Published in final edited form as:
Neurosurgery. 2013 November ; 73(5): 746–752. doi:10.1227/NEU.0000000000000097.

National Variability in Intracranial Pressure Monitoring and Craniotomy for Children With Moderate to Severe Traumatic Brain Injury

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Abstract

BACKGROUND—Traumatic brain injury (TBI) is a significant cause of mortality and disability in children. Intracranial pressure monitoring (ICPM) and craniotomy/craniectomy (CRANI) may

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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.

affect outcomes. Sources of variability in the use of these interventions remain incompletely understood.

OBJECTIVE—To analyze sources of variability in the use of ICPM and CRANI.

METHODS—Retrospective cross-sectional study of patients with moderate/severe pediatric TBI with the use of data submitted to the American College of Surgeons National Trauma Databank.

RESULTS—We analyzed data from 7140 children at 156 US hospitals during 7 continuous years. Of the children, 27.4% had ICPM, whereas 11.7% had a CRANI. Infants had lower rates of ICPM and CRANI than older children. A lower rate of ICPM was observed among children hospitalized at combined pediatric/adult trauma centers than among children treated at adult-only trauma centers (relative risk = 0.80; 95% confidence interval 0.66-0.97). For ICPM and CRANI, 18.5% and 11.6%, respectively, of residual model variance was explained by between-hospital variation in care delivery, but almost no correlation was observed between within-hospital tendency toward performing these procedures.

CONCLUSION—Infants received less ICPM than older children, and children hospitalized at pediatric trauma centers received less ICPM than children at adult-only trauma centers. In addition, significant between-hospital variability existed in the delivery of ICPM and CRANI to children with moderate-severe TBI.

Keywords

Decompressive craniectomy; Intracranial pressure monitoring

Recent estimates suggest that 1.7 million traumatic brain injuries (TBIs) occur annually in the United States, leading to approximately 53 000 deaths.[1] Among infants and children, TBI is both a major cause of mortality and of significant postinjury disability.[2] In the period following initial injury, patients with moderate and severe TBI frequently develop secondary insults to the brain due to hemorrhage, swelling, and disruption of normal autoregulation of cerebral blood flow, all of which may lead to increased intracranial pressure (ICP). Increased ICP further decreases blood flow and oxygen delivery to the already vulnerable brain, compounding the effects of the primary injury. Monitoring and medical/surgical management of increased ICP are hallmarks of modern neurosurgical and neurocritical care, and both are level III recommendations in peer-reviewed treatment guidelines for severe pediatric TBI published by the Brain Trauma Foundation.[3,4]

Despite the publication of evidence-based guidelines for the medical management of severe pediatric TBI in 2003, significant variability in the use of diagnostic and therapeutic technologies in the treatment of pediatric TBI has been documented in several studies.[3–7] Associations between lower rates of ICP monitoring and patient-level factors, especially young age, have been previously reported.[5–7] A possible link between higher volume of TBI care and increased use of ICP monitors has also been described.[5] To better analyze the sources of patient, hospital, and regional variability in the care delivered to US children with TBI, we undertook an analysis of the American College of Surgeons National Trauma Databank (NTDB). A priori, we elected to examine the incidence and variation of 2 neurosurgical markers of potential therapeutic intensity of care and guideline adherence in the care provided to children with moderate-severe TBI: ICP monitoring and craniotomy/ craniectomy for intractable intracranial hypertension.[3,4]

PATIENTS AND METHODS

Data Source

The NTDB is a registry of trauma patients hospitalized at voluntarily participating US trauma centers. NTDB data sets include demographic (eg, age, insurance coverage), administrative (eg, hospital trauma designation, discharge diagnosis codes), and measured (eg, admission Glasgow Coma Score) variables for injured patients. NTDB data sets are released on an annual basis, with variability in which hospitals participate during specific years. We analyzed NTDB data files from 2002 to 2008.

Inclusion Criteria

We included all patients younger than 18 years with an *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) discharge diagnosis code for TBI. We then utilized the Centers for Disease Control and Prevention definition of TBI, as has previously been used, to refine our sample.[1,5] In addition, to restrict our analysis to cases with moderate or severe injuries, we included only patients with both a head-specific Abbreviated Injury Score (AIS) ≥3 and an emergency room motor Glasgow Coma Score (GCS)≤3 (GCS motor 3 defined as flexor response to painful stimuli). NTDB records often, but not always, denote the presence of chemical sedation or paralysis during the GCS assessment. Our requirement of a high AIS and low GCS was designed to manage this possible source of selection bias. A sensitivity analysis adjusting for presence of sedation or paralysis was conducted as part of the multivariate analyses described below: no major changes in the interpretation of our analyses were observed.

Finally, because we sought to draw inferences from hospitals in which TBI care was relatively common, we included only cases cared for in hospitals that contributed at least 10 moderate/severe TBI cases to the NTDB during the year in which the patient was discharged. We specifically excluded patients who died in the emergency department and those who transferred from or to another acute-care hospital during their inpatient stay, because we sought to examine the care delivered to patients over the course of a single hospitalization at 1 facility. Transfers to rehabilitation or long-term care facilities were included.

Covariates and Outcomes

The NTDB provides demographic information including age, sex, insurance status, and clinical information that includes GCS. In addition, hospital-specific information is available, including the trauma designation (specified in our analysis as adult-only level I or II, adult and pediatric level I or II, pediatric only I or II, and grouping level III/IV and nontrauma centers) and hospital region (specified as Northeast, South, West, or Midwest, based on designations made by the American Trauma Society Trauma Information Exchange Program).[8] We adjusted for hospital TBI volume by counting the number of TBI cases at each hospital during each year. We then assigned hospitals to annual pediatric TBI volume tertiles (10-13 patients, 14-19 patients, and ≥20 patients). As potential confounders, we analyzed ICD-9 discharge and procedure codes to calculate head AIS, total body Injury Severity Score (ISS), and to determine whether patients had an inflicted injury or an extradural, subdural, or subarachnoid hemorrhage. Because of potential changes in hospitals participating in the NTDB on an annual basis, we controlled for discharge year. We studied 2 independent outcomes: placement of an ICP monitor (ICPM) and performance of craniotomy/craniectomy (CRANI). ICD-9 procedure codes do not allow for a clear separation of craniotomy and craniectomy procedures, and so we elected to group the 2 procedures for this analysis.

Software

STATA (version 11.2) was used for the creation of the analytic data set, as well as for calculation of the AIS and ISS scores using the publicly available ICDPIC software package.[9] The R statistical programming language, version 2.15.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for all subsequent data analysis, including the lme4 package for creation of hierarchical generalized linear models and the amelia package for multiple imputation.[10–12]

Statistical Analysis

Univariate statistics were analyzed by using counts and percentages. Bivariate statistics associating covariates and outcomes were calculated as relative risks with 95% confidence intervals. Confidence intervals excluding the value 1 were considered statistically significant. Given the likely within-hospital correlation of care delivery, we utilized multivariate hierarchical generalized linear models with hospitals specified as a random effect. This form of modeling assumes a constant effect of a predictor across hospitals, but allows each hospital its own intercept. Models utilized the Poisson error distribution with a log link in order to calculate relative risks for common outcomes.[13] All covariates were included in models a priori based on review of previous research and experience of the authors: no variable selection was performed during modeling. For univariate and bivariate analyses, missing categorical variables were managed by creation of “missing” categories. For multivariate analysis, missing data were assumed to be missing at random and managed by creation of 10 imputed data sets via chained equations: coefficient and confidence interval estimates were pooled and pooled estimates are reported in the text and tables. Separate imputation steps were performed for missing data at the hospital and patient levels to ensure that imputations at the hospital level were shared across all patients at that hospital.[14]

As a study of a publicly available database from which all patient identifiers have been expunged, this study was exempt from institutional review board review.

RESULTS

After application of the inclusion and exclusion criteria, the analytic data set included 7140 patients hospitalized at 156 different US hospitals. Demographic characteristics of the patients are depicted in Table 1. A plurality (46.8%) of patients was aged 13 to 17 years, and the majority was male. Most (81.0%) patients had an ISS suggestive of severe bodily injury (>15), and 65.1% had an intracranial hemorrhage. A large majority of patients were hospitalized at hospitals with a trauma designation of adult-only level I or II (36.4%) or adult-pediatric combined level I or II (42.1%).

ICP Monitoring

Positive bivariate associations with ICPM were observed for older age, presence of intracranial hemorrhage, and higher head and total body injury severity, whereas negative associations were observed for combined adult/pediatric trauma designation and several regions (Table 2). In a multivariate model adjusted for all covariates (Table 3), patients older than 1 year were more likely to receive ICPM than similarly injured infants (with infants as reference category, ages 1 to <5 years relative risk [RR] = 1.63, 95% confidence interval [CI] 1.29-2.06; 5 to <13 years RR = 1.53, 95% CI 1.20-1.95; and ≥13 years RR = 1.55, 95% CI 1.23-1.96). The negative association between combined adult/pediatric level I/II trauma designation compared with adult-only level I/II designation was preserved in the multivariate model, with a RR of 0.80 (95% CI 0.66-0.97); 18.5% of the residual variance in the hierarchical model was explained by between-hospital variability in the use of ICPM.

Craniotomy and Craniectomy

Positive bivariate associations of CRANI with sex, head and total body injury severity, and region were observed, whereas negative bivariate associations were observed for moderate annual TBI volumes but not highest (Table 2). In the multivariate model, a significantly increased RR for CRANI was observed for patients 1 to <5 years of age compared to infants (with infants as referent, age 1 to <5 year RR = 1.39, 95% CI 1.01-1.90). Patients with a head AIS of 4 were more likely to receive CRANI than those with head AIS = 3, but this effect was not observed for patients with a head AIS of 5/6. The presence of an intracranial hemorrhage was strongly associated with CRANI (RR = 3.32, 95% CI 2.66-4.16). Children at level III/IV or nontrauma centers were more likely to receive a CRANI than those at adult I/II trauma centers (RR = 1.56, 95% CI 1.02-2.38). In comparison with the ICPM model (18.5%), only 11.6% of the residual variance in the model was attributed to between-hospital variability.

Finally, we explored the correlation between adjusted hospital-specific relative risks of ICPM and CRANI by extracting hospital-specific intercepts from each hierarchical multivariate model and comparing each hospital's adjusted RR for ICPM with its adjusted RR for CRANI. The line of best fit (R^2 = 0.037, 95% CI 0.001-0.116) indicated little correlation for the within-hospital tendency toward performing each of these 2 procedures.

DISCUSSION

In this retrospective cohort study of children with moderate and severe TBI, we observed significant patient, hospital, and regional variation in rates of delivery of 2 neurosurgical interventions that have potential to modify outcomes. These results confirm and extend the results of previous studies showing variability in ICP monitoring in children with TBI, and have important implications in understanding the extent to which these treatments are provided to children with moderate-severe TBI.

Patient-level Variability

Previous studies have identified patient-level variability in ICPM for infants and children in both the United States and United Kingdom. In these studies, as in the present one, infants were consistently less likely than older children to receive ICPM after a TBI. Our study, as a broad national sample of care for children with TBI, substantially improves the generalizability of this observation. The main hypothesis offered to explain this consistent finding is the misconception of a pressure "pop off" provided by the open fontanel, despite evidence that infants with TBI remain at risk for elevated ICP and a lack of evidence for the reliability of the clinical examination in diagnosing intracranial hypertension.[15] This is particularly troubling in the light of survey evidence suggesting that physicians treating TBI generally agree with the recommendation to measure ICP in patients with severe TBI.[6] That same survey suggested that only 38% of physicians practice in settings with a clear TBI protocol: our supposition, which merits empiric study, is that patients treated in institutions with rigorous TBI protocols are more likely to receive guideline-supported care.

Hospital-level Variability

The present study identified a decreased incidence of ICPM associated with hospitalization at a combined adult/pediatric level I/II trauma center in comparison with an adult level I/II trauma center. The reason for this finding is not clear, but potential causes can be suggested. First, it is possible that centers with adult-only trauma designation are more aggressive (ie, they are more likely to surgically intervene) or comfortable with ICPM (ie, they use monitors more frequently, in general) than other centers. In part, this finding could be due to differences in the age distributions of patients hospitalized at each type of trauma center, but our adjustment for age should interrupt confounding owing to this association. It remains possible that, despite our adjustment procedures, residual confounding due to severity or mechanism of TBI affects our results. Fourth, the increased familiarity in caring for infants and children at hospitals with a pediatric trauma designation may be associated with less use of paralysis or sedation, or with generally greater comfort with bedside physical examination of children, and therefore a decreased requirement for ICPM. Unfortunately, the NTDB does not provide data on medication use, limiting our ability to test this assertion. Surprisingly, we identified an increased use of CRANI at hospitals classified as level III/IV or nontrauma centers. We have no clear explanation for this finding, but note that the number of these centers in our data set is small and that hospitals of this classification that participate in the NTDB may not be representative of national practices at otherwise similar hospitals. As attempts to decrease the variability in ICPM are instituted on the hospital, regional, and national level, an understanding of the factors that lead to differential treatment of children in adult and pediatric trauma centers would be of clear utility.

In our multivariate models, we did not identify a consistent relationship between volume of TBI patients and utilization of ICPM or CRANI, as has been previously identified for TBI[5] and other types of traumatic injury.[16,17] It is possible that our decision to restrict our data set to patients cared for at hospitals contributing a minimum of 10 patients per year led to this finding, or that the hospitals contributing to the NTDB represent a materially different population than the pediatric hospital consortium studied by Bennett and colleagues.[5] Similarly, we were unable to identify regional variability in the utilization of these procedures, despite the phenomenon of regional variability in health care delivery documented in multiple previous studies.[18,19] Trauma centers display regional variability in their distribution, which no doubt impacts the outcomes of children with TBI based on differences in time from injury to definitive care and access to specialized interventions.[8] Our need to impute region because of its frequent missingness from the NTDB data may provide the best explanation for a lack of observed regional differences in our models.

We found little correlation between within-hospital predisposition toward ICPM and CRANI. Although invasive monitoring and invasive therapy clearly differ in their indications, we expected hospitals predisposed to 1 decision to be likewise predisposed to the other. The absence of evidence for such a correlation in our data highlights the complexity of forces that shape decision-making for seriously or critically ill children with TBI. Physicians deciding how to care for injured children must also integrate evolving information about the effectiveness of available therapies. A recent randomized study of adults with TBI cared for in an intensive care unit setting did not observe a mortality benefit for ICP monitoring in comparison with care guided by clinical criteria.[20] Similarly, recent studies have highlighted the lack of high-quality evidence supporting decompressive craniotomy/craniectomy in adults with diffuse TBI.[21] It may be reasonable to hypothesize that in a well-staffed, mature intensive care unit setting, it will be difficult to demonstrate that, in isolation, either CRANI or ICPM lead to superior results. Although the continuous incremental advances in neurointensive care are challenging to study, they may prove to be a central determinant of patient outcomes.[22]

Limitations

As a retrospective review of administrative data, our study has certain well-understood limitations. First, we can make no claim regarding the directionality of the associations we have observed, and therefore cannot claim causal links between our covariates and our observed outcomes. This well-understood weakness of observational studies means that we encourage readers to interpret our findings as deserving of further confirmation. To do so would require larger and more comprehensive clinical databases tracking the care of brain-injured children, and we believe that the creation and adequate funding of such efforts deserves national attention.

Second, our ascertainment of TBI cases and both TBI and total injury severity (AIS/ISS) were based on ICD-9 codes, which introduces the possibility of nonrandom error (bias) at the time of code assignment. The use of these methods are supported both by the Centers for Disease Control and Prevention in its epidemiologic tracking of TBI and by the majority of large-scale TBI studies, and while we cannot exclude bias, we believe our study is no more affected than similar previous efforts.[1,23–25] As a voluntary registry, the NTDB must be considered a potentially biased source of information regarding the delivery of care to injured patients in the United States. The effect of that bias on our conclusions cannot be stated with certainty, but we believe that participating hospitals are more likely to provide high-quality and standards-adherent care than nonparticipators. As such, our estimates of variability likely under represent the variability present in the population as a whole. The absence of important clinical information in the NTDB, including pupillary examinations, physiological data, and indications for institution of ICPM or CRANI considerably lessens the granularity with which we can adjust our data and control for confounding. Balancing these limitations are our study's large sample size, our use of modern modeling techniques to control for within-hospital correlation, and the fact that our findings align well with previous research.

CONCLUSION

This study documents patient- and hospital-associated variability in the use of ICPM and CRANI for patients with moderate and severe TBI. In particular, adult trauma centers are more likely to institute ICPM than pediatric trauma centers, despite adjustment for probable confounders. Efforts to improve the care delivered to critically ill children with TBI will require a firm understanding of the institutional and regional factors associated with variability in the use of these invasive but potentially outcome-modifying technologies. Future efforts to understand the variability in care delivery to children with TBI would benefit from large data sets that consistently record highly granular clinical data.

Acknowledgments

This study was funded by the National Institutes of Health (NIH) 1R01NS072308 to 03.

ABBREVIATIONS

AIS	Abbreviated Injury Score
CRANI	craniotomy/craniectomy
GCS	Glasgow Coma Score
ICD-9-CM	*International Classification of Diseases, Ninth Revision, Clinical Modification*
ICP	intracranial pressure
ICPM	intracranial pressure monitoring
ISS	Injury Severity Score
NTDB	National Trauma Databank
TBI	traumatic brain injury

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TABLE 1

Characteristics of 7140 Children With Traumatic Brain Injury Hospitalized at 156 Different US Hospitals[a]

Covariate	**%**
Age	
Under 1 y (n = 582)	8.2
1 to <5 y (n = 1288)	18.0
5 to <13 y (n = 1927)	27.0
13 to <18 y (n = 3343)	46.8
Sex	
Female (n = 2574)	36.1
Male (n = 4566)	63.9
Insurance	
Government (n = 1780)	25.1
Private insurance (n = 1168)	33.0
Self-pay (n = 615)	8.6
Other (n = 1251)	17.5
Missing (n = 1168)	16.4
Inflicted injury (n = 766)	10.7
Intracranial hemorrhage (EDH, SDH, SAH) (n = 4650)	65.1
Head AIS	
3 (n = 2656)	37.2
4 (n = 3465)	48.5
5 or 6 (n = 1019)	14.3
Injury Severity Score (ISS) ≥15 (n = 5782)	81.0
Hospital trauma designation	
Adult I/II only (n = 2705)	36.4
Adult and Ped I/II (n = 3029)	42.1
Nontrauma center or both adult and pediatric level III/IV (n = 313)	4.4
Ped I/II only (n = 314)	4.4
Missing (n = 910)	12.7
Pediatric patients with TBI in same year at same hospital	
10-14 (n = 1294)	18.1
14-19 (n = 2021)	28.3
≥20 (n = 3825)	53.6
Region	
Northeast (n = 1055)	14.8
South (n = 2665)	37.3
West (n = 894)	12.5
Midwest (n = 1438)	20.1

Covariate	%
Missing (n = 1088)	15.2

[a]EDH, epidural hematoma; SDH, subdural hematoma; SAH, subarachnoid hematoma; AIS, Abbreviated Injury Score; TBI, traumatic brain injury; Ped, pediatric.

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TABLE 2

Unadjusted Association of Patient Characteristics With Use of ICP Monitors and With Craniotomy/Craniectomy[a]

Variable	ICP % n = 7140	RR	95% CI (Low)	95% CI (High)	CRANI % n = 7140	RR	95% CI (Low)	95% CI (High)
Overall	27.4				11.7			
Age								
Under 1 y	20.4	1.00	—	—	11.2	1.00	—	—
1 to <5 y	29.5	1.44	1.20	1.73	13.6	1.22	0.93	1.59
5 to <13 y	27.0	1.32	1.11	1.58	11.4	1.02	0.79	1.33
13 to <18 y	28.0	1.37	1.16	1.62	11.1	1.00	0.78	1.28
Sex								
Female	28.7	1.00	—	—	10.3	1.00	—	—
Male	26.7	0.93	0.86	1.01	12.4	1.20	1.05	1.38
Insurance								
Government	26.5	1.00	—	—	12.2	1.00	—	—
Private insurance	26.4	1.00	0.90	1.10	11.1	0.91	0.76	1.08
Self-pay	23.1	0.87	0.74	1.03	9.6	0.78	0.59	1.03
Other	30.9	1.17	1.04	1.31	12.6	1.03	0.85	1.25
Missing	29.5	1.11	0.99	1.25	11.9	0.97	0.80	1.19
Inflicted								
No	27.7	1.00	—	—	11.5	1.00	—	—
Yes	25.2	0.91	0.80	1.04	13.3	1.16	0.96	1.41
Intracranial hemorrhage (EDH, SDH, SAH)								
No	20.3	1.00	—	—	4.6	1.00	—	—
Yes	31.2	1.54	1.41	1.68	15.4	3.37	2.78	4.08
Head AIS								
3	22.6	1.00	—	—	9.4	1.00	—	—
4	30.5	1.35	1.24	1.48	13.6	1.45	1.26	1.68
5 or 6	29.4	1.31	1.16	1.47	10.9	1.16	0.94	1.44
Injury severity (ISS)								

Variable	ICP % n = 7140	RR	95% CI (Low)	95% CI (High)	CRANI % n = 7140	RR	95% CI (Low)	95% CI (High)
<15	18.9	1.00	—	—	9.8	1.00	—	—
≥15	29.4	1.55	1.38	1.75	12.1	1.23	1.04	1.47
Hospital trauma designation								
Adult I/II only	27.9	1.00	—	—	11.3	1.00	—	—
Adult and Ped I/II	25.7	0.92	0.84	1.00	10.7	0.95	0.82	1.10
Ped I/II only	26.8	0.96	0.79	1.16	15.0	1.33	1.00	1.77
NTC or both adult and ped	24.3	0.87	0.71	1.07	15.7	1.39	1.05	1.84
Missing	33.0	1.18	1.06	1.32	13.3	1.18	0.97	1.44
Hospital volume of TBI[i] patients								
10-13	27.3	1.00	—	—	13.8	1.00	—	—
14-19	25.6	0.94	0.84	1.06	11.0	0.80	0.66	0.96
≥20	28.4	1.04	0.94	1.15	11.3	0.82	0.70	0.97
Hospital region								
Northeast	32.4	1.00	—	—	14.7	1.00	—	—
South	24.1	0.74	0.66	0.83	10.3	0.70	0.58	0.84
West	24.4	0.75	0.65	0.87	10.5	0.72	0.56	0.91
Midwest	31.6	0.98	0.87	1.10	12.0	0.82	0.70	1.00
Missing	27.7	0.85	0.75	0.97	12.5	0.85	0.69	1.05

[a]ICP, intracranial pressure; RR, relative risk; CI, confidence interval; CRANI, craniotomy/craniectomy; EDH, epidural hematoma; SDH, subdural hematoma; SAH, subarachnoid hematoma; AIS, Abbreviated Injury Score; NTC, nontrauma center; TBI, traumatic brain injury.

TABLE 3

Adjusted Relative Risk of Intracranial Pressure Monitoring and Craniotomy/Craniectomy[a,b]

Variable	Relative Risk	95% CI
ICPM		
Age		
<1 y (referent)	1	—
1 to <5 y	1.63	(1.29-2.06)
5 to <13 y	1.53	(1.20-1.95)
13 to <18 y	1.55	(1.23-1.96)
Head AIS		
3 (referent)	1	—
5 or 6	1.11	(1.01-1.41)
Hospital trauma designation		
Adult I or II (referent)	1	—
Adult and Peds I or II	0.80	(0.66-0.97)
Discharge year		
2002 (referent)	1	—
2005	0.65	(0.45-0.93)
Other injury features		
Injury Severity Score >15	1.36	(1.14-1.63)
Intracranial hemorrhage (EDH, SDH, SAH)	1.57	(1.40-1.77)
CRANI		
Age		
<1 y (referent)	1	—
1 to <5 y	1.39	(.01-1.90)
Head AIS		
3 (referent)	1	—
4	1.33	(1.06-1.67)
Annual TBI case volume		
10-13 cases (referent)	1	—
14-19 cases	0.74	(0.58-0.93)
Hospital trauma designation		
Adult I or II (referent)	1	—
Level III/IV/nontrauma center	1.56	(1.02-2.38)
Other injury features		
Intracranial hemorrhage (EDH, SDH, SAH)	3.32	(2.66-4.16)

[a]ICP, intracranial pressure; RR, relative risk; CI, confidence interval; CRANI, craniotomy/craniectomy; EDH, epidural hematoma; SDH, subdural hematoma; SAH, subarachnoid hematoma; AIS, Abbreviated Injury Score; NTC, nontrauma center; TBI, traumatic brain injury.

[b]Included model covariates included age category, head AIS, sex, severe ISS, inflicted injury, presence of intracranial hemorrhage, insurance status, year of discharge, trauma designation, hospital region, and volume of TBI cases at the patient's hospital during that year. Only relative risk estimates with confidence intervals excluding 1 are considered significant and are displayed. In cases where nominal variables showed significant results, the referent category is listed for clarity of interpretation.