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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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A B S T R A C T

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 ≥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.

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 mcg 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

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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 summarise 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 finalise 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 (≥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] ≤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 to 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 ≥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 2828 patients not treated with TH, the two other reviews[12,17] included a total of 39 studies in 2564 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 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 Appendixes 3a–d*.

2.5.2. Recommendations

Recommendations in this document are stated as either strong ('we recommend') or weak ('we suggest').[24,25] The strength of the