

Factors Affecting Functional Outcome after Decompressive Craniectomy Performed for Traumatic Brain Injury: A Retrospective, Cross-sectional Study

Abstract

Background: Factors affecting functional outcome after decompressive craniectomy (DC) performed for traumatic brain injury (TBI) remain poorly understood. **Methods:** We conducted a retrospective study of all patients who underwent primary DC for TBI at our hospital between 2010 and 2014. Multivariate regression analyses were used to determine the predictors of functional outcome and overall survival. **Results:** A total of 98 patients with severe ($n = 81$, 82.6%) or moderate ($n = 17$, 17.4%) TBI underwent primary DC and were included in this study. The 30-day and overall mortality rates were 15.3% and 25.5%, respectively. At a median follow-up of 90 (interquartile range (IQR): 38–180) days, median Karnofsky Performance Status (KPS) and Glasgow outcome scale-extended (GOSE) scores were 50 (IQR: 20–70) and 5 (IQR: 3–7), respectively. Young age and severe TBI were predictors of mortality. Glasgow coma scale (GCS) score on discharge was a strong predictor of KPS and GOSE scores. **Conclusion:** Primary DC afforded an acceptable functional outcome (GOSE score ≥ 5) in 45.9% of patients. Young age and lower GCS at presentation were associated with worse survival. GCS score on discharge was a strong predictor of functional outcome.

Keywords: Decompressive craniectomy, functional outcome, head injury, traumatic brain injury

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Introduction

Traumatic brain injury (TBI) remains a major cause of morbidity and mortality worldwide.^[1] According to estimates, TBI is the cause of disability in approximately 5.3 million persons living in the United States.^[2] The direct and indirect cost of TBI in the United States is close to \$60 billion annually.^[3] In Australia, approximately 1000 patients sustain TBI annually, which eventually accounts for a lifetime cost of about \$1 billion.^[4] Even for patients who are hospitalized with severe TBI, almost 60% are affected by serious disability or mortality.^[5] Given the dismal outlook for patients with severe TBI, efforts have been made to identify effective treatment modalities for such patients.

As the damage inflicted by trauma in most patients with TBI cannot be reversed, medical and surgical therapies are primarily directed at reducing secondary neuronal injury. Increased intracranial pressure (ICP) as a consequence of TBI can lead to compression of brain parenchyma,

compromised cerebral perfusion, impaired CSF circulation, irreversible neuronal injury, and even brain herniation.^[6] To mitigate the detrimental consequences of increased ICP, several first-tier and second-tier measures have been recommended by the Brain Trauma Foundation.^[7] In patients with severe TBI and elevated ICP that is refractory to medical management, decompressive craniectomy (DC) is sometimes performed to relieve ICP and to provide space for brain tissue to expand.^[8]

Despite the theoretical promise of DC, its role in the management of patients with severe TBI and elevated ICP remains somewhat controversial. A Cochrane review published in 2006 concluded that performing DC in patients with severe TBI and elevated ICP does not improve functional outcomes.^[9] Subsequently, the results of the DC in Diffuse TBI (DECRA) trial further reinforced this proposition.^[10] Recent guidelines by the Brain Trauma Foundation did not recommend DC for the management of refractory intracranial hypertension in patients with TBI and diffuse injury.^[7] Results of the randomized

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evaluation of surgery with craniectomy for uncontrollable elevation of intracranial pressure (ResCue ICP) trial showed that DC may provide possible benefits in terms of survival when used as a last resort as compared to medical management alone, although functional outcome may be slightly worse.^[11]

Keeping the conflicting results from the DECRA^[10] and ResCue ICP^[11] trials in view, it seems likely that DC may afford a favorable functional outcome in carefully selected patients with TBI.^[7] Given that performing randomized trials in patients with TBI is technically challenging,^[12] results from observational studies have been given more weightage in this regard.^[13] In the present study, the aim was to ascertain factors that were predictive of a favorable functional outcome among patients who underwent DC for TBI at our institution.

Methods

Our hospital is a 522-bedded, tertiary care center located in an urban city of a developing country with an estimated population of over 23.5 million. After obtaining approval from the Institutional Ethics Review Committee, a retrospective, cross-sectional study was performed using the institutional medical records database. All files with an International Classification of Diseases, 9th Revision-Clinical Modification diagnosis code for “TBI” and procedure code for “DC” were retrieved. Patients diagnosed with a TBI between 2010 and 2014 were included in the study. Using a predesigned, structured pro forma, each medical record was systematically reviewed, and data relating to demographics, clinical features, laboratory and radiologic findings, medical and surgical management, hospital stay, and follow-up visits were systematically collected. Time from injury to arrival in the emergency department and time interval between arrival in the hospital and DC were also recorded. Charlson comorbidity index (CCI) was calculated and recorded for each patient,^[14] which was further categorized as 0, 1, 2, or ≥ 3 . For all patients, findings of computed tomography (CT) were categorized as per the Marshall classification.^[15] Revised Trauma Status (RTS) was recorded for each patient. The primary outcomes of interest were Karnofsky Performance Score (KPS) and Glasgow Outcome Scale-Extended (GOSE) at the last follow-up.

Statistical Package for Social Sciences (SPSS) version 20.0 (IBM; New York City, NY, United States) was used for performing statistical analysis. Frequencies were calculated for qualitative variables, while mean (standard deviation) or median (interquartile range [IQR]) were computed for quantitative variables. Statistical tests included Chi-square or Fisher’s exact test for comparison of proportions, Student’s *t*-test for comparison of means, and Wilcoxon signed rank-sum test for comparison of median ranks. Multivariate logistic regression analysis was performed to determine the predictors of survival using a stepwise forward approach. Moreover, multivariate linear regression

models were constructed to determine the predictors of KPS score and GOSE score (i.e., measures of functional outcome). For all comparisons, a $P < 0.05$ was considered statistically significant.

Results

A total of 98 patients who underwent DC during the study period were included in this study. Surgical procedures were performed by seven different neurosurgeons.

Patient characteristics

The median age of individuals included in our study was 30 (IQR: 22–45) years and 63 (64.3%) were male. Hypertension ($n = 15$, 15.3%) and diabetes ($n = 10$, 10.2%) were the most common comorbidities. Most patients had a CCI score of 0 ($n = 80$, 81.6%), 1 ($n = 10$, 10.2%), or 2 ($n = 6$, 6.1%). TBI in most individuals was secondary to road traffic accident ($n = 64$, 65.3%), fall from a height ($n = 17$, 17.4%), or firearm injury ($n = 8$, 8.2%). The median time interval between injury and arrival in the hospital was 1.5 (IQR: 1.0–2.4) hours. On arrival, median Glasgow coma scale (GCS) score of individuals was 5 (IQR: 4–7) and all patients had either severe ($n = 81$, 82.6%) or moderate ($n = 17$, 17.4%) TBI. Median heart rate, respiratory rate, and systolic blood pressure (BP) were 74 (IQR: 62–98) beats/min, 24 (IQR: 8–28) breaths/min and 150 (IQR: 138–164) mm Hg, respectively. Median RTS on arrival for patients was 10 (IQR: 8–11). Systemic injuries were noted in 25 (25.5%) patients. Findings on CT as per the Marshall classification were diffuse injury II ($n = 3$, 3.1%), diffuse injury III ($n = 7$, 7.1%), diffuse injury IV ($n = 5$, 5.1%), and mass lesion ($n = 83$, 84.7%). Subdural hematoma ($n = 59$, 60.2%), epidural hematoma ($n = 23$, 23.5%), subarachnoid hemorrhage ($n = 23$, 23.5%), and intraparenchymal hemorrhage ($n = 4$, 4.1%) were the most common types of mass lesions. These results are summarized in Table 1.

Management and outcome

Median time interval between arrival in the hospital and start of surgery (i.e., DC) was 2.3 (IQR: 1.3–4.0) hours, while the median interval between injury and start of DC was 4.8 (IQR: 3.2–12.0) hours. The median preoperative GCS score for study individuals was 5 (IQR: 3–7). Preoperative management strategies included hyperventilation to a target partial pressure of carbon dioxide of 32 mm Hg and use of mannitol (dose of 1 g/kg). Vasopressors were used (if necessary) to maintain an adequate systolic BP. Some patients received antiepileptic medications (levetiracetam or phenytoin) for control of seizures. Patients with manifestations of elevated ICP refractory to these measures were taken for DC. Unilateral frontotemporoparietal DC (hemicraniectomy) and bifrontal DC were performed in 75 (76.5%) and 23 (23.5%) patients, respectively. In all patients, a question mark incision was given to raise flap, and a wide

Table 1: Characteristics of patients included in our study cohort (n=98)

Characteristics	All subjects (n=98)	Subjects who died (n=25)
Age (median [IQR])	30 (22-45) years	48 (30-66) years
Sex, n (%)		
Male	63 (64.3)	18 (72.0)
Female	35 (35.7)	7 (28.0)
Co-morbidities*, n (%)		
None	80 (81.6)	10 (40.0)
Hypertension	15 (15.3)	8 (32.0)
Diabetes mellitus	10 (10.2)	6 (24.0)
Others	5 (5.1)	4 (16.0)
CCI, n (%)		
0	80 (81.6)	12 (48.0)
1	10 (10.2)	7 (28.0)
2	6 (6.1)	4 (16.0)
≥3	2 (2)	2 (8.0)
Mechanism of injury, n (%)		
Road traffic accident	64 (65.3)	14 (56.0)
Fall from height	17 (17.4)	9 (36.0)
Firearm injury	8 (8.2)	2 (8.0)
Hit by an animal	7 (7.1)	0
Hit by an object	2 (2.0)	0
Time from injury to arrival in hospital (median [IQR])	1.5 (1.0-2.4) h	2.3 (1.0-3.75) h
GCS on arrival (median [IQR])	5 (4-7)	5 (3-7)
Severity of TBI, n (%)		
Mild (GCS >12)	0	0
Moderate (GCS 9-12)	17 (17.4)	2 (8.0)
Severe (GCS ≤8)	81 (82.6)	23 (92.0)
Heart rate (median [IQR])	74 (62-98)	96 (82-118)
Systolic blood pressure (median [IQR])	150 (138-164)	123 (100-139)
Respiratory rate (median [IQR])	24 (8-28)	22 (8-28)
RTS (median [IQR])	10 (8-11)	9 (8-11)
Pupillary reflex intact, n (%)	64 (65.3)	16 (64.0)
Gag reflex intact, n (%)	60 (61.2)	15 (60.0)
Systemic injuries, n (%)	25 (25.5)	6 (24.0)
Marshall CT grade of TBI, n (%)		
Diffuse injury I	0	0
Diffuse injury II	3 (3.1)	0
Diffuse injury III	7 (7.1)	2 (8.0)
Diffuse injury IV	5 (5.1)	3 (12.0)
Mass lesion	83 (84.7)	20 (80.0)
Types of mass lesion†, n (%)		
Subdural hematoma	59 (60.2)	20 (80.0)
Epidural hematoma	23 (23.5)	6 (24.0)
Subarachnoid hemorrhage	23 (23.5)	10 (40.0)
Intraparenchymal hemorrhage	8 (8.2)	3 (12.0)

*Some patients had more than one comorbid condition, †Some patients had more than one type of mass lesion. IQR – Interquartile range; CCI – Charlson comorbidity index; GCS – Glasgow coma scale, TBI – Traumatic brain injury; RTS – Revised trauma score; CT – Computed tomographic

craniectomy was performed. In case of bilateral DC, a coronal incision was given, and a strip of bone was left in place over the superior sagittal sinus. Durotomy was performed in all cases, while duroplasty was performed in 58 (59.2%) cases using pericranium and surgical. The median number of days spent in the intensive care unit was

5 (IQR: 3–8) days with a median length of total hospital stay of 17 (IQR: 9–28) days.

Infectious and noninfectious complications occurred in 28 (28.6%) and 13 (13.3%) patients as mentioned in Table 2. The 30-day mortality rate in our study cohort was 15.3% [Figure 1], while on a long-term

Table 2: Interventions and outcome of study subjects (n=98)

Parameters	Results
Interventions	
Door-to-surgery time (median [IQR])	2.3 (1.3-4.0) h
Injury-to-surgery time (median [IQR])	4.8 (3.2-12.0) h
Preoperative GCS (median [IQR])	5 (3-7)
Type of DC performed, n (%)	
Frontotemporoparietal DC	75 (76.5%)
Bifrontal DC	23 (23.5%)
Duration of surgery (median [IQR])	3.7 (3.0-4.2) h
Estimated blood loss (median [IQR])	800 (500-1200) ml
Length of stay in ICU (median [IQR])	5 (3-8) days
Overall length of stay in hospital (median [IQR])	17 (9-28) days
Vasopressor support, n (%)	30 (30.6)
Tracheostomy, n (%)	59 (60.2)
Gastrostomy, n (%)	30 (30.6)
Outcome	
Overall mortality	25 (25.5)
Interval from TBI to death (median [IQR])	9 (3-47) days
Complications, n (%)	35 (35.7)
Infectious complications*, n (%)	
Pneumonia	7 (7.1)
Urinary tract infection	7 (7.1)
Wound infection	6 (6.1)
CNS infection	5 (5.1)
Other	2 (2.0)
Noninfectious complications*, n (%)	
Hydrocephalus	9 (9.2)
Subdural hematoma	6 (6.1)
Expansion of contusion	5 (5.1)
Deep vein thrombosis	3 (3.1)
GCS on discharge	9 (4-12)
Cranioplasty, n (%)	68 (69.4)
DC-to-cranioplasty time (median [IQR])	80 (42-120) days
Duration of follow-up (median [IQR])	90 (38-180) days
KPS score at last follow-up	50 (20-70)
GOSE score at last follow-up	5 (3-7)

*Some patients experienced more than one complication. CNS – Central nervous system; DC – Decompressive craniectomy; GCS – Glasgow coma scale; GOSE – Glasgow outcome scale-extended; ICU – Intensive Care Unit; IQR – Interquartile range; KPS – Karnofsky performance status; TBI – Traumatic brain injury

follow-up, a total of 25 (25.5%) patients died. Median GCS score for patients at discharge was 9 (IQR: 4–12). Cranioplasty was performed in 68 (69.4%) patients after a median period of 80 (IQR: 42–120) days. At a median follow-up of 90 (IQR: 38–180) days, median KPS and GOSE scores were 50 (IQR: 20–70) and 5 (IQR: 3–7), respectively.

Factors affecting outcome

Univariate analysis was performed using Chi-square or Fisher's exact test and variables were categorized for this purpose as follows age (0–39 years, 40–64 years,

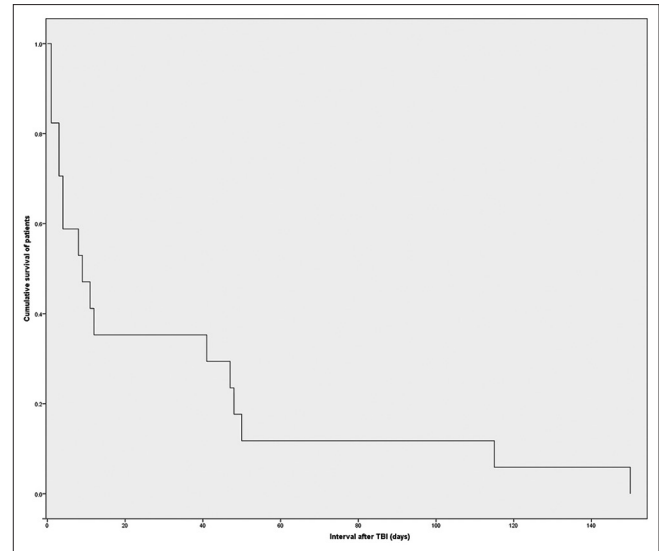


Figure 1: Kaplan–Meier survival curve depicting the survival of patients (Y-axis) in our cohort over time (X-axis)

and ≥ 65 years), comorbidities (none, one, or more than one), severity of TBI (moderate or severe), TBI-to-arrival in hospital interval (<1.5 h, 1.5–3 h, or >3 h), RTS (<9 or ≥ 9), mechanism of injury (fall from height, firearm injury, hit by an animal, hit by an object, or road traffic accident), GOSE score (<5 or ≥ 5), and KPS score (0%–20%, 21%–60%, or 61%–100%). Univariate analysis revealed that GOSE score was significantly affected by age group, severity of TBI, RTS, and TBI-to-arrival in hospital interval. KPS score was significantly affected by age group, presence of comorbidities, and severity of TBI and RTS. Overall mortality was significantly associated with age, presence of comorbidities, and severity of TBI. The *P* values for these analyses are provided in Table 3. Multivariate logistic regression analysis showed that young age (odds ratio: 16.78) and severe TBI (odds ratio: 90.91) were the only two statistically significant predictors of mortality. Multivariate linear regression analysis revealed that duration of surgery ($P = 0.043$), length of stay in hospital ($P = 0.008$), and GCS on discharge ($P < 0.001$) were predictors of KPS score. Likewise, multivariate linear regression analysis showed that GCS on discharge ($P < 0.001$) was the only predictor of GOSE score. These models accounted for 84.4% and 82.3% of variation in KPS and GOSE scores, respectively.

Discussion

In patients with TBI, neuronal injury and death secondary to the primary insult are irreversible. Secondary injury caused by raised ICP and cerebral edema can be potentially prevented and may provide an opportunity to salvage neurons and improve functional outcome.^[16] First-tier and second-tier interventions have been proposed to reduce ICP and control secondary neuronal injury.^[7] DC is a neurosurgical procedure in which decompression of the

Table 3: Factors affecting functional outcome and overall mortality in our patients

Factors	P*
Overall mortality	
Age group	0.001 [†]
Presence of comorbidities	0.031 [†]
Severity of TBI	0.034 [†]
TBI-to-arrival in hospital interval	0.290
RTS	0.879
Mechanism of injury	0.181
GOSE score	
Age group	0.012 [†]
Presence of comorbidities	0.073
Severity of TBI	<0.001 [†]
TBI-to-arrival in hospital interval	0.046 [†]
RTS	0.031 [†]
Mechanism of injury	0.182
KPS score	
Age group	<0.001 [†]
Presence of comorbidities	0.002 [†]
Severity of TBI	0.001 [†]
TBI-to-arrival in hospital interval	0.812
RTS	0.002 [†]
Mechanism of injury	0.173

*P values obtained using χ^2 or Fisher's exact test, [†]Indicates statistical significance (i.e., $P < 0.05$). TBI – Traumatic brain injury, RTS – Revised trauma score; GOSE – Glasgow outcome scale-extended, KPS – Karnofsky performance status

brain parenchyma is achieved by removing a piece of skull and opening the dura mater; this effectively reduces the ICP and theoretically can limit secondary neuronal injury.^[17] DC can be performed as either an early therapeutic intervention as part of a multi-tiered management protocol of TBI or it can be considered as a last-tier intervention to reduce ICP in patients for whom all other therapeutic maneuvers have failed.^[11]

In our study, 98 patients underwent DC for moderate or severe TBI and 45.9% had an acceptable functional outcome (i.e., GOSE score ≥ 5). The overall mortality rate in our patient cohort was 25.5%. These results are comparable to the results of the ResCue ICP trial.^[11] In the ResCue ICP trial, the overall mortality in the surgical group ($n = 202$) was 30.4% and 32% of patients had a GOSE score of ≥ 5 . However, it is important to note that all patients underwent primary DC in our study and the median time interval between arrival in the hospital and start of DC was 2.3 h. On the other hand, DC was performed as a last-tier intervention (i.e., secondary DC) in the ResCue ICP trial. Moreover, the proportion of patients with mass lesion (84.7%) in our study was much higher than that of the ResCue ICP trial (20%). This probably better represents the subset of patients with severe TBI who typically undergo DC in centers located in lower- to middle-income countries.^[18]

A few peculiarities were also notable in our study cohort. The bulk of our study sample consisted of men (64.3%), which may be a reflection of the male-dominated nature of the local society.^[19] All patients included in the study had moderate or severe TBI, which was expected as DC is not performed in cases of mild TBI. The median age of study individuals was 35 years and most had no comorbidities. These observations underscore the fact that TBI affects the healthy and most economically productive proportion of the society.^[20] This also explains the observation that young age was a predictor of mortality in our study. Most previously published studies have implicated increasing age as a predictor of mortality after TBI.^[21-24] However, in our study cohort, elderly patients comprised only 8.2% of the sample and were under-represented. This precluded us from drawing any meaningful conclusions about the geriatric population. A possible explanation for this observation may be that our center is a tertiary care center and in the absence of a structured prehospital triage system, most such patients succumbed before reaching the hospital.^[25] Another possible explanation is that the local population of our developing country has high fertility rates with limited life expectancy^[26] and geriatric patients represent a small subset of the population at large (in contrast to the aging populations of most developed countries).

GCS at the time of discharge was a strong predictor of functional outcome (both KPS and GOSE scores) in our study. GCS after TBI has been used as a measure of severity of TBI and as such, patients with a lower GCS are likely to have more severe neuronal injury. This, in turn, translates into a worse functional outcome in the long run. In a study by Williams *et al.*, immediate predecompression GCS score was noted to be a predictor of mortality.^[27] In another report, Murray *et al.* found that eye and verbal components of the GCS score were most useful prognostic markers for functional outcome.^[28] Moreover, in our study, KPS score was also influenced by duration of surgery and length of stay in the hospital. The duration of surgery may have an indirect impact on the degree of neuronal injury as *in vitro* studies have suggested that rapid expansion of swollen brain parenchyma can cause axonal stretch and injury.^[29-31]

There are a number of caveats to this study which should be kept in mind. First, our study was a retrospective study, and as such, the decision to perform DC was at the discretion of the treating neurosurgeon. Having said this, most neurosurgeons at our institution follow a protocol-based approach to the management of patients with TBI, which may have limited variability in patient selection. Second, we had a relatively small sample size ($n = 98$), which may have limited our ability to detect valid predictors of functional outcome and mortality. Despite this, we were able to identify a number of predictors of poor functional outcome (i.e., GCS at the time of discharge and duration of surgery). Third, our

study was conducted at a single tertiary care center of a developing country, and we had a relatively small number of geriatric patients. Therefore, it remains uncertain whether the favorable outcome noted in our study cohort can be generalized to the geriatric population. Finally, most patients in our study underwent primary DC (i.e., within the first few hours of arrival to the hospital); and thus, the results of this study may not be applicable in cases where DC is used as a last-tier intervention (i.e., secondary DC). Despite these limitations, this study is noteworthy in that it included a large subset of patients with mass lesions, which was in contrast to the typical patient populations included in randomized trials of DC.^[10,11] This probably represents the subset of patients with severe TBI who typically undergo DC in centers located in lower- to middle-income countries.^[18] Moreover, our study reported two measures of functional outcomes (KPS score and GOSE) for all patients and is one of the few studies to provide data on functional outcomes from a lower to middle income country. Overall, the results of our study suggest that severity of TBI, duration of surgery, and GCS at the time of discharge are strong predictors of long-term functional outcome.

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Conflicts of interest

There are no conflicts of interest.

References

- Ghajar J. Traumatic brain injury. *Lancet* 2000;356:923-9.
- Rutland-Brown W, Langlois JA, Thomas KE, Xi YL. Incidence of traumatic brain injury in the United States, 2003. *J Head Trauma Rehabil* 2006;21:544-8.
- Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: A brief overview. *J Head Trauma Rehabil* 2006;21:375-8.
- Myburgh JA, Cooper DJ, Finfer SR, Venkatesh B, Jones D, Higgins A; Australasian Traumatic Brain Injury Study (ATBIS) Investigators. Epidemiology and 12-month outcomes from traumatic brain injury in Australia and New Zealand. *J Trauma Acute Care Surg* 2008;64:854-62.
- Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. *Lancet Neurol* 2008;7:728-41.
- Dixon CE, Clifton GL, Lighthall JW, Yaghmai AA, Hayes RL. A controlled cortical impact model of traumatic brain injury in the rat. *J Neurosci Methods* 1991;39:253-62.
- Carney N, Totten AM, O'reilly C, Ullman JS, Hawryluk GW, Bell MJ *et al.* Guidelines for the management of severe traumatic brain injury. *Neurosurgery* 2017;80:6-15.
- Münch E, Horn P, Schürer L, Piepgras A, Paul T, Schmiedek P, *et al.* Management of severe traumatic brain injury by decompressive craniectomy. *Neurosurgery* 2000;47:315-22.
- Sahuquillo J, Arikian F. Decompressive craniectomy for the treatment of refractory high intracranial pressure in traumatic brain injury. *Cochrane Database Syst Rev* 2006;2006:CD003983.
- Cooper DJ, Rosenfeld JV, Murray L, Arabi YM, Davies AR, D'Urso P, *et al.* Decompressive craniectomy in diffuse traumatic brain injury. *N Engl J Med* 2011;364:1493-502.
- Hutchinson PJ, Kolias AG, Timofeev IS, Corteen EA, Czosnyka M, Timothy J, *et al.* Trial of decompressive craniectomy for traumatic intracranial hypertension. *N Engl J Med* 2016;375:1119-30.
- Maas AI, Roozenbeek B, Manley GT. Clinical trials in traumatic brain injury: Past experience and current developments. *Neurotherapeutics* 2010;7:115-26.
- Steyerberg EW, Mushkudiani N, Perel P, Butcher I, Lu J, McHugh GS, *et al.* Predicting outcome after traumatic brain injury: Development and international validation of prognostic scores based on admission characteristics. *PLoS Med* 2008;5:e165.
- Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994;47:1245-51.
- Maas AI, Hukkelhoven CW, Marshall LF, Steyerberg EW. Prediction of outcome in traumatic brain injury with computed tomographic characteristics: A comparison between the computed tomographic classification and combinations of computed tomographic predictors. *Neurosurgery* 2005;57:1173-82.
- Raghupathi R. Cell death mechanisms following traumatic brain injury. *Brain Pathol* 2004;14:215-22.
- Bayir H, Clark RS, Kochanek PM. Promising strategies to minimize secondary brain injury after head trauma. *Crit Care Med* 2003;31:S112-7.
- Servadei F. Clinical value of decompressive craniectomy. *N Engl J Med* 2011;364:1558-9.
- Nasrullah M, Bhatti JA. Gender inequalities and poor health outcomes in Pakistan: A need of priority for the national health research agenda. *J Coll Physicians Surg Pak* 2012;22:273-4.
- Humphreys I, Wood RL, Phillips CJ, Macey S. The costs of traumatic brain injury: A literature review. *Clinicoecon Outcomes Res* 2013;5:281-7.
- Hukkelhoven CW, Steyerberg EW, Rampen AJ, Farace E, Habbema JD, Marshall LF, *et al.* Patient age and outcome following severe traumatic brain injury: An analysis of 5600 patients. *J Neurosurg* 2003;99:666-73.
- Mosenthal AC, Lavery RF, Addis M, Kaul S, Ross S, Marburger R, *et al.* Isolated traumatic brain injury: Age is an independent predictor of mortality and early outcome. *J Trauma Acute Care Surg* 2002;52:907-11.
- Pompucci A, De Bonis P, Pettorini B, Petrella G, Di Chirico A, Anile C, *et al.* Decompressive craniectomy for traumatic brain injury: Patient age and outcome. *J Neurotrauma* 2007;24:1182-8.
- Susman M, Di Russo SM, Sullivan T, Risucci D, Nealon P, Cuff S, *et al.* Traumatic brain injury in the elderly: Increased mortality and worse functional outcome at discharge despite lower injury severity. *J Trauma Acute Care Surg* 2002;53:219-24.
- Shah AA, Rehman A, Sayyed RH, Haider AH, Bawa A, Zafar SN, *et al.* Impact of a predefined hospital mass casualty response plan in a limited resource setting with no pre-hospital care system. *Injury* 2015;46:156-61.
- Bhutta ZA, Hafeez A, Rizvi A, Ali N, Khan A, Ahmad F, *et al.* Reproductive, maternal, newborn, and child health in Pakistan: Challenges and opportunities. *Lancet* 2013;381:2207-18.
- Williams RF, Magnotti LJ, Croce MA, Hargraves BB, Fischer PE, Schroepel TJ, *et al.* Impact of decompressive craniectomy on functional outcome after severe traumatic brain injury. *J Trauma Acute Care Surg* 2009;66:1570-6.
- Murray GD, Butcher I, McHugh GS, Lu J, Mushkudiani NA, Maas AI, *et al.* Multivariable prognostic analysis in traumatic

- brain injury: Results from the IMPACT study. *J Neurotrauma* 2007;24:329-37.
29. Chung RS, Staal JA, McCormack GH, Dickson TC, Cozens MA, Chuckowree JA, *et al.* Mild axonal stretch injury *in vitro* induces a progressive series of neurofilament alterations ultimately leading to delayed axotomy. *J Neurotrauma* 2005;22:1081-91.
 30. Staal JA, Dickson TC, Gasperini R, Liu Y, Foa L, Vickers JC, *et al.* Initial calcium release from intracellular stores followed by calcium dysregulation is linked to secondary axotomy following transient axonal stretch injury. *J Neurochem* 2010;112:1147-55.
 31. Stiver SI. Complications of decompressive craniectomy for traumatic brain injury. *Neurosurg Focus* 2009;26:E7.