also high (27% [12–48]). Similar results were observed in TTM-treated patients.[18–20,30–33,35,36] Like the CR, the motor response can be suppressed by the effects of sedatives or neuromuscular blocking drugs.[18]

All predictors based on clinical examination have a high risk of self-fulfilling prophecy because they cannot be concealed from the treating team, and their corresponding level of evidence is consequently low. In addition, only a few prognostication studies reported suspension of sedation before clinical examination, and no study ruled out residual effects of neuromuscular blocking drugs using objective measurements such as median nerve stimulation train-of-four.

The ERC-ESICM panel recommended using the bilateral absence of both PLR and CR at 72 hours or more from ROSC to predict poor outcome in comatose survivors from CA, either TTM-treated or non-TTM-treated. Conversely, the panel suggested against using M $\leq$ 2 alone to predict poor outcome in those patients, given its high FPR. However, due to its high sensitivity, M $\leq$ 2 may be used to identify the population with the potential for poor neurologic status needing prognostication or to predict poor outcome in combination with other more robust predictors. When interference from residual sedation or paralysis is suspected, prolonging observation of clinical signs beyond 72 hours was recommended to minimize the risk of obtaining FPRs.

Myoclonus and Status Myoclonus

The ERC-ESICM panel detected wide inconsistency in the names and definitions of status myoclonus. Terms like status myoclonus, myoclonic status, generalized status myoclonicus, and myoclonus (or myoclonic) status epilepticus have been used interchangeably.[9] Because in postanoxic comatose patients clinical myoclonus is only inconsistently associated with epileptiform activity on EEG,[37,38] the panel refused the term "myoclonus status epilepticus" used in the AAN 2006 definition,[6] but adopted the associated criteria of continuity, whole-body manifestation, and prolonged duration. Although there is no definitive consensus in the literature on the duration or frequency of myoclonic jerks required to qualify as status myoclonus, in prognostication studies of comatose survivors of CA, the minimum reported duration is 30 minutes. Therefore, the ERC-ESICM panel suggested the term "status myoclonus" to indicate continuous and generalized myoclonus persisting for $\geq$ 30 minutes in comatose survivors of CA.

In TTM-treated patients, the presence of myoclonic jerks (not status myoclonus) within 72 hours from ROSC is inconsistently associated with poor outcome (FPR 5% [3–8]; sensitivity 33%).[35–37,39–41] A recent retrospective analysis of a large repository of TTM-treated patients also confirmed these findings.[42,43] Conversely, status myoclonus starting within 48 hours from ROSC was highly specific of poor outcome both in TTM-treated[18,37,44] (FPR 0.5% [0–3]; sensitivity 16%) and in non-TTM-treated patients[8,45,46] (FPR 0 [0–4]%; sensitivity 15%). However, several case reports of good neurologic recovery despite an early-onset, prolonged, and generalized myoclonus have been published. In some of these cases,[47–49] myoclonus persisted after awakening and evolved into a chronic action myoclonus (Lance-Adams syndrome). In others,[50,51] it disappeared with the recovery of consciousness. The exact time when recovery of consciousness occurred in these cases may have been masked by the myoclonus itself and by ongoing sedation. The ERC-ESICM Advisory Statement recommended using the presence of

status myoclonus within 48 hours from ROSC in combination with other predictors to predict poor outcome in comatose survivors of CA, either TTM-treated or non-TTM-treated. In those patients, an EEG recording can be useful to identify EEG signs of awareness and reactivity and to reveal coexistent epileptiform activity.

Evidence Concerning Other Predictors

The ERC-ESICM Advisory Statement also included evidence and recommendations on predictors not based on clinical examination. Different from neurologic signs, SSEPs, biomarkers, and imaging are not or are minimally influenced by TTM and sedative drugs. Although the EEG is more sensitive to these confounding factors, limited evidence suggests that some malignant patterns may be predictive even during TTM.[52,53]

As far as SSEPs are concerned, the panel confirmed that bilaterally absent N20 waves predict poor outcome with a very low FPR, especially when SSEPs are recorded after achieving normothermia.[9,24] However, the panel warned of the very high risk of self-fulfilling prophecy for SSEPs: SSEP results are more likely to influence physicians' and families' WLST decisions than results of the clinical examination or EEG.[54]

The ERC-ESICM panel confirmed the predictive value of EEG-based predictors like absence of reactivity and burst suppression, as suggested by the Swedish Resuscitation Council.[17] However, due to a lack of evidence in TTM-treated patients and the limited and very low-level evidence in non-TTM treated patients, the use of low-voltage EEG was not suggested. Instead, status epilepticus was added to the EEG predictors. Given the risk of interference on EEG from both TTM and profound sedation, the use of EEG-based predictors was not suggested before 72 hours from ROSC. In addition, their use was suggested only in combination (i.e., presence of burst suppression or status epilepticus plus an unreactive background) and only in association with other predictors.

As far as biomarkers were concerned, the ERC-ESICM review documented a wide variability of NSE thresholds for prediction of poor outcome with 0% FPR, especially in TTM-treated patients, in the first 72 hours after ROSC. For example, at 48 hours from ROSC, this threshold varied between 25 μg/L and 151.5 μg/L.[19,21,55–59] However, the distribution of NSE values in available studies[9,24,60] indicated that NSE values above 60 μg/L at 48 to 72 hours after ROSC are very rarely associated with good outcome. Limited evidence[56,61,62] suggested that the discriminative value of NSE levels at 48 to 72 hours was higher than at 24 hours. The ERC-ESICM panel suggested using high serum values of NSE at 48 to 72 hours from ROSC in combination with other predictors for prognosticating a poor neurologic outcome, regardless of TTM treatment. However, no threshold enabling prediction with a zero FPR could be recommended.

The ERC-ESICM panel confirmed the previous recommendations of the Swedish Resuscitation Council concerning imaging studies, and suggested using the presence of a marked reduction of the gray matter (GM)/white matter (WM) ratio or sulcal effacement on brain CT within 24 hours after ROSC or the presence of extensive restriction in diffusion on diffusion-weighted brain MRI at 2 to 5 days after ROSC in combination with other predictors to predict poor outcome in both TTM-treated and non-TTM-treated patients. However, given the limited number of patients studied, the spatial complexity of postanoxic changes in both CT and MRI, and the lack of standardization for quantitative measures of these changes, the use of brain imaging studies for prognostication was suggested only in centers where specific experience is available.

ERC-ESICM Prognostication Algorithm

Studies conducted in non-TTM-treated patients have shown that the process of brain recovery from anoxic-ischemic injury is generally completed within 72 hours from ROSC.[46,63] Consequently, in the absence of residual sedation, 72 hours after ROSC has been chosen as a suitable time for starting prognostication. However, when residual action of confounders is suspected, prognostication should be delayed until a reliable clinical examination can be made.

Since prognostication is indicated in patients with prolonged coma after resuscitation, the process should start with a thorough clinical examination to assess the level of consciousness.[64] The entry point of the ERC-ESICM algorithm is the presence of a Glasgow Coma Scale motor score ≤ 2 at ≥ 72 hours, given the high sensitivity of this sign. Results of earlier prognostic tests should also be considered at this time point.

The most robust predictors—bilaterally absent N20 SSEP waves at ≥ 24 hours after rewarming or bilaterally absent PLRs > 72 hours—should be evaluated first. If any of these predictors are present, a poor outcome is considered to be very likely (FPR $< 5\%$ with 95% CIs $< 5\%$ in TTM-treated patients). Based on expert opinion, the guidelines suggest combining the absence of PLR with the absence of CR for predicting poor outcome at this time point.

If none of the most robust predictors are present, the ERC-ESICM algorithm suggests considering a group of less accurate predictors. Based on expert opinion, these predictors should be assessed only after an additional 24-hour observation to allow additional time for clearance of lingering analgosedation and clinical improvement. These predictors have FPRs $< 5\%$ but wider 95% CIs than the previous predictors, and/or their definition/threshold is inconsistent in prognostication studies. Also based on expert opinion, the guidelines suggest combining at least two of these predictors for prognostication. These include the presence of early status myoclonus within 48 hours from ROSC, high values of serum NSE at 48 to 72 hours after ROSC, an unreactive malignant EEG pattern (burst suppression, status epilepticus) after rewarming, or diffuse signs of anoxic-ischemic injury on brain CT within 24 hours after ROSC or on brain MRI at 2 to 5 days after ROSC.

Different from the AAN 2006 guidelines, the ERC-ESICM algorithm is multimodal (►**Fig. 2**). This is because even the most robust predictors have a risk of leading to self-fulfilling prophecy. Apart from increasing safety, limited evidence[35,41,62,65] also suggests that multimodal prognostication increases sensitivity.

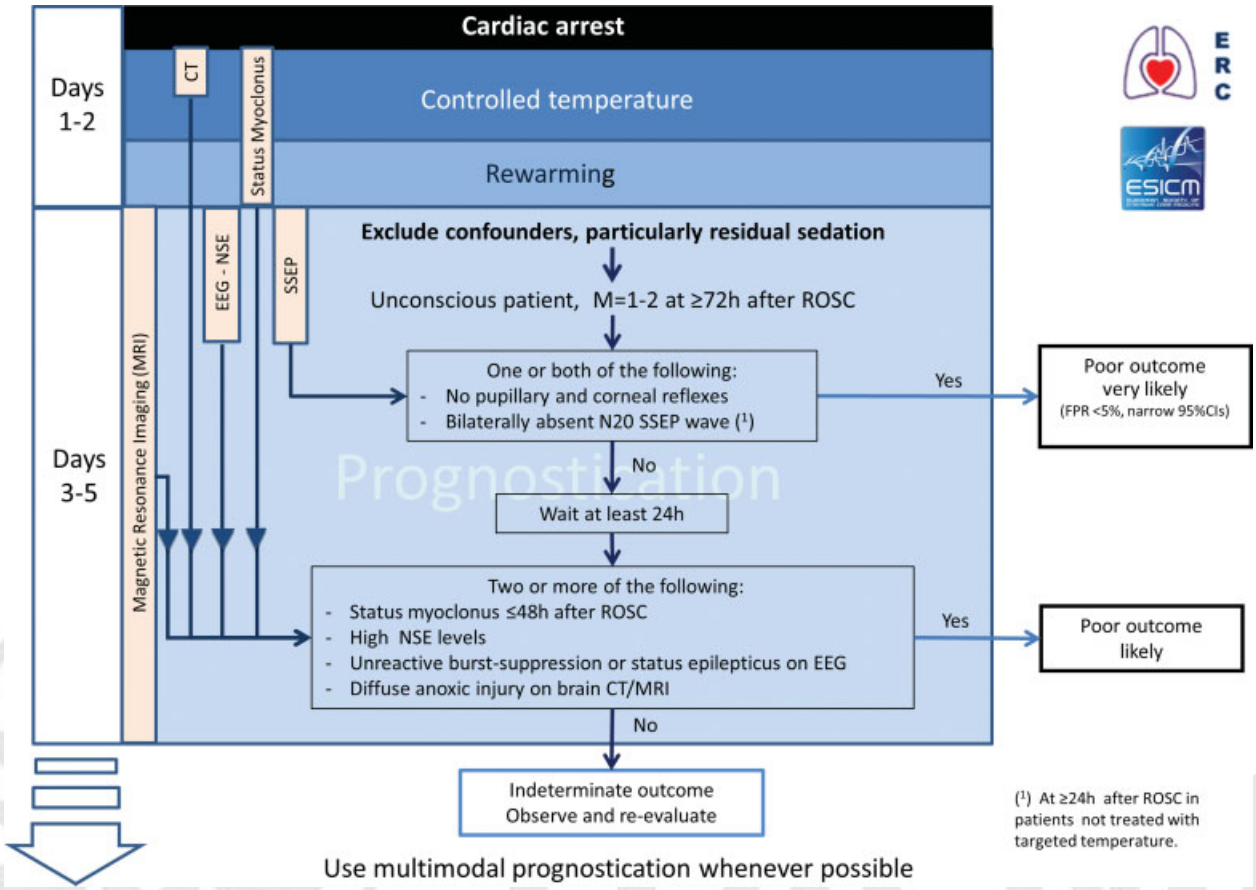

Fig. 2 European Resuscitation Council– European Society of Intensive Care Medicine (ERC-ESICM) prognostication algorithm. After the exclusion of confounders, prognostication starts at ≥ 72 hours after recovery of spontaneous circulation (ROSC) in patients who are unconscious with a M ≤ 2. Bilaterally absent pupillary light response and corneal reflex, or bilaterally absent N20 somatosensory evoked potential (SSEP) waves indicate a poor outcome is very likely. If none of these signs are present, two or more of the following indicate that a poor outcome is likely: status myoclonus ≤ 48 hours, high neuron-specific enolase (NSE) values, unreactive electroencephalography (EEG) with burst suppression or status epilepticus, diffuse anoxic injury on brain computed tomography (CT) and/or magnetic resonance imaging. If none of these criteria are met, the prognosis is indeterminate and prolonged observation with further re-evaluation is indicated. FPR, false-positive rate. (Reproduced from Sandroni et al[22].)

As per the AAN 2006 guidelines, prolonged observation is recommended for patients with indeterminate outcome. However, the absence of clinical improvement over time suggests a worse outcome. After the publication of the AAN 2006 guidelines, some evidence accumulated on the duration of unconsciousness after CA. Although awakening has been described as late as 25 days after arrest,[44,50,66] most survivors will recover consciousness within one week.[59,67–69] Time of awakening is influenced by several factors,[70] the most important of which are age, circulatory shock, and postresuscitation acute renal failure.[71] Especially when those factors are present, prolonged observation off sedation is indicated.

Conclusions

A careful clinical neurologic examination remains the foundation for prognostication of the comatose patient after CA.[64] In the pre-TTM era, a bilateral absence of pupillary and corneal reflexes or an absent or extensor motor response at 72 hours or later after ROSC, or a status myoclonus within 24 hours after ROSC had been recommended as robust predictors of poor neurologic outcome with 0% FPR and narrow confidence intervals. Recent reviews of evidence confirmed the high predictive value of absent pupillary and corneal reflexes in both TTM-treated and non-TTM-treated patients, whereas the specificity of motor response for the prediction of poor outcome was much lower than initially believed. However, an absent or extensor motor response at 72 hours after ROSC has a high sensitivity for poor neurologic outcome; it can therefore be used to identify the patients with the most severe neurologic injury needing prognostication. As far as an early status myoclonus is concerned, recent evidence confirmed its high specificity both in TTM-treated and in non-TTM treated patients. However, caution is needed when using this predictor, because of inconsistencies in its definition and possible confusion with other more benign forms of postanoxic myoclonus.

Clinical examination is prone to interference from body temperature and from residual effects of sedatives and/or neuromuscular blocking drugs. These confounders should be carefully ruled out before starting the prognostication process. Moreover, several other predictors that are not or are less sensitive to interference from drugs or body temperature

can usefully complement clinical examination. These include a bilaterally absent N20 SSEP wave, an unreactive burst suppression or status epilepticus on EEG, high and increasing blood levels of NSE, and a signs of diffuse anoxic-ischemic injury on imaging studies. Because even the most robust predictors do not singularly predict poor outcome with absolute certainty, a multimodal approach is always preferable, depending on locally available tests and expertise.

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