Optimal Out-of-Hospital Blood Pressure in Major Traumatic Brain Injury: A Challenge to the Current Understanding of Hypotension

Daniel W. Spaite, MD*; Chengcheng Hu, PhD; Bentley J. Bobrow, MD; Bruce Barnhart, MSN, RN; Vatsal Chikani, MPH; Joshua B. Gaither, MD; Kurt R. Denninghoff, MD; Gail H. Bradley, MD; Amber D. Rice, MD; Jeffrey T. Howard, PhD; Samuel M. Keim, MD

*Corresponding Author. E-mail: dan@aemrc.arizona.edu.

Study objective: Little is known about the out-of-hospital blood pressure ranges associated with optimal outcomes in traumatic brain injuries (TBI). Our objective was to evaluate the associations between out-of-hospital systolic blood pressure (SBP) and multiple hospital outcomes without assuming any predefined thresholds for hypotension, normotension, or hypertension.

Methods: This was a preplanned secondary analysis from the Excellence in Prehospital Injury Care (EPIC) TBI study. Among patients (age ≥10 years) with major TBIs (Barell Matrix type 1 and/or Abbreviated Injury Scale-head severity ≥3) and lowest out-of-hospital SBPs of 40 to 299 mmHg, we utilized generalized additive models to summarize the distributions of various outcomes as smoothed functions of SBP, adjusting for important and significant confounders. The subjects who were enrolled in the study phase after the out-of-hospital TBI guideline implementation were used to validate the models developed from the preimplementation cohort.

Results: Among 12,169 included cases, the mortality model revealed 3 distinct ranges: (1) a monotonically decreasing relationship between SBP and the adjusted probability of death from 40 to 130 mmHg, (2) lowest adjusted mortality from 130 to 180 mmHg, and (3) rapidly increasing mortality above 180 mmHg. A subanalysis of the cohorts with isolated TBIs and multisystem injuries with TBIs revealed SBP mortality patterns that were similar to each other and to that of the main analysis. While the specific SBP ranges varied somewhat for the nonmortality outcomes (hospital length of stay, ICU length of stay, discharge to skilled nursing/inpatient rehabilitation, and hospital charges), the patterns were very similar to that of mortality. In each model, validation was confirmed utilizing the postimplementation cohort.

Conclusion: Optimal adjusted mortality was associated with a surprisingly high SBP range (130 to 180 mmHg). Below this level, there was no point or range of inflection that would indicate a physiologically meaningful threshold for defining hypotension. Nonmortality outcomes showed very similar patterns. These findings highlight how sensitive the injured brain is to compromised perfusion at SBP levels that, heretofore, have been considered adequate or even normal. While the study design does did not allow us to conclude that the currently recommended treatment threshold (<90 mmHg) should be increased, the findings imply that the definition of hypotension in the setting of TBI is too low. Randomized trials evaluating treatment levels significantly higher than 90 mmHg are needed. [Ann Emerg Med. 2022;80:46-59.]

Please see page 47 for the Editor's Capsule Summary of this article.

Readers: click on the link to go directly to a survey in which you can provide **feedback** to *Annals* on this particular article.
A **podcast** for this article is available at www.annemergmed.com.
Continuing Medical Education exam for this article is available at http://www.acep.org/ACEPeCME/.

0196-0644/$-see front matter

https://doi.org/10.1016/j.annemergmed.2022.01.045

INTRODUCTION

Background and Importance

The societal burden of traumatic brain injuries (TBIs) is enormous—leading to 2.2 million emergency department visits, 280,000 hospitalizations, 52,000 deaths, and more than 60 billion dollars in economic costs in the United States each year.[1,2] In addition, more than 5 million Americans have major long-term disabilities as a result of TBIs.[1] The potential that early TBI management may improve outcomes has led to the promulgation of evidence-based out-of-hospital and inhospital TBI treatment guidelines for both children and adults.[3-6] The recently published Excellence in Prehospital Injury Care (EPIC) Study reported that the statewide implementation of the out-of-hospital guidelines was independently associated with a marked improvement in the adjusted odds of survival to hospital discharge among patients with severe TBIs.[7]

One major focus of the guidelines is the prevention and treatment of hypotension.[4,5] It is well established that even

Editor's Capsule Summary

What is already known on this topic

Hypotension that occurs early in the care of traumatic brain-injured patients is associated with worse outcomes. The optimal blood pressure for such patients is unclear.

What question this study addressed

Among 12,169 severe traumatic brain-injured patients 10 years and older, what was the association between probability of mortality and the lowest measured systolic blood pressure (SBP) during out-of-hospital care?

What this study adds to our knowledge

In this study population, 12% died. Probability of death decreased as the lowest measured SBP increased from 40 to approximately 130 mmHg. The probability of death remained fairly constant between 130 and 180 mmHg, and increased above 180 mmHg. SBP 90 to 120 mmHg was associated with greater probability of mortality than SBP 130 to 180 mmHg. Other, non-mortality outcome measures exhibited similar patterns.

How this is relevant to clinical practice

Early care of traumatic brain-injured patients should include focus on avoiding and treating low blood pressure, perhaps with a higher threshold than what is often considered hypotension.

a single episode of hypotension during the early management of a TBI is associated with a major increase in mortality.[3,8-27] However, this literature is comprised nearly exclusively of small studies that merely dichotomized cases into hypotensive and nonhypotensive cohorts (variously defined) and compared outcomes in the "low" versus "not low" groups. One of the central reasons there are no large emergency medical services (EMS) TBI studies evaluating blood pressure and outcomes is because of the challenge of linking out-of-hospital data to comprehensive inhospital information.[28] Unfortunately, this has limited our understanding of the effects of blood pressure on outcomes across the spectrum of potential values. Hence, while it is clear that low blood pressure during the early moments of TBI care is associated with worse outcomes, essentially nothing is known about whether "near hypotension" (or "low normotension") is harmful. Furthermore, no out-of-hospital studies have identified the range of pressures associated with the *best* outcomes. Answering such questions requires large numbers of patients so that blood pressure can be treated as a continuous variable (and not simply as a low/not-low categorical variable determined by an arbitrary cut point). The EPIC study database contained nearly 22,000 major TBI cases with linked out-of-hospital and hospital data and provided a unique opportunity to perform these analyses.[7,28]

Goals of This Investigation

Our objective was to analyze the associations between out-of-hospital blood pressure and outcomes across the entire range of values among older children and adults (age ≥10 years) enrolled in the EPIC study.[28] Specifically, we identified the out-of-hospital systolic blood pressure (SBP) range that is associated with optimal outcomes in major TBIs.

METHODS

Study Design, Setting, and Oversight

The parent study evaluated the effect of implementing the EMS TBI guidelines in patients with moderate, severe, or critical TBIs throughout Arizona. Because the methods have been reported in detail, we limit this description to the design attributes relevant to this specific, preplanned secondary analysis.[3-7,28-31]

Regulatory approvals were obtained from the Arizona Department of Health Services. The University of Arizona Institutional Review Board and the Arizona Department of Health Services Human Subjects Review Board approved the project and publication of deidentified data. While not a clinical trial, EPIC is registered at ClinicalTrials.gov (NCT01339702). The manuscript adheres to the Strengthening of Reporting of Observational studies in Epidemiology reporting guidelines. This was an observational, noninterventional analysis of a subset of the data in the EPIC study.

Data Collection

The Arizona State Trauma Registry (ASTR) contains extensive trauma center data on all patients transported to 1 of the 10 designated Level I trauma centers in the state. From the ASTR, all cases meeting the study criteria (described below) were entered into the EPIC Database. Each participating EMS agency then received a list of the EPIC patients who were cared for in their system. The cases were matched by incident date, name, and other patient identifiers, and the out-of-hospital patient care records (paper-based or electronic) were sent to the Study Data Center for entry into the database. This yielded an extensive data set of study patients that included both EMS and trauma center data (98.7% linkage rate).[7,28]

Selection of Participants

The inclusion criterion was enrollment in the preimplementation or postimplementation phases of the EPIC study. This included patients with physical trauma who (1) were transported directly or transferred to a Level I trauma center by participating EMS agencies, (2) had hospital diagnoses of TBIs (isolated or multisystem trauma that included TBI), and (3) met at least 1 of the following criteria: (a) Abbreviated Injury Scale (AIS)-head of ≥3, (b) Barell Matrix type 1, and (c) out-of-hospital positive pressure ventilation by bag-valve-mask device, endotracheal intubation, supraglottic airway, nasal intubation, or cricothyrotomy. Both patients with isolated TBI and those with TBI combined with multisystem injury were included in the analysis.

The exclusion criteria for the parent study were as follows: (1) nonmechanical mechanisms (eg, drowning); (2) choking/strangulation; (3) environmental injury (eg, hyperthermia); (4) poisoning (eg, drug overdose, carbon monoxide); (5) nontraumatic intracranial hemorrhage; and (6) other nontraumatic, acute neurological emergencies (eg, bacterial meningitis).[7,28]

The exclusion criteria for this subgroup analysis were as follows: age less than 10 years, interfacility transfers, and subjects with out-of-hospital SBPs of less than 40 mmHg. In addition, cases that were missing data for age, SBP, or trauma type (penetrating versus blunt) were excluded. The reason for excluding children under the age of 10 was because this significantly simplified the analysis because the threshold for defining hypotension (and the guideline-based treatment threshold) changes with each year of age from 0 to 9, while the threshold remains constant for older children and adults (age ≥10 years). To assess whether keeping older children in the analysis affected the findings, we performed a sensitivity analysis of the adult subjects only (age ≥18 years).

Outcomes

The primary outcome was inhospital mortality.[28] The secondary outcomes included hospital length of stay, ICU length of stay, hospital charges (US dollars), and discharge to a skilled nursing facility or to inpatient rehabilitation.

Analysis

Continuous variables were summarized by medians and interquartile ranges, and categorical variables by frequency and proportion. The risk-adjusted associations between binary outcome variables (death in the hospital, discharged to skilled nursing/rehabilitation facility) and the lowest out-of-hospital SBP were examined by logistic regression. The associations between the count outcome variables (hospital length of stay, ICU length of stay) and SBP were evaluated by negative binomial regression. Finally, the associations between (log transformed) total hospital charges and SBP were analyzed by linear regression. To prevent anomalies from monetary inflation, all charges were indexed to June 2015 US dollars using the hospital inpatient services Consumer Price Index from the US Bureau of Labor Statistics.[32-34] The regression models adjusted for important risk factors and potential confounders. Age, sex, race, ethnicity, out-of-hospital hypoxia, out-of-hospital airway management, Injury Severity Score (ISS), and head region injury score (International Classification of Diseases-Version 9) matched to AIS score were included, a priori, in the model (because they have been used nearly universally in trauma risk adjustment).[35-37] Trauma type (blunt versus penetrating), payment source, multisystem injury (TBI plus any nonhead body region with Regional Severity Score ≥3), out-of-hospital cardiopulmonary resuscitation, and treating trauma center were included because they have often been confounders in trauma outcome studies and were found to be significant covariates in previous EPIC reports.[7,28-31,38,39] The effects of continuous variables (SBP and age) in the regression models were fitted nonparametrically using penalized thin plate regression splines through the generalized additive model.[40] The model was penalized to avoid overfitting (excessive "wiggliness" in the transformation function due to random noise), and the smoothing parameters were chosen to optimize the Akaike Information Criterion, a measure of the predictive power of the model.[40]

Each model was fitted on the preimplementation (phase 1) data first; then, the fitted model was applied to the postimplementation data (phase 3) to calculate predicted outcome values and then compared to observed outcomes. The area under the receiver operating characteristic curve was used to assess the predictions by logistic regression models, and the Spearman rank correlation coefficient (rho) was estimated between the prediction (by each negative binomial regression or linear regression model) and the actual observations. Each model was then fitted on the combined phase 1 and phase 3 data. The fitted models were also assessed by deviance residual plots and collinearity checked using concurvity measures for the nonparametric term of SBP. The optimal SBP level was estimated as the value that optimized the fitted nonparametric function in the adjusted regression model of each outcome measure, with 95% confidence intervals obtained by the bootstrap method. The adjusted marginal mean of each outcome at any fixed value of SBP was estimated as the average of the predicted outcome values for all subjects in the data set with the SBP value changed to the fixed value and with values of all other covariates unchanged from the actual observed values. The unadjusted predicted mean and the adjusted marginal mean for each outcome measure were then plotted against the lowest SBP with pointwise 95% confidence bands.

The software environment R was used for the analysis, and the R package mgcv was used for the generalized additive model.[40-42] All tests were 2-sided with a significance level of 0.05.

Role of Funding Sources

The EPIC study was funded by an R01 ("EPIC") and an R01 Supplement ("EPIC4Kids") grant from the National Institutes of Health (NIH) (NIH/National Institute of Neurological Disorders and Stroke Grant #1R01NS071049). This secondary analysis was funded, in part, by the Department of Defense (DOD Contract #W81XWH-19-C-0058). Neither the NIH nor the DOD had any role in design or conduct of the study, including: (1) collection, management, analysis, or interpretation of the data, (2) preparation, review, or approval of the manuscript, and (3) decision to submit the manuscript for publication.

RESULTS

Characteristics of Study Subjects

There were 21,852 subjects enrolled in the preimplementation and postimplementation study phases from January 1, 2007 to June 30, 2015. After exclusions, 12,169 patients comprised the study group for this preplanned subanalysis (Figure 1).

Main Results

Table 1 summarizes the demographics and patient characteristics by survival status. Among the included cases, 1462 (12.0%) died, which reflects the focus of the EPIC study on major TBI. Table 2 shows all covariates in the model, and Figures 2 and 3 graphically express the unadjusted and adjusted probabilities of death, respectively, across the range of SBP values. The adjusted mortality plot (Figure 3) revealed 3 distinct attributes: first, a rapidly decreasing probability of death as the lowest EMS SBP increased from 40 mmHg to approximately 130 mmHg; second, a broad, flat valley of low death probability ranging up to approximately 180 mmHg; and third, a rapidly increasing mortality as the SBP increased above this value. This severely hypertensive cohort (SBP $\geq$180 mmHg) was much more likely to have very severe brain injuries (International Classification of Diseases-based Head Region Severity Score [AIS equivalent]: 4 to 6; 65.7% [61.1% to 70.1%]) than the normotensive group (120 to 179 mmHg; 48.5% [47.3% to 49.7%]).

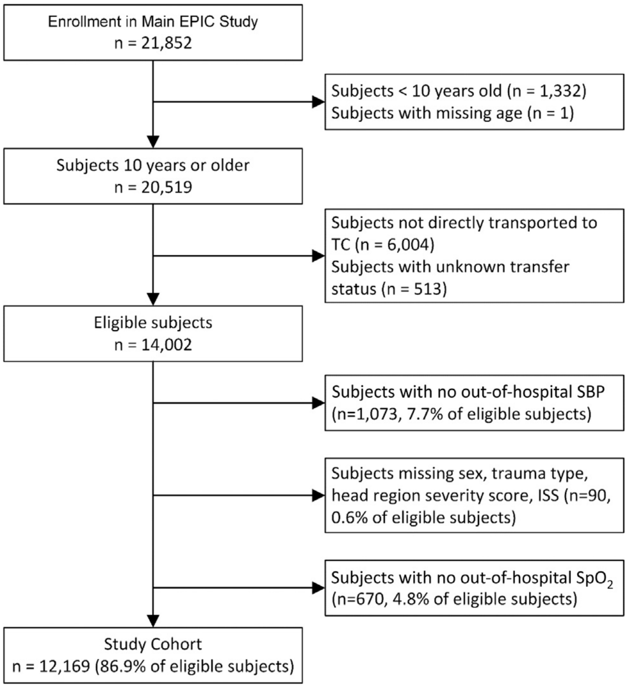

Figure 1. Enrollment tree. *ISS*, Injury Severity Score; *SpO_2*, blood oxygen saturation; *TC*, trauma center.

Figures 4 and 5 display the unadjusted and adjusted probabilities for the various nonmortality hospital outcomes, respectively. As expected, there was some variation. However, overall, there were significant similarities among the results of the plots for the mortality and nonmortality outcomes.

Because there may have been unidentified differences in risk adjustment and confounding among patents with penetrating versus blunt TBIs, we performed a sensitivity analysis by removing the patients with penetrating injuries. The resulting mortality-versus-SBP plots for the blunt-injury cohort were almost identical to those based on the full cohort (Figures 2 and 3). Furthermore, for all 4 nonmortality outcomes depicted in Figures 4 and 5, the adjusted and unadjusted plots based on the blunt-injury cohort were almost identical to those of the study group as a whole. Hence, there was no evidence that our results were substantially affected by differences in the penetrating-injury cohort, and we kept them in the main analysis because they were included in the primary study group in the parent study.

Table 1. Patient characteristics and outcomes by survival status.

Characteristic	All	Dead*	Alive*
Number of subjects	N=12,169	N=1462	N=10,707
Age (y)	44 (26-62)	47 (28-67)	44 (25-61)
Out-of-Hospital Characteristics			
Male			
No	3707 (30.5%)	403 (27.6%)	3304 (30.9%)
Yes	8462 (69.5%)	1059 (72.4%)	7403 (69.1%)
Race			
Black	427 (3.5%)	55 (3.8%)	372 (3.5%)
Asian	151 (1.2%)	18 (1.2%)	133 (1.2%)
American Indian/Alaska Nat.	622 (5.1%)	61 (4.2%)	561 (5.2%)
White	9438 (77.6%)	1097 (75%)	8341 (77.9%)
Other	1393 (11.4%)	180 (12.3%)	1213 (11.3%)
Unknown	138 (1.1%)	51 (3.5%)	87 (0.8%)
Hispanic			
No	9260 (76.1%)	1099 (75.2%)	8161 (76.2%)
Yes	2632 (21.6%)	298 (20.4%)	2334 (21.8%)
Unknown	277 (2.3%)	65 (4.4%)	212 (2%)
Payer			
Private	4421 (36.3%)	410 (28%)	4011 (37.5%)
AHCCCS/Medicaid	2945 (24.2%)	296 (20.2%)	2649 (24.7%)
Medicare	2252 (18.5%)	332 (22.7%)	1920 (17.9%)
Self-pay	1896 (15.6%)	323 (22.1%)	1573 (14.7%)
Other	493 (4.1%)	65 (4.4%)	428 (4%)
Unknown	162 (1.3%)	36 (2.5%)	126 (1.2%)
Trauma type			
Blunt	11,576 (95.1%)	1135 (77.6%)	10,441 (97.5%)
Penetrating	593 (4.9%)	327 (22.4%)	266 (2.5%)
Head Injury Severity Score (ICD)			
1 to 3	6085 (50%)	71 (4.9%)	6014 (56.2%)
4	3650 (30%)	107 (7.3%)	3543 (33.1%)
5 to 6	2434 (20%)	1284 (87.8%)	1150 (10.7%)
Injury Severity Score (ICD)			
1 to 14	4279 (35.2%)	13 (0.9%)	4266 (39.8%)
16 to 24	3848 (31.6%)	63 (4.3%)	3785 (35.4%)
25+	4042 (33.2%)	1386 (94.8%)	2656 (24.8%)
Body region			
Isolated TBI[‡]	8733 (71.8%)	793 (54.2%)	7940 (74.2%)
Multisystem TBI[§]	3436 (28.2%)	669 (45.8%)	2767 (25.8%)
CPR			
No	11,974 (98.4%)	1311 (89.7%)	10,663 (99.6%)
Yes	195 (1.6%)	151 (10.3%)	44 (0.4%)
Airway management			
No PPV	9528 (78.3%)	338 (23.1%)	9190 (85.8%)
BVM	592 (4.9%)	209 (14.3%)	383 (3.6%)
Advanced airway[‖]	2049 (16.8%)	915 (62.6%)	1134 (10.6%)
Min out-of-hospital SBP (mmHg)	124 (110-141)	116.5 (90-143)	125 (110-141)
Out-of-hospital hypotension			

Table 1. Continued.

Characteristic	All	Dead*	Alive*
No	11,243 (92.4%)	1123 (76.8%)	10,120 (94.5%)
Yes	926 (7.6%)	339 (23.2%)	587 (5.5%)
Min out-of-hospital SpO_2 (%)	97 (94, 98)	93 (85, 97)	97 (95, 98)
Outcomes			
Out-of-hospital hypoxia			
No	10880 (89.4%)	948 (64.8%)	9932 (92.8%)
Yes	1289 (10.6%)	514 (35.2%)	775 (7.2%)
Death before hospital admission			
No	11952 (98.2%)	1245 (85.2%)	10707 (100%)
Yes	217 (1.8%)	217 (14.8%)	0 (0%)
Hospital length of stay (days)	4 (2-9)	1 (1-4)	4 (2-10)
ICU admission			
No	2373 (19.5%)	266 (18.2%)	2107 (19.7%)
Yes	9796 (80.5%)	1196 (81.8%)	8600 (80.3%)
ICU length of stay (days)	2 (1-4)	1 (1-4)	2 (1-5)
Total hospital charges (US dollars)[†]	70,297 (37,486-159,514)	89,821 (46,045-170,516)	67,694 (36,724-157,035)
Discharged to home			
No	5371 (44.1%)	1462 (100%)	3909 (36.5%)
Yes	6784 (55.7%)	0 (0%)	6784 (63.4%)
Unknown	14 (0.1%)	0 (0%)	14 (0.1%)

AHCCCS, Arizona Health Care Cost Containment System; *BVM*, bag-valve-mask ventilation; *CPR*, cardiopulmonary resuscitation; *ICD*, International Classification of Diseases-Version 9; *PPV*, positive pressure ventilation (BVM or endotracheal intubation or supraglottic airway); *SpO_2*, blood oxygen saturation.
*Median (interquartile range) for continuous variables and count (percentage) for categorical variables.
†Adjusted for inflation to dollar of June 2015 based on Consumer Price Index of inpatient hospital services in US city average, all urban consumers, not seasonally adjusted.
‡Isolated TBI: Cases that met TBI inclusion criteria but had no injury with Regional Severity Score ≥3 in any other (nonhead) body region.
§Multisystem TBI: Cases that met TBI inclusion criteria and also had at least one nonhead region injury with Regional Severity Score ≥3.
ǀAdvanced airway includes both endotracheal intubation and supraglottic airways.

To evaluate whether the inclusion of older children consequentially changed the results or implications, we conducted a sensitivity analysis of the adult subjects (age ≥18 years) for the primary outcome of mortality and all 4 nonmortality outcomes. The resulting curves were almost identical to those presented in Figures 2 to 5.

LIMITATIONS

This study has limitations. First, the design was observational and we could not establish cause-and-effect relationships related to mortality or the treatment of hypotension. For instance, these data do not prove that the therapeutic target for blood pressure should be higher than the current recommendations. However, they do highlight the importance of perfusing the injured brain and that blood pressure is powerfully linked to a broad array of outcomes.[17,26,43] Furthermore, these results appear to support the statements in the TBI guidelines cautioning that the current recommendations may allow blood pressure to drop too low before intervention. Second, we could not make inferences from these findings to postresuscitation management that occurs in the hospital. The out-of-hospital management of blood pressure focuses solely on treating hypotension and typically lacks many resuscitative options that are available in the hospital (eg, whole blood).[4] In addition, this study did not answer questions related to ongoing ICU management or controversies, such as using pressors to enhance or optimize perfusion.[44,45] Third, while we adjusted for age in the analysis, there were other parameters associated with blood pressure and cardiovascular compensation that we could not factor into the model. For example, we did not directly account for comorbidities, such as baseline hypertension and heart disease, in the analysis. In addition, medications that might have affected the outcome were not adjusted for (eg, beta blockers, antihypertensives, anticoagulants). Fourth, there were some missing data. However, for an EMS study, the rate of missing data was extremely low (eg, no missing outcomes, missing risk adjusters/confounders in 0.6%, missing out-of-hospital SBP in only 7.7%). While

Table 2. Risk adjusters/confounders in the logistic regression model for death.

Variable	Levels	OR[#]	95% CI
Study phase 1* vs. phase 3[†]		1.2	(1.0-1.5)
Male	No	—	—
	Yes	0.9	(0.8-1.1)
Race	Black	—	—
	Asian	1.3	(0.6-2.9)
	American Indian/ Alaska Nat.	1.4	(0.8-2.6)
	White	1.0	(0.6-1.6)
	Other	1.0	(0.6-1.8)
	Unknown	2.4	(1.0-5.6)
Hispanic	No	—	—
	Yes	0.8	(0.6-1.0)
	Unknown	1.5	(0.8-2.6)
Payer	Private	—	—
	AHCCCS/Medicaid	1.0	(0.7-1.2)
	Medicare	1.2	(0.9-1.6)
	Self-pay	2.1	(1.6-2.7)
	Other	1.1	(0.7-1.6)
	Unknown	3.1	(1.6-5.9)
Trauma type	Blunt	—	—
	Penetrating	4.1	(3.1-5.5)
Head Region Injury Score (ICD)	1 to 3	—	—
	4	1.0	(0.7-1.4)
	5 to 6	13.0	(9.2-18.5)
Injury Severity Score (ICD)	1 to 14	—	—
	16 to 24	3.7	(1.9–7.1)
	25+	10.1	(5.2-19.6)
Body region	Isolated TBI[§]	—	—
	Multisystem TBI[|]	1.1	(0.9-1.4)
Hypoxia	No	—	—
	Yes	1.7	(1.4-2.1)
Airway management	No PPV	—	—
	BVM	4.4	(3.4-5.8)
	Advanced airway[¶]	5.3	(4.3-6.5)
CPR	No	—	—
	Yes	5.2	(3.2-8.6)
Hospital[‡]	Not shown		
SBP (mmHg)	Nonparametric function		
Age (y)	Nonparametric function		

*Phase 1: Preintervention phase of main study.
[†]Phase 3: Postintervention phase of main study.
[‡]Hospital (treating trauma center) was highly significant. The numbers are not shown to prevent any identification or inference of facility-specific outcome differences.
[§]Isolated TBI: Cases that met TBI inclusion criteria but had no injury with Regional Severity Score ≥3 in any other (nonhead) body region.
[|]Multisystem TBI: Cases that met TBI inclusion criteria and also had at least one nonhead region injury with Regional Severity Score ≥3.
[¶]Advanced airway includes both endotracheal intubation and supraglottic airways.
[#]Odds ratio for death compared to the reference category.

this missing data rate is very low, there is still the possibility that excluding cases with missing vital signs could have potentially introduced bias into the analysis. Thus, we evaluated the subjects who had no out-of-hospital measurements of SBP or blood oxygen saturation. This group tended to be slightly younger, slightly more likely to be male, more likely to have had penetrating injuries, and more likely to have had more severe injuries. Fifth, this study relied on information documented by EMS. Thus, we could not know for sure that the reported measurements reflected the actual lowest SBPs. Finally, we could not independently verify the accuracy of the blood pressure measurements. However, this is true of essentially all EMS studies.[46] In fact, a strength of EPIC is that the data team abstracted the EMS patient care records directly and comprehensively. This level of data

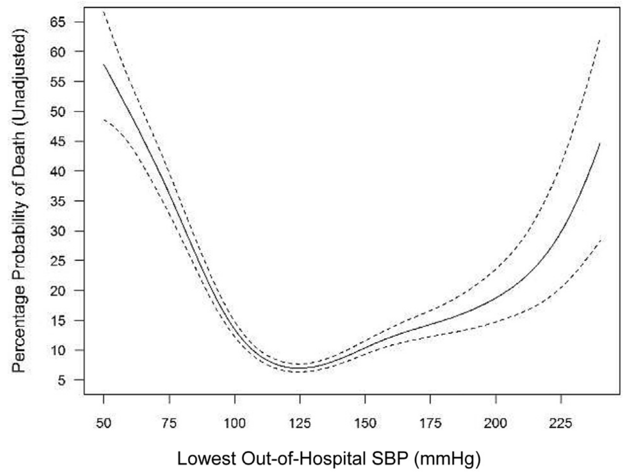

Figure 2. Unadjusted analysis of probability of death by SBP. Unadjusted analysis of the probability of dying in the hospital plotted against lowest out-of-hospital SBP. The dotted lines represent 95% confidence bands.

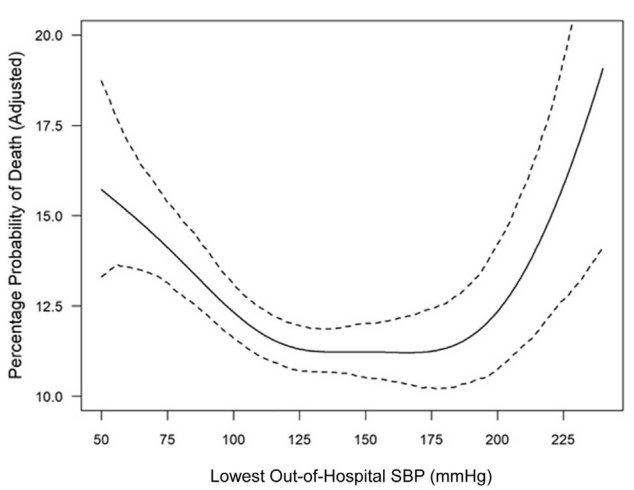

Figure 3. Adjusted analysis of probability of death by SBP. Adjusted analysis of the probability of dying in the hospital plotted against lowest out-of-hospital SBP. The dotted lines represent 95% confidence bands.

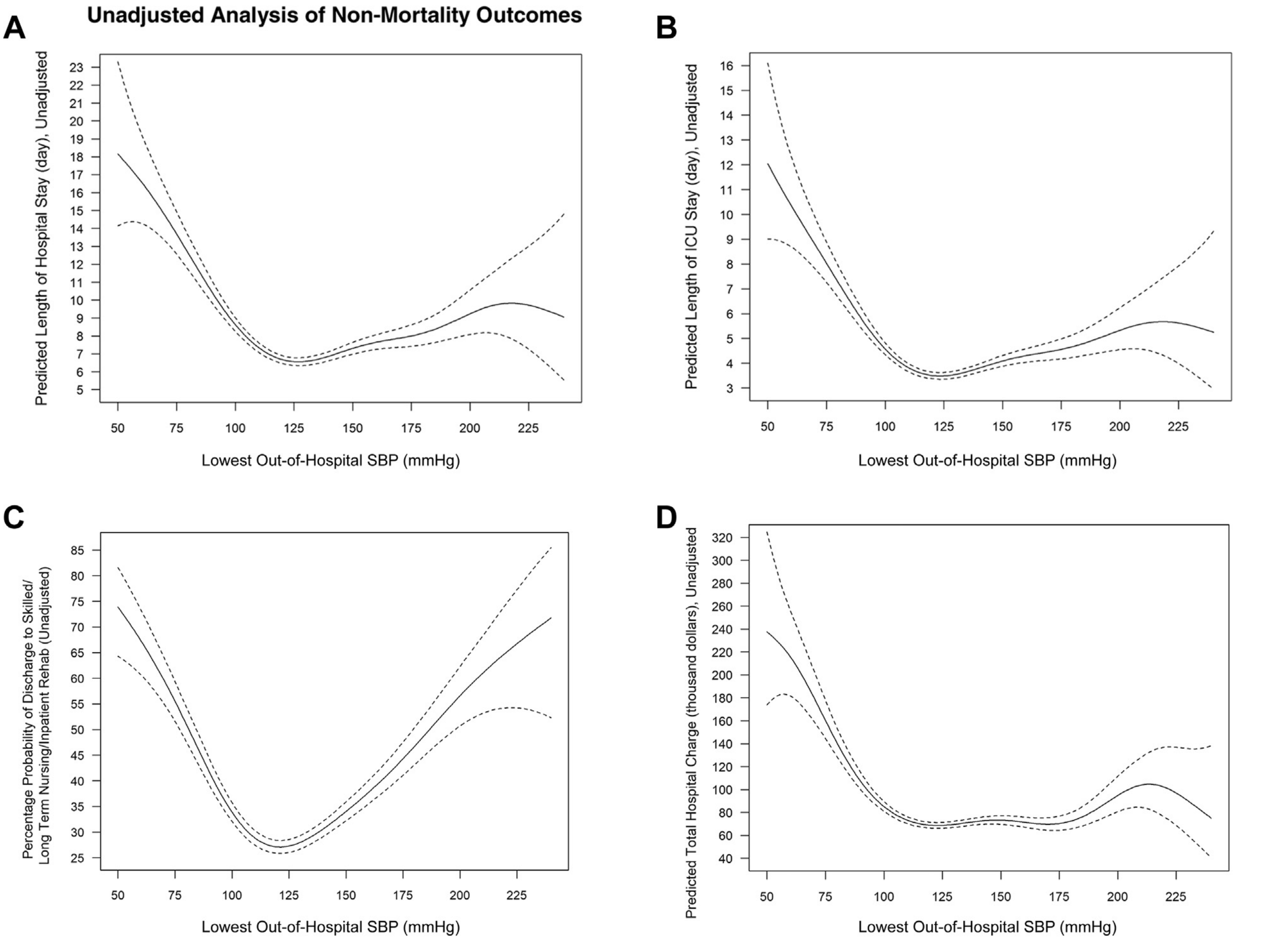

Figure 4. Unadjusted analysis of nonmortality outcomes. *A,* Hospital length of stay: Unadjusted analysis of the number of days of hospitalization plotted against lowest out-of-hospital SBP. The dotted lines represent 95% confidence bands. *B,* ICU length of stay: Unadjusted analysis of the number of days of intensive care plotted against lowest out-of-hospital SBP. *C,* Discharge to skilled nursing/long-term care/inpatient Rehabilitation: Unadjusted analysis of the probability of requiring skilled nursing/inpatient rehabilitation after hospital discharge plotted against lowest out-of-hospital SBP. *D,* Hospital charges: Unadjusted analysis of total hospital charges (indexed to June 2015 US dollars) plotted against lowest out-of-hospital SBP.

scrutiny and consistency is rare in out-of-hospital research.[46]

DISCUSSION

Historically, the EMS literature evaluating blood-pressure–related effects in TBIs has focused nearly entirely on hypotension.[7-15,17-31] This is a result of 2 primary factors: (1) the well-established fact that inadequate perfusion causes secondary brain injury and is associated with poor outcomes and (2) the evaluation of questions related to "normal" (or optimal) blood pressure requires studies with very large patient numbers so it can be treated as a continuous variable.[28,29,31] Because linking out-of-hospital data to hospital outcomes is notoriously difficult, most EMS studies have been small.[46-48] Unfortunately, the resulting literature has focused solely on hypotension and this has created the impression that blood pressure has little effect on TBI outcomes unless it is critically low. However, in a previous report from the preimplementation cohort of the EPIC study, 2 findings brought this concept into question.[31] First, no blood pressure-versus-mortality threshold was identifiable at any point between 40 and 120 mmHg. In fact, the association between SBP and the adjusted log odds of death was linear, with an adjusted odds ratio of 0.81 for mortality associated with a 10 mmHg increase, regardless of the SBP range being evaluated. In other words, an SBP difference of 10 mmHg (say, 115 versus 105, 90 versus 80, or 75 versus 65) was associated with a 19% difference in the adjusted odds of death across the entire SBP range. The second finding that raised questions about how "hypotension" has typically

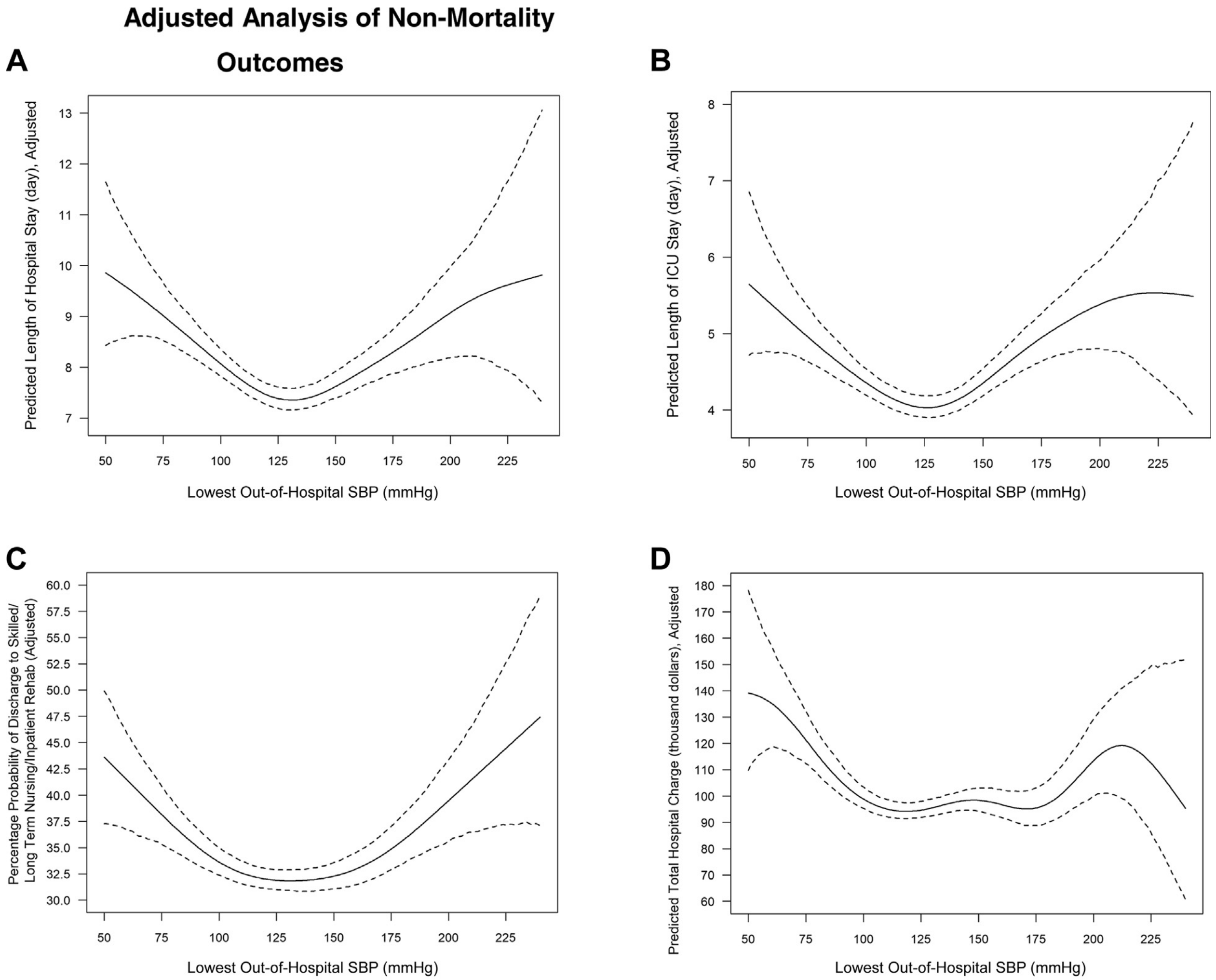

Figure 5. Adjusted analysis of nonmortality outcomes. *A,* Hospital length of stay: Adjusted analysis of the number of days of hospitalization plotted against lowest out-of-hospital SBP. The dotted lines represent 95% confidence bands. *B,* ICU length of stay: Adjusted analysis of the number of days of intensive care plotted against lowest out-of-hospital SBP. *C,* Discharge to skilled nursing/ long-term care/inpatient rehabilitation: Adjusted analysis of the probability of requiring skilled nursing/inpatient rehabilitation after hospital discharge plotted against lowest out-of-hospital SBP. *D,* Hospital charges: Adjusted analysis of total hospital charges (indexed to June 2015 US dollars) plotted against lowest out-of-hospital SBP.

been defined was the fact that dichotomizing “low” versus “not low” at cut points spanning the entire range from 60 mmHg to 135 mmHg yielded statistically worse mortality in each “low” cohort.[31] Hence, the idea that only *very* low blood pressure influences outcomes in TBIs may be wrong.

In the current study, the pattern of adjusted mortality revealed 3 distinct features across the spectrum of pressures (Figure 3): (1) steady improvement in mortality across the entire range from 40 to at least 125 mmHg, (2) a very broad range of low mortality from 130 to 180 mmHg, and (3) a rapid increase in mortality above 180 mmHg.

The evaluation of the left side of the plot is instructive and reveals improvement in the associated outcomes to an SBP level far above the “classic” definition for hypotension (90 mmHg). It also demonstrates an absence of any SBP-versus-mortality inflection point or threshold below at least 125 mmHg, a finding that confirms our previous report from the preimplementation cohort.[31] Furthermore, we found that patients with TBIs who were “nearly hypotensive” were at a significantly increased risk of death. Notably, while the classically hypotensive cohort (<90 mmHg) represented only 7.7% of the EPIC population, the nearly-hypotensive group (90 to 119 mmHg) comprised 36.1% of cases. So, while the less-than-90-mmHg cohort had a higher mortality rate, the significant size of the nearly-hypotensive group accounted for a large number of deaths. Hence, "near hypotension" may be highly consequential in TBI mortality, because it occurs in so many patients.

The center of the adjusted mortality plot is remarkable in 2 ways (Figure 3). First, there is a very wide, and nearly flat, range of low mortality—a finding that has not been previously reported in the EMS literature. Second, the left side of this low mortality plateau begins at blood pressures far above any levels that have been typically utilized as thresholds for defining hypotension (approximately 130 mmHg). While EPIC was not designed to compare the effectiveness of the current guideline threshold compared to other possible levels (eg, 100, 110, etc), the surprisingly high "optimal" blood pressure range clearly shows that the risks associated with poor perfusion begin at levels far above the current definition for hypotension. This adds to the concerns discussed in the EMS TBI guidelines document: "The value of 90 mmHg as a threshold for hypotension has been defined by blood pressure distributions for *normal* adults (emphasis added). Thus, this is more a statistical than physiological finding…Given the influence of cerebral perfusion pressure on outcome, it is possible that SBP higher than 90 mmHg would be desirable during the out-of-hospital and resuscitation phase, but no studies have been performed to corroborate this."[5] The lack of clarity surrounding this issue led the guideline authors to give it high priority in the section on "Key Issues for Future Investigation." In the listing of recommended future research, topic number one is the identification of "the level of hypotension that correlates with poor outcome."[5]

The finding that the "optimal" range in the middle of the SBP plot extends up to pressures around 180 mmHg is intriguing, particularly because this analysis evaluated the lowest-recorded EMS SBPs. While we cannot establish cause and effect, this may well reflect the key role that perfusion plays in the outcome of brain-injured patients. The fact that cerebral blood flow is so important in TBIs has led to attempts to improve outcomes through the enhancement of perfusion (eg, phenylephrine, dopamine, and norepinephrine). However, the efficacy of these therapeutic interventions remains unproven.[44,45,49-52] In any case, regardless of whether interventions that increase perfusion will ultimately be found to be effective, it is clear that cerebral blood flow is critically important for good outcomes. Furthermore, the historical approach that has focused solely on avoiding very low blood pressure in out-of-hospital TBI management may have underestimated the negative effect of near hypotension. Our findings clearly point to the need for future clinical trials comparing the current treatment threshold with higher targets (potentially up to levels as high as 110 to 120 mmHg).

The right side of the SBP plot (Figure 3) probably represents the pathophysiological converse of the left side. That is, while *low* blood pressure strongly *contributes* to mortality (left side), *high* pressures *reflect* critical brain injury (right side). This concept is supported by the severity patterns—the severely hypertensive cohort (SBP $\geq$180 mmHg) was much more likely to have very severe brain injuries than the normotensive group (see Results). This is consistent with the concept in the current literature revealing that severe hypertension is often reflective of critical brain injury, the loss of autoregulation, and the cardiovascular system's attempt to maintain cerebral blood flow in the setting of markedly increased intracranial pressure.[5,53] Once this severe hypertensive pattern is established in an attempt to improve brain perfusion, unless intracranial pressure is significantly reduced, the extreme hypertension then contributes to additional brain edema in a vicious cycle that leads to death.[5]

Because the factors that affect mortality in multisystem TBIs are more complex than those in isolated TBIs, we performed a subanalysis, evaluating these 2 cohorts separately. Not surprisingly, the mortality rate associated with multisystem TBIs was higher (19.5% [18.2% to 20.8%]) than that of the isolated TBI cohort (9.1% [8.5% to 9.7%]). Consequently, the unadjusted and adjusted probabilities of death, across the range of blood pressures, were higher in multisystem TBIs than in isolated. However, other than the higher death probabilities in multisystem, the blood pressure plots showed similar patterns compared to the overall main analysis (Figures 2 and 3). The shapes and patterns of the unadjusted analyses are shown in Figure 6 and of the adjusted plots in Figure 7 (multisystem) and Figure 8 (isolated). As can be seen in the figures, the results from both multisystem and isolated TBIs are consistent with the findings and implications of the combined analysis. The adjusted mortality plots reveal (1) a down-sloping left side that is lowest at SBP levels far higher than 90 mmHg, (2) a low adjusted mortality in the 130- to-160 mmHg range, and (3) a rapidly increasing risk of death with severe hypertension. Consequently, while patients with multisystem TBIs have an overall higher probability of death than those with isolated TBIs, the blood pressure ranges associated with the death probability patterns across the range of SBP are very similar and support the findings of the combined analysis. Thus, it appears that blood pressure may be associated with mortality in similar ways in multisystem and isolated TBIs. This would be consistent with the well-established understanding of the importance of brain perfusion that would be expected, regardless of whether a patient had multiple body injuries or isolated brain trauma.

The associations between out-of-hospital blood pressure and nonmortality outcomes (hospital length of stay, ICU length of stay, discharge to a skilled nursing facility or

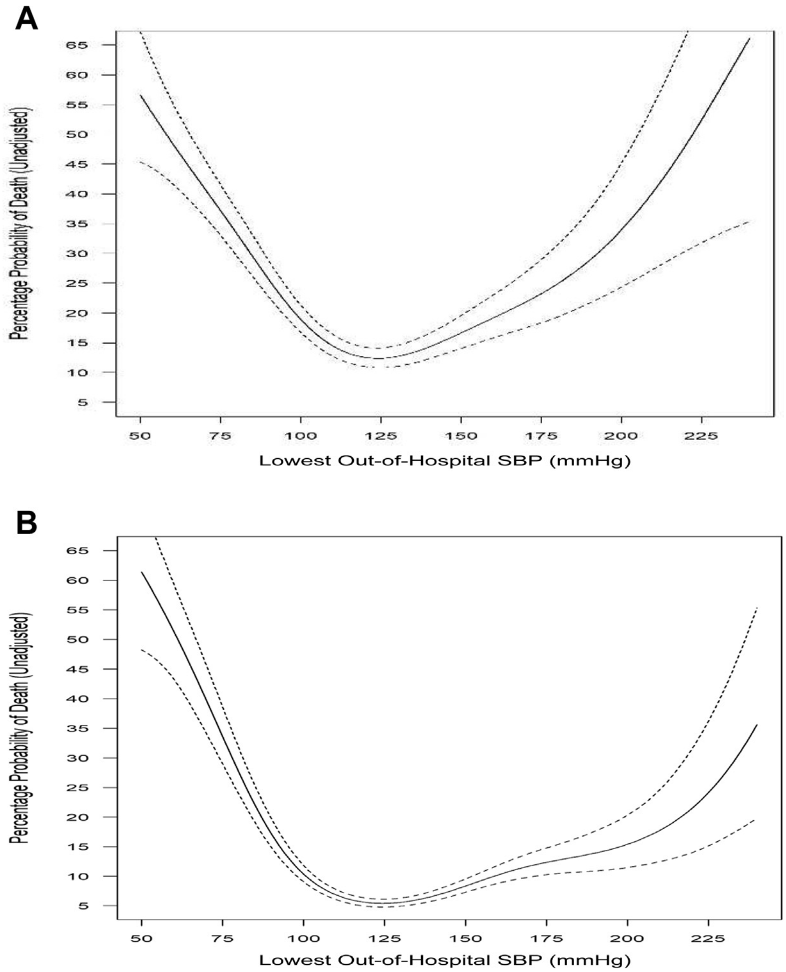

Figure 6. Analysis of unadjusted probability of death by SBP (multisystem and isolated). Unadjusted analysis of the probability of dying in the hospital plotted against lowest out-of-hospital SBP. The dotted lines represent 95% confidence bands. *A,* Multisystem TBI: Unadjusted plot. *B,* Isolated TBI: Unadjusted plot. *TBI,* traumatic brain injury.

inpatient rehabilitation, hospital charges) are shown in Figures 4 and 5. While some variations exist, there is a remarkable similarity between the SBP plots for mortality and the nonmortality outcomes. Below approximately 125 mmHg, increases in blood pressure are associated with marked improvements in outcomes. As with mortality, the "optimal" ranges for SBP are far higher than the 90 mmHg hypotension threshold—in the range of approximately 125 to 160 mmHg. And finally, the pattern of markedly worse outcomes with extreme hypertension is seen with nonmortality outcomes in patterns consistent with mortality.

The very strong associations between a single out-of-hospital physiological parameter (lowest SBP) and distal outcomes are striking. These findings are made even more remarkable by the fact that the average amount of time EMS providers spent with the patients was only 33 minutes. Given that the mean length of inpatient care was 7.1 days (more than 300 times longer), it appears that factors associated with perfusion of the injured brain during the first few minutes of TBI management may have disproportionate influences on distal outcomes.

The one exception to the typical high-low-high mortality pattern was found with hospital charges (Figures 4 and 5). It is important to note that the apparent pattern of reduced hospital costs at the extremely high range of SBPs was based on very few data points. That is, only 53 of the 12,169 subjects had lowest SBPs higher than 210 mmHg. The 95% confidence bands were very wide in that range, and the upper bounds did not go down. Thus, it is possible that this was simply a statistical anomaly. Nonetheless, the point estimate line for cost did tend to go downward in the setting of extreme hypertension. If this trend is real, there are several plausible reasons that could explain the pattern. First, a massive brain or overall body injury often leads to early death and the cessation of

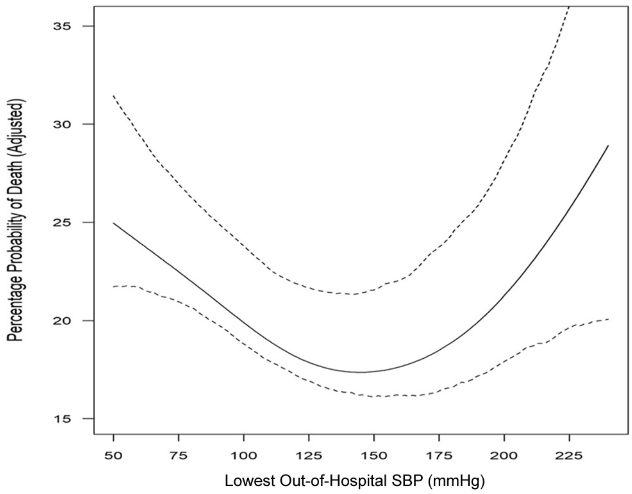

Figure 7. Analysis of adjusted probability of death by SBP (multisystem TBI). Adjusted analysis of the probability of dying in the hospital plotted against lowest out-of-hospital SBP. The dotted lines represent 95% confidence bands.

"heroic" (and expensive) measures. Second, patients with critical TBIs (head region severity scores of 5 to 6) or overall injuries (ISS ≥25) died sooner than those who died from less-severe injuries. The median hospital length of stay in the critical TBI cohort that died (head region severity score of 5 to 6) was 1.0 (95% confidence interval, 1.0 to 1.0) days, compared to 3.0 (2.0 to 4.0) days for those who died from less-severe TBIs. This was also true of critical overall injury (the median length of stay for the ISS ≥25 cohort was 1.0 [1.0 to 1.0] days, compared to 4.0 [2.5 to 6.0] days for those with ISS <25). The above combination of factors may explain the "paradoxical" finding that the

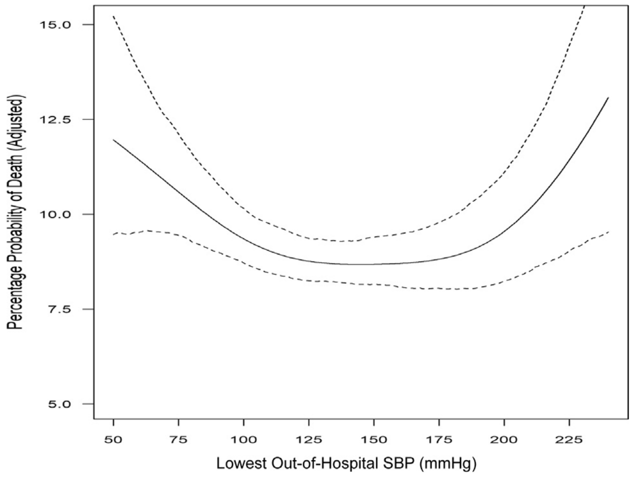

Figure 8. Analysis of adjusted probability of death by SBP (isolated TBI). Adjusted analysis of the probability of dying in the hospital plotted against lowest out-of-hospital SBP. The dotted lines represent 95% confidence bands.

hospital cost was reduced in the setting of extreme hypertension.

In summary, the analysis of the association between out-of-hospital blood pressure and outcomes in more than 12,000 patients with major TBIs yielded several distinct patterns. The adjusted mortality decreased monotonically between 40 and 130 mmHg, remained low up to 180 mmHg, and rapidly increased above this level. There was no evidence of a physiologic inflection point anywhere near the classic hypotension threshold of 90 mmHg. This overall pattern also occurred consistently among multiple nonmortality outcomes. Taken together, these findings bring into question the historical understanding of how low blood pressure can be allowed to go before intervention during the early resuscitation of patients with TBIs. Levels that are currently considered adequate or normal may negatively affect outcomes, and the optimal blood pressure may be far higher than what has been reflected in the literature. Given the unexpectedly strong association between out-of-hospital blood pressure and outcomes in the range between 90 and 130 mmHg, trials that randomize patients at significantly higher treatment thresholds are sorely needed.

Supervising editor: Theodore R. Delbridge, MD, MPH. Specific detailed information about possible conflict of interest for individual editors is available at https://www.annemergmed.com/editors.

Author affiliations: From the Arizona Emergency Medicine Research Center, College of Medicine–Phoenix, The University of Arizona, Phoenix, AZ (Spaite, Hu, Barnhart, Gaither, Denninghoff, Rice, Keim); the Department of Emergency Medicine, College of Medicine, The University of Arizona, Tucson, AZ (Spaite, Gaither, Denninghoff, Rice, Keim); the Mel and Enid Zuckerman College of Public Health, The University of Arizona, Tucson, AZ (Hu); the Department of Emergency Medicine, McGovern Medical School at UT Health, Houston, TX (Bobrow, Bradley); the Arizona Department of Health Services, Bureau of Emergency Medical Services, Phoenix, AZ (Chikani); and the Department of Public Health, University of Texas at San Antonio, San Antonio, TX (Howard).

Author contributions: CH and DWS had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. DWS drafted and submitted the manuscript, and all authors contributed substantially to its revision. DWS takes responsibility for the paper as a whole.

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The University of Arizona received funding from the NIH and DOD supporting the EPIC study. This includes support for the following authors from their academic appointments: DWS, CH, BJB, VC, BB, JBG, and KRD. GHB, ADR, JTH, and SMK have no conflicts of interest to report. Supported by the US Army Medical Research and Materiel Command under Contract No. W81XWH-19-C-0058. The data collection and linkage for the original EPIC study, from which the EPIC Database came, were funded, in part, by a grant from the National Institutes of Health (NIH/NINDS Grant # 1R01NS071049).

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation. Furthermore, the content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Neither the DOD nor the NIH had any role in the following: (1) design and conduct of the study, (2) collection, management, analysis, and interpretation of the data, (3) preparation, review, or approval of the manuscript, or (4) the decision to submit the manuscript for publication.

Publication dates: Received for publication June 24, 2021. Revisions received November 16, 2021, and January 17, 2022. Accepted for publication January 26, 2022.

Trial registration number: NCT01339702.

Presented, in part, at the Annual Scientific Assembly of the National Association of EMS Physicians, January 13 to 16, 2021.

REFERENCES

1. Bell JMBM, Jenkins EL, Haarbauer-Krupa J. Traumatic Brain Injury In the United States: Epidemiology and Rehabilitation. National Center for Injury Prevention and Control, Division of Unintentional Injury Prevention, Centers for Disease Control; 2014.
2. Finkelstein E, Corso PS, Miller TR. *The Incidence and Economic Burden of Injuries in the United States*. Oxford University Press; 2006.
3. Adelson PD, Bratton SL, Carney NA, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. Chapter 12. Use of hyperventilation in the acute management of severe pediatric traumatic brain injury. *Pediatr Crit Care Med*. 2003;4:S45-S48.
4. Badjatia N, Carney N, Crocco TJ, et al. Guidelines for prehospital management of traumatic brain injury 2nd edition. *Prehosp Emerg Care*. 2008;12(Suppl 1):S1-S52.
5. Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons. Guidelines for the management of severe traumatic brain injury. *J Neurotrauma*. 2007;24(Suppl 1):S1-S106.
6. Kochanek PM, Carney N, Adelson PD, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents–second edition. *Pediatr Crit Care Med*. 2012;13(Suppl 1):S1-S82.
7. Spaite DW, Bobrow BJ, Keim SM, et al. Association of statewide implementation of the prehospital traumatic brain injury treatment guidelines with patient survival following traumatic brain injury: the Excellence in Prehospital Injury Care (EPIC) Study. *JAMA Surg*. 2019;154:e191152.
8. Chesnut RM, Marshall LF, Klauber MR, et al. The role of secondary brain injury in determining outcome from severe head injury. *J Trauma*. 1993;34:216-222.
9. Fearnside MR, Cook RJ, McDougall P, et al. The Westmead Head Injury Project outcome in severe head injury. A comparative analysis of pre-hospital, clinical and CT variables. *Br J Neurosurg*. 1993;7:267-279.
10. Shutter LA, Narayan RK. Blood pressure management in traumatic brain injury. *Ann Emerg Med*. 2008;51(Suppl):S37-S38.
11. Jankowitz BT, Adelson PD. Pediatric traumatic brain injury: past, present and future. *Dev Neurosci*. 2006;28:264-275.
12. Gentleman D. Causes and effects of systemic complications among severely head injured patients transferred to a neurosurgical unit. *Int Surg*. 1992;77:297-302.
13. Pigula FA, Wald SL, Shackford SR, et al. The effect of hypotension and hypoxia on children with severe head injuries. *J Pediatr Surg*. 1993;28:310-314; discussion 315-316.
14. Kokoska ER, Smith GS, Pittman T, et al. Early hypotension worsens neurological outcome in pediatric patients with moderately severe head trauma. *J Pediatr Surg*. 1998;33:333-338.
15. Miller JD, Becker DP. Secondary insults to the injured brain. *J R Coll Surg Edinb*. 1982;27:292-298.
16. Barton CW, Hemphill JC, Morabito D, et al. A novel method of evaluating the impact of secondary brain insults on functional outcomes in traumatic brain-injured patients. *Acad Emerg Med*. 2005;12:1-6.
17. Manley G, Knudson MM, Morabito D, et al. Hypotension, hypoxia, and head injury: frequency, duration, and consequences. *Arch Surg*. 2001;136:1118-1123.
18. Price DJ, Murray A. The influence of hypoxia and hypotension on recovery from head injury. *Injury*. 1972;3:218-224.
19. Stocchetti N, Furlan A, Volta F. Hypoxemia and arterial hypotension at the accident scene in head injury. *J Trauma*. 1996;40:764-767.
20. Carrel M, Moeschler O, Ravussin P, et al. Prehospital air ambulance and systemic secondary cerebral damage in severe craniocerebral injuries. *Ann Fr Anesth Reanim*. 1994;13:326-335.
21. Kohi YM, Mendelow AD, Teasdale GM, et al. Extracranial insults and outcome in patients with acute head injury–relationship to the Glasgow Coma Scale. *Injury*. 1984;16:25-29.
22. Rose J, Valtonen S, Jennett B. Avoidable factors contributing to death after head injury. *Br Med J*. 1977;2:615-618.
23. Chesnut RM, Ghajar J, Maas AIR, et al. Part 2: early indicators of prognosis in severe traumatic brain injury. *J Neurotrauma*. 2000;17:555-627.
24. Hill DA, Abraham KJ, West RH. Factors affecting outcome in the resuscitation of severely injured patients. *Aust N Z J Surg*. 1993;63:604-609.
25. Chesnut RM, Marshall SB, Piek J, et al. Early and late systemic hypotension as a frequent and fundamental source of cerebral ischemia following severe brain injury in the Traumatic Coma Data Bank. *Acta Neurochir Suppl (Wien)*. 1993;59:121-125.
26. McHugh GS, Engel DC, Butcher I, et al. Prognostic value of secondary insults in traumatic brain injury: results from the IMPACT study. *J Neurotrauma*. 2007;24:287-293.
27. Miller JD, Sweet RC, Narayan R, et al. Early insults to the injured brain. *JAMA*. 1978;240:439-442.
28. Spaite DW, Bobrow BJ, Stolz U, et al. Evaluation of the impact of implementing the emergency medical services traumatic brain injury guidelines in Arizona: the Excellence in Prehospital Injury Care (EPIC) study methodology. *Acad Emerg Med*. 2014;21:818-830.
29. Spaite DW, Hu C, Bobrow BJ, et al. Association of out-of-hospital hypotension depth and duration with traumatic brain injury mortality. *Ann Emerg Med*. 2017;70:522-530.e1.
30. Spaite DW, Hu C, Bobrow BJ, et al. The effect of combined out-of-hospital hypotension and hypoxia on mortality in major traumatic brain injury. *Ann Emerg Med*. 2017;69:62-72.

31. Spaite DW, Hu C, Bobrow BJ, et al. Mortality and prehospital blood pressure in patients with major traumatic brain injury: implications for the hypotension threshold. *JAMA Surg*. 2017;152:360-368.
32. Consumer Price Index (CPI). Inpatient hospital services in U.S. city average, all urban consumers, not seasonally adjusted (series ID: CUUR0000SS5702). United States Department of Labor. Accessed October 29, 2020. https://beta.bls.gov/dataViewer/view/timeseries/CUUR0000SS5702
33. Lerner EB, Nichol G, Spaite DW, et al. A comprehensive framework for determining the cost of an emergency medical services system. *Ann Emerg Med*. 2007;49:304-313.
34. Lerner EB, Garrison HG, Nichol G, et al. An economic toolkit for identifying the cost of emergency medical services (EMS) systems: detailed methodology of the EMS Cost Analysis Project (EMSCAP). *Acad Emerg Med*. 2012;19:210-216.
35. Hannan EL, Waller CH, Farrell LS, et al. A comparison among the abilities of various injury severity measures to predict mortality with and without accompanying physiologic information. *J Trauma*. 2005;58:244-251.
36. MacKenzie EJ, Steinwachs DM, Shankar B. Classifying trauma severity based on hospital discharge diagnoses. Validation of an ICD-9CM to AIS-85 conversion table. *Med Care*. 1989;27:412-422.
37. Stewart KE, Cowan LD, Thompson DM. Changing to AIS 2005 and agreement of injury severity scores in a trauma registry with scores based on manual chart review. *Injury*. 2011;42:934-939.
38. Newgard CD, Fildes JJ, Wu L, et al. Methodology and analytic rationale for the American College of Surgeons Trauma Quality Improvement Program. *J Am Coll Surg*. 2013;216:147-157.
39. Nathens AB, Jurkovich GJ, Maier RV, et al. Relationship between trauma center volume and outcomes. *JAMA*. 2001;285:1164-1171.
40. Wood SN. *Generalized Additive Models: An Introduction with R*. 2nd ed. Chapman and Hall/CRC; 2017.
41. R: a language and environment for statistical computing: version 3.5.3. R Foundation for Statistical Computing. Accessed August 2, 2020. https://www.r-project.org
42. Wood SN. Fast stable restricted maximum likelihood and marginal likelihood estimation of semiparametric generalized linear models. *J R Stat Soc B*. 2011;73:3-36.
43. Berry C, Ley EJ, Bukur M, et al. Redefining hypotension in traumatic brain injury. *Injury*. 2012;43:1833-1837.
44. Robertson CS, Valadka AB, Hannay HJ, et al. Prevention of secondary ischemic insults after severe head injury. *Crit Care Med*. 1999;27:2086-2095.
45. Howells T, Elf K, Jones PA, et al. Pressure reactivity as a guide in the treatment of cerebral perfusion pressure in patients with brain trauma. *J Neurosurg*. 2005;102:311-317.
46. Spaite DW, Valenzuela TD, Meislin HW. Barriers to EMS system evaluation: problems associated with field data collection. *Prehosp Disaster Med*. 1993;8:S35-S40.
47. Spaite D, Benoit R, Brown D, et al. Uniform prehospital data elements and definitions: a report from the uniform prehospital emergency medical services data conference. *Ann Emerg Med*. 1995;25:525-534.
48. Spaite DW. The future of emergency care in the United States: the Institute of Medicine Subcommittee on Prehospital Emergency Medical Services. *Ann Emerg Med*. 2006;48:126-130.
49. Steiner LA, Johnston AJ, Czosnyka M, et al. Direct comparison of cerebrovascular effects of norepinephrine and dopamine in head-injured patients. *Crit Care Med*. 2004;32:1049-1054.
50. Johnston AJ, Steiner LA, Chatfield DA, et al. Effect of cerebral perfusion pressure augmentation with dopamine and norepinephrine on global and focal brain oxygenation after traumatic brain injury. *Intensive Care Med*. 2004;30:791-797.
51. Di Gennaro JL, Mack CD, Malakouti A, et al. Use and effect of vasopressors after pediatric traumatic brain injury. *Dev Neurosci*. 2010;32:420-430.
52. Allen BB, Chiu YL, Gerber LM, et al. Age-specific cerebral perfusion pressure thresholds and survival in children and adolescents with severe traumatic brain injury. *Pediatr Crit Care Med*. 2014;15:62-70.
53. Butcher I, McHugh GS, Lu J, et al. Prognostic value of cause of injury in traumatic brain injury: results from the IMPACT study. *J Neurotrauma*. 2007;24:281-286.