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Clinical paper

The prognostic value of quantitative diffusion-weighted MRI after pediatric cardiopulmonary arrest

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Abstract

Objectives: The prognostic value of quantitative diffusion-weighted magnetic resonance imaging (DWI MRI) in predicting neurologic outcomes after pediatric cardiopulmonary arrest (CPA) has not been determined. The aim of this study was to identify a DWI MRI threshold for brain volume percent that correlates with neurologic outcome in children who remain comatose or display significant neurologic deficits immediately after resuscitation from CPA.

Methods: This single-center retrospective study analyzed DWI MRIs of pediatric patients who remained neurologically impaired after CPA. Any MRI obtained within 2 weeks after CPA was analyzed. The apparent diffusion coefficient (ADC) value of each voxel within the brain was determined. Percentage brain volume with voxels below each ADC threshold between 300 and 1200 $\times 10^{-6}$ mm^2/s with a step of 50 were calculated. Area under the receiver operating characteristics curve (AUC) was used to identify optimal DWI MRI thresholds for brain volume percent most predictive of poor neurologic outcome. The primary outcome measure was neurologic outcome 6-months after CPA based on Pediatric Cerebral Performance Category (PCPC) score. Poor neurologic outcome was defined as PCPC score of 3–6, or a worsening from baseline score $\geq$1 if baseline PCPC score was $\geq$3.

Results: Twenty-six patients were included in this study. The median age was 8.5 years (2.2–14) and median time from CPA to MRI was 4 days (2–7). Two ADC thresholds for brain volume percent had the largest AUC for predicting poor neurologic outcome. An ADC threshold of $<600 \times 10^{-6}$ mm^2/s in $\geq$7% of brain volume; and $<650 \times 10^{-6}$ mm^2/s in $\geq$11% of brain volume both demonstrated a specificity of 1.0 (0.76–1.0, 95% CI) and a sensitivity of 0.8 (0.44–0.96, 95% CI) for poor outcome.

Conclusions: In pediatric patients who remain comatose or have significant neurologic deficits after CPA, quantitative DWI MRI correlates with neurologic outcome. Both an ADC threshold of $<600 \times 10^{-6}$ mm^2/s in $\geq$7% of brain volume and $<650 \times 10^{-6}$ mm^2/s in $\geq$11% of brain volume are highly specific for predicting poor neurologic outcome. A prospective trial to validate these thresholds is needed.

Keywords: DWI, Neurologic outcome, Pediatric cardiopulmonary arrest, Prognosis, Quantitative brain MRI

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Introduction

Out-of-hospital cardiopulmonary arrest (CPA) affects about 16,000 children in the United States every year.[1] In addition, an estimated 5800 children experience in-hospital CPA every year[2]. Despite improvement in the quality of cardiopulmonary resuscitation, CPA often results in death or poor long-term neurologic outcome in survivors.[3] Hypoxic-ischemic neurological injury after CPA is a significant cause of death and neurologic morbidity.[4–11] In practice, clinical care decisions often depend on the degree of neurological compromise and the early and long-term prognosis, thus the ability to reliably and accurately predict clinical outcome is critical. However, rendering neurologic prognosis in the first few days after arrest is challenging, particularly in patients who remain comatose or display severe neurological deficits. Acknowledging the limits of prognostication is important to prevent premature or inappropriately pessimistic prognostication leading to care limitations. One study demonstrated that prediction accuracy was poor on initial presentation after CPA and improved over the first 7 days of care.[12] Multiple prognostic variables (e.g. neurologic examination, neurophysiologic tests, and serum biomarkers of brain injury) are currently used.[13–16] However, these have significant limitations because they identify only a subset of poor outcome patients with high specificity.[17,18] In addition, the neurologic examination and the results of neurophysiologic tests may be confounded by the effects of sedation, analgesia, neuromuscular blockade, or metabolic derangements. And serum biomarkers may be susceptible to false-positive test results and are not yet readily available in many institutions.[19]

Neuroimaging, specifically magnetic resonance imaging (MRI), is performed after CPA to evaluate for hypoxic-ischemic brain injury. Combining qualitative MRI findings with neurological scales, such as Glasgow coma scale, may improve poor outcome prediction.[20] However, qualitative MRI may not be useful in the very early period after CPA when findings can be subtle or absent.[21,22] In the early evaluation of ischemia, lesions are better identified using diffusion weighted imaging (DWI) MRI which measures the diffusion of water molecules reflecting random (Brownian) motion, capillary flow, and transcellular active transport. Cytotoxic edema after ischemia results in decreased or restricted movement of water along the studied plane in this sequence. DWI MRI can therefore be used to diagnose global hypoxic-ischemic brain injury and may provide valuable prognostic information regarding short- and long-term outcome as the radiographic findings correlate with neuropathological changes.[23,24]

The rate of diffusion can be quantified by the apparent diffusion coefficient (ADC) which is an additional sequence that summarizes the diffusion in all three dimensions.[25] ADC values in different structures in normal brain have been identified, as have the thresholds to identify ischemic brain.[26,27] In adult comatose CPA survivors, whole brain ADC values correlate with outcome.[28,29] One single-center study found that an ADC threshold $<650 \times 10^{-6}\,mm^2/s$ in >10% of whole brain volume is correlated with poor outcome defined as death or vegetative state. This degree of severe ADC restriction identified poor outcome with a 100% specificity and 81% sensitivity.[29] A follow up multi-center study confirmed that an ADC value of $<650 \times 10^{-6}\,mm^2/s$ in ≥10% of brain volume can differentiate comatose post-cardiac arrest patients with poor versus good outcomes with a high specificity (91%, 95% CI 75–98%) and good sensitivity (72%, 95% CI 61–80%).[30]

In pediatric CPA survivors, abnormal DWI MRI in the cortex and basal ganglia based on qualitative MRI interpretation was shown to correlate with poor outcome.[31] On quantitative DWI MRI, global and regional ADC was decreased in children with unfavorable outcome.[32] However, quantitative whole brain ADC and brain volume thresholds that correlate with outcome have not been determined in pediatric CPA survivors. The aim of this study was to use quantitative DWI MRI to identify ADC and brain volume thresholds that correlate with neurologic outcome in pediatric survivors of CPA.

Methods

Patient population and data collection

This was an IRB-approved single center retrospective study of pediatric patients admitted to the pediatric or pediatric cardiovascular intensive care unit who remained neurologically impaired after CPA. We defined a CPA event as any out-of-hospital or in-hospital event with at least 2 min of chest compressions for pulselessness. Patients >1 week to ≤18 years of age who received a clinically-indicated brain MRI within 2 weeks after CPA between May 2014–June 2017 were included. Post-resuscitation care was provided per standard of care by the primary treatment team and included prevention of secondary neurologic injury, evaluation and treatment of the underlying cause of CPA, maintenance of normoxemia, normocarbia, and normal mean arterial blood pressure for age, use of rectal and/or esophageal temperature probes for continuous temperature measurement, maintenance of normothermia, and aggressive treatment of fever (>38 °C). Pain and agitation were treated, and medications were used at the discretion of the treatment team. MRIs were obtained as part of clinical care when the patient was deemed safe for transport.

Patients were identified using an existing prospective CPA database. Demographic and clinical data were captured using chart review and recorded and managed using REDCap electronic data capture tools hosted at Stanford University.[33] Data collected included patient demographics, CPA characteristics, resuscitation details, post-resuscitation care, serial neurological exam findings, ICU course and length of stay, hospital length of stay, MRI results, neurologic outcome reported as Pediatric Cerebral Performance Category (PCPC) Score at hospital discharge and at 6-month post CPA, and date and cause of death.

Neurologic outcomes

The primary outcome measure was neurologic outcome 6-months after CPA based on the Pediatric Cerebral Performance Category (PCPC) score. The PCPC is a validated 6-point scale of functional morbidity and cognitive impairment after illness or injury. The categories are: (1) normal; (2) mild disability; (3) moderate disability; (4) severe disability; (5) coma and vegetative state; and (6) death.[34] Poor neurologic outcome was defined as PCPC score of 3–6, or a worsening from baseline score ≥1 if baseline score was ≥3. Baseline PCPC score was determined from the electronic medical record based on an admission report or, when available, a pre-arrest physical exam or prior medical visits. PCPC score 6-months after CPA was determined based on pediatric neurologists' assessments during follow-up visits.

Magnetic resonance imaging protocol

Twenty-four to 42 contiguous DWI sections per patient were acquired using a 1.5T GE Optima MR450w or 3T DISCOVERY MR750 scanners (GE Medical Systems, Waukesha, WI). Images were acquired with spin-echo planar imaging: 256 × 256 matrix; field of view 200–250 mm; slice thickness 4 mm (one scan 5 mm) with gap 0–1.5 mm; flip angle 90, *x*-, *y*-, *z*-axes averaged; b0 and 1000 s/mm^2. ADC maps created by the manufacturer standard software were used. To skull strip scan and extract brain mask, we used MRIcron software (MRIcron, Version 1, June 2015, Chris Rorden, University of South Carolina), which implements Brain Extraction Tool. Brain masks were created from b0 images and saved. Using in-house created software in Matlab version R2017a (The MathWorks, Inc., Natick, MA), we applied brain masks to ADC images. To minimize artifacts, noise, and fluid component we considered ADC $<2000 \times 10^{-6}$ mm^2/s for the brain volume and ADC between 200–1200 $\times 10^{-6}$ mm^2/s for the ADC distribution analysis within the brain tissue. The program produced spreadsheets with the total brain volume, the mean brain ADC value, and the percentage of voxels below different ADC thresholds.

Statistical analysis

Mann–Whitney U test was used to determine differences between the two groups on continuous or ordinal variables, while Fisher Exact test was used to compare categorical data. Empirical receiver operating characteristic (ROC) analysis was used to analyze brain volume percentages below each ADC threshold to determine the best correlation with poor neurologic outcome. Youden's index was used to determine the optimal volume and ADC cut-offs, defined as the cut-point that achieved the highest combined sensitivity and specificity.[35] Variables significant at $\alpha < 0.05$ in univariable analysis were included to test the independence of the MRI ADC thresholds as predictors of the outcome when adjusted individually for each factor in the logistic regression analysis. All statistical tests were two-sided and considered significant at $\alpha < 0.05$. Statistical analysis was conducted with IBM SPSS Statistics, version 24 (IBM Corp., Armonk, N.Y., USA)

Results

Sixty-three children were identified with CPA between May 2014–June 2017 and 26 met inclusion criteria for this analysis (Fig. 1). Patient and CPA characteristics are shown in Table 1. The median age was 8.5 years (IQR 2.2–14) and 18 (69%) were male. Sixteen (62%) patients had an out-of-hospital CPA. Causes of pre-arrest PCPC >1 are summarized in Table 2 and the distribution of the pre-arrest PCPC score is shown in Fig. 2. Twenty-one (81%) patients had a pre-arrest PCPC score of 1–2 (normal or mild disability) and 5 (19%) had a pre-arrest PCPC score of 3–4 (moderate or severe disability).

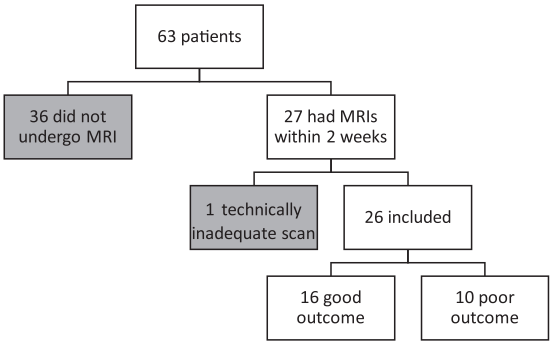

Fig. 1 – Enrollment flowchart.

Sixteen (62%) patients had a favorable outcome at 6-month post-arrest. Of 10 patients with unfavorable outcome, 7 died. Six patients died following withdrawal of life-sustaining therapies due to perceived poor neurologic prognosis; and 1 died of multi-organ failure. Fig. 2 summarizes PCPC score pre-arrest, at hospital discharge, and at 6-months following CPA for the study population

Median time to MRI was 4 days (IQR 2–7) after CPA. Patients with poor outcome had a longer duration of CPR than patients with good outcome and were more likely to have had an unwitnessed CPA. The cause of cardiac arrest differed between outcome groups with more arrhythmias (ventricular fibrillation, ventricular tachycardia) in the good outcome group compared to more respiratory causes/hypoxia in the poor outcome group. The number of epinephrine doses, initial lactate level, and lowest pH 24-h following CPA were not significantly different between the outcome groups.

Qualitative MRI results differed between outcome groups. In the good outcome group, 3 patients (19%) had abnormal MRIs, but only one showed findings consistent with hypoxic-ischemic injury with abnormal T2 signal in the basal ganglia bilaterally. In the poor outcome group, 9 patients (90%) had abnormal MRIs and all abnormal MRIs had findings consistent with hypoxic-ischemic injury patterns. Findings on these abnormal MRIs in the poor outcome group were: abnormal DWI in the cortex and deep grey (n = 2), abnormal DWI in deep grey only (n = 1), and abnormal T2 and DWI in the cortex and/or deep grey (n = 6).

Two ADC thresholds for brain volume percent had the largest area under the receiver operating characteristics curve (AUC) for predicting poor neurologic outcome. An ADC threshold of $<600 \times 10^{-6}$ mm^2/s in $\geq$7% of brain volume; and ADC threshold $<650 \times 10^{-6}$ mm^2/s in $\geq$11% of brain volume were both 100% specific (95% CI 76–100) and 80% sensitive (95% CI 44–96) for poor outcome, with a positive predictive value of 100% (95% CI 60–100), and a negative predictive value of 89% (95% CI 64–98).

If $\geq$7% of brain volume had an ADC $<600 \times 10^{-6}$ mm^2/s, or $\geq$11% of brain volume had an ADC $<650 \times 10^{-6}$ mm^2/s, the odds ratio of having a poor outcome was 112 (95% CI 5–2611). ROC analysis showed that ADC thresholds of $<600 \times 10^{-6}$ mm^2/s and $<650 \times 10^{-6}$ mm^2/s were good predictors of poor outcome with AUC of 0.95 (95% CI 0.88–1.0) for the former and AUC of 0.95 (95% CI 0.87–1.0) for the latter (Fig. 3).

Univariable analysis revealed three individually significant predictors of outcome in our study population (duration of CPR, witnessed CA, and cause of CA) (Table 1). We were unable to perform a full multivariable analysis including all variables that were significant alone due to limited sample size. Therefore, we tested independence of the ADC threshold predictor in combination with each of the 3 individually significant predictors of outcome. In each combination, ADC cutoffs of $\geq$7% $<600 \times 10^{-6}$ mm^2/s and $\geq$11% $<650 \times 10^{-6}$ mm^2/s remained to be independent predictors of poor outcome while any other predictor was not a significant predictor anymore in combination with the ADC predictor. In particular, *p*-value for each individually significant clinical characteristic when entered in the model together with the ADC cutoff defined by $<600 \times 10^{-6}$ mm^2/s and $<650 \times 10^{-6}$ mm^2/s thresholds were: duration of CPR −0.327, witnessed CA −0.783, and cause of CA −0.789, while corresponding *p*-values for ADC were 0.024, 0.033, and 0.027.

Table 1 – Patient and event characteristics.*

	All subjects (n = 26)	Good outcome (n = 16)	Poor outcome (n = 10)	*P* value
Age (years)	8.5 (2.2–14)	8.5 (2.6–13.2)	7 (2.8–14.8)	0.907
Sex, male/female (% male)	18/8 (69)	11/5 (69)	7/3 (70)	1.0
Location of CPA, n (%) In-hospital	10 (38)	7 (44)	3 (30)	0.683
Witnessed, n (%)	19 (73)	15 (94)	4 (40)	0.005
CPR to ROSC (min)	16.5 (8–40)	13 (7–18)	24 (20–48)	0.016
Cause of CPA, n (%)				0.039
■ Arrhythmia (VF/VT)	9 (35)	8 (50)	1 (10)	
■ Respiratory/hypoxia	10 (39)	5 (31)	5 (50)	
■ Hypotension/shock	3 (12)	2 (13)	1 (10)	
■ Other	1 (4)	1 (6)	0 (0)	
■ Unknown	3 (12)	0 (0)	3 (30)	
Initial rhythm, n (%)				0.102
■ VF/VT	11 (42)	9 (56)	2 (20)	
■ Bradycardia	6 (23)	4 (25)	2 (20)	
■ PEA/Asystole	7 (27)	3 (19)	4 (40)	
■ Unknown	2 (8)	0 (0)	2 (20)	
CPA to MRI (days)	4 (2–7)	3.5 (2–9)	4 (3–5)	0.969
PICU/CVICU LOS (days)	16.5 (6–40)	15.5 (5.5–41)	19.5 (6–25)	0.746
Hospital LOS (days)	29 (8–65)	28 (8–72.5)	29.5 (6–47)	0.887
Survival to HD, n (%)	19 (73)	16 (100)	3 (30)	<0.001

CPA, cardiopulmonary arrest; CPR, cardiopulmonary resuscitation; HD, hospital discharge; LOS, length of stay; ROSC, return of spontaneous circulation.
* Values expressed as median (interquartile range) unless otherwise indicated.

Table 2 – Causes of mild, moderate, and severe disability.

PCPC	Cause of disability
2	■ Noonan syndrome ■ Congenital myopathy ■ Attention deficit hyperactivity disorder (ADHD) and tic disorder ■ De novo sequence variant in TRAF7 gene with multiple congenital anomalies ■ Duchenne muscular dystrophy (DMD) ■ VACTERL[a] association ■ Tetralogy of Fallot with pulmonary atresia and major aortopulmonary collateral arteries (TOF/PA/MAPCAs)
3	■ Carnitine acylcarnitine translocate deficiency ■ Duchenne muscular dystrophy (DMD) ■ Wolff Hirschhorn syndrome (4p deletion syndrome) ■ Beckwith–Wiedemann syndrome
4	■ Cerebral palsy (CP)

[a] VACTERL: Vertebral anomalies, Anal atresia, Cardiac defects, TE (tracheoesophageal) fistula, Renal defects, and Limb defects.

Discussion

In this study, whole brain ADC thresholds that correlate with outcome in pediatric CPA survivors were identified. A threshold of $<600 \times 10^{-6}$ mm^2/s in $\geq$7% of brain volume or $<650 \times 10^{-6}$ mm^2/s in $\geq$11% of brain volume was highly specific and had good sensitivity for predicting poor neurologic outcome. Interestingly, the ADC threshold of $<650 \times 10^{-6}$ mm^2/s in $\geq$11% of brain volume is very similar to the threshold identified in comatose adults after CPA where several studies have shown that an ADC threshold of $<650 \times 10^{-6}$ mm^2/s in $\geq$10% of brain volume differentiated survivors with poor versus good

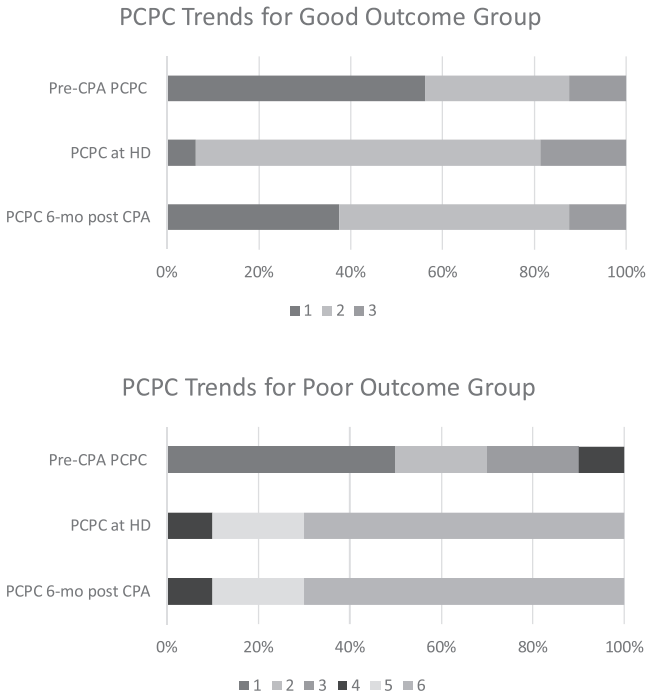

Fig. 2 – Pediatric cerebral performance category score.

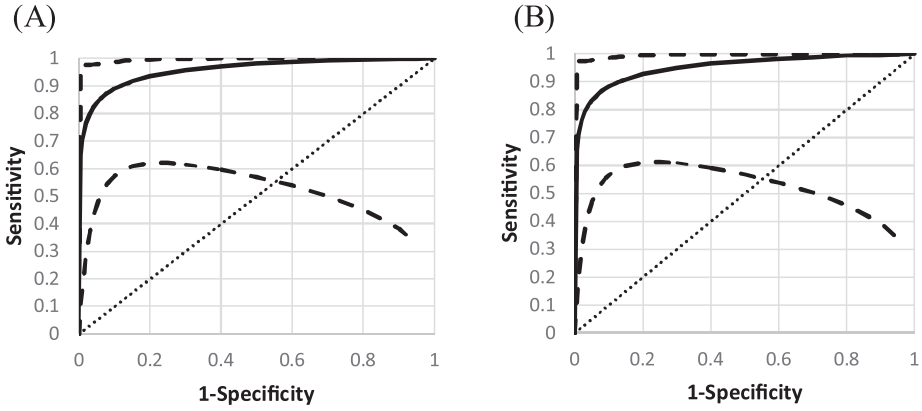

Fig. 3 – Receiver operating characteristic (ROC) curve for brain volume percent at (A) ADC $<600 \times 10^{-6}$ mm^2/s to predict poor outcome (AUC 0.95, 95% CI 0.88–1.0); and (B) ADC $<650 \times 10^{-6}$ mm^2/s to predict poor outcome (AUC 0.95, 95% CI 0.87–1.0).
Solid line represents fitted ROC curve and dashed lines represent 95% CI for the curve.

neurologic outcome.[29,30] This supports the idea that whole brain ADC maps and thresholds may be clinically useful in the prognostic evaluation of pediatric patients after CPA.

This study is unique as to our knowledge it is the first to evaluate quantitative ADC and brain volume thresholds as prognostic tools in the pediatric CPA population. The technique we used to analyze whole brain ADC values and to determine specific thresholds was simple and semi-automatic, allowing for potential ease of wider implementation. Incorporating this analysis in a multimodal approach may improve prognostication after pediatric CPA and may be especially helpful in patients who do not have other clinical or laboratory predictors of poor outcome.

Despite this promising initial result, several limitations are important to address. This was a single center retrospective study with a relatively small cohort. Validating ADC and brain volume thresholds to predict neurologic outcome in a larger, prospective multicenter sample of children is necessary to assess the generalizability of the identified thresholds. While the above mentioned adult study of coma after cardiac arrest was also able to identify an ADC threshold and a brain volume cutoff that predicted the degree of functional recovery among survivors,[30] our small sample size limited our ability to attempt determining similar thresholds, and this would be a valuable pursuit in a larger sample. Additionally, the potential for a self-fulfilling prophecy biasing the results exists since the providers were not blinded to the MRI results. The clinical team did not know the quantitative whole brain ADC values, but the qualitative MRI results were available to the clinical treatment team and could have influenced discussions about predicted outcome and decisions for withdrawal of life sustaining therapies.

Time from CPA to MRI in our study varied, which can result in variability in ADC values. If imaging is obtained too early after CPA, DWI changes may be absent, and if imaging is obtained >6 days post-arrest, a "pseudo-normalization" of ADC may occur whereby some lesions have low ADC values and others have higher ADC values due to a progressive increase in vasogenic edema and loss of cellular membrane integrity.[36,37] For these reasons, the adult literature has investigated optimal timing of obtaining DWI MRI for prognostication and obtaining MRI between 2 and 4.5 days after arrest may be an optimal window.[29] Protocolizing time from CPA to MRI when possible will help eliminate this factor in future studies. Future work should also study ADC thresholds in different aged subgroups, given that brain ADC values decrease throughout childhood and especially over the first two years of life as myelination occurs.[38] It is unclear what effect this may have on ADC thresholds that correlate with prognosis in post-CPA hypoxic-ischemic injury.

Lastly, outcomes were measured 6 months after CPA using PCPC. Many patients may go on to have significant meaningful long-term recovery over years.[39,40] Future studies should incorporate longer-term follow up and use more specific neuropsychological tests as measures of outcome to cover the broad range of developmental stages in childhood and the range of lasting neuro-cognitive sequelae after hypoxic-ischemic brain injury. It is important to recognize that boundaries between outcome categories may not be clear. Each family has values, beliefs, and their own concepts of good and poor outcome. These concepts may be subject to change over time as people adapt or incorporate disability into a meaningful life. Thus, we advocate that any prognostic discussion in a brain-injured child after cardiopulmonary arrest include both discussions of individual values and the limitations of prognostic capabilities.

Conclusions

In summary, quantitative DWI MRI is correlated with outcome and may be a useful prognostic adjunct in pediatric patients with moderate to severe neurologic deficits after CPA. Specific ADC thresholds and brain volume thresholds can help differentiate patients with poor versus good outcome with high specificity. Quantitative DWI MRI should not be used in isolation as a prognostic variable, but the technique is feasible, and incorporating quantitative DWI MRI findings with other prognostic variables may facilitate better outcome prediction after pediatric CPA.

Conflict of interest

The authors declare that they have no conflict of interest.

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