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ORIGINAL RESEARCH

Trauma

Changes in neurologic status after traumatic brain injury in the Resuscitation Outcomes Consortium Hypertonic Saline trial

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Abstract

Objectives: Traumatic brain injury (TBI) is an important public health problem resulting in significant death and disability. Emergency medical services (EMS) personnel often provide initial treatment for TBI, but only limited data describe the long-term course and outcomes of this care. We sought to characterize changes in neurologic status among adults with TBI patients enrolled in the Resuscitation Outcomes Consortium Hypertonic Saline (ROC-HS) trial.

Methods: We used data from the TBI cohort of the ROC-HS trial. The trial included adults with TBI, with Glasgow Coma Scale (GCS) ≤8, and excluded those with shock (systolic blood pressure [SBP] ≤70 or SBP 71–90 with a heart rate [HR] ≥108). The primary outcome was Glasgow Outcome Scale–Extended (GOS-E; 1 = dead, 8 = no disability) determined at (a) hospital discharge and (b) 6-month follow-up. We assessed changes in GOS-E between hospital discharge and 6-month follow-up using descriptive statistics and Sankey graphs.

Results: Among 1279 TBI included in the analysis, GOS-E categories at hospital discharge were as follows: favorable (GOS-E 5–8) 220 (17.2%), unfavorable (GOS-E 2–4) 664 (51.9%), dead (GOS-E 1) 321 (25.1%), and missing 74 (5.8%). GOS-E categories at 6-month follow-up were as follows: favorable 459 (35.9%), unfavorable 279 (21.8%), dead 346 (27.1%), and missing 195 (15.2%). Among initial TBI survivors with complete GOS-E, >96% followed one of three neurologic recovery patterns: (1) favorable to favorable (20.0%), (2) unfavorable to favorable (40.3%), and (3) unfavorable to unfavorable (36.0%). Few patients deteriorated from favorable to unfavorable neurologic status, and there were few additional deaths.

Conclusions: Among TBI receiving initial prehospital care in the ROC-HS trial, changes in 6-month neurologic status followed distinct patterns. Among TBI with unfavorable neurologic status at hospital discharge, almost half improved to favorable neurologic status at 6 months. Among those with favorable neurologic status at discharge, very

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few worsened or died at 6 months. These findings have important implications for TBI clinical care, research, and trial design.

KEYWORDS
outcomes, recovery, traumatic brain injury

1 | INTRODUCTION

1.1 | Background

The annual burden of traumatic brain injury (TBI) in the United States is enormous, associated with 2.2 million emergency department visits, 280,000 hospitalizations, 52,000 deaths, and more than $60 billion in economic costs.[1,2] While early mitigation of secondary injury is a priority, few interventions have proven effective for TBI treatment. Clinical trials offer information to support the effectiveness of novel medical therapies. An essential consideration in clinical trial design is the selection of appropriate outcomes, which must be relevant to the disease, plausibly linked to the intervention, objectively measurable, and pertinent to patients and caregivers.

1.2 | Importance

Emergency medical services (EMS) personnel often provide initial lifesaving care for acute TBI. Measures performed by EMS may include establishment of airway, support of oxygenation and ventilation, and treatment of hypotension, among others.[3] Select clinical trials have tested TBI interventions in the prehospital setting, such as hypertonic saline and tranexamic acid.[4,5] The timing of outcomes is important in TBI trials as functional recovery from TBI may take months, or even years after the initial injury.[6–16] Measurement of outcomes at hospital discharge is feasible but may fail to capture subsequent neurologic changes. Measurement of outcomes at later endpoints may better capture changes in health status but is logistically difficult, increasing the complexity of trial design and deployment. Understanding the course of TBI recovery is important for several reasons, including informing long-term clinical care as well as guiding the design of prehospital TBI clinical trials. There are few studies characterizing changes in neurologic or vital status after prehospital TBI treatment.

1.3 | Goals of this investigation

The Resuscitation Outcomes Consortium Hypertonic Saline (ROC-HS) trial tested the effectiveness of prehospital hypertonic saline in the treatment of acute TBI.[4] We sought to characterize changes in neurologic status among adults with TBI enrolled in the ROC-HS trial.

2 | METHODS

2.1 | Study design

We conducted a secondary analysis of the TBI cohort enrolled in the ROC-HS trial. This analysis was classified as not human subject research by the University of Arizona Institutional Review Board.

2.2 | Setting—The Resuscitation Outcomes Consortium Hypertonic Saline trial

The ROC-HS was a multicenter clinical trial testing the effectiveness of prehospital hypertonic fluids upon outcomes after severe TBI and hemorrhagic shock.[4,17] ROC consisted of 114 EMS agencies from 11 communities in the United States and Canada. The trial included enrollment of two cohorts: (1) TBI and (2) hemorrhagic shock. Inclusion criteria for the TBI cohort were as follows: blunt mechanism of injury, age 15 years or older, Glasgow Coma Scale (GCS) score $\leq$ 8, and ineligibility for the hemorrhagic shock cohort. The hemorrhagic shock cohort included patients with systolic blood pressure of $\leq$70 mm Hg or 71–90 mmHg with a concomitant heart rate $\geq$ 108 beats per minute. Key exclusion criteria included known or suspected pregnancy, prisoners, transferred patients, out-of-hospital cardiopulmonary resuscitation, administration of >2000 mL of crystalloid intravenous fluid, or any amount of colloid or blood products. Patients with concomitant head injury and hypotension were included in the shock cohort.

The three blinded trial interventions included a 250 mL bolus of (1) 7.5% saline (hypertonic saline), (2) 7.5% saline with 6% dextran 70 (hypertonic saline/dextran), and (3) 0.9% saline (normal saline), randomized in a ratio of 1:1:1.4. Study fluids were provided in identical intravenous bags; EMS providers were blinded to the fluid contents. The trial met prespecified criteria for futility in 28-day survival or 6-month neurologic outcomes after enrollment of 1282 and 853 patients in the TBI and hemorrhagic shock cohorts, respectively. Patient enrollment occurred during 2006–2009.

2.3 | Selection of participants

We included all patients enrolled in the TBI cohort of the parent trial.

2.4 | Outcomes

The outcomes of interest for this analysis were neurologic outcome and death at (1) hospital discharge and (2) 6-month follow-up. The trial determined neurologic status using the Glasgow Outcome Scale–Extended (GOS-E).[18,19] The Glasgow Outcome Scale (GOS) was first described by Jennett and Bond as an assessment of global neurologic outcome and death after severe brain injury and consisted of the five categories: 1 = dead, 2 = vegetative state, 3 = severe disability, 4 = moderate disability, 5 = good recovery.[20] Later efforts modified the GOS to GOS-E with eight categories to improve its sensitivity: 1 = dead, 2 = vegetative state, 3 = lower severe disability, 4 = upper severe disability, 5 = lower moderate disability, 6 = upper moderate disability, 7 = lower good recovery, and 8 = upper good recovery.[18,19] Research teams determined GOS-E at hospital discharge using a structured telephone survey.[21] If the patient was unable to respond to the survey, family members or caregivers provided the requested information, an approach that has been previously validated.[21,22] For patients who died after hospital discharge, we assigned a 6-month GOS-E = 1. For patients who died before hospital discharge, we assigned GOS-E = 1 for both hospital and 6-month follow-up. The trial did not assess outcomes after 6-month follow-up.

2.5 | Data analysis

We excluded patients where hospital discharge occurred after the 6-month follow-up. Characteristics described by the parent trial included patient demographics (age, sex), clinical presentation (injury mechanism, prehospital GCS, revised trauma score [RTS], injury severity score [ISS], head abbreviated injury score [AIS], Marshall head computed tomography [CT] classification), EMS care (air medical transport, advanced airway placement, the prehospital time interval), and outcomes (hospital survival, 28-day survival, intensive care unit-free days at 28 days, and GOS-E at hospital discharge and 6 months).[23–27] We determined GOS-E changes between hospital discharge and 6 months by examining median changes with exact 95% CIs and means change with bootstrapped 95% CIs. We stratified neurologic status according to severity categories: GOS-E 1 = dead, GOS-E 2–4 = unfavorable neurologic status, and GOS-E 5–8 = favorable neurologic status. We also used Sankey graphs to depict transitions between GOS-E categories at hospital discharge and 6 months.[28]

In an additional analysis, we focused on the subset of patients with unfavorable neurologic status at hospital discharge, distinguishing (1) those who improved to favorable neurologic status from (2) those who remained in unfavorable neurologic status at 6-month follow-up. Using multicovariate logistic regression, we identified the baseline characteristics independently associated with improvement to favorable 6-month neurologic function through a backward elimination process starting from a model including all baseline characteristics that were associated with the outcome in univariate analysis at the significance level of 0.20.

The Bottom Line

Limited data exist on long-term outcomes of patients with traumatic brain injury (TBI) treated by emergency medical services (EMS). The authors used data from a randomized trial of prehospital hypertonic saline for TBI to examine changes in functional outcome from the time of hospital discharge to 6-month follow-up. Almost half of patients with unfavorable functional outcome at hospital discharge improved by 6 months and very few with favorable outcome at discharge worsened or died by 6 months, findings that will be important for future clinical care and trials.

Some authors advocate extending the GOS-E range to 4–8 for classifying favorable neurologic status, noting that many patients with GOS-E = 4 (upper severe disability) are able to function at home without supervision for more than 8 h daily.[7] In a sensitivity analysis, we repeated the analysis of the full cohort defining favorable neurologic status as GOS-E 4–8 and unfavorable neurologic status as GOS-E 2–3.

We conducted all analyses using SAS and Microsoft Excel with the Power–User add-in (Power-User SAS).

3 | RESULTS

The parent trial enrolled a total of 1282 TBI patients. We excluded three patients who were discharged from the hospital more than six months after injury, leaving 1279 in the analysis. Trial interventions were as follows: hypertonic saline + dextrose 357 (27.9%), hypertonic saline 340 (26.6%), and normal saline 582 (45.5%). Enrolled subjects were mostly male and suffered primarily blunt injury (Table 1). The acuity of the population was high, with high RTS and ISS. Approximately 40% underwent air medical transport. One-third of the population experienced severe TBI (head AIS 3 or 4), and one-third suffered critical TBI (head AIS 5–6). Approximately one-fifth of the population did not have a significant brain injury (head AIS = 0). Approximately three-fourths were alive at 28-days after injury. Among the 945 patients alive at hospital discharge, median time from injury to discharge was 14 days (interquartile range [IQR] 4, 30), and median time from hospital discharge to 6-month outcome interview was 176 days (IQR 158, 190).

At hospital discharge, favorable neurologic status, unfavorable neurologic status, and death comprised 17.2%, 51.9%, and 25.1% of the full cohort (Table 2). At 6-month follow-up favorable neurologic status, unfavorable neurologic status and death comprised 35.9%, 21.8%, and 27.1% of the cohort.

Neurologic status was available at both hospital discharge and 6-month follow-up for 1066 of 1279 (83.3%) subjects. Of this subset, 30.1% were dead at hospital discharge. Of the remaining survivors, most (>96%) followed one of three neurologic status trajectories: (1) favorable to favorable (20.0%), (2) unfavorable to favorable (40.3%),

TABLE 1 Characteristics of 1279 patients enrolled in the Resuscitation Outcomes Consortium Hypertonic Saline Traumatic Brain Injury (TBI) trial.

Characteristic	Frequency
Age (year), mean (SD)	39 (18.5)
Sex, *n* (%)	
Male	973 (76.1%)
Female	304 (23.7%)
Unknown	2 (0.2%)
Race	
Asian	40 (3.1%)
Black	109 (8.5%)
White	629 (49.2%)
Other	45 (3.5%)
Unknown	456 (35.7%)
Hispanic	
No	662 (51.8%)
Yes	126 (9.9%)
Unknown/not noted	491 (38.4%)
Injury mechanism, *n* (%)	
Blunt	1258 (98.4%)
Penetrating	18 (1.4%)
Unknown	3 (0.2%)
Prehospital Glasgow Coma Scale, median (IQR)	5 (3, 7)
Hospital Admission Glasgow Coma Scale, median (IQR)	3 (3, 7)
Lowest Prehospital Systolic Blood Pressure, mm Hg, median (IQR)	120 (102, 136)
Lowest Emergency Department Systolic Blood Pressure, mm Hg, median (IQR)	111 (94, 126)
Systolic Blood Pressure on Hospital Admission, median (IQR)	140 (121, 157)
Systolic Blood Pressure on Hospital Admission, mean (SD)	139.2 (33.1)
Revised trauma score (RTS), mean (SD)	5 (1.2)
Injury severity score (ISS), median (IQR)	26 (16, 36)
Maximum head abbreviated injury score (AIS), *n* (%)	
0	236 (18.5%)
1	6 (0.5%)
2	113 (8.8%)
3	161 (12.6%)
4	274 (21.4%)
5	452 (35.3%)
6	5 (0.4%)
Unknown	32 (2.5%)
Marshall score, first head CT, n (%)	
Diffuse injury I	373 (29.2%)
Diffuse injury II	433 (33.9%)
Diffuse injury III	151 (11.8%)
Diffuse injury IV	51 (4.0%)
Mass lesion	207 (16.1%)
Other	16 (1.3%)
Unknown	48 (3.8%)
Air transport, *n* (%)	
No	772 (60.4%)
Yes	504 (39.4%)
Unknown	3 (0.2%)
Total prehospital time (min), median (IQR)	50 (38, 67)
Trial intervention, *n* (%)	
Hypertonic saline + dextran	357 (27.9%)
Hypertonic saline	340 (26.6%)
Normal saline	582 (45.4%)
Survival at hospital discharge, *n* (%)	
No	321 (25.1%)
Yes	945 (73.9%)
Unknown	13 (1.0%)
28-Day survival, *n* (%)	
No	312 (24.4%)
Yes	957 (74.8%)
Unknown	10 (0.8%)
ICU-free days through day 28, median (IQR)	19 (0, 27)

and (3) unfavorable to unfavorable (36.0%). (Table 3, Figure 1). Of the 220 patients with favorable neurologic status at hospital discharge, only seven (1.0%) deteriorated to unfavorable neurologic status or death. Compared with hospital discharge, there were only 23 additional deaths at 6-month follow-up.

In the full cohort, younger age, higher RTS, lower head AIS score, lower Marshall score, and absence of hypotension in the emergency department (ED) were independently associated with progression from unfavorable neurologic status (GOS-E 2–4) at hospital discharge to good neurologic status (GOS-E 5–8) at 6-month follow-up[26] (Supporting Information Appendix 1, Table 4). The parent trial interventions (hypertonic saline, hypertonic saline/dextrose, and normal saline) were not associated with progression in neurologic status.

In a sensitivity analysis recategorizing favorable neurologic status as GOS-E 4–8 and unfavorable neurologic status as GOS-E 2–3, there were only minimal differences in the percentage of surviving patients transitioning from unfavorable to favorable neurologic status (41.5%) (Appendices 2 and 3).

TABLE 2 Comparison of neurologic status (Glasgow Outcome Scale-Extended [GOS-E]) at hospital discharge and 6-month follow-up among patients enrolled in the Resuscitation Outcomes Consortium Hypertonic Saline Traumatic Brain Injury (TBI) trial. It includes full cohort ($n = 1279$).

		GOS-E at 6-month follow-up									
		GOS-E classification									
		Favorable, $n = 459$ (35.9%)				Unfavorable, $n = 279$ (21.8%)			Dead, $n = 346$ (27.1%)	Missing, $n = 195$ (15.2%)	
GOS-E classification	GOS-E at hospital discharge	8	7	6	5	4	3	2	1	Missing	Total
Favorable, $n = 200$ (17.2%)	8	57	9	6	3	2	0	0	0	39	116
	7	17	4	1	3	0	0	0	0	9	34
	6	20	6	3	6	1	0	0	1	12	49
	5	4	7	2	1	1	1	0	1	4	21
Unfavorable, $n = 664$ (51.9%)	4	35	16	9	11	17	8	0	0	14	110
	3	78	48	58	44	77	131	1	9	52	498
	2	1	0	0	0	3	25	6	12	9	56
Dead, $n = 321$ (25.1%)	1	0	0	0	0	0	0	0	321	0	321
Missing, $n = 74$ (5.8%)	Missing	6	2	1	1	1	4	1	2	56	74
	Total	218	92	80	69	102	169	8	346	195	1279

Note: No change between favorable/unfavorable status or death. Improvement in neurologic status. Decline in neurologic status or death. Dead GOS-E: 1; GOS-E 2–4: unfavorable neurologic status; GOS-E 5–8: favorable neurologic status. Shaded cells indicate transitions between favorable and unfavorable neurologic status or death.

TABLE 3 Patterns of neurologic status change between hospital discharge and 6-month follow-up among patients enrolled in the Resuscitation Outcomes Consortium Hypertonic Saline Traumatic Brain Injury (TBI) trial. It includes 1066 of 1279 TBI subjects with complete neurologic status at both hospital discharge and 6-month follow-up. Neurologic status defined as: Dead GOS-E: 1, unfavorable GOS-E: 2–4, favorable GOS-E: 5–8.

Change in neurologic status (Hospital discharge → 6-month follow-up)	Full cohort, N (%)	Hospital survivors only, N (%)
1) Favorable (GOS-E 5–8) → Favorable (GOS-E 5–8)	149 (14.0%)	149 (20.0%)
2) Favorable (GOS-E 5–8) → Unfavorable (GOS-E 2–4)	5 (0.5%)	5 (0.7%)
3) Favorable (GOS-E 5–8) → Dead (GOS-E 1)	2 (0.2%)	2 (0.3%)
4) Unfavorable (GOS-E 2–4) → Favorable (GOS-E 5–8)	300 (28.1%)	300 (40.3%)
5) Unfavorable (GOS-E 2–4) → Unfavorable (GOS-E 2–4)	268 (25.1%)	268 (36.0%)
6) Unfavorable (GOS-E 2–4) → Dead (GOS-E 1)	21 (2.0%)	21 (2.8%)
7) Dead at hospital discharge (GOS-E 1)	321 (30.1%)	Not applicable

4 | LIMITATIONS

As expected, a portion of subjects in the trial did not exhibit intracranial injuries on CT imaging. Enrollment in a prehospital TBI clinical trial is based upon initial clinical presentation, not verified radiologic findings. The ROC-HS trial included TBI with an initial presenting GCS ≤8. Thus, the trial may have included some unconscious subjects without intracranial injuries (e.g. those with intoxication masquerading as TBI) as well as seemingly conscious patients with severe intracranial injuries. This may partially explain the lower death rate seen in our study (1.8%) compared with prior cohorts.[7,9]

We did not adjust for potential confounders such as patient characteristics, severity of injury, EMS treatment (e.g. airway management or volume of intravenous fluids), or the intervention group of the parent trial. Adjustment for confounding would be important if we were comparing outcomes between different exposure subsets in the study data set. However, our objective was to describe the natural history and transitions of neurologic status in the overall study population; one would not expect confounding to alter these observations. Given the random assignment of treatment groups in the parent ROC-HS trial, we would expect few if any differences in the natural course of neurologic status between trial treatment intervention groups. While the

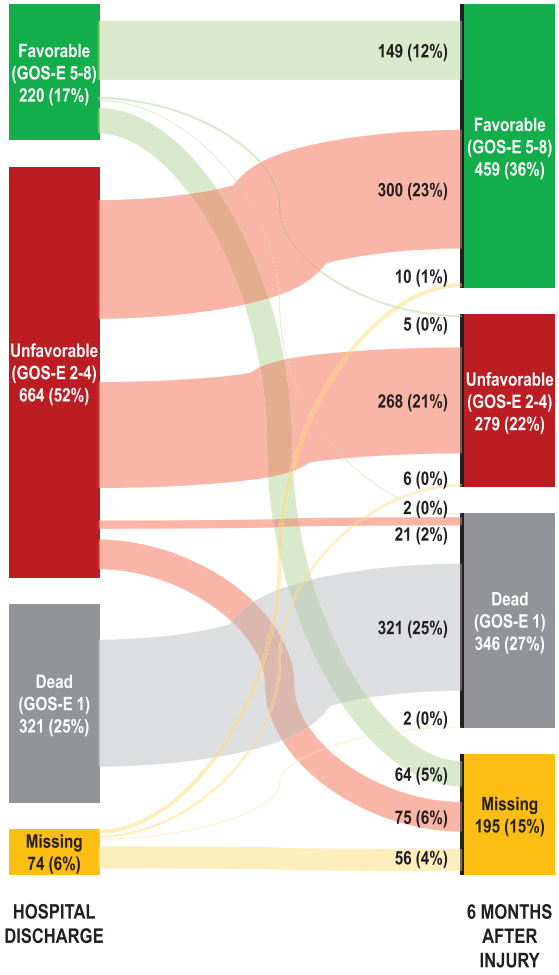

FIGURE 1 Sankey graph depicting changes in neurologic status (Glasgow Outcome Scale-Extended [GOS-E]) between hospital discharge and 6-month follow-up among patients enrolled in the Resuscitation Outcomes Consortium Hypertonic Saline trial. N = 1279 patients.

early termination of the parent trial could have altered the makeup of each intervention group, the description of the parent trial indicated few if any differences in baseline characteristics or outcomes between the intervention groups.[4]

Missingness of GOS-E was also prevalent, influencing 17% of the cohort. We note missing 6-month GOS-E was more common among those with initial good neurologic status (32%) than those with poor neurologic status (11%); the reasons for these differences are unclear. We surmise that individuals with an initially poor neurologic status may be easier to track in the long term if they are connected with TBI rehabilitation services. If all the missing values were included in sensitivity analyses as "favorable" or "unfavorable" neurologic status, this would have slightly shifted the proportion of patients in each neurologic trajectory. We did not study other measures of neurologic and functional status such as the Functional Independence Measure, the Disability Rating Scale, or quality of life.[6,29] We also did not study other neurologic sequelae such as seizures, dementia, and Parkinsonism.[30]

TABLE 4 Multicovariate logistic regression of factors associated with improvement from unfavorable (GOS-E 2–4) to favorable neurologic outcome (GOS-E 5–8) among patients enrolled in the Resuscitation Outcomes Consortium Hypertonic Saline Traumatic Brain Injury (TBI) trial. It is limited to subset with unfavorable neurologic status at hospital discharge (GOS-E 2–4).

Variable	OR (95% CI)
Age (year)	0.97 (0.96, 0.98)
Revised trauma score (RTS)	1.44 (1.20, 1.72)
Maximum head abbreviated injury score (AIS)	
0	Reference
1–3	1.40 (0.75, 2.62)
4	1.06 (0.57, 1.97)
5	0.61 (0.32, 1.14)
Marshall score, first head CT	
Diffuse injury I/II	Reference
Diffuse injury III/IV	0.50 (0.29, 0.85)
Mass lesion	0.52 (0.28, 0.98)
Hypotension at ED (lowest SBP < 90 mm Hg)	
No	Reference
Yes	0.56 (0.34, 0.94)

Abbreviations: CI, confidence interval; OR, odds ratio; SBP, systolic blood pressure.

5 | DISCUSSION

In this analysis of data from the ROC-HS trial, we observed that the majority of TBI patients alive at hospital discharge subsequently exhibited one of three neurologic recovery patterns: (1) good neurologic status at both hospital discharge and 6-month follow-up, (2) poor neurologic status at hospital discharge improving to good neurologic outcome at 6-month follow-up, and (3) poor neurologic status at both hospital discharge and 6-month follow-up. These findings have important implications for both the care and prognostication of TBI as well as the design of prehospital TBI intervention trials.

While the ROC-HS trial took place over 15 years ago, compared with other TBI series, the data had important distinctions and strengths that were well suited to our objectives. We aimed to study TBI patients receiving initial care in the prehospital setting; these patients present with the higher acuity and undergo early resuscitative care. Clinical trials also tend to have higher accuracy and lower missingness; rates of GOS-E missingness in the current series were 6%–15%, much lower than the 30%–50% missingness observed in prior cohorts.[7–9] Most importantly, the subjects in the ROC-HS trial were enrolled under Exception from Informed Consent, ensuring inclusion of the highest acuity patients without recruitment biases. We conducted this analysis using the ROC-HS data because of its availability and suitability for our defined objectives. We expect others to replicate and validate our analytic methods with more contemporary prehospital TBI data. However, given the distinctions of the prehospital TBI population, analyses of TBI

identified in other settings (i.e., in the hospital) may arrive at slightly different results.

Our findings reinforce existing perspectives regarding the trajectories of TBI neurologic recovery. As suggested by the current and prior studies, the general ominous prognosis of patients with poor neurologic status at hospital discharge may be unwarranted.[7–16] Among those with initially unfavorable neurologic status, almost half improved to favorable neurologic status. Very few patients with favorable neurologic status at hospital discharge deteriorated or died at 6-month follow-up. There were also few additional deaths at 6-month follow-up. In an analysis of 484 patients from the TRACK-TBI cohort study, McCrea et al. found that at 12 months, 52% of patients with severe TBI (defined as initial GCS 3–8) achieved favorable neurologic outcomes.[7] In an analysis of 4624 TBI in the TBI Model Systems National Database, Dams-O'Connor et al. observed functional improvement in the first 2 years after TBI followed by a decline and decreased independence by year 5.[15] Similarly, Puffer et al. analyzed recovery trajectories of 640 TBI in the Citicoline Brain Injury Treatment trial, reporting substantial improvement in all severity groups within 6 months.[8,11] Clinicians and families should use these observations to guide decisions regarding long-term care and recovery after TBI.

We also observed many findings relevant to TBI clinical trial design. As expected with prehospital TBI trials, given the limitations of the prehospital setting, a portion of enrolled patients will present with low GCS but have no demonstrable brain CT abnormalities. Trial sample sizes must account for this possibility. We affirmed the shift in distribution of neurologic status between hospital discharge and 6-month follow-up. If the objective of a novel trial intervention is to mitigate death after TBI, then hospital survival may be suitable as the primary research outcome, as the overall number of deaths does not significantly increase at 6 months. For interventions targeting optimization of neurologic outcome, extending observation to 6 months or later may be necessary. To plan for the logistics of long-term follow-up, research teams should focus on the subset with unfavorable neurologic status at hospital discharge. Our secondary findings highlight the baseline characteristics of TBI most likely to improve to favorable neurologic status, offering additional targets of focus for research teams. One could conceivably use neurologic status at hospital discharge as the primary outcome; our study suggests that observed differences in neurologic status at hospital discharge would likely widen at later time points. While the rates of missing GOS-E are lower than in prior studies, it is still high enough to bias inferences; trial design must account for missingness when estimating sample sizes.

We also offer an important novel analytic approach to better depict and conceptualize neurologic recovery after TBI. Prior studies presented the distribution of GOS-E categories at discrete time points, characterizing the heterogeneity of the population but not specifically identifying the transitions of neurological status between discharge and follow-up.[7–9] Other studies have characterized TBI trajectories using a range of sophisticated analytic techniques, such as quadratic models and least absolute shrinkage and selection operator.[10,12] We believe that our use of Sankey graphs is simple, intuitive, and clarifies dominant patterns of neurologic recovery. While incremental changes in GOS-E are of interest, in the context of clinical trial design, shifts between broad categories are potentially more useful. In the sensitivity analysis, when shifting the range for good neurologic outcome from GOS-E 5–8 to GOS-E 4–8, the percentage of total trial TBI patients improving from unfavorable to favorable neurologic status remained similar (29% vs. 28%); this observation supports the robustness of our approach.

In conclusion, in this analysis of the ROC-HS TBI trial cohort, neurologic recovery after TBI followed distinct patterns. Among TBI with unfavorable neurologic status at hospital discharge, almost half progressed to favorable neurologic status at 6 months. Very few TBI worsened or died at 6 months. These observations offer key perspectives to guide TBI care, research, and clinical trial design.

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to all of the following: (1) the conception and design of the study, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be submitted.

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CONFLICT OF INTEREST STATEMENT

There is no overlap with previous publications other than the parent Resuscitation Outcomes Consortium Hypertonic Saline trial, and we confirm that the manuscript, including related data, figures, and tables, has not been published previously and that the manuscript is not under consideration elsewhere at this time. Dr. Wang is Editor in Chief of *JACEP Open* and had no role in the editorial assessment of or decision to publish this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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