Editorial

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Updated information on neuro-prognosticative tools to predict outcomes for patients with hypoxic-ischemic encephalopathy induced by cardiac arrest

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SUMMARY Hypoxic-ischemic encephalopathy (HIE), caused by cardiac arrest (CA) is a refractory condition in clinical settings. The clinician and family members have to make a hard decision: continue expensive life-sustaining therapy or withdraw the expensive intervention. The core problem lies in "whether this patient can still be awakened and achieve neurological recovery". This study briefly summarizes the use of mainstream neuro-prognosticative tools thus far with the latest available evidence. To gain a better understanding of the pathophysiological state of patients with HIE, comprehensive use of these tools and repeated assessments are recommended. The final decision should be made cautiously and comprehensively in light of the patient's medical history, pathophysiological state, results of neuro-prognosticative evaluations, and the clinician's clinical experience *per se*. Novel computerized technologies such as artificial intelligence, big data, and machine learning should be used to develop neuro-prognosticative tools for refractory CA-induced HIE.

Keywords hypoxic-ischemic encephalopathy (HIE), cardiac arrest (CA), neuro-prognosticative tools, awaken, neurological recovery

1. Introduction

Hypoxic-ischemic encephalopathy (HIE) in adults is a refractory condition that is commonly caused by cardiac arrest (CA). Survivors usually fall into a coma or unresponsive wakefulness syndrome. Approximately 40–66% of HIE survivors cannot be awakened (*1*) and have to undergo expensive intensive care and life-sustaining therapy. This situation might compel the clinician and family members to make a hard decision: continue such expensive treatment or withdraw it. The core issue lies in whether the patient can be awakened and recover even after prolonged treatment. Neuro-prognosticative evaluations play a vital role in making this decision, which can differentiate a state of prolonged coma from a state of irreversible cerebral damage.

2. Available neuro-prognosticative tools

By far, the available neuro-prognosticative tools can be classified into four types: *i*) clinical assessments, *ii*) electrophysiological tools, *iii*) biomarkers, and *iv*) neuroimaging tools (Figure 1).

Clinical assessments should include Glasgow Coma Scale motor response (GCS-M) and brainstem reflexes, and corneal and pupillary reflexes (*2*). Scores of GCS-M < 2 (*3,4*) and absence of bilateral brainstem reflexes (4) may indicate a poor prognosis. Conversely, Kamps *et al*. pointed out that the response to pain stimulation and corneal reflex are not a reliable tool for the early prediction of poor outcomes in patients undergoing hypothermia therapy (*3*). However, a later study verified that quantitative pupillometry is an excellent tool to predict HIE with a poor prognosis on day one after CA (*5*).

Electrophysiological tools include somatosensory evoked potentials (SSEP) and electroencephalography (EEG). In terms of SSEP, the most commonly used index is the N20 response in SSEP assessments. The N20 response is measured as the response from the primary somatosensory cortex after 20 ms of stimulation of the median nerve at the wrist (*2*). Early in 2003, Robinson *et al*. reported less than 1% changes in awakening in coma of HIE patients with absent somatosensory evoked potential response (*6*). Oddo and Friberg also pointed out that the absence of a bilateral

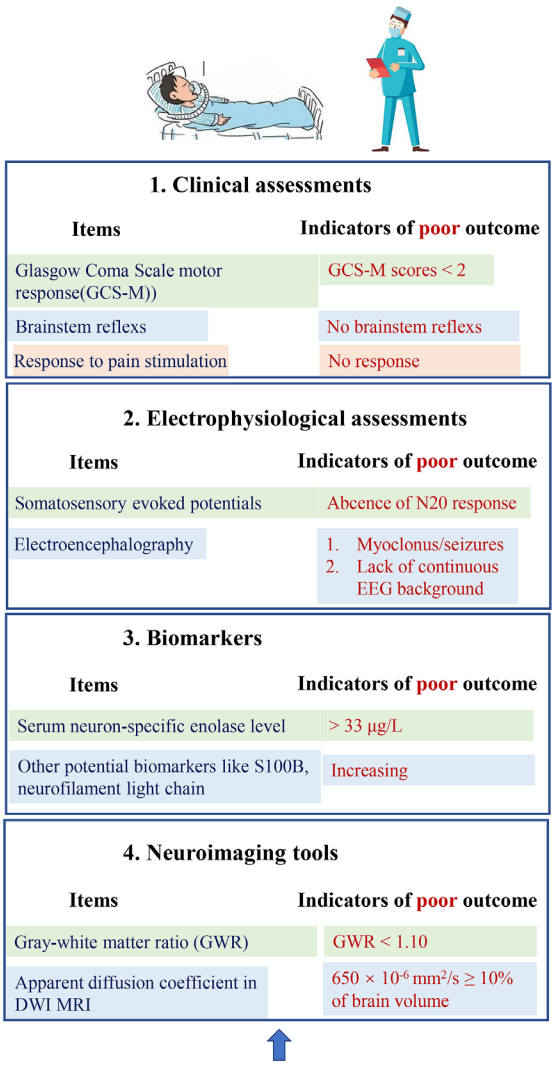

Figure 1. The recommended neuro-prognosticative tools for predicting the outcome HIE induced by CA

N20 response can predict 100% HIE with a poor prognosis (*2*). In addition, a later study found that the combined use of N60 and mismatch negativity achieved satisfactory sensitivity (82.7%) and specificity (82.0%) at predicting whether patients could be awakened (*7*). The limitations of the use of such SSEP indices lie in: *i*) they are easily affected by injuries to the cervical spinal cord and isolated lesions in the brain stem (*1*); *ii*) they have low sensitivity at predicting a good prognosis (*2*); and *iii*) interpretation of the evoked potentials may sometimes be subjective. Accordingly, EEG is, owing to its noninvasive and inexpensive nature, another commonly used electrophysiological tool to predict the clinical outcomes of HIE. In addition, EEG can be used in patients undergoing hypothermia therapy. However, there is still a lack of a "standard predictive model/pattern" of EEG in such patients with HIE. Generally, earlier recovery of continuous EEG background activity and later onset of myoclonus/seizures are indicators of a better outcome, whereas severe and frequent myoclonus/seizures indicate a worse outcome (*8*). Suppressed EEG, burst suppression, and generalized periodic discharges superimposed on a suppressed background have been observed in patients with severe HIE (*9*). A later study evaluated the changes in EEG patterns affected by pain stimulation. It found that awakening patients after pain stimuli had a higher γ, β, and α spectral power in the frontal and parietal lobes, a lower δ and θ spectral power in the bilateral temporal and occipital lobes, higher entropy in the frontal and parietal lobes, lower entropy in the temporal occipital lobes, and stronger γ and β connectivity in nearly the whole brain, but weaker θ and δ connectivity in some brain regions in comparison to unawakening patients (*1*). These patterns may be useful in predicting the prognosis for HIE.

The most important biomarker for predicting HIE is concentration of serum neuron-specific enolase (NSE). A serum level > 33 μg/L was identified as the cutoff value to indicate a poor outcome for HIE 24–72 h after CA (*10,11*). However, the thresholds of NSE levels to predict a poor outcome vary among different studies. Stammet *et al*. reported 50 μg/L 72 h after CA (*12*), and Streitberger *et al*. reported that 90 μg/L is better, considering specificity and sensitivity (*13*). Endisch *et al*. found that patients with serum NSE levels > 67 μg/L 48 h after CA had severe HIE (9). However, elevated serum NSE levels undoubtedly indicate a poorer outcome.

Computed tomography (CT) and magnetic resonance imaging (MRI) are commonly used neuroimaging tools to examine HIE. Considering potential confounding factors such as edema in the early stages, however, CT and MRI are more commonly used in patients with HIE > 7 days after CA (*2*). For better observation/quantification of brain injury following CA-induced HIE in the early stage, diffusion-weighted imaging (DWI) MRI is recommended to identify abnormalities in the brain structure and predict HIE prognosis. Hirsch *et al*. found that an apparent diffusion coefficient of 650 × 10^{-6} mm^2/s ≥ 10% of brain volume is a threshold indicating a poor prognosis in patients with HIE (*14*). However, the most widely accepted index is the gray-white matter ratio (GWR). A GWR < 1.10 in patients with HIE indicated a poor outcome because over 70% of patients with a GWR < 1.10 were found to have "near-complete cortical and hippocampal neuronal death" (*9*). Conversely, GWR > 1.3 might predict a good outcome even in patients with severe HIE (*9*).

In addition to the aforementioned tools, several non-mainstream tools have been mentioned in sporadic studies. For example, Preuß *et al*. evaluated the association between mean arterial blood pressure (MAP) and HIE severity after CA. They found that MAP was associated with CA survival but not with HIE severity. Patients with HIE who have fewer vasopressor requirements might have a higher chance of being awakened from a coma (*15*). Potential HIE-related biomarkers include S100B (*16*), neurofilament light

chains (*17,18*), and glial fibrillary acidic protein (*18*). However, the value of these promising predictive tools requires further investigation.

3. Insights and conclusion

The clinical outcomes of HIE caused by CA remain poor. Indeed, neurological recovery is rare in these patients (*11*) even they received prolonged intensive care and a spectrum of therapies, such as electrical stimulation, hyperbaric oxygen therapy, acupuncture, and electroacupuncture, have been attempted. Thus, selection of patients potentially having a good outcome as a result of further active treatment or selection of patients potentially having a hopeless outcome necessitating withdrawal of expensive interventions might be a knotty problem faced by all clinicians. Indeed, "withdrawal of expensive interventions" might lead to ethical/humanistic problems. Hence, the evaluation/prediction of HIE outcomes must be performed cautiously and rigorously. Several suggestions have been proposed for the future prediction of HIE outcomes.

i) Comprehensive evaluation using multimodal approaches. As described earlier, each evaluation tool has its particular advantages and disadvantages. To reach a robust conclusion, a battery of tools should be used to evaluate a given patient (Figure 1) to avoid possible bias and misjudgment. Reduplicative evaluations should be performed at different times. We should keep in mind that all the "assessment results" are for reference only, and the final decision should be made cautiously and comprehensively in light of the patient's medical history, pathophysiological state, results of the neuro-prognosticative evaluations, and the clinician's clinical experience *per se*.

ii) Owing to novel computerized technologies, such as artificial intelligence, big data, and machine learning, more precise and reliable evaluation is possible. Recently, Gramespacher *et al*. described a novel automated cerebral CT (CCT) analysis based on supervised machine learning to predict the clinical outcomes of patients with HIE caused by out-of-hospital CA (*19*). They found that machine learning-assisted gray matter analysis of CCT images might be a reliable and time-independent approach to predict outcomes along with conventional prognostic assessments (*19*). The development of such a novel assessment tool should be a future direction for predicting the clinical outcomes of HIE.

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