Prognostication in comatose survivors of cardiac arrest: An advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine

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Abstract *Objectives:* To review and update the evidence on predictors of poor outcome (death, persistent vegetative state or severe neurological disability) in adult comatose survivors of cardiac arrest, either treated or not treated with controlled temperature, to identify knowledge gaps and to suggest a reliable prognostication strategy. *Methods:* GRADE-based systematic review followed by expert consensus achieved using Web-based Delphi methodology, conference calls and face-to-face meetings. Predictors based on clinical examination, electrophysiology, biomarkers and imaging were included. *Results and conclusions:* Evidence from a total of 73 studies was reviewed. The quality of evidence was low or very low for almost all studies. In patients who are comatose with absent or extensor motor response at $\geq$72 h from arrest, either treated or not treated with controlled temperature, bilateral absence of either pupillary and corneal reflexes or N20 wave of short-latency somatosensory evoked potentials were identified as the most robust predictors. Early status myoclonus, elevated values of neuron-specific enolase at 48–72 h from arrest, unreactive malignant EEG patterns after rewarming, and presence of diffuse signs of postanoxic injury on either computed tomography or magnetic resonance imaging were identified as useful but less robust predictors. Prolonged observation and repeated assessments should be considered when results of initial assessment are inconclusive. Although no specific combination of predictors is sufficiently supported by available evidence, a multimodal prognostication approach is recommended in all patients.

Keywords Heart arrest · Coma · Prognosis · Clinical examination · Somatosensory evoked potentials · Neuron specific enolase · CT scan · Magnetic resonance

1 Introduction

Severe neurological impairment caused by hypoxic-ischaemic brain injury is common after resuscitation from cardiac arrest [1]. Early identification of patients with no chance of a good neurological recovery will help to avoid inappropriate treatment and provide information for relatives.

In 2006 [2], a landmark review from the Quality Standards Subcommittee of the American Academy of Neurology (AAN) recommended a sequential algorithm to predict poor neurological outcome in comatose survivors within the first 72 h after cardiopulmonary resuscitation (CPR). According to that algorithm, the presence of myoclonus status epilepticus on day 1, the bilateral absence of the N20 wave of somatosensory evoked potentials (SSEPs) or a blood concentration of neuron specific enolase (NSE) above 33 μg L^{-1} at days 1–3, and absent pupillary and corneal reflexes or a motor response no better than extension (M1–2) at day 3 accurately predicted poor outcome. However, the AAN recommendations need updating:

1. The AAN 2006 review was based on studies conducted before the advent of therapeutic hypothermia (TH) for post-resuscitation care. Both TH itself and sedatives or neuromuscular blocking drugs used to maintain it may potentially interfere with prognostication indices, especially clinical examination [3]. The predictive value of those indices therefore needs to be re-evaluated in TH-treated patients.
2. Studies conducted both before [4] and after [5, 6] the AAN 2006 review showed that the previously recommended thresholds for outcome prediction using biomarkers were inconsistent [7].
3. Evidence for some prognostic tools such as EEG [8] and imaging studies was limited at the time of the 2006 AAN review, and needs re-evaluation.
4. The AAN 2006 review and previous reviews 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) [9].

Given the limitations of the current literature and the need for up-to-date clinical guidance, members 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 Neurological Prognostication in comatose survivors of cardiac arrest. The aims of this statement are to:

1. Update and summarize the available evidence on this topic, including that on TH-treated patients;
2. Provide practical recommendations on the most reliable prognostication strategies, based on a more robust analysis of the evidence, in anticipation of the next ERC Guidelines on Resuscitation to be published in October 2015;
3. Identify knowledge gaps and suggest directions for future research.

2 Methods

2.1 Panel selection

The panel for this Advisory Statement included medical specialists experienced in the management of comatose resuscitated patients. All the panel members are authors of original studies on prognostication in post-resuscitation care or have previous experience in guideline development or systematic evidence review. Panel members completed a conflict of interest declaration, as recommended [10, 11].

2.2 Group process

Following an initial conference call and a face-to-face meeting, the panel members agreed on criteria for study inclusion, grading methods, and the process timeline. Subsequent consensus on the evidence and the recommendations was achieved using a Web-based Delphi method. The document was written using a Web-based collaborative process and collectively reviewed for content and wording. A final face-to-face meeting was held to finalize the statements.

2.3 Inclusion criteria and definitions

Given the paucity of evidence on neurological prognostication in children with coma after cardiac arrest, the evidence evaluation was restricted to adults. Inclusion criteria are described in detail elsewhere [12]. Briefly, all studies on adult ($\geq$16 years) patients who were comatose following resuscitation from cardiac arrest and were treated with TH were considered for inclusion. Patients defined as unconscious, unresponsive, or having a Glasgow Coma Scale score (GCS) [13] $\leq$8, were considered as comatose. Studies including non-comatose patients or patients in hypoxic coma from causes other than cardiac arrest (e.g., respiratory arrest, carbon monoxide intoxication, drowning, and hanging) were excluded, except when a subpopulation of cardiac arrest patients could be evaluated separately.

Studies were considered for inclusion regardless of both the cause of arrest and treatment with TH. Pooling of

data was stratified according to timing of prognostication and TH treatment. Poor neurological outcome was defined as a Cerebral Performance Category (CPC) [14] of 3–5 (severe neurological disability, persistent vegetative state or death) as opposed to CPC 1–2 (absent, mild or moderate neurological disability; see ESM Appendix 1 for a detailed CPC description). In some studies, a CPC 4–5 was defined as a poor outcome. When original data were not available to correct outcome as CPC 3–5, a CPC 4–5 was accepted as a surrogate poor outcome, assigning the study an indirectness score. When the outcome was expressed using a modified Rankin Score (mRS) [15], an equivalent CPC was calculated based on the equivalence mRS $\geq 4 =$ CPC ≥ 3 [16].

2.4 Data source

Results from three recent systematic reviews [7, 12, 17] on post-arrest prognostication were used as a data source. One of these [7] included 50 studies on 2,828 patients not treated with TH, the two other reviews [12, 17] included a total of 39 studies in 2,564 TH-treated patients. In order to identify further studies published during the grading and consensus process, the automatic alert system of PubMed was maintained active and the tables of contents of relevant journals were screened. This led to the inclusion of five additional studies [18–22].

2.5 Grading

Grading was made according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria [23–28]. The grading process for included studies is described in detail in the ESM Appendix 2.

2.5.1 Quality of evidence

According to GRADE, the quality of evidence (QOE) was graded as high, moderate, low or very low according to the presence of limitations, indirectness, inconsistency, and imprecision. Publication bias was not considered, given the difficulty of measuring it in prognostic studies [29].

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 to decide to WLST.

Imprecision was graded as serious when the upper limit of the 95 % confidence intervals (CIs) of the estimate of the false positive rate (FPR) was greater than 5 %, and very serious when this value was more than 10 %. Confidence intervals were calculated using the F distribution method, according to Blyth [30].

This advisory statement covers the four main categories of prognostic tests: clinical examination, electrophysiology, biomarkers and imaging. The relevant Evidence Profile tables are included in the ESM Appendices 3a–d.

2.6 Recommendations

Recommendations in this document are stated as either strong ('we recommend') or weak ('we suggest') [24, 25]. The strength of the recommendations was based on the following factors [25]: (1) the balance between true and false predictions given by that test, i.e. the test performance as estimated by its sensitivity and specificity; (2) the confidence in the magnitude of the estimates (i.e., the quality of evidence); and (3) the resource use, i.e. the cost of the strategy under evaluation.

3 Clinical examination

3.1 Evidence (ESM Table 1)

3.1.1 Ocular reflexes

Bilateral absence of pupillary light reflex immediately after recovery of spontaneous circulation (ROSC) [31–33] has a very limited value in predicting poor outcome [FPR is 8 (1–25) %]. Conversely, at 72 h from ROSC [3, 18, 33–40], a bilaterally absent pupillary light reflex predicts poor outcome with 0 % FPR, both in TH-treated and in non-TH-treated patients (95 % CIs 0–2 and 0–8, respectively); however, its sensitivity is low (24 and 18 % respectively).

A bilaterally absent corneal reflex is slightly less specific than the pupillary reflex for prediction of poor outcome. One reason for this could be the sensitivity of the corneal reflex to interference from residual effects of sedatives [3] or neuromuscular blocking drugs. At 72 h from ROSC, the FPR was 5 (0–25) % in one study [35] in non-TH-treated patients and 4 (1–7) % in 7 studies [3, 18, 36–40] in TH-treated patients; sensitivities were 29 and 34 % respectively.

3.1.2 Motor response to pain

In non-TH-treated patients [35, 41], an absent or extensor motor response to pain, corresponding to a motor score 1 or 2 of the Glasgow Coma Scale ($M \leq 2$) at 72 h 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 TH-treated patients [3, 18, 36–40, 42–44]. Like the corneal reflex, the motor response can be suppressed by the effects of sedatives or neuromuscular blocking drugs [3].

Only a few prognostication studies [3, 18, 21, 38, 42, 44] 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. No study evaluated the interobserver agreement in clinical examination. In coma due to multiple causes, this agreement is only moderate (kappa from 0.42 to 0.79) [45].

While predictors of poor outcome based on clinical examination are inexpensive and easy to use, they cannot be concealed from the treating team and therefore their results may potentially influence clinical management and cause a self-fulfilling prophecy.

3.2 Recommendations

We recommend:

- Using the bilateral absence of both pupillary and corneal reflexes at 72 h or more from ROSC to predict poor outcome in comatose survivors from cardiac arrest, either TH-treated or non-TH-treated.
- Prolonging observation of clinical signs beyond 72 h when interference from residual sedation or paralysis is suspected, so that the possibility of obtaining false positive results is minimised.

We do not suggest using an absent or extensor motor response to pain ($M \leq 2$) alone to predict poor outcome in those patients, given its high false positive rate. However, due to its high sensitivity, this sign may be used to identify the population with poor neurological status needing prognostication or to predict poor outcome in combination with other more robust predictors.

3.3 Knowledge gaps

- Prospective studies are needed to investigate the pharmacokinetics of sedative drugs and neuromuscular blocking drugs in post-cardiac arrest patients, especially those treated with controlled temperature.
- Clinical studies are needed to evaluate the reproducibility of clinical signs used to predict outcome in comatose post-arrest patients. In particular, clinical examination tends to underestimate the presence of pupillary reflex, which can be detected and quantified using pupillometry [46, 47].

4 Myoclonus and status myoclonus

4.1 Evidence (ESM Table 1)

Myoclonus is a clinical phenomenon consisting of sudden, brief, involuntary jerks caused by muscular contractions or inhibitions. A prolonged period of continuous and generalised myoclonic jerks is commonly described as status myoclonus. There is no definitive consensus on the duration or frequency of myoclonic jerks required to qualify as status myoclonus; however, in prognostication studies in comatose survivors of cardiac arrest, the minimum reported duration is 30 min. The names and definitions used for status myoclonus vary among those studies (see ESM Appendix 4). Terms like status myoclonus, myoclonic status, generalised status myoclonicus, and myoclonus (or myoclonic) status epilepticus have been used interchangeably. Although the term myoclonic status epilepticus may suggest an epileptiform nature for this phenomenon, in post-anoxic comatose patients clinical myoclonus is only inconsistently associated with epileptiform activity on EEG [48, 49].

In comatose survivors of cardiac arrest treated with TH [21, 42, 44, 48, 50, 51], the presence of myoclonic jerks (not status myoclonus) within 72 h from ROSC is not consistently associated with poor outcome [FPR 5 (3–8) %; sensitivity 33 %]. In one study [36], the presence of myoclonic jerks within 7 days from ROSC was compatible with neurological recovery [FPR 11 (3–26) %; sensitivity 54 %].

A status myoclonus starting within 48 h from ROSC was consistently associated with a poor outcome [FPR 0 (0–4) %; sensitivity 15 %] in prognostication studies made in non-TH-treated patients [35, 52, 53], and is also highly predictive [FPR 0.5 (0–3) %; sensitivity 16 %] in TH-treated patients [3, 48, 54]. However, several case reports of good neurological recovery despite an early-onset, prolonged and generalised myoclonus have been published. In some of these cases, [55–60] myoclonus persisted after awakening and evolved into a chronic action myoclonus (Lance–Adams syndrome). In others [61, 62], it disappeared with 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.

4.2 Recommendations

We suggest:

- Using the term status myoclonus [52] to indicate a continuous and generalized myoclonus persisting for ≥30 min in comatose survivors of cardiac arrest.
- Using the presence of a status myoclonus within 48 h from ROSC in combination with other predictors to predict poor outcome in comatose survivors of cardiac arrest, either TH-treated or non-TH-treated.
- Evaluating patients with post-arrest status myoclonus off sedation whenever possible; in those patients, EEG recording can be useful to identify EEG signs of awareness and reactivity [61] and to reveal a coexistent epileptiform activity.

4.3 Knowledge gaps

- A consensus-based, uniform nomenclature and definition for status myoclonus is needed.
- The distinctive pathophysiological and electrophysiological features of postanoxic status myoclonus, in comparison with more benign forms of myoclonus, like the Lance–Adams syndrome, need to be further investigated.

5 Bilateral absence of SSEP N20 wave

5.1 Evidence (ESM Table 2)

In non-TH-treated post-arrest comatose patients, bilateral absence of the N20 wave of short-latency somatosensory evoked potentials (SSEPs) predicts death or vegetative state (CPC 4–5) with 0 (0–5) % FPR as early as 24 h from ROSC [35, 63, 64], and it remains predictive during the following 48 h with a consistent sensitivity (45–46 %) [4, 35, 63, 65, 66]. Among a total of 287 patients with no N20 SSEP wave at ≤72 h from ROSC, there was only one false positive result [67] [positive predictive value 99.7 (98–100) %].

In TH-treated patients, a bilaterally absent N20 wave accurately predicts poor outcome both during TH [FPR 0 (0–2) %] and after rewarming (at 72 h from ROSC) [FPR 0.4 (0–2) %], even if two isolated cases of false positive prediction have been reported [68, 69]. In the largest observational study on SSEP in TH-treated patients [38], three patients with a bilaterally absent N20 during TH rapidly recovered consciousness after rewarming and ultimately had a good outcome. In a post hoc assessment, two experienced neurophysiologists reviewed blindly the original tracings and concluded that the SSEP recordings were undeterminable because of excessive noise. Correction of the results after this reassessment led to a FPR of 0 (0–3) %.

Interobserver agreement for SSEPs in anoxic-ischaemic coma is moderate to good but is influenced by noise [70, 71].

In most prognostication studies, absence of the N20 wave after rewarming has been used—alone or in combination—as a criterion for deciding on WLST, with a consequent risk of self-fulfilling prophecy (see ESM Appendix 3b). SSEP results are more likely to influence physicians' and families' WLST decisions than those of clinical examination or EEG [72].

5.2 Recommendations

We recommend:

- Using bilateral absence of N20 SSEP wave at ≥72 h from ROSC to predict poor outcome in comatose survivors from cardiac arrest treated with controlled temperature.

We suggest:

- Using SSEP at ≥24 h after ROSC to predict poor outcome in comatose survivors from cardiac arrest not treated with controlled temperature.

SSEP recording requires appropriate skills and experience, and utmost care should be taken to avoid electrical interference from muscle artefacts or from the ICU environment.

5.3 Knowledge gaps

- Most of prognostic accuracy studies on SSEPs in postanoxic coma were not blinded, which may have led to an overestimation of the SSEP prognostic accuracy due to a self-fulfilling prophecy. Blinded studies will be needed to assess the relevance of this bias.

6 Electroencephalogram (EEG)

6.1 Evidence (ESM Table 2)

6.1.1 Absence of EEG reactivity

In TH-treated patients, absence of EEG background reactivity during TH is almost invariably associated with poor outcome [FPR 2 (1–7) %; [21, 44, 50]] while, after rewarming at 48–72 h from ROSC, it predicts a poor outcome with 0 (0–3) % FPR [42, 44, 50]. However, in one study in posthypoxic myoclonus [48], three patients with no EEG reactivity after rewarming from TH had a good outcome. Among four prognostication studies on absent EEG reactivity after cardiac arrest included in this document, three [21, 42, 44] were made by the same group of investigators. Limitations of EEG reactivity include being operator-dependent and non-quantitative, and lacking standardization. Techniques for automated analysis of EEG background reactivity are under investigation [73].

6.1.2 Status epilepticus

In TH-treated patients, the presence of status epilepticus (SE), i.e., a prolonged epileptiform activity, during TH or immediately after rewarming [51, 54, 74] is almost invariably followed by poor outcome (FPR from 0 to 6 %). Among those patients, absence of EEG reactivity [51, 75] or a discontinuous EEG background [76] predicted no chance of neurological recovery. All studies on

SE included only a few patients. Definitions of SE were inconsistent among those studies (see ESM Appendix 5).

6.1.3 Low voltage EEG

According to recent guidelines [77], the voltage of background EEG is defined as low when most or all activity is <20 μV (measured from peak to trough) in longitudinal bipolar with standard 10–20 electrodes, while suppression is defined as all voltage being <10 μV.

In two studies [35, 67] in non-TH-treated patients, a low-voltage EEG (≤20–21 μV) at 1–3 days after ROSC predicted poor outcome with 0 [0–6] % FPR. In one of these studies [35], however, the presence of this EEG pattern was used as a criterion for WLST.

In two studies [76, 78] in TH-treated patients, a flat or low-voltage tracing on continuous EEG recorded during TH or immediately after rewarming was inconsistently associated to a poor outcome (FPR from 0 to 6 %). In two studies [79, 80], a bispectral index (BIS) value of 6 or less recorded during TH, corresponding to a flat or low-amplitude EEG, predicted poor outcome with 0 (0–6) % FPR, while higher BIS values were less specific [81]. However, in a subsequent study [82], a BIS ≤6 was not 100 % reliable (FPR 17 % [7–32]). There is limited evidence [76, 82] on the predictive value of low EEG voltage after rewarming from TH.

Amplitude of the EEG signal may depend on the effect of drugs, body temperature, and on a variety of technical conditions such as skin and scalp impedance, inter-electrode distances, size, type and placement of the exploring electrodes, and type of filters adopted, as well as patient-specific issues [83].

6.1.4 Burst-suppression

According to a recent definition [77], burst-suppression is defined as more than 50 % of the EEG record consisting of periods of EEG voltage <10μV, with alternating bursts. In comatose survivors of cardiac arrest, either TH-treated or non-TH-treated, burst-suppression is usually a transient finding. During the first 24–48 h after ROSC [67] in non-TH-treated patients or during TH [44, 78, 84], burst-suppression is common and it may be compatible with neurological recovery, while at ≥72 h from ROSC [35, 76, 85] a persisting burst-suppression pattern is less common, but is consistently associated with poor outcome. In one case [61], a good recovery was reported despite an EEG burst-suppression pattern recorded at 72 h from ROSC; in that case, EEG reactivity was maintained. Definitions of burst-suppression were inconsistent among prognostication studies (see ESM Appendix 6).

6.2 Recommendations

We suggest:

- Using EEG-based predictors such as absence of EEG reactivity to external stimuli, presence of burst-suppression or status epilepticus at ≥72 h after ROSC to predict poor outcome in comatose survivors from cardiac arrest.
- Using these predictors only in combination (i.e. presence of burst-suppression or status epilepticus *plus* an unreactive background) and combining them with other predictors, since these criteria lack standardisation and the relevant evidence is limited to a few studies performed by experienced electrophysiologists.
- Not using a low EEG voltage to predict outcome in comatose survivors of cardiac arrest, because of the limited evidence and the risk of interference from hypothermia, ongoing sedation and technical factors.

We recommend not using burst-suppression for prognostication during the first 24–36 h after ROSC or during TH in comatose survivors of cardiac arrest.

Apart from its prognostic significance, recording of EEG—either continuous or intermittent—in comatose survivors of cardiac arrest both during TH and after rewarming is helpful to assess the level of consciousness—which may be masked by prolonged sedation, neuromuscular dysfunction or myoclonus—and to detect and treat non-convulsive seizures [8], which may occur in about one-quarter of comatose survivors of cardiac arrest [54, 76, 86].

6.3 Knowledge gaps

- Larger prospective studies on the prevalence and the predictive value of EEG changes in comatose survivors of cardiac arrest are needed, especially in patients who have been rewarmed from controlled temperature.
- The definition of SE and the modalities for eliciting and evaluating EEG reactivity need standardisation. In future studies, definitions of burst suppression and low-voltage EEG should comply with recent recommendations [77].
- It is not clear whether postanoxic SE is only a marker of brain injury or whether it contributes directly to neurological injury, nor if anti-epileptic treatments may potentially improve its outcome.

7 Biomarkers

NSE and S-100B are protein biomarkers that are released following injury to neurons and glial cells, respectively.

Blood values of NSE or S-100B after cardiac arrest are likely to correlate with the extent of anoxic-ischaemic neurological injury from cardiac arrest and, therefore, with the severity of neurological outcome.

Advantages of biomarkers over both EEG and clinical examination include quantitative results and likely independence from the effects of sedatives. Their main limitation as prognosticators is that it is difficult to find a consistent threshold for identifying patients destined to a poor outcome with a high degree of certainty. In fact, serum concentrations of biomarkers are per se continuous variables, which limits their applicability for predicting a dichotomous outcome, especially when a threshold for 0 % FPR is required.

7.1 Evidence (ESM Table 3)

7.1.1 Neuron-specific enolase (NSE)

In non-TH-treated patients, the 2006 AAN review [2] identified an NSE threshold of 33 μg L^{-1} at days 1–3 from ROSC as an accurate predictor of poor outcome with 0 % FPR. However, in a study [4] included in that review, this threshold was 47.6 μg L^{-1} at 24 h, while, in a large cohort study [5] published after the AAN review, this threshold was 65.0 μg L^{-1} at 48 h and 80 μg L^{-1} at 72 h. In three other studies [3, 63, 87], values of NSE between 65 and 85 μg L^{-1} at 3–5 days were reported as compatible with recovery of consciousness.

In TH-treated patients, the threshold for 0 % FPR varied between 38.1 and 80.8 μg L^{-1} at 24 h [20, 74, 88–90], between 25 and 151.5 μg L^{-1} at 48 h [20, 22, 38, 74, 88–93], and between 27.3 and 78.9 μg L^{-1} at 72 h [6, 90, 91]. However, the distribution of NSE values in available studies [5, 6, 22, 38, 88, 91] indicates that NSE values above 60 μg L^{-1} at 48–72 h from ROSC are very rarely associated with good outcome. Limited evidence [20, 89, 94] suggests that the discriminative value of NSE levels at 48–72 h is higher than at 24 h.

7.1.2 S-100B

S-100B is less well documented than is NSE. As for NSE, inconsistencies were found in its thresholds for 0 % FPR. In non-TH-treated patients, these thresholds ranged from 0.19 to 5.2 μg L^{-1} at 24 h [4, 92, 95] and from 0.12 to 0.25 μg L^{-1} at 48 h [92, 96, 97]. Precision was very low in all studies.

In TH-treated patients, the thresholds for a 0 % FPR ranged from 0.18 to 1.15 μg L^{-1} at 24 h after ROSC [90, 92, 98], and from 0.30 to 2.15 μg L^{-1} at 48 h [82, 90]. Finally, in one study [90], the threshold for 0 % FPR at 72 h was 0.92 μg L^{-1}.

The main reasons for the observed variability in biomarker thresholds may include the use of heterogeneous measurement techniques [99, 100], the presence of extra-neuronal sources of biomarkers (haemolysis and neuroendocrine tumours for NSE [101], muscle and adipose tissue breakdown for S-100B [102]), and the incomplete knowledge of the kinetics of their blood concentrations in the first few days after ROSC. Some evidence [89, 90, 94] suggests that not only the biomarkers' absolute concentrations but also their trends over time may have predictive value.

7.2 Recommendations

We suggest:

- Using high serum values of NSE at 48–72 h from ROSC in combination with other predictors for prognosticating a poor neurological outcome in comatose survivors from cardiac arrest, either TH-treated or non-TH-treated. However, no threshold enabling prediction with zero FPR can be recommended.
- Using utmost care and preferably sampling at multiple time points when assessing NSE to avoid false positive results due to haemolysis.

7.3 Knowledge gaps

- There is a need for standardisation of the measuring techniques for NSE and S-100 in cardiac arrest patients.
- Little information is available on the kinetics of the blood concentrations of biomarkers in the first few days after cardiac arrest.

8 Imaging

8.1 Evidence (ESM Table 4)

8.1.1 Brain CT

Brain CT is often performed in resuscitated comatose patients, mainly to exclude further causes of coma, such as subarachnoid haemorrhage [103]. The main CT finding of global anoxic-ischaemic cerebral insult following cardiac arrest is cerebral oedema [104], which appears as a reduction in the depth of cerebral sulci (sulcal effacement) and an attenuation of the grey matter/white matter (GM/WM) interface, due to a decreased density of the GM. In one study [105], the presence of this pattern on brain CT performed immediately after resuscitation predicted poor outcome with 81 % sensitivity and 8 (0–38) % FPR. The attenuation of the GM/WM interface has been quantitatively measured as the ratio (GWR)

between the GM and the WM densities. The GWR threshold below which poor outcome was predicted with 0 % FPR ranged between 1.12 and 1.22 [20, 33, 106]. The methods for GWR calculation were inconsistent among studies.

8.1.2 MRI

Advantages of MRI over brain CT include a better spatial definition and a high sensitivity for identifying ischaemic brain injury; however, its use can be problematic in the most clinically unstable patients [107].

The earliest post-ischaemic MRI change is hyperintensity in cortical areas or basal ganglia on diffusion weighted imaging (DWI) sequences. In two small studies [108, 109], the presence of large multilobar changes on DWI or FLAIR MRI sequences performed within 5 days from ROSC was consistently associated with death or vegetative state while focal or small volume lesions were not [93]. In patients with poor outcome after resuscitation from cardiac arrest, MRI can reveal extensive changes when results of other predictors such as SSEP or ocular reflexes are normal [93, 107].

Apparent diffusion coefficient (ADC) is a quantitative measure of ischaemic DWI changes. ADC values between 700 and 800 $\times$ 10^{-6} mm^2/s are considered to be normal [107]. Several methods have been used to quantify the DWI changes following cardiac arrest in order to predict outcome. Measured parameters include whole-brain ADC [110], the proportion of brain volume with low ADC [111] and the lowest ADC value in specific brain areas, such as the cortical occipital area and the putamen [88, 112]. The ADC thresholds associated with 0 % FPR vary among studies. These methods depend partly on subjective human decision in identifying the region of interest to be studied and in the interpretation of results, although automated analysis has recently been proposed [19]. According to one study [109], the optimal time window for prognostication based on ADC is 3–5 days from ROSC in the cortical structures and 6–8 days in the subcortical structures. Both the timing and severity of MRI changes after arrest differ between cortical areas.

Advanced MRI techniques, such as fractional anisotropy [113] and axial diffusivity in diffusion-tensor (DT) imaging [114], have recently been tested in humans to evaluate the white matter disorganisation and the axonal damage following diffuse anoxic-ischemic brain injury, respectively. Limited evidence shows that these techniques may be useful to predict outcome in patients who are persistently comatose after cardiac arrest and that their accuracy is comparable or superior to that of ADC [113].

All studies on prognostication after cardiac arrest using imaging have a small sample size with a consequent low precision, and a very low quality of evidence. Most of those studies are retrospective, and brain CT or MRI had been made at discretion of the treating physician, which may have caused a selection bias and overestimated their performance.

8.2 Recommendations

We suggest:

- Using the presence of a marked reduction of the GM/WM ratio or sulcal effacement on brain CT within 24 h after ROSC, or the presence of extensive reduction in diffusion on brain MRI at 2–5 days after ROSC, to predict a poor outcome in patients who are comatose after resuscitation from cardiac arrest both TH-treated or non-TH-treated.
- Using brain CT and MRI for prognosticating poor outcome after cardiac arrest only in combination with other predictors.
- Using brain imaging studies for prognostication only in centres where specific experience is available, given the limited number of studied patients, the spatial and temporal variability of post-anoxic changes in both CT and MRI, and the lack of standardisation for quantitative measures of these changes.

8.3 Knowledge gaps

- Evidence on imaging studies in comatose survivors of cardiac arrest is limited by small sample size and likely selection bias. Larger prospective studies are needed to confirm the results of the currently available studies.
- The severity of brain CT and MRI changes after global ischaemic injury will need a standardised description, e.g. using scoring systems similar to those used for traumatic brain injury [115].
- The prognostic value of quantitative vector indices derived from DT imaging, such as fractional anisotropy and axial diffusivity, need to be evaluated in future studies.

9 Self-fulfilling prophecy

Almost all prognostication studies reviewed in this document were assigned a low or very low quality of evidence (see Evidence Profile Tables on ESM Appendix 3a–d) the main reason being the risk of self-fulfilling prophecy. In fact, only 9/73 studies (12 %)—3 of which are from the same group—reported blinding of the treating team from the results of the predictor under investigation. In 2 of these studies [37, 38], results of the predictor (absence of N20 SSEP wave) recorded during

TH were not disclosed, but if patients remained comatose after rewarming, a second SSEP was performed and results were disclosed to the treating team, who used this information for treatment decisions. A treatment suspension policy was reported in 37/73 studies (51 %), although only 27 of those studies described the criteria for WLST. In 14/37 studies (38 %), the treatment suspension policy was based, at least in part, on one or more of the predictors under investigation (see ESM Table 5). Treatment limitations were applied at a minimum of 3 days or less from cardiac arrest in 12 studies and from 3 to 7 days in 9 studies, while in the remaining studies the minimal duration of life support measures was not reported.

Prevention of self-fulfilling prophecy bias would require blinding of test results to the treating team and providing sufficiently prolonged life support in patients who do not recover consciousness after resuscitation and rewarming. Both those tasks are difficult to accomplish. Some predictors, such as results of clinical examination, cannot be concealed to the treating team. Others, such as EEG, should not be concealed as they can reveal the presence of potentially treatable complications, like seizures. In some institutions, having a dedicated investigator not involved in patient management who will ensure blinding of collected data may not be feasible [80]. On the other hand, indefinite supportive care in potentially hopeless patients raises both ethical and financial concerns. However, even when the risk of self-fulfilling prophecy cannot be avoided in order to adequately account for this bias, it is desirable that future prognostic accuracy studies report in detail the criteria for withdrawal or limitation of life-sustaining treatment, as has been done in recent trials [116].

10 Practical approach: suggested prognostication strategy

Prognostication is indicated in patients with prolonged coma after resuscitation. A thorough clinical examination should be performed daily to detect signs of neurological recovery such as purposeful movements or to identify a clinical picture suggesting that brain death has occurred.

Following global post-anoxic injury, the brain will make a gradual recovery. Brainstem reflexes return first, then the motor response to pain and, finally, cortical activity and consciousness [117]. This process is completed within 72 h from arrest [53, 117]. Consequently, in the absence of residual sedation, 72 h after ROSC seems to be a suitable time for prognostication. However, in patients who have received sedatives $\leq$12 h before the 72 h neurological assessment, the reliability of clinical examination may be reduced [3]. Special care must be taken in TH-treated patients, since hypothermia prolongs the effects of both opiates [118] and neuromuscular blocking drugs [119, 120].

Before decisive assessment is performed, major confounders must be excluded [121, 122]; apart from sedation and neuromuscular blockade, these include hypothermia, severe hypotension, hypoglycaemia, and metabolic and respiratory derangements. Sedatives and neuromuscular blocking drugs should be suspended long enough to avoid interference with clinical examination. Short-acting drugs are preferred whenever possible. When residual sedation/paralysis is suspected, consider using antidotes to reverse the effects of these drugs. Be careful if using flumazenil to reverse the effects of benzodiazepines, since this drug may lower the seizure threshold.

We suggest using the prognostication strategy outlined in the algorithm on Fig. 1 in all comatose patients with an absent or extensor motor response to pain at $\geq$72 h from ROSC. Results of earlier prognostic tests should also be considered at this time point.

Evaluate the most robust predictors first. These predictors have the highest specificity and precision (FPR $<$5 % with 95 % CIs $<$5 % in patients treated with controlled temperature) and have been documented in $>$5 studies from at least three different groups of investigators. They include bilaterally absent pupillary reflexes at $\geq$72 h from ROSC and bilaterally absent SSEP N20 wave after rewarming (this last sign can be evaluated at $\geq$24 h from ROSC in patients who have not been treated with controlled temperature). Based on exert opinion, we suggest combining the absence of pupillary reflexes with those of corneal reflexes for predicting poor outcome at this time point. Both these predictors maintain their predictive value irrespective of hypothermia treatment [18].

If none of the signs above is present, a group of less accurate predictors can be evaluated, but the degree of confidence in their prediction will be lower. These have FPR $<$5 % but wider 95 % CIs than the previous predictors, and/or their definition/threshold is inconsistent in prognostication studies. These predictors include the presence of early status myoclonus (within 48 h from ROSC), high values of serum NSE at 48–72 h after ROSC, an unreactive malignant EEG pattern (burst-suppression, status epilepticus) after rewarming, the presence of a marked reduction of the GM/WM ratio or sulcal effacement on brain CT within 24 h after ROSC or the presence of diffuse ischemic changes on brain MRI at 2–5 days after ROSC. Based on expert opinion, we suggest waiting at least 24 h after the first prognostication assessment and confirming unconsciousness with M1–2 before using this second set of predictors. We also suggest combining at least two of these predictors for prognostication.

No specific NSE threshold for prediction of poor outcome with 0 % FPR can be recommended at present, although, in all the studies we analysed, NSE values

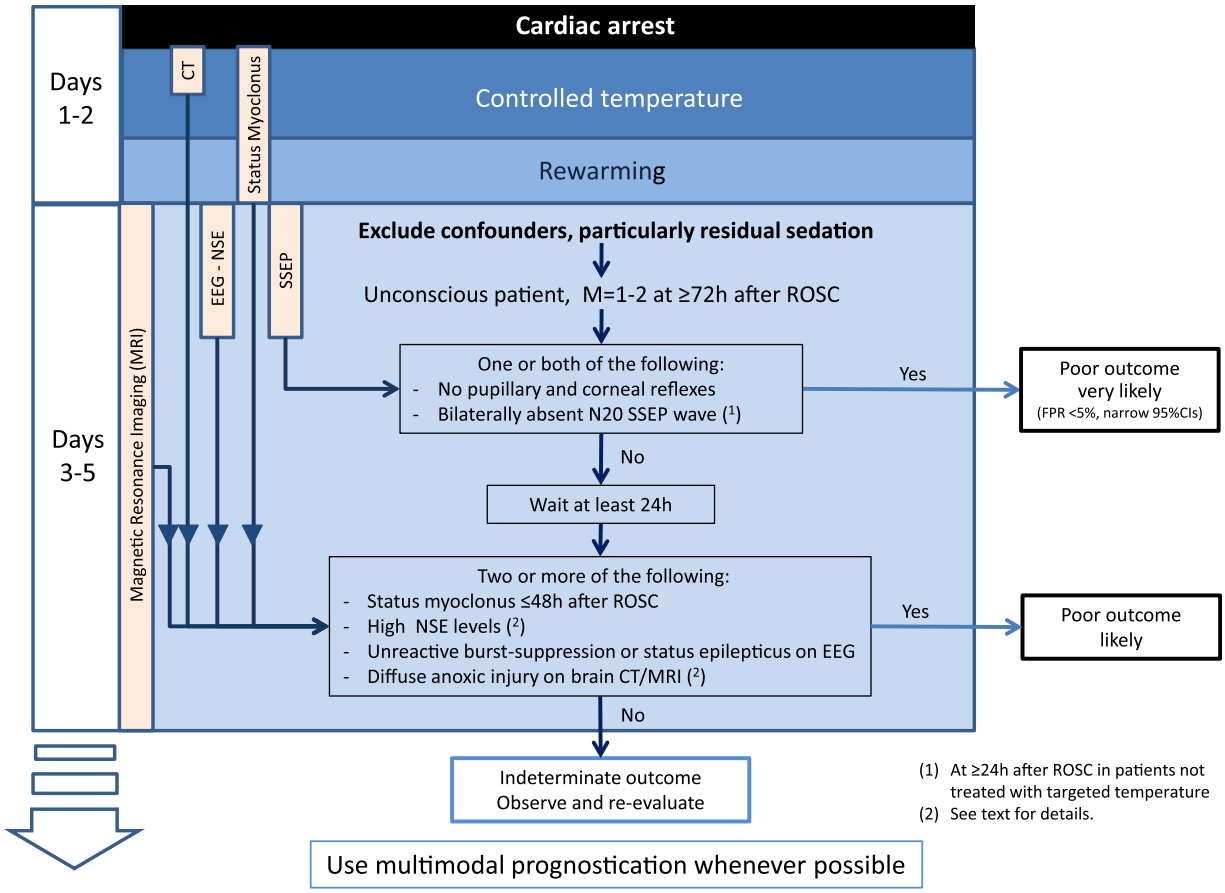

Fig. 1 Suggested prognostication algorithm. The algorithm is entered ≥72 h after ROSC if, after the exclusion of confounders (particularly residual sedation), the patient remains unconscious with a Glasgow Motor Score of 1 or 2. The absence of pupillary and corneal reflexes, and/or bilaterally absent N20 SSEP wave, indicates a poor outcome is very likely. If neither of the features is present, wait at least 24 h before reassessing. At this stage, two or more of the following indicate that a poor outcome is likely: status myoclonus ≤48 h; high neuron-specific enolase values; unreactive EEG with burst suppression or status epilepticus; diffuse anoxic injury on brain CT and/or MRI. If none of these criteria are met consider continue to observe and re-evaluate

greater than 60 μg L^{-1} at 48–72 h were very rarely associated with a false positive prediction. Ideally, every laboratory hospital assessing NSE should create its own normal values and cut-off levels based on the test kit used. Care should be taken to avoid haemolysis when sampling NSE.

Although the most robust predictors showed no false positives in most studies, none of them singularly predicts poor outcome with absolute certainty when the relevant comprehensive evidence is considered. Moreover, those predictors have often been used for WLST decisions, with the risk of a self-fulfilling prophecy. For this reason, we recommend that prognostication should be multimodal whenever possible, even in the presence of one of these predictors. Apart from increasing safety, limited evidence [20, 21, 42, 82] also suggests that multimodal prognostication increases sensitivity.

When prolonged sedation and/or paralysis is necessary, for example because of the need to treat severe respiratory insufficiency, we recommend postponing prognostication until a reliable clinical examination can be performed. Biomarkers, SSEP and imaging studies may play a role in this context, since they are insensitive to drug interference.

When dealing with an uncertain outcome, clinicians should consider prolonged observation. Absence of clinical improvement over time suggests a worse outcome. Although awakening has been described as late as 25 days after arrest [54, 61, 123], most survivors will recover consciousness within 1 week [93, 124–126]. In a recent observational study [126], 94 % of patients awoke

within 4.5 days from rewarming and the remaining 6 % awoke within 10 days.

11 Conclusions

A careful clinical neurological examination remains the foundation for prognostication of the comatose patient after cardiac arrest [127]. Adequate time should be given initially for the early awakeners to regain consciousness and to avoid interference from residual effects of sedatives and/or neuromuscular blocking drugs. This implies waiting until 72 h or more after ROSC before predicting poor outcome, although some indicators can be evaluated earlier. Whenever possible, prognosticate using multiple predictors, depending on locally available tests and expertise. If the results of prognostic tests produce conflicting results or prognostication is uncertain, we recommend further clinical observation and re-evaluation.

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Conflict of interest

- Claudio Sandroni is a member of the Editorial Board of the journal *Resuscitation* (unpaid); evidence reviewer of the Advanced Life Support Task Force, International Liaison Committee on Resuscitation (ILCOR) (unpaid). He is the first author of two systematic reviews on prognostication in comatose patients resuscitated from cardiac arrest.
- Alain Cariou is the Deputy of Trauma and Emergency Medicine (TEM) Section of the European Society of Intensive Care Medicine (ESICM) and Delegate from the ESICM in the General Assembly of the European Resuscitation Council (ERC). He received academic research grants from the French Ministry of Health for conducting clinical research in the field of cardiac arrest (all data controlled by the investigators).
- Fabio Cavallaro is a co-author of two systematic reviews on prognostication in comatose patients resuscitated from cardiac arrest.
- Tobias Cronberg is the Coordinator of recommendations on prognostication after cardiac arrest, Swedish Resuscitation Council. He received academic research grants from multiple non-profit organisations for the conduct of a cognitive sub-study and EEG sub-study of the Target Temperature Management trial (all data controlled by the investigators).
- Hans Friberg received lecture fees from Natus, Inc. (manufacturer of NervusMonitor, cont. EEG/aEEG) and from Bard Medical. He received grants from the EU Interreg. Programme IV A and academic research grants from multiple non-profit organisations for the Target Temperature Management trial (all data controlled by the investigators). He is the chair of the working party "Care after cardiac arrest", Swedish Resuscitation Council.
- Cornelia Hoedemaekers is co-author of a systematic review on diagnostic tools for prediction of poor outcome after cardiopulmonary resuscitation.
- Janneke Horn received a grant from the Dutch Heart Foundation (2007B039) for the PROPAC II study and from the Dutch Brain Foundation (14F06.48) for research on SSEP during hypothermia treatment after cardiac arrest (data controlled by the investigator and no restrictions on publication). She is the principal investigator of the PROPACII study and co-author of a systematic review on diagnostic tools for prediction of poor outcome after cardiopulmonary resuscitation.
- Jerry Nolan is the Editor-in-Chief of *Resuscitation* and Vice-Chair, European Resuscitation Council.
- Andrea Rossetti received a grant from the Swiss National Science Foundation (grant no. CR32I3_143780).
- Jasmeet Soar is the Editor of *Resuscitation* (Honorarium). He is member of the Executive Committee, Resuscitation Council (UK) (unpaid); Chair of the ERC ALS Working Group (unpaid); and Co-chair of the ALS ILCOR Task Force (unpaid).

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