Review article

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Neuroprognostication strategies after cardiac arrest: A review of current evidence

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Abstract

Cardiac arrest is the most important cause of death worldwide. Often, those who survive have an increased mortality and disability risk that is mainly associated with the development of hypoxic-ischemic brain injury (HIBI). This review examines current methods and recent advancements in neuroprognostication after cardiac arrest, focusing on the multimodal approach recommended by current guidelines.

Recent studies have shown that a multimodal approach for neuroprognostication has the highest specificity to determine unfavorable outcomes after cardiac arrest. New biomarkers, such as neurofilament light chain alongside advancements in machine learning models, have shown promising results in predicting outcomes. Although several prognostic scoring systems have been developed to predict neurological outcomes as early as hospital admission, their prognostic efficacy is still being determined due to several associated limitations.

Although several strategies for improving neurological outcomes during and after cardiac arrest exist, HIBI remains the leading cause of disability among survivors. A multimodal approach, including at least two diagnostic modalities, is crucial for accurate prognostication. Emerging technologies, including machine learning models and biomarkers, offer potential improvements to existing prognostic strategies, emphasizing the need for consistent guideline adherence to optimize patient care.

Key words: Cardiac arrest, hypoxic-ischemic brain injury, neuroprognostication.

Introduction

The most prevalent cause of death and disability after cardiac arrest is hypoxic-ischemic brain injury (HIBI). (1-3) Cardiac arrest results in the cessation of blood flow to all vital organs and the brain, initiating a cascade of multiple pathological events that result in neuronal damage and cell death. This process continues, even after the return of spontaneous circulation (ROSC), and is known as post-cardiac arrest syndrome (PCAS) (**Figure 1**). (2,4) PCAS occurs due to ischemia-reperfusion injury, involves multiple pathways, and is mainly mediated by the production of free radicals in the absence of oxygen. (4) Both ischemia and reperfusion injury are essential mechanisms responsible for the development of brain injury and poor neurological outcomes in cardiac arrest survivors. Therefore, neuroprognostication is essential to determine the injury's extent and appropriate therapeutic measures.

The assessment of neurological outcome after cardiac arrest is commonly measured with the Cerebral Performance Category (CPC) score and the Modified Rankin Scale (mRS). (2) These scores determine the degree of consciousness and disability after cardiac arrest. Yet, assigning a numerical value

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does not adequately predict the prognosis of patients with poor neurological outcomes. Current guidelines on post-resuscitation care suggest using a multimodal approach to prognostication to minimize the rate of false positives and self-fulfilling prophecy bias and to avoid premature discussions on withdrawal of life-sustaining therapy. (5)

Predicting neurological outcome with scoring systems

One of the original methods of neuroprognostication after cardiac arrest mainly consisted of a thorough clinical examination. (6) Since then, multiple prognostic scoring systems have been developed to aid in risk stratification and outcome prediction in cardiac arrest survivors (**Table 1**). However, these scoring systems may have several limitations, such as reliance on variables that may not be readily available or accurately measured in all clinical settings, lack of validation in diverse patient populations, and assessment of mortality during hospital admission, which can be considered as to early by guidelines and limited ability to predict long-term neurological outcomes. (7-15)

Multimodal approach for neuroprognostication

The 2021 guidelines from the European Resuscitation Council (ERC) and the European Society of Intensive Care Medicine (ESICM) recommend using a multimodal approach for neuroprognostication after cardiac arrest. (16) The proposed algorithm encompasses multiple diagnostic modalities (clinical examination, imaging, neurophysiology, and biomarkers) (**Figure 2**), which should be performed three days after ROSC and in the absence of confounders, such as residual sedation, therapeutic hypothermia, neuromuscular blockade, severe hypotension, hypoglycemia, sepsis, and metabolic abnormalities. (16)

Clinical examination

Calculation of the Glasgow Coma Scale Motor Score (GCS-M) is the first step in the neuroprognostication algorithm. (16) A GCS-M≤3 at 72 hours after ROSC signals a multimodal prognostication approach initiation. (16) This scoring system has demonstrated good sensitivity and specificity (77.1% and 92.8%, respectively). However, its prognostic accuracy improves when combined with other diagnostic modalities, such as brain imaging, neurophysiology studies, and biomarkers. (17)

One specific clinical sign that improves accuracy is the presence of bilateral absence of pupillary light reflex and corneal reflex. Individually, this sign has a 100% specificity for predicting a poor outcome. (17) This is due to the relative resistance of the brainstem to anoxic injury. (2) Therefore, its absence signifies profound neurological damage. (2) Status myoclonus within 72-96 hours is associated with a poor neurological outcome. (16)

Imaging

Common radiological signs of poor outcome include generalized brain edema, which can be observed as a reduction of the grey/white matter ratio (GWR) on brain computed tomography (CT) and extensive diffusion restriction on brain magnetic resonance imaging (MRI). (16) In one study, brain CT and MRI demonstrated a low sensitivity and high specificity to determine neurological outcomes (32.3%, 98.3%, 13%, and 100%, respectively). (17) Quantitative (measurement of GWR) interpretation of CT scans has shown to be superior to qualitative interpretation due to variability between observers. (18) Qualitative interpretation focuses on observing subjective signs, such as the loss of boundary between grey and white matter, sulcal effacement, and pseudo-subarachnoid hemorrhage. (19) Kirsch and coinvestigators showed that a GWR cutoff value of 1.17 after 12 hours of ROSC could predict a poor neurological outcome with 100% specificity. (20)

Quantitative interpretation of MRI in post-arrest patients can be achieved by measuring the apparent diffusion coefficient (ADC), which is decreased after cardiac arrest, particularly an ACD reduction in the occipital lobes, which has been associated with decreased consciousness. (21) Besides quantitative interpretation, various artificial intelligence algorithms have been developed in the last few years to enhance accuracy. (22,23) Machine learning models have shown promising results for predicting awakening and mortality (23) and the risk of developing HIBI in post-cardiac arrest patients. (23,24)

Neurophysiology

Current clinical guidelines suggest that an electroencephalogram (EEG) should be performed on patients who remain comatose after cardiac arrest. (16) EEG evaluation can be performed by continuous EEG monitoring or intermittent 30-minute routine EEG. (25) Specific patterns associated with poor neurological outcomes have been widely described. (26) Standardized terminology for their interpretation in critically ill patients has been provided by the American Clinical Neurophysiology Society (ACNS), which was recently revised in 2021. (26) The classical EEG criteria were introduced by Westhall and colleagues in 2016 and have been included in current guidelines. (17,27) **Figure 3** depicts these commonly used criteria.

Interestingly, few studies have been done to determine which patterns suggest a good neurological prognosis. (28) Favorable neurological outcomes are generally described as the absence of malignant patterns. After cardiac arrest, most patients will present with a suppressed background on EEG; however, if, within 12-72 hours after ROSC, there is an increase in amplitude and continuity with no abundant discharges, a good neurological outcome is likely. (25,29) A study by Fenter and colleagues revealed that a more permissive benign EEG definition may improve the sensitivity to detect patients with favorable outcomes. (28) In this study, Westhall's EEG classification was compared to a modified benign EEG classification in 381 patients, showing that the modified definition had a higher sensitivity for identifying those with a good outcome (97% vs 71%). (28)

EEG interpretation can be complex; newer technologies, such as machine learning models, can aid in understanding and predicting outcomes. (30) In one study, the use of convolutional neural networks (CNN), a deep learning algorithm to predict the likelihood of awakening in comatose patients following cardiac arrest, showed good predictive power and discriminative ability to predict awakening in both therapeutic hypothermia (TH) and normothermia. (30)

Somatosensory evoked potentials (SSEP) have also been used for neuroprognostication. They reflect the activation of the primary sensory cortex when the median nerve is stimulated. (2) This method for prognostication is not highly affected by sedatives, antiepileptic medications, and targeted temperature management (TTM). (16) Therefore, SSEP can be performed 24 hours after ROSC. Using neuromuscular blockers is recommended to avoid artifacts caused by muscular activity. (17,31) The bilateral absence of the N20 wave indicates severe HIBI and is consistent with a poor neurological outcome. (16) Neurophysiology prognostication modalities offer higher specificity when used together. A prospective study (ProNeCA) revealed 100% specificity for EEG and SSEP as early as 12 and 72 hours after ROSC; although sensitivity was not high when these two methods were combined for prognostication, sensitivity increased to 79%. (32)

Biomarkers

The most studied blood biomarkers for neuroprognostication are neuron-specific enolase (NSE) and protein S100 beta (S100β). (33) These biomarkers have gained interest because their release correlates to the severity of brain injury and because they are unaffected by confounders and interpretation bias. (25) S100β is a calcium-binding protein derived from astrocytes. In post-ROSC patients, increased plasma values of S100β have been associated with hypoxemic brain injury. (4)

NSE is an intracellular neuronal enzyme of glucose metabolism. Currently, only the measurement of NSE plasma values is recommended in the guidelines on post-resuscitation care. (16) Increasing values at 24 to 72 hours indicate a poor prognosis, specifically NSE>60 μg/l at 48h or 72h. (16) In a recent meta-analysis, NSE showed a reasonable degree of specificity to predict when a poor outcome was likely. (34) Patients who survived hospital discharge had lower NSE levels than those who did not survive. Moreover, among all patients who survived, those with a poor neurological outcome had a higher NSE when compared with patients with a good neurological outcome. (34)

Other novel biomarkers, such as tau and neurofilaments (axonal injury markers), have recently gained more clinical attention for the prediction of neurological outcomes. A recent meta-analysis showed that neurofilament light chain (NF-L) and tau had the highest area under the receiver operating characteristic curves (AUCs) for predicting a poor outcome compared to NSE, S100β, glial fibrillary protein, and ubiquitin carboxyl hydrolase L1. (35) High serum levels of tau after cardiac arrest have been associated with poor neurological outcomes and decreased survival rates. (36) Neurofilaments have been shown to increase in cerebrospinal fluid and blood after neuronal damage and neurodegeneration. (37) These filaments provide dendrites and axons with tensile strength. (38) The prognostic value of NF-L plasma values after cardiac arrest has been evaluated in various studies. (35) Moseby-Knappe and colleagues evaluated the neurological outcome in 717 patients from the TTM trial. (37) NF-L plasma values were measured 24-72 hours after cardiac arrest. In this study, serum NF-L demonstrated consistently high performance in predicting a poor outcome across all time points. Furthermore, it performed superior to NSE, S100β, and tau (p=0.001). (37) A post hoc sensitivity analysis on 112 patients of the COMCARE trial (39,40) revealed that NF-L serum concentrations were significantly higher in patients with poor neurological outcomes at 24, 48, and 72 hours. (40,41) This was particularly noticeable at 48 hours. Moreover, NF-L could predict death from hypoxic-ischemic brain injury, and its diagnostic accuracy was not affected by TTM. (41)

It is important to note that no diagnostic modality offers complete accuracy in determining neurological outcomes. (16) In 2020, the ERC/ESICM 4-step algorithm's performance was evaluated using data

from the patient cohort of the TTM (n=585). (17) In this study, the algorithm exhibited an overall sensitivity of 38.7% and a specificity of 100%; a higher sensitivity of 42.5% was achieved when prognostication was made regardless of the GCS-M. Moreover, when diagnostic modalities were analyzed separately, early status myoclonus had the lowest sensitivity (6.8%), while NSE and GCS-M<2 had the highest sensitivity for poor outcome prediction. (17) In a study conducted by Pouplet and colleagues, incorporating NF-L plasma values into the 2021 ERC/ESICM algorithm increased sensitivity. (42) Specifically, at a threshold of 500 pg/ml, sensitivity increased from 53% to 74%, and at a threshold of 1,200 pg/ml, it reached 68%. (42)

While a multimodal approach is crucial to accurately perform neuroprognostication and prevent premature withdrawal of life support, inconsistent adherence to prognostic guidelines is common. A recent retrospective study by Elmer and colleagues, encompassing multiple hospitals in the United States and including 34,585 patients, revealed that merely 2% of patients underwent at least two diagnostic modalities, 9% underwent a single diagnostic test, and only 5% were evaluated by a neurologist. (43) Notably, CT scans were the predominant prognostic test in the study. However, an observed trend indicated an increasing testing frequency over time. (43) Studies have shown that combining multiple modalities significantly enhances specificity and sensitivity. Therefore, consistent adherence to guidelines may help achieve accurate prognostication, helping to identify patients who would benefit from extensive treatment and who would not.

Conclusions

Cardiac arrest remains a prevalent situation. A large majority of deaths of patients who survive are attributed to HIBI. The pathophysiological processes underlying HIBI are complex and occur both during and after cardiac arrest. Accurate neuroprognostication, involving the timely assessment and utilization of at least two distinct diagnostic modalities, enhances sensitivity and specificity in determining neurological outcomes. Emerging technologies, such as machine learning models and biomarkers, are currently being researched and can potentially improve the existing multimodal approach.

Table 1. Scoring systems developed for risk stratification and outcome prediction after cardiac arrest

Score/year	Categories/variables	Interpretation	Application time	Outcome
OHCA/2006 (7)	• Initial rhythm • Time from collapse to CPR • Duration of CPR • Serum creatinine • Arterial lactate	• All variables associated with poor outcome	Hospital admission	Neurological outcome at hospital discharge
FOUR/2010 (8,45,46)	• Eye response • Motor response • Brainstem reflexes • Respiration pattern	• ≤4 high mortality • >8 associated with survival • Improvement >2 in serial exams is associated with survival	3-5 days after ROSC	In-hospital mortality Long term outcome
PCAC*/2011 (9,10)	• Awake • Coma with mild cardiopulmonary failure • Coma with severe cardiopulmonary failure • Deep coma	• 80% • 60% • 40% • 10%	First 6 hours after ROSC	Rate of survival, neurological outcome, and development of MOF
5-R score (11)	• Initial rhythm • Starting resuscitation (≤5 min) • ROSC (≤30 min) • Light reflex • Absence of re-arrest	• ≥4 good neurological outcome	Hospital admission	Neurological outcome in patients treated with TH
CAHP/2016 (12)	• Age • Male sex • Non-shockable rhythm • Time from collapse-BLS • Time from BLS to ROSC • Location of cardiac arrest • Epinephrine dose • Arterial pH	• <150 low risk • 150-200 medium risk • ≥200 high risk	Hospital admission	Neurological outcome at discharge
C-GRApH/2017 (13)	• Coronary artery disease • Glucose ≥200 mg/dl • Rhythm of arrest (not VT/VF) • Age>45 • pH<7.0	• >4 poor prognosis • <1 good prognosis	Hospital admission	Neurological outcome in patients treated with TH
CRASS/2020 (14)	• Age • Rhythm • Etiology • Support • Epinephrine dose • Pre-emergency status • Location • Amiodarone • Status at admission • Witnessed • Duration of CPR • The time between collapse and CPR	• Probability of good outcome= $1/(1+e^{-X})$*	Hospital admission	Probability of survival with good neurological outcome in OHCA at hospital discharge

KORHN-CASS (15)	HIBI • Unwitnessed arrest • Non-shockable rhythm • Epinephrine • Arrest time ≥29 min • Noncardiac etiology • Absence of brainstem reflexes • Shock	• ≥6 HIBI • ≥7 IHD	Hospital admission	Development of HIBI and IHD

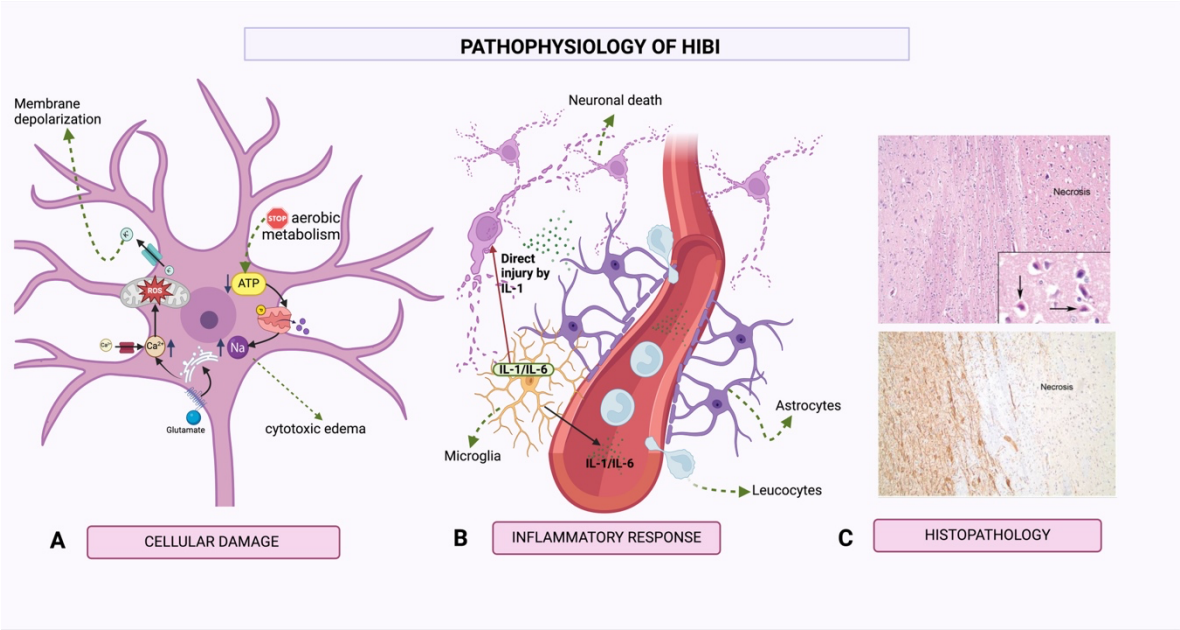
Legend: OHCA=out-of-hospital cardiac arrest; CPR=cardio-pulmonary resuscitation; FOUR=Full Outline if UnResponsiveness; PCAC=Pittsburgh cardiac arrest category; ROSC=restore of spontaneous circulation; MOF=multiple organ failure; TH=therapeutic hypothermia; CAHP=cardiac arrest hospital prognosis; BLS=basic life support; VT=ventricular tachycardia; VF=ventricular fibrillation; CRASS=CaRdiac Arrest Survival Score; KORHN-CASS=Korean Hypothermia Network-cardiac arrest severity score; HIBI=hypoxic-ischemic brain injury; IHD=ischemic heart disease.
*The probability of hospital discharge with a good neurological outcome formula; e=Euler's number; X=sum of the independent variables.

Table 2. Definitions for EEG patterns according to Westhall et al., Nolan et al., and Fenter et al.

EEG patterns	Westhall et al. (27)	Nolan et al. (16)	Fenter et al. (28)
Highly malignant	• Suppressed background without discharges • Suppressed background with continuous periodic discharges • Burst suppression background with or without discharges	• Suppressed background with or without periodic discharges • Burst suppression	• Westhall's criteria
Malignant	• Malignant periodic or rhythmic patterns* • Malignant background** • Unreactive EEG8***	• Unequivocal seizures during the first 72 hours (poor prognosis)	• Westhall's criteria
Benign	• Absence of any malignant criteria	• Continuous, normal voltage, and reactive background	• Reactive background • Absence of malignant periodic or rhythmic patterns*

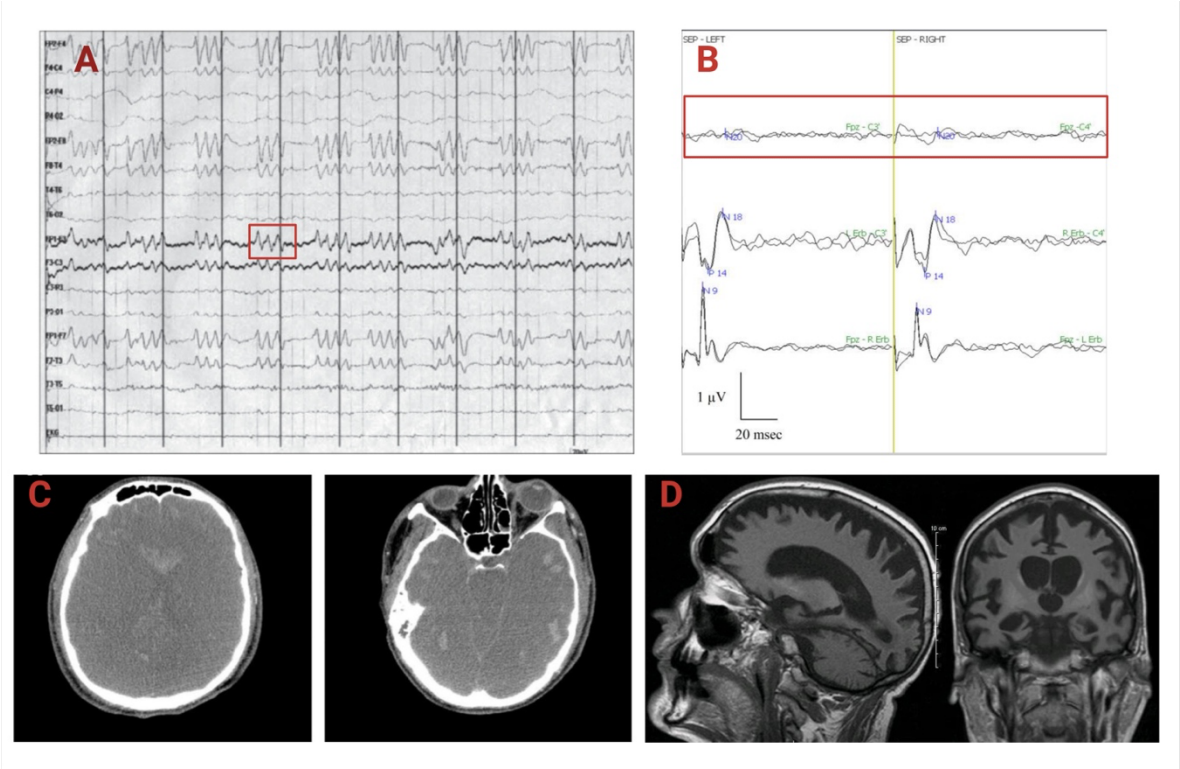
Legend: EEG=electroencephalogram.
*Abundant periodic discharges; abundant rhythmic polyspike-/spike-/sharp-and-wave; unequivocal electrographic seizure.
**Discontinuous background; low-voltage background; reversed anterior-posterior gradient.
***Absence of background reactivity or only stimulus-induced discharges.

Figure 1. Pathophysiology of hypoxic-ischemic brain injury



Legend:
A) Cessation of blood flow and oxygen delivery halts aerobic metabolism, which results in depletion of adenosine triphosphate (ATP) and ion pump dysfunction, resulting in cytotoxic intracellular edema and potassium efflux, which generates membrane depolarization. As a result, voltage-gated Ca^{2+} channels open, and intracellular Ca^{2+} concentration increases, stimulating glutamate secretion. Glutamate binds to its receptors (mGlur and NMDA) and further increases the release of Ca^{2+} from the endoplasmic reticulum. (2) During reperfusion injury, Ca^{2+} activates lipases and proteases and increases the production of oxygen reactive species (ROS) and nitric oxide, which causes cellular injury by damage to mitochondria, cellular membranes, and DNA. (4)
B) Activation of the innate immune system and subsequent inflammatory response caused by neuronal cell death. Microglia and circulating leucocytes release inflammatory cytokines (IL-6/IL-1). IL-1 release can result in direct neuronal injury. Complement activation further releases inflammatory cytokines, leucocyte, and endothelial activation. (44)
C) Histopathologic evidence of HIBI in a piglet model showing early necrosis with shrunken and eosinophilic neurons (arrows) (image sourced from the National Library of Medicine's Open-I platform. Licensed under CC BY 2.0).
For more information, visit https://openi.nlm.nih.gov/detailedresult?img=PMC2582156_srad49-1049-f6&query=hypoxic%20ischemic%20encephalopathy%20pathology&it=xg&req=4&npos=50

Figure 2. Neurophysiology and brain imaging findings are suggestive of poor neurological outcomes



Legend:
A) EEG was performed one hour after cardiac arrest, and periodic sharp waves in clusters of triplets (red square) and quadruplets were observed with attenuation of background activity.
B) Somatosensory evoked potentials showing bilateral absence of N20 wave one month after cardiac arrest.
C) Brain CT scan showing diffuse cerebral edema with ventricular and sulcal effacement.
D) MRI of a patient in a persistent vegetative state after cardiac arrest showing cerebral atrophy with diffuse grey matter loss.
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https://openi.nlm.nih.gov/detailedresult?img=PMC3355043_1757-7241-20-22-7&query=somatosensory%20evoked%20potentials&it=xg&req=4&npos=23
https://openi.nlm.nih.gov/detailedresult?img=PMC3521820_cln-67-12-1511-g002&query=Diffuse%20Cerebral%20Edema%20from%20cardiac%20arrest&it=xg&req=4&npos=8

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