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Correlation between prehospital and in-hospital hypotension and outcomes after traumatic brain injury

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ABSTRACT

Background and objective: Hypotension has a powerful effect on patient outcome after traumatic brain injury (TBI). The relative impact of hypotension occurring in the field versus during early hospital resuscitation is unknown. We evaluated the association between hypotension and mortality and non-mortality outcomes in four cohorts defined by where the hypotension occurred [neither prehospital nor hospital, prehospital only, hospital only, both prehospital and hospital].
Methods: Subjects ≥10 years with major TBI were included. Standard statistics were used for unadjusted analyses. We used logistic regression, controlling for significant confounders, to determine the adjusted odds (aOR) for outcomes in each of the three cohorts.
Results: Included were 12,582 subjects (69.8% male; median age 44 (IQR 26–61). Mortality by hypotension status: No hypotension: 9.2% (95%CI: 8.7–9.8%); EMS hypotension only: 27.8% (24.6–31.2%); hospital hypotension only: 45.6% (39.1–52.1%); combined EMS/hospital hypotension 57.6% (50.0–65.0%); ($p < 0.0001$). The aOR for death reflected the same progression: 1.0 (reference-no hypotension), 1.8 (1.39–2.33), 2.61 (1.73–3.94), and 4.36 (2.78–6.84), respectively. The proportion of subjects having hospital hypotension was 19.0% (16.5–21.7%) in those with EMS hypotension compared to 2.0% (1.8–2.3%) for those without ($p < 0.0001$). Additionally, the proportion of patients with TC hypotension was increased even with EMS "near hypotension" up to an SBP of 120 mmHg [(aOR 3.78 (2.97, 4.82)].
Conclusion: While patients with hypotension in the field or on arrival at the trauma center had markedly increased risk of death compared to those with no hypotension, those with prehospital hypotension that was not resolved before hospital arrival had, by far, the highest odds of death. Furthermore, TBI patients who had prehospital hypotension were five times more likely to arrive hypotensive at the trauma center than those who did not. Finally, even "near-hypotension" in the field was strongly and independently associated the risk of a hypotensive hospital arrival (<90 mmHg). These findings are supportive of the prehospital guidelines that recommend aggressive prevention and treatment of hypotension in major TBI.

1. Introduction

The burden of traumatic brain injury (TBI) is enormous, affecting an estimated 69 million individuals throughout the world each year, with an estimated 11% of those sustaining severe TBI [1]. Annually in the United States, TBI leads to 2.2 million emergency department (ED) visits, 280,000 hospitalizations, 52,000 deaths, and over $60 billion in economic costs [2,3]. While improving outcomes has been difficult [4], early management may help mitigate secondary brain injury [4-8] and this has led to the promulgation of evidence based TBI guidelines for prehospital care [5-7,9,10]. Prior to the recently reported results of the Excellence in Prehospital Injury Care (EPIC) study, no large, controlled

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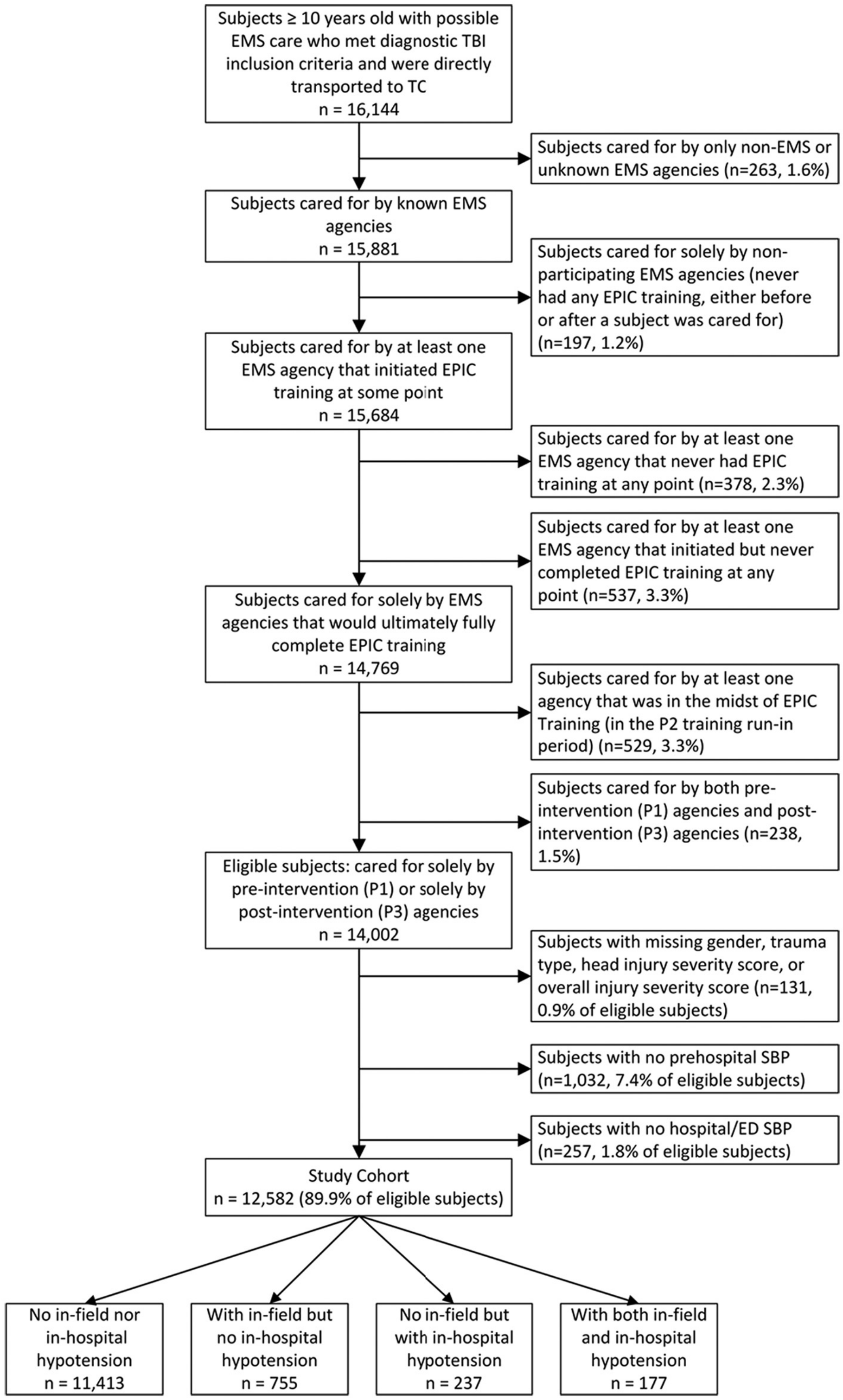

Fig. 1. Case inclusion/exclusion flow chart.
EMS indicates emergency medical services; SBP, systolic blood pressure; EPIC, Excellence In Prehospital Injury Care study; P1, study phase 1 (pre-implementation phase); P2, study phase 2 (training run-in phase; for each EMS agency, time from initiation to completion of training); P3, study phase 3 (postimplementation phase); TBI, traumatic brain injury.

evaluation of the guidelines had been published. EPIC demonstrated that implementation of the EMS guidelines was associated with significant improvement in adjusted odds of survival to hospital discharge among patients with severe TBI [11,12]. A primary component of these guidelines is the immediate prevention and treatment of hypotension.

Hypotension in the setting of TBI causes secondary brain injury and has been associated with poorer outcomes when occurring during the prehospital and early trauma center care [11,13-41]. Recent research has also established the dose-dependent effects of hypotension on TBI mortality [42]. Little is known about the association between prehospital hypotension and hypotension occurring during initial resuscitation at the trauma center. We are unaware of any reports assessing the relative impact on outcome when hypotension occurs in the field versus after trauma center arrival.

2. Methods

2.1. Setting

This study is a sub-analysis of data collected as part of the Excellence in Prehospital Injury Care (EPIC) Study. EPIC was a statewide study using a controlled, before-after, multisystem, intention-to-treat design. The details of the methodology have been previously published [11,42-45]. The main study [11,12] evaluated the association of implementing the EMS TBI guidelines on outcome [10,47,48]. EPIC included any patient meeting the following criteria: treated by a participating EMS agency AND transported to a level I trauma center AND had hospital diagnosis(es) consistent with TBI (isolated or multisystem) AND met at least one of the following definitions for major TBI: a) CDC Barell Matrix-Type 1 [49,50], b) Abbreviated Injury Scale-Head ≥3. As part of the study, detailed prehospital data were collected and linked to trauma center patient care information and outcomes (Jan 1, 2007-June 30, 2015).

The complete EPIC dataset was used for this secondary analysis. The main EPIC study was funded by the National Institutes of Health and is registered at ClinicalTrials.gov (NCT01339702). This secondary analysis was funded by the Department of Defense (DoD-FOA: W81XWH-17-R-BAA1).

2.2. Selection of participants

Subjects included in this secondary analysis were those in both the pre-implementation and post-implementation cohorts. Exclusions: Age < 10 years; missing data [age, sex, trauma type, International Classification of Diseases (ICD, version 9)-head severity, injury severity score (ISS), in-field systolic blood pressure (SBP), in-hospital SBP] patients who were cared for by EMS agencies who had never received or did not complete EPIC training at any point. Patients <10 years of age were excluded to simplify the analysis since the definition for hypotension changes with each year between 0 and 9 years.

2.3. Outcome measures

The primary outcome was mortality (death in hospital). Secondary outcomes included total hospital days, ICU days, and ventilator days. Deaths that might have occurred after hospital discharge were not known and were not included in the analysis.

2.4. Data collection and processing

All EMS data were collected and abstracted by the EPIC data team using a structured process to insure consistent data entry across agencies. These were linked to trauma center data (with more than a 98% linkage rate). Details about the EPIC database development and structure have previously been described in detail [42,43,45].

2.5. Primary data analysis

Demographics, injury characteristics, intervention (guideline implementation), prehospital and initial emergency department (ED)/trauma center (TC) vital measures, and clinical outcome measures were summarized using median and interquartile range (IQR) for continuous variables and frequency and proportion for categorical variables. The correlation of prehospital hypotension and hypotension at the initial ED/TC assessment was evaluated by comparing the ED/TC hypotension rate between subjects with and without EMS hypotension using the Chi-squared test. Clopper-Pearson confidence interval (CI) for any proportion estimate like the ED/TC hypotension proportion and death proportion was obtained for the full cohort and/or various subgroups by EMS hypotension status.

To study the association between outcome measures and prehospital and ED/TC hypotension, four groups of hypotension status were defined: 1) those with neither prehospital nor initial trauma center hypotension, 2) those with prehospital hypotension but no initial ED/TC hypotension, 3) those without prehospital hypotension but with initial ED/TC hypotension, and 4) those with both prehospital and initial ED/TC hypotension. Unadjusted analysis associating death and hypotension status was performed using Chi-squared test and unadjusted logistic regression. The risk-adjusted associations between death and in-field/trauma center hypotension status was evaluated by a logistic regression model with death as the response and with covariates including prehospital and trauma center hypotension status and other important risk factors and potential confounders [age, sex, race, ethnicity, payment source, trauma type (blunt or penetrating), head region severity score (ICD-9) matched to Abbreviated Injury Scale), ISS, multisystem TBI (any body region other than head with a severity score of at least 3), intervention of guideline implementation, prehospital hypoxia, prehospital CPR, and treating trauma center]. The effects of continuous variable (age) in the regression models was fitted non-parametrically using penalized thin plate regression splines through the generalized additive model [51,52].

Unadjusted and adjusted analyses were performed to associate non-mortality outcomes with hypotension status on the subgroup of subjects discharged alive from the hospital. Logistic regression was used for the binary outcome of discharge to skilled nursing facility or inpatient rehabilitation, negative binomial regression used for count outcomes (total hospital days, ICU days, and ventilator days), and linear regression for the continuous variable of log-transformed total hospital charges (adjusted for inflation to dollar of June 2015 based on consumer price index of inpatient hospital services in U.S. city average, all urban consumers, not seasonally adjusted). Risk-adjusted association between each of these outcome measures and the hypotension pattern was examined by the appropriate regression model with adjustment for important risk factors and potential confounders shown above for the mortality outcome. The software environment R (version 3.6.3) with R package mgcv (version 1.8–31) was used for the analysis [52-54]. All tests were two-sided with significance level 0.05.

The project and the public reporting of de-identified data were approved by the Institutional Review Board for both the a.

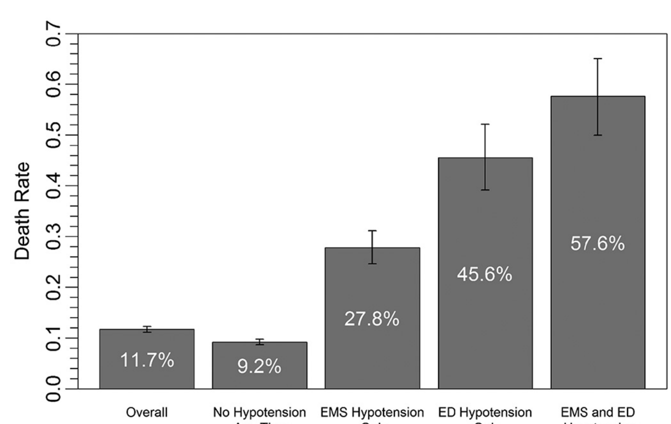

Fig. 2. Unadjusted mortality by hypotension group.
EMS: emergency medical services.
ED: Emergency Department.
Error bars represent 95% confidence intervals.

Table 1
Patient characteristics by hypotension status.

	No hypotension*	EMS hypotension only*	ED hypotension only*	EMS + ED hypotension*
	11,413	755	237	177
Intervention group				
Pre-implementation	8117 (71.1%)	476 (63%)	155 (65.4%)	112 (63.3%)
Post-implementation	3296 (28.9%)	279 (37%)	82 (34.6%)	65 (36.7%)
Age, y	44 (26, 62)	39 (24, 56)	44 (28, 62)	39 (27, 57)
Male patient				
No	3434 (30.1%)	246 (32.6%)	71 (30%)	48 (27.1%)
Yes	7979 (69.9%)	509 (67.4%)	166 (70%)	129 (72.9%)
Race				
Black	417 (3.7%)	23 (3%)	6 (2.5%)	7 (4%)
Asian	143 (1.3%)	10 (1.3%)	1 (0.4%)	2 (1.1%)
American Indian/Alaska Nat.	575 (5%)	36 (4.8%)	7 (3%)	18 (10.2%)
White	8832 (77.4%)	580 (76.8%)	184 (77.6%)	132 (74.6%)
Other	1329 (11.6%)	89 (11.8%)	37 (15.6%)	11 (6.2%)
Unknown	117 (1%)	17 (2.3%)	2 (0.8%)	7 (4%)
Hispanic				
No	8678 (76%)	559 (74%)	173 (73%)	136 (76.8%)
Yes	2466 (21.6%)	168 (22.3%)	57 (24.1%)	34 (19.2%)
Unknown	269 (2.4%)	28 (3.7%)	7 (3%)	7 (4%)
Payer				
Private	4152 (36.4%)	266 (35.2%)	85 (35.9%)	58 (32.8%)
AHCCCS/	2772 (24.3%)	211 (27.9%)	52 (21.9%)	47 (26.6%)
Medicaid				
Medicare	2128 (18.6%)	105 (13.9%)	39 (16.5%)	21 (11.9%)
Self-Pay	1759 (15.4%)	121 (16%)	42 (17.7%)	37 (20.9%)
Other	443 (3.9%)	37 (4.9%)	15 (6.3%)	10 (5.6%)
Unknown	159 (1.4%)	15 (2%)	4 (1.7%)	4 (2.3%)
Trauma type				
Blunt	10,974 (96.2%)	667 (88.3%)	189 (79.7%)	139 (78.5%)
Penetrating	439 (3.8%)	88 (11.7%)	48 (20.3%)	38 (21.5%)
Head injury severity score (ICD&)				
1 to 3	5908 (51.8%)	276 (36.6%)	64 (27%)	38 (21.5%)
4	3510 (30.8%)	200 (26.5%)	49 (20.7%)	35 (19.8%)
5 to 6	1995 (17.5%)	279 (37%)	124 (52.3%)	104 (58.8%)
Injury severity score (ICD)				
1 to 14	4264 (37.4%)	121 (16%)	25 (10.5%)	5 (2.8%)
16 to 24	3757 (32.9%)	175 (23.2%)	38 (16%)	14 (7.9%)
25+	3392 (29.7%)	459 (60.8%)	174 (73.4%)	158 (89.3%)
Body region				
Isolated TBI	8494 (74.4%)	351 (46.5%)	105 (44.3%)	55 (31.1%)
Multisystem TBI	2919 (25.6%)	404 (53.5%)	132 (55.7%)	122 (68.9%)
CPR				
No	11,325 (99.2%)	716 (94.8%)	215 (90.7%)	161 (91%)
Yes	88 (0.8%)	39 (5.2%)	22 (9.3%)	16 (9%)
Airway management				
No PPV	9364 (82%)	382 (50.6%)	94 (39.7%)	39 (22%)
BVM	534 (4.7%)	54 (7.2%)	23 (9.7%)	14 (7.9%)
Intubation	1515 (13.3%)	319 (42.3%)	120 (50.6%)	124 (70.1%)
Number of EMS IV fluid boluses				
	0 (0,0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Any EMS IV fluid bolus				
No	10,765 (94.3%)	593 (78.5%)	218 (92%)	149 (84.2%)
Yes	648 (5.7%)	162 (21.5%)	19 (8%)	28 (15.8%)
Total EMS isotonic IV fluid volume (ml)				
	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Total EMS isotonic IV fluid volume category				
0–249 ml	10,952 (96%)	624 (82.6%)	220 (92.8%)	156 (88.1%)
250–499 ml	221 (1.9%)	50 (6.6%)	9 (3.8%)	6 (3.4%)
500–749 ml	158 (1.4%)	48 (6.4%)	6 (2.5%)	8 (4.5%)
750–999 ml	27 (0.2%)	8 (1.1%)	0 (0%)	2 (1.1%)
1000 ml or above	55 (0.5%)	25 (3.3%)	2 (0.8%)	5 (2.8%)
Min EMS SBP (mmHg)	128 (113, 143)	78 (69.5, 83.5)	114 (100,131)	70 (60, 81)
EMS hypotension				
No	11,413 (100%)	0 (0%)	237 (100%)	0 (0%)
Yes	0 (0%)	755 (100%)	0 (0%)	177 (100%)
ED/Hospital initial SBP (mmHg)	140 (126, 157)	123 (107, 144)	80 (69, 84)	79 (67, 84)
Hypotension at ED/Hospital				
No	11,413 (100%)	755 (100%)	0 (0%)	0 (0%)
Yes	0 (0%)	0 (0%)	237 (100%)	177 (100%)
Min EMS O2 Saturation (%)	97 (95, 98)	95 (88, 98)	94 (85, 97)	92 (80.2, 97)
EMS hypoxia				
No	10,069 (88.2%)	509 (67.4%)	134 (56.5%)	87 (49.2%)
Yes	863 (7.6%)	189 (25%)	72 (30.4%)	67 (37.9%)
Unknown	481 (4.2%)	57 (7.5%)	31 (13.1%)	23 (13%)
ED/Hospital Initial O2 Saturation(%)	98 (96, 100)	98 (95, 100)	98 (94, 100)	97 (93, 100)

Table 1 (*continued*)

	No hypotension*	EMS hypotension only*	ED hypotension only*	EMS + ED hypotension*
Hypoxia at ED/HOSPITAL				
No	9241 (81%)	582 (77.1%)	176 (74.3%)	118 (66.7%)
Yes	337 (3%)	65 (8.6%)	25 (10.5%)	29 (16.4%)
Unknown	1835 (16.1%)	108 (14.3%)	36 (15.2%)	30 (16.9%)
ED/Hospital initial GCS	14 (10, 15)	8 (3, 15)	3 (3, 14)	3 (3, 6)
ED/Hospital initial heart rate (bpm)	92 (79, 107)	101 (80, 122)	102 (83.5, 127)	107 (85, 131)
ED/Hospital initial HR				
60–129 bpm	10,174 (89.1%)	560 (74.2%)	172 (72.6%)	111 (62.7%)
below 60 bpm	376 (3.3%)	40 (5.3%)	11 (4.6%)	11 (6.2%)
130 bpm or above	773 (6.8%)	139 (18.4%)	52 (21.9%)	47 (26.6%)
Unknown	90 (0.8%)	16 (2.1%)	2 (0.8%)	8 (4.5%)
ED/Hospital initial respiratory rate (bpm)	18 (16, 21)	18 (14, 22)	17 (12,22)	15 (12, 19)
Death before discharge				
No	10,362 (90.8%)	545 (72.2%)	129 (54.4%)	75 (42.4%)
Yes	1051 (9.2%)	210 (27.8%)	108 (45.6%)	102 (57.6%)
Death before hospital admission				
No	11,351 (99.5%)	719 (95.2%)	216 (91.1%)	159 (89.8%)
Yes	62 (0.5%)	36 (4.8%)	21 (8.9%)	18 (10.2%)
Hospital length of stay (day)	4 (2, 9)	5 (1, 14)	3 (1, 15)	2 (1, 14)
ICU length of stay (day)	2 (1, 4)	3 (1, 9)	2 (1,11)	2 (1, 8)
Time on ventilator (day)	0 (0,2)	1 (0, 6)	1 (1, 7)	1 (1, 6)
Total hospital charge (dollar)	54,742.9 (29,169, 120,527.6)	98,071.1 (45,858.3, 246,687.3)	106,077.7 (45,791.2, 274,049.5)	109,103 (44,527.9, 286,698)
Discharged to home				
No	4713 (41.3%)	509 (67.4%)	187 (78.9%)	160 (90.4%)
Yes	6685 (58.6%)	246 (32.6%)	50 (21.1%)	17 (9.6%)
Unknown	15 (0.1%)	0 (0%)	0 (0%)	0 (0%)

* median (interquartile range) for continuous variables and count (percentage) for categorical variables.

3. Results

There were 16,144 cases of major TBI in the dataset and 12,582 met all inclusion criteria (Fig. 1). Median age was 44 years (IQR: 26–61), 69.8% were male, and the overall mortality was 11.7% (95% CI: 11.1–12.3%). The death rate was highest in the group with both EMS and TC hypotension (Fig. 2). There were 11,413 patients who had no hypotension in the field or on initial TC evaluation and this group had the lowest mortality rate [9.2% (8.7–9.8%)]. Mortality increased across the three hypotension groups as follows: EMS hypotension without initial TC hypotension [27.8% (24.6–31.2%)]; no EMS hypotension but with initial TC hypotension [45.6% (39.1–52.1%)]; both EMS and initial TC hypotension [57.6% (50.0–65.0%); $p < 0.0001$ for comparison of all groups].

Table 1 summarizes the demographics and patient characteristics by hypotension status and Table 2 shows the results of the regression analysis for the mortality outcome. The results reveal the same progression from the group with no hypotension having the lowest adjusted mortality risk, through the various hypotension cohorts, to the highest adjusted mortality occurring in the subjects who had both EMS and initial TC hypotension. Fig. 3 shows the results for both the unadjusted and adjusted odds of death by hypotension cohort.

Table 3 shows the adjusted analyses for the non-mortality outcomes across the four hypotension subgroups. The most seriously injured patients died earlier in their hospital course. For this reason, there was not the same stepwise progression in hospital length of stay, ICU length of stay, ventilator days and charges.

Table 4 shows the probability of patients arriving at the TC with various levels of "near-hypotension" (e.g., SBP <95, <100, <105 mmHg), based upon whether they experienced an SBP of <90 mmHg in the field. Regardless of which threshold is evaluated, the likelihood of arriving with near-hypotension is significantly increased in patients who experienced prehospital hypotension (i.e., <90 mmHg; Table 4). Analysis also shows that there is a significantly increased odds of arriving to the TC with hypotension, even in patients who merely experienced near-hypotension in the field (Fig. 4). Highly-significant associations with TC hypotension remain throughout the *entire* range of "normal" EMS SBP [adjusted ORs: <90 vs. >90 mmHg: 5.11 (4.05, 6.44); <95 vs. >95 mmHg: 5.04 (4.03, 6.29); <100 vs. >100 mmHg: 4.77 (3.83, 5.93); <105 vs. >105 mmHg: 4.40 (3.53, 5.48); <110 vs. >110 mmHg: 4.15 (3.32, 5.18); <115 vs. >115 mmHg: 3.81 (3.03, 4.81); <120 vs. >120 mmHg: 3.78 (2.97, 4.82)].

4. Discussion

We believe this is the first study to evaluate and compare the associated outcomes in severe TBI patients who experienced hypotension, based upon when the hypotension occurred during their early care. The previous literature evaluating the effects of hypotension on patients with TBI have consisted of studies focused either on hypotension that occurred in the prehospital setting or after arrival at the hospital [14,15,17,20,24,25,29-34,36,37,55-59]. No large study has evaluated the question of whether correlations exist between prehospital hypotension, in-hospital hypotension, and outcomes. The main reason for this absence of knowledge is because none of the large trauma databases, worldwide, have been able to reliably link in-field data to comprehensive trauma center information. That is, while almost all of them attempt to make this linkage, the missing EMS data rate is so high in these databases that all attempts to make conclusions from analyses of the prehospital data suffer from major selection bias induced by missing information.

The focus of this study was to identify associations between where hypotension occurred (i.e., prehospital versus at the trauma center) and outcome. The risk of dying was progressively worse if hypotension extended from the prehospital setting into the hospital. Furthermore, the increased mortality associated with having both prehospital and initial TC hypotension [unadjusted OR 13.4 (95% CI: 9.9–18.2); adjusted OR 4.4 (2.8–6.8)] was dramatically greater than that which has been historically reported from hypotension occurring either in the prehospital or TC setting (typically 1.3–2.0) [14,34,37]. The fact that having either prehospital or initial in-hospital hypotension is associated with an intermediate increase in mortality (between having no hypotension or both EMS and ED hypotension) is consistent with previous published work from the EPIC study showing that the duration of hypotension is strongly associated with TBI mortality [42].

Table 2
Logistic regression model for mortality.

Covariates		OR	95% CI
Hypotension Status	No hypotension	–	–
	EMS but no ED hypotension	1.8	(1.39, 2.33)
	ED but no EMS hypotension	2.61	(1.73, 3.94)
	EMS and ED hypotension	4.36	(2.78, 6.84)
Intervention	Pre-implementation of guidelines	–	–
	Post-implementation of guidelines	1.1	(0.925, 1.30)
Male	No	–	–
	Yes	0.966	(0.810, 1.15)
Race	Black	–	–
	Asian	0.991	(0.456, 2.16)
	American Indian/Alaska Nat.	1.17	(0.673, 2.03)
	White	0.962	(0.635, 1.46)
	Other	1.06	(0.648, 1.74)
	Unknown	2.16	(0.977, 4.77)
Hispanic	No	–	–
	Yes	0.789	(0.624, 0.996)
	Unknown	1.18	(0.700, 1.99)
Payer	Private	–	–
	AHCCCS/Medicaid	0.886	(0.714, 1.10)
	Medicare	1.18	(0.901, 1.55)
	Self Pay	1.96	(1.53, 2.50)
	Other	1.08	(0.727, 1.59)
	Unknown	3.22	(1.79, 5.79)
Trauma type	Blunt	–	–
	Penetrating	5.37	(4.12, 6.99)
Head injury severity score (ICD)	1 to 3	–	–
	4	1.11	(0.787, 1.57)
	5 to 6	21.3	(15.1, 30.1)
Injury severity score (ICD)	1 to 14	–	–
	16 to 24	3.18	(1.72, 5.91)
	25+	8.93	(4.79, 16.7)
Body region	Isolated TBI	–	–
	Multisystem TBI	1.39	(1.15, 1.67)
CPR	No	–	–
	Yes	7.03	(4.16, 11.9)
Prehospital hypoxia	No	–	–
	Yes	2.11	(1.73, 2.58)
	Unknown	2.07	(1.53, 2.80)

Also adjusted for age as a nonparametric function ($p < 0.0001$), and adjusted for the reporting trauma center ($p < 0.0001$; to protect mandated anonymity of the participating hospitals, the numbers are not shown to prevent any possible identification or inference of facility-specific outcome differences).

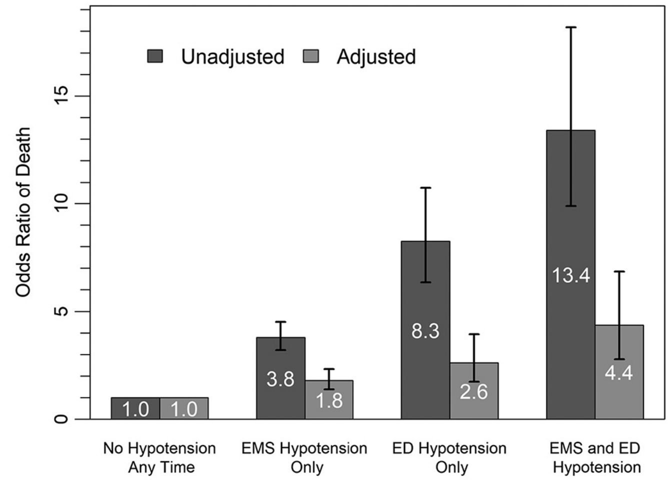

Fig. 3. Odds ratio for mortality by hypotension status.
EMS: emergency medical services.
ED: Emergency Department.
Reference group was the cohort with no prehospital or trauma center hypotension.
Error bars represent 95% confidence intervals.

This analysis revealed that hypotension occurring during EMS care carried a dramatically increased risk of still being hypotensive at the time of arrival at the TC. Those who had no hypotension in the field had only a 1 in 50 chance of arriving hypotensive at the hospital compared to a 1 in 5 chance for those who did experience prehospital hypotension ($p < 0.0001$).

Although this analysis does not allow evaluation of whether treatment of prehospital hypotension would reduce the incidence of early trauma center hypotension, it does lend support the current guidelines that recommend the prevention of prehospital hypotension in patients with traumatic brain injury.

Our findings also have other clinical implications. In particular, the existence of hypotension in the field should be clearly communicated to the receiving facility in advance of arrival so that proper preparations (e.g., ensuring the immediate availability of blood products) are underway prior to receiving the patient, so that there is not a delay in continuing adequate resuscitation for a patient who is at risk for arriving with hypotension.

Recent reports have brought into question whether the current threshold for defining and treating hypotension ought to be increased to a level above 90 mmHg [47,61]. While the "classic" threshold recommendation has remained unchanged in most of the official guidelines for at least 25 years, this analysis adds to the growing evidence that deleterious effects from hypotension in patients with TBI occur at levels above, and perhaps far above, 90 mmHg [44,47,61-66]. Given this emerging concern, our findings are provocative (Table 4, Fig. 4). Among patients who experienced prehospital hypotension (<90 mmHg), the likelihood of arriving at the trauma center with near-hypotension (regardless of which cut-point was used between 95 and 120 mmHg) were dramatically increased compared to patients who had not experienced a prehospital SBP < 90 mmHg. For example, among patients who experienced prehospital hypotension, 30% of them arrived at the trauma center with an SBP < 100 and over 40% arrived with an SBP < 110.

Even more striking was the converse of these prehospital/hospital blood pressure findings. Among patients who never had a prehospital SBP < 90 mmHg, there was a much higher likelihood of arriving hypotensive at the trauma center if they experienced *any* level of "near-hypotension" in the field. Even a single EMS SBP below 120 mmHg was associated with nearly a quadrupling of the odds of arriving at the TC with hypotension (<90 mmHg) compared to the risk in the cohort whose prehospital blood pressure never fell below this level. We believe this is the first time that any of these "near-hypotension" findings have been reported in the literature.

We also think that this is the first large study to report the associations between early hypotension (either prehospital or initial trauma center) and non-mortality outcomes. While we did not find the same distinctly "progressive" pattern (i.e., no hypotension, EMS hypotension only, trauma center hypotension only, and combined EMS and trauma center hypotension) that occurred with mortality, the non-mortality outcomes did show highly significant increases in detrimental outcome with hospital length of stay, ICU length of stay, and being discharged to skilled nursing or inpatient rehabilitation (Table 3). Cost (specifically, hospital charges) was the one outcome that showed a different trend. This was due to the fact that many very severely injured patients died in the ED, thus limiting the hospital costs in many of the most hypotensive patients.

This study has several limitations. First, the design is observational, and we are unable to establish causality. Thus, while the associations between mortality and EMS/initial trauma center hypotension are strong, both separately and in combination, this is not proof of cause-and-effect. Second, we do not have data on hypotension that may have occurred after the initial resuscitation. While hypotension occurring later during the hospital course could have affected outcomes, we are not able to identify such impact. Third, the parent study was a before/after interventional evaluation. Thus, the approach to treating hypotension changed in the post-intervention phase. While we adjusted for the study phase in the analysis, we cannot know for sure whether the

Table 3
Adjusted non-mortality outcomes by hypotension status.

	No hypotension	Prehospital hypotension	trauma center hypotension	Prehospital + trauma center hypotension	
Hospital LOS**	Ref	1.29 (1.19, 1.39)	1.42 (1.22, 1.65)	1.35 (1.11, 1.64)	<0.0001
ICU LOS **	Ref	1.31 (1.20, 1.43)	1.53 (1.30, 1.81)	1.36 (1.10, 1.69)	<0.0001
Ventilator Days**	Ref	1.63 (1.33, 1.98)	2.16 (1.47, 3.16)	1.59 (0.964, 2.63)	<0.0001
Discharged to SNF/Rehab*	Ref	1.58 (1.29, 1.95)	1.57 (1.02, 2.42)	3.03 (1.67, 5.52)	<0.0001
Hospital Charges***	Ref	1.34 (1.23, 1.46)	1.67 (1.42, 1.97)	1.59 (1.28, 1.97)	<0.0001

LOS, Length of stay; ICU, Intensive care unit.
SNF/Rehab: Skilled nursing facility or inpatient rehabilitation.
Ref: The no hypotension cohort was the reference group for all comparisons.
* Adjusted odds ratio.
** Adjusted ratio of means.
*** Adjusted ratio of medians.

Table 4
Proportions of patients with EMS hypotension that arrive at the trauma center with various levels of "near-hypotension".

Outcome	Subgroup	n	Proportion (95% CI)	*p*-value	OR (95%CI)
Trauma center SBP < 90	All	12,582	3.3% (3.0%, 3.6%)	<0.0001	11.3 (9.17, 13.9)
	No Prehospital Hypotension	11,650	2.0% (1.8%, 2.3%)		
	Prehospital Hypotension	932	19.0% (16.5%, 21.7%)		
Trauma center SBP < 95	All	12,582	4.6% (4.2%, 5.0%)	<0.0001	11.0 (9.20, 13.3)
	No Prehospital Hypotension	11,650	3.0% (2.7%, 3.3%)		
	Prehospital Hypotension	932	25.2% (22.5%, 28.1%)		
Trauma center SBP < 100	All	12,582	6.0% (5.6%, 6.4%)	<0.0001	9.98 (8.44, 11.8)
	No Prehospital Hypotension	11,650	4.1% (3.7%, 4.5%)		
	Prehospital Hypotension	932	29.8% (26.9%, 32.9%)		
Trauma center SBP < 105	All	12,582	8.8% (8.3%, 9.3%)	<0.0001	8.26 (7.10, 9.62)
	No Prehospital Hypotension	11,650	6.6% (6.1%, 7.0%)		
	Prehospital Hypotension	932	36.8% (33.7%, 40.0%)		
Trauma center SBP < 110	All	12,582	11.3% (10.8%, 11.9%)	<0.0001	7.33 (6.34, 8.48)
	No Prehospital Hypotension	11,650	8.9% (8.4%, 9.4%)		
	Prehospital Hypotension	932	41.7% (38.5%, 45.0%)		
Trauma center SBP < 115	All	12,582	15.8% (15.1%, 16.4%)	<0.0001	6.60 (5.74, 7.59)
	No Prehospital Hypotension	11,650	13.1% (12.4%, 13.7%)		
	Prehospital Hypotension	932	49.8% (46.5%, 53.0%)		
Trauma center SBP < 120	All	12,582	20.1% (19.4%, 20.8%)	<0.0001	5.48 (4.77, 6.28)
	No Prehospital Hypotension	11,650	17.5% (16.8%, 18.2%)		
	Prehospital Hypotension	932	53.6% (50.4%, 56.9%)		

The proportion of patients with EMS hypotension (at least one prehospital SBP < 90 mmHg) arriving at the trauma center with hypotension (SBP < 90 mmHg) or near-hypotension (variably defined in increments of 5 mmHg between 95 and 120 mmHg).

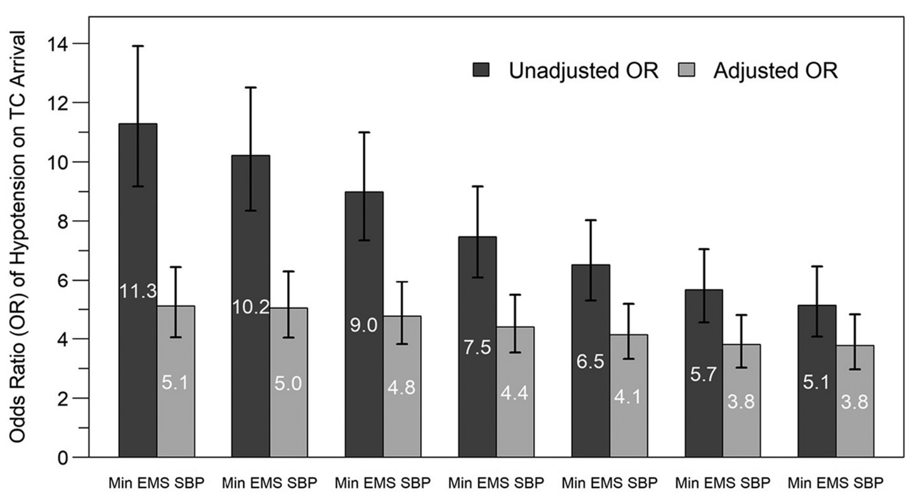

Fig. 4. Unadjusted and adjusted odds of being hypotensive (SBP < 90) on arrival at the Trauma Center, based upon lowest reported prehospital SBP.
EMS: emergency medical services.
TC: Trauma Center.
Error bars represent 95% confidence intervals.

findings were affected by guideline implementation. To assess this, we performed a sensitivity analysis, evaluating the pre-implementation and post-implementation phases separately (See online supplement). While the point estimates differed somewhat in these analyses (mortality was slightly higher in the post-implementation cohort), the results did not differ significantly. The patterns observed were similar between the pre and post-implementation cohorts (and similar to that in the combined cohort). The implications of the findings were the same as the combined analysis. Fourth, although patient outcomes depend upon inpatient as well as prehospital care, we were not able to control for the effects of inpatient care. Given the stability of the trauma system in Arizona (over 40 years since its inception), there is no reason to believe that there were any major, systematic, statewide changes in hospital care during the study period. Fifth, because data are collected in the prehospital setting, it is not possible to independently verify the measurements taken and recorded by EMS providers. The EPIC database, however, utilized a single data team to abstract data directly from the patient care record via a standardized process. This consistency is unusual in EMS studies. Finally, there were missing data. However, only 10.1% of subjects were excluded for this reason. In a setting requiring linked prehospital and hospital data, this is a very low missing data rate [67,68].

5. Conclusions

While patients with hypotension in the field or on arrival at the trauma center had markedly increased risk of dying compared to those with no hypotension, those with prehospital hypotension that was not resolved before hospital arrival had, the highest likelihood of death. TBI patients with prehospital hypotension were five times more likely to arrive at the trauma center with hypotension, compared to those who were never hypotensive in the field. These findings are consistent with other prehospital literature that highlight the risks of hypotension in major TBI.

Prior presentations

National Association of EMS Physicians Annual Meeting January 2022.

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CRediT authorship contribution statement

Amber D. Rice: Writing – original draft, Investigation. **Chengcheng Hu:** Formal analysis, Data curation, Conceptualization. **Daniel W. Spaite:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Bruce J. Barnhart:** Writing – review & editing, Project administration. **Vatsal Chikani:** Writing – review & editing. **Joshua B. Gaither:** Writing – review & editing, Investigation. **Kurt R. Denninghoff:** Writing – review & editing, Funding acquisition. **Gail H. Bradley:** Writing – review & editing. **Jeffrey T. Howard:** Writing – review & editing. **Samuel M. Keim:** Writing – review & editing, Supervision. **Bentley J. Bobrow:** Writing – review & editing, Project administration, Investigation, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2022.12.015.

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