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Prognostication in Post-Cardiac Arrest Patients

Dilok Piyayotai and Sombat Muengtaweepongsa

Abstract

After resuscitation from cardiac arrest, a combination of the complex pathophysiologic process, known as post-cardiac arrest syndrome (PCAS), is attributed to multiple organ damage. Global ischemic cascade occurs in the brain due to generalized ischemia during cardiac arrest and the reperfusion process after the return of spontaneous circulation (ROSC), leading to hypoxic/ ischemic brain injury. Targeted temperature management (TTM) is a well-known neuroprotective therapy for ischemic/hypoxic brain injury. This global brain injury is a significant cause of death in PCAS. The implementation of TTM for PCAS leads to a reduction in mortality and better clinical outcomes among survivors. Prognostication is an essential part of post-resuscitation care. Before the TTM era, physicians relied on the algorithm for prognostication in comatose patients released by the American Academy of Neurology in 2006. However, TTM also announced more significant uncertainty during prognostication. During this TTM era, prognostication should not rely on just a solitary parameter. The trend of prognostication turns into a multimodal strategy integrating physical examination with supplementary methods, consisting of electrophysiology such as somatosensory evoked potential (SSEP) and electroencephalography (EEG), blood biomarkers, particularly serum neuron-specific enolase (NSE), and neuro-radiography including brain imaging with CT/ MRI, to enhance prognostic accuracy.

Keywords: prognosis, cardiac arrest, therapeutic hypothermia, neurological outcomes, hypoxic-ischemic encephalopathy, restore of spontaneous circulation, reperfusion

1. Introduction

Cardiac arrest is the leading cause of ischemic and hypoxic encephalopathy, as the brain is the organ that receives blood from the heart at 25% of all the blood that leaves the heart. Regardless of the underlying cause, patients with cardiac arrest often experience neurological complications, both short-term and long-term. Therefore, neurological monitoring is essential and essential in cardiac arrest patients for proper care and accurate prognosis [1].

The prognostication after cardiac arrest consists of (1) neurological examination, (2) neurophysiologic evaluation, (3) neuro-radiologic evaluation, (4) biochemical markers.

The algorithm for prognostication in post-cardiac arrest (PCAS) patients with restoring spontaneous circulation (ROSC) invented by the American Academy of Neurology in 2006 (as shown in **Figure 1**) has become a landmark guideline [2]. The

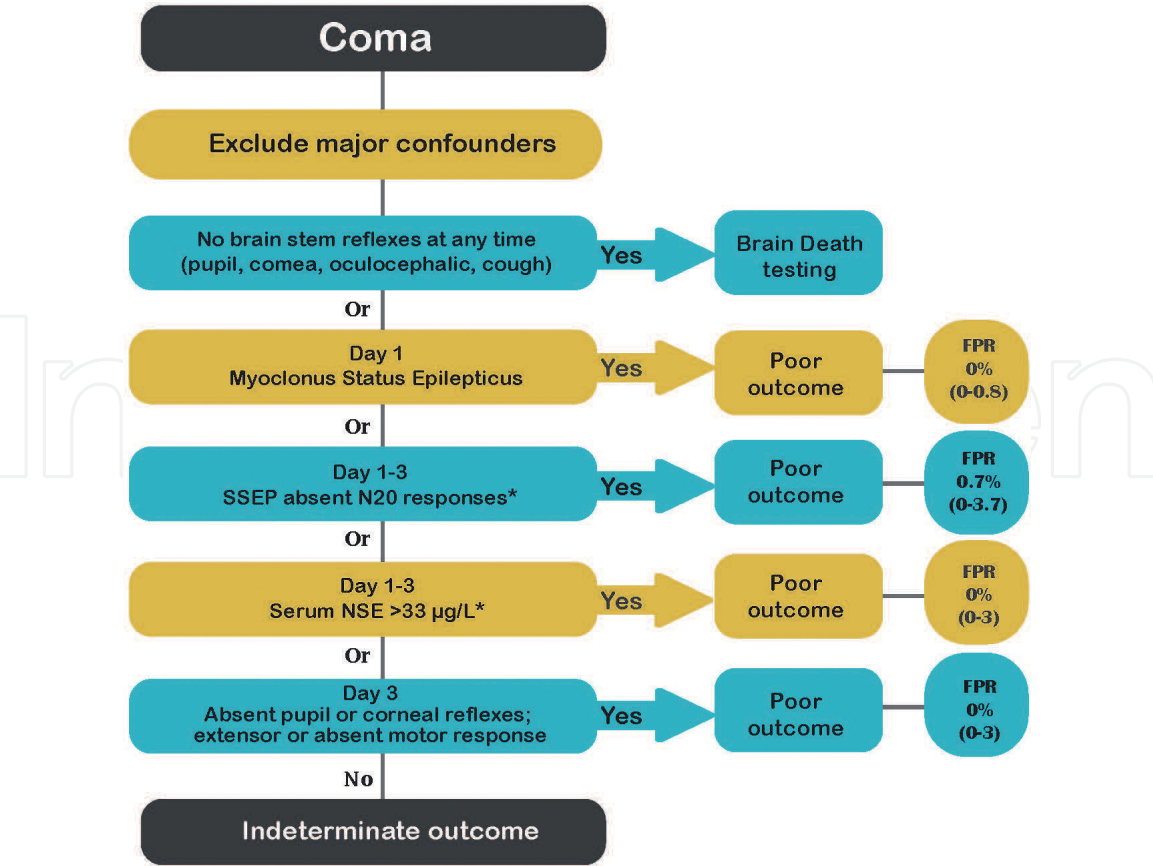


Figure 1.
The algorithm for prognostication in post-cardiac arrest (PCAS) patients with restoring spontaneous circulation (ROSC) was invented by the American Academy of Neurology in 2006.

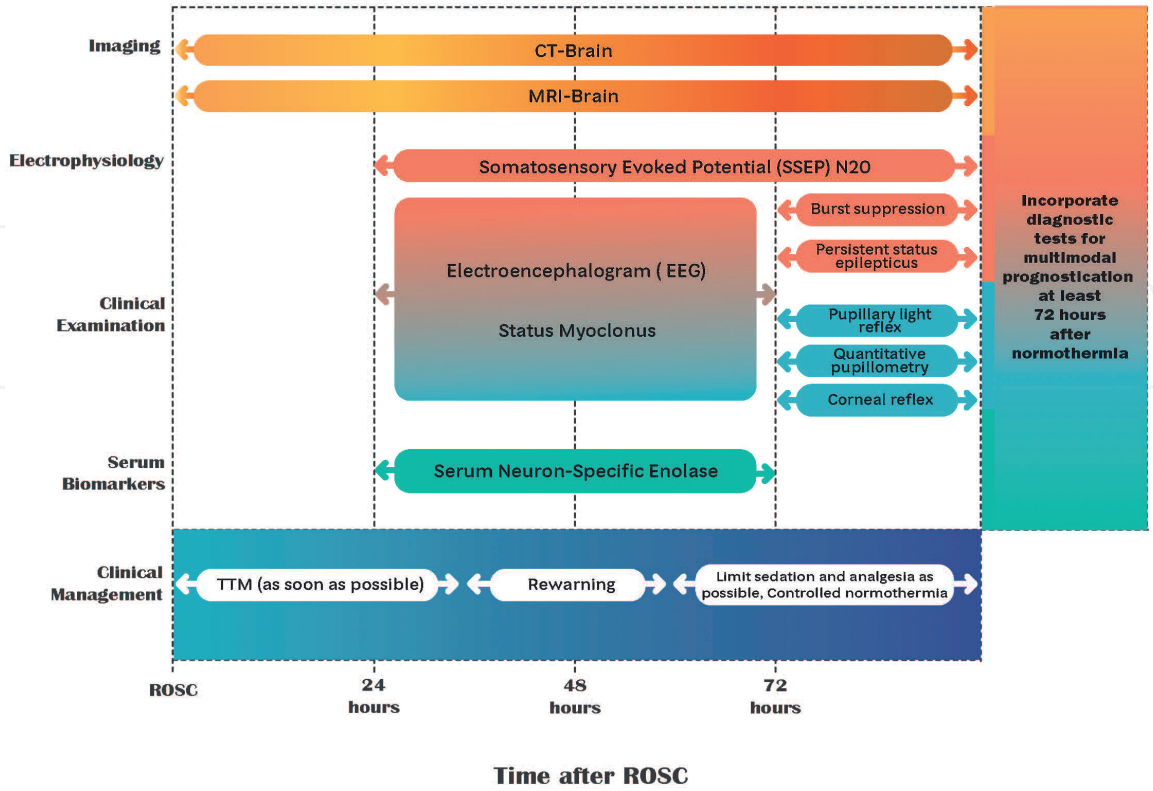


Figure 2.
The algorithm for prognostication in post-cardiac arrest (PCAS) patients with restoring spontaneous circulation (ROSC) was invented by the American Heart Association in 2020.

primary purpose of the algorithm is to determine the poor outcomes for withdrawal of life-sustaining treatment, although most of the PCAS patients fall into indeterminate outcomes. However, due to improved outcomes with targeted temperature management (TTM), clinical and surrogate makers in the algorithm need to be interpreted more carefully in patients treated with TTM [1, 3]. The recent resuscitation guidelines updated the algorithm using multimodal evaluation (as shown in **Figure 2**) to ensure better accuracy in determining the prognosis in post-cardiac arrest patients treated with TTM [4]. The predicting tool for prognostication in post-cardiac arrest patients is available [5]. In contrast, the prognostication in coma patients outside post-cardiac arrest is much less established [6]. In general, for patients who remain coma for more than four weeks, the chance to achieve a meaningful recovery is low.

2. Neurological examination

The neurological examination remains essential for prognostication in PCAS patients, which indicates the degree of hypoxic-ischemic brain injury. Therefore, physicians usually use the overall neurological signs to predict the outcomes after ROSC. The optimal time to predict the outcomes with neurological examination is three days after ROSC in PCAS patients not treated with TTM [2]. In contrast, the neurological examination should get delayed until five days after ROSC or three days after normothermia in PCAS patients treated with TTM [7].

2.1 Glasgow coma scale (GCS)

The initial purpose of the Glasgow Coma Scale (GCS) was to measure the level of consciousness in traumatic brain injuries; however, it is also helpful for predicting outcomes in PCAS [8]. Serial improvement of GCS in PCAS patients is usually associated with good outcomes [9]. Therefore, predicting tools for outcomes in PCAS usually included the GCS [10]. The GCS motor scores less than three at three days after ROSC in PCAS patients not treated with TTM strongly predict poor outcomes (false positive rate 0–3%) [2]. On the other hand, in PCAS patients treated with TTM, the GCS motor scores less than three at three days after normothermia or five days after ROSC may not always predict poor outcomes (false positive rate 19%) [11, 12]. The GCS motor scores more than three before initiation of TTM strongly predict good outcomes [13].

2.2 Pupillary light reflex (PLR)

Intact pupillary light reflex (PLR) indicates proper midbrain function. The absence of PLR three days after ROSC in PCAS patients not treated with TTM strongly predicts poor outcomes (false positive rate 0–3%) [2]. On the other hand, in PCAS patients treated with TTM, the absence of PLR at three days after normothermia or five days after ROSC remains predictive for poor outcomes with a 2.1% false-positive rate [11, 14]. Thus, early absent PLR after ROSC before initiation of TTM may not always predict poor outcomes [15]. Abnormal Neurological Pupil index and PLR quantitative measurements by pupillometry early after ROSC increase accuracy for the predictor of poor outcomes [16, 17].

2.3 Corneal reflex

The corneal reflex indicates the degree of intactness of the pathway from the ophthalmic branch of the fifth cranial nerve through the pons to the seventh cranial

nerve and facial muscles [18]. Gently touching the cornea with a thin wisp of sterile cotton will aggravate, leading to involuntary closure of the ipsilateral eye, as well as the closing of the other eye (consensual response). Therefore, the accuracy of the technique is crucial for declaring the corneal reflex present or absent [19]. The absence of bilateral corneal reflex three days after ROSC in PCAS patients not treated with TTM strongly predicts poor outcomes (false positive rate 0–3%) [2]. On the other hand, in PCAS patients treated with TTM, the absence of bilateral corneal reflex at three days after normothermia or five days after ROSC remains predictive for poor outcomes with a 2.2% false-positive rate [11].

2.4 Oculocephalic reflex (Doll's eye movement)

The intact reaction of oculocephalic reflexes (Doll's eye movement) consists of the deviation of both ocular globes towards the opposite direction of cephalic turning. A fully conscious patient does not have oculocephalic reflex due to voluntary suppression. Once an unconscious PCAS patient does not express these symptoms, a lesion must be located at either the afferent or efferent arm of the reflex loop. The afferent arm includes the labyrinthine complex, vestibular nerve (CN VIII), and neck proprioceptors. The efferent arm includes the oculomotor nerve (CN III), trochlear (CN IV), and abducens nerve (CN VI), and their responsible muscles. If the connective pathways between the afferent and efferent arms in the pons and medulla become interrupted in unconscious PCAS patients, the doll's eyes reflex will also be absent. Physicians usually use the lack of oculocephalic reflex together with the absence of other brainstem reflexes to indicate poor outcomes for withdrawal of life support in PCAS patients [20].

2.5 Vestibulo-ocular reflex

Irrigating one tympanic membrane with cold water or saline introduces ipsilateral deviation of both eyes with contralateral fast phase nystagmus lasting for one to two minutes. While switching to hot water produces the opposite reaction: contralateral deviation, with ipsilateral fast phase nystagmus. Bilateral irrigating with cold water or saline gives rise to a downward deviation with upward nystagmus. In contrast, bilateral irrigating with hot water or saline, the opposite reaction occurs. Patients with inflammations and traumatic lesions within the outer and middle ear are contra-indicated to get the vestibulo-ocular reflex test. The absence of any or abnormal responses indicates brainstem dysfunction [21]. The absence of vestibulo-ocular reflex at more than 24 h after ROSC in PCAS patients not treated with TTM usually predicts poor outcomes with a false positive rate of 14% [22].

2.6 Myoclonus status epilepticus (MSE)

Myoclonic movement disorders occurred after hypoxic-ischemic brain injury in PCAS patients entitles post-hypoxic myoclonus. The post-hypoxic myoclonus is divided into the malignant, the so-called Myoclonus Status Epilepticus (MSE), and the benign, the so-called Lance Adam Syndrome (LAS), subtypes. MSE indicates more severe hypoxic-ischemic brain damage than LAS. Clinical features of the post-anoxic myoclonus alone are difficult to discriminate between MSE and LAS. The electrophysiologic studies help enhance the accuracy of the post-anoxic myoclonus diagnosis [23]. The early presence of MSE within 24 h after ROSC in PCAS patients not treated with TTM predicts poor outcomes (false positive rate 0–8.8%) [2]. However, an increasing number of studies report good outcomes in PCAS patients with initial MSE treated with TTM [24, 25]. Therefore, the early presence of post-anoxic myoclonus should not discourage the use of TTM in PCAS patients [25].

3. Neurophysiologic studies

3.1 Somatosensory evoked potentials (SSEPs)

Somatosensory evoked potentials (SSEPs) consist of electronic waves that result from the stimulation of neural structures along the somatosensory tracks. The stimulation sites typically performed for prognostic SSEPs studies are the median nerve at the wrist. The measurement sites are the N20 wave at the contralateral parietal cortex, as shown in **Figure 3** [26]. The artifacts and low amplitude of the N20 wave are the limitations of SSEP interpretation [27]. The absence of N20 wave within three days after ROSC in PCAS patients not treated with TTM strongly predicts poor outcomes (false positive rate 0–3.7%) [2]. An increasing number of cases reported initial absence but the later presence of N20 wave and good outcomes in PCAS patients treated with TTM [28, 29]. Series of SSEPs with the absence of N20 wave until six days after ROSC provide better accuracy for poor outcomes in PCAS patients treated with TTM [30]. Visual Evoked Potentials may be as valuable as SSEPs for outcomes predictor in PCAS patients [31].

3.2 Electroencephalogram (EEG)

EEG has been used together with other prognostic tools for the outcomes predictor in PCAS patients for more than five decades. EEG patterns, which can be found in PCAS patients, include iso-electric, low voltage (less than 20 milli-volts), burst suppression, epileptiform, continuous activity with frequency less than eight Hertz, and continuous activity with frequency less than eight frequency more than or equal to eight Hertz [32]. The first three patterns are considered malignant EEG and predict poor outcomes in PCAS patients [33]. However, malignant EEG alone may not accurately predict poor outcomes (false positive rate 0.9 to 11) (2). Reactivity

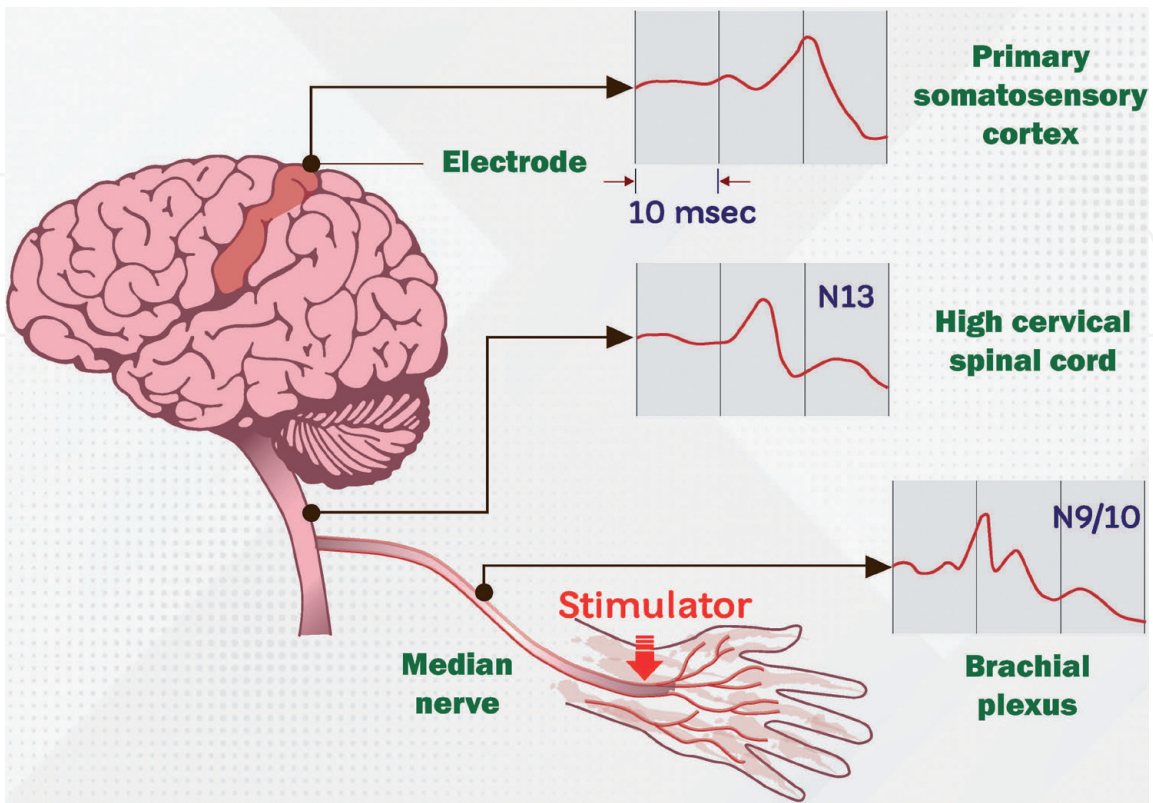


Figure 3.
The somatosensory evoked potential (SSEP).

is a significant change in background EEG activity following external stimuli [34]. EEG reactivity following clapping or sternal rubbing indicates good outcomes in PCAS patients [35].

4. Neuroimaging studies

4.1 Computer tomography (CT-brain)

CT-brain is convenient to obtain early in PCAS patients, and the results are not disturbed by any treatment during resuscitation. CT-brain is beneficial to help determine some neurological causes of cardiac arrests, such as an intracranial hemorrhage. However, CT-brain is not sensitive enough to detect the early phase of hypoxic-ischemic brain injury. The apparent abnormalities such as diffuse cerebral edema with effacement of the basal cisterns and sulci, loss of cortical gray-white differentiation, bilateral hypodensities involving the deep gray nuclei or the arterial border zones (as shown in **Figure 4**), take a few days or weeks to show up in CT-brain [36]. The measurement of gray-white matter ratio (GWR) by the Hounsfield units is helpful to detect the unvisualized early cerebral edema from hypoxic-ischemic brain injury in CT-brain. Many previous studies have shown that if the GWR is low in the CT-brain, it indicates an initial sign of severe hypoxic-ischemic brain injury and a PCAS patient's likelihood of death [37]. The area of the brain used for GWR calculation is varied among studies [38]. In general, the average GWR of less than 1.14 is highly predictive for poor outcomes with 100% specificity and 100% positive predictive value [39].

CT-brain without contrast in PCAS patients with profound brain swelling from severe hypoxic-ischemic insults may mimic subarachnoid hemorrhage [40], as shown in **Figure 5**. Pseudo-subarachnoid hemorrhage was postulated to define this phenomenon [41]. The transposition of edematous brain tissue into the subarachnoid space, transposition of cerebrospinal fluid, and distension of superficial pial veins should be the mechanisms of this appearance CT-brain [42]. Hyperdensity area suspected blood at Sylvian fissure is usually less than 35 Hounsfield unit in pseudo-subarachnoid hemorrhage, but more than 50 Hounsfield unit in actual subarachnoid hemorrhage [43–45].

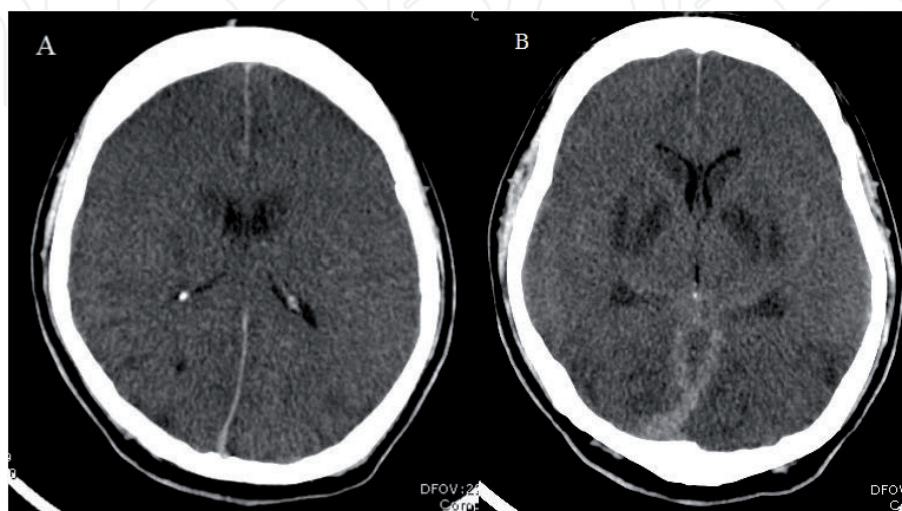


Figure 4. CT-Brain in a patient with severe hypoxic/ischemic brain injury: diffuse cerebral edema with effacement of the gyri and sulci (A), loss of cortical gray-white differentiation, bilateral hypodensities involving the deep gray nuclei (B).

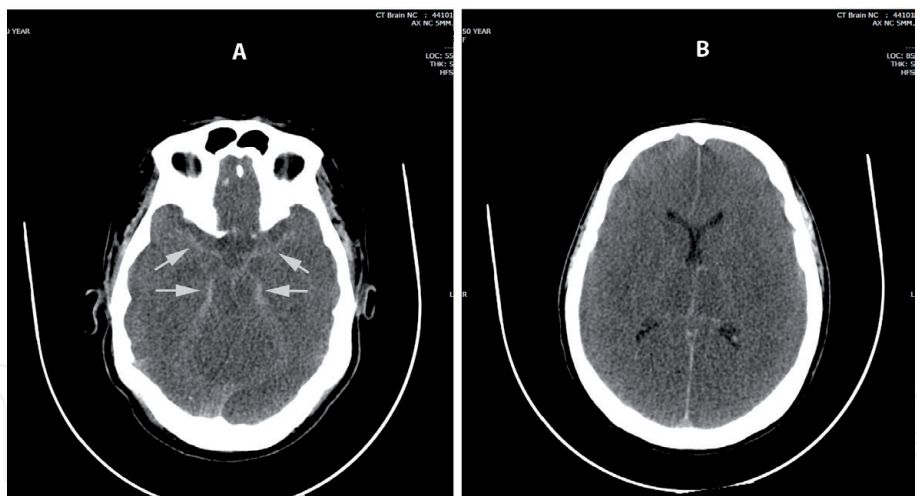


Figure 5.
Pseudo-subarachnoid hemorrhage (A, arrows) in CT-brain without contrast from PCAS patients with profound brain swelling (B) from severe hypoxic-ischemic insults.

4.2 Magnetic resonance imaging (MRI-brain)

MRI-brain is more sensitive than CT-brain for detection of early hypoxic-ischemic brain injury. However, MRI-brain is not as convenient as CT-brain to obtain early in PCAS patients [46]. Diffusion-Weighted Imaging (DWI) sequences of MRI-brain are the most sensitive for cytotoxic injury from hypoxic-ischemic brain insults [47]. Restricted water molecules within ischemic brain tissue cause DWI restriction leading to hypersignal intensity appearance (**Figure 6**) [48]. DWI restriction threshold of $650 \times 10^{-6} \text{ mm}^2/\text{s}$ in more than 9 percent of brain volume determines poor outcomes [49]. Diffusion Tensor Imaging (DTI) plays a significant role in white matter tractography with a similar principle of intercellular water diffusion in DWI [50]. Fractional anisotropy, a DTI parameter, is a quantitative measurement for white matter abnormality [51]. Quantitative whole-brain white matter fractional anisotropy measured by DTI between days seven and 28 after cardiac arrest can predict long-term neurological outcomes [52, 53]. The fluid-attenuated inversion recovery (FLAIR) sequences of MRI-brain can also detect cytotoxic injury from hypoxic-ischemic brain insults [54]. The appearance of hypoxic-ischemic brain injury detected by FLAIR adds up the specificity to DWI in predicting unfavorable outcomes [55].

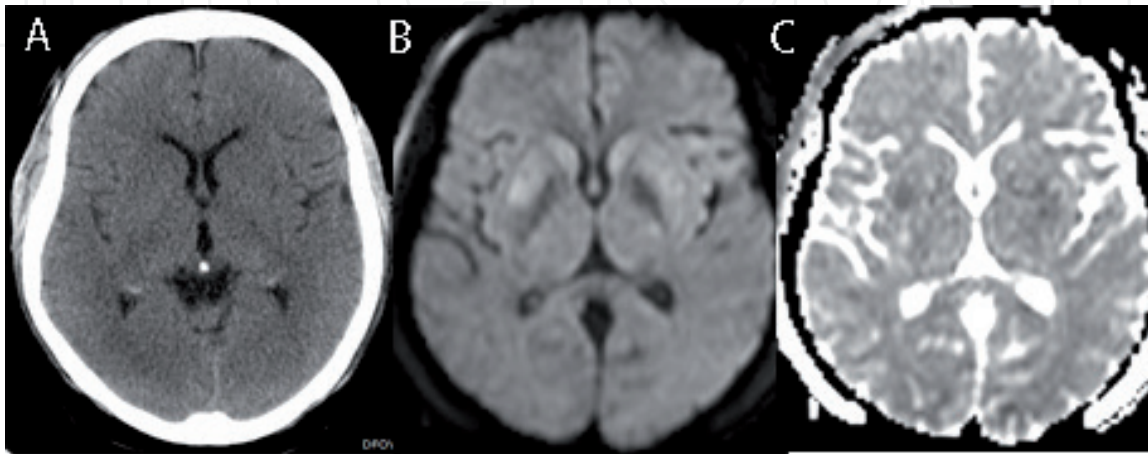


Figure 6.
Imaging of a PCAS patient on five days after ROSC: CT-brain (A) showed no hypodensity lesion, DWI (B) showed hyperintensity in deep nuclei corresponded with hypointensity in Apparent Diffusion Coefficient sequences (C).

5. Biochemical makers

Several previous studies have shown that many chemicals are secreted from the brain into the bloodstream and cerebrospinal fluid (CSF) following hypoxic-ischemic brain insults, including neuron-specific enolase (NSE), S100B protein, Tau, neurofilament light chain, and glial fibrillary acidic protein.

5.1 Neuron-specific enolase (NSE)

NSE is an isoenzyme of the glycolytic pathway found in neurons. Hypoxic-ischemic brain injuries anaerobically upregulate glycolysis, producing and releasing NSE from damaged neurons into the bloodstream [56]. Blood NSE levels were correlated with the severity of hypoxic-ischemic brain injury [57]. Serum NSE is the most useful biochemical marker for cardiac arrest prognostication [2, 4]. In PCAS patients not treated with TTM, serum NSE more than 33 µg/L between 24 and 72 h after ROSC predicts poor outcome (false positive rate 0–3%) [2]. The predictive value for poor outcome (false positive rate 0%) becomes more specific when using the cutoff level at more than 80 µg/L [57]. The cutoff level of serum NSE for poor outcome prediction became inconclusive, ranging from 33 to 120 µg/L in PCAS patients treated with TTM [4]. Serial serum NSE at 24, 48, and 72 h after ROSC was proposed to improve outcome prediction accuracy in PCAS patients treated with TTM [58, 59].

5.2 Other biochemical markers

Other biochemical markers rather than NSE have limited data to use for prognostication in PCAS patients. S100B, a glial-derived protein, more than 0.2 µg/L in serum within 72 h after ROSC may predict poor outcomes [60]. Serial serum S100B at 24, 48, and 72 h after ROSC did not add any predictive accuracy to serial serum NSE [61]. The accuracy of serial serum Tau, a neuron-derived protein, at 24, 48, and 72 h after ROSC is comparable with serial serum NSE for predicting poor outcomes [62]. However, the role of serum Tau fragments, Tau-A and Tau-C, in cardiac arrest prognostication remains uncertain [63]. Serial plasma neurofilament light chain at 24, 48, and 72 h after ROSC with the respective cutoff value of 127, 263, and 344 pg/ml is predictive for poor outcomes [64]. The specificity of serial plasma neurofilament light chain for poor outcome prediction is comparable with other standard methods used in the guidelines [65]. Glial fibrillary acidic protein, another glial-derived protein, is released into the bloodstream only in the presence of pathologic conditions and is more specific to acute brain damage than NSE or S100B [66]. Elevated serum glial fibrillary acidic protein more than 0.8 µg/L at 48 h after ROSC predicts poor outcomes [67].

6. Other tools

6.1 Intracerebral monitoring

Intracranial pressure (ICP) monitoring is rarely applied in PCAS patients. The reliable ICP monitoring techniques, including intraventricular catheter and intracerebral transducer, are solely invasive. Non-invasive techniques using transcranial Doppler, optic nerve sheath diameter ultrasound, and jugular venous pulse pressure are available but have low accuracy [68]. The benefit of ICP monitoring in treatment or prognostication in PCAS patients is uncertain [69]. Persistent elevated ICP above 20 mmHg is usually associated with poor outcomes in PCAS patients [70].

6.2 Autonomic nervous system assessment

Sinus bradycardia during TTM treatment reflects intact autonomic response and predicts good outcomes in PCAS patients [71, 72]. The difference in heart rate during the hypothermic maintenance and normothermic phase of TTM also reflects the intact autonomic response to temperature change and predicts good outcomes [73]. Heart rate variability (HRV) is a conventional method for autonomic function assessment [74]. HRV is feasible to apply in PCAS patients [75]. However, the role of HRV in cardiac arrest prognostication remains uncertain.

6.3 Miscellaneous

The role of aging in PCAS prognostication remains controversial [76]. Advanced age should not be the indication for withdrawal of care in PCAS patients. Also, the role of the pulse index contour cardiac output monitoring system in PCAS prognostication and treatment remains controversial [77].

7. Conclusions

It is essential to determine PCAS patients with poor outcomes for the decision of care withdrawal. There are several methods of prognostication after the cardiac arrest that should be combined to assist in proper prediction. A multimodal approach using Neurological examination, Neurophysiologic evaluation, Neuro-radiologic evaluation, and Biochemical markers is recommended to provide the most accuracy for poor outcome prediction. Most of the data used in prognostication studies derive from the out-of-hospital cardiac arrest subgroup. However, the data can be applied to other subgroups of cardiac arrest. Even though a multimodal approach has been used, the prognosis of most PCAS patients still falls into indeterminate outcomes.

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Conflict of interest

The authors declare no conflict of interest.

Acronyms and abbreviations

PCAS	post-cardiac arrest syndrome
ROSC	return of spontaneous circulation
OHCA	out-of-hospital cardiac arrest
IHCA	in-hospital cardiac arrest
TTM	targeted temperature management
AAN	American Academy of Neurology
SSEP	somatosensory evoked potential
EEG	electroencephalography

NSE	neuron specific enolase
TCD	transcranial Doppler
GCS	Glasgow Coma Scale
PLR	pupillary light reflex
MSE	myoclonus status epilepticus
LAS	Lance Adam Syndrome
GWR	gray-white matter ratio
DWI	diffusion-weighted imaging
DTI	diffusion tensor imaging
FLAIR	fluid-attenuated inversion recovery
CSF	cerebrospinal fluid
ICP	intracranial pressure.

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