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CONCEPTS

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Early risk stratification after resuscitation from cardiac arrest

Patrick J. Coppler PA-C[1] | **Clifton W. Callaway MD, PhD**[1] | **Francis X. Guyette MD, MS**[1] | **Maria Baldwin MD**[2] | **Jonathan Elmer MD, MS**[1,2,3]

[1]Department of Emergency Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

[2]Department of Neurology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

[3]Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Correspondence
Patrick James Coppler, PA-C, Department for Emergency Medicine, University of Pittsburgh School of Medicine, 3600 Forbes Avenue, Iroquois Building Suite 400A, Pittsburgh, PA 15260, USA.
Email: copplerpj@upmc.edu

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[Correction added on 6 May 2020, after first online publication: the citation of Figure 3 is replaced with Figure 4 in the sentence "Recent work illustrates how subtypes of post-arrest myoclonus can be differentiated using EEG (Figure 3).[76]" of Section 5.]

[Correction added on 14 May 2020, after first online publication: the value of overall survival (%) for PCAC 3 in Table 1 is changed from 30 to 40.]

Abstract

Emergency clinicians often resuscitate cardiac arrest patients, and after acute resuscitation, clinicians face multiple decisions regarding disposition. Recent evidence suggests that out-of-hospital cardiac arrest patients with return of spontaneous circulation have higher odds of survival to hospital discharge, long-term survival, and improved functional outcomes when treated at centers that can provide advanced multidisciplinary care. For community clinicians, a high volume cardiac arrest center may be hours away. While current guidelines recommend against neurological prognostication in the first hours or days after return of spontaneous circulation, there are early findings suggestive of irrecoverable brain injury in which the patient would receive no benefit from transfer. In this Concepts article, we describe a simplified approach to quickly evaluate neurological status in cardiac arrest patients and identify findings concerning for irrecoverable brain injury. Characteristics of the arrest and resuscitation, initial neurological assessment, and brain computed tomography together can identify patients with high likelihood of irrecoverable anoxic injury. Patients who may benefit from centers with access to continuous electroencephalography are discussed. This approach can be used to identify patients who may benefit from rapid transfer to cardiac arrest centers versus those who may benefit from care close to home. Risk stratification also can provide realistic expectations for recovery to families.

KEYWORDS

anoxic brain injury, brain CT, cardiac arrest, electroencephelography, Lance–Adams syndrome, myoclonus, neurological prognostication, outcome, seizure

1 | INTRODUCTION

Emergency clinicians often manage patients resuscitated from cardiac arrest.[1] Like acute myocardial infarction,[2] ischemic stroke,[3] and trauma,[4] management of out-of-hospital cardiac arrest patients is complex and requires a multidisciplinary system of care capable of providing time-sensitive interventions. Patients treated at high volume centers with organized systems of care have better survival and neurological recovery.[5-15] Although considerable between-center variability persists,[16-18] nearly half of patients resuscitated from out-of-hospital cardiac arrest can survive. Nevertheless, some patients resuscitated from out-of-hospital cardiac arrest exhibit early signs of irrecoverable brain injury. These patients are unlikely to derive benefit from aggressive interventions or transfer to specialty care.[19] It falls upon emergency department clinicians to perform early risk stratification after return of spontaneous circulation to identify patients likely to benefit from aggressive care.

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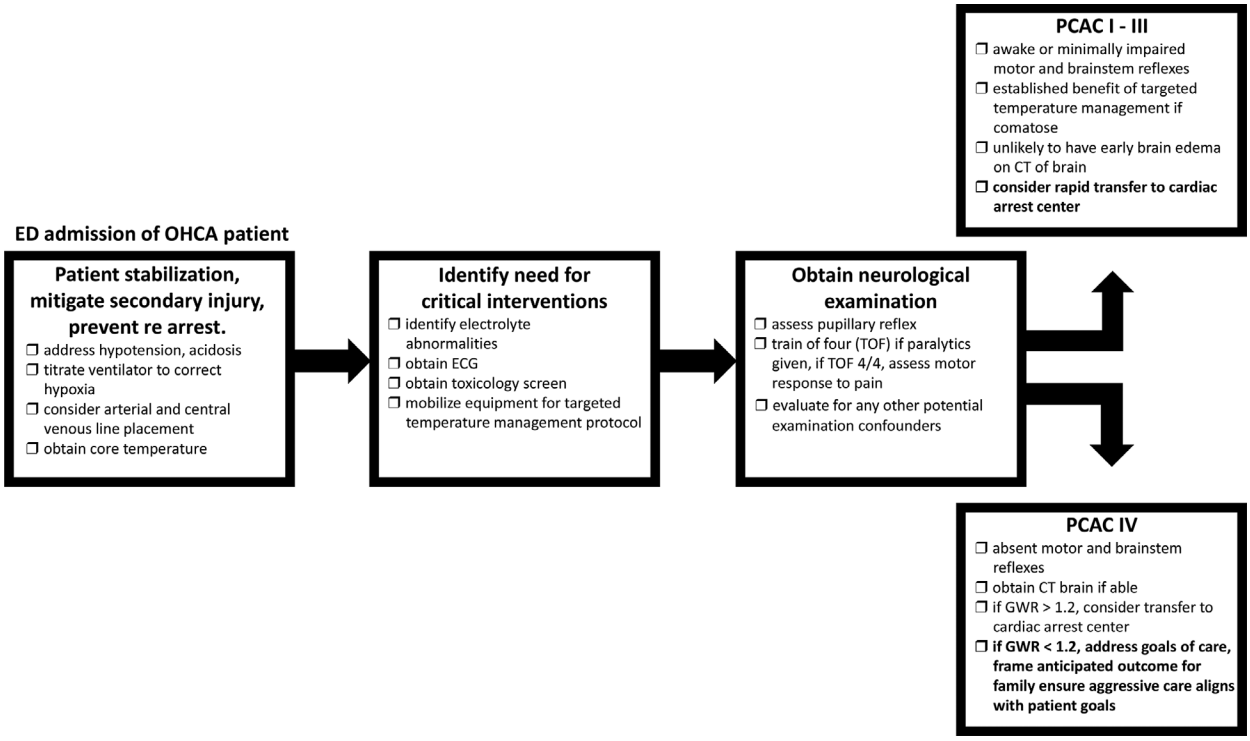

FIGURE 1 Flow diagram of post-cardiac arrest patient evaluation. Abbreviations: CT, computed tomography; ECG, electrocardiograph; ED, emergency department; GWR, gray-white ratio; OHCA, out-of-hospital cardiac arrest; PCAC, Pittsburgh Cardiac Arrest Category

Consensus guidelines recommend delaying neurological prognostication after cardiac arrest for days after return of spontaneous circulation.[20-22] These guidelines aim to limit the risk that patients who are capable of recovery will undergo premature withdrawal of life-sustaining therapies. Guidelines also highlight potential for shock, hypothermia, and medications to obscure accurate neurological assessment and emphasize a dearth of highly specific tests early after return of spontaneous circulation that definitively preclude recovery. Nevertheless, recent research suggests early risk stratification is possible in most post-arrest patients. This review provides an overview of early neurological evaluation in post-anoxic coma and describes an accessible approach to early neurological risk stratification (Figure 1).

2 | ARREST CHARACTERISTICS

Emergency medical services (EMS) can provide an array of prognostic information to emergency clinicians. Characteristics including witnessed collapse,[23] provision of bystander cardiopulmonary resuscitation (CPR) and automated external defibrillator shocks,[24-26] shockable initial rhythm,[27] and short resuscitations are associated with better outcomes.[28] Whether there are characteristics (eg, unwitnessed asystolic arrests) or thresholds (eg, a particularly arrest duration) that preclude recovery is less clear.

A secondary analysis of the Resuscitation Outcomes Consortium Prehospital Resuscitation Using an Impedance Valve and Early Versus Delayed (ROC-PRIMED) trial explored the relationship between CPR duration and out-of-hospital cardiac arrest outcomes. They found survival to hospital discharge worsened with each additional minute of CPR. Of 905 subjects with favorable functional outcomes at discharge, 90% achieved return of spontaneous circulation within 20 min, and 99% achieved return of spontaneous circulation within 37 min. Patients who underwent prolonged CPR (20–40 min) and recovered had other favorable arrest characteristics (witnessed arrests, bystander CPR, and/or shockable initial rhythms).

These data highlight the complex interaction between time-dependent and time-invariant arrest characteristics that affect brain injury severity. Unfortunately, reports of certain arrest characteristics (eg, duration) are unreliable or may require retrieval of records that are not immediately available in the emegency department (ED). [29] Our approach is to corroborate historical indicators of arrest characteristics with objective measures including initial serum lactate, shock severity, and baseline neurological assessment (see below) rather than relying on only historical details for medical decision making. When a patient appears better than the historical report (eg, lactate is low and neurological exam is vigorous), we would always discount the bad historical features in favor of providing more aggressive care for the patient.

In general, patients with multiple unfavorable characteristics (>40 min CPR, unwitnessed arrest, and a non-shockable initial rhythm) are very likely also to have significant brain injury on examination. These patients may not benefit from additional treatments (see below, Table 1). Conversely, patients with witnessed arrest, shockable initial rhythms, and/or brief arrest durations are likely to present with lower illness severity and have higher probability of favorable outcomes. It is reasonable to proceed rapidly with aggressive resuscitative measures,

TABLE 1 Stratification of cardiac arrest illness severity with the Pittsburgh Cardiac Arrest Category and consideration for initial neurological workup and triage

	Examination	Common reported arrest characteristics	Overall survival (%)	Care considerations
PCAC 1	Awake: follows simple commands, purposeful movements	Witnessed arrest, bystander CPR, shockable initial rhythm, brief arrest (5–10 min), few if any ACLS drugs given	80	Care and triage directed at etiology of arrest, minimal immediate neurological injury concern
PCAC 2	Coma with mild cardiopulmonary failure: minimal difficulty maintaining oxygenation, ventilation, and norepinephrine ≤0.1 μg/kg/min or equivalent dose	Witnessed arrest, shockable or non-shockable initial rhythm, moderate CPR time (10–20 min), <5 epinephrine administered	60	Consider triage to high volume center with cardiac catheterization and EEG capability; monitor for any abnormal movements concerning for seizure activity
PCAC 3	Coma with severe cardiopulmonary failure: hypoxemia with high ventilator requirements, high doses of vasopressors >0.1 μg/kg/min or equivalent dose	Witnessed arrest, shockable or non-shockable initial rhythm, moderate CPR time (10–20 min), <5 epinephrine administered	40	Focus on immediate stabilization; consider triage to high volume center with cardiac catheterization and EEG capability; monitor for any abnormal movements concerning for seizure activity
PCAC 4	Deep coma: absent pupil and/or corneal responses with no movement of extremities regardless of cardiopulmonary status	Unwitnessed, non-shockable, prolonged CPR time (>30 min), >5 epinephrine administered, possible drug overdose-related arrest	10	Consider CT brain to evaluate for malignant cerebral edema; if edema diagnosed, consider triage options with likely outcome in mind; confirm with decision makers code status, aggressive care in line with patient preferences and goals

Abbreviations: EEG, electroencephalography; CPR, cardiopulmonary resuscitation; CT, computed tomography; PCAC, Pittsburgh Cardiac Arrest Category.

coronary revascularization (if indicated) and transfer to specialty care without delay for additional diagnostics and treatment. The association of prolonged CPR with worse chance of recovery does not apply to all patient subgroups, particularly those with hypothermia from exposure [30–32] or refractory ventricular dysrhythmias,[32,33] both of which may do well despite prolonged resuscitation efforts.

3 | PHYSICAL EXAMINATION

Permanent brain injury begins within minutes of cardiac arrest.[34] Only about one quarter of resuscitated patients have brief arrest durations (eg, a single automated external defibrillator shock) and are awake on ED arrival.[35] We define awake as following commands or making purposeful movements (eg, gesturing or using fine motor control to pull at lines and devices). The remainder of patients are comatose. A focused early neurological assessment of brainstem reflexes and motor examination can quantify severity of coma. Of note, a substantial proportion of patients without neurological responses in the minutes after return of spontaneous circulation regain some or all function during the subsequent hours.[36] Therefore, repeated assessments are more informative than a single exam. The full outline of unresponsiveness (FOUR) score is one well-validated instrument designed for assessing any comatose patient that includes a full and thorough cranial nerve and motor assessment.[37,38] For the comatose post-cardiac arrest patient, assessment of motor response to pain and pupillary reflex are key components of the FOUR score that can drive decision making regarding further neurological testing as we further discuss below.

Organ dysfunction and shock are also key findings on initial examination that can stratify illness severity and probability of recovery. The Sequential Organ Failure Assessment (SOFA) score is one instrument that quantifies multiple organ systems and has been used for stratification of many critical illnesses.[35,39] In post-cardiac arrest patients, initial cardiovascular and pulmonary subscales of the SOFA score are associated with survival and recovery.[35,40] In practice, clinicians will titrate the ventilator and vasoactive drugs during resuscitation and during the first hours after return of spontaneous circulation. Clinical assessment of the cardiovascular and pulmonary SOFA subscales requires simply inspection of the fraction of inspired oxygen and doses of vasopressors currently required to maintain adequate oxygenation and blood pressure.

We developed a simple scheme to risk-stratify post-arrest illness based on the best neurological exam within the first 6 h after return of spontaneous circulation and severity of cardiopulmonary failure (Table 1). The Pittsburgh Cardiac Arrest Category (PCAC) is a validated illness severity tool that is highly predictive of survival and functional outcome at hospital discharge.[35,40] This score is based on the motor and brainstem subscales of the FOUR score,[38] and cardiovascular and respiratory subscales of the SOFA score.[39] Illness severity ranges from: PCAC I, awake and following commands; PCAC II, comatose without cardiopulmonary failure; PCAC III, comatose with cardiopulmonary failure (severe hypotension and/or hypoxemia); and PCAC IV, severe coma with loss of some brainstem reflexes regardless of cardiopulmonary status. Survival decreases in a stepwise fashion. PCAC I patients have 80% survival, with mortality mostly due to underlying cardiac arrest etiology and comorbidities. PCAC IV patients have 10%

survival, 5% good neurological and functional recovery, and deaths are generally due to severity of brain injury. An advantage of PCAC compared to other illness severity scores[41-45] is that only requires data that are readily obtainable in the ED, rather than arrest characteristics that may be unavailable or conflicting via verbal handoff and written report.[29]

Assessing PCAC within the first 6 h after return of spontaneous circulation allows initial resuscitative efforts to correct confounders such as profound acidosis or shock and allows some reconstitution of neuronal energetics and function.[46] Although the optimal timing of targeted temperature management is uncertain,[47] studies demonstrating benefit to targeted temperature management have initiated cooling within 6–8 h of return of spontaneous circulation.[48-50] Therefore, neurological assessment within 6 h of resuscitation does not excessively delay time to definitive treatment and can be done as equipment for targeted temperature management is mobilized and interventions to correct hypotension, hypocarbia, and hypoxemia are used to limit secondary brain injury. As multisystem organ failure is addressed, the neurological assessment may improve such that an initial PCAC IV may regain some motor function or brainstem reflexes and be re-categorized as a less severely injured classification. We perform neurological assessments on admission to the emergency department then typically again after procedures and diagnostics such as central venous lines, arterial lines, chest radiography, or computed tomography (CT) imaging are performed.

In practice, PCAC can inform clinical decision making. In our prior work, we found that patients receiving care at a high volume center have better long-term outcomes, regardless of PCAC.[7,51] At our institution, PCAC types I–III have higher survival after urgent coronary angiography when a cardiac etiology is suspected, whereas PCAC IV patients have no benefit from emergency angiography.[19] We discuss these expectations when advising families about decisions for procedures and interventions in comatose patients. In the future, this approach of selecting therapies based on illness severity may guide other interventions and therapies.[52] Regardless, PCAC provides some initial information regarding general, early expectations of severity of illness and potential for recovery for families or surrogate decision makers. PCAC also sets the pre-test likelihood of survival for the treating team, who can then revise this estimate during the next few days when additional prognostic tests or information become available.

Clinicians should use extreme caution when there are confounding variables that may affect physical examination findings. Acidosis, hypotension, hypoxemia, intoxicants such as prescription or recreational drugs, or pre-existing conditions can cloud the initial examination. We serially examine patients as we address and correct their multisystem organ failure to evaluate for improvements in neurological assessment. We specifically ask EMS about any sedatives or paralytics given during transport. If a patient has no obvious movement, we use a nerve stimulator (train of 4) to exclude residual neuromuscular blockade, as drug clearance can be severely impaired after cardiac arrest, during hypothermia, and following liver injury.[53,54] Overdose-related cardiac arrests are common.[55] In a prior analysis, we found that overdose-related cardiac arrest patients present with deeper coma compared to non-overdose-related arrests.[56] Despite this, functional outcomes at hospital discharge are similar. A comprehensive urine drug screen, even if overdose is not suspected, can identify sedating medications. Small pupils should raise suspicion of opioid overdose, administration of fentanyl prior to examination, as well as the possibility for a neurological etiology of arrest such as pontine hemorrhage. Dilated pupils may be due to atropine administered during resuscitation. However, mid-position fixed pupils are likely due to anoxic injury.[57] Bedside pupil assessments have limitations. When compared to infrared pupillometry, pupil reactivity assessments with pen lights can be inaccurate, especially with small pupil sizes such that reactivity is falsely absent.[58,59] There is no physical examination finding immediately post-return of spontaneous circulation associated with universal futility.[60,61] For example, a recent study of >10,000 post-arrest patients in France showed that 64% had nonreactive pupils on presentation, of whom 10% enjoyed favorable recoveries.[62] A core temperature, preferably esophageal or bladder, may reveal accidental hypothermic cardiac arrest. These patients require a fundamentally different treatment strategy and can have a survival rate >70% despite initial moribund appearance.[63]

4 | BRAIN COMPUTED TOMOGRAPHY

Brain CT imaging is a useful early diagnostic and prognostic modality that is available in every ED. CT is objective and not confounded by medications, shock, or other limitations of history and physical exam. In 5%–10% of cases, CT identifies the inciting etiology of arrest (eg, subarachnoid hemorrhage).[64] Moreover, early severe cerebral edema is strongly prognostic after cardiac arrest.[65] Loss of blood flow, oxygen, and glucose delivery to neurons results in energetic failure and loss of necessary adenosine triphosphate for active ion transport channels.[66] This dysfunction results in higher concentrations of intracellular water (cytotoxic or anoxic edema). When mild, this edema may be reversible, but, when early and severe, this edema can result in irreversible loss of cerebral perfusion or herniation.

The radiographic density of gray matter is a radiographic correlate of cerebral edema, because gray matter attenuation of X-rays decreases as tissue water increases. This radiographic change appears as a decrease in the ratio of X-ray attenuation (Hounsfield units) in anatomically well-defined gray matter versus white matter structures: the gray–white ratio.[67] Simple locations to measure this ratio are at the level of the basal ganglia, where the caudate nucleus and posterior limb of the internal capsule can be measured in a single CT slice (Figure 2). In normal brain CTs, gray–white ratio is ≈1.30–1.40. Although intact gray–white ratio does not necessarily forecast a good neurological outcome, loss of differentiation with a gray–white ratio <1.20 is associated with much lower probability of neurological recovery,[65,67,68] and a gray–white ratio <1.10 is 100%- specific for poor neurological outcome.[69]

Qualitative signs of severe edema, which correlate with lower gray–white ratio, include effacement of the cerebral sulci, loss of basal cisterns including the prepontine space and quadrigeminal plate,

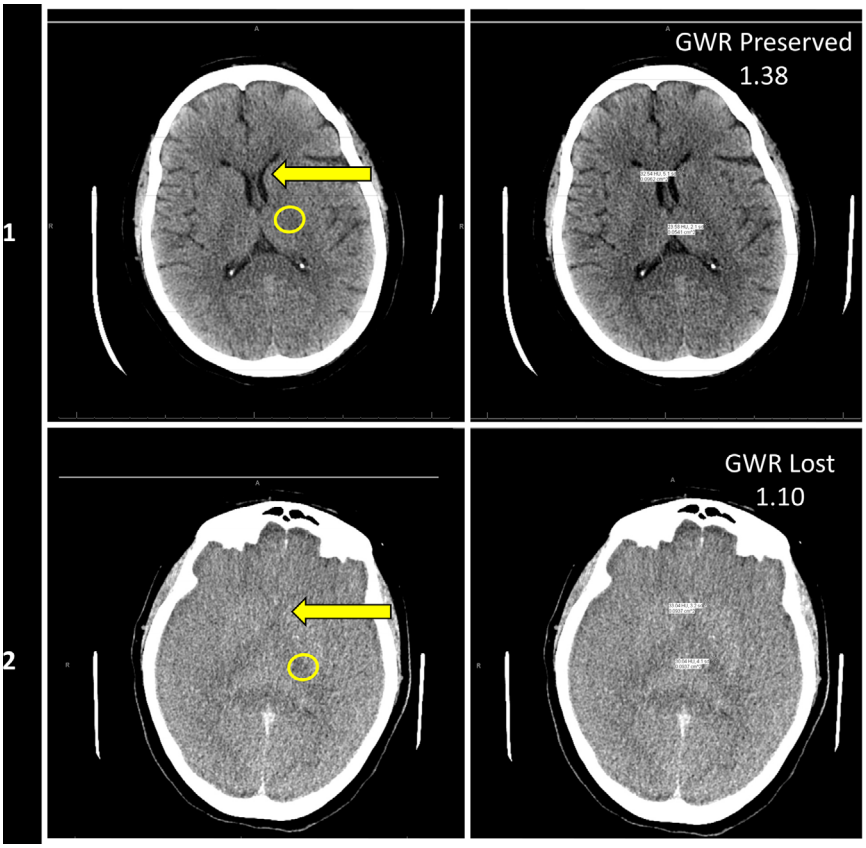

FIGURE 2 Calculation of gray–white ratio on brain computed tomography (CT). Two patients cared for at our facility status post-cardiac arrest for which CT brain was obtained. Gray–white ratio calculated by placing a region of interest on the head of the caudate nucleus (yellow arrow) and on the posterior limb of the internal capsule (yellow ring). Patient 1 with preserved gray–white ratio and patient 2 with sulcal effacement, absence of basal cisterns, and loss gray–white ratio

crowding of the foreman magnum, and pseudosubarachnoid hemorrhage (Figure 3). If encountered, these findings are highly concerning for irrecoverable brain injury.[70,71] Unless overt hemodynamic instability precludes a CT scan, we obtain initial brain imaging in all comatose post-arrest patients. Patients with >30 min of CPR have >40% prevalence of cerebral edema on initial CT brain.[72]

5 | ELECTROENCEPHALOGRAPHY MONITORING AND SEIZURES

Post-arrest patients develop epileptiform electroencephalography (EEG) activity or seizures in 25%–50% of cases.[73,74] Abnormal EEG patterns often do not have any clinical correlate and can only be identified with EEG monitoring (non-convulsive status epilepticus). Presence of seizures is a sign of worse brain injury, which influences assessment of illness severity. However, some post-cardiac arrest seizures are amenable to treatment, and patients with convulsive or non-convulsive seizures can recover with aggressive treatment and comprehensive supportive care.[79] We consider EEG monitoring critical during early evaluation of post-cardiac arrest coma.

Post-arrest myoclonus is another clinical entity, which is probably distinct from post-cardiac arrest seizures. Myoclonic jerking has historically been viewed as ominous but about 10% of patients with myoclonus can have full recovery.[75] Myoclonus varies from dramatic whole body jerks to subtle eyelid fluttering. Recent work illustrates how subtypes of post-arrest myoclonus can be differentiated using EEG (Figure 4).[76] Malignant myoclonus that occurs in association with high-amplitude polyspike bursts ("burst-suppression with identical bursts") portends a dismal prognosis and is likely a sign of catastrophic brain injury. In contrast, Lance-Adams syndrome is a post-anoxic movement disorder in which the patients have cortical background activity on EEG, with or without narrow spike wave discharges. Nearly half of cases with Lance-Adams syndrome will ultimately awaken from coma, but awakening may be delayed up to 2–4 weeks post-arrest.[76] Physical examination findings alone cannot differentiate between malignant myoclonus and Lance-Adams syndrome. Identifying the subtype of post-anoxic myoclonus is critical to distinguish patients with and without reasonable expectations of recovery, and identification requires expertise in interpreting the neurophysiological findings (Figure 4).

When we encounter abnormal movements that are concerning for myoclonus or seizure activity, we use propofol with or without ketamine to suppress the motor manifestations. It does not appear at this time that early antiepileptic drugs change the natural history of malignant myoclonus or Lance-Adams syndrome, and therefore, we do not add these drugs routinely.[78] If there is clinical concern for true status epilepticus, we treat with bolus doses of benzodiazepines and conventional anti-epileptics. [77] There is no established role for prophylactic anticonvulsants in patients with no clinical or EEG findings of seizures. All comatose patients should be admitted to a setting where serial or continuous EEG is available.

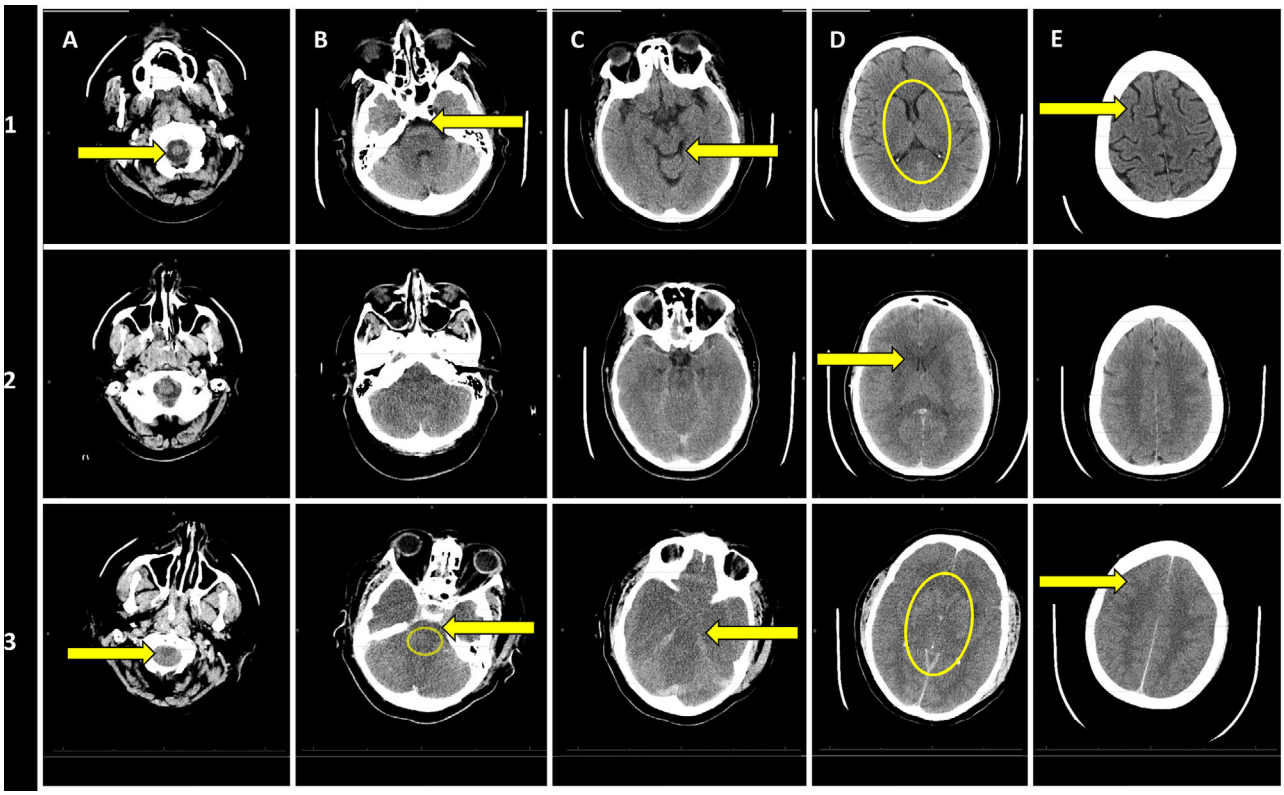

FIGURE 3 Qualitative characteristics concerning for malignant brain edema. Three patients cared for at our facility status post-cardiac arrest for which computed tomography (CT) brain was obtained representative of (1) normal appearance, (2) intermediate anoxic findings, and (3) severe anoxic injury. Patient 1: (column A) open foreman magnum (arrow); (column B) open prepontine space (arrow); (column C) quadrigeminal plate open (arrow); (column D) normal appearing lateral ventricles (oval); and (column E) normal appearing cortical sulci. Patient 2: (column A) low hanging cerebellar tonsils without herniation; (column B) absent prepontine space; (column C) absent quadrigeminal plate; (column D) narrow lateral ventricles, early caudate nucleus infarction (arrow); and (column E) incomplete effacement of cortical sulci. Patient 3: (column A) foreman crowded with cerebellar tonsils concerning for tonsillar herniation; (column B) effaced prepontine space and hypodense brainstem (circle); (column C) quadrigeminal plate effaced, pseudosubarachnoid sign (arrow); (column D) absence of lateral ventricles (oval), infarction of the basal ganglia; and (column E) complete effacement of cortical sulci

6 | INTEGRATED APPROACH TO RISK STRATIFICATION

After resuscitation and stabilization of vasoactive medications and ventilation, clinicians should assess post-cardiac arrest patients using physical examination. Based on this examination, CT of the brain and EEG should be considered (Figure 1). Awake patients (PCAC I) have an excellent (80%) chance of recovery, and aggressive treatment of the underlying cause of arrest should be expedited. Mild-moderate comatose patients with preserved pupillary and other brain stem reflexes and some motor response (PCAC II) have a 60% chance of recovery, and also will benefit from aggressive support and treatment. If severe cardiopulmonary dysfunction is present with mild-moderate coma (PCAC III), expected survival is reduced to 30% and will require advanced cardiopulmonary support. Among deeply comatose patients with missing pupil responses and brainstem reflexes (PCAC IV), expected survival is only 10% and some procedures may not improve this rate.

CT of the brain will identify a subset of the PCAC IV patients with severe cerebral edema (gray–white ratio <1.1, sulcal effacement, loss of cisterns) with negligible chance of recovery or benefit from any non-experimental treatments (Figures 2 and 3). These CTs also will identify some patients with devastating intracranial hemorrhage or stroke that also alters prognosis. Borderline cerebral edema (gray–white ratio 1.1–1.2) on CT scan has a low chance of recovery and only with very aggressive neurocritical care. Finally, jerking movements may represent a seizure or myoclonus. Early EEG, with expert interpretation, can distinguish malignant myoclonus with negligible chance of recovery from Lance-Adams syndrome or more benign movements. Aggressive treatment of seizures or non-convulsive status epilepticus identified on EEG also allows survival for some patients.

7 | CONCLUSION

Resuscitated cardiac arrest patients are frequently encountered in all EDs. Emergency clinicians are tasked with immediate stabilization, diagnostic workup, and triage to either the local intensive care unit or transfer to facilities capable of providing required interventions. We provide a simple approach for risk stratification, using initial

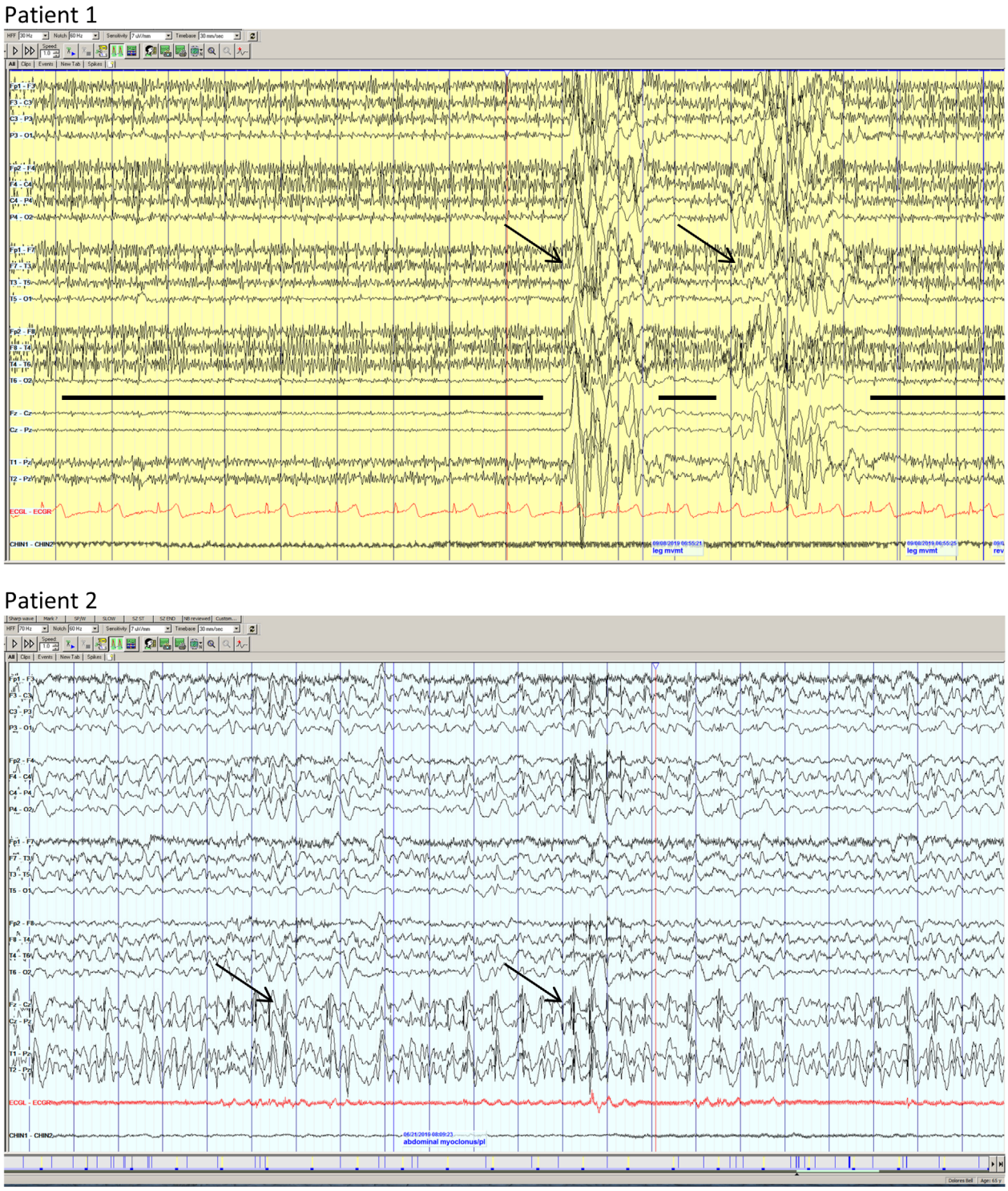

FIGURE 4 Electroencephalography (EEG) characteristics of malignant myoclonus versus early Lance-Adams syndrome. Two patients cared for at our facility post-cardiac arrest. Both patients developed similar appearing intermittent axial muscle jerks and associate eye opening. Patient 1 with suppression burst pattern with identical polyspike wave bursts time locked to movements, diagnostic of malignant myoclonus. EEG suppression (bars) with identical polyspoke wave bursts (arrows). Patient 2 with continuous, reactive background with intermittent central spikes time locked to movements (arrows), diagnostic of early Lance-Adams syndrome

neurological examination, assessment of cardiopulmonary dysfunction, CT of the brain, and early EEG. This approach can guide clinicians and families through decisions regarding procedures, transfer or admission to local hospital, and this approach can provide a starting point for the prognostic testing over the subsequent days.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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