Functional Neurologic Outcomes Change Over the First 6 Months After Cardiac Arrest

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Objectives: To determine the longitudinal changes in functional outcome and compare ordinal outcome scale assessments in comatose cardiac arrest survivors.

Design: Prospective observational study of comatose cardiac arrest survivors. Subjects who survived to 1 month were included.

Setting: Academic medical center ICU.

Patients: Ninety-eight consecutive patients who remained comatose after resuscitation from cardiac arrest; 45 patients survived to 1 month.

Interventions: None.

Measurements and Main Results: Patients' functional neurologic outcomes were assessed by phone call or in-person clinic visit at 1, 3, 6, and 12 months postcardiac arrest using the modified Rankin Scale, Glasgow Outcome Scale, and Barthel Index. A "good" outcome was defined as modified Rankin Scale 0–3, Barthel Index 70–100, and Glasgow Outcome Scale 4–5. Changes in dichotomized outcomes and shifts on each outcome scale were analyzed. The mean age of survivors was 51 ± 19 years and 18 (40%) were women. Five (19%) out of 26 patients with data available at all timepoints improved to good modified Rankin Scale outcome and none worsened to poor outcome between postarrest months 1 and 6 ($p = 0.06$). Thirteen patients (50%) improved on the modified Rankin Scale by 1–3 points and four (15%) worsened by 1–2 points between months 1 and 6 (overall improvement by 0.5 points; 95% CI, 0–1; $p = 0.04$). From postarrest months 6 to 12, there was no change in the number of patients with good versus poor outcomes. The modified Rankin Scale and Barthel Index were more sensitive to detecting changes in outcome than the Glasgow Outcome Scale.

Conclusions: In initially comatose cardiac arrest survivors, improvements in functional status occur over the first 6 months after the event. There was no significant change in outcome between postarrest months 6 and 12. The modified Rankin Scale is a sensitive outcome scale in this population. (*Crit Care Med* 2016; 44:e1202–e1207)

Key Words: cardiac arrest; coma; neurologic injury; outcomes; postresuscitation care

Over 600,000 patients suffer a cardiac arrest annually in the United States (1–3). Current survival rates with the use of therapeutic hypothermia vary from 30% to 60%, though even survivors classified as having "good" neurologic outcomes often experience significant long-term cognitive deficits or "postresuscitation encephalopathy" (4–10). In the era of therapeutic hypothermia and targeted temperature management for comatose cardiac arrest survivors, increasing numbers of patients who remain comatose after resuscitation go on to have favorable neurologic outcomes (11–13).

Given the historically grim prognosis of cardiac arrest, early resuscitation research used mortality and surrogate physiologic measures to define postcardiac arrest outcomes (14, 15). As resuscitation and the management of postcardiac arrest syndrome improved, the need for patient-focused outcomes that better assess neurologic function has developed. The optimal method and timing of neurologic outcome assessment have not been established (14). The American Heart Association consensus statement recommends that a 90-day outcome be used "coupled with neurocognitive and quality-of-life assessments." (14) The Cerebral Performance Category (CPC) or modified Rankin Scale (mRS) is suggested as a global outcome assessment of neurologic function, though the authors

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acknowledge a significant lack of evidence to support a single scale or timepoint (14). Additionally, there are limited data characterizing the natural history of neurologic recovery after cardiac arrest, as most studies lack serial follow-up. One study showed that Mini-Mental State Examination scores improved initially after cardiac arrest but did not significantly change between 3 months and 1 year postarrest (7). However, like much of the previous research in long-term functional outcome after cardiac arrest, this work was performed prior to the era of therapeutic hypothermia.

Determining longitudinal changes in functional status in postcardiac arrest survivors can provide valuable clinical information for care providers, patients, and family members, and comparing three ordinal outcome scales used longitudinally at different timepoints may help define and standardize research outcomes. Therefore, we sought to describe the functional neurologic outcome as measured by three performance scales over a 12-month period in patients who were initially comatose after resuscitation from cardiac arrest. The objective of the current study was to determine longitudinal changes in patients' functional outcomes at 1, 3, 6, and 12 months after cardiac arrest and to compare performance of three functional outcomes scales (mRS, Barthel Index [BI], and Glasgow Outcome Score [GOS]).

MATERIALS AND METHODS

This is a single-center prospective observational study of functional outcomes in patients who initially remained comatose following resuscitation from cardiac arrest.

Subjects

Consecutive comatose postcardiac arrest patients were prospectively enrolled. Adult patients who remained comatose after initial resuscitation for cardiac arrest were eligible if they met the following inclusion criteria: men and nonpregnant women at least 18 years old, resuscitation for primary and secondary cardiac arrest, and persistent coma defined as no eye opening to voice and inability to follow commands after return of perfusing cardiac rhythm. Patients who regained consciousness following return of spontaneous circulation were not included. Exclusion criteria were preexisting "do not resuscitate" status, prearrest mRS of greater than or equal to 3, receiving investigational drug or procedures, severe coexisting systemic disease limiting life expectancy, and brain death. The study was approved by the institutional review board, and written informed consent was obtained from a legally authorized representative. The patients also gave written informed consent if they regained consciousness and sufficient cognitive status to allow for the informed consent process.

Clinical Care

All patients who remain comatose after resuscitation from cardiac arrest are comanaged by the neurocritical care team who work closely with the primary teams to provide postresuscitation care. If patients met the criteria for therapeutic hypothermia, they were cooled to a target temperature of 33°C ± 0.5°C for 24 hours and then underwent controlled rewarming. Optimization of hemodynamics and workup and treatment of an underlying cause of the arrest were performed per institutional protocol. Decisions regarding limitations of life-sustaining treatment were at the discretion of the treating team in conjunction with authorized patient representative and guided by the following framework: decisions to limit life-sustaining treatment based on multiple organ failure, perceived poor prognosis from a nonneurologic standpoint, or patient's/family's wishes were accepted at any timepoint postarrest. Decisions to limit maximal care based on perceived neurologic prognosis were guided by an algorithm in which maximal care was continued for 72 hours postarrest. After therapeutic hypothermia was completed, sedation was minimized to ensure patient comfort but preserve neurologic assessments as much as possible. If patients met historical predictors of poor prognosis at 72 hours postarrest and after at least 24 hours of normothermia, then the team talked with family about likely poor prognosis and discussed options for limitations of care. Historical predictors of poor neurologic prognosis were considered any of the following: Glasgow Coma Scale motor score of less than or equal to 2, no pupillary reflexes, no corneal reflexes, burst suppression or electrocerebral silence on electroencephalogram in the absence of sedating medication, and absent N20 cortical response on somatosensory evoked potentials. If these findings were not present, then care was recommended to continue maximally until reassessment at postarrest day 7.

After the initial hospitalization, clinical care and decisions about changing overall goals of care were left to the discretion of the clinical treating team. The cause of death was recorded for all patients.

Outcome Assessment

Functional outcomes were measured by mRS, BI, and GOS, obtained via a structured telephone interview at 1, 3, and 12 months and an in-person clinic follow-up at 6 months. Patients who were unable to come to clinic at 6 months were assessed with structured telephone interviews. The outcome scales were performed by a physician or research coordinator blinded to the clinical data and certified in the administration of these assessments. Outcomes were dichotomized to good versus poor, and good outcomes were predefined as mRS 0–3, GOS 4–5, or BI of 70–100. Because dichotomized outcomes may not capture the clinical benefit associated with a shift of at least one grade on the mRS (16), we also determined the likelihood of transitioning between grades on the mRS between timepoints (so-called shift analysis) (17–19).

The mRS is a seven-point scale ranging from 0 to 6, in which a patient with a score of 0 has no residual symptoms and is able to carry out daily-life activities independently, whereas a 6 represents death (20–22). The BI is a scale that ranges from 0 to 100 with 10 categories that assess independence in activities of daily living: feeding, bathing, grooming, dressing, bladder, toilet use, moving from bed to chair, and ability to walk (22–24). The GOS is a five-point scale that ranges from 1 (death) to 5 (good recovery, able to return to normal activities) (25).

Patients who were alive at 1 month postarrest were included in this analysis. Patients with incomplete datasets had data carried backward and forward for sensitivity analyses, and these results are reported separately. For the patients to be included in the analyses, outcomes had to be assessed at least at one timepoint. No patients were completely lost to follow-up.

Statistical Analysis

Changes in the dichotomized outcomes (good vs poor) over time were analyzed with McNemar test. For the full range of each outcome scale, we estimated magnitude of the shifts in the patient outcome scores between assessment timepoints using Hodges-Lehmann estimates for the median differences with 95% CIs and then assessed them for significance using Wilcoxon signed rank test (for two timepoints) or Friedman test (for multiple timepoints). We also estimated the general odds ratio (OR_G, a generalization of the odds ratio for ordinal data) for improvement versus worsening by at least one point between assessments. Cases without change in the score were accounted as ties. Asymptotic 95% CI was estimated using logarithmic transformation to improve the normal approximation to the statistic OR_G (26, 27). A p value of less than 0.05 was defined as significant. IBM SPSS Statistics version 22 software (IBM, Armonk, NY) was used for all analyses.

RESULTS

One hundred patients were enrolled between 2008 and 2014. One patient was ultimately determined to have been unlikely to have had a cardiac arrest, and another patient withdrew from the study, leaving 98 patients included in the final analysis. The overall mortality rate for the entire duration of the 1-year study was 59%. Fifty-three of the patients (54%) died during the initial hospitalization, and four survived to hospital discharge but died between 1 and 12 months postarrest.

Of 45 patients who were alive at 1 month postarrest, 26 patients (58%) completed follow-up at all timepoints (1, 3, 6, and 12 mo). Nineteen patients had incomplete follow-up data: 38 (84%) were assessed at 1 month, 38 (84%) were assessed at 3 months, 40 (89%) were assessed at 6 months, and 35 (78%) were assessed at 12 months. Thirty-five patients had adequate data for a "last observation carried backwards" analysis, and 43 patients had enough data for a "last observation carried forward" analysis.

The mean age was 51 ± 19 years and 18 (40%) were women. Thirty-one patients (31/45; 69%) had out-of-hospital cardiac arrest, and ventricular fibrillation was the most common underlying rhythm (n = 20; 44%). Thirty-eight (84%) were treated with therapeutic hypothermia. Seven patients did not undergo hypothermia due to developing clinical responsiveness despite early coma (n = 3), refractory ventricular arrhythmia (n = 1), severe coagulopathy (n = 1), and hemodynamic instability (n = 2). Additional patient characteristics are reported in **Table 1**.

TABLE 1. Demographic and Clinical Factors

Demographics	n = 45
Gender (women), n (%)	18 (40)
Age, mean ± SD	51 ± 19
Race, n (%)	
White	33 (73)
Black	5 (11)
Asian	5 (11)
Native Hawaiian/Pacific Islander	2 (4)
Ethnicity (Hispanic), n (%)	10 (22)
Historic rankin, median (IQR)	1 (0–2)
Cardiac Arrest Details	
Out-of-hospital cardiac arrest	31 (69)
Therapeutic hypothermia	38 (84)
Type of cardiac arrest	
Ventricular fibrillation	20 (44)
Ventricular tachycardia	1 (2)
Pulseless electrical activity	16 (36)
Asystole	4 (9)
Other	4 (9)
Coma duration > 3 d, n (%)	14 (31)
Return of spontaneous circulation (min)	22 ± 15

IQR = interquartile range.

mRS

In the dichotomized analysis, 12 of the 26 patients (46%) with data available from all timepoints had a good functional outcome (mRS, 0–3) at 1 month. There were no statistically significant differences in dichotomized outcome between months 1 and 3 and months 3 and 6. However, between 1 and 6 months, five patients (36%; 95% CI, 16–61%) improved sufficiently to be reclassified from poor to good functional outcome leading to an increase in the percentage of patients with good functional outcome from 46% to 65% (strong trend for significance with p = 0.063). Although four patients worsened (15%; 95% CI, 6–34%) on the overall mRS between postarrest months 1 and 6, the worsening did not result in reclassified into a different primary outcome group (0%; 95% CI, 0–24%). Three of the four patients with worsening on the mRS died, going from a mRS of 5 to 6 (n = 2) or mRS of 4 to 6 (n = 1). Causes of death for the three patients who died between postarrest months 1 and 6 were nonneurologic: acute renal failure, acute respiratory failure, and acute systolic heart failure. From months 6 to 12, there was no change in the number of patients with good versus poor outcomes: one patient improved from poor to good outcome and one patient worsened from good to poor outcome, leaving overall 17 patients (65%) remaining in the good outcome category (p = 1.0).

On the full mRS scale, shift analysis showed 13 patients (50%) improved between postarrest months 1 and 6 (**Fig. 1**).

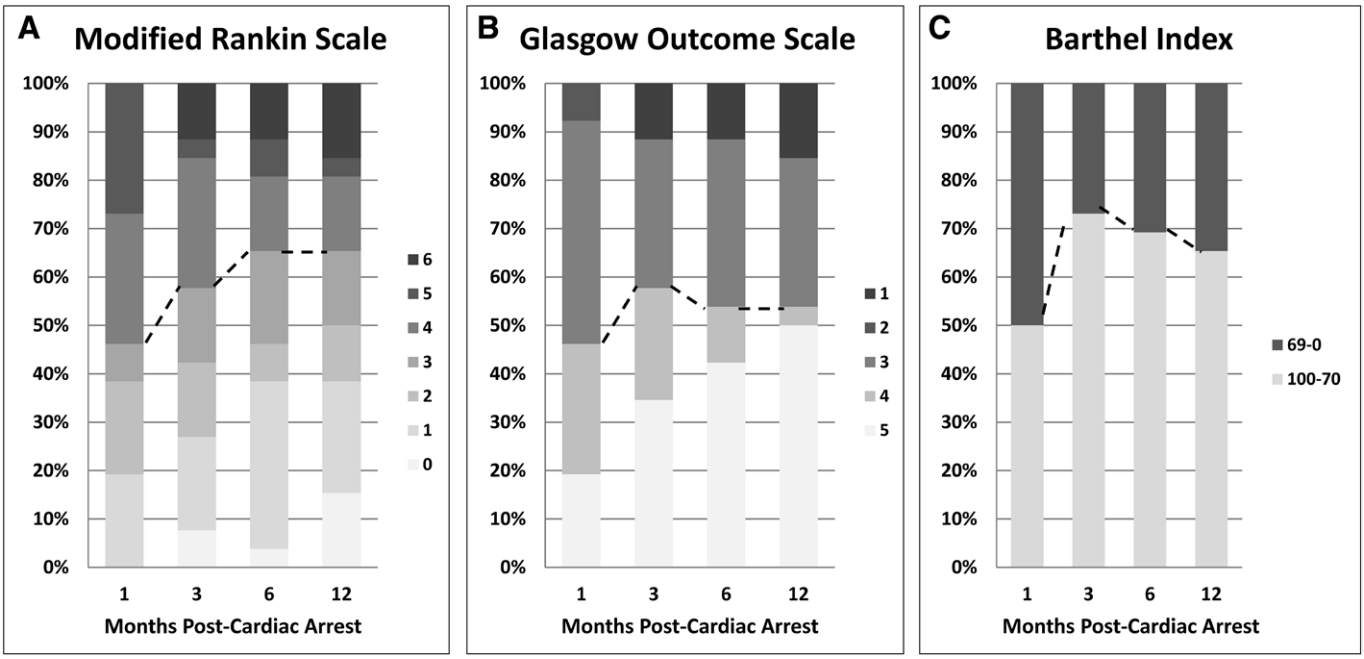

Figure 1. Change in outcome distribution over 12 mo: **A**, Modified Rankin Scale, **B**) Glasgow Outcome Scale, and **C**) Barthel Index. *n* value is equal to 26.

TABLE 2. Individual Patient Changes in Modified Rankin Scale Between Postarrest Months 1 and 6

		mRS at 6 Mo							
		0	**1**	**2**	**3**	**4**	**5**	**6**	**Total**
mRS at 1 Mo	**1**	1	4	0	0	0	0	0	5
	2	0	4	0	1	0	0	0	5
	3	0	0	1	1	0	0	0	2
	4	0	1	1	2	2	0	1	7
	5	0	0	0	1	2	2	2	7
	Total	1	9	2	5	4	2	3	26

mRS = modified Rankin Scale.

Changes in modified Rankin Scale between postarrest months 1 and 6. Numbers to the left of the shaded boxes denote number of patients who improved, whereas numbers to the right of the shaded boxes denote number of patients who worsened.

Ten patients improved by one point, two patients improved by two points, and one patient improved by three points (**Table 2**). Overall, there was a median 0.5 (95% CI, 0–1) shift in mRS toward improvement between months 1 and 6 ($p = 0.04$), with OR_G for improvement by at least one point was 2.06 (95% CI, 0.91–4.67). Between months 6 and 12 postarrest, individual patients continued to improve on the full mRS scale. Five out of 23 alive patients at 6 months postarrest improved further by month 12 (22%; 95% CI, 10–42%): three patients with a score of 1 improved to 0, one patient improved from mRS of 3–1, and one patient improved from 4 to 3. In the same time period (between 6 and 12 mo postarrest), three patients (13%; 95% CI, 5–32%) worsened on the full scale, one patient worsened from 1 to 2, one from 3 to 4, and one patient with a mRS of 5 at 6 months had died by 12 months. There was no overall shift in the mRS scores between 6 and 12 months: median (95% CI) difference of 0 (0–0.5), p value equal to 0.366; OR_G for improvement by at least one point was 1.17 (95% CI, 0.54–2.52).

When data were not available for all follow-up timepoints, but were available for at least one timepoint, data were carried forward or backward. Using the inferred data, the overall results were similar to the results from patients with a complete dataset. On the dichotomized scale, the proportion of patients with good outcome again did not change significantly between 1 and 3 months (51–63%, $p = 0.063$, carried forward data; 57–66%, $p = 0.250$, carried backward data) but significantly increased from 1 to 6 months in the carried forward/backward datasets: from 57% to 71% ($p = 0.063$) when carried backward; and from 51% to 72% ($p = 0.004$) when carried forward. Meanwhile, the proportion of patients with good outcome remained unchanged from 6 to 12 months in both datasets ($p = 1.0$). There was overall improvement on mRS

scale between 1 and 6 months by 0.5 (0–1.0) (median [95% CI]) ($p = 0.012$) for carried backward and 0.5 (0–1) ($p = 0.008$) for carried forward analyses. There was still no change between 1 and 3 months ($p = 0.262$, carried forward; $p = 0.084$, carried backward) and between 6 and 12 months ($p = 0.366$ carried backward and carried forward).

GOS

When GOS outcomes were assessed in dichotomized analyses, there was no difference in the proportion of patients with good and poor outcomes at 1, 3, 6, and 12 months (46%, 58%, 54%, and 54%, respectively, with good outcome) (Fig. 1). Similarly, there was no significant difference in shift in the GOS scores between all four timepoints, p value equal to 0.44. At an individual level, between months 1 and 3, three patients worsened and six patients improved (median shift, 0; 95% CI, 0–0.5). Between months 1 and 6, eight patients (31%; 95% CI, 17–50%) had improvements in their GOS, and four patients (15%; 95% CI, 6–34%) worsened on the GOS scale, but there was no significant overall shift ($p = 0.356$ for overall GOS shift between 1 and 6 mo). In the patients who did improve, five patients improved from a 4 (moderate disability) to 5 (mild disability), two patients from 3 (severe disability) to 4, and one patient from 3 to 5. Of the four patients who worsened, one patient worsened from 4 to 3, and one patient with GOS of 3 and two with GOS of 2 (persistent vegetative state) died. Between months 6 and 12, only two patients (8%) improved from GOS of 4–5 and one patient with GOS of 3 died, and these changes were not statistically significant. Results did not change when patients with carried-forward or backward data were included.

BI

When functional status was assessed using the BI, the proportion of patients with good outcome increased between months 1 and 3 (13 [50%] to 19 [73%]; $p = 0.03$). There were no additional changes in the dichotomized outcome groups between months 3 and 6 and months 6 and 12. In the shift analysis, when looking at the continuous scale, there was significant improvement between months 1 and 3 on the full Barthel scale: index increased by 7.5 points (95% CI, 0–30; $p = 0.021$). There was no change in the overall index between months 3 and 6 and months 6 and 12. Using carried-forward and carried-backward data, the results were similar in that there was a significant shift toward improvement from 1 to 3 months but no significant changes after five points (95% CI, 0–20; $p = 0.01$), carried-forward; 2.5 points (0–12.5; $p = 0.05$), carried-backward.

DISCUSSION

The results of this prospective study of 45 survivors of cardiac arrest who were initially comatose after resuscitation show functional outcomes improve over the first 6 months postarrest. On the mRS scale, a strong trend toward improvement was seen between postarrest months 1 and 6 using a dichotomized outcome, and there was a significant difference in outcomes between 1 and 6 months postarrest when assessing outcome changes on the full mRS scale. Interestingly, there was not a significant change between the shorter intervals of months 1–3 and 3–6, but the improvement became significant when outcomes were compared between months 1 and 6. From postarrest months 6 to 12, there was no significant change in the total number of patients in the dichotomized outcome groups by mRS, but individuals within the good outcome group continued to see improvements in mRS during this time period. Other outcome scales also supported this finding of longitudinal improvements in functional outcome. There were significant improvements in functional outcomes by BI seen by 3 months postarrest, though these improvements stabilized and did not show significant further improvements at month 6 or 12. When outcomes were assessed by the GOS, there was a nonsignificant trend toward improved outcomes between postarrest months 1 and 6.

Although the majority of long-term disability in survivors of cardiac arrest is due to neurologic dysfunction, there are little data about optimal timing or methodology of assessing functional outcome. This study is significant because patients were followed prospectively over 1 year after cardiac arrest, and functional outcomes were assessed at multiple timepoints with multiple assessment scales. It provides information on the chances of long-term improvement beyond the acute injury period, which can offer valuable prognostic information to survivors and their families. It also provides critical information about the trajectory of recovery and supports previous studies in patients with brain injury due to other types of insults (trauma, stroke), showing that the majority of functional improvement occurs during the first 6 months after injury, but there is still potential for long-term recovery (28). Most patients who attain a good outcome will do so within the first 6 months. The results also suggest that the mRS and the BI are more sensitive for detecting improvements than the GOS. The GOS may not be an adequately refined outcome scale to assess functional status in this population.

Several limitations are important to address. Despite enrolling 100 patients in a consecutive prospective sample, only 45 patients (45%) survived to 1 month follow-up and were eligible for inclusion. This relatively low patient number from a single center limits generalizability. We also used structured phone interviews for the majority of the follow-ups and performed in-person evaluations at the 6-month follow-up if patients could come in to clinic. Although structured phone interviews have been validated as a reliable assessment methodology (29, 30), in-person assessments likely provide the best opportunity for evaluation. Future research should include longitudinal in-person evaluations and make use of technology for telemedicine evaluation if travel to the clinical center is not feasible.

Finally, although outcomes were assessed with three different outcomes scales at each timepoint, other commonly used outcome measures such as the CPC were not used. However, the GOS has essentially the same number, description, and categories of outcome as the CPC, and in fact, the CPC was adapted for hypoxic-ischemic brain injury patients based on the originally described GOS (31). As such, the results seen here

using the GOS would also likely be replicated if the CPC were used, but further research is needed. It is also important to note that recovery that is meaningful to a patient or family member occurs in a more nuanced manner than what may be measurable by coarse outcomes scales. Recovery in cognition, independence, and other areas that lead to improvement in a patient's quality of life are also important to assess, and future studies should include more subjective quality-of-life assessments.

This study provides important information about the timing and trajectory of functional neurologic recovery in survivors of cardiac arrest who initially remain comatose. Given that a significant proportion of patients see functional improvements through postarrest month 6, future research should consider the following patients to at least a 6-month outcome assessment. Additionally, there were differences in the results between assessments with the GOS versus the mRS, despite overall similar trends. Assessments using the mRS showed significant changes in outcome, whereas those using the GOS did not. Additional work is necessary to identify the optimal assessment tool(s) to quantify neurologic recovery after hypoxic-ischemic brain injury, and more nuanced scales are likely to prove beneficial.

CONCLUSIONS

In this prospective study of long-term functional outcome in initially comatose cardiac arrest survivors, improvements in functional status may occur over the first 6 months after the event. There is little evidence for significant changes in outcome between postarrest months 6 and 12. The mRS may be a more sensitive ordinal outcome scale than the GOS or CPC in this patient population, but additional research is needed. Future resuscitation research should incorporate a 6-month outcome assessment of functional neurologic status.

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