Recent Advances in Critical Care



Edited by
David Ashton-Cleary • William English

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Chapter 3

Prognostication following cardiac arrest

Matthew Thomas, Nick Kane

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) has a poor prognosis. In the UK approximately 10% of people who suffer an OHCA and have active resuscitation survive to be discharged from hospital in a good neurological condition [1]. However rates of survival across the world differ considerably, with some countries having nearly double the number of survivors seen in the UK [2]. Accurate prediction of neurological prognosis is vital to guide appropriate therapy and facilitate honest communication with the families of OHCA survivors.

Historically it has been difficult to identify which patients with return of spontaneous circulation (ROSC) following an OHCA are likely to survive, and there has been prognostic pessimism surrounding this diagnosis. In the past, decisions for withdrawal of life sustaining therapy (WLST) have been made as early as 24 hours after a cardiac arrest. More recently, the growing number of previously unexpected survivors has prompted reconsideration of this approach.

A number of modalities exist that may assist accurate prediction of neurological outcome following cardiac arrest. These include radiology, neurophysiology and serum biochemical tests. There have been numerous attempts to examine the performance and offer formal guidance on the relative merits of these tests. An important contribution was the American Academy of Neurology guidelines produced in 2006 [3]. These guidelines have recently been revised and updated by the European Resuscitation Council (ERC) and the European Society of Intensive Care Medicine (ESICM) [4].

BACKGROUND

Accurate prediction of outcome following cardiac arrest is extremely important. Most initial survivors of cardiac arrest will have a period of coma following ROSC. If active treatment is continued in every survivor of cardiac arrest, high numbers of patients will survive with severe neurological damage, some of whom may be ventilator dependent or in a persistent

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vegetative state. These outcomes are ones that most patients and societies wish to avoid, but not at the cost of reducing the proportion of survivors.

The aim of every predictive test is to have maximal sensitivity and specificity. Tests that have 100% sensitivity and specificity result in false positive and false negative rates of 0%. In the context of prognostication following cardiac arrest, false prediction of poor neurological outcome is particularly important, as tests that predict poor outcome may prompt WLST and ultimately, premature patient death [5]. The frequency with which a test falsely predicts poor outcome is known as the false prediction rate (FPR). An alternative way of describing the FPR is that it is the inverse of the positive predictive value. An understanding of this concept is required in order to compare the performance of the variety of different tests that have been described for prognostication following cardiac arrest. In this context, false positive rates of > 5% are generally considered unacceptable. The development of widely available tests that have an FPR as close to 0% as possible, with narrow confidence intervals, would represent a very significant advance in critical care medicine.

The various strategies that can be used to help prognostication following cardiac arrest range from simple clinical observation and examination to advanced and sometimes expensive biochemical, neurophysiology and imaging tests. The availability of these tests varies widely. Whilst staff in every hospital in the world should be able to complete a Glasgow Coma Scale (GCS) motor score on a daily basis, limited numbers of hospitals can offer functional MRI or somatosensory evoked potentials (SSEPs).

To date, clinical examination at 72 hours post-cardiac arrest has been widely used to guide prognostication following OHCA, with a GCS motor score of 2 or 1 being associated with a poor prognosis [6]. However, the studies in which this was validated were often performed before the advent of cooling [7] and there are concerns that whilst cooling may improve neurological recovery, it may also delay awakening. This delay in awakening could be as a result of both the cooling itself and cooling induced alterations in metabolism of sedative medications. We advise caution in relying on the GCS motor score alone for prognostication and the potential pitfalls of this approach will be discussed further.

CURRENT DEVELOPMENTS

Circumstances of the arrest

There are many aspects of the circumstances surrounding cardiac arrest that are associated with a better or worse outcome. These include the following; presence of bystander cardiopulmonary resuscitation (CPR), duration of CPR, age and co-morbidity of the patient, lactate on admission and presenting rhythm. Unfortunately when taken in isolation these factors are not sufficient to guide prognosis. They have, however, proven useful in defining a subset of patients within research studies who have features consistent with a good outcome. The outcomes of these patients can then be easily compared with each other. An example of this is the Utstein comparator group which describes a group of patients who have a suspected cardiac cause of arrest, receive bystander CPR and have an initial presenting rhythm of ventricular fibrillation (VF) or ventricular tachycardia (VT) [8]. Notably the survival for this group of patients is significantly greater than that of patients who do not meet these criteria.

Other scores based on premorbid factors such as the prognosis after resuscitation (PAR) score have been described [9]. The PAR score (**Table 3.1**) was developed from a

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Table 3.1 The prognosis after resuscitation score

Variable	Score
Metastatic malignancy	10
Nonmetastatic malignancy	3
Sepsis	5
Dependent functional status	5
Pneumonia	3
Creatinine > 130 mmol/L	3
Age > 70 years	2
Acute myocardial infarction	–2

A score > 5 suggests non-survival

retrospective cohort of in-hospital cardiac arrests. Whilst the score itself is simple to calculate, with a score > 5 suggesting non–survival, the score is not sufficiently accurate to be the sole factor to guide decisions on the appropriateness of critical care admission and continued active treatment. Additionally, all these scores have other inherent problems. The cut-off score used can be set very high giving a very low sensitivity of around 20% but a low FPR. But if the cut-off score is set at the optimal value on a receiver operator characteristic (ROC) curve, several false positives occur [10]. The famous case of the UK footballer, Fabrice Muamba, who made a full recovery after receiving 72 minutes of CPR could be taken to further illustrate this point; despite duration of resuscitation being associated with outcome there are several outliers [10,11].

Imaging

Computerised tomography

CT of the brain is often performed soon after ROSC in order to rule out a potential neurological cause of the cardiac arrest. In some studies, neurological causes of cardiac arrest have been reported to have occurred in up to 16% of cardiac arrest patients [12]. CT scanning may also be used to look for evidence of cerebral damage. Loss of sulcal effacement and lack of grey/white matter differentiation are the two well described features [13].

However, there are similar inherent problems in relying on these radiology prognostic tests as they too utilise a designated cut-off value to distinguish good from poor outcomes. Clearly, the cut-off value chosen will alter the performance of the test. An example of this is the assessment and scoring of changes in grey/white matter ratios in different areas of the brain following cardiac arrest [13]. If the grey/white matter ratio is set low, suggesting complete loss of differentiation, a false positive rate of 0% can be achieved but sensitivity is low (reported at <20%). Large trials with prospective validation of this technique have not been performed. As a result of these issues, CT in isolation should not be relied on as a predictor of poor outcome following OHCA [4,14].

Magnetic resonance imaging

MRI is not commonly performed in survivors of OHCA despite the development of some objective measures of cerebral ischaemia, such as the apparent diffusion coefficient (ADC). The ADC is a quantitative measure of water activity that has been used extensively

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as a marker of cell necrosis and brain damage in both stroke medicine and neonatology. Unfortunately, studies examining the utility of ADC in prognostication following cardiac arrest remain generally small-scale and retrospective in nature, so its current use also cannot be recommended [13,15].

Neurophysiology

The main neurophysiology tests used to aid prognostication are electroencephalography (EEG) and somatosensory–evoked potentials (SSEPs).

Electroencephalography

An EEG is a recording of the electrical activity of the brain, usually obtained from 21 small-disc electrodes placed on the scalp. When performed in a minimally sedated patient after cardiac arrest a continuous EEG pattern with normal voltage physiological oscillations (such as α rhythm and sleep spindles) portends a favourable neurological outcome [35], particularly when reactive to external stimulation [36]. Lack of EEG reactivity to external stimuli (i.e. calling the patient's name or painful sensory stimulation) is predictive of a poor neurological outcome. Additionally there are four principal 'malignant' EEG patterns associated with poor outcome of comatose patients following cardiac arrest. The reliability of abnormal EEG patterns in predicting poor neurological outcome was investigated in a study by Amorim et al., of 364 admissions due to cardiac arrest of whom 120 (29.9%) survived [34]. These abnormal ECG patterns are discussed in turn.

i. *Generalised periodic epileptiform discharges (GPEDs) or generalised periodic discharges (GPDs)* – stereotypic repetitive GPEDs/GPDs (**Figure 3.1**) are very commonly seen after cardiac arrest. Whilst they generally carry a poor prognosis, survivors with these EEG patterns have been reported. In Amorim's series 2 of the 10 patients with GPEDs had good outcomes (Cerebral Performance Category, CPC 1 or 2)[34].
ii. *Burst suppression (BS)* – BS is a relatively common pattern where paroxysms of spikes, sharpened theta and/or delta waves alternate with intervening periods of low voltage EEG (i.e. suppressed ≤ 10 μV) for more than 50% of the recording (**Figure 3.2**). In the context of OHCA survivors, BS with identical bursts is usually associated with a poor outcome [35,36]. However, BS cannot be reliably used as a prognostic tool as it can be due to accumulation of sedative agents (especially propofol) and survivors with BS have occasionally been seen. In Amorim's series 8 of the 22 patients with survived with good outcomes (CPC 1 or 2) [34]. This clearly highlights the potential pitfall of reliance on single EEG measures for predicting poor outcome.
iii. *Status epilepticus (SE)* – myoclonic SE (**Figure 3.3**), SE and non-convulsive seizures have been reported to occur in 10–30% of OHCA patients with ROSC, and they have been reported to be independently associated with poor outcome [16]. When present, these abnormalities should be aggressively treated with intravenous anticonvulsants, usually in combination. Persistent SE is rare and associated with a poor prognosis, particularly when seen 'early' after OHCA (i.e. first 48 hours post CA), but there have been some reported survivors with good functional outcome [17].
iv. *Low voltage EEG* – a low voltage (≤ 20 μV) or suppressed (≤ 10 μV) EEG, which in its extreme form indicates electro-cerebral inactivity (or an isoelectric EEG), is associated with an even worse outcome than BS. When present it is the most reliable EEG prognostic biomarker predictive of a poor neurological outcome post OHCA [36].

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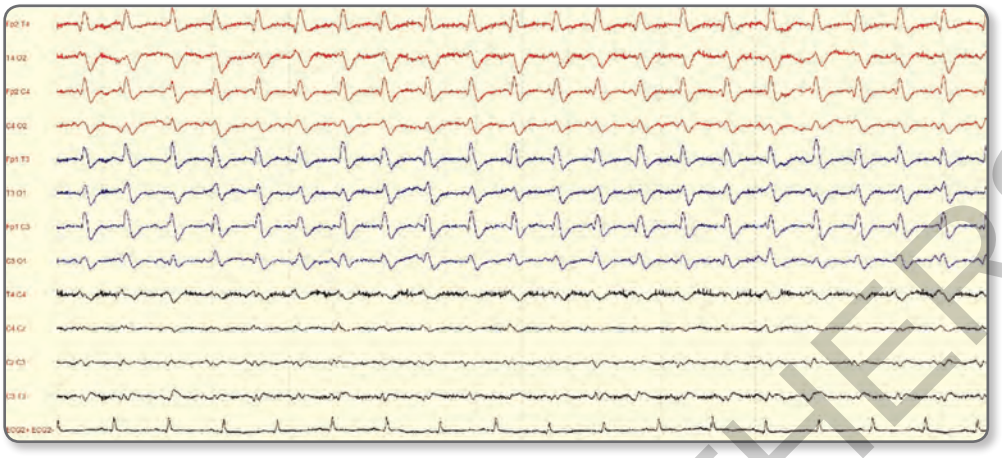

Figure 3.1 Generalised periodic epileptiform discharges (GPED/GPSs) after OHCA (the EEG pattern was attenuated by propofol but the patient died).

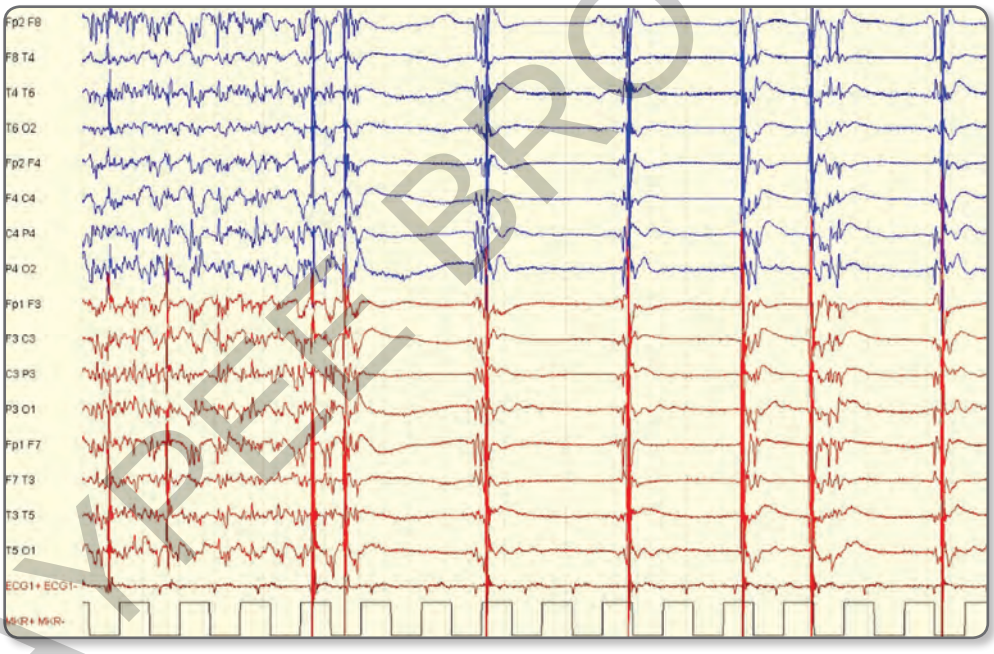

Figure 3.2 Burst suppression (BS) after OHCA (the EEG pattern was refractory to treatment and the patient died).

Somatosensory-evoked potentials

Somatosensory-evoked potentials are the waves or complexes generated by the cortex in response to an electrical stimulus delivered to a sensory nerve (see **Figure 3.4**). They have been widely used in the assessment of multiple sclerosis and are increasingly used in the assessment of hypoxic ischaemic encephalopathy after OHCA. The N20 response to

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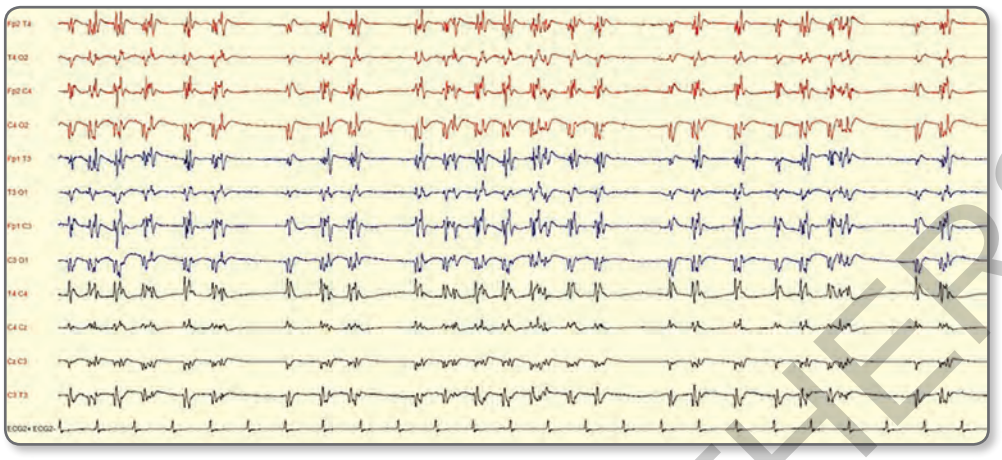

Figure 3.3 Myoclonic status epilepticus after OHCA (the EEG pattern was refractory to treatment and the patient died).

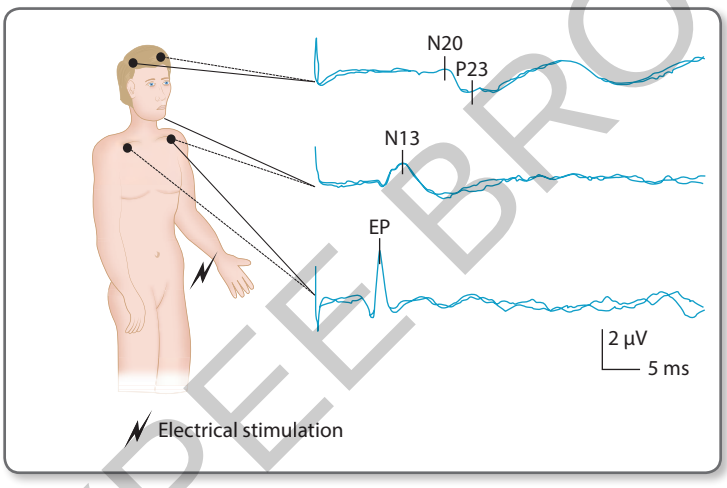

Figure 3.4 Median nerve SSEP. With permission from Walsh, Kane and Butler, 2005.

stimulation of the median nerve is the most frequently measured cortical waveform, and can be dichotomised into present or absent.

Meta-analysis of current literature found that the reliability of SSEPs is comparable in patients treated with or without hypothermia [18]. This test has been reported to have an FPR of 0.007% (95% CI 0.001-0047) in patients treated with therapeutic hypothermia [18]. Whilst in general it is a reliable test, it is prone to some inter-observer variability, with a kappa coefficient of 0.52 (range 0.2 to 0.65) [19]. False positive results to SSEP N20 have been reported in adults following hypoxic ischaemic encephalopathy [20], but there often appears to have been confounding factors, such as an early assessment (i.e. <72 hours post arrest).

Despite the fact that it appears that bilaterally absent SSEP N20 potentials are the single best predictor of poor neurological outcome following OHCA, several issues remain. Firstly the test is not widely available: whilst there are over 50 EEG departments

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within the UK, only about 5% of hospitals in the UK have routine access to SSEPs [21]. As a result, the performance and analysis of SSEPs will require extra investment; both in equipment and in trained clinicians who are able to perform the investigation and interpret the results. Secondly, in a number of studies, absence of SSEP N20 was used to determine whether WLST should occur. This has created concern that the test can become a self-fulfilling prophecy.

Blood tests

Two biochemical markers show promise for prognostication; neuron specific enolase (NSE) and S100 beta. Of the two, the role that the former may have in prognostication following cardiac arrest has been more closely evaluated.

Neuron specific enolase was first discovered in patients with neuroendocrine tumours, but it is now understood to be released when there is destruction of neuronal tissues. In hypoxic brain injury following cardiac arrest, the level of NSE has been demonstrated to correlate with the degree of brain injury [22].

Unlike SSEPs, which are either present or absent, NSE measurement provides a discrete value. In the 2006 review of prediction of outcome following cardiac arrest, a threshold of 33 ng/mL was used [3]. However, subsequent to this, a large cohort study has suggested that in order to minimise the FPR, a cut-off of 80 ng/mL is used [23]. In addition, differing values according to the different testing modalities have also been described [23].

Despite some persisting uncertainty as to the correct cut-off value to be used, NSE has the additional benefit that it is a peripheral blood test that can be performed at low cost. However, it is still not widely used in the UK although the reasons for this remain unclear, particularly seeing as it has the potential to make multimodal prognostication possible.

S100 beta is another neuronal protein whose serum values have been shown to increase with neurological injury. It has shown considerable promise as a marker of brain injury following cardiac arrest [24], but it is not widely used either as a research tool or in clinical practice. As such, and in contrast to NSE, the 2015 guidelines do not recommend its use [25].

Clinical examination

The principal advantage of using clinical examination to predict outcome is that it is reproducible and requires minimal equipment. It can therefore be reliably performed worldwide. The two principal aspects of clinical examination that are used to determine outcome are the pupillary response to light and the motor response to pain. Other components of the GCS and corneal reflexes have been investigated but are not sufficiently specific to be used.

An absent pupillary response to light is common immediately following ROSC and of virtually no predictive value at that stage, due to a combination of hypoxia and administration of adrenaline. At 72 hours, absent pupillary response to light is a very reliable predictive test. Studies show a 0% FPR for this feature but it is an uncommon clinical finding, only occurring in around 11% of patients, thus it has low sensitivity [4,26].

The motor response to pain is also a useful predictor. A GCS motor score of 1 or 2, (no response or an extensor response to painful stimulus) is probably the commonest test used to predict poor outcome worldwide. It is one of the most sensitive, with a sensitivity of > 70%, but when used alone it is far from the perfect, possessing a higher false positive rate (12–48%) than many other tests [4,26,27].

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Myoclonus

Myoclonus is a rhythmic, sustained contraction of muscles. Myoclonic status epilepticus represents a specific clinical entity which, when present, was suggested in the 2006 guidance to have a FPR of 0% for poor neurological outcome [3]. There have, however, been increasing case reports of a good outcome despite the presence of myoclonus, including cases of suspected myoclonic status epilepticus [28]. In such cases, the movement disorder either became a chronic active myoclonus (Lance-Adams syndrome) or actually disappeared altogether once consciousness was regained [29]. Current recommendations have decreased the importance attached to the presence of myoclonus. Importantly they also suggest that myoclonic status epilepticus should be an EEG rather than a clinical diagnosis.

TIMING OF PROGNOSTICATION

The initial management of patients after ROSC should involve stabilisation, identification and treatment of any precipitating cause and targeted temperature management. In general, prognostication should be delayed for a minimum of 72 hours post-OHCA. It is important to ensure that sedative medication is given an adequate time to clear; a minimum of 12 hours has been recommended [30]. As when assessing suitability to perform brain stem death tests, experienced clinicians with knowledge of the pharmacology of sedative infusions are best placed to determine the suitability of an individual patient for a prognostic assessment.

The GCS motor score of 1–2 is a simple but useful screening tool. In patients with a higher score, outcome will remain indeterminate, therefore further assessment for suitability for WLST is not advised at that time, as a good outcome is possible. In patients with a low GCS motor score, further tests are advisable. A low GCS motor score combined with absent pupillary reflexes or an absent SSEP N20 is associated with a universally poor prognosis and in these cases withdrawal of life sustaining therapy should be considered.

The guidelines by the ERC and ESICM contain a flow diagram that provides a useful approach to prognostication tests in general as well as useful guidance on the timing of prognostication [4,25]. However, these guidelines are of limited use in units where multimodal testing is unavailable. Patients in units that do not have access to multimodal assessment who maintain pupillary reflexes and are not in myoclonus status epilepticus should be regarded as having an indeterminate outcome. Evaluation every 24 hours is recommended in these cases.

As there currently is not a satisfactory set of simple, universally available tests for this common situation, there is continued reliance on the expertise and experience of front-line clinicians. These staff continue to make difficult decisions on prognostication and the appropriateness of on-going, active medical treatment. The use of a second opinion is helpful in these situations [31].

FUTURE DEVELOPMENTS

Accurate prognostication following OHCA has been identified as an area for further research by all resuscitation councils [32], and new developments are regularly being made in the field of prognostication following cardiac arrest. There are over a dozen trials registered on ClinicalTrials.gov related to prognostication. There will undoubtedly

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be further research into the promising areas of neurophysiology and blood testing, with SSEP and neuron specific enolase likely to become far more readily available over the next few years. In addition, as the resuscitation for out of hospital cardiac arrest patients is becoming increasingly invasive (involving the use of mechanical CPR and on occasions extracorporeal life support), improved ability to predict which cardiac arrest patients would benefit from these techniques is also required [33].

SUMMARY

Prognostication following cardiac arrest is difficult. It is clear that a structured approach offers the best solution. It is important that in patients treated with therapeutic hypothermia, prognostication should be delayed to allow adequate rewarming and to ensure that sedative medication has worn off.

The very best approach is a multimodal one, combining elements of the clinical examination, especially GCS motor score and pupillary response to light, with neurophysiological tests, ideally SSEPs. Of the serum markers, neuron specific enolase represents the most promising test. Because of the recognised difficulties with accurate prognostication, it is important to maintain good lines of communication with the relatives of survivors of OHCA, explaining that uncertainty still remains in some cases.

Key points for clinical practice

- In all but exceptional circumstances prognostication should be delayed for a minimum of 72 hours after the return of spontaneous circulation.
- Sedative medication must be allowed to fully wear off before prognostic tests are performed.
- As advised by the ERC, a multimodal assessment should be used for prognostication. This assessment should ideally incorporate both clinical examination and specialised tests.
- GCS motor score alone is not a good early predictor of outcome.
- Of the more specialised tests, the most promising are somatosensory-evoked potentials and serum neuron specific enolase, but neither is universally available.

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