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Risk Factors and Neurological Outcomes Associated With Circulatory Shock After Moderate–Severe Traumatic Brain Injury: A TRACK-TBI Study

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BACKGROUND: Extracranial multisystem organ failure is a common sequela of severe traumatic brain injury (TBI). Risk factors for developing circulatory shock and long-term functional outcomes of this patient subset are poorly understood.

OBJECTIVE: To identify emergency department predictors of circulatory shock after moderate–severe TBI and examine long-term functional outcomes in patients with moderate–severe TBI who developed circulatory shock.

METHODS: We conducted a retrospective cohort study using the Transforming Clinical Research and Knowledge in TBI database for adult patients with moderate–severe TBI, defined as a Glasgow Coma Scale (GCS) score of <13 and stratified by the development of circulatory shock within 72 hours of hospital admission (Sequential Organ Failure Assessment score ≥2). Demographic and clinical data were assessed with descriptive statistics. A forward selection regression model examined risk factors for the development of circulatory shock. Functional outcomes were examined using multivariable regression models.

RESULTS: Of our moderate–severe TBI population (n = 407), 168 (41.2%) developed circulatory shock. Our predictive model suggested that race, computed tomography Rotterdam scores <3, GCS in the emergency department, and development of hypotension in the emergency department were associated with developing circulatory shock. Those who developed shock had less favorable 6-month functional outcomes measured by the 6-month GCS-Extended (odds ratio 0.36, $P = .002$) and 6-month Disability Rating Scale score (Diff. in means 3.86, $P = .002$) and a longer length of hospital stay (Diff. in means 11.0 days, $P < .001$).

CONCLUSION: We report potential risk factors for circulatory shock after moderate–severe TBI. Our study suggests that developing circulatory shock after moderate–severe TBI is associated with poor long-term functional outcomes.

KEY WORDS: Circulatory shock, Critical care, Multiorgan dysfunction, Traumatic brain injury

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Traumatic brain injury (TBI) is a leading cause of death and disability in the United States.[1] Critical care of moderate–severe TBI is aimed at limiting damage from primary brain injury and reducing secondary brain injuries, including maintaining hemodynamic stability and preventing multiorgan dysfunction.[2,3] Severe brain injury may result in disruption of autonomic tone and catecholamine surge. This maladaptive state is a potential mechanism for development of early circulatory shock after TBI and is associated with cerebral ischemia and disrupted cerebral hemodynamics.[4-9] Although early circulatory shock is associated with increased in-hospital mortality after severe TBI,[10] limited clinical data exist for impact of circulatory shock on long-term neurological outcomes.

Prevention and management of circulatory shock may reduce secondary brain injury and

ABBREVIATIONS: ABG, arterial blood gas; **BP,** blood pressure; **DRS,** Disability Rating Scale; **ED,** emergency department; **GOSE,** Glasgow Outcome Scale-Extended; **ISS,** Injury Severity Score; **MCC,** motorcycle collision; **MVC,** motor vehicle collision; **SBP,** systolic blood pressure; **SOFA,** sequential organ failure assessment; **TBI,** traumatic brain injury; **TRACK-TBI,** Transforming Clinical Research and Knowledge in TBI; **VS,** vegetative state; **WBC,** white blood cell count.

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improve outcomes after severe TBI through prompt recognition and goal-directed hemodynamic management of potentially modifiable factors. Identifying clinical risk factors in the acute period may facilitate recognition of patients at risk of circulatory shock after TBI and thereby improve both short-term and long-term neurological outcomes. To address these gaps, the aims of this study were to examine (1) emergency department (ED) risk factors for circulatory shock after moderate–severe TBI and (2) the association between circulatory shock and long-term clinical and functional outcomes after TBI.

METHODS

Database and Study Design

On approval from the Duke University Institutional Review Board, we conducted a retrospective cohort study using the Transforming Clinical Research and Knowledge in TBI (TRACK-TBI) database. TRACK-TBI is a prospective multicenter cohort study consisting of patients enrolled from emergency departments of level 1 trauma center. All patients within the data set were enrolled within 24 hours of TBI exposure. All participants or their legal authorized representatives provided written informed consent. Research questions for this study were generated after the design and completion of the TRACK-TBI study. The following criteria warranted exclusion from the TRACK-TBI cohort: any injury classified as American Spinal Injury Association Impairment Scale score of C or worse,[11] patients with debilitating neurological disease, patients who were incarcerated or in custody, patients who were pregnant, patients placed on in-patient psychiatric hold, or those enrolled in an interventional trial. Data that support the findings of this study are available on request.

Study Population

We examined adults and older adolescents (age ≥17 years) in the TRACK-TBI cohort with moderate–severe TBI, defined as a Glasgow Coma Scale (GCS) score of <13 after initial resuscitation, admitted to the intensive care unit (ICU) from the ED. We excluded patients with significant extracranial injury, defined as nonhead/neck Abbreviated Injury Scale scores >3, to examine the impact of brain injury itself. To identify patients who developed circulatory shock after hospital admission, we excluded patients requiring vasopressors before ED discharge.

Exposure, Outcomes, and Covariates

For our first aim, we identified risk factors for development of circulatory shock after moderate–severe TBI. Primary exposures were demographic characteristics (age, sex, race, and ethnicity), medical comorbidities (hypertension, cardiovascular disease, diabetes, neurological disease, and pulmonary disease), injury characteristics (injury cause, Injury Severity Score, and Rotterdam computed tomography [CT] score), and ED clinical variables. The primary outcome of interest was development of circulatory shock, as defined by scores ≥2 on the cardiovascular component of the sequential organ failure assessment (SOFA) (indicating at least the need for a vasopressor) within 72 hours of hospital admission.

For our second aim, we examined associations between development of circulatory shock and long-term outcomes. The primary exposure was development of circulatory shock, as defined above. Long-term outcomes were assessed through dichotomized 6-month Glasgow Outcome Scale-Extended (GOSE). GOSE 1 to 4 indicated poor long-term outcomes whereas GOSE 5 to 8 was considered good long-term outcomes.[12,13] In addition, we examined the length of hospital stay, ICU length of stay, in-hospital mortality, and 6-month score on the Disability Rating Scale (DRS).[14]

Statistical Methods

Descriptive statistics were used to examine demographic and clinical characteristics and ED clinical variables. Categorical variables are reported as number (percentage), and continuous variables are reported as mean (SD). Differences between subjects with and without circulatory shock were assessed using Fisher's exact tests for categorical variables and Mann–Whitney tests for continuous and ordinal variables (Table 1). Variables that were considered for a forward selection regression model for predicting circulatory shock had an entry criterion of P-value <.05. Results of the forward regression model are presented as odds ratios (OR) with 95% CI (Table 2).

We examined the association between the development of circulatory shock and long-term functional outcomes using multivariable logistic regression for binary outcomes, linear regression for continuous outcomes, and Cox proportional hazards regression for length of stay accounting for censoring because of in-hospital deaths (Table 3). Models were adjusted for age, sex, race, radiographic characteristics (Rotterdam CT score), ISS of nonhead, administration of any intravenous mannitol, and GCS score in the ED. To reduce possibility of type I errors (false positives), significance values were adjusted using a false discovery rate of 5%, per the Benjamini–Hochberg method. Sensitivity analyses were performed by examining variations of each outcome model for covariate adjustment and missingness (**Supplemental Table 1**, http://links.lww.com/NEU/D203). Propensity-weighted models used boosted regression to weight followed subjects according to how closely their demographic and injury characteristics resembled those of subjects who were lost to follow-up, whereas multiple imputation models used these characteristics to impute missing baseline and outcome values using chained equations and 10 imputed data sets. A P-value <.05 was considered statistically significant, and all analyses were performed using SPSS version 26.

RESULTS

Demographic and Clinical Characteristics of the Study Population

The final study population included 407 subjects from 18 different clinical sites in the TRACK-TBI cohort (Figure 1).

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TABLE 1. Demographic and Clinical Characteristics of the Study Population and Predictors of Circulatory Shock

Variable	Total	Circulatory shock		*P* value
		No	Yes	
Subjects	407	239	168	
Demographic characteristics				
Age (No. [%])				
Mean (SD)	40.4 (16.8)	38.9 (16.6)	42.4 (16.9)	.021
17-39 y	216 (53%)	134 (56%)	82 (49%)	.377
41-60 y	139 (34%)	77 (32%)	62 (37%)	
>60 y	52 (13%)	28 (12%)	24 (14%)	
Sex (No. [%])				
Male	324 (80%)	191 (80%)	133 (79%)	.901
Female	83 (20%)	48 (20%)	35 (21%)	
Race (No. [%])				
White	317 (80%)	179 (77%)	138 (85%)	<.001
Black	48 (12%)	40 (17%)	8 (5%)	
Others	29 (7%)	13 (6%)	16 (10%)	
Unknown	13	7	6	
Hispanic (No. [%])				
No	313 (79%)	175 (76%)	138 (84%)	.45
Yes	82 (21%)	56 (24%)	26 (16%)	
Unknown	12	8	4	
Medical history (No. [%])				
Cardiovascular (any)	68 (18%)	34 (15%)	34 (22%)	.101
Hypertension	57 (15%)	26 (12%)	31 (20%)	.028
Diabetes type I	1 (0%)	1 (0%)	0 (0%)	1.000
Diabetes type II	25 (7%)	12 (5%)	13 (8%)	.293
Neurological (any)	43 (11%)	21 (9%)	22 (14%)	.142
Pulmonary (any)	35 (9%)	20 (9%)	15 (10%)	.857
Unknown	29	15	14	
Injury characteristics				
Injury cause (No. [%])				
MVC occupant	101 (25%)	64 (27%)	37 (22%)	.179
MCC	55 (14%)	33 (14%)	22 (13%)	
MVC (cyclist or pedestrian)	63 (15%)	32 (13%)	31 (18%)	
Fall	99 (24%)	58 (24%)	41 (24%)	
Assault	34 (8%)	25 (10%)	9 (5%)	
Others/unknown	55 (14%)	27 (11%)	28 (17%)	
Injury cause (No. [%])				
Acceleration/deceleration	194 (48%)	109 (46%)	85 (51%)	.364
Blow to head	110 (27%)	59 (25%)	51 (30%)	.214
Head against object	268 (66%)	158 (66%)	110 (65%)	.916
Crush	10 (2%)	3 (1%)	7 (4%)	.100
Ground level fall	68 (17%)	45 (19%)	23 (14%)	.180
Fall from height	107 (26%)	59 (25%)	48 (29%)	.424
Other mechanisms	24 (6%)	14 (6%)	10 (6%)	1.000
ISS of nonhead/neck				
Mean (SD)	5.8 (6.4)	5.4 (6.3)	6.4 (6.4)	.172
Rotterdam CT score (No. [%])				
Mean (SD)	3.4 (1.2)	3.1 (1.1)	3.8 (1.3)	<.001
1	4 (1%)	4 (2%)	0 (0%)	
2	85 (23%)	65 (29%)	20 (13%)	
3	153 (41%)	96 (43%)	57 (38%)	
4	52 (14%)	26 (12%)	26 (17%)	
5	49 (13%)	20 (9%)	29 (19%)	
6	32 (9%)	12 (5%)	20 (13%)	
Unknown	32	16	16	
ED variables				

TABLE 1. Continued.

Variable	Total	Circulatory shock		*P* value
		No	Yes	
GCS ED arrival (No. [%])				
Mean (SD)	5.8 (3.1)	6.3 (3.2)	5.1 (2.9)	<.001
Severe (3-8)	305 (75%)	168 (70%)	137 (82%)	.011
Moderate (9-12)	102 (25%)	71 (30%)	31 (18%)	
ED reactive pupils (No. [%])				
Mean (SD)	1.48 (0.83)	1.58 (0.77)	1.36 (0.90)	.016
0	79 (22%)	35 (17%)	44 (29%)	.036
1	25 (7%)	15 (7%)	10 (7%)	
2	251 (71%)	153 (75%)	98 (64%)	
Unknown	52	36	16	
ED arrival SBP				
Mean (SD)	141.1 (29.2)	141.2 (29.0)	140.9 (29.6)	.922
Unknown	8	3	5	
ED arrival DBP				
Mean (SD)	87.7 (21.7)	86.3 (21.3)	89.9 (22.3)	.183
Unknown	45	17	28	
ED arrival heart rate				
Mean (SD)	92.0 (27.4)	93.4 (26.1)	90.0 (29.1)	.141
Unknown	12	6	6	
ED rate-pressure product				
Mean (SD)	12 969 (4938)	13 141 (4664)	12 719 (5314)	.169
Unknown	13	6	7	
ED temperature (°C)				
Mean (SD)	36.4 (0.9)	36.5 (0.8)	36.3 (1.0)	.095
Unknown	154	75	79	
ED WBC >12 (No. [%])				
No	147 (39%)	102 (46%)	45 (29%)	.001
Yes	230 (61%)	120 (54%)	110 (71%)	
Unknown	30	17	13	
ED lactate (units)				
Mean (SD)	11.4 (14.3)	13.5 (16.1)	8.8 (10.9)	.197
Unknown	193	118	75	
ABG pH (No. [%])				
≤7.2	154 (93%)	99 (94%)	55 (90%)	.332
>7.2	12 (7%)	6 (6%)	6 (10%)	
Unknown	253	143	110	
Tox screen (No. [%])				
Negative	80 (41%)	51 (39%)	29 (45%)	.441
Positive	114 (59%)	79 (61%)	35 (55%)	
Unknown	213	109	104	
Tox screen positives (No. [%])				
Opioids	23 (12%)	16 (12%)	7 (11%)	1.000
Benzodiazepines	64 (32%)	43 (32%)	21 (33%)	1.000
Cannabis	45 (23%)	34 (26%)	11 (17%)	.206
Amphetamines	10 (5%)	7 (5%)	3 (5%)	1.000
Cocaine	16 (8%)	14 (11%)	2 (3%)	.095
Barbiturates	2 (1%)	2 (2%)	0 (0%)	1.000
PCP	3 (2%)	2 (2%)	1 (2%)	1.000
Methadone	1 (1%)	1 (1%)	0 (0%)	1.000
Others	10 (5%)	6 (5%)	4 (6%)	.732
Unknown	213	109	104	
Blood EtOH–positive (No. [%])				
No	168 (54%)	98 (51%)	70 (59%)	.198
Yes	144 (46%)	95 (49%)	49 (41%)	
Unknown	95	46	49	

TABLE 1. Continued.

Variable	Total	Circulatory shock		*P* value
		No	Yes	
ED IV blood (No. [%])				
No	356 (87%)	220 (92%)	136 (81%)	.001
Yes	51 (13%)	19 (8%)	32 (19%)	
ED IV mannitol (No. [%])				
No	362 (89%)	224 (94%)	138 (82%)	<.001
Yes	45 (11%)	15 (6%)	30 (18%)	
ED cardiopulmonary arrest (No. [%])				
No	400 (99%)	237 (100%)	163 (98%)	.310
Yes	4 (1%)	1 (0%)	3 (2%)	
Unknown	3	1	2	
Intubated in ED (No. [%])				
No	233 (61%)	146 (65%)	87 (55%)	.043
Yes	148 (39%)	77 (35%)	71 (45%)	
Unknown	26	16	10	
ED/field hypotension (No. [%])				
No	342 (85%)	212 (89%)	130 (78%)	.002
Yes	62 (15%)	25 (11%)	37 (22%)	
Unknown	3	2	1	
ED/field hypoxia (No. [%])				
No	342 (85%)	212 (89%)	130 (78%)	.210
Yes	62 (15%)	25 (11%)	37 (22%)	
Unknown	3	2	1	
ED/field seizures (No. [%])				
No	368 (91%)	215 (90%)	153 (92%)	.728
Yes	37 (9%)	23 (10%)	14 (8%)	
Unknown	2	1	1	

ABG, arterial blood gas; CT, computed tomography; DBP, diastolic blood pressure; ED, emergency department; EtOH, ethyl alcohol; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; MCC, motorcycle collision; MVC, motor vehicle collision; SBP; systolic blood pressure; WBC, white blood cell count.
The baseline characteristics of those with and without circulatory shock are shown.

Details of demographic and clinical characteristics of the study population stratified by the presence of circulatory shock within 72 hours after admission are given in Table 1. The mean age for all patients was 40.4 ± 16.8 years; 324 (79.6%) patients were male; 317 (77.8%) were White race; and 82 (20.1%) identified as Hispanic ethnicity. The study population had a mean (±SD) ISS of nonhead/neck of 5.8 ± 6.4 and a Rotterdam CT Score of 3.4 ± 1.2. The mean GCS on arrival was 5.8 ± 3.1, and the ED arrival systolic blood pressure was 141.1 ± 29.2 mm Hg.

Predictors of Circulatory Shock

Of the 407 with moderate–severe TBI admitted to the ICU, 168 (41.2%) developed circulatory shock within 72 hours of admission. Several demographic and clinical characteristics were associated with the development of circulatory shock, as shown in Table 1: race ($P < .001$), CT Rotterdam score ($P < .001$), mean GCS on ED arrival ($P < .001$), mean pupil reactivity in the ERs ($P = .016$), white blood cell count in ED above 12 ($P = .001$), blood transfusion in ED ($P = .001$), mannitol administration in ED ($P < .001$), and development of hypotension in the ED ($P = .002$). Table 2 shows the results of the forward selection regression model identifying 4 significant variables: race, Rotterdam CT score, GCS in ED, and development of hypotension in ED.

Clinical and Functional Outcomes

Table 3 shows primary and secondary outcomes among patients who developed circulatory shock within 72 hours of admission and those who did not. Patients who developed early circulatory shock had a crude in-hospital mortality of 23%, compared with 12% for those who did not. Among patients who developed circulatory shock, 35% had a favorable 6-month GOSE, compared with 66% who did not develop circulatory shock.

Figure 2 shows the Kaplan–Meier curve depicting cumulative survival. Patients who developed circulatory shock had increased mortality at 6 months postinjury. Figure 3 shows the distribution of 6-month GOSE among patients with and without circulatory shock. After multivariable regression analysis, development of circulatory shock was associated with decreased odds for favorable

TABLE 2. Forward Selection Regression Model Identifying Risk Factors for Circulatory Shock Development

Variable	B	SE	Wald	df	*P*-value	Exp(B)[a] 95% CI
Constant	−0.70	0.35	4.00	1	.045	0.50 (0.25, 0.99)
Race (vs White)			13.69	3	.003	
Black	−1.37	0.42	10.60	1	.001	0.26 (0.11, 0.58)
Others	0.51	0.43	1.42	1	.234	1.66 (0.72, 3.81)
Unknown	−0.64	0.60	1.13	1	.288	0.53 (0.16, 1.71)
Rotterdam			24.34	5	<.001	
3	0.71	0.32	4.99	1	.026	2.03 (1.09, 3.78)
4	1.27	0.40	10.16	1	.001	3.56 (1.63, 7.76)
5	1.71	0.41	17.12	1	<.001	5.50 (2.45, 12.35)
6	1.59	0.47	11.50	1	.001	4.88 (1.95, 12.21)
Unknown	1.27	0.46	7.78	1	.005	3.57 (1.46, 8.74)
GCS ED (per 1 pt)	−0.10	0.04	7.24	1	.007	0.90 (0.84, 0.97)
Hypotension (vs no)			9.15	2	.010	
Yes	0.93	0.31	9.15	1	.002	2.53 (1.39, 4.62)
Unknown	0.15	1.26	0.01	1	.908	1.16 (0.10, 13.72)

ED, emergency department; GCS, Glasgow Coma Scale.
[a]Odds ratio.
Forward selection regression model examining associations between clinical and demographic risk factors and the development of circulatory shock.

6-month GOSE (OR 0.36, 95% CI 0.20-0.65, P = .002), worse 6-month DRS score (Diff. in means 3.86, 95% CI 1.62-6.11, P = .002), and longer length of stay (Diff. in means 11.0, 95% CI 5.7-13.8, P < .001). Sensitivity analysis for all models demonstrated robust risk estimates (**Supplementary Table 1**, http://links.lww.com/NEU/D203).

DISCUSSION

Key Results

We conducted a retrospective multicenter cohort study to describe ED risk factors for circulatory shock in patients with moderate–severe TBI and associations between early circulatory shock and long-term clinical and functional outcomes after injury. We found that (1) development of circulatory shock is common and is associated with multiple demographic and ED clinical variables and (2) development of circulatory shock is associated with poor long-term functional outcomes after TBI.

Interpretation

Circulatory shock has a multifactorial etiology after moderate–severe TBI.[3,15] Evidence suggests that after severe TBI, autonomic and inflammatory mediators are released into the circulation, resulting in widespread organ dysfunction.[4,16] Brain injury results in changes in autonomic tone and widespread catecholamine release.[3,17-19] It is hypothesized that this sympathomimetic state may be driving the failure of the cardiovascular, pulmonary, and renal systems.[3,20] Although sympathetic activation may initially be protective by preserving blood flow to the brain and other organs, this may eventually become maladaptive and result in systemic vasoconstriction and cardiac dysfunction.[21-23] The incidence of cardiac dysfunction after severe TBI is reported to be as high as 22% using traditional echocardiographic assessments and between 10% and 38% when more sensitive parameters of left

TABLE 3. Association of Circulatory Shock With Primary and Secondary Outcomes

Outcomes	N Total	Circulatory shock No	Circulatory shock Yes	Unadjusted Effect	Unadjusted *P*	Adjusted Effect	Adjusted *P*[a]	Adjusted 95% CI	Adjusted *P*[b]
Discharged alive[c]	407	88%	77%	Odds ratio 0.44	.002	Odds ratio 1.12	.765	Odds ratio 0.54-2.31	.765
6-mo GOSE 5-8[c]	306	66%	35%	Odds ratio 0.27	<.001	Odds ratio 0.36	.001	Odds ratio 0.20-0.65	.002
Length of stay[d], d	338	14.9	25.9	Diff. in means 11.0	<.001	Diff. in means 9.7	<.001	Diff. in means 5.7-13.8	<.001
6-mo DRS[d]	237	5.54	10.99	Diff. in means 5.45	<.001	Diff. in means 3.86	.001	Diff. in means 1.62-6.11	.002
Mortality through 6 mo[e]	407	12%	28%	Hazard ratio 2.67	<.001	Hazard ratio 1.14	.633	Hazard ratio 0.66-1.99	.765

DRS, Disability Rating Scale; GOSE, Glasgow Outcome Scale-Extended.
[a]Analysis adjusted for age, sex, race, Rotterdam score, ISS of nonhead, ED mannitol, and ED GCS.
[b]Multiple comparisons were used to further adjust significance values (Benjamini–Hochberg, m = 5).
[c]Dichotomous outcomes were analyzed through logistic regression and reported as odds ratios.
[d]Continuous outcomes were analyzed through linear regression and reported as difference in means.
[e]Outcomes in survival were analyzed through Cox regression with hazard ratios reported.
Regression models depicting the relationship of clinical outcomes and the development of circulatory shock.

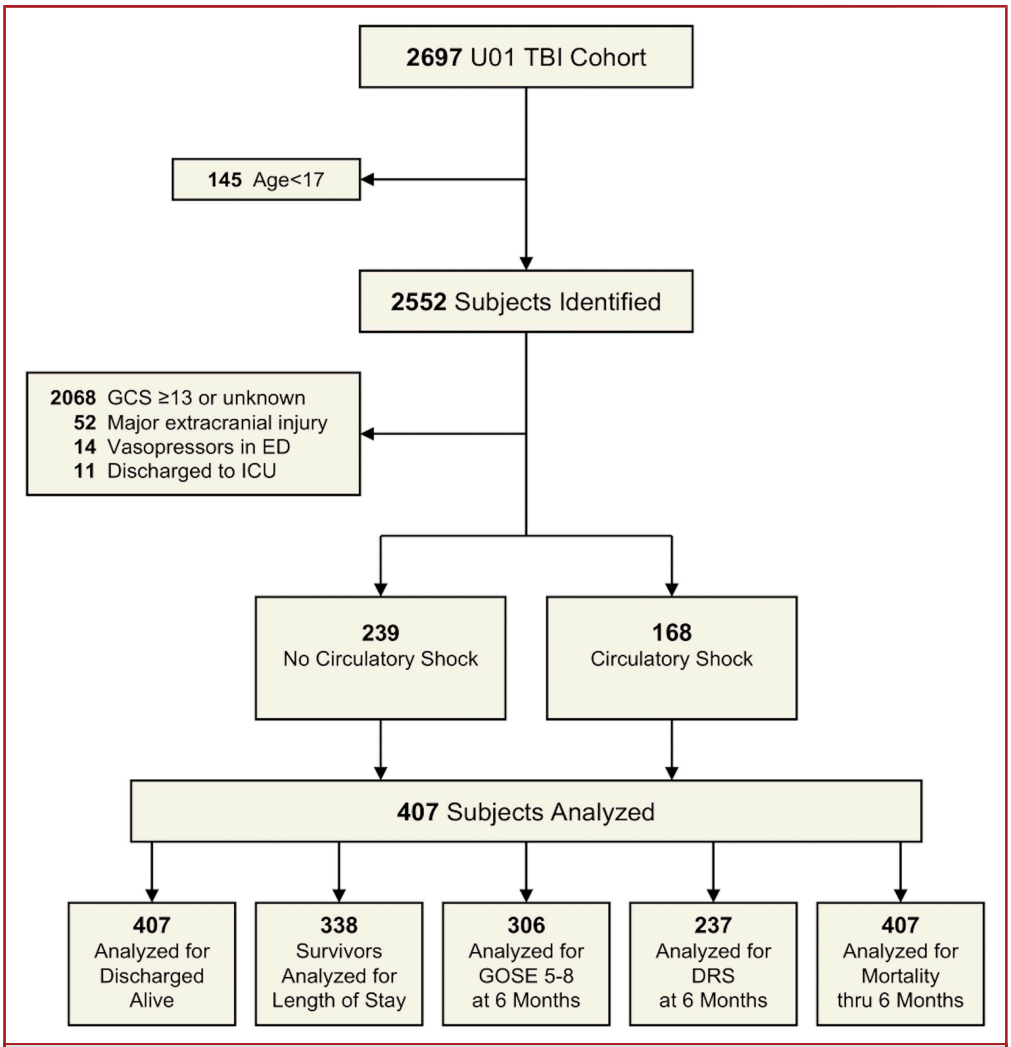

FIGURE 1. *Strengthening the Reporting of Observational Studies in Epidemiology inclusion and exclusion criteria. Flowchart of inclusion and exclusion designations for final subject analysis. DRS, Disability Rating Scale; ED, emergency department; GCS, Glasgow Coma Scale; GOSE, Glasgow Outcome Scale-Extended; ICU, intensive care unit; TBI, traumatic brain injury.*

ventricular functions are used.[23,24] Circulatory dysfunction is associated with development of multiorgan dysfunction within 72 hours after TBI and increased mortality.[3,16,22-32]

This widespread circulatory dysfunction manifests as episodes of hypotension after injury, where decreases in mean arterial pressures put the brain at risk of hypoxic and metabolic injury. An estimated 20% to 66% of patients with moderate to severe brain injury have at least 1 episode of early hypotension after TBI.[9,10,27,32] Current TBI guidelines for hemodynamic management suggest maintaining the systolic blood pressure at ≥100 mm Hg or ≥110 mm Hg depending on the patient age.[2] In cases of severe circulatory dysfunction, vasopressors may be used to restore and maintain adequate cerebral perfusion pressure by increasing mean arterial pressures.[2,33] Recent data suggest that vasopressors can be used initially to avoid hypotensive states and support cerebral perfusion pressure, but there is no association with improved survival.[34] Further work examining the impact of both endogenous and exogenous catecholamines in severe TBI is warranted.

We found that the development of circulatory shock after moderate–severe TBI is common and is associated with a variety of clinical variables at admission. Of the study population, 41.2% developed circulatory shock requiring intravenous vasopressors within 72 hours of admission. Possible predictors of the development of circulatory shock include 4 clinical variables identified using the forward selection process: Rotterdam CT scores above 2, development of hypotension, and low GCS on ED admission, and Black race was associated with decreased odds of developing circulatory shock.

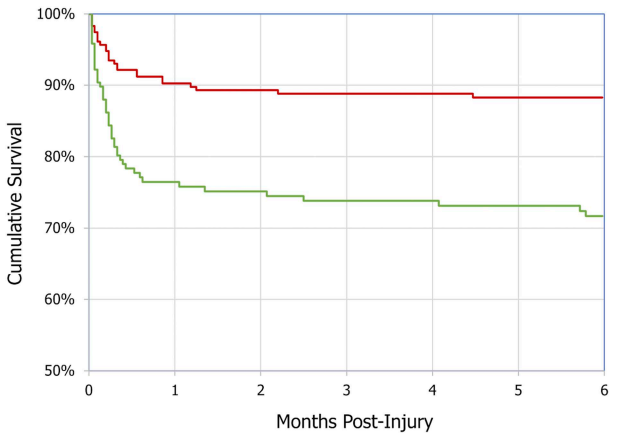

FIGURE 2. *Cumulative survival. Kaplan–Meier curve depicting cumulative survival after development of circulatory shock after severe TBI. The green line denotes patients who developed circulatory shock, and the red line denotes patients who did not develop circulatory shock. TBI, traumatic brain injury.*

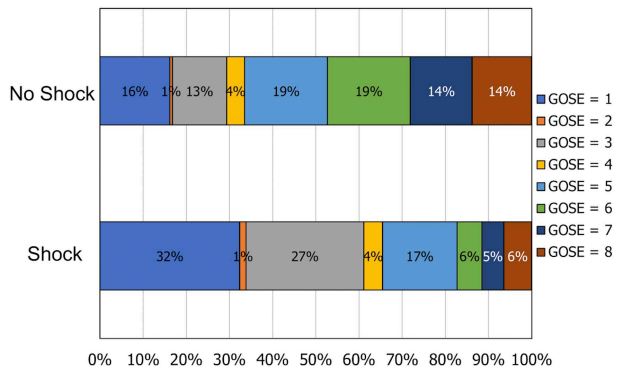

FIGURE 3. *Distribution of 6-month GOSE (shock vs no shock). Depiction of GOSE scores. The top bar denotes patients who did not develop circulatory shock, and the bottom bar denotes patients who developed circulatory shock. GOSE score: 1 = dead; 2 = VS; 3 = lower severe disability (lower SD); 4 = upper severe disability (upper SD); 5 = lower moderate disability (lower MD); 6 = upper moderate disability (upper MD); 7 = lower good recovery (lower GR); 8 = upper good recovery (upper GR). GOSE, Glasgow Outcome Scale-Extended; VS, vegetative state.*

Increased Rotterdam CT scores have been associated with increased mortality in adult patients with mild-to-severe TBI.[35-37] Ours is the first model to suggest a relationship between Rotterdam CT scores and development of circulatory shock. Our model suggests that higher GCS on admission to the ED may decrease odds of developing circulatory shock. Initial GCS is a well-known efficient predictor of in-hospital mortality after trauma.[27,38] No studies thus far have examined the predictive value of GCS in development of shock in moderate–severe TBI.

Our model suggests that Black race decreased the odds of developing circulatory shock. Given that the criterion for circulatory shock in this study was a SOFA score >2 defined by the initiation of vasopressors, a possible explanation is that the Black population in our data set was less likely to receive vasopressors. Perhaps this is secondary to increased prevalence of hypertension among the Black population and a lower likelihood of meeting the threshold for vasopressor use.[39] Alternatively, this finding may be secondary to racial disparities and inequitable utilization of vasopressors during hospitalization. Given the limited scope of our study, future work will be critical in examining racial and ethical health disparities related to TBI.

In our analysis of outcomes, we found that development of early circulatory shock was associated with worse scores on 6-month GOSE, 6-month DRS, and longer length of hospital stay compared with those who did not develop shock. Previous work analyzing associations of cardiovascular dysfunction and outcomes has mainly focused on the strong association of hypotension and in-hospital mortality.[6,7,27,32,40] Butcher et al[7] were first to demonstrate that low admission blood pressure (BP) was associated with the worse GOS score at 6 months. In a small retrospective cohort study, Schirmer-Mikalsen et al[10] found that hypotension (<90 mm Hg) within 24 hours of admission predicted an unfavorable GOS at 6 months. They support current guidelines to avoid instances of early hypotension in severe TBI; however, they are unable to comment on the relationship between the development of circulatory shock and the utilization of vasopressors with long-term functional outcomes. Indeed, this is the first multicenter study to analyze circulatory shock within 72 hours of admission and its association with 6-month GOSE and 6-month DRS scores. Our study suggests the presence of multivariate risk factors for the development of circulatory shock after TBI beyond BP that may affect long-term outcomes and confirms the importance of early recognition and prompt management of circulatory shock after TBI. Future studies should expand on this work and look to further elucidate the mechanisms of circulatory shock after severe TBI, develop directed treatments for this pathology, and assess racial and ethnic biases, which may affect clinical treatment and outcomes.

Limitations

First, the retrospective nature of this study limits conclusions that can be established and creates the risk of residual confounding. Second, although detailed information on pharmaceutical exposures (ie, vasopressor use) was available, we could not ascertain the underlying mechanisms for hypotension; therefore, the underlying shock state could not be assessed. Vasopressor utilization proxied circulatory dysfunction because detailed information on the exact shock state and episodes of hypotension could not be gathered. In addition, the requirement of vasopressors as defined by a SOFA score >2 does not distinguish between populations of patients receiving vasopressors for refractory intracranial hypertension with impaired cerebral

perfusion pressure or intraoperative blood loss vs hemodynamically unstable patients. Third, several clinical variables, such as BP and temperature, are recorded by automatic devices, which may misestimate true vital sign values.[41] Fourth, our analysis is limited to the presence or absence of circulatory shock 72 hours after admission and was not powered to conduct an analysis of mediators such as duration. Fifth, significance values are generally invalid in stepwise regression models. Although our model suggests 4 predictors of shock, these are subject to bias; further modeling is needed in future studies. Our study suggests that there may be a relationship between race and development of circulatory shock. Future studies with increased population sizes and attention to differential outcomes by race in morbidity and mortality are warranted. Finally, a relatively small number of cases met study entry criteria, and although the TRACK-TBI database uses a robust sample size, there is the potential for diminished accuracy in the risk estimates given a lack of statistical power.

Generalizability

We derived our cohort from the TRACK-TBI database, which is composed of an 18-center prospective study conducted from 2014 to 2020. We believe that the cohort is representative of high-volume tertiary-care centers and the results are generalizable to modern neurosurgical and critical care practices.

CONCLUSION

In a multicenter population of moderate–severe TBI patients, we observed that development of early circulatory shock was common and associated with several demographic and ED clinical variables. Patients who developed circulatory shock had worse functional outcomes at 6 months. Prompt recognition and management of early hemodynamic instability may help improve outcomes for these patients.

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Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES

1. Prevention CfDCa. *Surveillance Report of Traumatic Brain Injury-Related Emergency Department Visits, Hospitalizations, and Deaths-United States, 2014*. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services; 2019.
2. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury, Fourth Edition. *Neurosurgery.* 2017;80(1):6-15.
3. Krishnamoorthy V, Komisarow JM, Laskowitz DT, Vavilala MS. Multi-organ dysfunction following severe traumatic brain injury: epidemiology, mechanisms, and clinical management. *Chest.* 2021;160(3):956-964.
4. Vavilala MS, Lee LA, Lam AM. Cerebral blood flow and vascular physiology. *Anesthesiol Clin North Am.* 2002;20(2):247-264, v.
5. Czosnyka M, Smielewski P, Piechnik S, Steiner LA, Pickard JD. Cerebral autoregulation following head injury. *J Neurosurg.* 2001;95(5):756-763.
6. Miller JD, Sweet RC, Narayan R, Becker DP. Early insults to the injured brain. *JAMA.* 1978;240(5):439-442.
7. Butcher I, Maas AI, Lu J, et al. Prognostic value of admission blood pressure in traumatic brain injury: results from the IMPACT study. *J Neurotrauma.* 2007;24(2):294-302.
8. Brenner M, Stein DM, Hu PF, Aarabi B, Sheth K, Scalea TM. Traditional systolic blood pressure targets underestimate hypotension-induced secondary brain injury. *J Trauma Acute Care Surg.* 2012;72(5):1135-1139.
9. Manley G, Knudson MM, Morabito D, Damron S, Erickson V, Pitts L. Hypotension, hypoxia, and head injury: frequency, duration, and consequences. *Arch Surg.* 2001;136(10):1118-1123.
10. Schirmer-Mikalsen K, Vik A, Gisvold SE, Skandsen T, Hynne H, Klepstad P. Severe head injury: control of physiological variables, organ failure and complications in the intensive care unit. *Acta Anaesthesiol Scand.* 2007;51(9):1194-1201.
11. El Masry WS, Tsubo M, Katoh S, El Miligui YH, Khan A. Validation of the American Spinal Injury Association (ASIA) motor score and the National Acute Spinal Cord Injury Study (NASCIS) motor score. *Spine (Phila Pa 1976).* 1996;21(5):614-619.
12. Levin HS, Boake C, Song J, et al. Validity and sensitivity to change of the extended Glasgow Outcome Scale in mild to moderate traumatic brain injury. *J Neurotrauma.* 2001;18(6):575-584.
13. Shukla D, Devi BI, Agrawal A. Outcome measures for traumatic brain injury. *Clin Neurol Neurosurg.* 2011;113(6):435-441.
14. Rappaport M, Hall KM, Hopkins K, Belleza T, Cope DN. Disability rating scale for severe head trauma: coma to community. *Arch Phys Med Rehabil.* 1982;63(3):118-123.
15. Vincent JL, De Backer D. Circulatory shock. *N Engl J Med.* 2013;369(18):1726-1734.
16. Lee S, Hwang H, Yamal JM, et al. IMPACT probability of poor outcome and plasma cytokine concentrations are associated with multiple organ dysfunction syndrome following traumatic brain injury. *J Neurosurg.* 2019;131(6):1931-1937.
17. Rosner MJ, Newsome HH, Becker DP. Mechanical brain injury: the sympathoadrenal response. *J Neurosurg.* 1984;61(1):76-86.
18. Kõiv L, Merisalu E, Zilmer K, Tomberg T, Kaasik AE. Changes of sympathoadrenal and hypothalamo-pituitary-adrenocortical system in patients with head injury. *Acta Neurol Scand.* 1997;96(1):52-58.
19. McDonald SJ, Sharkey JM, Sun M, et al. Beyond the brain: peripheral interactions after traumatic brain injury. *J Neurotrauma.* 2020;37(5):770-781.
20. Tracey KJ. The inflammatory reflex. *Nature.* 2002;420(6917):853-859.
21. Krishnamoorthy V, Mackensen GB, Gibbons EF, Vavilala MS. Cardiac dysfunction after neurologic injury: what do we know and where are we going? *Chest.* 2016;149(5):1325-1331.
22. Krishnamoorthy V, Rowhani-Rahbar A, Chaikittisilpa N, et al. Association of early hemodynamic profile and the development of systolic dysfunction following traumatic brain injury. *Neurocrit Care.* 2017;26(3):379-387.
23. Krishnamoorthy V, Rowhani-Rahbar A, Gibbons EF, et al. Early systolic dysfunction following traumatic brain injury: a cohort study. *Crit Care Med.* 2017;45(6):1028-1036.
24. Prathep S, Sharma D, Hallman M, et al. Preliminary report on cardiac dysfunction after isolated traumatic brain injury. *Crit Care Med.* 2014;42(1):142-147.
25. Aisiku IP, Yamal JM, Doshi P, et al. The incidence of ARDS and associated mortality in severe TBI using the Berlin definition. *J Trauma Acute Care Surg.* 2016;80(2):308-312.
26. Bratton SL, Davis RL. Acute lung injury in isolated traumatic brain injury. *Neurosurgery.* 1997;40(4):707-712; discussion 712.
27. Corral L, Javierre CF, Ventura JL, Marcos P, Herrero JI, Mañez R. Impact of non-neurological complications in severe traumatic brain injury outcome. *Crit Care.* 2012;16(2):R44.

28. Holland MC, Mackersie RC, Morabito D, et al. The development of acute lung injury is associated with worse neurologic outcome in patients with severe traumatic brain injury. *J Trauma.* 2003;55(1):106-111.
29. Moore EM, Bellomo R, Nichol A, Harley N, Macisaac C, Cooper DJ. The incidence of acute kidney injury in patients with traumatic brain injury. *Ren Fail.* 2010;32(9):1060-1065.
30. Ramtinfar S, Chabok SY, Chari AJ, Reihanian Z, Leili EK, Alizadeh A. Early detection of nonneurologic organ failure in patients with severe traumatic brain injury: multiple organ dysfunction score or sequential organ failure assessment?. *Indian J Crit Care Med.* 2016;20(10):575-580.
31. Mascia L, Sakr Y, Pasero D, Payen D, Reinhart K, Vincent JL. Extracranial complications in patients with acute brain injury: a post-hoc analysis of the SOAP study. *Intensive Care Med.* 2008;34(4):720-727.
32. Jeremitsky E, Omert L, Dunham CM, Protetch J, Rodriguez A. Harbingers of poor outcome the day after severe brain injury: hypothermia, hypoxia, and hypoperfusion. *J Trauma.* 2003;54(2):312-319.
33. Sookplung P, Siriussawakul A, Malakouti A, et al. Vasopressor use and effect on blood pressure after severe adult traumatic brain injury. *Neurocrit Care.* 2011;15(1):46-54.
34. Dhillon NK, Huang R, Mason R, et al. Vasopressors in traumatic brain injury: quantifying their effect on mortality. *Am J Surg.* 2020;220(6):1498-1502.
35. Mohammadifard M, Ghaemi K, Hanif H, Sharifzadeh G, Haghparast M. Marshall and Rotterdam computed tomography scores in predicting early deaths after brain trauma. *Eur J Transl Myol.* 2018;28(3):7542.
36. Mata-Mbemba D, Mugikura S, Nakagawa A, et al. Early CT findings to predict early death in patients with traumatic brain injury: Marshall and Rotterdam CT scoring systems compared in the major academic tertiary care hospital in northeastern Japan. *Acad Radiol.* 2014;21(5):605-611.
37. Katar S, Aydin Ozturk P, Ozel M, et al. The use of Rotterdam CT score for prediction of outcomes in pediatric traumatic brain injury patients admitted to emergency service. *Pediatr Neurosurg.* 2020;55(5):1-7.
38. Moore L, Lavoie A, Camden S, et al. Statistical validation of the Glasgow Coma Score. *J Trauma.* 2006;60(6):1238-1243; discussion 1243-1234.
39. Lackland DT. Racial differences in hypertension: implications for high blood pressure management. *Am J Med Sci.* 2014;348(2):135-138.
40. Chesnut RM. Avoidance of hypotension: conditio sine qua non of successful severe head-injury management. *J Trauma.* 1997;42(5 suppl):S4-S9.
41. Cienki JJ, DeLuca LA, Daniel N. The validity of emergency department triage blood pressure measurements. *Acad Emerg Med.* 2004;11(3):237-243.

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Supplemental Table 1. Sensitivity analysis. Sensitivity analyses examining variations of each outcome model for covariate adjustment and missingness. **A**, Dichotomous outcome, logistic regression; **B**, Continuous outcome, linear regression; **C**, Survival, Cox proportional hazards regression; DRS, Disability Rating Scale; GOSE, Glasgow Outcome Scale-Extended; MI, multiple imputation.

COMMENT

The authors have presented a "retrospective multicenter cohort study to describe ED risk factors for circulatory shock in patients with moderate–severe TBI and associations between early circulatory shock and long-term clinical and functional outcomes following injury."

This work is important and serves as a foundation for better understanding of a current knowledge gap. The conclusion that "Prompt recognition and management of early hemodynamic instability may help improve outcomes for these patients" is agreed. These findings, however, are not particularly novel in the field. The more interesting aspects of this work are derived from the identified limitations: the role of race, the specifics of the hypotension, etc. An additional area not addressed in the manuscript is the decision to limit the scope to the moderate–severe cohort. Inclusion of the risk associated with mild TBI patients and a more comprehensive assessment of the TBI patient would also be of value.

Overall, this is a strong manuscript, focusing on an important clinical question. Although the conclusions do not offer anything additional in our current management of TBI in limiting secondary injuries, the findings allow a foundation from which additional studies might be launched. There are many unanswered questions, and this work nicely frames further investigations.

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