The Effect of Combined Out-of-Hospital Hypotension and Hypoxia on Mortality in Major Traumatic Brain Injury

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Study objective: Survival is significantly reduced by either hypotension or hypoxia during the out-of-hospital management of major traumatic brain injury. However, only a handful of small studies have investigated the influence of the combination of both hypotension and hypoxia occurring together. In patients with major traumatic brain injury, we evaluate the associations between mortality and out-of-hospital hypotension and hypoxia separately and in combination.

Methods: All moderate or severe traumatic brain injury cases in the preimplementation cohort of the Excellence in Prehospital Injury Care study (a statewide, before/after, controlled study of the effect of implementing the out-of-hospital traumatic brain injury treatment guidelines) from January 1, 2007, to March 31, 2014, were evaluated (exclusions: $<$10 years, out-of-hospital oxygen saturation $\leq$10%, and out-of-hospital systolic blood pressure $<$40 or $>$200 mm Hg). The relationship between mortality and hypotension (systolic blood pressure $<$90 mm Hg) or hypoxia (saturation $<$90%) was assessed with multivariable logistic regression, controlling for Injury Severity Score, head region severity, injury type (blunt versus penetrating), age, sex, race, ethnicity, payer, interhospital transfer, and trauma center.

Results: Among the 13,151 patients who met inclusion criteria (median age 45 years; 68.6% men), 11,545 (87.8%) had neither hypotension nor hypoxia, 604 (4.6%) had hypotension only, 790 (6.0%) had hypoxia only, and 212 (1.6%) had both hypotension and hypoxia. Mortality for the 4 study cohorts was 5.6%, 20.7%, 28.1%, and 43.9%, respectively. The crude and adjusted odds ratios for death within the cohorts, using the patients with neither hypotension nor hypoxia as the reference, were 4.4 and 2.5, 6.6 and 3.0, and 13.2 and 6.1, respectively. Evaluation for an interaction between hypotension and hypoxia revealed that the effects were additive on the log odds of death.

Conclusion: In this statewide analysis of major traumatic brain injury, combined out-of-hospital hypotension and hypoxia were associated with significantly increased mortality. This effect on survival persisted even after controlling for multiple potential confounders. In fact, the adjusted odds of death for patients with both hypotension and hypoxia were more than 2 times greater than for those with either hypotension or hypoxia alone. These findings seem supportive of the emphasis on aggressive prevention and treatment of hypotension and hypoxia reflected in the current emergency medical services traumatic brain injury treatment guidelines but clearly reveal the need for further study to determine their influence on outcome. [Ann Emerg Med. 2017;69:62-72.]

Please see page 63 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background and Importance

Traumatic brain injury is a massive public health problem, leading to more than 50,000 deaths and enormous health care expenditures each year in the United States.[1,2] The Centers for Disease Control and Prevention (CDC) estimates that at least 5.3 million Americans, approximately 2% of the US population, are living with a major, permanent, traumatic brain injury–related disability.[2,3]

During the out-of-hospital care of patients with traumatic brain injury, hypoxia occurs frequently[4-9] and significantly increases mortality.[6,7,10-16] It is independently associated with a higher risk of death even if the hypoxemic episode is reflected by only a single measurement of low

Editor's Capsule Summary

What is already known on this topic

Both hypotension and hypoxia are independently associated with higher mortality among out-of-hospital patients with traumatic brain injury.

What question this study addressed

For out-of-hospital patients with traumatic brain injury, what is the effect on survival of the combination of hypotension and hypoxia compared with either factor alone?

What this study adds to our knowledge

Among 13,151 out-of-hospital patients with traumatic brain injury during a 7-year period, only 1.6% experienced both hypotension and hypoxia. Mortality was 5.6% for patients with neither but 43.9% when the combination of hypotension and hypoxia occurred. The adjusted odds ratio for death was 6.1 (95% confidence interval [CI] 4.2 to 8.9) for the combination, 2.5 (95% CI 1.9 to 3.3) for hypotension alone, and 3.0 (95% CI 2.4 to 3.8) for hypoxia alone.

How this is relevant to clinical practice

Emphasis should be placed on avoiding hypotension and hypoxia in patients with traumatic brain injury, and additional attention should be paid to preventing their combination.

oxygen saturation.[10,12,17] Stocchetti found that the presence of out-of-hospital hypoxia more than tripled the likelihood of death among victims of severe traumatic brain injury.[6] Hypotension is also very common early in the care of traumatic brain injury[7,10,11,18] and significantly affects survival.[6,10,11,14,15,18-39] A single episode of hypotension doubles mortality, and this risk increases significantly with repeated episodes (an odds ratio [OR] of 8.1 for death in one study).[26]

Although the negative effect of hypotension and hypoxia has been well documented in the literature, little is known about their combination. Thus, it is unknown whether, together, they have no additional effect, an additive effect, or some intermediate influence on outcomes. Even though it is known that hypotension and hypoxia independently increase mortality, this is not the same as showing that the combination of the two is additive in its effect in patients who actually experience both. In fact, some authors have suggested that, because there are great similarities at the cellular level in the effect of hypoxia and hypotension (reduced oxygen delivery to the neuron), having both may add little to the risk of death because the physiologic insult may be similar with either or both.[16,22,26] With the exception of a meta-analysis that had major issues with study heterogeneity and missing data,[39] the reports that have examined the effect of hypotension combined with hypoxia in traumatic brain injury have included few cases.[6,16,22,26,28,35,40] Furthermore, even less is known about this problem in the out-of-hospital setting. To our knowledge, only 2 previous studies specifically evaluated the hypotension and hypoxia combination with out-of-hospital data.[6,16] A key reason for evaluating the effect of blood pressure and oxygenation measured before hospital arrival is because the injured brain is so highly sensitive to changes in perfusion and oxygenation and the timeframe during which neuronal damage begins is so short. It is well established that secondary brain injury is initiated by even brief periods of compromised blood flow or hypoxia.[20,22,23,28,35,40-43] Thus, decreased perfusion or hypoxia occurring during the out-of-hospital interval may have a profound effect on outcome.

Goals of This Investigation

The objective of this investigation was to evaluate the association between survival and out-of-hospital hypotension, hypoxia, or both in patients with major traumatic brain injury.[41]

In major traumatic brain injury, the combination of both out-of-hospital hypotension (systolic blood pressure <90 mm Hg) and hypoxia (oxygen saturation <90%) has additional negative influence on survival compared with either factor alone.

MATERIALS AND METHODS

The Excellence in Prehospital Injury Care (EPIC) study has been described in detail elsewhere.[41] It is funded by the National Institutes of Health, and, although not a randomized trial, it is registered at ClinicalTrials.gov (NCT01339702). Rather than reiterating the details of the parent study, here we limit the description to the design attributes relevant to this specific evaluation.

Setting

The EPIC study is evaluating the effect of implementing the out-of-hospital traumatic brain injury guidelines[42-45] in patients with moderate or severe ("major") traumatic brain injury throughout Arizona, using a before-after, controlled, multisystem, observational design. The patients in this evaluation are in the preimplementation cohort of EPIC (treated by an emergency medical services [EMS] agency between January 1, 2007, and March 31, 2014, without receiving EPIC study interventions). Cases in the interventional cohort were excluded for 2 reasons. First, inclusion of postintervention cases in this observational evaluation would encroach on several of the main hypotheses of the primary parent study, and the analysis plan does not allow multiple "looks" at the interventional data. Second, because two of the emphases of guideline implementation are the prevention and aggressive treatment of hypotension and hypoxia, including postimplementation cases might significantly bias the results.

Study Design and Selection of Participants

The EPIC database is made up of the subset of patients from the Arizona State Trauma Registry meeting EPIC study criteria for major traumatic brain injury (described below). The registry has detailed inhospital data on all trauma patients transported to the 8 state-designated Level I trauma centers in Arizona. The EPIC database contains both Arizona State Trauma Registry data and linked, detailed, out-of-hospital data. The necessary regulatory approvals for the EPIC project were obtained from the Arizona Department of Health Services and the state attorney general. The University of Arizona Institutional Review Board and the Arizona Department of Health Services Human Subjects Review Board approved the project; determined that, by virtue of being a public health initiative, neither the interventions nor their evaluation constitutes human subjects research; and approved the publication of deidentified data.

Patients aged 10 years or older with physical trauma who had a trauma center diagnosis consistent with traumatic brain injury (either isolated or multisystem trauma that included traumatic brain injury) and met at least 1 of the following definitions for moderate or severe traumatic brain injury were included: CDC Barell matrix type 1; *International Classification of Diseases, Ninth Revision* head region severity score greater than or equal to 3; and Abbreviated Injury Scale–head region score greater than or equal to 3.[41]

Excluded were patients younger than 10 years; those missing EMS systolic blood pressure, oxygen saturation, or other important confounders; those with lowest systolic blood pressure less than 40 or greater than 200 mm Hg; those with oxygen saturation less than or equal to 10%; and those who were transferred out of the reporting trauma center.

The age cutoff of less than 10 years was used primarily to simplify the analysis. For patients younger than 10 years, hypotension is defined as a systolic blood pressure less than 70 mm Hg+(age×2).[43,45] Given that this represents only 6.8% of the EPIC population, it would markedly increase the complexity of the analysis without substantially adding to the size of the study cohort. Younger than 10 years also makes sense as an age cutoff because we were not yet examining treatment (the purpose of the main study). The related cutoffs (such as <15 years and having ventilation rates=20 breaths/min versus ≥15 years and 10 breaths/min) are not relevant to this analysis.

Interventions

This was an evaluation of the preimplementation EPIC cohort and entailed no interventions.

Outcome Measures

The main outcome was survival to hospital discharge.[41]

Data Collection and Processing

The Arizona State Trauma Registry contains extensive trauma center data on all patients transported to the designated Level I trauma centers in the state. From the registry, all cases meeting study criteria (described above) are entered into the EPIC database. Each participating EMS agency then receives a list of the EPIC patients who were cared for in their system. The cases are matched by incident date, name, and other patient identifiers. Either scanned copies (paper-based patient care records) or electronic data files (electronic patient care records) are then sent to the EPIC study data center. Database personnel then use a comprehensive data collection tool to abstract the data and enter them into the EPIC database. This provides an extensive, linked data set for study patients that includes both out-of-hospital and trauma center data. The entire process of case identification, EMS and trauma center linkage, accessing EMS patient care records, trauma center and EMS data entry, data quality management, and the structure of the EPIC database are described in detail in the study methods article.[41] More than 20,000 cases have been enrolled in EPIC, and more than 31,000 EMS patient care records have been entered into the database. There are more patient care records than cases because many patients are cared for by more than 1 EMS agency. The successful linkage rate is exceptionally high (for example, throughout the study, the rate of cases with missing EMS systolic blood pressure has been consistently <5%).

Blood pressure and oxygen saturation data were evaluated by including every documented out-of-hospital measurement for each patient. This could include data from 1 or several EMS agencies for a given patient. Patients who had at least 1 systolic blood pressure measurement less than 90 mm Hg or oxygen saturation less than 90% within their entire set of out-of-hospital measurements became, respectively, the group with "hypotension" or "hypoxia." The "combined hypotension and hypoxia" cohort included all patients who had at least 1 hypoxic measurement and at least 1 hypotensive measurement during the entire duration of their out-of-hospital care.

Primary Data Analysis

Continuous variables were summarized by median and interquartile range within each of the 2 subgroups of patients who survived or died and also within each of the 4 groups defined by hypotension and hypoxia status (neither hypotension nor hypoxia, hypotension only, hypoxia only, and both hypotension and hypoxia). Categorical variables were summarized by frequency and proportion (with 95% confidence intervals [CIs] when appropriate) with each of the subgroups described above. Association between mortality and hypotension and hypoxia status was examined by logistic regression, with or without adjustment, for important independent risk factors and potential confounders (age, sex, race, ethnicity, payment source, trauma type [blunt versus penetrating], head region injury score [*International Classification of Diseases, Ninth Revision* matched to the Abbreviated Injury Scale], Injury Severity Score, interfacility transfer, and treating trauma center). Age, sex, race, ethnicity, head region injury score, Injury Severity Score, and interfacility transfer were included a priori in the model (regardless of whether they were found to be significant), whereas payment source, trauma type, and treating trauma center were included because they were found to be significant covariates. The effect of age in the logistic regression was fitted nonparametrically with penalized thin plate regression splines through the generalized additive model,[46] with the smoothing parameter chosen to optimize the Akaike information criterion. The software environment R (version 3.2.3; The R Foundation, Vienna, Austria) was used for the analysis[47] and the R package mgcv (version 1.8-12; Simon Wood, Bristol, UK)[46,48] was used for the generalized additive model. *P* values were calculated from a Wald-type test with the Bayesian covariance matrix.[49] The fitted model was assessed by deviance residual plots, as well as the area under the receiver operating characteristic curve. The 95% CIs of the area under the receiver operating characteristic curve were obtained by the Delong method.[50] Collinearity was checked with variance inflation factors for the parametric terms and concurvity for the nonparametric term. Mixed-effect models were used to assess the correlation of subjects treated by the same trauma center, and multiple imputation procedures were used to evaluate the effect of missing covariates.

Main Results

There were 17,105 subjects in the preintervention group (from January 1, 2007, through March 31, 2014), of whom 13,151 (76.9%) met inclusion criteria (study cohort; Figure 1 shows the details of excluded cases). The median age was 45 years (interquartile range 26 to 64 years), 68.6% were men, and 8.2% died. Among patients in the study group, 11,545 (87.8%) had neither hypotension nor hypoxia, 604 (4.6%) had hypotension only, 790 (6.0%) had hypoxia only, and 212 (1.6%) had both hypotension and hypoxia. Figure 2 shows the raw, unadjusted cohort mortality by the existence of neither hypotension nor hypoxia, hypotension only, hypoxia only, and both hypotension and hypoxia. The mortality rates ranged from a low of 5.6% for patients with neither hypoxia nor hypotension to a high of 43.9% for those with both. Table 1 summarizes the demographics and patient characteristics by survival status. Table 2 summarizes the same variables by hypotension and hypoxia status. All factors associated with risk of death were also associated with the hypotension and hypoxia status. The specific data by treating trauma center are not shown in Tables 1 or 2. Because absolute anonymity is required by state regulations and the institutional review board (for all subjects, EMS agencies, and hospitals), we were not able to report specific trauma-center-related data, even generically, because trauma center patient volumes in Arizona are a matter of public record. Thus, presentation of these data could lead to certain hospital-specific information's being inferred or identified (eg, because of comparisons of the sizes of the 95% CIs). Although the data are not shown, because treating trauma center was a significant confounder, we adjusted for it in the model.

Logistic regression was used to examine the independent associations between hypotension and hypoxia status and mortality risk, controlling for potential confounders and significant risk measures (Table 1). The results of the regression analysis are shown in Table 3. Figure 3 shows the crude (unadjusted) and adjusted ORs (cORs and aORs, respectively) for death for the subcohorts defined by hypotension and hypoxia status, using the patients with neither hypotension nor hypoxia as the reference. Compared with this group, the cohort with both hypotension and hypoxia had a cOR for death of 13.2 (95% CI 10.0 to 17.5) and an aOR of 6.1 (95% CI 4.2 to 8.9). These represent at least a doubling of the corresponding ORs for either hypotension (cOR 4.4 [95% CI 3.6 to 5.5]; aOR 2.5 [95% CI 1.9 to 3.3]) or hypoxia (cOR 6.6 [95% CI 5.6-7.9]; aOR 3.0 [95% CI 2.4-3.8]) alone (Figure 3). Testing for an interaction term between hypotension and hypoxia was not significant in the logistic regression model (P=.43), indicating that the effects of hypotension and hypoxia were additive on the scale of log odds.

Deviance residual plots did not indicate any deviation from the model assumptions. The only continuous

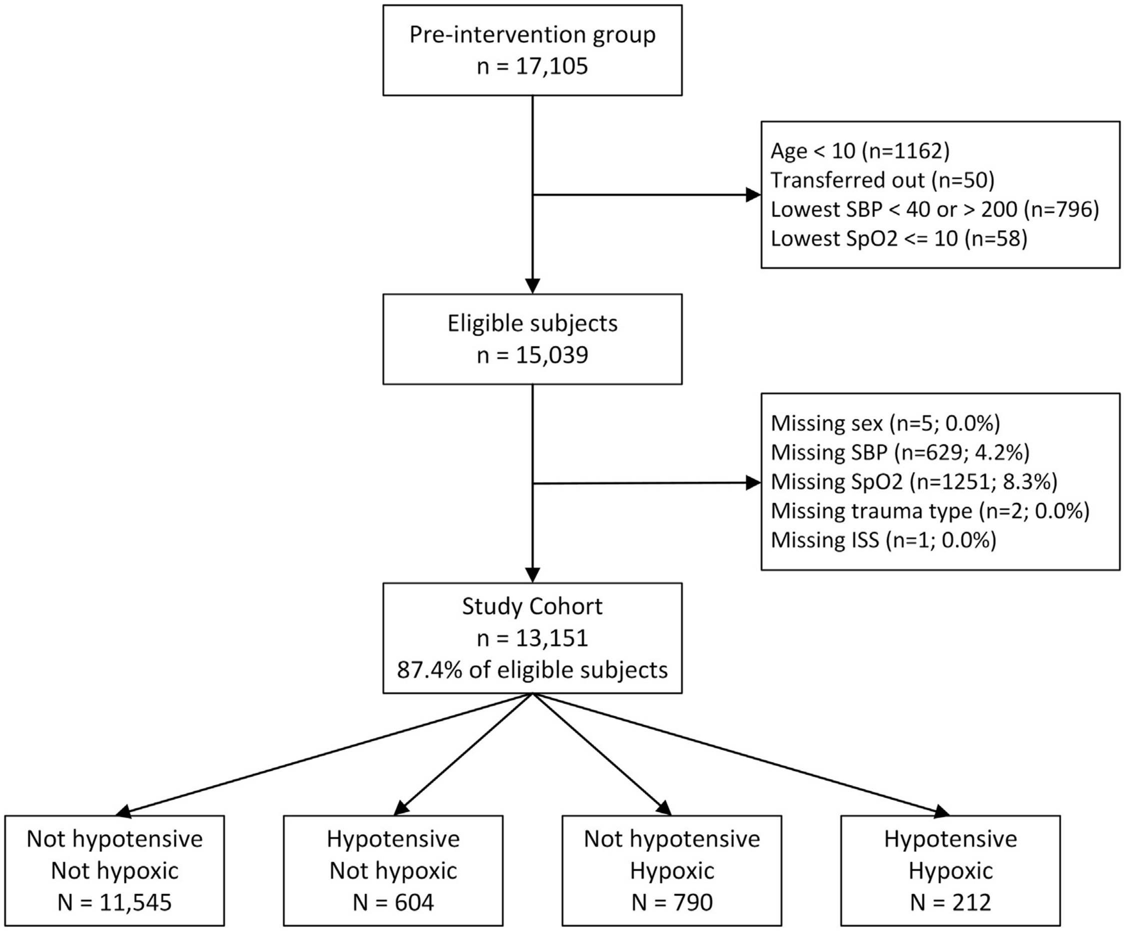

Figure 1. Details of study population inclusion and exclusion. *SBP*, Systolic blood pressure; *Sp02*, % oxygen saturation; *Trauma type*, Blunt or penetrating injury; *ISS*, Injury severity score.

covariate in the model, age, was fitted nonparametrically. The area under the receiver operating characteristic curve was estimated to be 0.938 (95% CI 0.932 to 0.945), indicating a high discriminative ability of the model. In addition, no multicollinearity in the covariates was detected.

As a sensitivity analysis, random trauma center effects were added to the logistic regression model to explore the potential correlation among subjects treated by the same trauma center. There was minimal difference in the results: the largest change in the estimated ORs was 1.5% for the 3 groups of hypotension only, hypoxia only, and both conditions compared with the referent group of no hypotension or hypoxia. Also, the largest change in the standard error estimates for the 3 corresponding regression coefficients was 0.2%. As another sensitivity analysis, we applied the multiple imputation procedure to explore the effects of missing data and observed only small changes. The largest change in the estimated ORs was 10.5%, and the lower limit of the 95% CI for each OR remained above 1.

LIMITATIONS

This study had limitations. First, the design was observational, and we were unable to establish cause-and-effect relationships related to treatment. Thus, the results cannot be used to determine whether the treatment of hypotension or hypoxia is effective at reducing mortality (this is part of the primary hypothesis of the main, parent study). The current analysis simply allowed us to identify associations between hypotension, hypoxia, and outcome.

Second, there are some missing data. However, for an out-of-hospital study, the rates for missing data were very low[51] (Figure 1). In addition, the use of multiple imputation resulted in minimal differences in the analysis compared with that of the actual data set.

Third, the database contains only those measurements of blood pressure and oxygen saturation that were documented by EMS personnel, and there is no way to independently verify the accuracy of the measurements. Thus, we could not know for certain that all hypotensive or hypoxic patients were identified, and hence there could be

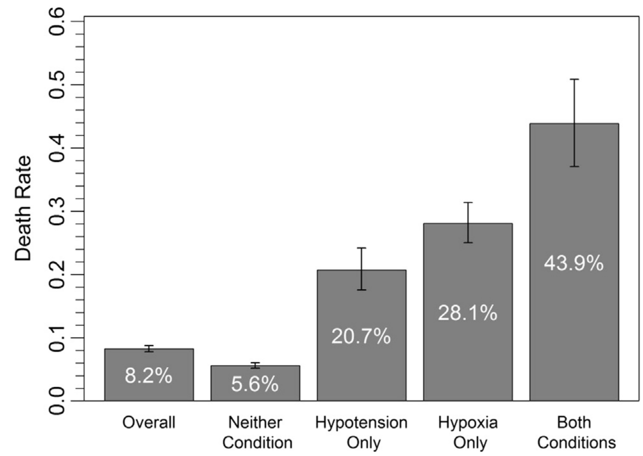

Figure 2. Crude mortality rate by hypotension and hypoxia status. Error bars represent 95% CIs.

some misclassification of patients among the 4 groups (hypotension, hypoxia, neither, and both). However, these issues related to data documentation and accuracy are true of essentially all EMS studies. One strength of EPIC is that the data are abstracted directly, consistently, and comprehensively from the patient care records. This level of scrutiny and consistency of data collection is rare in out-of-hospital research.[51]

Fourth, there could have been some "leakage" in practice changes during the preimplementation timeframe because the guidelines have been available for more than a decade. However, we believe it is unlikely that this is a factor. We conducted a prestudy evaluation of traumatic brain injury protocol changes and implementation before the EPIC project implementation to identify whether partial or full implementation was occurring in Arizona. Information from 51 agencies (responsible for EMS response to 4.8 million residents [75% of the population]) was gathered related to traumatic brain injury EMS care. Only half had protocols specifying appropriate ranges for oxygen saturation or blood pressure, and only one third had any specific treatment protocols. Even among agencies with traumatic brain injury protocols, the monitoring and treatment recommendations were highly variable, and no agency had implemented or was planning to implement the official traumatic brain injury guidelines.

Fifth, the definition for hypotension and hypoxia required only that there be at least a single low reading (<90 mm Hg/<90% saturation). Thus, the absence of time-sequence analysis means that we treated patients who may have had multiple low readings the same as those who had only a single abnormal measurement.

Sixth, we did not evaluate whether interventions were performed in an attempt to treat blood pressure or oxygenation.

Table 1. Patient and injury characteristics by survival status.*

Characteristics	All, 13,151	Alive, 12,067	Dead, 1,084
Age, y	45 (26–64)	44 (25–64)	50 (28–72)
Male patient			
No	4,135 (31.4)	3,808 (31.6)	327 (30.2)
Yes	9,016 (68.6)	8,259 (68.4)	757 (69.8)
Race			
Black	386 (2.9)	358 (3)	28 (2.6)
American Indian/ Alaska Native	1,087 (8.3)	1,007 (8.3)	80 (7.4)
Asian	129 (1)	118 (1)	11 (1)
White	9,868 (75)	9,047 (75)	821 (75.7)
Other	1,570 (11.9)	1,444 (12)	126 (11.6)
Unknown	111 (0.8)	93 (0.8)	18 (1.7)
Hispanic			
No	10,083 (76.7)	9,264 (76.8)	819 (75.6)
Yes	2,743 (20.9)	2,528 (20.9)	215 (19.8)
Unknown	325 (2.5)	275 (2.3)	50 (4.6)
Payer			
Private	4,292 (32.6)	4,037 (3,3.5)	255 (23.5)
AHCCCS/Medicaid	3,415 (26)	3,165 (26.2)	250 (23.1)
Medicare	2,846 (21.6)	2,544 (21.1)	302 (27.9)
Self-pay	1,698 (12.9)	1,515 (12.6)	183 (16.9)
Other	633 (4.8)	581 (4.8)	52 (4.8)
Unknown	267 (2)	225 (1.9)	42 (3.9)
Trauma type			
Blunt	12,665 (96.3)	11,782 (97.6)	883 (81.5)
Penetrating	486 (3.7)	285 (2.4)	201 (18.5)
Head ISS (*ICD-9*)			
1–3	7,182 (54.6)	7,104 (58.9)	78 (7.2)
4	3,874 (29.5)	3,747 (31.1)	127 (11.7)
5–6	1,962 (14.9)	1,099 (9.1)	863 (79.6)
Unknown	133 (1)	117 (1)	16 (1.5)
ISS (*ICD-9*)			
1–14	5,372 (40.8)	5,349 (44.3)	23 (2.1)
16–24	4,381 (33.3)	4,299 (35.6)	82 (7.6)
≥25	3,398 (25.8)	2,419 (20)	979 (90.3)
Hypotension			
No	12,335 (93.8)	11,469 (95)	866 (79.9)
Yes	816 (6.2)	598 (5)	218 (20.1)
Hypoxia			
No	12,149 (92.4)	11,380 (94.3)	769 (70.9)
Yes	1,002 (7.6)	687 (5.7)	315 (29.1)
Hypotension and hypoxia			
No	12,939 (98.4)	11,948 (99)	991 (91.4)
Yes	212 (1.6)	119 (1)	93 (8.6)
Interfacility transfer			
No	8,890 (67.6)	8,051 (66.7)	839 (77.4)
Yes	4,176 (31.8)	3,932 (32.6)	244 (22.5)
Unknown	85 (0.6)	84 (0.7)	1 (0.1)

AHCCCS, Arizona Health Care Cost Containment System; *ICD-9*, *International Classification of Diseases, Ninth Revision*.
*Data are presented as median (interquartile range) for continuous variables and No. (%) for categorical variables.

DISCUSSION

The detrimental effects of hypotension and hypoxia during the early care of patients with major traumatic brain injury have been well established.[6,7,10-40] However, there is almost nothing known about the effect of these factors

Table 2. Patient and injury characteristics by hypotension and hypoxia status.*

Characteristics	All, 13,151	No Hypotension or Hypoxia, 11,545	Hypotension Only, 604	Hypoxia Only, 790	Both Conditions, 212
Dead					
No	12,067 (91.8)	10,901 (94.4)	479 (79.3)	568 (71.9)	119 (56.1)
Yes	1,084 (8.2)	644 (5.6)	125 (20.7)	222 (28.1)	93 (43.9)
Age, y	45 (26–64)	45 (26–65)	44 (25–62)	48 (28.2–66)	32.5 (21–50)
Male patient					
No	4,135 (31.4)	3,633 (31.5)	202 (33.4)	236 (29.9)	64 (30.2)
Yes	9,016 (68.6)	7,912 (68.5)	402 (66.6)	554 (70.1)	148 (69.8)
Race					
Black	386 (2.9)	341 (3)	11 (1.8)	31 (3.9)	3 (1.4)
American Indian/Alaska Native	1,087 (8.3)	950 (8.2)	59 (9.8)	52 (6.6)	26 (12.3)
Asian	129 (1)	114 (1)	6 (1)	7 (0.9)	2 (0.9)
White	9,868 (75)	8,646 (74.9)	453 (75)	610 (77.2)	159 (75)
Other	1,570 (11.9)	1,405 (12.2)	69 (11.4)	78 (9.9)	18 (8.5)
Unknown	111 (0.8)	89 (0.8)	6 (1)	12 (1.5)	4 (1.9)
Hispanic					
No	10,083 (76.7)	8,837 (76.5)	456 (75.5)	625 (79.1)	165 (77.8)
Yes	2,743 (20.9)	2,430 (21)	124 (20.5)	145 (18.4)	44 (20.8)
Unknown	325 (2.5)	278 (2.4)	24 (4)	20 (2.5)	3 (1.4)
Payer					
Private	4,292 (32.6)	3,782 (32.8)	190 (31.5)	243 (30.8)	77 (36.3)
AHCCCS/Medicaid	3,415 (26)	2,958 (25.6)	180 (29.8)	208 (26.3)	69 (32.5)
Medicare	2,846 (21.6)	2,537 (22)	113 (18.7)	177 (22.4)	19 (9)
Self-pay	1,698 (12.9)	1,487 (12.9)	82 (13.6)	101 (12.8)	28 (13.2)
Other	633 (4.8)	552 (4.8)	22 (3.6)	44 (5.6)	15 (7.1)
Unknown	267 (2)	229 (2)	17 (2.8)	17 (2.2)	4 (1.9)
Trauma type					
Blunt	12,665 (96.3)	11,213 (97.1)	541 (89.6)	720 (91.1)	191 (90.1)
Penetrating	486 (3.7)	332 (2.9)	63 (10.4)	70 (8.9)	21 (9.9)
Head ISS (*ICD-9*)					
1–3	7,182 (54.6)	6,573 (56.9)	284 (47)	274 (34.7)	51 (24.1)
4	3,874 (29.5)	3,476 (30.1)	139 (23)	208 (26.3)	51 (24.1)
5–6	1,962 (14.9)	1,391 (12)	165 (27.3)	299 (37.8)	107 (50.5)
Unknown	133 (1)	105 (0.9)	16 (2.6)	9 (1.1)	3 (1.4)
ISS (*ICD-9*)					
1–14	5,372 (40.8)	5,090 (44.1)	137 (22.7)	132 (16.7)	13 (6.1)
16–24	4,381 (33.3)	3,986 (34.5)	168 (27.8)	198 (25.1)	29 (13.7)
≥25	3,398 (25.8)	2,469 (21.4)	299 (49.5)	460 (58.2)	170 (80.2)
Interfacility transfer					
No	8,890 (67.6)	7,662 (66.4)	410 (67.9)	641 (81.1)	177 (83.5)
Yes	4,176 (31.8)	3,808 (33)	191 (31.6)	144 (18.2)	33 (15.6)
Unknown	85 (0.6)	75 (0.6)	3 (0.5)	5 (0.6)	2 (0.9)

*Data are presented as median (interquartile range) for continuous variables and No. (%) for categorical variables.

when they both occur in patients before arrival at the hospital because the hypotension and hypoxia combination is an unusual occurrence, and studying this question requires the analysis of large numbers of patients with traumatic brain injury and linked out-of-hospital data. Although there are large trauma-center-based databases that can be queried for ED and inhospital information, these have limited or no out-of-hospital data.[22,38,39,52-57] Because the EPIC database has extensive out-of-hospital data and is very large, it provides the opportunity to ask EMS-related questions in small patient subgroups.[41]

We have been able to find only 2 previous studies that reported specifically on the combined effect of out-of-hospital hypotension and hypoxia on outcome.[6,16] In the investigation of 49 patients by Stocchetti et al,[6] 27 had an oxygen saturation less than 90% on the scene and 12 had a systolic blood pressure less than 100 mm Hg (their definition for hypotension). Unfortunately, the study does not report the number of patients who had both hypotension and hypoxia. However, at least some of the patients must have had both because the authors concluded that "outcome was significantly worse in cases of hypotension, desaturation, or both." They gave no information about the relative rates of mortality among the cohorts. Chi et al[16] studied 150 patients with severe traumatic brain injury who were transported by helicopter.

Table 3. Logistic regression model for death.

Covariates*	OR	95% CI
Hypotension and hypoxia status		
Neither hypotension nor Hypoxia	Reference	NA
Hypotension only	2.49	(1.87–3.32)
Hypoxia only	3.00	(2.37–3.78)
Both conditions	6.10	(4.20–8.86)
Male patient		
No	Reference	NA
Yes	0.98	(0.82–1.17)
Race		
Black	Reference	NA
American Indian/Alaska Native	1.82	(1.00–3.32)
Asian	1.31	(0.51–3.35)
White	1.72	(1.02–2.91)
Other	1.94	(1.06–3.56)
Unknown	2.23	(0.89–5.60)
Hispanic		
No	Reference	NA
Yes	0.73	(0.56–0.94)
Unknown	1.78	(1.08–2.93)
Payer		
Private	Reference	NA
AHCCCS/Medicaid	1.08	(0.85–1.37)
Medicare	1.29	(0.97–1.72)
Self-pay	2.49	(1.89–3.29)
Other	1.18	(0.79–1.76)
Unknown	2.75	(1.62–4.66)
Trauma type		
Blunt	Reference	NA
Penetrating	4.73	(3.55–6.31)
Head ISS (*ICD-9*)		
1–3	Reference	NA
4	1.34	(0.96–1.87)
5–6	12.35	(9.05–16.85)
Unknown	5.76	(2.97–11.16)
ISS (*ICD-9*)		
1–14	Reference	NA
16–24	3.08	(1.81–5.25)
≥25	12.93	(7.82–21.38)
Interfacility transfer		
No	Reference	NA
Yes	0.62	(0.50–0.77)
Unknown	0.25	(0.03–2.02)

NA, Not applicable

*Age was fitted nonparametrically and trauma center was also included (details not shown).

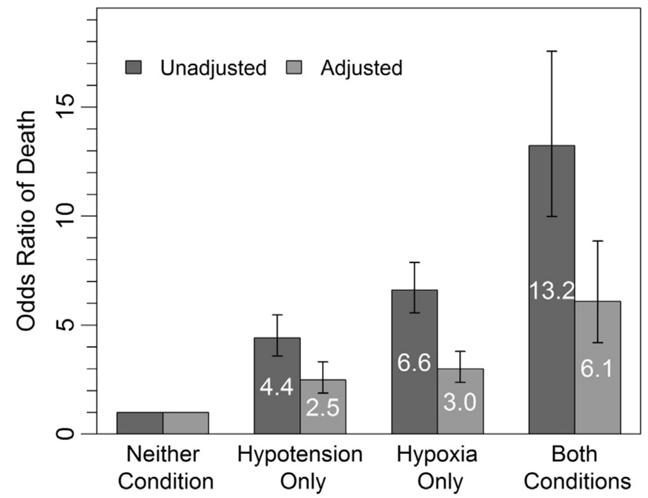

Figure 3. ORs for mortality by hypotension and hypoxia status. Reference group was the cohort with neither hypotension nor hypoxia. Error bars represent 95% CIs.

Fourteen patients had only hypotension, 37 had only hypoxia (oxygen saturation <92%), and 6 had both. Mortality for cases with neither hypotension nor hypoxia was 20% compared with 8% for hypotension-only patients, 37% for hypoxia-only patients, and 24% for those with both. These wide-ranging (and even paradoxic) results were likely due to the very small numbers, and thus this study could make no conclusions about the effect of the combination of hypotension and hypoxia on outcome. Both Fearnside et al[11] and Stassen and Welzel[40] also obtained out-of-hospital clinical data in their evaluations of severe traumatic brain injury. However, they made no comment about the relative influence of the combination of hypotension and hypoxia. In the classic study by Chesnut et al[10] on secondary brain injury, the authors attempted to assess the effect of physiologic insults in the EMS setting. Unfortunately, the out-of-hospital data were compromised by the fact that they did not actually obtain measurements of oxygenation. Rather, out-of-hospital "hypoxia" was merely identified as the presence of cyanosis or apnea when this was documented by EMS personnel.[10]

The studies that report inhospital data from the ED or the ICU give slightly more information about the combination of hypotension and hypoxia, but the findings have been variable and inconclusive. Manley et al[26] studied 107 patients with traumatic brain injury, using physiologic measurements in the ED and inpatient settings. Among the 14 patients who had both hypotension and hypoxia, they found that "…the combination of hypotension and hypoxia…[was] not additive." Unfortunately, with such small numbers, the statistical power behind such a conclusion was limited. Pigula et al[22] evaluated 451 children with severe traumatic brain injury in the National Pediatric Trauma Registry, using inhospital physiologic parameters. Mortality was 61% among children with hypotension only, 21% among those with hypoxia only, and 85% among the small number (20) who had both hypotension and hypoxia. They concluded that "[i]f both hypotension and hypoxia were found together, mortality was only slightly increased over those children with hypotension alone (p=0.056)." Kohi et al[35] found that the combination of hypotension and hypoxia in patients with severe traumatic brain injury was universally fatal.

However, there were only 6 patients in this cohort and all of the measurements of blood pressure and oxygenation were obtained in the ICU. Thus, this study was reflective of patients with "late" hypotension and hypoxia, but provided no information about physiologic insults occurring earlier in the course and, perhaps, before irreversible injury had occurred. In a meta-analysis, McHugh et al[39] reported on 465 patients with combined hypotension and hypoxia and found a slight increase in mortality among those who had both (54.6%) compared with those with hypotension only (48.5%). However, they used a mixture of ED admission data and an unspecified amount of EMS data. There was also significant heterogeneity among the investigations that were included in the final meta-analysis (eg, differing definitions of hypotension). Furthermore, some of the studies had missing data rates exceeding 30%, creating substantial risks for selection bias.

In the current study of 13,151 patients with major traumatic brain injury, 604 (4.6%) experienced hypotension without hypoxia in the field, 790 (6.0%) had hypoxia without hypotension, and 212 (1.6%) experienced both. We believe this is the largest evaluation of out-of-hospital hypotension and hypoxia yet conducted in patients with traumatic brain injury, and this allowed us to examine detailed interactions that the previous studies could not (the largest report in the extant EMS literature had no more than 12 patients with combined hypotension/hypoxia[6,16]). In the EPIC population, the combination of hypotension and hypoxia is associated with a significantly increased likelihood of dying (cOR 13.2; aOR 6.1) compared with the cohorts who have only hypotension (cOR 4.4; aOR 2.5) or hypoxia (cOR 6.6; aOR 3.0) (Figure 3). This means that the combination is associated with more than a doubling of the risk of death compared with having either alone. The clinical implications of this are further supported by the fact that there is no interaction on the log odds scale. In other words, hypoxia does not modify the effect of hypotension and, conversely, hypotension does not modify the effect of hypoxia. Thus, in patients who experience both hypotension and hypoxia, the combination of these physiologic insults has a profound influence on outcome, with an additive influence on the log odds of death.

As stated in the study hypothesis, the primary focus of this evaluation was to identify whether the hypotension and hypoxia combination adds additional risk above that of either alone. However, this analysis also revealed another important finding: the associations between the secondary physiologic insults and mortality are significantly stronger than have been generally reported. Although there is variation, both the crude and adjusted odds of death for patients experiencing hypoxia alone have typically been approximately 2.[7,10-13,17,20] However, in the EPIC population, the cOR is 6.6 and the aOR is 3.0 (Figure 3). Furthermore, the odds of mortality in patients with hypotension only have generally been in the range of 1.3 to 2.[10,11,14,15,18-38] In contrast, we identified significantly higher odds of death in hypotensive patients (cOR 4.4; aOR 2.5) (Figure 3). There are several potential reasons for this. First, perhaps the previous studies were simply too small to identify an accurate influence of these factors. Second, many of the studies that depended on obtaining data from trauma center databases had access to only 1 or 2 out-of-hospital vital signs measurements. Thus, it is unclear whether hypotension or hypoxia was reliably identified because in previous studies it was unclear whether the EMS measurements recorded in the database were the first, last, highest, or lowest for each patient. By comparison, in the EPIC database, there is no limit to the number of vital signs measurements that can be recorded. For example, there are cases in the EPIC database that have more than 30 recorded out-of-hospital blood pressure measurements. Finally, most of the previous studies used blood pressure and oxygen saturation data obtained after arrival at the hospital. Thus, it is possible that the EPIC study, by specifically evaluating the out-of-hospital treatment interval, has identified patients who become hypotensive or hypoxic earlier in their course. In this case, the effects of these insults may be magnified by occurring earlier and perhaps lasting longer, and thus may affect the brain to a greater extent.

The design of the current study does not allow confident statements about the effect of EMS treatment aimed at preventing or reversing hypotension or hypoxia. However, it does bring up some interesting questions. Because the combination appears to be so detrimental, this raises the specter that if either hypoxia or hypotension can be prevented or treated, there may be the potential to significantly improve survival even if the other parameter is not improved. For example, the prevention of hypoxia by management of oxygenation may decrease a given patient's risk of death from a highly fatal aOR of 6.1 (if he or she experienced both hypotension and hypoxia) to a far more "favorable" aOR of 2.5 (if he or she experienced only hypotension). The same might be relevant in the prevention or treatment of hypotension in a patient who has hypoxia that cannot be improved.

In summary, this statewide study evaluating out-of-hospital hypotension and hypoxia in victims of major traumatic brain injury found a greater risk for death from either of these insults than has generally been reported in the previous literature. Furthermore, the combination of hypotension and hypoxia occurring before arrival at the hospital is associated with a significant increase in both the crude and adjusted odds of death compared with either physiologic insult alone. In fact, the effects are additive on the log odds of death. These findings seem supportive of the emphasis on aggressive prevention and treatment of hypotension and hypoxia reflected in the current EMS traumatic brain injury treatment guidelines but clearly reveal the need for further study to determine their influence on outcome.[42-45]

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