Prognostic value of diffusion-weighted MRI for post-cardiac arrest coma

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Abstract

Objective

To validate quantitative diffusion-weighted imaging (DWI) MRI thresholds that correlate with poor outcome in comatose cardiac arrest survivors, we conducted a clinician-blinded study and prospectively obtained MRIs from comatose patients after cardiac arrest.

Methods

Consecutive comatose post-cardiac arrest adult patients were prospectively enrolled. MRIs obtained within 7 days after arrest were evaluated. The clinical team was blinded to the DWI MRI results and followed a prescribed prognostication algorithm. Apparent diffusion coefficient (ADC) values and thresholds differentiating good and poor outcome were analyzed. Poor outcome was defined as a Glasgow Outcome Scale score of ≤ 2 at 6 months after arrest.

Results

Ninety-seven patients were included, and 75 patients (77%) had MRIs. In 51 patients with MRI completed by postarrest day 7, the prespecified threshold of $>10\%$ of brain tissue with an ADC $<650 \times 10^{-6} \text{ mm}^2/\text{s}$ was highly predictive for poor outcome with a sensitivity of 0.63 (95% confidence interval [CI] 0.42–0.80), a specificity of 0.96 (95% CI 0.77–0.998), and a positive predictive value (PPV) of 0.94 (95% CI 0.71–0.997). The mean whole-brain ADC was higher among patients with good outcomes. Receiver operating characteristic curve analysis showed that ADC $<650 \times 10^{-6} \text{ mm}^2/\text{s}$ had an area under the curve of 0.79 (95% CI 0.65–0.93, $p < 0.001$). Quantitative DWI MRI data improved prognostication of both good and poor outcomes.

Conclusions

This prospective, clinician-blinded study validates previous research showing that an ADC $<650 \times 10^{-6} \text{ mm}^2/\text{s}$ in $>10\%$ of brain tissue in an MRI obtained by postarrest day 7 is highly specific for poor outcome in comatose patients after cardiac arrest.

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Glossary

ADC = apparent diffusion coefficient; AUC = area under the curve; CI = confidence interval; DWI = diffusion-weighted imaging; GOS = Glasgow Outcome Scale; IQR = interquartile range; NPV = negative predictive value; PPV = positive predictive value; ROC = receiver operating characteristic curve; SSEP = somatosensory evoked potential.

Hypoxic-ischemic brain damage is the leading cause of morbidity and mortality in survivors of cardiac arrest.^{1–3} With >600,000 cardiac arrests in the United States each year and up to 80% of survivors of cardiac arrest initially remaining in a coma, post-cardiac arrest hypoxic-ischemic encephalopathy is a significant neurologic illness and public health burden.^{4–6}

The critically important ability to accurately and reliably predict neurologic outcome during the acute period after cardiac arrest is limited.^{7,8} Previously validated prognostic paradigms are no longer applicable to many patients in the era of targeted temperature management and current critical care management paradigms. Despite the potential for uncertainty, inappropriate early pessimistic prognostication may occur, which contributes to decisions to limit care and to withdrawal of life-sustaining measures.^{9,10} A multimodal prediction model is recommended,^{11–14} although most currently available prognostic methods have significant limitations. Better prognostic tools with high sensitivity and specificity are needed.

Diffusion-weighted imaging (DWI) MRI estimates the degree of cortical injury after cardiac arrest and provides important prognostic information.^{15–17} Specific quantitative DWI thresholds that appear to be predictive of outcome have been identified and include both the severity of apparent diffusion coefficient (ADC) reduction and the percentage of brain tissue with low ADC values.^{17,18} An ADC of $<650 \times 10^{-6} \text{ mm}^2/\text{s}$ in >10% of brain tissue differentiated patients with good and poor outcomes in a single-center study^{16,17} and in a subsequent multicenter cohort.¹⁹ However, the thresholds have not been validated in a prospective cohort, and previous studies had methodologic limitations.

We conducted a clinician-blinded study designed to prospectively evaluate quantitative DWI MRI thresholds that correlate with poor outcome in patients who remain comatose after cardiac arrest. The primary analysis sought to determine whether the previously identified threshold of having >10% of brain tissue with an ADC value $<650 \times 10^{-6} \text{ mm}^2/\text{s}$ identified patients with poor outcome. We also evaluated the previously identified threshold of $\leq 0.2\%$ of brain volume with an ADC value $<450 \times 10^{-6} \text{ mm}^2/\text{s}$ to determine whether this could differentiate functional status in the patients with good outcome.

Methods

Standard protocol approvals, registrations, and patient consents

The Institutional Review Board approved the study. Written consent was required from a legally authorized representative,

and patients were consented for ongoing participation if they regained sufficient cognitive status to participate in the informed consent process.

Clinical care and withdrawal of life-sustaining therapies

Consecutive patients with cardiac arrest who remained comatose after return of spontaneous circulation were prospectively enrolled over a 5-year period (2009–2014). Inclusion and exclusion criteria are shown in table 1. The neurocritical care team comanaged all comatose cardiac arrest survivors and identified patients for the study. The adult intensive care units were also screened daily for potential patients.

All comatose post-cardiac arrest patients were admitted to an intensive care unit with neurocritical care team comanagement. The underlying cause of the cardiac arrest was treated per standard care. Patients who qualified were treated with targeted temperature management to a target temperature of $33 \pm 0.5^\circ\text{C}$ for 24 hours and then rewarmed in a controlled manner over the subsequent 24 hours. Hemodynamic parameters were supported per routine intensive care unit care.

Patients underwent a detailed history and physical examination by a neurocritical care or stroke neurologist on admission. Clinical and neurophysiologic studies were obtained prospectively at predefined times (figure 1). Study-specific neurologic examination was performed daily by a neurointensivist or stroke neurologist during the first 3 days after the cardiac arrest and again at days 7 and 14 after arrest if the patient remained hospitalized. The study-specific neurologic examination included the Glasgow Coma Scale score and assessment of brainstem reflexes and motor function.

The clinical neurocritical care team was responsible for all clinical decision-making and discussions about withdrawal of life-sustaining measures; the study team was not involved in any related discussions. The clinical team was blinded to the results of the DWI MRI; all other clinical and neurophysiologic diagnostics were available. Decisions on limitations of life-sustaining treatment were at the discretion of the treating team in conjunction with authorized patient representatives and were guided by the following framework: decisions to limit life-sustaining treatment on the basis of multiorgan failure, perceived poor prognosis from a nonneurologic standpoint, or patient's/family's wishes at any time point after arrest. Decisions to limit maximal care on the basis of perceived neurologic prognosis were guided by an algorithm in which maximal care was continued for 72 hours after arrest. Sedation and analgesia

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age ≥ 18 y	Preexisting "do not resuscitate" status
Status after return of spontaneous circulation after in- or out-of-hospital cardiac arrest	Prearrest modified Rankin Scale score ≥ 3
Persistent coma defined as no response to verbal commands and no comprehensible speech	Severe coexisting or terminal disease that would be expected to interfere with long-term outcome assessments
	Pregnancy
	Brain death determined before MRI

were minimized to ensure patient comfort but preserve neurologic assessments as much as possible. If patients met historical predictors of poor prognosis at 72 hours after arrest and after at least 24 hours of normothermia, then the team talked with the family about likely poor prognosis and discussed options for palliative focused care. Historical predictors of poor neurologic prognosis considered were any of the following: a motor score on the Glasgow Coma Scale ≤ 2 , no pupillary reflexes, no corneal reflexes, electrocerebral silence on EEG in the absence of sedating medication, and absent N20 cortical response on somatosensory evoked potentials (SSEPs). If these findings were not present, then care was recommended to continue maximally until postarrest day 7. If prognosis was again rendered indeterminate, then care was recommended to continue and be reassessed every 48 hours thereafter.

The primary outcome was the Glasgow Outcome Scale (GOS) score assessed at 6 months after arrest. The assessment was performed by in-person clinical visits by a neurologist who was blinded to the MRI results. If patients were unable to come to the clinic, the GOS was assessed by structured telephone interview by a certified rater who was blinded to the MRI results. If the 6-month outcome assessment could not be completed, data from the 1- or 3-month follow-up were carried forward. The 6-month functional outcome was dichotomized to good and poor outcome, with good outcome

defined as a GOS score of 3 to 5 and poor outcome defined as a GOS score of 1 to 2. The GOS was subclassified within the good outcome group to define favorable functional outcome as a GOS score of 4 to 5 and impaired functional outcome as a GOS score of 3 (figure 2). Additional outcome measures were the modified Rankin Scale, Barthel Index, and neuropsychological testing, which were also assessed by structured telephone interview at 1, 3, and 12 months after arrest.²⁰

MRI and image processing

The target time for obtaining MRI examinations was between postarrest days 2 and 4 (36–96 hours after arrest), according to our previous research showing that quantitative DWI analysis is most sensitive and specific during this window,¹⁷ but all MRI examinations obtained within the first 7 days after arrest were analyzed. All magnetic resonance studies were obtained on 1.5T or 3T GE Signa Horizon scanners (GE Medical Systems, Waukesha, WI). Twenty to 23 contiguous DWI sections per patient were acquired with spin-echo echo planar imaging (128×128 acquisition matrix, field of view 24×24 cm, slice thickness/gap 5/1.5 or 5/2.5 mm, $b = 0$ and $1,000 \text{ s/mm}^2$) and diffusion-encoding along the 3 principal axes. Individual images with diffusion-encoding along the 3 principal axes were then averaged to produce isotropic DWIs.

The brain was automatically outlined on b_0 images, and corresponding masks were saved with the Brain Extraction Tool (FSL, Oxford, UK) in MRICron software (McCauley Center, Chris Rorden's Neuropsychology Lab, University of South Carolina, Columbia). The ADC maps were uniformly recreated by RAPID software (iSchemaView, Menlo Park, CA). Percentage brain volume with voxels below each ADC threshold between 200 and $1,200 \times 10^{-6} \text{ mm}^2/\text{s}$ with a step of 50 were calculated. To minimize artifacts, noise, and fluid component, we considered $\text{ADC} < 2,000 \times 10^{-6} \text{ mm}^2/\text{s}$ for the brain volume and ADC between 200 and $1,200 \times 10^{-6} \text{ mm}^2/\text{s}$ for the ADC distribution analysis within the brain tissue. The total brain volume, ADC value in each brain voxel, mean brain ADC value, and percentage of voxels below different ADC thresholds within outlined brain tissue masks were automatically calculated with in-house created software in Matlab

Figure 1 Timing of targeted temperature management and clinical diagnostics

EEG = electroencephalogram; NSE = neuron specific enolase; SSEP = somatosensory evoked potential; TH = therapeutic hypothermia.

Figure 2 Outcome groups

GOS = Glasgow Outcome Scale.

(The MathWorks, Natick, MA). Brain masks were corrected in 3 cases to exclude identified artifacts.

All images were independently reviewed for technical quality by a neurointensivist (K.G.H.) and a neuroradiologist (N.F.) who were blinded to the patient's clinical course and outcome. Technically inadequate scans were removed from the analysis. If there was disagreement about the technical adequacy, the 2 investigators reviewed the DWI MRI together and reached a consensus.

Data analysis

To determine the safety and feasibility of obtaining MRI, reasons for not obtaining MRI were documented. Adverse events during transport or during acquisition of the MRI were recorded.

We evaluated MRIs obtained in the target window of post-arrest days 2 to 4 and MRIs obtained within 7 days after arrest. The prognostic performance of the previously determined threshold of >10% of brain tissue with an ADC value $<650 \times 10^{-6} \text{ mm}^2/\text{s}$ for predicting poor outcome was evaluated. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. To determine whether the previously defined threshold of $\leq 0.2\%$ of brain volume with an ADC value $<450 \times 10^{-6} \text{ mm}^2/\text{s}$ identified patients in the good neurologic outcome group with favorable functional outcome (GOS score 4–5), the prognostic value of the MRIs meeting this criterion was determined. We also performed receiver operating characteristic curve (ROC) analysis to examine the optimal ADC threshold differentiating patients with good (GOS score 3–5) and poor (GOS score 1–2) outcomes and for differentiating survivors with favorable (GOS 4–5) vs impaired (GOS 3) functional outcome, and we compared mean brain ADC values among outcome groups.

The predictive value of DWI MRI was compared with the predictive value of historic predictors. Historic predictors of poor outcome were considered SSEPs absent at 72 hours, pupillary responses and/or corneal reflexes absent at 72 hours in the absence of sedation/paralysis, motor response extensor or worse at 72 hours in the absence of sedation/paralysis, and/or isoelectric EEG at 72 hours in the absence of sedation.

The sensitivity, specificity, PPV, and NPV of historic predictors were calculated.

Statistical analysis was performed with IBM SPSS Statistics 25 (SPSS, Chicago, IL). One-way analysis of variance and Kruskal-Wallis analysis of variance on ranks were used to compare differences between the good and poor outcome groups and between the impaired functional outcome and favorable functional outcome groups. Differences between 2 groups were determined with the *t* test or Mann-Whitney *U* test. The McNemar test was used to compare related dichotomous variables. Statistical significance was defined as $\alpha < 0.05$, and all tests were 2 sided.

Data availability

Anonymized data will be shared by request with qualified investigators.

Results

Patients

One hundred ninety-two comatose survivors of cardiac arrest were evaluated, and 100 patients were enrolled. One patient regained consciousness and withdrew from the study, and 1 patient was later determined not to have had a cardiac arrest, yielding 98 patients in the final analysis. One additional patient refused to participate in follow-up after hospital discharge but allowed collected data to be analyzed. Thus, 98 patients were included in the descriptive sections but 97 patients included in the outcomes analyses.

The mean age was 57 ± 18 years (mean $\pm$ SD); 39 (40%) were female; and 55 (56%) had poor outcome. Patients in the good outcome group were younger than those in the poor outcome group (52 ± 18 vs 61 ± 17 years, good vs poor, $p < 0.01$). The mean arrest duration overall was 22 ± 15 minutes, and the duration did not differ between good and poor outcome groups (22 ± 15 vs 23 ± 15 minutes, good vs poor, $p = 0.68$). There was no difference in the proportion of patients who had medical comorbid conditions or underwent targeted temperature management (table 2).

MRI safety and feasibility

Seventy-five patients (77%) had MRIs after the cardiac arrest. Of the 23 patients who did not undergo brain MRI, reasons included medical instability ($n = 6$), withdrawal of life support ($n = 4$), presence of incompatible metal object ($n = 12$), and logistical issues ($n = 1$, patient's body habitus precluded MRI). Of the 75 MRIs that were obtained, 12 were technically inadequate for quantitative analysis and were excluded from the analyses. Reasons for technical inadequacy included severe distortion or shading artifacts in the frontal or temporal lobes due to ghosting or coil dysfunction, patient motion, and software problems, including with image reconstruction and development of ADC maps. These were not detected while the patient was still on the magnetic resonance scanner or soon thereafter due in part to the fact that images were not being sent to our picture archiving and

Table 2 Patient demographics and clinical information

	Overall (n = 98)	Outcome ^a	
		Good (n = 42)	Poor (n = 55)
Age (mean ± SD), y	57 ± 18	52 ± 18	61 ± 17
Female sex, n (%)	39 (40)	18 (43)	20 (36)
Arrest duration (mean ± SD), min	22 ± 15	22 ± 15	23 ± 15
In-hospital arrest location, n (%)	37 (38)	12 (29)	25 (46)
Targeted temperature management, n (%)	79 (81)	36 (86)	42 (76)
Time to first MRI, median (interquartile range), h	73 (53–101)	78 (53–122)	71 (53–81)
Medical comorbid conditions, n (%)			
Diabetes mellitus	22 (22)	7 (17)	15 (27)
Hypertension	46 (47)	19 (45)	27 (49)
Coronary artery disease	22 (22)	7 (17)	15 (27)

^a One patient refused follow-up but allowed collected data to be included. Thus, there are 98 patients in the descriptive statistics but 97 patients between the outcome groups.

communication system for clinical review so that blinding of the clinical teams could be preserved. Fifty-one patients had technically adequate MRIs completed by postarrest day 7, and 41 of those MRIs were completed within target window of postarrest days 2 to 4. The primary reasons for completing MRI outside the target time were medical instability, presence of a temporary device that was MRI incompatible, or delayed transfer to our facility from an outside hospital.

MRI analysis for predicting poor outcome

In the cohort of 41 patients with MRIs done on postarrest days 2 to 4, the percent of brain tissue with an ADC $<650 \times 10^{-6} \text{ mm}^2/\text{s}$ differed significantly between patients in the good outcome group and those in the poor outcome group (5.8% [5.0%–6.2%] vs 13.0% [7.9%–46.6%], median [interquartile range (IQR)], good vs poor, $p = 0.004$). The brain volume cutoff of $>10\%$ of brain tissue with an ADC $<650 \times 10^{-6} \text{ mm}^2/\text{s}$ was highly predictive of poor outcome, with a sensitivity of 0.64 (95% confidence interval [CI] 0.43–0.81), a specificity of 0.94 (95% CI 0.68–0.997), and a PPV of 0.94 (95% CI 0.69–0.997). The mean ADC of brain tissue was higher among patients with the good outcome: $837 \times 10^{-6} \text{ mm}^2/\text{s}$ (IQR 830–852 mm^2/s) vs $801 \times 10^{-6} \text{ mm}^2/\text{s}$ (IQR 648–835 mm^2/s) (median, good vs poor, $p = 0.026$).

In the cohort of 51 patients with MRIs done within 7 days after arrest, the percent of brain tissue with an ADC $<650 \times 10^{-6} \text{ mm}^2/\text{s}$ differed significantly between patients in the good and those in the poor outcome group (5.8% [IQR 5.0%–6.3%] vs 13.0% [IQR 7.4%–48.3%], median, good vs poor, $p < 0.001$) (figure 3). The volume cutoff of $>10\%$ of brain tissue with an

ADC $<650 \times 10^{-6} \text{ mm}^2/\text{s}$ was highly predictive of poor outcome with a sensitivity of 0.63 (95% CI 0.42–0.80), a specificity of 0.96 (95% CI 0.77–0.998), and a PPV of 0.94 (95% CI 0.71–0.997). Only 1 patient with good outcome had an ADC $<650 \times 10^{-6} \text{ mm}^2/\text{s}$ in $>10\%$ of brain tissue, and the MRI in this patient was felt to be of poor technical quality but did not meet criteria for removal from analysis when it was screened blindly by the adjudicators. The mean ADC of brain tissue was higher among patients with a good outcome: $836 \times 10^{-6} \text{ mm}^2/\text{s}$ (IQR 827–853 mm^2/s) vs $801 \times 10^{-6} \text{ mm}^2/\text{s}$ (IQR 638–832 mm^2/s) (median good vs poor, $p = 0.006$).

In addition to validating the previously defined thresholds, we re-evaluated all ADC and brain volume thresholds in ROC analysis. For the 41 scans completed 2 to 4 days after arrest, the highest areas under the curve (AUCs) across all ADC thresholds were in ADC $<650 \times 10^{-6} \text{ mm}^2/\text{s}$ (AUC 0.77 [95% CI 0.62–0.92]) and $<550 \times 10^{-6} \text{ mm}^2/\text{s}$ (AUC 0.77 [95% CI 0.63–0.91], $p = 0.004$). The optimal brain volume cutoff of $>9\%$ of ADC $<650 \times 10^{-6} \text{ mm}^2/\text{s}$ differentiated poor outcome on par with the predefined volume cutoff of $>10\%$ (sensitivity 0.68 [0.46–0.82], specificity 0.94 [0.68–0.997], PPV 0.94 [0.71–0.997], NPV 0.65 [0.43–0.83]).

When all ADC and brain volume thresholds in the ROC analysis for the 51 scans completed within 7 days were re-evaluated, ADC $<550 \times 10^{-6} \text{ mm}^2/\text{s}$ had the highest AUC at 0.80 (0.68–0.93, $p < 0.001$). The optimal brain volume cutoff at the ADC $<550 \times 10^{-6} \text{ mm}^2/\text{s}$ was $>6\%$, which had a sensitivity of 0.48 (0.29–0.68), specificity of 0.96 (0.77–0.998), PPV of 0.93 (0.64–0.996), and NPV of 0.62 (0.45–0.77). However, ADC $<650 \times 10^{-6} \text{ mm}^2/\text{s}$ had a comparable AUC of 0.79 (0.65–0.93, $p < 0.001$) and at a cutoff of $>9\%$ had a sensitivity of 0.67 (0.46–0.83), specificity of 0.96 (0.77–0.998), PPV of 0.95 (0.72–0.997), and NPV of 0.72

Figure 3 Percent of brain tissue with an ADC $<650 \times 10^{-6} \text{ mm}^2/\text{s}$ differs between outcome groups

ADC = apparent diffusion coefficient; GOS = Glasgow Outcome Scale.

(0.53–0.86). This was comparable to the performance of the predefined >10% volume cutoff at $\text{ADC} < 650 \times 10^{-6} \text{ mm}^2/\text{s}$ and to the performance of the threshold of $\text{ADC} < 550 \times 10^{-6} \text{ mm}^2/\text{s}$ in >6% of brain (figure 4).

MRI analysis for predicting functional status within the good outcome group

We also evaluated whether the previously defined threshold of $\leq 0.2\%$ of brain volume with an ADC value $< 450 \times 10^{-6} \text{ mm}^2/\text{s}$ differentiated favorable from impaired functional outcome. There were 16 survivors who had MRI completed in the window of postarrest days 2 to 4, and of those, 10 (62.5%) patients had favorable functional outcome (GOS score 4–5) and 6 (37.5%) patients had impaired functional outcome (GOS score 3). Only 1 of those patients had $\leq 0.2\%$ of brain tissue with $\text{ADC} < 450 \times 10^{-6} \text{ mm}^2/\text{s}$; thus, we were unable to validate the previously defined threshold. The mean ADC values and the brain volume thresholds and ADC cutoffs did not differentiate favorable from impaired outcome patients with acceptable precision because all AUCs were not significant. The same was true in the cohort of 24 survivors who had MRI completed by postarrest day 7.

Nonimaging biomarkers

The predictive values of absent pupillary response, best motor response of extension or no movement, and absent SSEPs

within 72 hours after arrest were evaluated. The receipt of any sedation or analgesic medication within the 12 hours before the diagnostic maneuver was also recorded.

We analyzed the predictive value of nonimaging biomarkers in the cohort of patients with MRI done on postarrest days 2 to 4, those with MRIs done on postarrest days 2 to 7, and the full cohort of 98 patients. The sensitivity, specificity, NPV, and PPV of historic outcome predictors were similar in all the subgroups, and the results of the group with MRIs done on postarrest days 2 to 7 are shown in table 3. Overall, the presence of ≥ 1 historic outcome predictor was 100% specific for poor outcome in patients who did not receive any sedation or analgesia in the preceding 12 hours but only 81% specific for poor outcome in patients who had received any sedation or analgesic medications within 12 hours. In the combined cohort of all participants who had and had not received sedation, the presence of ≥ 1 historic outcome predictor had a sensitivity of 0.75 (0.60–0.85), specificity of 0.85 (0.70–0.94), PPV of 0.86 (0.72–0.94), and NPV of 0.73 (0.58–0.84).

Nonimaging biomarkers combined with MRI

In patients with MRI done on postarrest days 2 to 7, the threshold of $\text{ADC} < 650 \times 10^{-6} \text{ mm}^2/\text{s}$ in >10% of brain tissue allowed the identification of 1 additional patient with poor outcome when added to the historic predictors (sensitivity increased from 0.86 to 0.91 for poor outcome prediction). The

Figure 4 Receiver operating characteristic curve and performance of optimal brain volume thresholds of $\text{ADC} < 550 \times 10^{-6} \text{ mm}^2/\text{s}$ in >6% of brain and $\text{ADC} < 650 \times 10^{-6} \text{ mm}^2/\text{s}$ in >10% of brain

Based on 51 MRIs done within 7 days after arrest. For percentage of apparent diffusion coefficient (ADC) $< 550 \times 10^{-6} \text{ mm}^2/\text{s}$, the area under the curve (AUC) was 0.80 (95% confidence interval [CI] 0.68–0.93, $p < 0.001$), with a sensitivity of 0.48 (95% CI 0.29–0.68) and specificity of 0.96 (95% CI 0.77–0.998) in >6% of brain. For percentage of ADC $< 650 \times 10^{-6} \text{ mm}^2/\text{s}$, the AUC was 0.79 (95% CI 0.65–0.93, $p < 0.001$), with a sensitivity of 0.63 (95% CI 0.42–0.80) and specificity of 0.96 (95% CI 0.77–0.998) in >10% of brain.

Table 3 Predictive value of historic outcome predictors and quantitative MRI

A	Good outcome	Poor outcome	Sensitivity	Specificity
Received sedation within the last 12 h				
Pupillary reactivity				
Pupils reactive	18	12	0.25 (0.08–0.53)	1.0 (0.78–1.0)
Pupils unreactive	0	4		
Best motor response				
M3–M6	15	2	0.875 (0.60–0.98)	0.83 (0.58–0.96)
M1–M2	3	14		
SSEP				
SSEP present	4	6	0.57 (0.29–0.81)	1.0 (0.40–1.0)
SSEP absent	0	8		
Any historic poor outcome predictor				
None present	15	2	0.875 (0.60–0.98)	0.83 (0.58–0.96)
≥1 Present	3	14		
No sedation within the last 12 h				
Pupillary reactivity				
Pupils reactive	6	7	0.36 (0.12–0.68)	1.0 (0.52–1.0)
Pupils unreactive	0	4		
Best motor response				
M3–M6	6	2	0.82 (0.48–0.97)	1.0 (0.52–1.0)
M1–M2	0	9		
SSEP				
SSEP present	0	2	0.67 (0.24–0.94)	NA
SSEP absent	0	4		
Any historic poor outcome predictor				
None present	6	2	0.82 (0.48–0.97)	1.0 (0.52–1.0)
≥1 Present	0	9		
All patients with MRI done on postarrest days 1–7				
Pupillary reactivity				
Pupils reactive	24	19	0.30 (0.14–0.50)	1.0 (0.83–1.0)
Pupils unreactive	0	8		
Best motor response				
M3–M6	21	4	0.85 (0.65–0.95)	0.875 (0.67–0.97)
M1–M2	3	23		
SSEP (n = 24)				
SSEP present	4	8	0.6 (0.36–0.80)	1.0 (0.4–1.0)
SSEP absent	0	12		
Any historic poor outcome predictor				

Continued

Table 3 Predictive value of historic outcome predictors and quantitative MRI (continued)

A		Good outcome	Poor outcome	Sensitivity	Specificity
	None present	21	4	0.85 (0.65–0.95)	0.875 (0.67–0.97)
	≥1 present	3	23		
B		<10% with ADC <650	>10% with ADC <650		
Poor outcome					
	Any historic predictor				
	≥1 Present	7	16	Sensitivity 0.89, Specificity 1.0 for poor outcome.	
	All absent	3	1 ^a		
Good outcome					
	Any historic predictor				
	≥1 Present	3 ^b	0		
	All absent	20	1		

Abbreviation: SSEP = somatosensory evoked potential.

A: In 51 patients with MRI completed on postarrest days 1 to 7, the predictive value of historic outcome predictors depended on whether the patient had received any sedation within the prior 12 hours.

B: In 51 patients with MRI completed on postarrest days 1 to 7, the use of an MRI threshold of ADC $<650 \times 10^{-6}$ mm²/s in >10% of brain in combination with historic outcome predictors improved outcome prediction. MRI allowed identification of ^a1 additional patient with poor outcome and correctly identified ^b3 patients with good outcome who would have been incorrectly classified as having poor outcome by historic outcome predictors. The sensitivity and specificity of MRI remained high.

threshold of ADC $<650 \times 10^{-6}$ mm²/s in >10% of brain tissue also allowed the identification of 3 patients with good outcome who were predicted to have poor outcome on the basis of nonimaging biomarkers. All 3 of these patients had received sedation within the 12 hours before the examination, and all 3 patients had <10% of brain tissue with ADC $<650 \times 10^{-6}$ mm²/s.

Discussion

The predictive value of specific quantitative thresholds for DWI MRI was examined in comatose survivors of cardiac arrest. An ADC $<650 \times 10^{-6}$ mm²/s in >10% of brain tissue, which was the threshold identified in an earlier cohort,¹⁷ was highly specific and had good sensitivity when the MRI was of good technical quality and obtained between days 2 and 7 after arrest. This threshold identifies patients who will have long-term poor outcome, defined as those who die or do not regain consciousness. We deliberately adhered to a prescribed prognostication algorithm to avoid self-fulfilling prophecies of poor prognosis and premature prognostication in the setting of temperature management and sedation, facilitated by having the clinical team blinded to the DWI MRI. Quantitative DWI MRI added to the sensitivity and specificity of outcome prediction when combined with nonimaging biomarkers. Unlike nonimaging biomarkers, including the neurologic examination and electrophysiologic prognostic tests, quantitative DWI MRI offers a sensitive and specific tool that is not affected by temperature management and sedation.

This study is unique from prior work studying quantitative DWI MRI in post-cardiac arrest coma for several reasons: it is the largest prospectively collected cohort; there were standardized clinical care paradigms for end-of-life decisions and withdrawal of life-sustaining therapies; the clinicians were blinded to the DWI MRI so as not to introduce bias and the potential for a self-fulfilling prophecy; and the primary outcome was 6-month functional neurologic outcome.

While obtaining MRI in intubated, critically ill patients was overall safe and feasible, we found several limitations. First, several patients were unable to obtain MRI at all due to the presence of metal devices (permanent pacemakers being most common), which is particularly relevant in the post-cardiac arrest population. Updated management strategies regarding MRI device compatibility should facilitate this in future practice.^{21,22} Second, in patients who were eligible to undergo MRI, medical instability and the presence of a temporary MRI-incompatible device precluded imaging in the ideal early time window (36–96 hours). Finally, the technical quality of several of the scans was inadequate for quantitative analysis, although qualitative interpretation could still be performed. This was a particular problem with this study design because the MRIs were never sent to the clinical radiology system for a qualitative review for technical adequacy given the blinding paradigm; thus, we had a higher rate of technically inadequate scans than would be expected.

This study validates previous research showing that an ADC $<650 \times 10^{-6} \text{ mm}^2/\text{s}$ in $>10\%$ of brain tissue in an MRI obtained between days 2 and 7 after arrest is highly specific for poor outcome in comatose patients after cardiac arrest. There are several benefits to a quantitative MRI-based prognostic tool, including the objective evaluation and the lack of confounding by sedation. Quantitative DWI MRI analysis may be used with other multimodal biomarkers to facilitate outcome prediction in comatose patients within the first week after cardiac arrest.

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Disclosure

K. Hirsch, N. Fischbein, M. Mlynash, and S. Kemp report no disclosures. R. Bammer has equity interest in and serves as a consultant for iSchemaView. I. Eyngorn, J. Tong, M. Moseley, and C. Venkatasubramanian report no disclosures. G. Albers has equity interest in and serves as a consultant for iSchemaView. Go to Neurology.org/N for full disclosures.

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Karen G. Hirsch, MD	Stanford University, CA	Data collection, analysis, interpretation; drafting manuscript
Nancy Fischbein, MD	Stanford University, CA	Conception and study design; data collection, analysis, interpretation; drafting manuscript
Michael Mlynash, MD, MS	Stanford University, CA	Data collection, analysis, interpretation
Stephanie Kemp, BA	Stanford University, CA	Data collection, analysis, interpretation
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Julia Tong, MD	University of California, Los Angeles	Data collection, analysis, interpretation

Appendix (continued)

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