Effect of Implementing the Out-of-Hospital Traumatic Brain Injury Treatment Guidelines: The Excellence in Prehospital Injury Care for Children Study (EPIC4Kids)

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Study objective: We evaluate the effect of implementing the out-of-hospital pediatric traumatic brain injury guidelines on outcomes in children with major traumatic brain injury.

Methods: The Excellence in Prehospital Injury Care for Children study is the preplanned secondary analysis of the Excellence in Prehospital Injury Care study, a multisystem, intention-to-treat study using a before-after controlled design. This subanalysis included children younger than 18 years who were transported to Level I trauma centers by participating out-of-hospital agencies between January 1, 2007, and June 30, 2015, throughout Arizona. The primary and secondary outcomes were survival to hospital discharge or admission for children with major traumatic brain injury and in 3 subgroups, defined a priori as those with moderate, severe, and critical traumatic brain injury. Outcomes in the preimplementation and postimplementation cohorts were compared with logistic regression, adjusting for risk factors and confounders.

Results: There were 2,801 subjects, 2,041 in preimplementation and 760 in postimplementation. The primary analysis (postimplementation versus preimplementation) yielded an adjusted odds ratio of 1.16 (95% confidence interval 0.70 to 1.92) for survival to hospital discharge and 2.41 (95% confidence interval 1.17 to 5.21) for survival to hospital admission. In the severe traumatic brain injury cohort (Regional Severity Score–Head 3 or 4), but not the moderate or critical subgroups, survival to discharge significantly improved after guideline implementation (adjusted odds ratio = 8.42; 95% confidence interval 1.01 to 100+). The improvement in survival to discharge among patients with severe traumatic brain injury who received positive-pressure ventilation did not reach significance (adjusted odds ratio = 9.13; 95% confidence interval 0.79 to 100+).

Conclusion: Implementation of the pediatric out-of-hospital traumatic brain injury guidelines was not associated with improved survival when the entire spectrum of severity was analyzed as a whole (moderate, severe, and critical). However, both adjusted survival to hospital admission and discharge improved in children with severe traumatic brain injury, indicating a potential severity-based interventional opportunity for guideline effectiveness. These findings support the widespread implementation of the out-of-hospital pediatric traumatic brain injury guidelines. [Ann Emerg Med. 2020;■:1-15.]

Please see page XX for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background and Importance

The burden of traumatic brain injury is enormous, affecting more than 2.8 million individuals in the United States annually. Among children younger than 18 years, it results in 812,000 emergency department (ED) visits, 23,000 hospitalizations, and 2,500 deaths each year,[1,2] making it a leading cause of pediatric death and disability.[3] Although improving outcomes has been difficult,[4-11] early management may help mitigate secondary brain injury.[3,12-17] This has led to promulgation of evidence-based traumatic brain injury treatment guidelines for the out-of-hospital care provided in emergency medical services (EMS) systems.[12-14,16] Before the recently reported results of the Excellence in Prehospital Injury Care (EPIC) Study,[18] no large, controlled evaluation of the guidelines had been published for any age group. EPIC demonstrated that implementation of the EMS guidelines (among all ages combined) was associated with

Editor's Capsule Summary

What is already known on this topic

Approximately 2,500 children die of head trauma in the United States annually.

What question this study addressed

What was the effect of implementing an out-of-hospital trauma care guideline for children with a traumatic brain injury treated in Arizona?

What this study adds to our knowledge

Implementation of the traumatic brain injury out-of-hospital guidelines was not associated with improved overall survival. Survival to hospital admission and improved overall survival was observed in the severe (but not moderate or critically-severe) head-injured children.

How this is relevant to clinical practice

Implementation of guidelines might improve survival of children with severe head injuries, but not that of those with less severe or devastating injuries.

significant improvement in adjusted survival to hospital discharge among patients with severe traumatic brain injury.[18] Here, we report the preplanned pediatric subanalysis, the Excellence in Prehospital Injury Care for Children ("EPIC4Kids") study.

Goals of This Investigation

The objective of this study was to implement the nationally vetted out-of-hospital traumatic brain injury guidelines[13] among the EMS agencies of Arizona and compare before-after risk-adjusted outcomes in children with moderate, severe, and critical traumatic brain injury. This pediatric subgroup analysis was planned a priori during the conception of the study.

MATERIALS AND METHODS

Study Design and Setting

The EPIC study evaluated the effect of statewide traumatic brain injury guideline implementation across all ages, using a controlled, before-after, multisystem, intention-to-treat design.[18-20] This report (Excellence in Prehospital Injury Care for Children [EPIC4Kids]) is the evaluation of implementing the guidelines in children younger than 18 years. We also report several main results on individuals younger than 21 years because this was the original age definition for children (as specified by the National Institutes of Health). The study methods have previously been reported in detail.[18,21-24]

The University of Arizona institutional review board and Arizona Department of Health Services Human Subjects Review Board approved the project and the publication of deidentified data.[21-24] The Strengthening the Reporting of Observational Studies in Epidemiology checklist (http://www.strobe-statement.org) was used to improve this article.

Data Collection and Processing

The Arizona State Trauma Registry contains extensive data on patients taken to Level I trauma centers. From this data set, cases meeting inclusion criteria between January 1, 2007, and June 30, 2015, were linked to EMS data by accessing paper-based or electronic patient care reports from participating agencies. The linkage and combination of these data yielded a comprehensive out-of-hospital and trauma center database. Detailed descriptions of the data collection and linkage processes have been reported previously.[21]

Selection of Participants

For this analysis, children with major traumatic brain injury were defined as patients younger than 18 years with physical trauma who were transported directly or transferred to a Level I trauma center by participating agencies, had hospital diagnosis(es) consistent with traumatic brain injury (isolated or multisystem), and met at least one of the following definitions for major traumatic brain injury: Centers for Disease Control and Prevention Barell matrix type 1 injury[25-27] or Abbreviated Injury Scale–Head score greater than or equal to 3. To prevent selection bias, all subjects meeting injury criteria were included whether EMS data were obtained or not.[28,29] The same analysis was performed with the National Institutes of Health definition for children (<21 years) and, as designed in the original analysis plan, these results are provided in Figures E1 to E3 (available online at http://www.annemergmed.com). Subjects with major traumatic brain injury were then grouped into 3 cohorts by Regional Severity Score–Head: moderate traumatic brain injury (score 1 or 2), severe traumatic brain injury (score 3 or 4), and critical traumatic brain injury (score 5 or 6). Clinical examples of injuries that would be in each group include cerebral contusion and skull fracture (moderate traumatic brain injury), moderate-sized epidural hematoma (severe traumatic brain injury), and brain stem contusion or large subdural hematoma with extensive diffuse axonal injury (critical traumatic brain injury).

Interventions

All Arizona EMS agencies were invited to participate. Participation required adoption of the out-of-hospital pediatric traumatic brain injury guideline–based treatment protocols with agreement to implement the guidelines using a train-the-trainer strategy and a commitment to provide EMS data. Every agency participated in all 3 study phases and provided data regardless of which phase they were in. The willingness and ability to provide access to EMS data from July 1, 2007, through the end of enrollment in the study (June 30, 2015) was required. Training emphasized guideline use in patients with physical trauma, reported or apparent loss of consciousness, and injury sufficient to warrant transport to a hospital.[21]

Guideline-based, age-specific protocols and algorithms (Figure 1 and Figure E1, available online at http://www.annemergmed.com) grouped patients into infants (0 to 24 months), children (2 to 14 years), and adolescents (15 to 20 years). The clinical protocols focused on 4 interventions: (1) prevention and treatment of hypoxia through early, high-flow oxygen administration; (2) airway interventions to optimize oxygenation and ventilation (bag-valve-mask and intubation or extraglottic/supraglottic airways reserved for cases in which basic airway interventions were inadequate); (3) prevention of hyperventilation by using age-appropriate ventilation rates and ventilation adjuncts (eg, visual cue ventilation rate timers, flow-controlled ventilation bags); and (4) avoidance and aggressive treatment of hypotension by infusing isotonic fluids.[21] For patients younger than 10 years, age-specific thresholds for treatment of hypotension and fluid resuscitation were used.

Outcome Measures

The primary outcome was survival to hospital discharge ("survival"). The secondary outcome was survival to hospital admission (meaning survival long enough to be admitted from the ED to the operating room, inpatient bed status, or both, or being discharged alive from the ED).

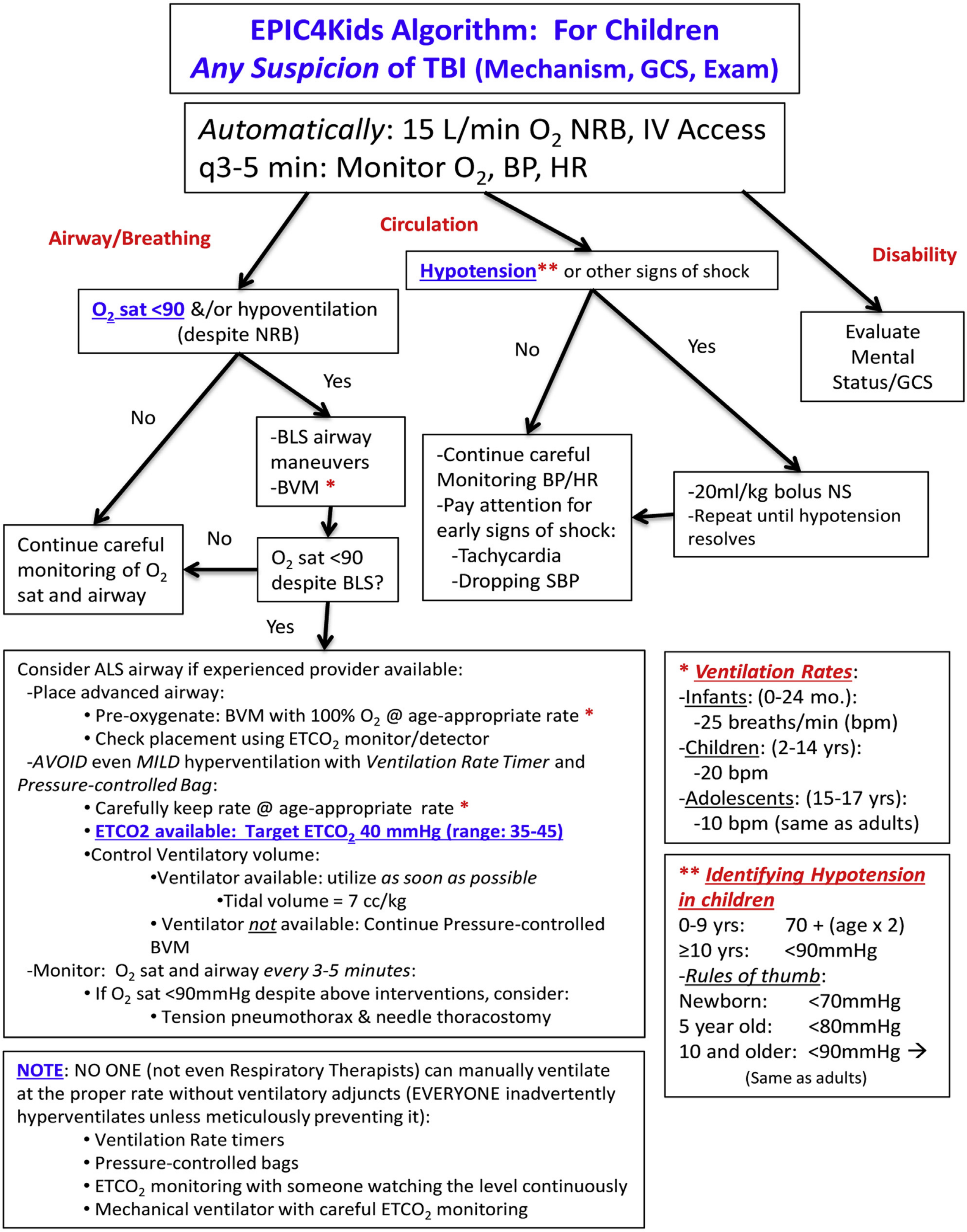
Primary Data Analysis

Continuous variables were summarized by median and interquartile range (IQR), and 95% confidence intervals (CIs) were obtained by the bootstrap method. Categoric variables were summarized by frequency and proportion (with 95% Clopper-Pearson CI), and differences between 2 groups were evaluated with difference in proportions (risk difference) and odds ratio, with 95% CI obtained by either the score method or the melded method for small number of events.[30,31]

The analysis compared outcomes in the preimplementation phase with those in the postimplementation phase. Subjects presenting during phase 2 (the timeframe from initiation of training at an EMS agency until training was complete) were excluded from the analysis. The study phases were based on each agency's training schedule. To limit the potential for contamination of the phases, the beginning and ending dates for training in each agency were meticulously identified by specific, ongoing communication between study coordinating personnel and training officials from each agency. This ensured that subjects were not enrolled in preimplementation after any training had begun in an agency, and also that no subjects were enrolled in postimplementation before training was completed. Thus, preimplementation and postimplementation were kept "pure" by careful categorization of each patient in phase 2 (the run-in phase, which was excluded from the analysis) if they were cared for by any agency that had begun, but not yet completed, training.

The associations between survival and survival to hospital admission and intervention were examined by logistic regression, adjusting for important risk factors and potential confounders (age, sex, race, ethnicity, Regional Severity Score–Head, Injury Severity Score, trauma type, direct transport versus transfer to a trauma center, payment source, multisystem injury, out-of-hospital cardiopulmonary resuscitation [CPR], and treating trauma center). These covariates were all included a priori in the model regardless of statistical significance, based on the extant trauma literature and the previous observational studies published from the preimplementation EPIC cohort.[22-24] The effect of age (continuous variable) was fitted nonparametrically, using penalized thin plate splines through the generalized additive model.[32] Fitted models were assessed by deviance residual plots and area under the receiver operating characteristic (ROC) curve, with 95% CI obtained by the DeLong method. Collinearity was checked with variance inflation factors for the parametric terms and concurvity for the nonparametric term. Mixed-effect models for survival/survival to hospital admission were used to assess the effect of potential correlation of subjects treated by the same EMS agency. The 8 trauma centers of this study were included in the models as fixed effects because they were the only Level I trauma centers in Arizona at the design phase of this study (ie, not a random sample of trauma centers from a larger group).

In preplanned secondary analyses (ie, moderate-, severe-, and critical-severity-based cohorts), standard logistic regression was used when there were at least 200 subjects with the event (survival/survival to hospital admission) and



Consider ALS airway if experienced provider available:

- Place advanced airway:
  - Pre-oxygenate: BVM with 100% O_2 @ age-appropriate rate *
  - Check placement using $ETCO_2$ monitor/detector
- *AVOID* even *MILD* hyperventilation with *Ventilation Rate Timer* and *Pressure-controlled Bag*:
  - Carefully keep rate @ age-appropriate rate *
  - **ETCO2 available: Target $ETCO_2$ 40 mmHg (range: 35-45)**
  - Control Ventilatory volume:
    - Ventilator available: utilize *as soon as possible*
      - Tidal volume = 7 cc/kg
    - Ventilator *not* available: Continue Pressure-controlled BVM
- Monitor: O_2 sat and airway *every 3-5 minutes*:
  - If O_2 sat <90mmHg despite above interventions, consider:
    - Tension pneumothorax & needle thoracostomy

NOTE: NO ONE (not even Respiratory Therapists) can manually ventilate at the proper rate without ventilatory adjuncts (EVERYONE inadvertently hyperventilates unless meticulously preventing it):

- Ventilation Rate timers
- Pressure-controlled bags
- $ETCO_2$ monitoring with someone watching the level continuously
- Mechanical ventilator with careful $ETCO_2$ monitoring

*** *Ventilation Rates***:
-Infants: (0-24 mo.):
-25 breaths/min (bpm)
-Children: (2-14 yrs):
-20 bpm
-Adolescents: (15-17 yrs):
-10 bpm (same as adults)

***** Identifying Hypotension in children***

0-9 yrs:	70 + (age x 2)
≥10 yrs:	<90mmHg

-*Rules of thumb*:

Newborn:	<70mmHg
5 year old:	<80mmHg
10 and older:	<90mmHg → (Same as adults)

Figure 1. Out-of-hospital traumatic brain injury treatment algorithm for children. *EPIC4Kids,* Excellence in Prehospital Injury Care for Children; *TBI*, traumatic brain injury; *GCS*, Glasgow Coma Scale score; O_2, oxygen; *NRB*, non-rebreather; *IV*, intravenous; *BP*, blood pressure; *HR*, heart rate; *BLS*, basic life support; *BVM*, bag-valve-mask; *SBP*, systolic blood pressure; *NS*, normal saline; *mo*, months; *ETCO2*, end-tidal carbon dioxide; *yrs*, years; *cc*, mililiters; *kg*, kilogram.

200 without. Otherwise, Firth's penalized-likelihood logistic regression was used.[33,34]

We used software environment R (R Foundation for Stastical Computing, Vienna, Austria) for the analysis.[35] Packages boot for bootstrap,[36] PropCIs,[37] exact2x2,[38] and epitools were used for unadjusted analysis[39]; mgcv,[32] gamm4,[40] and logistf for regression models[41]; and pROC for area under the ROC curve analysis.[42] All tests were 2 sided with α=.05, except for the primary analysis, which was .04 (1 interim analysis was conducted with α=.01).

RESULTS

Characteristics of Study Subjects

Total enrollment in EPIC was 26,873, including 3,470 children. In this analysis, 669 subjects were excluded (Figure 2), leaving 2,801 as the study group (preimplementation 2,041; postimplementation 760). Preimplementation began for all agencies on January 1, 2007. Phase 2 began and ended at different times for each agency (the first agency began training February 22, 2012; the last agency completed training on January 23, 2015). The median training interval was 43 days (IQR 16 to 99 days). Although there was variation in the time required to complete training (phase 2), the majority of agencies were efficient at doing so. This is reflected by the fact that only 2.4% of patients were excluded owing to being cared for by an agency in the run-in period (phase 2). Among all 3,291 children with eligible injuries who arrived at trauma centers by EMS, only 255 (7.7%) were cared for by nonparticipating agencies (nearly all nonparticipants were very small rural agencies). Both ground-based and air agencies participated and care was provided by basic and advanced emergency medical technicians, paramedics, critical care paramedics, and nurses. Greater than 130 fire departments and EMS agencies participated in EPIC and 92 of them cared for pediatric subjects. Of the 92 agencies, 55 cared for subjects in both preimplementation and postimplementation. These tended to be larger agencies, as reflected by the fact that they cared for 96% of all included subjects. Patients meeting study inclusion criteria were taken to 8 trauma centers, 1 of which was a pediatric Level I trauma center. Trauma centers are distributed across the 3 major population centers in Arizona and serve the northern, central, and southern regions. Hospital data were linked to out-of-hospital patient care reports, with a 98.7% linkage rate.[21]

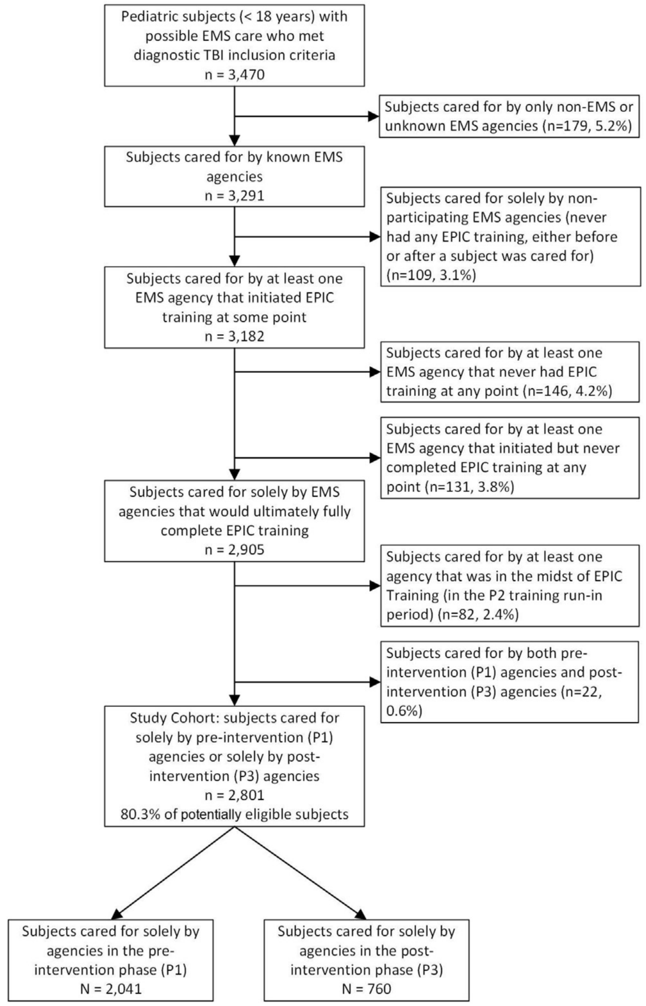


Figure 2. Enrollment tree. *P2*, Study phase 2 (training run-in phase; for each EMS agency, period from initiation to completion of training); *P1*, study phase 1 (preimplementation phase); *P3*, study phase 3 (postimplementation phase).

Table 1 shows subject demographics and clinical characteristics. Median age was lower in postimplementation (8 years; IQR 2 to 14 years) than preimplementation (12 years; IQR 3 to 16 years), with a difference in median age of –4 years (95% CI –6 to –3 years; bootstrap). Brain injury severity was greater in the postimplementation cohort (Regional Severity Score–Head=4; 27.3% [95% CI 25.4% to 29.3%] preimplementation versus 32.2% [95% CI 28.9% to 35.7%] postimplementation; absolute change 4.9% [95% CI 1.2% to 8.8%]; Regional Severity Score–Head=5 to 6; 16.1% [95% CI 14.5% to 17.8%] preimplementation versus 17.6% [95% CI 15.0% to 20.5%] postimplementation, change 1.5% [95% CI –1.5% to 4.8%]). Within the severe traumatic brain injury cohort, there were 1,405 cases (70.2%) in preimplementation and 596 (29.8%) in postimplementation. Among these, the proportions of subjects receiving positive-pressure ventilation were

Table 1. Subject characteristics.

Characteristic	Categories	Pre,*	Post,*
		N=2,041	N=760
Age, y		12 (3–16)	8 (2–14)
Sex	Girls	756 (37)	283 (37.2)
	Boys	1,285 (63)	477 (62.8)
Race	Black	90 (4.4)	47 (6.2)
	Asian	15 (0.7)	15 (2)
	American Indian/Alaska Native	143 (7)	37 (4.9)
	White	1,335 (65.4)	475 (62.5)
	Other	445 (21.8)	164 (21.6)
	Unknown	13 (0.6)	22 (2.9)
Hispanic	No	1,228 (60.2)	465 (61.2)
	Yes	733 (35.9)	294 (38.7)
	Unknown	80 (3.9)	1 (0.1)
Payer	Private	827 (40.5)	285 (37.5)
	AHCCCS/Medicaid	921 (45.1)	408 (53.7)
	Self-pay	196 (9.6)	48 (6.3)
	Other	63 (3.1)	18 (2.4)
	Unknown	34 (1.7)	1 (0.1)
Trauma type	Blunt	1,972 (96.6)	731 (96.2)
	Penetrating	69 (3.4)	28 (3.7)
	Burn	0	1 (0.1)
Regional Severity Score–Head *(ICD-9)*	1–3	1,130 (55.4)	374 (49.2)
	4	557 (27.3)	245 (32.2)
	5–6	329 (16.1)	134 (17.6)
	Unknown	25 (1.2)	7 (0.9)
ISS *(ICD-9)*	1–14	930 (45.6)	323 (42.5)
	16–24	579 (28.4)	247 (32.5)
	≥25	530 (26)	188 (24.7)
	Unknown	2 (0.1)	2 (0.3)
Body region	Isolated TBI	1,602 (78.5)	637 (83.8)
	Multisystem TBI	439 (21.5)	123 (16.2)
Transfer	No	1,271 (62.3)	419 (55.1)
	Yes	684 (33.5)	341 (44.9)
	Unknown	86 (4.2)	0
CPR	No	1,945 (95.3)	714 (93.9)
	Yes	96 (4.7)	46 (6.1)
Airway management	No PPV	1,534 (75.2)	586 (77.1)
	BVM	73 (3.6)	49 (6.4)
	SGA	5 (0.2)	5 (0.7)
	Intubation	429 (21)	120 (15.8)

AHCCCS, Arizona Health Care Cost Containment System; *ICD-9, International Classification of Diseases, Ninth Revision*; *PPV*, positive-pressure ventilation (patients received active ventilation regardless of basic or advanced airway type); *SGA*, supraglottic airway (eg, Laryngeal Mask Airway, King Airway).

"Pre"=study phase 1 (preimplementation), "post"=study phase 3 (postimplementation). Isolated TBI: Cases that met TBI inclusion criteria but had no injury with Regional Severity Score greater than or equal to 3 in any other (nonhead) body region. Multisystem TBI: Cases that met TBI inclusion criteria and also had at least 1 nonhead region injury with Regional Severity Score greater than or equal to 3. BVM=basic airway providing positive-pressure ventilation. Treating trauma center was also highly significant ($P<.001$). To protect the mandated anonymity of the participating hospitals, the numbers are not shown (preventing any possible identification or inference of facility).

*Data are presented as median (IQR) for numeric variables and No. (%) for categoric variables.

14.8% (208) in preimplementation and 11.7% (70) in postimplementation (Table 2).

Main Results

The overall (all-severity) analysis, illustrated in Table 3, revealed an adjusted odds ratio (aOR) for survival of 1.16 (95% CI 0.70 to 1.92). The odds of survival to hospital admission, illustrated in Table 4, improved (aOR=2.41; 95% CI 1.17 to 5.21).

There were 305 children (11.0%) with moderate traumatic brain injury, 2,001 (72.3%) with severe traumatic brain injury, and 463 (16.7%) with critical traumatic brain injury. The severe traumatic brain injury subgroup showed significant improvement in adjusted odds of survival to

Table 2. Unadjusted risk differences and odds ratios for survival in children younger than 18 years after traumatic brain injury.

Outcome	Group	P1 Survival Proportion (n/Total) (95% CI)	P3 Survival Proportion (n/Total) (95% CI)	Effect Measures	
Survival to hospital discharge	All subjects	0.894 (1,825/2,041) (0.880–0.907)	0.901 (685/760) (0.878–0.922)	RD	0.007 (−0.020 to 0.032)
				OR	1.081 (0.815 to 1.447)
	Severe TBI	0.986 (1,385/1,405) (0.978–0.991)	1.000 (596/596) (0.994–1.000)	RD	0.014 (0.008 to 0.022)
				OR	Inf (2.236 to Inf)
	Severe TBI and PPV	0.909 (189/208) (0.861 to 0.944)	1.000 (70/70) (0.949 to 1.000)	RD	0.091 (0.038 to 0.138)
				OR	Inf (1.805 to Inf)
Survival to hospital admission	All subjects	0.960 (1,959/2,041) (0.950 to 0.968)	0.976 (742/760) (0.963 to 0.986)	RD	0.016 (0.001 to 0.030)
				OR	1.725 (1.018 to 3.077)
	Severe TBI	0.994 (1,396/1,405) (0.988 to 0.997)	1.000 (596/596) (0.994 to 1.000)	RD	0.006 (−0.000 to 0.012)
				OR	Inf (0.997 to Inf)
	Severe TBI and PPV	0.957 (199/208) (0.919 to 0.980)	1.000 (70/70) (0.949 to 1.000)	RD	0.043 (−0.010 to 0.080)
				OR	Inf (0.808 to Inf)

RD, Risk difference; *OR*, odds ratio; *Inf*, infinity.
Clopper-Pearson CI for proportions. CI for RD and OR by the score method or the melded method for small samples.

discharge after implementation (aOR=8.42; 95% CI 1.01 to 100+), whereas the moderate and critical groups did not. The results for survival and survival to hospital admission are shown in Figure 3. The same analysis for children younger than 21 years yielded similar results for survival in patients with severe traumatic brain injury (aOR=5.03; 95% CI 1.37 to 29.7) (Figure E2, available online at http://www.annemergmed.com).

We evaluated the nonmortality outcome of survivors being discharged to home. This represents a positive functional outcome compared with other dispositions such as being discharged to a skilled nursing facility or inpatient rehabilitation. The aORs for discharge to home were similar between preimplementation and postimplementation (Figure 4).

Among patients with severe traumatic brain injury who received positive-pressure ventilation (bag-valve-mask ventilation, supraglottic airway, or intubation), the improvement in adjusted survival after implementation did not reach significance (aOR=9.13; 95% CI 0.79 to 100+) (Figure 5). However, in the cohort younger than 21 years, the improvement was significant (aOR=7.48; 95% CI 1.41 to 93.4) (Figure E3, available online at http://www.annemergmed.com).

Implementation of the traumatic brain injury guidelines was associated with changes in patient care. Overall, the treatment-related changes among children were consistent with the all-age findings from the main EPIC study. Because this substudy analyzed only 12.8% of the EPIC population, some findings did not reach statistical significance. However, even the smaller pediatric cohort showed good evidence of changes in care after guideline training. For example, despite greater brain injury severity in postimplementation (Table 1), patients were less likely to be intubated (15.8%; 13.3%, 18.6%) than in preimplementation (21.0%, 19.3%, 22.9%; absolute reduction in proportion of intubated patients=5.2%, 2.0%, 8.3%; odds ratio=0.71, 0.56, 0.88); relative reduction=24.9%, 9.9%, 37.6%). Furthermore, among intubated patients in postimplementation who experienced profound out-of-hospital hypoxia (SpO_2 <70%), all of them arrived at the hospital having had their hypoxia reversed (compared with less than half experiencing reversal of profound hypoxia in preimplementation).

LIMITATIONS

This study has limitations. First, it was not randomized. Although a randomized trial might have definitively identified optimal treatment, it was not feasible. Because existing studies overwhelmingly report detrimental effects of hypoxia, hypotension, and hyperventilation, randomization (to nonguideline care) would be unacceptable to the majority of EMS systems. Use of a pragmatic trial design (eg, stepped wedge or cluster randomized)[43] was also nonfeasible because the timing of EPIC training had to be determined primarily by agency-specific operational factors. Second, as with many pediatric studies, the CIs were wide because of limited patient numbers. However, Excellence in Prehospital Injury Care for Children is much larger than any previous pediatric EMS traumatic brain injury study (by at least an order of magnitude in most cases). Furthermore, this is the first controlled study of any size that directly evaluated the effectiveness of the EMS guidelines in children, to our knowledge. Third, because the guidelines were implemented as a "bundle," we cannot identify the relative influence of specific interventions (eg, oxygenation/preoxygenation, fluid administration) because

Table 3. aORs for survival to hospital discharge (primary analysis) for patients younger than 18 years in phase 3 versus phase 1.

Variable in Adjusted Model	Categories	OR	95% CI
Intervention	No	—	—
	Yes	1.16	(0.697–1.92)
Sex	Girls	—	—
	Boys	1.13	(0.731–1.74)
Race	Black	—	—
	Asian	0.146	(0.021–0.998)
	American Indian/ Alaska Native	0.837	(0.244–2.87)
	White	0.861	(0.338–2.19)
	Other	1.01	(0.333–3.08)
	Unknown	1.78	(0.256–12.4)
Hispanic	No	—	—
	Yes	0.886	(0.513–1.53)
	Unknown	1.02	(0.319–3.24)
Payer	Private	—	—
	AHCCCS/ Medicaid	0.936	(0.570–1.54)
	Self-pay	0.281	(0.140–0.565)
	Other	0.571	(0.217–1.50)
	Unknown	0.316	(0.069–1.44)
Trauma type	Blunt	—	—
	Penetrating	0.267	(0.126–0.566)
Head ISS *(ICD-9)*	1–3	—	—
	4	0.268	(0.068–1.05)
	5–6	0.008	(0.002–0.031)
ISS *(ICD-9)*	1–14	—	—
	16–24	0.933	(0.180–4.83)
	≥25	0.445	(0.091–2.17)
Body region	Isolated TBI	—	—
	Multisystem TBI	0.518	(0.322–0.833)
Transfer	No	—	—
	Yes	2.30	(1.33–3.97)
	Unknown	0.459	(0.146–1.44)
CPR	No	—	—
	Yes	0.043	(0.021–0.086)
Hospital		Not shown	
Age, y		Nonparametric function	

Isolated TBI: Cases that met TBI inclusion criteria but had no injury with Regional Severity Score greater than or equal to 3 in any other (nonhead) body region. Multisystem TBI: Cases that met TBI inclusion criteria and also had at least 1 nonhead region injury with Regional Severity Score greater than or equal to 3. To protect the mandated anonymity of the participating hospitals (treating trauma centers), the ORs and CIs comparing different hospitals are not shown (preventing any possible identification or inference of facility-specific outcome differences). Dashes represent use of a category as a reference for statistical comparison.

Table 4. aORs for survival to hospital admission for patients younger than 18 years in phase 3 versus phase 1.

Variable in Adjusted Model	Categories	OR	95% CI
Intervention	No	—	—
	Yes	2.41	(1.17–5.21)
Boys	No	—	—
	Yes	0.928	(0.492–1.73)
Race	Black	—	—
	Asian	0.139	(0.010–20.1)
	American Indian/ Alaska Native	1.54	(0.201–14.7)
	White	0.462	(0.119–1.60)
	Other	1.1	(0.238–4.75)
	Unknown	8.15	(0.320–1540.)
Hispanic	No	—	—
	Yes	0.517	(0.231–1.13)
	Unknown	0.505	(0.128–2.41)
Payer	Private	—	—
	AHCCCS/Medicaid	1.41	(0.686–2.92)
	Self-pay	0.567	(0.243–1.33)
	Other	0.317	(0.090–1.22)
	Unknown	0.823	(0.145–6.20)
Trauma type	Blunt	—	—
	Penetrating	0.432	(0.176–1.08)
Head ISS *(ICD-9)*	1–3	—	—
	4	0.007	(0.000–0.168)
	5–6	0.003	(0.000–0.063)
ISS *(ICD-9)*	1–14	—	—
	16–24	13.1	(0.741–141.)
	≥25	2.78	(0.186–24.5)
Body region	Isolated TBI	—	—
	Multisystem TBI	2.01	(1.03–4.02)
Transfer	No	—	—
	Yes	19.9	(4.69–189.)
	Unknown	0.906	(0.229–5.60)
CPR	No	—	—
	Yes	0.048	(0.025–0.089)
Age, y		1.00	(0.947–1.06)
Hospital		Not shown	

Isolated TBI: Cases that met TBI inclusion criteria but had no injury with Regional Severity Score greater than or equal to 3 in any other (nonhead) body region. Multisystem TBI: Cases that met TBI inclusion criteria and also had at least 1 nonhead region injury with Regional Severity Score greater than or equal to 3. To protect the mandated anonymity of the participating hospitals (treating trauma centers), the ORs and CIs comparing different hospitals are not shown (preventing any possible identification or inference of facility-specific outcome differences). Dashes represent use of a category as a reference for statistical comparison.

this would have required stepwise, intervention-specific implementation. Fourth, it is possible that changes in trauma center care or other secular trends affected the results. In the full EPIC patient population, this issue was evaluated in 2 cohorts that met diagnostic inclusion criteria but were unaffected by EPIC: outcomes for patients cared for by nonparticipating EMS agencies, and outcomes for patients brought to trauma centers by privately owned vehicle. These were compared across the early (January 1, 2007, to December 31, 2012) and late EPIC study periods (January 1, 2013, to June 30, 2015). Neither of these analyses yielded any evidence of secular outcome improvement over time. Indeed, there was a

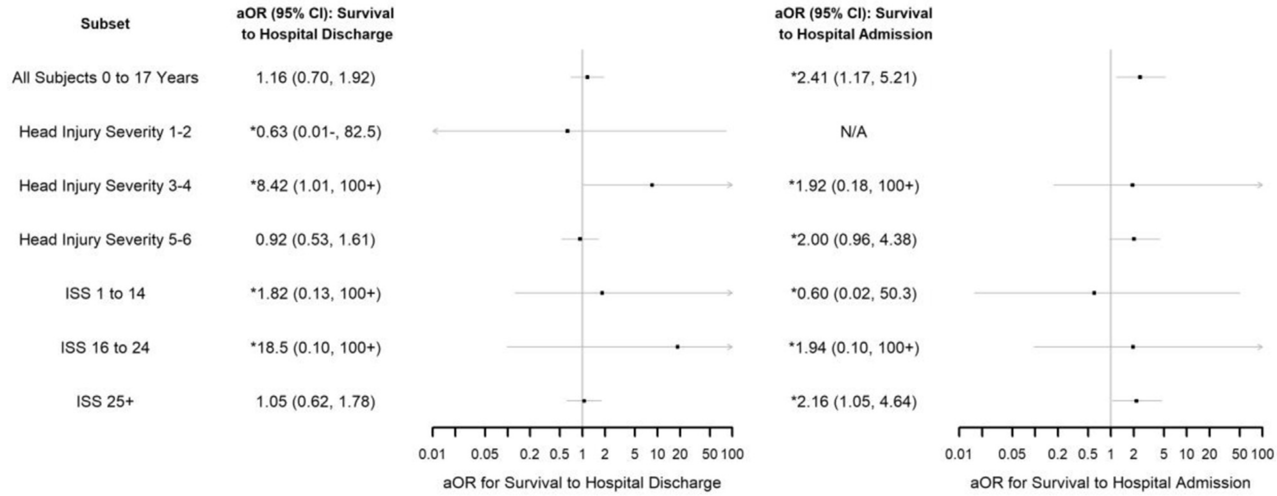


Figure 3. Primary analysis—adjusted survival. Postintervention adjusted odds of survival to hospital discharge or admission for the "moderate" (Regional Severity Score–Head of 1 or 2; ISS of 1 to 14), "severe" (Regional Severity Score–Head of 3 or 4; ISS of 16 to 24), and "critical" (Regional Severity Score–Head of 5 or 6; ISS of 25 to 75) injury cohorts. N/A because numbers were too small for adjusted analysis. Analyses without an asterisk: Logistic regression was used when there were at least 200 subjects with the event (eg, survived to discharge) and 200 without it (eg, did not survive to discharge). Analyses with an asterisk: In comparisons that did not meet the criteria of at least 200 subjects with the event and 200 without, Firth's penalized-likelihood logistic regression was used.

Number of events/number of subjects in each subgroup:

- All subjects aged 0 to 17 y: survival to hospital discharge 2,510/2,801; survival to hospital admission 2,701/2,801
- Head ISS 1 to 2: survival to hospital discharge 304/305; survival to hospital admission 305/305
- Head ISS 3 to 4: survival to hospital discharge 1,981/2,001; survival to hospital admission 1,992/2,001
- Head ISS 5 to 6: survival to hospital discharge 204/463; survival to hospital admission 379/463
- ISS 1 to 14: survival to hospital discharge 1,248/1,253; survival to hospital admission 1,252/1,253
- ISS 16 to 24: survival to hospital discharge 816/826; survival to hospital admission 822/826
- ISS $\geq$25: survival to hospital discharge 442/718; survival to hospital admission 623/718

N/A, Not applicable; *ISS*, Injury Severity Score.

nonsignificant worsening of outcomes in the late group.[18] Although the pediatric cohorts were too small to provide conclusive results in parallel analyses, the fact that the all-age evaluations yielded no evidence of secular improvement as an explanation for the positive study results is supportive of the conclusion that the association between guideline implementation and improved outcome in children may reflect true effectiveness of the interventions. We did not adjust for multiple testing in secondary analyses, and thus the subanalyses should be interpreted as exploratory. Fifth, we were not able to evaluate functional outcomes. Although survival to hospital discharge was always the primary outcome for this study, unfortunately, we had to suspend our plan to obtain 12-month functional outcome (Glasgow Outcome Scale–Extended) because of a reduction in funding. Sixth, we could not control for the effects of inpatient care. Thus, we cannot know conclusively that the improvements were directly caused by EMS interventions. However, the concurrent increase in survival to hospital admission, an outcome that is proximate to the out-of-hospital interventions, is supportive of the conclusion that EMS implementation led to the improvements in final outcome.

DISCUSSION

The out-of-hospital pediatric traumatic brain injury guidelines emphasize prevention and treatment of hypoxia, hypotension, and hyperventilation.[13] These recommendations are based on observational studies demonstrating increased traumatic brain injury mortality from these insults (hypoxia,[15,44-51] hypotension,[3,15,45,46,49-57] and hyperventilation[15,17,47,58-64]). However, the supporting evidence remains weak because, to our knowledge, no controlled out-of-hospital studies have directly evaluated the effect of guideline-based care in children.[13,14]

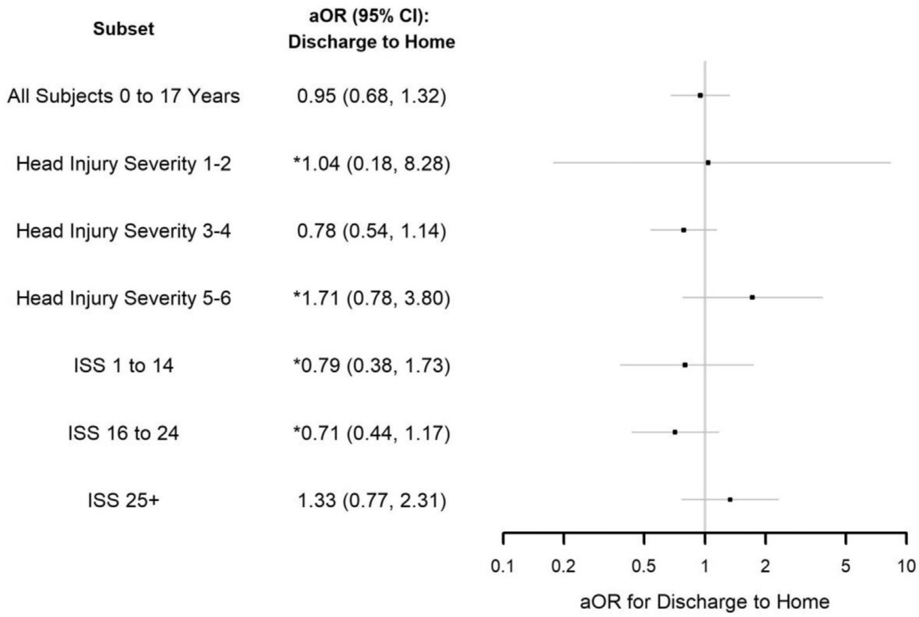


Figure 4. Discharge to home.

- All subjects aged 0 to 17 y: discharge to home 2,104/2,507
- Head ISS 1 to 2: discharge to home 279/302
- Head ISS 3 to 4: discharge to home 1,724/1,980
- Head ISS 5 to 6: discharge to home 85/204
- ISS 1 to 14: discharge to home 1,189/1,246
- ISS 16 to 24: discharge to home 693/815
- ISS $\geq$25: discharge to home 220/442

In Arizona, the pediatric and adult out-of-hospital traumatic brain injury guidelines were implemented simultaneously as a statewide initiative in which EMS providers were trained to provide guideline-based care for patients with any injury-associated loss of consciousness.[12-14,16] This inclusive approach at the individual patient level was taken because traumatic brain injury can be difficult to identify in the field and its severity may not be immediately apparent.[12-14,16,65-70] An intention-to-treat design was used because participation from more than 100 EMS agencies was expected and there was no guarantee that out-of-hospital records documenting EMS care would be available in a high percentage of cases.[18,29,71]

The main (all-age) EPIC study revealed strong evidence that guideline-based care was actually implemented and that it was associated with improvement of treatment-related physiologic parameters.[18] Across all ages, implementation was associated with a lower rate of intubation, a much higher rate of bag-valve-mask ventilation among patients with positive-pressure ventilation, a greater reduction of hypoxia at hospital arrival, a greater likelihood of receiving a fluid bolus and a greater volume of bolus in hypotensive and near-hypotensive patients, and a lower proportion of patients with hypocapnia/hyperventilation when intubated.[18] Despite its smaller size, this pediatric substudy also revealed good evidence that there were meaningful, guideline-based changes in care among children.

The primary analysis (across the entire traumatic brain injury severity spectrum) did not show significant improvement in survival. This appears to be due to the broad inclusion criteria (moderate through critical traumatic brain injury). We were aware of the risk of this happening, but still intentionally included a broad spectrum of "major" traumatic brain injury because it was not known which severity subgroups would benefit.[5,6,8-13,65,69,70,72] This inclusive approach prevented unknowingly excluding patients who might benefit if the criteria were too narrow. However, it had the risk of "diluting" the treatment effect (by including nonresponding cohorts). Thus, we planned a priori to evaluate the moderate, severe, and critical traumatic brain injury cohorts separately to prevent some subgroups from potentially "hiding" the effectiveness of others. Indeed, this approach identified that implementation was strongly

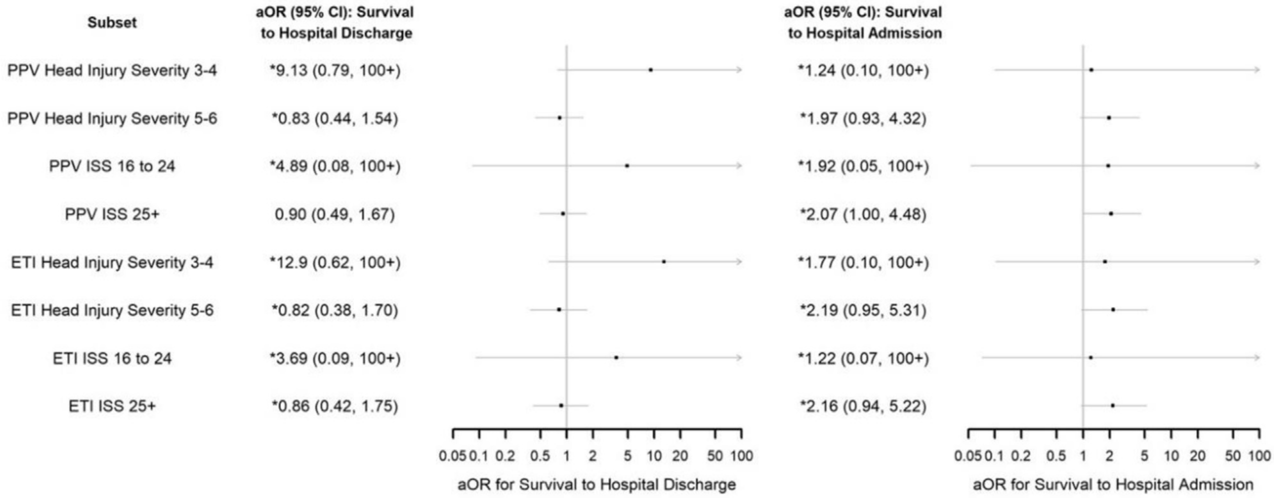


Figure 5. Survival among patients with positive-pressure ventilation. Postintervention adjusted odds of survival to hospital discharge or admission for the severe (Regional Severity Score–Head of 3 or 4; ISS of 16 to 24), and critical (Regional Severity Score–Head of 5 or 6; ISS of 25–75) injury cohorts. Analyses without an asterisk: Logistic regression was used when there were at least 200 subjects with the event (eg, survived to discharge) and 200 without it (eg, did not survive to discharge). Analyses with an asterisk: In comparisons that did not meet the criteria of at least 200 subjects with the event and 200 without it, Firth's penalized-likelihood logistic regression was used.

Number of events/number of subjects in each subgroup:

- PPV head ISS 3 to 4: survival to hospital discharge 259/278; survival to hospital admission 269/278
- PPV head ISS 5 to 6: survival to hospital discharge 114/363; survival to hospital admission 280/363
- PPV ISS 16 to 24: survival to hospital discharge 122/131; survival to hospital admission 127/131
- PPV ISS $\geq$25: survival to hospital discharge 203/469; survival to hospital admission 375/469
- ETI head ISS 3 to 4: survival to hospital discharge 200/217; survival to hospital admission 209/217
- ETI head ISS 5 to 6: survival to hospital discharge 88/298; survival to hospital admission 224/298
- ETI ISS 16 to 24: survival to hospital discharge 91/99; survival to hospital admission 95/99
- ETI ISS $\geq$25: survival to hospital discharge 156/382; survival to hospital admission 298/382

PPV, Positive-pressure ventilation; *ETI*, intubation.

associated with improvement in severe traumatic brain injury.

In the cohort of children with severe brain injury, the aOR for survival to hospital discharge improved significantly (Figure 3). As with many pediatric studies, the relatively wide CIs raise concerns about sample size. However, we believe that looking at the patterns for the 2 preplanned pediatric-age-based analyses and the all-age main study strengthens the confidence that the improvement is real. The aORs and 95% CIs for survival were: all ages (aOR 2.03; 95% CI 1.52 to 2.72),[18] younger than 21 years (aOR 5.03; 95% CI 1.37 to 29.7), and younger than 18 years (aOR 8.42; 95% CI 1.01 to 100+). Two clear trends emerged from these findings. First, the point estimate for the independent association between guideline implementation and survival increased as the age of the cohort became younger. It is plausible that this trend in improved outcome is real because it is widely believed that there is greater neurologic resilience (often termed "plasticity") in younger brain-injured patients and that they are more likely to experience improvement after a cerebral insult. Second, the CIs became wider as the age cut point decreased. This trend, of course, was entirely expected because of a smaller sample size (thus inherently widening the CIs) and a larger aOR (even when the width of the CI stays the same for log[aOR] [ie, if sample size were fixed], the width of the CIs for aOR will increase quickly because of exponentiation as the log [aOR] moves farther away from 1). Because of this, even if the true effect of implementation is positive in children, when that effect is studied, there obviously comes a point at which decreasing the age of inclusion leads to a small enough group that the analysis yields very broad CIs. This is true regardless of how strong the true survival effect is. Although these arguments do not remove all concerns related to the size of the study, we believe that the finding of improved outcome's being associated with guideline implementation in children is plausible and consistent with the emerging understanding of neurologic plasticity in pediatric brain injury.

The overall increase in survival to hospital *admission* (aOR=2.14; 95% CI 1.17 to 5.21) is important because this outcome occurs within minutes to hours of the out-of-hospital interventions and likely reflects changes in EMS care. Early outcomes have been recognized to have value for evaluating the effect of out-of-hospital interventions in other serious, time-sensitive conditions.[73-77] In addition, improved early survival creates the potential for patients to benefit from subsequent specialized care.[75,76,78-80]

During the conception of the study, we planned to evaluate 12-month functional outcomes. Unfortunately, changes in funding precluded this. However, given the marked improvement in survival among severe cases, it is promising that the adjusted odds of being discharged to home during the postimplementation period were similar to that found in the preimplementation phase (Figure 4). It appears that the improvements in survival were not associated with a higher incidence of morbid neurologic impairment.

The findings in the severe cohort support a concept of an interventional opportunity between the extremes of traumatic brain injury severity. At the moderate end of the spectrum, detection of differences in mortality is unlikely because nearly all of these patients will survive regardless of EMS care. On the other hand, in patients with critical traumatic brain injury, even optimal treatment aimed at preventing secondary brain injury may have little influence on survival because the initial, primary injury is so severe. Furthermore, in the critical cohort, there appear to be other factors that contribute to a lack of treatment effect. The overall EPIC study identified that treatment-related physiologic improvement was less likely to be achieved in critical patients than in severe ones.[18] For example, although the proportion of intubated patients with at least 1 oxygen saturation level of 100% increased significantly after implementation (preimplementation 44.2% with 95% CI 42.2% to 46.3%; postimplementation 54.5% with 95% CI 51.1% to 57.8%), this increase varied with severity. In the severe group, the proportion increased from 50.7% (95% CI 47.5% to 53.9%) in preimplementation to 66.9% (95% CI 61.4% to 72.0%) in postimplementation, a 16.1% absolute increase (95% CI 10.0% to, 22.0%). However, in the critical cohort, this proportion only increased from 39.4% (95% CI 36.6% to 42.2%) to 46.5% (95% CI 42.2% to, 50.8%); change 7.1% (95% CI 2.1% to 12.2%). Another factor that might have limited the likelihood of identifying improvement in the critical subgroup was the Stocchetti effect.[81,82] That is, improvements in out-of-hospital trauma care may lead to a paradoxic effect of improved out-of-hospital survival, but no increase (or even a decrease) in hospital survival. This can occur because critical patients who previously died in the field may survive to hospital admission, but then die inhospital from extremely severe injury and reduce the rate of survival to hospital discharge. The greater increase in survival to hospital admission compared with survival to discharge in the critical traumatic brain injury cohort supports this as a possible factor.

Out-of-hospital intubation in children with traumatic brain injury has been controversial for decades.[14,16,19,65,83-88] However, in studies associating intubation with negative outcomes,[19,60,65,83,87] it is unclear whether the primary issue was the procedure itself or the high proportion of patients with inadvertent hyperventilation postintubation.[17,44,63,64,84,89] In EPIC, training emphasized reserving intubation for patients with markedly depressed level of consciousness and in whom basic interventions were inadequate for airway protection and oxygenation.[12-14,16] As would be expected if this training were successful, the intubation rate decreased after implementation and the bag-valve-mask device–only rate increased.

Although the improvement in adjusted survival among severe traumatic brain injury patients who received positive-pressure ventilation (bag-valve-mask/supraglottic airway/intubation) was not significant in the cohort younger than 18 years (aOR=9.13; 95% CI 0.79 to 100+) (Figure 5), it was significant in both the full EPIC population (aOR=3.52; 95% CI 1.96 to 6.34) and among patients younger than 21 years (aOR=7.48; 95% CI 1.41 to 93.4) (Figure E3, available online at http://www.annemergmed.com). These findings suggest that a combination of an emphasis on preoxygenation/high-flow oxygenation, an emphasis on basic airway management followed by advanced airway management only when proper oxygenation or ventilation is impossible, and meticulous prevention of hyperventilation (with the use of visual ventilation rate timers, flow-controlled ventilation bags, and attention to end tidal carbon dioxide [ETCO_2] monitoring) may be the optimal approach to out-of-hospital airway/ventilation management in children with major traumatic brain injury.

These findings do not answer the questions surrounding when children with traumatic brain injury ought, or ought not, to be intubated in the field. As would be expected from the emphasis placed on reserving advanced airways for patients who do not respond successfully to basic interventions, there was a significant (and probably appropriate) reduction in the proportion of intubations before hospital arrival. Although the improvement in adjusted survival was not statistically significant (aOR=12.9; 95% CI 0.62 to 100+), the point estimate was positive and consistent with the highly significant improvement identified in the overall (all-age) severe, intubated traumatic brain injury cohort (aOR=3.14; 95% CI 1.65 to 5.98).[18] We caution against misinterpreting (in either direction) the implications of these findings. EPIC compared outcomes among patients who were intubated in preimplementation and postimplementation but did not randomize treatment. Hence, despite improvement in the all-age airway analysis, our findings related to pediatric traumatic brain injury do not answer the question of whether patients should have been intubated. Clearly, the many questions surrounding this issue require further study and no confident conclusion can be made from these data about when children with traumatic brain injury benefit from out-of-hospital intubation over basic airway management. However, these findings do provide evidence that, regardless of the decision made about which airway intervention to use, prevention of hyperventilation is likely associated with improved outcome.

In summary, statewide implementation of the pediatric out-of-hospital traumatic brain injury guidelines did not improve overall survival among children with major (combined moderate, severe, and critical) traumatic brain injury. However, adjusted odds of survival improved significantly among patients with severe traumatic brain injury. These findings may indicate a severity-based interventional opportunity for guideline effectiveness and support widespread implementation of the out-of-hospital pediatric traumatic brain injury guidelines.

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