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Original Contribution

Effect of hypoxia on mortality and disability in traumatic brain injury according to shock status: A cross-sectional analysis

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ABSTRACT

Objectives: This study aimed to test the association between hypoxia level and outcomes according to shock status in traumatic brain injury (TBI) patients.
Methods: Adult TBI patients transported by emergency medical services in 10 provinces were enrolled. Hypoxia was a main exposure; three groups by oxygen saturation (SaO2, non-hypoxia (≥94%), mild hypoxia (90 ≤ SaO2 < 94%)), and severe hypoxia (<90%). Shock status (<systolic blood pressure 90 mmHg) was an interactive exposure. The outcomes were hospital mortality and worsened disability (a 2-point increase of Glasgow Outcome Scale). Multivariable logistic regression was used to calculate the adjusted odds (AORs) with 95% Confidence intervals (CIs).
Results: Of the 6125 patients, the mortality/disability rates were 49.4%/69.0% in severe hypoxia, 30.7%/46.9% in mild hypoxia, and 18.5%/27.5% in normoxia ($p < 0.0001$). Mortality/disability rates were 47.1%/57.1% in shock status and 20.5%/31.4% in non-shock status ($p < 0.0001$). AORs (95% CIs) for worsened disability/mortality compared with normoxia (reference) were 3.23 (2.47–4.21)/2.24 (1.70–2.96) in patients with severe hypoxia and 2.11 (1.63–2.74)/1.84 (1.39–2.45) in those with mild hypoxia. AORs (95% CIs) for worsened disability/mortality was 1.58 (1.20–2.09)/1.33 (1.01–1.76) by severe hypoxia than normoxia in patient with only non-shock status in the interaction analysis.
Conclusions: There was a trend toward worsened outcomes with mild and severe hypoxia in patient with and without shock, however, the only met statistical significance for patients with both severe hypoxia and non-shock status.

1. Introduction

Traumatic brain injury (TBI) is one of the most serious health problems worldwide. The most recent estimates indicate that 1.1 million Americans are treated in emergency departments. About 2.5–6.5 million people currently live with physical, cognitive, or psychological impairment, and 50,000 individuals die due to TBI each year [1-4]. Similar patterns of an increased burden of TBI resulting from its high fatality have also been reported in many other countries [5-7].

The extent of neurological injury after TBI is not determined solely by the traumatic impact itself, but by time. Secondary brain injury occurs as a result of a complex process that began with primary injury and is characterized by neuroinflammation, ischemia/reperfusion injury, cerebral edema, intracranial hemorrhage, and intracranial hypertension. Patients who survive early TBI are very vulnerable to secondary insult to the damaged brain, primarily due to hypoxia and hypotension during the initial period of resuscitation [2]. Cerebral hypoxia and hypotension are known to cause adverse outcomes in TBI patients [8-14]. In major TBIs, mortality is much more important when two parameters are combined. The adjusted mortality probability for both hypotension and hypoxia were two times higher than for patients with hypotension or hypoxia only [15].

To prevent brain damage caused by hypoxia, sufficient oxygen must be supplied through the blood and sufficient blood pressure must be maintained for optimal brain perfusion. Optimal cerebral perfusion is determined by the difference between mean arterial pressure (MAP) and intracranial pressure (ICP). However, ICP cannot be accurately

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measured in the pre-hospital environment. Rather, it can be estimated based on brain damage. Oxygen saturation and MAP can determine oxygen delivery to the brain and the amount of oxygen delivered to the brain is directly related to hypoxic brain damage.

The current definition of hypoxia and protocols for oxygen delivery suggests 90% or 94% oxygen saturation as a uniform standard of oxygen supply without taking into account these complex factors affecting cerebral perfusion [16-18]. In previous studies involving non-traumatic cases, 90% oxygen saturation was used to define hypoxia. On the other hand, 94% was recommended as the optimal level of oxygen supply for long-term preservation in other studies on trauma patients. In particular, hypoxia in shock has not been thoroughly investigated, particularly with respect to optimal oxygen levels that do not require oxygen supply. It is unclear how many percent oxygen saturation is required for oxygenation in patients with TBI. We hypothesized that hypoxic effects are dependent on the presence of shock and the extent of intracranial injury.

2. Methods

This study was approved by the Institutional Review Board at the research site. This material has been approved for use in Korea Centers for Disease Control and Prevention (CDC). The patient's informational consent was waivered because the data did not contain any personal information and caused minimal risk to the subject.

2.1. Study design and data source

This study is a cross-sectional observational study. Data from the Emergency Medical Services-treated Severe Trauma Registry (EMS-STR) database were used and collected from 10 provinces in Korea from 2012 to 2013. The EMS-STR was developed to monitor the incidence and outcomes of severe trauma patients transported by EMS in Korea by the Korea CDC and the Central Fire Services (CFSs). The index cases with an abnormal revised trauma score (RTS), which was defined as shock (systolic blood pressure <90 mmHg), abnormal respiration rate (<10 or >29 respirations/min), or abnormal mental status (non-alert response using the AVPU scale), were extracted from the EMS run sheet All cases meeting the criteria for abnormal RTSs were reviewed for the individuals' hospital medical records by the expert reviewers of the Korea CDC.

Data variables included demographic and socioeconomic variables, administrative EMS variables, prehospital clinical variables, emergency care-related variables in the hospital, injury variables, and hospital outcomes. A data quality management (DQM) committee was formed to maintain the data quality. The DQM committee consisted of emergency physicians, injury epidemiologists, trauma surgeons and biostatistical experts. During the medical record review, the DQM committee offered advice regarding the questions and provided feedback about the collected data using a quality assurance protocol.

2.2. Study setting

Emergency medical services (EMS) in this study setting were similar to those provided by emergency medical technicians (EMT) - basic or intermediate. EMTs were able to supply oxygen through either basic airway, back-vale mask ventilation, or intubation under direct medical control [19]. EMS medical directors in all EMS agencies that were overseen by the fire department of each county were employed to provide medical oversight for trauma care as well as other serious emergency conditions. The directors usually visited the fire department to review the EMS run sheet and severe trauma registry and score the quality of the prehospital care provided by the EMTs of the EMS agency. Trauma care equipment in most ambulances included basic airways (oropharyngeal airway, nasopharyngeal airway), advanced airways (supraglottic airway, endotracheal tube), ventilation devices (portable oxygen tank, facial or bag-valve mask), circulation devices and materials (intravenous set), vital sign monitors (non-invasive blood pressure monitor, oxygen saturation monitor), and a defibrillator. The country has approximately 1400 ambulances that are operated by a province's fire department headquarters on a tax-based budget [20]. Level 1 emergency medical technicians are the top providers in this setting, and their service level is equivalent to an intermediate level EMT in the USA. The EMS level 1 technician can provide basic life support and limited advanced life support including intravenous fluid resuscitation and advanced airway under direct medical supervision. They are capable of transporting all patients to the ED and providing CPR during ambulance transport unless the patients achieve a return of spontaneous circulation at the scene. All EMTs are required to fulfill 40 h of continuing medical education to maintain relevant medical skills and knowledge in accordance with the Rescue and Fire EMS Act [19]. The national trauma protocol requires EMTs to minimize patients' movement to prevent further injury, stay and treat within 10 min in the field, and transport patients who meet the criteria of the trauma triage scheme of the US CDC to a higher level of emergency department or regional trauma center. The recording of details of prehospital trauma care and relevant information in the EMS trauma registry is encouraged [20].

Approximately 400 EDs are designated by the Ministry of Health and Welfare as levels 1 through 3 according to the emergency care capacity and resource measures including staffing, equipment, and size of the department space. Level 1 and 2 EDs have more resources and better facilities for emergency care and must be staffed by emergency physicians 24 h for 365 days a year to provide high-quality care, whereas level 3 EDs can be staffed by general physicians [20]. Additionally, there are EDs in small hospitals that provide lower levels of services that are not formally designated by the government as EDs [19]. Those hospitals manage the primary care of minimally injured patients.

2.3. Study subjects

The study subjects were TBI patients who were 15 years old or above and admitted to the study from EDs across the 10 provinces from 2012 to 2013. TBI patients were defined according to the International Classification of Disease (ICD)-10th version, including all patients with diagnosis codes of S06.0-S06.9 (concussion, traumatic cerebral edema, diffuse brain injury, focal brain injury, epidural hemorrhage, traumatic subdural hemorrhage, traumatic subarachnoid hemorrhage, intracranial injury with prolonged coma, other intracranial injuries, and unspecified intracranial injury). If a patient had another injury code as well as the TBI code, the patient was considered a TBI patient (see http://apps.who.int/classifications/icd10/browse/2016/en#/S00-S09). Patients whose information about oxygen saturation, blood pressure, injury severity or hospital outcomes (mortality and disability) was unknown or unmeasured were excluded.

2.4. Variables

Study variables included demographic factors (age, gender, and urbanization level), injury factors (mechanism, intent, and event date and time), EMS elapsed time intervals (response time, scene time, and transport time), prehospital clinical parameters (blood pressure, respiratory rate, pulse rate, oxygen saturation, AVPU scale score in the field), prehospital care (airway management, oxygen supply, fluid therapy, and CPR), and hospital care factors (level of ED, systolic blood pressure, respiratory rate and heart rate at ED, AVPU scale score in the ED, intervention or operation, transfusion, CPR, and intensive care), hospital outcomes (final diagnosis, mortality, and disability measured using the Glasgow Outcome Scale (GOS) at pre-event and at hospital discharge).

Hypoxia as a main exposure was defined as a decrease below normal levels of oxygen in inspired gases, arterial blood, or tissues without reaching anoxia. This definition did not include the concept of an oxygen level that adversely affected the brain. In this study, the hypoxia

state was divided into three levels of oxygen saturation (SaO2) measured in the field as follows: non-hypoxia (94% or higher SaO2), mild hypoxia (90–93% SaO2), and severe hypoxia (<90% SaO2). Another exposure, shock, was defined as an interaction term as a systolic blood pressure lower than 90 mmHg in the field.

2.5. Outcome measures

The primary outcome was hospital mortality. The secondary outcome was worsened disability, which was defined as a case in which the difference between GOS score at discharge and pre-event GOS score was 2 points or more or the patient died at hospital discharge. The outcomes were measured by the medical record reviewers of the Korea CDC based on medical records written by duty physicians, surgeons, or registered nurses.

2.6. Statistical analysis

Demographic findings were compared among the three hypoxia groups and shock vs. non-shock groups for the distribution of risk factors and outcomes. The continuous variables were compared using the Wilcoxon sum-rank test, and categorical variables were compared using a chi-square test.

We determined the association between SaO2 and hospital outcomes using restricted cubic spline analysis for calculating the log odds of outcomes according to the change in oxygen saturation level. The method was also used for systolic blood pressure and outcomes.

A multivariable logistic analysis was used to determine the association between the main exposure and outcomes for the strata of injury severity and hospital care groups. The crude odds ratios (ORs) with 95% confidence intervals (CIs) for hospital outcomes of the hypoxia group in Model 1 were calculated without adjustment. AORs with 95% CIs adjusted for age and gender (Model 2) and adjusted for age, gender, metropolis, mechanism of injury, season and week of injury, time of injury, response time interval, scene time interval, advanced airway, fluid therapy, and shock status (Model 3) were calculated for the outcomes.

To compare the effect size, a final interaction analysis was performed to calculate the AORs (95% CIs) of the hypoxia groups according to shock status for hospital outcomes.

3. Results

3.1. Demographic findings

Of 8306 adult TBI patients, 6125 patients were analyzed; exclusions included 793 patients without SaO2 values, 658 without SBP values, 224 with traumatic cardiac arrest, 150 without NISS (New Injury Severity Scale) scores, and 772 without GOS scores (Fig. 1).

The demographic characteristics of the patients according to hypoxia status were summarized in Table 1 and Supplementary Table 1. Among 6125 patients, 636 patients (10.4%) had severe hypoxia, 554 patients (9.0%) had mild hypoxia, and 4935 patients (80.6%) were in normoxia status. Of these patients, 49.4%, 30.7%, and 18.5% of them with severe hypoxia, mild hypoxia and normoxia died, respectively. Totals of 69.0%, 46.9%, and 27.5% of patients with severe hypoxia, mild hypoxia, and normoxia, respectively, resulted in worsened disability (each $p < 0.0001$).

The demographic findings of the patients according to shock status were compared in Table 2 and Supplementary Table 2. Of the total number of patients, 8.5% of them suffered from shock, and 91.5% were classified as having non-shock status. Hospital mortality and worsened disability were 47.1% and 57.1% in the shock status group, respectively, and 20.5% and 31.4% in the non-shock group, respectively ($p < 0.0001$).

3.2. Main analysis

The main results of the multivariable logistic regression analysis are shown in Table 3. In the full model (Model 3), AORs (95% CIs) for worsened disability/mortality compared with normoxia (reference) were 3.23 (2.47–4.21)/2.24 (1.70–2.96) in severe hypoxia and 2.11 (1.63–2.74)/1.84 (1.39–2.45) in mild hypoxia. AORs (95% CIs) by shock status were 2.07 (1.45–2.96) for worsened disability and 2.14 (1.48–3.10) for mortality.

3.3. Interaction analysis

AORs (95% CIs) for worsened disability/mortality were significantly different according to shock status as follows: 1.35 (0.73–2.52)/1.26 (0.68–2.32) in patients with mild hypoxia and shock status, 1.49 (0.88–2.51)/1.31 (0.79–2.20) in patients with severe hypoxia and

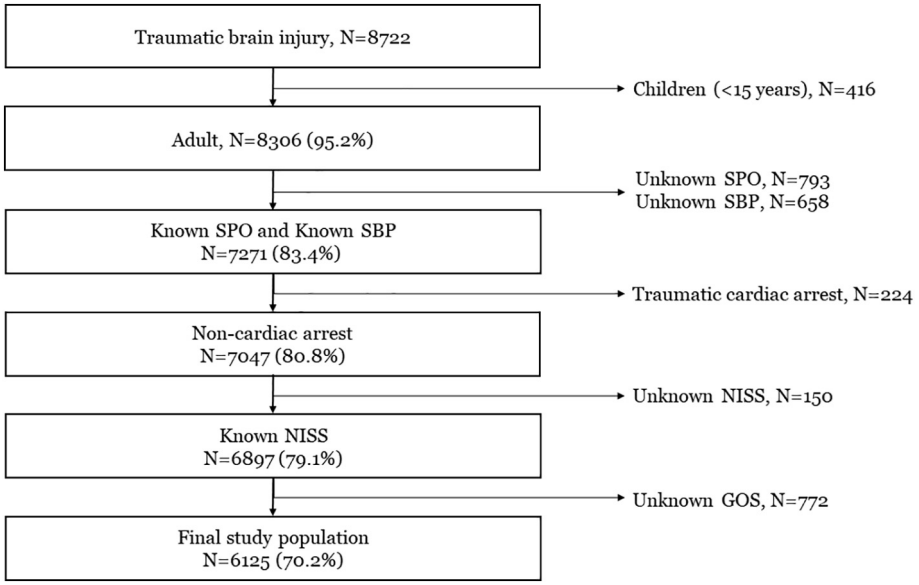

Fig. 1. Study population. SPO, saturation of peripheral oxygenation SBP, systolic blood pressure NISS, new injury severity GOS, Glasgow Outcome Scale.

Table 1
Demographic findings of the study population among exposure groups.

Variable	All		Severe Hypoxia		Mild Hypoxia		Normoxia		p-Value
	N	%	N	%	N	%	N	%	
All	6125	100.0	636	100.0	554	100.0	4935	100.0	
Gender									<0.0001
Male	4431	72.3	491	77.2	433	78.2	3507	71.1	
Female	1694	27.7	145	22.8	121	21.8	1428	28.9	
Age group, years									0.0001
15 ~ 24	659	10.8	57	9.0	34	6.1	568	11.5	
25 ~ 34	642	10.5	73	11.5	44	7.9	525	10.6	
35 ~ 44	720	11.8	68	10.7	56	10.1	596	12.1	
45 ~ 54	1250	20.4	124	19.5	116	20.9	1010	20.5	
55 ~ 64	1178	19.2	119	18.7	118	21.3	941	19.1	
65 ~ 74	968	15.8	107	16.8	116	20.9	745	15.1	
75~	708	11.6	88	13.8	70	12.6	550	11.1	
Metropolis									0.2745
No	3559	58.1	382	60.1	334	60.3	2843	57.6	
Yes	2566	41.9	254	39.9	220	39.7	2092	42.4	
Injury mechanism									<0.0001
Traffic accident	3317	54.2	377	59.3	289	52.2	2651	53.7	
Fall or slip	2233	36.5	197	31.0	219	39.5	1817	36.8	
Collision	331	5.4	26	4.1	17	3.1	288	5.8	
Other mechanism	244	4.0	36	5.7	29	5.2	179	3.6	
Mental status in the field									<0.0001
Alert	1603	26.2	56	8.8	82	14.8	1465	29.7	
Verbal response	2426	39.6	109	17.1	210	37.9	2107	42.7	
Pain response	1607	26.2	223	35.1	214	38.6	1170	23.7	
No response	489	8.0	248	39.0	48	8.7	193	3.9	
Shock status									<0.0001
Yes (SBP < 90 mmHg)	518	8.5	241	37.9	51	9.2	226	4.6	
No (SBP ≥ 90 mmHg)	5607	91.5	395	62.1	503	90.8	4709	95.4	
Treatment at EMS location									
Bleeding control	2879	47.0	269	42.3	301	54.3	2309	46.8	0.0001
Wound care	2495	40.7	201	31.6	244	44.0	2050	41.5	<0.0001
Intravenous fluid	295	4.8	45	7.1	38	6.9	212	4.3	0.0005
Charlson comorbidity									0.1044
None	5663	92.5	597	93.9	502	90.6	4564	92.5	
1 or more	462	7.5	39	6.1	52	9.4	371	7.5	
Mental status at ED									<0.0001
Alert	2517	41.1	75	11.8	151	27.3	2291	46.4	
Verbal response	1307	21.3	87	13.7	121	21.8	1099	22.3	
Pain response	1299	21.2	141	22.2	161	29.1	997	20.2	
No response	1002	16.4	333	52.4	121	21.8	548	11.1	
AIS ≥ 3									
Head	3291	53.7	496	78.0	402	72.6	2393	48.5	<0.0001
Chest	832	13.6	219	34.4	140	25.3	473	9.6	<0.0001
Abdomen	44	0.7	16	2.5	4	0.7	24	0.5	<0.0001
Spine	84	1.4	14	2.2	8	1.4	62	1.3	0.1539
Extremity	317	5.2	60	9.4	43	7.8	214	4.3	<0.0001
Outcomes									
Hospital death	1396	22.8	314	49.4	170	30.7	912	18.5	<0.0001
Disability, (GOS ≤ 3)	2054	33.5	439	69.0	260	46.9	1355	27.5	<0.0001

SBP, systolic blood pressure; EMS, emergency medical service; ED, emergency department; AIS, Abbreviate injury scale; GOS, Glasgow Outcome Scale.

shock status, 1.22 (0.88–1.69)/1.20 (0.87–1.66) in patients with mild hypoxia and non-shock status, and 1.58 (1.20–2.09)/1.33 (1.01–1.76) in those with severe hypoxia and non-shock status (Table 4).

Table 2
Demographic findings of the study population between shock status groups.

Variable	All		Shock		Normal		p-Value
	N	%	N	%	N	%	
All	6125	100.0	518	100.0	5607	100.0	
Gender							0.5889
Male	4431	72.3	380	73.4	4051	72.2	
Female	1694	27.7	138	26.6	1556	27.8	
Age group, years							0.1906
15 ~ 24	659	10.8	65	12.5	594	10.6	
25 ~ 34	642	10.5	66	12.7	576	10.3	
35 ~ 44	720	11.8	62	12.0	658	11.7	
45 ~ 54	1250	20.4	94	18.1	1156	20.6	
55 ~ 64	1178	19.2	86	16.6	1092	19.5	
65 ~ 74	968	15.8	79	15.3	889	15.9	
75~	708	11.6	66	12.7	642	11.4	
Metropolis							0.3525
No	3559	58.1	291	56.2	3268	58.3	
Yes	2566	41.9	227	43.8	2339	41.7	
Injury mechanism							0.0008
Traffic accident	3317	54.2	315	60.8	3002	53.5	
Fall or slip down	2233	36.5	146	28.2	2087	37.2	
Collision	331	5.4	33	6.4	298	5.3	
Other mechanism	244	4.0	24	4.6	220	3.9	
Mental status at the field							<0.0001
Alert	1603	26.2	175	33.8	1428	25.5	
Verbal response	2426	39.6	49	9.5	2377	42.4	
Pain response	1607	26.2	102	19.7	1505	26.8	
No response	489	8.0	192	37.1	297	5.3	
Hypoxia status							<0.0001
Severe Hypoxia	636	10.4	241	46.5	395	7.0	
Mild Hypoxia	554	9.0	51	9.8	503	9.0	
Normoxia	4935	80.6	226	43.6	4709	84.0	
Treatment at EMS location							
Bleeding control	2879	47.0	240	46.3	2639	47.1	0.7487
Wound care	2495	40.7	191	36.9	2304	41.1	0.0615
Intravenous fluid	295	4.8	58	11.2	237	4.2	<0.0001
Charlson comorbidity							0.0144
None	5663	92.5	493	95.2	5170	92.2	
1 or more	462	7.5	25	4.8	437	7.8	
Mental status at the ED							<0.0001
Alert	2517	41.1	160	30.9	2357	42.0	
Verbal response	1307	21.3	53	10.2	1254	22.4	
Pain response	1299	21.2	69	13.3	1230	21.9	
No response	1002	16.4	236	45.6	766	13.7	
AIS ≥ 3							
Head	3291	53.7	321	62.0	2970	53.0	<0.0001
Chest	832	13.6	153	29.5	679	12.1	<0.0001
Abdomen	44	0.7	8	1.5	36	0.6	0.02
Spine	84	1.4	13	2.5	71	1.3	0.0199
Extremity	317	5.2	57	11.0	260	4.6	<0.0001
Outcomes							
Hospital death	1396	22.8	244	47.1	1152	20.5	<0.0001
Disability, (GOS ≤ 3)	2054	33.5	296	57.1	1758	31.4	<0.0001

EMS, emergency medical service; ED, emergency department; AIS, Abbreviate injury scale; GOS, Glasgow Outcome Scale.

4. Discussion

Both exposures, hypoxia and shock status, revealed significant increases in disability and mortality rates. Severe hypoxia followed by mild hypoxia was significantly associated with poor hospital outcomes. However, hypoxia groups with shock status were not significantly associated with poor outcomes. Only severe hypoxia with non-shock status was associated with an increase in disability and mortality in the interaction models.

From this study, we found that the effect size of hypoxia for outcomes in TBI patients was different according to shock status. In patients already suffering from shock, hypoxia did not add any significant effect. However, if TBI patients were not in shock, severe hypoxia <90% SaO2 significantly affected brain damage to result in disability and mortality.

Spaite DW et al. studied the associations between mortality and out-of-hospital hypotension and hypoxia separately and in combination [15]. Mortality for the four study groups (neither hypotension nor

Table 3
Multivariable logistic regression analysis for outcomes by hypoxia and shock status.

Exposure	Outcomes	Group	Total	Outcomes		Model 1			Model 2			Model 3		
			N	n	%	AOR	95% CI		AOR	95% CI		AOR	95% CI	
Hypoxia														
	Disability	Total	6125	2054	33.5									
		Normoxia	4935	1355	27.5	1.00			1.00			1.00		
		Severe hypoxia	554	260	46.9	3.45	2.66	4.47	3.38	2.60	4.39	3.23	2.47	4.21
		Mild hypoxia	636	439	69.0	2.29	1.78	2.94	2.12	1.64	2.73	2.11	1.63	2.74
	Mortality	Total	6125	1396	22.8									
		Normoxia	4935	912	18.5	1.00			1.00			1.00		
		Severe hypoxia	554	170	30.7	2.43	1.86	3.18	2.35	1.79	3.08	2.24	1.70	2.96
		Mild hypoxia	636	314	49.4	1.92	1.46	2.52	1.82	1.38	2.39	1.84	1.39	2.45
Shock status														
	Disability	Total	6125	2054	33.5									
		Normal	5607	1758	31.4	1.00			1.00			1.00		
		Shock	518	296	57.1	2.10	1.49	2.96	2.19	1.54	3.11	2.07	1.45	2.96
	Mortality	Total	6125	1396	22.8									
		Normal	5607	1152	20.5	1.00			1.00			1.00		
		Shock	518	244	47.1	2.29	1.60	3.27	2.32	1.62	3.33	2.14	1.48	3.10

AOR, adjusted odds ratio.
95% CI, 95% confidence interval.
Model 1; not adjusted (crude).
Model 2; adjusted for age and gender.
Model 3; adjusted for shock status, gender, age, injury mechanism and intent, event time - season, weekday, and hour - and response time interval.

hypoxia, hypotension only, hypoxia only, and both hypotension and hypoxia) was 5.6%, 20.7%, 28.1%, and 43.9%, respectively. The results that combined out-of-hospital hypotension and hypoxia were associated with significantly increased mortality, which was consistent with the findings of this study. Their exclusion criteria (exclusions: <10 years of age, out-of-hospital oxygen saturation ≤10%, and out-of-hospital systolic blood pressure <40 or >200 mmHg) and definition of exposure (systolic blood pressure <90 mmHg and SaO2 <90% each) were different from those in our study. The overall effects of hypoxia or hypotension were similar with those of our study. However, they did not compare the effect size of hypoxia under hypotension status.

Zebrack M et al. studied severe traumatic brain injury in children (N = 299) [21]. They found that untreated hypoxia was not significantly associated with death or disability, except in the setting of hypotension. These findings may be contrary to our study findings. They used the exposure (hypoxia and hypotension) measured at the time when the patients visited the level 1 trauma center. However, blood pressure (31%) and oxygenation (34%) were not recorded during some portion of "early care." Documented hypotension occurred in 118 children (39%). An attempt to treat documented hypotension was made in 48% of cases (57 of 118 children). Documented hypoxia occurred in 131 children (44%). Untreated hypotension was associated with increased mortality, but untreated hypoxia without hypotension was not significantly associated with outcomes. This study had a significant limitation because more than half of the patients had no information on hypoxia and hypotension, which could have resulted in selection bias. A number of patients might have had significant hypoxia status that was not measured in the clinical setting. Even though this study was performed at a single center retrospectively, the effect size of hypoxia under normal blood pressure in TBI patients may be controversial.

Fuller G et al. aimed to fully characterize the association between admission SBP and mortality (N = 5057) [10]. Admission SBP demonstrated a smooth u-shaped association with outcomes in a bivariate analysis, with increasing mortality at both lower and higher values and no evidence of any threshold effect. Adjustment for confounding factors slightly attenuated the association between mortality and SBP at levels <120 mmHg and abolished the relationship for higher SBP values. Case-mix adjusted odds of death were 1.5 times greater at <120 mmHg, doubled at <100 mmHg, tripled at <90 mmHg and was six times greater at SBP < 70 mmHg, $p < 0.01$. We used the cut-off value of 90 mmHg for shock status. If we used different cut-off values such as 120 mmHg, 100 mmHg, or 70 mmHg, the effect might have been different.

We used the parameters for oxygen saturation and blood pressure that were measured by EMS personnel in the field. Numerous studies involving trauma care for patients suffering from shock or hypoxia were compared between physician-staffed and paramedic-staffed services because the providers offer a different level of services when the patients are suffering from shock or hypoxia or both. In studies favoring physician-staffed ambulance or helicopter services, the paramedic-staffed services resulted in better outcomes [22,23]. From the observational study during the 6-year study period, 458 total patients showed that one-year mortality was higher in the paramedic-staffed EMS group compared to the physician-staffed group, 57% vs. 42%, respectively. This system difference affected the outcomes of the study. Our study had lower levels of service providers, and the mortality and disability due to secondary injury followed by hypoxia or hypotension might have been more significant.

Prehospital hypoxia can be prevented by appropriate management such as providing a basic airway and oxygen therapy or advanced airway for patients with severe hypoxia status. A secondary analysis from the ProTECT III trial (a multicenter randomized, double-blind, placebo-controlled trial of early administration of progesterone in 882 patients with acute moderate-to-severe nonpenetrating TBI) showed better outcomes in the advanced airway management group than the non-advanced airway group in a prehospital setting (mortality 13.8% v. 19.5%, respectively, $p = 0.03$) [24]. In our study setting, the placement

Table 4
Interaction effect of shock with hypoxia status on outcomes in traumatic brain injury.

Outcomes	Shock status	Hypoxia					
		Mild			Severe		
		AOR	95% CI		AOR	95% CI	
Disability							
	Shock	1.35	0.73	2.52	1.49	0.88	2.51
	Normal	1.22	0.88	1.69	1.58	1.20	2.09
Mortality							
	Shock	1.26	0.68	2.32	1.31	0.79	2.20
	Normal	1.20	0.87	1.66	1.33	1.01	1.76

AOR, adjusted odds ratio.
95% CI, 95% confidence interval.
AORs and 95% CIs were calculated from models with adjustment for shock status, gender, age, injury mechanism and intent, event time - season, weekday, and hour - and response time interval.

of a prehospital advanced airway by an EMT was allowed for only traumatic cardiac arrest patients who were excluded from the study. Therefore, most patients did not receive advanced airway management. This study setting will be considered when interpreting the findings.

This study recommends a change in the hospital protocol for TBI patients with hypoxia or shock. If the patient is suffering from hypoxia without shock, it is recommended that the SaO2 of the patient be maintained above the level of 94% through vigorous treatment using basic or advanced airway management for adequate oxygen supply. In many EMS systems in Asia, advanced airway protocols are limited to patients in cardiac arrest and not for non-arrest traumas [25,26]. To prevent hypoxia and maintain a normal oxygen level in TBI patients, the protocol would need to be changed. Further studies are recommended to search for the exact cut-off value for hypoxia (90% v. 94%) or to determine the effect of consecutive episodes of hypoxia in TBI patients with shock or non-shock status.

4.1. Limitations

As this study excluded patients whose medical records on oxygen saturation, blood pressure, injury severity or hospital outcomes were unknown or unmeasured, it is possible that their inclusion might have altered the results. Moreover, as the study only included those who were 15 years old or above, the results might not be applicable to pediatric patients. Those exclusions would affect the outcomes and contribute to selection bias. Data about SaO2, shock status, mental status, and of TBI patients were collected by EMTs, duty physicians, surgeons, and registered nurses using the EMS run sheet. Despite the existence of a standard measurement manual, the devices differ by hospital, and the measurer's judgment might differ from person to person. This measurement bias was not considered in the study. As we mentioned, the study was performed at the low-to-intermediate level of EMS, which is different from the EMS level in Western countries or North America. Caution should be taken when generalizing these findings to different settings. Finally, we should consider the limited sample size to interpret the results. It appears that the hypoxia was associated with higher mortality/disability in the shock group than the non-shock group. However, the confidence intervals are larger in the shock group because there are fewer patients.

5. Conclusion

The study found that both prehospital shock (SBP <90 mmHg) and hypoxia (SaO2 <90% or <94%) consistently had a non-favorable effect on outcomes after TBI. Hypoxia resulted in different effect sizes between shock and non-shock status. Hypoxia without shock status was significantly associated with poor outcomes, and hypoxia with shock was not associated with poor outcomes in the interaction model.

Author contributions

Ms. Seo and Dr. Shin had full access to all of the data in the study and assumed responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Dr. Shin.

Acquisition, analysis, or interpretation of the data: Dr. Shin and Ms. Seo.

Drafting of the manuscript: Ms. Seo.

Critical revision of the manuscript for important intellectual content: Drs. Song, Ro, and Park.

Statistical analysis: Dr. Shin.

Obtainment of funding: Dr. Shin.

Manuscript approval: all authors.

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Conflict of interest

The authors declare no conflicts of interest relevant to this paper.

Data sharing statement

The Korea Centers for Disease Control and Prevention (CDC) approved the use of the database in this study. Data sharing should be approved by the Korea CDC

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2018.12.022.

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