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Cushing's sign and severe traumatic brain injury in children after blunt trauma: a nationwide retrospective cohort study in Japan

Tetsuya Yumoto,[1,2] Hiromichi Naito,[1] Takashi Yorifuji,[3] Hiroki Maeyama,[2] Yoshinori Kosaki,[1] Hirotsugu Yamamoto,[1] Kohei Tsukahara,[1] Takaaki Osako,[1] Atsunori Nakao[1,2]

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[1]Advanced Emergency and Critical Care Medical Center, Okayama University Hospital, Okayama, Japan
[2]Department of Emergency and Critical Care Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan
[3]Department of Human Ecology, Okayama University Graduate School of Environmental and Life Science, Okayama, Japan

Correspondence to
Dr Tetsuya Yumoto; tyumoto@cc.okayama-u.ac.jp

ABSTRACT

Objective We tested whether Cushing's sign could predict severe traumatic brain injury (TBI) requiring immediate neurosurgical intervention (BI-NSI) in children after blunt trauma.

Design Retrospective cohort study using Japan Trauma Data Bank.

Setting Emergency and critical care centres in secondary and tertiary hospitals in Japan.

Participants Children between the ages of 2 and 15 years with Glasgow Coma Scale motor scores of 5 or less at presentation after blunt trauma from 2004 to 2015 were included. A total of 1480 paediatric patients were analysed.

Primary outcome measures Patients requiring neurosurgical intervention within 24 hours of hospital arrival and patients who died due to isolated severe TBI were defined as BI-NSI. The combination of systolic blood pressure (SBP) and heart rate (HR) on arrival, which were respectively divided into tertiles, and its correlation with BI-NSI were investigated using a multiple logistic regression model.

Results In the study cohort, 297 (20.1%) exhibited BI-NSI. After adjusting for sex, age category and with or without haemorrhage shock, groups with higher SBP and lower HR (SBP ≥135 mm Hg; HR ≤92 bpm) were significantly associated with BI-NSI (OR 2.84, 95% CI 1.68 to 4.80, P<0.001) compared with the patients with normal vital signs. In age-specific analysis, hypertension and bradycardia were significantly associated with BI-NSI in a group of 7–10 and 11–15 years of age; however, no significant association was observed in a group of 2–6 years of age.

Conclusions Cushing's sign after blunt trauma was significantly associated with BI-NSI in school-age children and young adolescents.

Strength and limitations of this study

- ► A nationwide retrospective cohort study from Japan Trauma Data Bank.
- ► Relationship between Cushing's sign and severe traumatic brain injury requiring immediate neurosurgical intervention in paediatric patients with traumatic brain injury using a multiple logistic regression model.
- ► A large number of patients were excluded due to missing data.
- ► Detailed injury patterns based on CT classification, type of craniotomy, cause of death and information on whether intracranial pressure was monitored and the actual data if measured were unavailable due to its nature of retrospective analysis.

INTRODUCTION

Traumatic brain injury (TBI) is a critical global public health problem, given the number of children and youth affected.[1 2] Early diagnosis and management of severe TBI is crucial to reduce mortality and morbidity.[3]

The efficacy of intracranial pressure monitoring in paediatric patients with severe TBI remains controversial[4]; however, intracranial hypertension is associated with high mortality and unfavourable neurological outcomes.[5–9] If intracranial pressure increases after TBI, systemic blood pressure rises as a compensatory mechanism to maintain cerebral perfusion pressure.[10] Cushing's triad of respiratory irregularity, hypertension and bradycardia is a classic sign of intracranial hypertension.[11] It usually serves as a warning sign of brain herniation. Hypotension in paediatric patients with severe TBI is also associated with poor outcomes due to decreased cerebral perfusion pressure.[12 13]

Although evidence is scant, as early decompressive surgery may be beneficial in children with severe TBI,[14] rapid identification of those who require surgical intervention plays an important role in improving outcomes. Cushing's sign has been demonstrated to be a weak but important predictor of the requirement for urgent neurosurgical treatment in adult

TBI.[15] However, its clinical importance in the paediatric population has not been elucidated. We hypothesised that Cushing's sign at emergency department presentation could predict severe TBI requiring immediate neurosurgical intervention (BI-NSI) in children. The purpose of this study was to investigate the combination of systolic blood pressure (SBP) and heart rate (HR) in paediatric patients with altered mental status on admission after TBI and its correlation with BI-NSI.

METHODS

Study design and data collection

This was a nationwide retrospective cohort study using data from the Japan Trauma Data Bank (JTDB), which represents one of the largest trauma databases in the world.[16] The JTDB was created in 2003 with the Japanese Association for Acute Medicine (Committee for Clinical Care Evaluation) and the Japanese Association for the Surgery of Trauma (Trauma Surgery Committee).[17] As of March 2016, 256 emergency and critical care centres in secondary and tertiary hospitals participated in Japanese trauma care and research. The registry database includes patient demographics, mechanism of injury, vital signs on arrival, Injury Severity Score (ISS), surgical procedures and discharge status. The Okayama University Hospital ethical committee approved this study (ID 1708–001). Because of the anonymous nature of the data, they waived the requirement for informed consent.

Participants and definitions

All trauma patients logged in the JTDB from January 2004 to December 2015 were assessed for eligibility. In this study, the paediatric population was defined as children under 16 years of age. Children who were younger than 2 years old were excluded because of rapid changes in physiology in the first 2 years of life.[18 19] Patients presenting with blunt trauma, who were directly transported from the injury location, and with Glasgow Coma Scale (GCS) motor scores of 5 or less, which implicates severe TBI, were included.[20] Patients who arrived in cardiac arrest or with head Abbreviated Injury Scale (AIS) score of 6 were excluded. Patients were also excluded if demographic or vital sign data were missing.

BI-NSI was defined as severe TBI needing craniotomy or burr hole evacuation within the first 24 hours of admission.[21–24] To minimise survivorship bias, non-surviving patients with head AIS score of 5 and ISS lower than 34 who were considered dead due to isolated severe TBI were also defined as having BI-NSI.[15] As inaccuracies in respiratory measurement in children have been demonstrated,[25] the combination of SBP and HR were assessed to determine the clinical significance of Cushing's sign.

Patients were divided into three age groups: 2–6 years old, 7–10 years old and 11–15 years old based on age-specific mean arterial pressure or cerebral perfusion pressure thresholds.[18 19 26]

Statistical analysis

Data are shown as numbers and percentages for categorical variables, mean and SD, or median and IQRs for continuous variables depending on their distributions. BI-NSI and non–BI-NSI group patients were compared in the overall population and in the age-specific groups. Comparisons between the groups were made using the X^2 test, Student's t-test or Mann-Whitney U test as appropriate.

We first evaluated the associations of SBP and HR with BI-NSI independently using a restricted cubic spline function. We used four knots for SBP and HR to incorporate the spline functions into multiple logistic regression models, which adjusted for sex, age category and with or without the need for emergency thoracotomy, laparotomy or transcatheter arterial embolisation (TAE) to control haemorrhage. We then obtained the adjusted ORs with their 95% CIs for each SBP and HR using the medians of both indicators (ie, 124 mm Hg for SBP and 105 beats/min for HR) as our reference.

Overall population and each age group were, respectively, categorised into nine groups according to each tertile (low, normal and high) of SBP and HR to assess the associations of the combination of SBP and HR with BI-NSI. To determine the adjusted ORs with their 95% CIs for BI-NSI in overall population according to the categories of the combination of SBP and HR, we developed a multiple logistic regression model after adjusting for age groups (2–6 vs 7–10 vs 11–15 years old), sex and with or without the need for emergency thoracotomy, laparotomy or TAE to control haemorrhage,[15 27] with normal SBP and normal HR group as the reference category.[28 29] Age group-specific adjusted ORs and their 95% CIs were also evaluated after adjusting for sex and with or without the need for emergency thoracotomy, laparotomy or TAE to control haemorrhage. The Hosmer-Lemeshow test was used for assessing the calibration of the models. The Nagelkerke's R^2 value was calculated to evaluate the goodness of fit of the models.

A sensitivity analysis was performed that excluded subjects who required emergency thoracotomy, laparotomy or TAE to control haemorrhage and the patients with spinal cord injury for overall population and each age group.

A two-tailed p value of <0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics V.25 (IBM SPSS, Chicago, Illinois, USA) except for spline analyses, which was conducted by Stata SE V.15 statistical software (StataCorp., College Station, Texas, USA).

RESULTS

Study population

A total of 236 101 trauma patients were registered in the JTDB during the study period. Among them, 1480

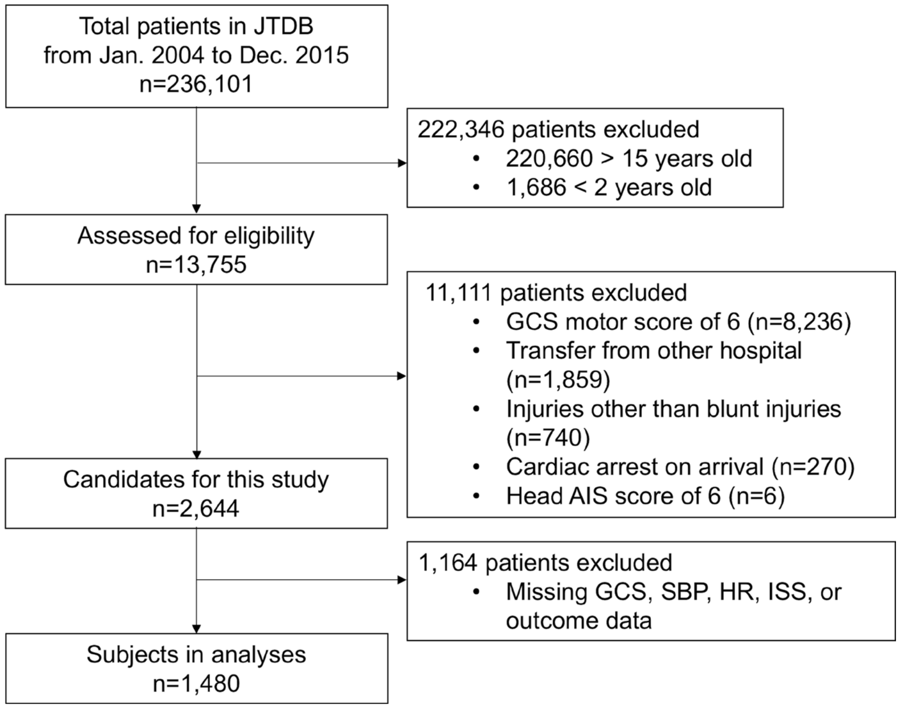

Figure 1 Flow diagram of the study population. AIS, Abbreviated Injury Scale; GCS, Glasgow Coma Scale; HR, heart rate; ISS, Injury Severity Score; JTDB, Japan Trauma Data Bank; SBP, systolic blood pressure.

paediatric trauma patients met the inclusion criteria. Figure 1 shows a flow diagram of the study population. Study population characteristics are summarised in online supplementary table 1S. The 2–6, 7–10 and 11–15 years old age groups included 418, 493 and 569 patients, respectively. Of the study cohort, 297 (20.1%) exhibited BI-NSI. Of 297 patients, 268 patients required burr hole evacuation (n=93) and/or craniotomy (n=202) and 29 patients were considered dead due to isolated severe TBI without neurosurgical intervention.

Comparison between BI-NSI group and non–BI-NSI group

In the overall population, patients with BI-NSI were compared with the non–BI-NSI group (table 1). The BI-NSI group had higher SBP (128 vs 123 mm Hg, P=0.009) and lower HR (98 vs 107 beats/min, P<0.001). In age-specific analysis, there was no significant difference in the 2–6 and the 7–10 years old age groups with respect to SBP (118 vs 120 mm Hg, P=0.599, 123 vs 122 mm Hg, P=0.307, respectively).

Multivariable relationship between SBP or HR and BI-NSI

As shown in figure 2A,B, the associations of SBP and HR with BI-NSI using cubic splines were J-shaped. In particular, higher values of SBP and lower values of HR were associated with increased risk of BI-NSI.

Multivariable relationship between the combination of SBP and HR and BI-NSI

In overall population, patients with higher SBP and lower HR (SBP ≥135 mm Hg; HR ≤92 beats/min, OR 2.84, 95% CI 1.68 to 4.80, P<0.001) were significantly associated with BI-NSI compared with the reference group, which was defined as patients with normal vital signs (table 2). The non-significant result of Hosmer-Lemeshow test (χ^2=7.528, df=8, P=0.481) showed that the model had a good fit to the data. The Nagelkerke's R^2 value was 0.040.

In age-specific analysis, although no significant association was observed between the combination of SBP and HR and BI-NSI in a group of 2–6 years of age (table 3A), hypertension and bradycardia were significantly associated with BI-NSI in a group of 7–10 and 11–15 years of age (table 3B,C). The non-significant result of Hosmer-Lemeshow test (2–6 years old; χ^2=5.28, df=8, P=0.727, 7–10 years old; χ^2=2.967, df=8, P=0.936, 11–15 years old; χ^2=2.48, df=8, P=0.963) also demonstrated that the model had a good fit to the data. The Nagelkerke's R^2 values was 0.038, 0.058 and 0.074, respectively.

Similar results were obtained for the sensitivity analysis in which the patients who required emergency thoracotomy, laparotomy or TAE to control haemorrhage and the patients with spinal cord injury were removed from the analysis (see online supplementary table 2S).

DISCUSSION

In this nationwide retrospective cohort study, we found that the combination of bradycardia and hypertension, which are the components of Cushing's sign, with abnormal GCS motor score at presentation in school-age children and young adolescents after severe blunt trauma was a significant predictor of BI-NSI, which was defined as severe TBI requiring immediate neurosurgical intervention, or death due to possible isolated severe TBI.

Table 1 Overall and age-specific characteristics of the severe traumatic brain injury requiring immediate neurosurgical intervention (BI-NSI) and non-BI-NSI groups

	Overall			2 to 6 years old		
	BI-NSI	Non BI-NSI	P value	BI-NSI	Non BI-NSI	P value
	n=297	n=1183		n=62	n=356	
Age (years)	9.7 (3.9)	8.9 (4.0)	0.002	4.0 (1.6)	4.0 (1.5)	0.860
Male, n (%)	209 (70.4)	798 (67.5)	0.366	44 (71.0)	237 (66.6)	0.559
Mechanism of injury			0.273			0.001
Traffic accident, n (%)	204 (68.7)	846 (71.5)		22 (35.5)	208 (58.4)	
Fall, n (%)	68 (22.9)	272 (23.0)		33 (53.2)	133 (37.4)	
Other, n (%)	25 (8.4)	65 (5.5)		7 (11.3)	15 (4.2)	
SBP (mm Hg)	128 (111, 147)	123 (110, 138)	0.009	118 (100, 139)	120 (109, 135)	0.599
HR (beats/min)	98 (78, 120)	107 (89, 128)	<0.001	114 (86, 135)	120 (100, 143)	0.029
GCS	6 (4, 8)	9 (7, 11)	<0.001	6 (4, 8)	10 (7, 12)	<0.001
*Surgery or TAE, n (%)	13 (4.4)	70 (5.9)	0.397	1 (1.6)	18 (5.1)	0.332
Spinal cord injury, n (%)	3 (1.0)	6 (0.5)	0.396	0 (0.0)	1 (0.3)	1
ISS	25 (20, 33)	18 (10, 29)	<0.001	25 (16, 27)	17 (9, 25)	<0.001
Hospital mortality, n (%)	67 (21.9)	68 (5.8)	<0.001	15 (24.2)	14 (4.0)	<0.001
	7 to 10 years old			**11 to 15 years old**		
	n=103	n=390		n=132	n=437	
Age (years)	8.4 (1.1)	8.3 (1.1)	0.468	13.4 (1.4)	13.3 (1.4)	0.696
Male, n (%)	69 (67.0)	266 (68.4)	0.813	96 (72.7)	295 (67.5)	0.285
Mechanism of injury			0.141			0.881
Traffic accident, n (%)	80 (77.7)	317 (81.3)		102 (77.3)	321 (73.5)	
Fall, n (%)	14 (13.6)	56 (14.4)		21 (15.9)	83 (19.0)	
Other, n (%)	9 (8.7)	17 (4.3)		9 (6.8)	33 (7.5)	
SBP (mm Hg)	123 (112, 142)	122 (110, 136)	0.307	135 (117, 151)	127 (113, 142)	0.006
HR (beats/min)	95 (79, 120)	108 (89, 127)	<0.001	92 (73, 117)	96 (80, 115)	0.183
GCS	6 (4, 8)	9 (7, 11)	<0.001	7 (4, 8)	8 (6, 10)	<0.001
*Surgery or TAE, n (%)	3 (2.9)	25 (6.4)	0.233	9 (6.8)	27 (6.2)	0.838
Spinal cord injury, n (%)	0 (0.0)	1 (0.3)	1.000	3 (2.3)	4 (0.9)	0.206
ISS	25 (20, 32)	20 (10, 29)	<0.001	26 (25, 35)	21 (14, 30)	<0.001
Hospital mortality, n (%)	26 (25.2)	20 (5.1)	<0.001	24 (18.2)	34 (7.8)	0.001

*Emergency thoracotomy, laparotomy or TAE to control haemorrhage.
GCS, Glasgow Coma Scale; HR, heart rate; ISS, Injury Severity Score; SBP, systolic blood pressure; TAE, transcatheter arterial embolisation.

As initial management can significantly affect outcomes of severe TBI in children, early identification and treatment are necessary to prevent secondary injury specifically induced by hypotension and hypoxia.[3 30] Several immediate screening methods to determine the presence of severe TBI in paediatric patients are available.[31–33] No motor response or fixed and bilaterally dilated pupils were associated with a higher mortality rate in paediatric patients with severe TBI.[31] On physical examination in the emergency department, the presence of altered mental status, signs of skull base fracture and vomiting have been reported as significant predictors of moderate to severe TBI in children.[32] In a large cohort of minor TBI children 2 years of age or older with GCS scores of 14–15, findings including normal mental status, no loss of consciousness, no severe mechanism of injury, no vomiting, no severe headache and no signs of basilar skull fracture were associated with a very low risk of significant TBI.[33]

As for physiological parameters, the study population in our cohort (median ISS, 21) exhibited higher SBP and relatively higher HR for each age group compared with normal children at rest, which was consistent with data from prior studies.[34 35] In comparison between the groups, children with BI-NSI showed significantly higher SBP and lower HR to some extent compared with the non-BI-NSI group, but these differences may not necessarily be clinically significant. Similar results have been observed, so the relative bradycardia after

 Yumoto T, et al. BMJ Open 2018;8:e020781. doi:10.1136/bmjopen-2017-020781

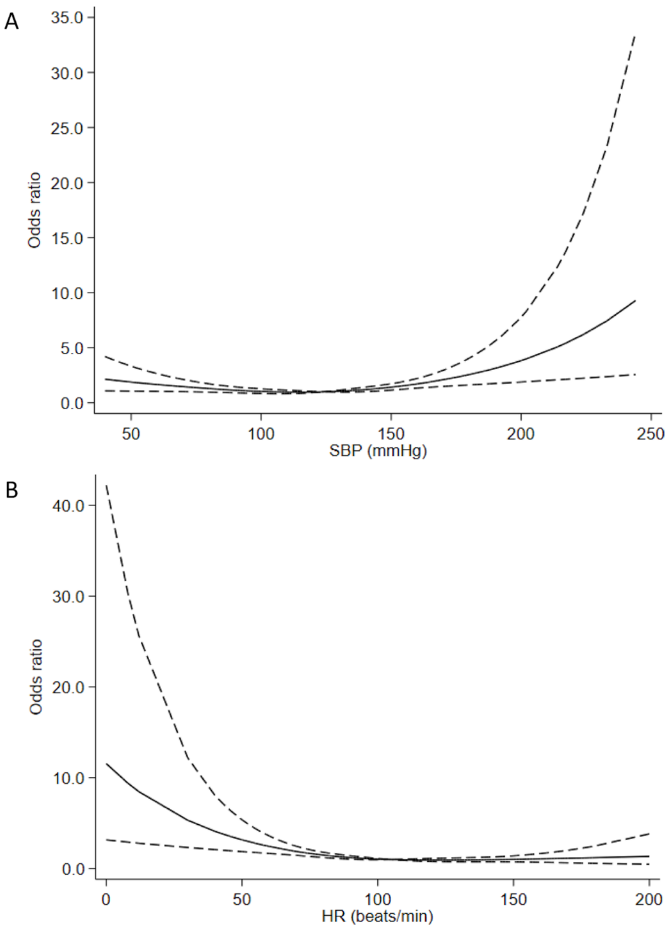

Figure 2 Spline plot of ORs for relationship between severe traumatic brain injury requiring immediate neurosurgical intervention (BI-NSI) and systolic blood pressure (SBP) (A) and BI-NSI and heart rate (HR) (B). Both models were adjusted for sex, age category and with or without the need for emergency thoracotomy, laparotomy or transcatheter arterial embolisation to control haemorrhage. The reference category for each OR is the median values (ie, 124 mm Hg for SBP and 105 beats/min for HR). The dashed lines represent 95% CIs.

blunt trauma in the younger children was suggested to be an early warning sign of severe TBI.[34] After analysis of the combination of SBP and HR, our study showed that the higher SBP and lower HR were a significant predictor for BI-NSI in a group of 7–10 years of age and 11–15 years of age, considering the children with normal vital signs in each group as the reference category. Cushing's triad (ie, respiratory irregularity, bradycardia and hypertension) is a classical and physical sign of impending brain herniation. In adult patients with blunt trauma, prehospital Cushing's sign with altered mental status was described as a significant predictor of severe TBI, implicating brain herniation.[15] The same results were obtained in a cohort of school age children and young adolescents. Acker *et al* demonstrated that the presence of either elevated shock index, paediatric age-adjusted or abnormal GCS motor scores could identify children with severe TBI.[20]

At an initial phase of impaired cerebral perfusion, the simultaneous onset of hypertension and tachycardia was observed during endoscopic neurosurgical procedures.[36] Conversely, our results showed no significant relationship between tachycardia and BI-NSI. This difference may be explained by the fact that our outcome variable focused on the 'life-threatening' TBI requiring immediate neurosurgical intervention or death due to isolated severe TBI.

In the clinical setting, the presence of hypertension and bradycardia in paediatric patients, particularly school-age children and young adolescents, suggestive of head injury at emergency department presentation may be useful to determine severe TBI that may require subsequent neurosurgical surgeries, which may help clinicians provide quick further diagnostic study and treatment. These traditional signs of SBP and HR are still useful for the immediate prediction of fatal conditions.

This study had several limitations that should be acknowledged. First, a large number of patients were

Table 2 Adjusted ORs and 95% CIs for severe traumatic brain injury requiring immediate neurosurgical intervention according to the combination of systolic blood pressure (SBP) and heart rate (HR)

SBP (mm Hg)	HR (beats/min) Low (≤92)	Normal (93–119)	High (120≤)
High (135≤)	2.84 (1.68–4.80) P<0.001	1.22 (0.68–2.18) P=0.507	1.35 (0.76–2.37) P=0.303
Normal (117–134)	1.43 (0.83–2.49) P=0.200	Reference	0.93 (0.49–1.76) P=0.822
Low (≤116)	1.67 (0.97–2.89) P=0.066	1.26 (0.71–2.25) P=0.427	1.08 (0.60–1.95) P=0.793

Covariates were adjusted for sex, age category and with or without the need for emergency thoracotomy, laparotomy or transcatheter arterial embolisation to control haemorrhage, with SBP of 117 to 134 mm Hg and HR of 93 to 119 beat/min as the reference category.

Table 3 Age-specific adjusted ORs and 95% CIs for severe traumatic brain injury requiring immediate neurosurgical intervention (BI-NSI) according to the combination of systolic blood pressure (SBP) and heart rate (HR)

A. 2–6 years old				
1.86 (0.61–5.70) P=0.278	0.91 (0.27–3.10) P=0.877	0.73 (0.21–2.46) P=0.607	High (131≤)	SBP (mm Hg)
1.43 (0.49–4.18) P=0.516	2.02 (0.69–5.87) P=0.197	1.42 (0.47–4.29) P=0.534	Low (≤112)	
1.17 (0.39–3.49) P=0.784	Reference	0.39 (0.08–2.01) P=0.262	Normal (113–130)	
Low (≤106)	Normal (107–134)	High (135≤)		
	HR (beats/min)			
B. 7–10 years old				
4.22 (1.69–10.53) P=0.002	1.41 (0.53–3.78) P=0.492	1.45 (0.54–3.90) P=0.459	High (133≤)	SBP (mm Hg)
2.47 (0.99–6.16) P=0.053	Reference	0.83 (0.26–2.67) P=0.752	Normal (117–132)	
1.50 (0.58–3.86) P=0.401	1.90 (0.74–4.87) P=0.181	1.37 (0.49–3.80) P=0.549	Low (≤116)	
Low (≤93)	Normal (94–120)	High (121≤)		
	HR (beats/min)			
C. 11–15 years old				
4.07 (1.80–9.19) P=0.001	1.22 (0.49–3.03) P=0.667	1.96 (0.86–4.45) P=0.108	High (141≤)	SBP (mm Hg)
0.98 (0.40–2.41) P=0.962	Reference	1.92 (0.81–4.57) P=0.139	Normal (121–140)	
1.72 (0.76–3.88) P=0.193	0.64 (0.25–1.69) P=0.370	0.93 (0.38–2.28) P=0.870	Low (≤120)	
Low (≤85)	Normal (86–109)	High (110≤)		
	HR (beats/min)			

Covariates were adjusted for sex and with or without the need for emergency thoracotomy, laparotomy or transcatheter arterial embolisation to control haemorrhage, with each normal vital sign as the reference category.

excluded due to missing data, as this was a retrospective database study. Second, detailed injury patterns based on CT classification, type of craniotomy and cause of death were unknown. In addition, information on whether intracranial pressure was monitored and the actual data if measured was unavailable from the JTDB. These factors should have been considered to reflect the relationship between Cushing's sign and impending brain herniation. Finally, transfer time or prehospital interventions including fluid resuscitation and sedatives or analgesics were not accounted for, which would have affected vital signs on arrival.

CONCLUSIONS

Cushing's sign with abnormal GCS motor score at emergency department presentation in school-age children and young adolescents after severe blunt trauma was a significant predictor of BI-NSI, which was defined as severe TBI requiring immediate neurosurgical intervention or death due to possible isolated severe TBI.

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Contributors TYu, HN, KT, and HY designed the study. TYu, HN, YK and AN conducted data acquisition. TYu, TYo, HM, TO and AN analysed and interpreted the data. All authors contributed to drafting the article and revising it critically for important intellectual content. All authors approved the final version of the manuscript.

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Competing interests None declared.

Patient consent Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

Ethics approval Okayama University Hospital ethical committee (ID 1708–001).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The data that support the findings of this study are available from JTDB but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of JTDB.

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