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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.

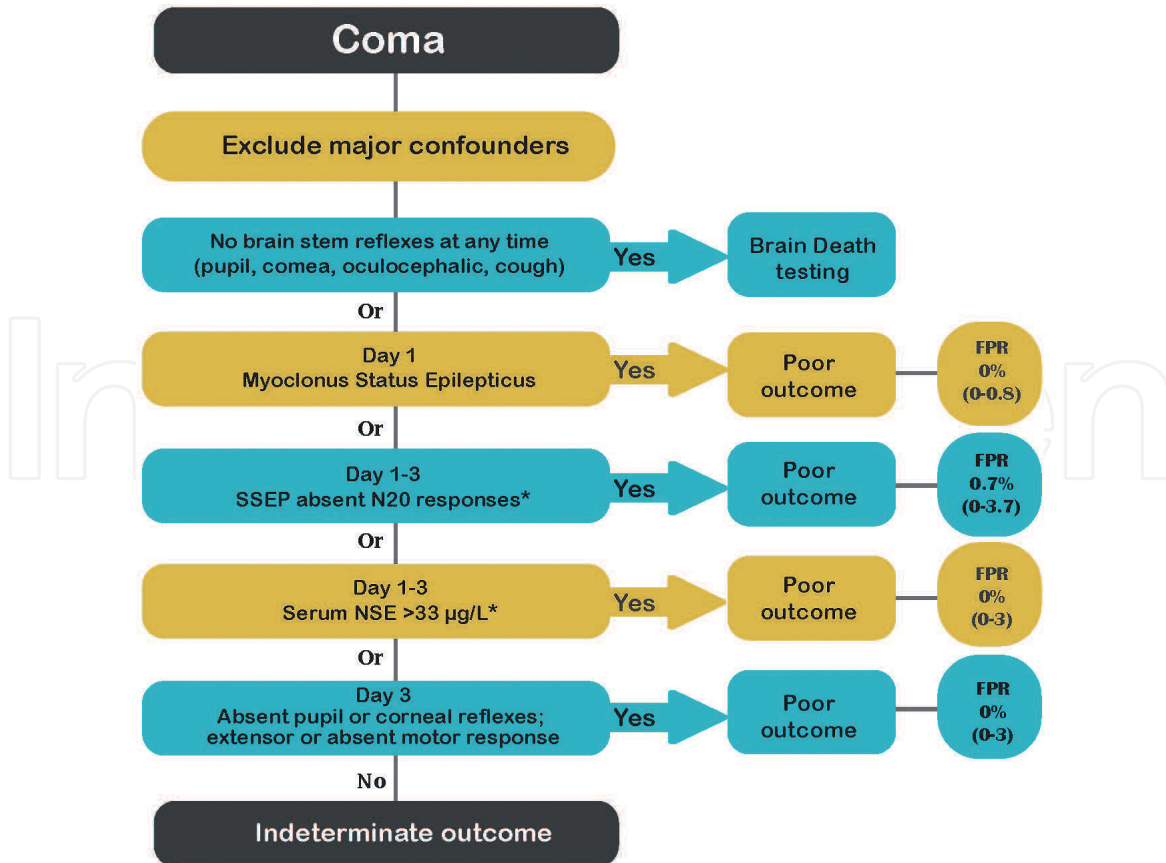
**Keywords:** prognosis, cardiac arrest, therapeutic hypothermia, neurological outcomes, hypoxic-ischemic encephalopathy, restore of spontaneous circulation, reperfusion

## 1. Introduction

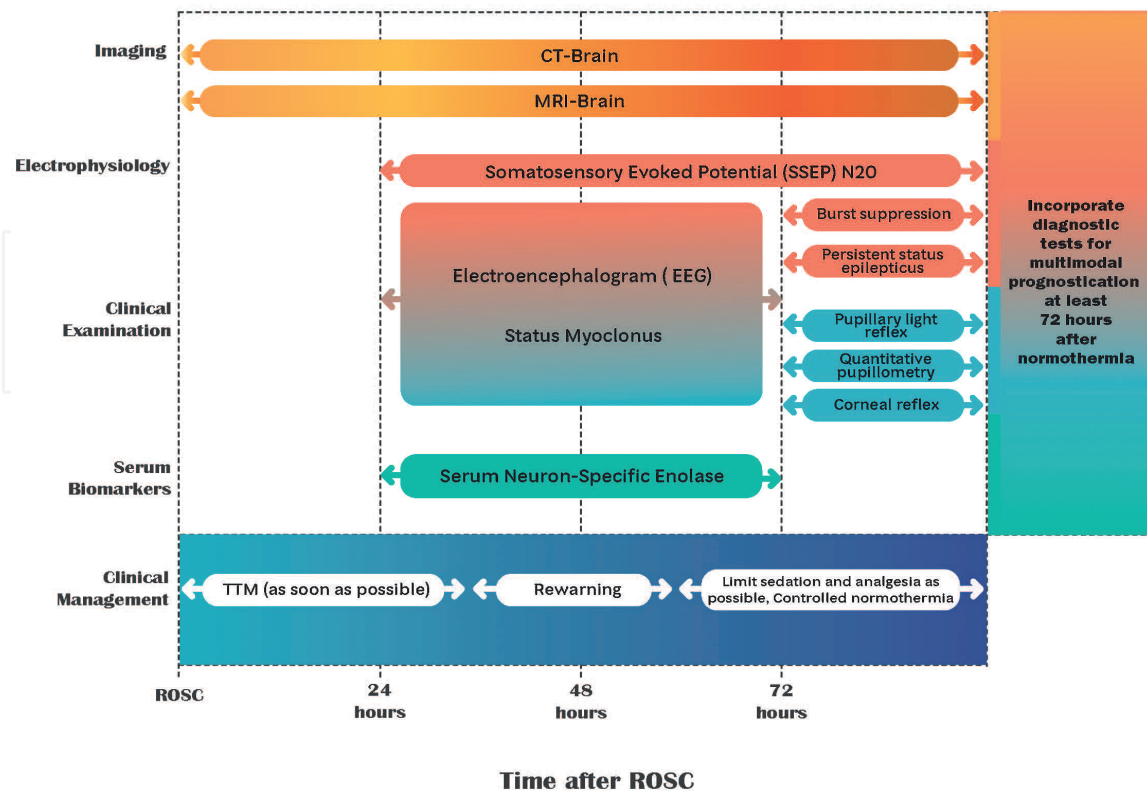
Cardiac arrest is the leading cause of ischemic and hypoxic encephalopathy, as the brain is the organ that receives blood from the heart at 25% of all the blood that leaves the heart. Regardless of the underlying cause, patients with cardiac arrest often experience neurological complications, both short-term 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].

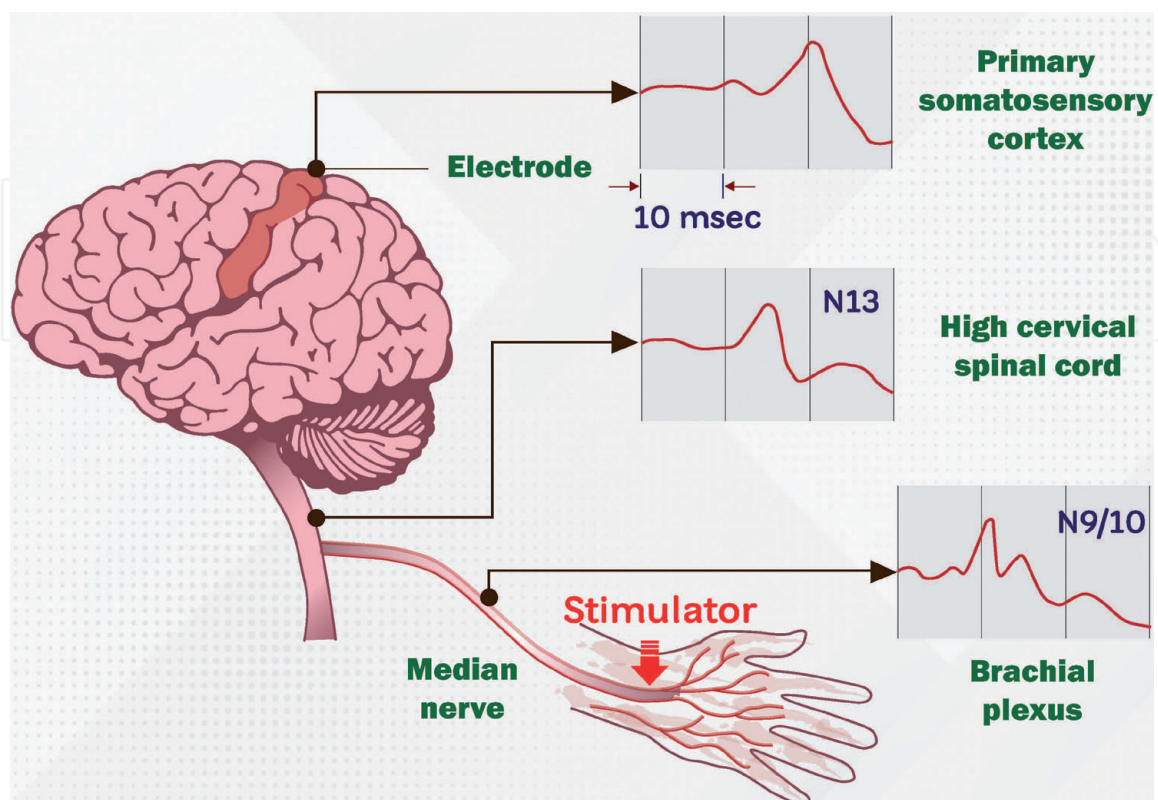
### 3. Neurophysiologic studies

#### 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).*

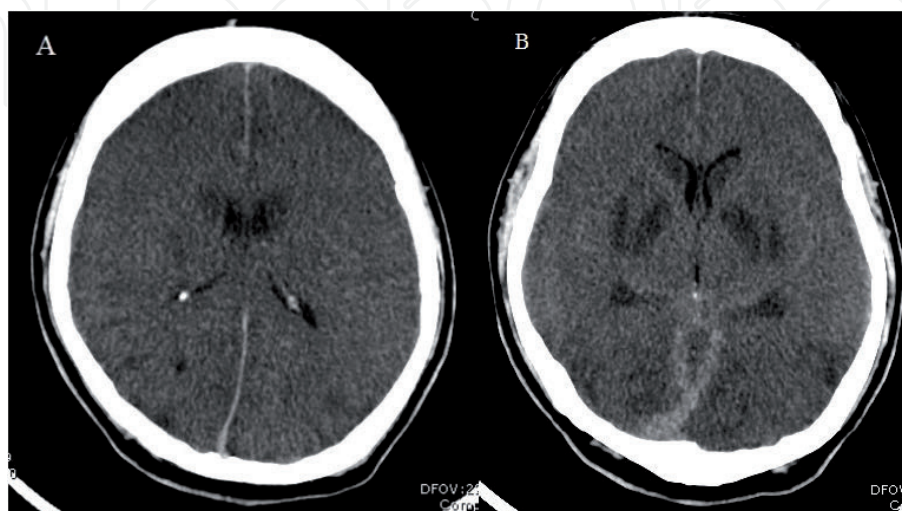
is a significant change in background EEG activity following external stimuli [34]. EEG reactivity following clapping or sternal rubbing indicates good outcomes in PCAS patients [35].

## 4. Neuroimaging studies

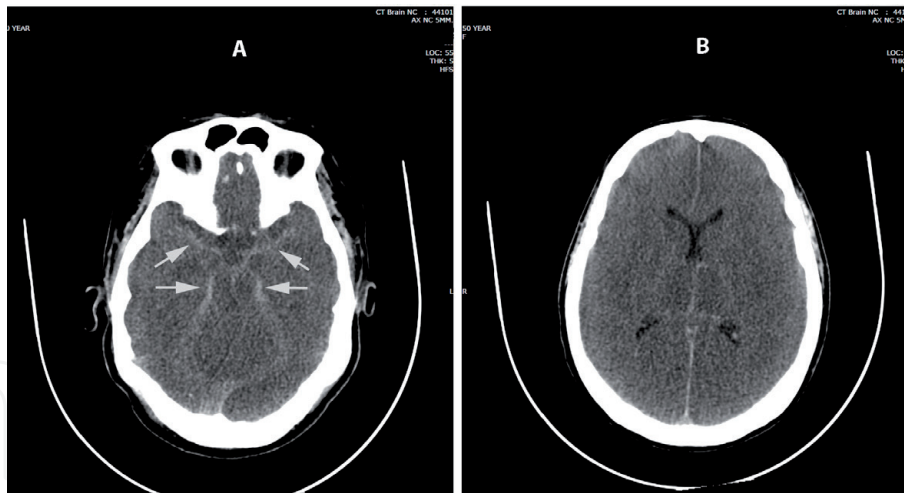
### 4.1 Computer tomography (CT-brain)

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].



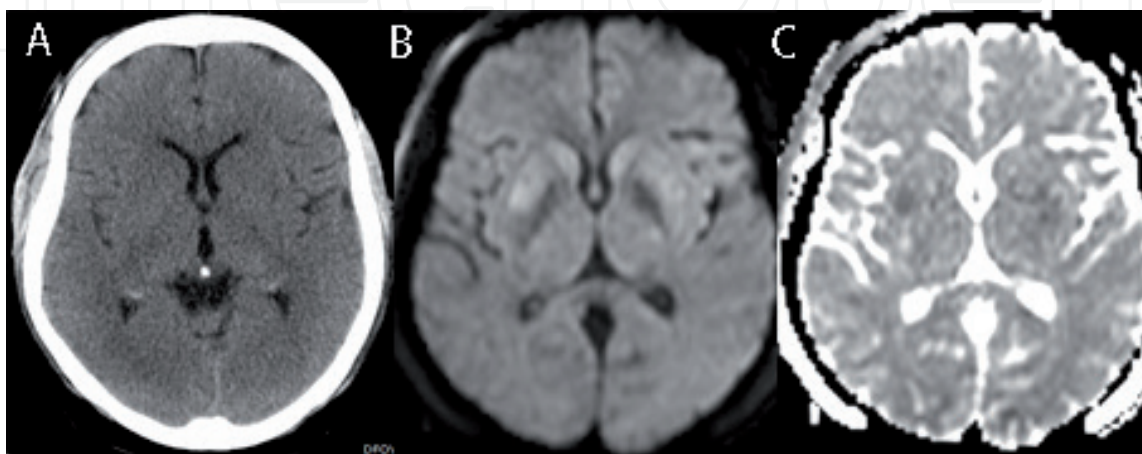
**Figure 4.** CT-Brain in a patient with severe hypoxic/ischemic brain injury: diffuse cerebral edema with effacement of the gyri and sulci (A), loss of cortical gray-white differentiation, bilateral hypodensities involving the deep gray nuclei (B).



**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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## References

- [1] Muengtaweepongsa S. Methods and clinical applications of targeted temperature management. *Neurology Asia*. 2015;**20**(4):325-333
- [2] Wijdicks EFM, Hijdra A, Young GB, Bassetti CL, Wiebe S. Practice parameter: Prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review). *Neurology*. 2006;**67**(2):203-210. DOI: 10.1212/01.wnl.0000227183.21314.cd
- [3] De Georgia M, Raad B. Prognosis of coma after cardiac arrest in the era of hypothermia. *Continuum (Minneapolis, Minn)*. 2012;**18**(3):515-531. DOI: 10.1212/01.CON.0000415425.68900.c6
- [4] Panchal AR, Bartos JA, Cabañas JG, Donnino MW, Drennan IR, Hirsch KG, et al. Part 3: Adult basic and advanced life support: 2020 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2020;**142**(16\_suppl\_2). DOI: 10.1161/cir.0000000000000916
- [5] Seewald S, Wnent J, Lefering R, Fischer M, Bohn A, Jantzen T, et al. CaRdiac Arrest Survival Score (CRASS)—A tool to predict good neurological outcome after out-of-hospital cardiac arrest. *Resuscitation*. 2020;**146**:66-73. Epub 2019/11/16. DOI: 10.1016/j.resuscitation.2019.10.036
- [6] Estraneo A, Moretta P, Loreto V, Santoro L, Trojano L. Clinical and neuropsychological long-term outcomes after late recovery of responsiveness: A case series. *Archives of Physical Medicine and Rehabilitation*. 2014;**95**(4):711-716. DOI: 10.1016/j.apmr.2013.11.004
- [7] Matthews E, Magid-Bernstein J, Velazquez A, Falo C, Park S, Claassen J, et al. Prognostic value of the neurological exam in cardiac arrest patients treated with therapeutic hypothermia (S46. 008). *Neurology*. 2016;**86**(16 Supplement):S46. 008
- [8] Mullie A, Verstringe P, Buylaert W, Houbrechts H, Michem N, Deloof H, et al. Predictive value of Glasgow coma score for awakening after out-of-hospital cardiac arrest. *Cerebral Resuscitation Study Group of the Belgian Society for Intensive Care*. *Lancet*. 1988;**1**(8578):137-140. Epub 1988/01/23
- [9] Schefold JC, Storm C, Krüger A, Ploner CJ, Hasper D. The Glasgow Coma Score is a predictor of good outcome in cardiac arrest patients treated with therapeutic hypothermia. *Resuscitation*. 2009;**80**(6):658-661. Epub 2009/04/14. DOI: 10.1016/j.resuscitation.2009.03.006
- [10] Fugate JE, Rabinstein AA, Claassen DO, White RD, Wijdicks EFM. The FOUR score predicts outcome in patients after cardiac arrest. *Neurocritical Care*. 2010;**13**(2):205-210. DOI: 10.1007/s12028-010-9407-5
- [11] Dragancea I, Horn J, Kuiper M, Friberg H, Ullén S, Wetterslev J, et al. Neurological prognostication after cardiac arrest and targeted temperature management 33°C versus 36°C: Results from a randomised controlled clinical trial. *Resuscitation*. 2015;**93**:164-170. DOI: 10.1016/j.resuscitation.2015.04.013
- [12] Al Thenayan E, Savard M, Sharpe M, Norton L, Young B. Predictors of poor neurologic outcome after induced mild hypothermia following cardiac arrest. *Neurology*. 2008;**71**(19):1535-1537. Epub 2008/11/05. DOI: 10.1212/01.wnl.0000334205.81148.31
- [13] Hifumi T, Kuroda Y, Kawakita K, Sawano H, Tahara Y, Hase M, et al.

Effect of admission glasgow coma scale motor score on neurological outcome in out-of-hospital cardiac arrest patients receiving therapeutic hypothermia. *Circulation Journal*. 2015;**79**(10):2201-2208. DOI: 10.1253/circj.cj-15-0308

[14] Martinell L, Nielsen N, Herlitz J, Karlsson T, Horn J, Wise MP, et al. Early predictors of poor outcome after out-of-hospital cardiac arrest. *Critical Care*. 2017;**21**(1):96. DOI: 10.1186/s13054-017-1677-2

[15] Dhakal LP, Sen A, Stanko CM, Rawal B, Heckman MG, Hoyne JB, et al. Early absent pupillary light reflexes after cardiac arrest in patients treated with therapeutic hypothermia. *Therapeutic Hypothermia and Temperature Management*. 2016;**6**(3):116-121. DOI: 10.1089/ther.2015.0035

[16] Riker RR, Sawyer ME, Fischman VG, May T, Lord C, Eldridge A, et al. Neurological pupil index and pupillary light reflex by pupillometry predict outcome early after cardiac arrest. *Neurocritical Care*. 2020;**32**(1):152-161. Epub 2019/05/10. DOI: 10.1007/s12028-019-00717-4

[17] Tamura T, Namiki J, Sugawara Y, Sekine K, Yo K, Kanaya T, et al. Early outcome prediction with quantitative pupillary response parameters after out-of-hospital cardiac arrest: A multicenter prospective observational study. *PLoS One*. 2020;**15**(3):e0228224. Epub 2020/03/20. DOI: 10.1371/journal.pone.0228224

[18] Greer DG, Donofrio PD. CHAPTER 16 - Electrophysiological evaluations. In: Dobbs MR, editor. *Clinical Neurotoxicology*. Philadelphia: W.B. Saunders; 2009. pp. 201-212

[19] Geocadin RG, Callaway CW, Fink EL, Golan E, Greer DM, Ko NU, et al. Standards for studies of neurological prognostication in

comatose survivors of cardiac arrest: A Scientific Statement From the American Heart Association. *Circulation*. 2019;**140**(9):e517-e42. DOI: 10.1161/cir.0000000000000702

[20] Geocadin RG, Buitrago MM, Torbey MT, Chandra-Strobos N, Williams MA, Kaplan PW. Neurologic prognosis and withdrawal of life support after resuscitation from cardiac arrest. *Neurology*. 2006;**67**(1):105-108. DOI: 10.1212/01.wnl.0000223335.86166.b4

[21] Rzewnicki I, Łebkowski W, Kordecki JK. Evaluation of vestibulo-ocular reflex in patients with damage to the central nervous system (GCS score 5-3). *Advances in Medical Sciences*. 2015;**60**(1):107-111. DOI: 10.1016/j.advms.2014.12.001

[22] Peberdy MA, Callaway CW, Neumar RW, Geocadin RG, Zimmerman JL, Donnino M, et al. Part 9: Post-cardiac arrest care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;**122**(18 Suppl 3):S768-S786. Epub 2010/10/22. DOI: 10.1161/CIRCULATIONAHA.110.971002

[23] Freund B, Kaplan PW. Post-hypoxic myoclonus: Differentiating benign and malignant etiologies in diagnosis and prognosis. *Clinical Neurophysiology Practice*. 2017;**2**:98-102. DOI: 10.1016/j.cnp.2017.03.003

[24] Lucas JM, Cocchi MN, Saliccioli J, Stanbridge JA, Geocadin RG, Herman ST, et al. Neurologic recovery after therapeutic hypothermia in patients with post-cardiac arrest myoclonus. *Resuscitation*. 2012;**83**(2):265-269. DOI: 10.1016/j.resuscitation.2011.09.017

[25] Seder DB, Sunde K, Rubertsson S, Mooney M, Stammet P, Riker RR, et al.

Neurologic outcomes and postresuscitation care of patients with myoclonus following cardiac arrest. *Critical Care Medicine*. 2015;**43**(5):965-972. Epub 2015/02/06. DOI: 10.1097/ccm.0000000000000880. PubMed PMID: 25654176

[26] Muengtawepong S. General Principles of Somatosensory Evoked Potentials. 2019. eMedicine, Medscape. 26 Feb 2019. Available from: <https://emedicine.medscape.com/article/1139906-overview>.

[27] Pfeifer R, Weitzel S, Günther A, Berrouschot J, Fischer M, Isenmann S, et al. Investigation of the inter-observer variability effect on the prognostic value of somatosensory evoked potentials of the median nerve (SSEP) in cardiac arrest survivors using an SSEP classification. *Resuscitation*. 2013; **84**(10):1375-1381. DOI: 10.1016/j.resuscitation.2013.05.016

[28] Amorim E, Ghassemi MM, Lee JW, Greer DM, Kaplan PW, Cole AJ, et al. Estimating the false positive rate of absent somatosensory evoked potentials in cardiac arrest prognostication. *Critical Care Medicine*. 2018;**46**(12): e1213-e121. Epub 2018/09/25. DOI: 10.1097/ccm.00000000000003436

[29] Habeych ME, Moshayedi P, Rittenberger JC, Gunn SR. Initial absence of N20 waveforms from median nerve somatosensory evoked potentials in a patient with cardiac arrest and good outcomes. *Clinical and Experimental Emergency Medicine*. 2019;**6**:177-182. Epub 2019/02/12. DOI: 10.15441/ceem.18.015

[30] Sandroni C, D'Arrigo S, Cacciola S, Hoedemaekers CWE, Kamps MJA, Oddo M, et al. Prediction of poor neurological outcome in comatose survivors of cardiac arrest: A systematic review. *Intensive Care Medicine*. 2020;**46**(10):1803-1851. DOI: 10.1007/s00134-020-06198-w

[31] Choi SP, Park KN, Wee JH, Park JH, Youn CS, Kim HJ, et al. Can somatosensory and visual evoked potentials predict neurological outcome during targeted temperature management in post cardiac arrest patients? *Resuscitation*. 2017;**119**:70-75. Epub 2017/06/27. DOI: 10.1016/j.resuscitation.2017.06.022

[32] Hofmeijer J, Van Putten MJAM. EEG in postanoxic coma: Prognostic and diagnostic value. *Clinical Neurophysiology*. 2016;**127**(4):2047-2055. DOI: 10.1016/j.clinph.2016.02.002

[33] Westhall E, Rossetti AO, Van Rootselaar A-F, Wesenberg Kjaer T, Horn J, Ullén S, et al. Standardized EEG interpretation accurately predicts prognosis after cardiac arrest. *Neurology*. 2016;**86**(16):1482-1490. DOI: 10.1212/wnl.00000000000002462

[34] Liu G, Su Y, Liu Y, Jiang M, Zhang Y, Zhang Y, et al. Predicting outcome in comatose patients: The role of EEG reactivity to quantifiable electrical stimuli. *Evidence-based Complementary and Alternative Medicine*. 2016;**2016**:1-7. DOI: 10.1155/2016/8273716

[35] Admiraal MM, Horn J, Hofmeijer J, Hoedemaekers CWE, van Kaam CR, Keijzer HM, et al. EEG reactivity testing for prediction of good outcome in patients after cardiac arrest. *Neurology*. 2020;**95**(6):e653-ee61. DOI: 10.1212/wnl.00000000000009991

[36] Kjos BO, Brant-Zawadzki M, Young RG. Early CT findings of global central nervous system hypoperfusion. *AJR American Journal of Roentgenology*. 1983;**141**(6):1227-1232. Epub 1983/12/01

[37] Torbey MT, Selim M, Knorr J, Bigelow C, Recht L. Quantitative analysis of the loss of distinction between gray and white matter in comatose patients after cardiac arrest.

Stroke. 2000;**31**(9):2163-2167. Epub 2000/09/08

[38] Torbey MT, Geocadin R, Bhardwaj A. Brain arrest neurological outcome scale (BrANOS): Predicting mortality and severe disability following cardiac arrest. Resuscitation. 2004;**63**(1):55-63. Epub 2004/09/29. DOI: 10.1016/j.resuscitation.2004.03.021

[39] Kim S, Choi S, Park K, Youn C, Oh S, Choi S. Early brain computed tomography findings are associated with outcome in patients treated with therapeutic hypothermia after out-of-hospital cardiac arrest. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine. 2013;**21**(1):57. DOI: 10.1186/1757-7241-21-57

[40] Given CA, Burdette JH, Elster AD, Williams DW. Pseudo-subarachnoid hemorrhage: A potential imaging pitfall associated with diffuse cerebral edema. American Journal of Neuroradiology. 2003;**24**(2):254-256

[41] You JS, Park S, Park YS, Chung SP. Pseudo-subarachnoid hemorrhage. The American Journal of Emergency Medicine. 2008;**26**(4):521 e1-521 e2. DOI: 10.1016/j.ajem.2007.08.031

[42] Platt A, Collins J, Ramos E, Goldenberg FD. Pseudosubarachnoid hemorrhage: A systematic review of causes, diagnostic modalities, and outcomes in patients who present with pseudosubarachnoid hemorrhage. Surgical Neurology International. 2021;**12**:29. Epub 2021/02/19. DOI: 10.25259/sni\_905\_2020

[43] Yuzawa H, Higano S, Mugikura S, Umetsu A, Murata T, Nakagawa A, et al. Pseudo-subarachnoid hemorrhage found in patients with postresuscitation encephalopathy: Characteristics of CT findings and clinical importance. American Journal of Neuroradiology. 2008;**29**(8):1544-1549. DOI: 10.3174/ajnr.a1167

[44] Ahn J, Choi S, Jung Y, Min Y. Clinical characteristics of patients with pseudo-subarachnoid haemorrhage who were successfully resuscitated from out-of-hospital cardiopulmonary arrest. Hong Kong Journal of Emergency Medicine. 2012;**19**(2):85-91. DOI: 10.1177/102490791201900202

[45] Choi KS, Won YD, Yi HJ, Lim TH, Lee YJ, Chun HJ. Therapeutic and prognostic implications of subarachnoid hemorrhage in patients who suffered cardiopulmonary arrest and underwent cardiopulmonary resuscitation during an emergency room stay. Clinical Neurology and Neurosurgery. 2013;**115**(10):2088-2093. Epub 2013/08/13. DOI: 10.1016/j.clineuro.2013.07.024

[46] Zhou SE, Maciel CB, Ormseth CH, Beekman R, Gilmore EJ, Greer DM. Distinct predictive values of current neuroprognostic guidelines in post-cardiac arrest patients. Resuscitation. 2019;**139**:343-350. DOI: 10.1016/j.resuscitation.2019.03.035

[47] Obenaus A, Badaut J. Chapter 3 - Noninvasive Imaging Techniques for Brain Edema: From Basic Science to the Clinic. In: Badaut J, Plesnila N, editors. Brain Edema. San Diego: Academic Press; 2017. pp. 51-69

[48] Patil S, Melkundi SS, Govinda RBT. Evaluation of intracranial lesions by diffusion weighted imaging. Journal of Evolution of Medical and Dental Sciences. 2015;**4**:12505

[49] Hirsch KG, Mlynash M, Eyngorn I, Pirsaheli R, Okada A, Komshian S, et al. Multi-center study of diffusion-weighted imaging in coma after cardiac arrest. Neurocritical Care. 2016;**24**(1):82-89. Epub 2015/07/15. DOI: 10.1007/s12028-015-0179-9

[50] Alexander AL, Lee JE, Lazar M, Field AS. Diffusion tensor imaging of the brain. Neurotherapeutics.

2007;4(3):316-329. DOI: 10.1016/j.nurt.2007.05.011

[51] Van Der Eerden AW, Khalilzadeh O, Perlberg V, Dinkel J, Sanchez P, Vos PE, et al. White matter changes in comatose survivors of anoxic ischemic encephalopathy and traumatic brain injury: Comparative diffusion-tensor imaging study. *Radiology*. 2014;270(2):506-516. DOI: 10.1148/radiol.13122720

[52] Luyt CE, Galanaud D, Perlberg V, Vanhaudenhuyse A, Stevens RD, Gupta R, et al. Diffusion tensor imaging to predict long-term outcome after cardiac arrest: A bicentric pilot study. *Anesthesiology*. 2012;117(6):1311-1321. Epub 2012/11/09. DOI: 10.1097/ALN.0b013e318275148c

[53] Velly L, Perlberg V, Boulier T, Adam N, Delphine S, Luyt CE, et al. Use of brain diffusion tensor imaging for the prediction of long-term neurological outcomes in patients after cardiac arrest: A multicentre, international, prospective, observational, cohort study. *Lancet Neurology*. 2018;17(4):317-326. Epub 2018/03/04. DOI: 10.1016/S1474-4422(18)30027-9

[54] Saranathan M, Worters PW, Rettmann DW, Winegar B, Becker J. Physics for clinicians: Fluid-attenuated inversion recovery (FLAIR) and double inversion recovery (DIR) Imaging. *Journal of Magnetic Resonance Imaging*. 2017;46(6):1590-1600. DOI: 10.1002/jmri.25737

[55] Lopez Soto C, Dragoi L, Heyn CC, Kramer A, Pinto R, Adhikari NKJ, et al. Imaging for neuroprognostication after cardiac arrest: Systematic review and meta-analysis. *Neurocritical Care*. 2020;32(1):206-216. DOI: 10.1007/s12028-019-00842-0

[56] Haque A, Polcyn R, Matzelle D, Banik NL. New insights into the role of neuron-specific enolase in

neuro-inflammation, neurodegeneration, and neuroprotection. *Brain Sciences*. 2018;8(2):33. DOI: 10.3390/brainsci8020033

[57] Almaraz AC, Bobrow BJ, Wingerchuk DM, Wellik KE, Demaerschalk BM. Serum neuron specific enolase to predict neurological outcome after cardiopulmonary resuscitation: A critically appraised topic. *The Neurologist*. 2009;15(1):44-48. DOI: 10.1097/NRL.0b013e318191f810

[58] Stammet P, Collignon O, Hassager C, Wise MP, Hovdenes J, Aneman A, et al. Neuron-specific enolase as a predictor of death or poor neurological outcome after out-of-hospital cardiac arrest and targeted temperature management at 33 degrees C and 36 degrees C. *Journal of the American College of Cardiology*. 2015;65(19):2104-2114. Epub 2015/05/16. DOI: 10.1016/j.jacc.2015.03.538

[59] Ryoo SM, Kim YJ, Sohn CH, Ahn S, Seo DW, Kim WY. Prognostic abilities of serial neuron-specific enolase and lactate and their combination in cardiac arrest survivors during targeted temperature management. *Journal of Clinical Medicine*. 2020;9(1):159. Epub 2020/01/16. DOI: 10.3390/jcm9010159

[60] Jang JH, Park WB, Lim YS, Choi JY, Cho JS, Woo JH, et al. Combination of S100B and procalcitonin improves prognostic performance compared to either alone in patients with cardiac arrest: A prospective observational study. *Medicine (Baltimore)*. 2019;98(6):e14496. Epub 2019/02/09. DOI: 10.1097/MD.00000000000014496

[61] Stammet P, Dankiewicz J, Nielsen N, Fays F, Collignon O, Hassager C, et al. Protein S100 as outcome predictor after out-of-hospital cardiac arrest and targeted temperature management at



- 33 °C and 36 °C. *Critical Care*. 2017;**21**(1): 153. DOI: 10.1186/s13054-017-1729-7
- [62] Mattsson N, Zetterberg H, Nielsen N, Blennow K, Dankiewicz J, Friberg H, et al. Serum tau and neurological outcome in cardiac arrest. *Annals of Neurology*. 2017;**82**(5):665-675. Epub 2017/10/06. DOI: 10.1002/ana.25067
- [63] Grand J, Kjaergaard J, Nielsen N, Friberg H, Cronberg T, Bro-Jeppesen J, et al. Serum tau fragments as predictors of death or poor neurological outcome after out-of-hospital cardiac arrest. *Biomarkers*. 2019;**24**(6):584-591. DOI: 10.1080/1354750x.2019.1609580
- [64] Wihersaari L, Ashton NJ, Reinikainen M, Jakkula P, Pettila V, Hastbacka J, et al. Neurofilament light as an outcome predictor after cardiac arrest: A post hoc analysis of the COMACARE trial. *Intensive Care Medicine*. 2021;**47**(1):39-48. Epub 2020/08/28. DOI: 10.1007/s00134-020-06218-9
- [65] Moseby-Knappe M, Mattsson N, Nielsen N, Zetterberg H, Blennow K, Dankiewicz J, et al. Serum neurofilament light chain for prognosis of outcome after cardiac arrest. *JAMA Neurology*. 2019;**76**(1):64-71. Epub 2018/11/02. DOI: 10.1001/jamaneurol.2018.3223
- [66] Hol EM, Pekny M. Glial fibrillary acidic protein (GFAP) and the astrocyte intermediate filament system in diseases of the central nervous system. *Current Opinion in Cell Biology*. 2015;**32**: 121-130. Epub 2015/03/03. DOI: 10.1016/j.ceb.2015.02.004
- [67] Helwig K, Seeger F, Holschermann H, Lischke V, Gerriets T, Niessner M, et al. Elevated serum glial fibrillary acidic protein (GFAP) is associated with poor functional outcome after cardiopulmonary resuscitation. *Neurocritical Care*. 2017;**27**(1):68-74. Epub 2017/01/06. DOI: 10.1007/s12028-016-0371-6
- [68] Cardim D, Griesdale DE, Ainslie PN, Robba C, Calviello L, Czosnyka M, et al. A comparison of non-invasive versus invasive measures of intracranial pressure in hypoxic ischaemic brain injury after cardiac arrest. *Resuscitation*. 2019;**137**:221-228. DOI: 10.1016/j.resuscitation.2019.01.002
- [69] Sekhon MS, Griesdale DE, Ainslie PN, Gooderham P, Foster D, Czosnyka M, et al. Intracranial pressure and compliance in hypoxic ischemic brain injury patients after cardiac arrest. *Resuscitation*. 2019;**141**:96-103. DOI: 10.1016/j.resuscitation.2019.05.036
- [70] Reis C, Akyol O, Araujo C, Huang L, Enkhjargal B, Malaguit J, et al. Pathophysiology and the monitoring methods for cardiac arrest associated brain injury. *International Journal of Molecular Sciences*. 2017;**18**(1):129. DOI: 10.3390/ijms18010129
- [71] Thomsen JH, Hassager C, Bro-Jeppesen J, Soholm H, Nielsen N, Wanscher M, et al. Sinus bradycardia during hypothermia in comatose survivors of out-of-hospital cardiac arrest - a new early marker of favorable outcome? *Resuscitation*. 2015;**89**:36-42. DOI: 10.1016/j.resuscitation.2014.12.031
- [72] Thomsen JH, Nielsen N, Hassager C, Wanscher M, Pehrson S, Kober L, et al. Bradycardia during targeted temperature management: An early marker of lower mortality and favorable neurologic outcome in comatose out-of-hospital cardiac arrest patients. *Critical Care Medicine*. 2016;**44**(2):308-318. Epub 2015/10/16. DOI: 10.1097/CCM.0000000000001390
- [73] Muengtaweepongsa S, Jantanukul A, Suwanprasert K. Should the heart rate including the heart rate variability be important prognosticators in cardiac arrest? *Resuscitation*.

2016;**98**:e15. Epub 2015/11/26.  
DOI: 10.1016/j.resuscitation.2015.08.026

[74] Mejía-Mejía E, Budidha K, Abay TY, May JM, Kyriacou PA. Heart rate variability (HRV) and pulse rate variability (PRV) for the assessment of autonomic responses. *Frontiers in Physiology*. 2020;**11**:779. DOI: 10.3389/fphys.2020.00779

[75] Jantanukul A, Muengtaweepongsa S, Suwanprasert K, editors. Suppression of autonomic drive determined by nonlinear HRV analysis in therapeutic hypothermia after cardiac arrest. The 6th 2013 Biomedical Engineering International Conference Krabi. IEEE; 2013. DOI: 10.1109/bmeicon.2013.6687657

[76] Kovacs E, Pilecky D, Szakal-Toth Z, Fekete-Gyor A, Gyarmathy VA, Geller L, et al. The role of age in post-cardiac arrest therapy in an elderly patient population. *Physiology International*. 2020;**107**(2):319-336. Epub 2020/07/22. DOI: 10.1556/2060.2020.00027

[77] Kovacs E, Gyarmathy VA, Pilecky D, Fekete-Gyor A, Szakal-Toth Z, Geller L, et al. An interaction effect analysis of thermodilution-guided hemodynamic optimization, patient condition, and mortality after successful cardiopulmonary resuscitation. *International Journal of Environmental Research and Public Health*. 2021;**18**(10):5223. Epub 2021/06/03. DOI: 10.3390/ijerph18105223