Prognostic Significance of Magnetic Resonance Imaging in Patients with Severe Nonpenetrating Traumatic Brain Injury Requiring Decompressive Craniectomy

Kwok M. Ho[1-3], *Stephen Honeybul*[4], *Ravi Ambati*[1]

BACKGROUND: **Diffuse axonal injury (DAI) detected on magnetic resonance imaging (MRI) may be useful to predict outcome after traumatic brain injury (TBI).**

METHODS: **This study compared the ability of the International Mission for Prognosis and Analysis of Clinical Trials (IMPACT) prognostic model with DAI on MRI to predict the 18-month neurologic outcome in 56 patients who had required decompressive craniectomy after TBI.**

RESULTS: **Of the 56 patients included in the study (19 scans occurred within 14 days; median time for all patients 24 days, interquartile range 14–42), 18 (32%) had evidence of DAI on the MRI scans. The presence of DAI on the MRI diffusion-weighted (DW) T2*-weighted gradient echo and susceptibility-weighted (SWI) sequences was associated with an increased risk of unfavorable outcome at 18 months compared with patients without DAI (44% vs. 17%, difference = 27%, 95% confidence interval 2.4–46.7%; $P = 0.032$), particularly when the brainstem was involved. However, neither the grading (I to IV) nor the number of brain regions with DAI was as good as the IMPACT model in discriminating between patients with unfavorable and favorable outcomes (area under the receiver operating characteristic curve: 0.625 and 0.621 vs. 0.918, respectively; $P < 0.001$ for both comparisons). After adjustment for the IMPACT prognostic risks, DAI in different brain regions and the grading of DAI were also not independently associated with unfavorable outcome.**

CONCLUSIONS: **The prognostic significance of DAI on MRI may, in part, be captured by the IMPACT prognostic model. More research is needed before MRI should be routinely used to prognosticate the outcomes in patients with TBI requiring decompressive craniectomy.**

INTRODUCTION

Predicting long-term outcome after severe traumatic brain injury (TBI) is difficult, but accurate assessment is important for medical decision making, quality assurance, and research purposes.[1-4] Traditionally, this has been based on individual clinical and radiologic parameters that have been shown to have prognostic significance. These include age, initial post-resuscitation Glasgow Coma Score (GCS), pupillary reaction to light, episodes of hypoxia and hypotension that may contribute to secondary brain injury, and computed tomographic (CT) brain features such as traumatic subarachnoid blood and petechial hemorrhage.

More recently, improvements in statistical analysis combined with access to large clinical datasets has enabled investigators to develop sophisticated web-based outcome prediction models. The CRASH (Corticosteroid Randomization After Significant Head injury) and IMPACT (International Mission for Prognosis and Analysis of Clinical Trials) models incorporate all these prognostic factors to provide a prediction of unfavorable neurologic outcome at 6 months (defined on the Glasgow outcome scale as severely

Key words
- Adult brain injury
- Axonal injury
- Head trauma
- Magnetic resonance imaging
- Prognostic model

Abbreviations and Acronyms
AUROC: Area under the receiver operating characteristic
CRASH: Corticosteroid Randomization After Significant Head injury
DAI: Diffuse axonal injury
DWI: Diffusion-weighted I
GCS: Glasgow Coma Score
IMPACT: International Mission for Prognosis and Analysis of Clinical Trials
MRI: Magnetic resonance imaging
SWI: Susceptibility-weighted imaging
TBI: Traumatic brain injury

From the [1]Department of Intensive Care Medicine, Royal Perth Hospital; [2]School of Population and Global Health, University of Western Australia; [3]School of Veterinary and Life Sciences, Murdoch University; and [4]Department of Neurosurgery, Royal Perth Hospital, Perth, Western Australia, Australia

To whom correspondence should be addressed: Kwok M. Ho, Ph.D. [E-mail: kwok.ho@health.wa.gov.au]

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disabled, vegetative, or dead).[5,6] A number of studies have subsequently externally validated these models.[7-9]

Although these 2 models have excellent ability to discriminate between patients with and without long-term unfavorable outcome (with area under the receiver operating characteristic [AUROC] curve >0.80),[7-9] their calibration remains far from perfect, limiting their utility in medical decision making.[10,11] One possible way to improve the accuracy of the current prognostic models is to incorporate magnetic resonance imaging (MRI) findings. It is well established that diffuse axonal injury (DAI). caused by angular or rotational acceleration/deceleration forces to the brain, can induce severe cerebral edema and also multiple petechial hemorrhage. Whereas CT brain imaging is very good at demonstrating DAI if it is associated with generalized cerebral edema, it has limitations when detecting microhemorrhages, especially when they occur in the brainstem.[12,13] More importantly, recent studies have shown that DAI detected on MRI may offer additional prognostic significance, over and above the aforementioned clinical and CT brain parameters.[12-14]

We hypothesized that the number of brain regions with DAI or the grading of DAI on MRI scan can discriminate between patients with and without 18-month unfavorable neurologic outcome after severe TBI requiring decompressive craniectomy. Specifically, we wanted to compare the prognostic significance of DAI on MRI with the IMPACT prognostic model. We used the IMPACT model rather than the CRASH model because we previously demonstrated that the IMPACT model was better calibrated in this group of patients. Finally, we wanted to assess whether the ability of the IMPACT prognostic model to predict long-term neurologic outcome could be improved by adding the DAI parameters.

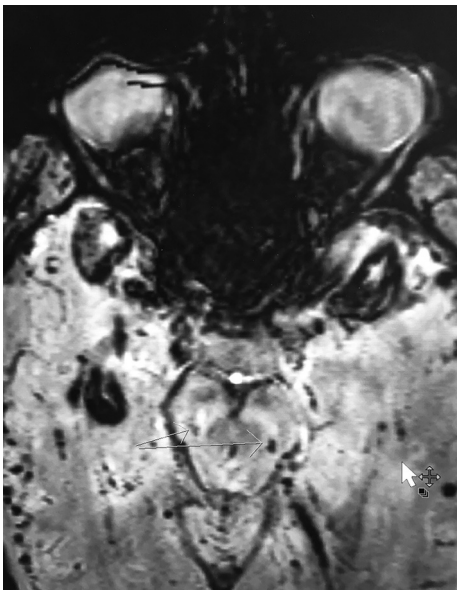


Figure 1. Diffuse axonal injury in the substantia nigra on susceptibility-weighted imaging sequences of the magnetic resonance image. The *arrows* illustrate the locations of the DAI lesions.

METHODS

After this audit was registered with the Royal Perth Hospital Clinical Quality and Safety Unit (No. 22378), the MRI data of patients who had undergone MRI within 10 weeks after severe TBI requiring decompressive craniectomy, between 2008 and 2016, at the 2 tertiary neurosurgical referral centers in Western Australia, were retrieved and merged with the existing neurosurgical administrative database. The database contains all the clinical (age, pupil reactivity, motor score, hypoxia, and hypotension), laboratory (plasma glucose, hemoglobin concentrations), and radiologic information (presence of epidural hematoma and subarachnoid hemorrhage, Marshall CT grading) on admission to the study centers that was needed to calculate the predicted risks of unfavorable outcome at 6 months, using either the CRASH or IMPACT model (including full laboratory and CT brain data). The IMPACT model calculator is freely available on the Internet (http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.0050165#s5). We had previously validated the accuracy of the CRASH and IMPACT models in predicting the neurologic outcome 18 months after decompressive craniectomy.[8,9] The 2 neurosurgical study centers are the only adult neurotrauma centers in the state of Western Australia and serve a population of about 2.1 million.

All MRI images in the T2*-weighted gradient-echo (TR 504 ms, TE 29.2 ms, slice thickness 6 mm, flip angle 15°, resolution 320), diffusion-weighted I (DWI) Resolve (TR 5500 ms, TE 65 ms, slice thickness 5 mm, flip angle 180°, resolution 176), DWI EPI (TR 9600 ms, TE 94 ms, slice thickness 4 mm, resolution 192), and susceptibility-weighted imaging (SWI) sequences (TR 49 ms, TE 40 ms, flip angle 15°, slice thickness 2 mm, resolution 256) (Magnetom Aera, Siemens, Erlangen, Germany) were used to report the presence of DAI.

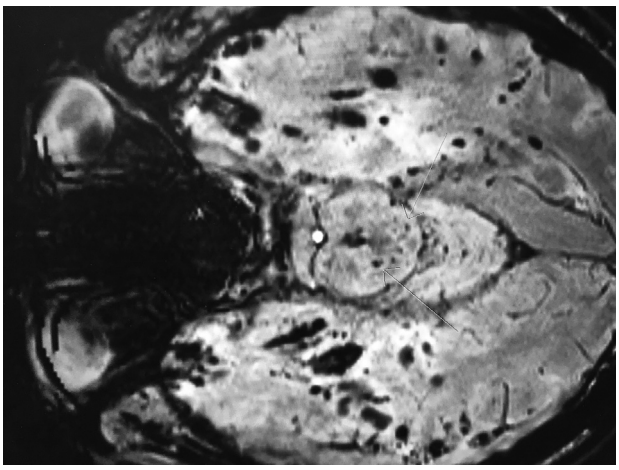


Figure 2. Diffuse axonal injury in the brainstem on susceptibility-weighted imaging sequences of the magnetic resonance image. The *arrows* illustrate the locations of the DAI lesions.

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Table 1. Difference in Characteristics Between Patients with Favorable and Unfavorable Outcome 18 Months After Decompressive Craniectomy for Severe Traumatic Brain Injury

Variable	All Patients (N = 56)	Unfavorable (n = 32)	Favorable (n = 24)	*P* Value*
Age, years (IQR)	29 (20–45)	26 (20–48)	33 (19–43)	0.914
Male, number (%)	43 (77)	24 (75)	19 (79)	0.760
GCS (IQR)	5 (4–8)	5 (3–6)	8 (5–11)	0.001
Pupil reactivity, number (%)				0.004
None	9 (16)	8 (25)	1 (4)	
1	9 (16)	8 (25)	1 (4)	
2	38 (68)	16 (50)	22 (92)	
CT brain findings, number (%)				
tSAH	51 (91)	31 (97)	20 (83)	0.079
Midline shift	46 (82)	28 (88)	18 (75)	0.227
Epidural hematoma	2 (4)	0 (0)	2 (8)	0.096
Unevacuated hematoma	23 (41)	14 (44)	9 (38)	0.638
Effaced basal cistern	12 (21)	10 (31)	2 (8)	0.039
Petechial hemorrhage	51 (91)	31 (97)	20 (83)	0.079
Major extracranial injury, number (%)	26 (46)	18 (56)	8 (33)	0.089
Bifrontal craniectomy, number (%)	25 (45)	13 (41)	12 (50)	0.485
Length of ICU stay, days (IQR)	12 (10–16)	14 (12–16)	10 (6–14)	0.010
Length of ward stay, days (IQR)	54 (19–114)	90 (34–145)	21 (13–55)	0.001
CRASH predicted unfavorable outcome risk 6 months, % (IQR)	70 (54–86)	85 (73–88)	54 (42–61)	0.001
IMPACT predicted unfavorable outcome risk at 6 months, % (IQR)	52 (35–76)	71 (52–86)	34 (28–46)	0.001

IQR, interquartile range; CT, computed tomography; tSAH, traumatic subarachnoid haemorrhage; GCS, Glasgow Coma Score; ICU, intensive care unit; CRASH, Corticosteroid Randomization After Significant Head injury; IMPACT, International Mission for Prognosis and Analysis of Clinical Trials.
**P* values generated by χ^2 or Mann-Whitney test.

The severity of DAI was graded as I (cerebral hemispheres only), II (corpus callosum), III (brainstem), or IV (substantia nigra or mesencephalic tegmentum).[14] The number of brain regions with DAI was summed (1 to 6: scored 1 for each of the following areas either unilaterally or bilaterally: frontal lobes, tempoparietal lobes, occipital lobes, corpus callosum, brainstem, and substantia nigra or mesencephalic tegmentum) without considering the size of each lesion (Figures 1 and 2). Incidental vascular anomalies and partial volume averaging of true vessels were not considered as DAI lesions, and SWI was considered the most sensitive MRI imaging sequence in detecting DAI in the study centers. DAI resulting from cerebral microbleeds can be visualized as small, round, and homogenous low-signal lesions on echo T2*-weighted gradient-echo or SWI images that are not consistent with bones, vessels, or MRI artifacts.[15] The consultant radiologists who reported the MRI were not aware of the IMPACT predicted risk of the study patients.

Statistical Analyses

Categoric and skewed continuous data were analyzed by χ^2 and Mann-Whitney tests, respectively. AUROC was used to define the ability of the grading of DAI, number of brain regions with DAI, and the predicted risks of the IMPACT model to discriminate between patients with and without unfavorable outcome 18 months after severe TBI. Similar to all TBI outcome studies, unfavorable outcome was defined as dependence in average daily activities. The difference in AUROC derived from the same cases was estimated according to the method suggested by Hanley and McNeil.[16] In addition, we also assessed whether the 1) grading of DAI, 2) number of brain regions with DAI, and presence of DAI in 3) brainstem, 4) substantia nigra, or mesencephalic tegmentum were significantly associated with unfavorable outcome at 18 months while adjustment was made for the IMPACT predicted risk of unfavorable outcome in a multivariate logistic regression.

As a sensitivity analysis to assess whether the timing of the MRI scan would affect our results, the AUROC of the grading of DAI, number of brain regions with DAI, the predicted risks of the IMPACT model to discriminate between patients with and without unfavorable outcome 18 months after surgery were analyzed again by restricting to patients who had the MRI scan within 2 weeks of decompressive craniectomy. All statistical analyses were performed by SPSS for Windows (version 24.0, IBM, Armonk, NY,

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Table 2. Difference in Magnetic Resonance Imaging Findings Including Areas of Involvement with Diffuse Axonal Injuries (DAI) Between Those with Favorable and Unfavorable Outcome 18 Months After Decompressive Craniectomy for Severe Traumatic Brain Injury

Variable	All Patients (N = 56)	Unfavorable (n = 32)	Favorable (n = 24)	*P* value*
Presence of DAI, number (%)	18 (32)	14 (44)	4 (17)	0.032
Corpus callosum, number (%)	12 (21)	9 (28)	3 (13)	0.158
Frontal lobes, number (%)	11 (20)	8 (25)	3 (13)	0.244
Tempoparietal lobes, number (%)	12 (21)	9 (28)	3 (13)	0.158
Occipital lobes, number (%)	3 (5)	2 (6)	1 (4)	0.732
Brainstem, number (%)	9 (16)	8 (25)	1 (4)	0.036
Substantia nigra or mesencephalic tegmentum, number (%)	4 (7)	3 (9)	1 (4)	0.454
Number of the above regions involved, number (IQR)	0 (0–2)	0 (0–2)	0 (0–0)	0.032
Grading of DAI				0.178
0	38 (68)	18 (56)	20 (83)	
I	4 (7)	3 (9)	1 (4)	
II	5 (9)	3 (9)	2 (8)	
III	5 (9)	5 (16)	0 (0)	
IV	4 (7)	3 (9)	1 (4)	

Grading of DAI: 0, no DAI; I, Cerebral hemispheres; II, Corpus callosum; III, Brainstem; IV, Substantia nigra or mesencephalic region.
IQR, interquartile range.
*P values generated by χ^2 or Mann-Whitney test.

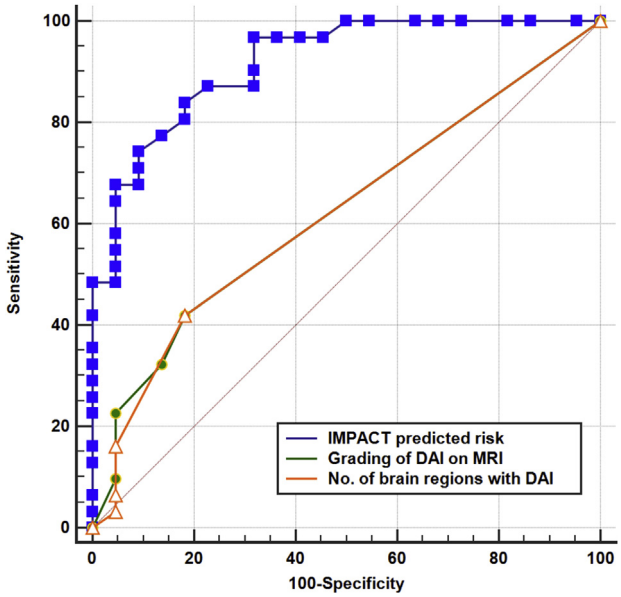


Figure 3. Area under the receiver operating characteristic (AUROC) curves of the grading and number of brain regions with diffuse axonal injury (DAI) on magnetic resonance imaging (MRI) and the International Mission for Prognosis and Analysis of Clinical Trials (IMPACT) predicted risk. IMPACT predicted risk: AUROC = 0.918 (95% confidence interval [CI] 0.809–0.976). Grading of DAI on MRI: AUROC = 0.625 (95% CI 0.481–0.754). Number of brain regions with DAI: AUROC = 0.621 (95% CI 0.477–0.751). The IMPACT predicted risk was significantly better than grading of DAI (difference in AUROC = 0.293, 95% CI 0.156–0.431; $P < 0.001$) or number of brain regions with DAI (difference in AUROC = 0.297, 95% CI 0.159–0.435; $P < 0.001$) in differentiating between patients with favorable and unfavorable outcome 18 months after decompressive craniectomy.

USA) and MedCalc for Windows (version 12.5, Ostend, Belgium); and a 2-tailed α-error of <5% was taken as significant.

RESULTS

A total of 56 patients had a MRI brain scan for diagnostic or prognostic purposes after their decompressive craniectomy during the study period (median 24 days, interquartile range [IQR] 14–42). Of the 56 patients included in the study, 25 (45%) had bifrontal decompression. The median age and IMPACT predicted risk of unfavorable outcome of all the patients were 29 years old (IQR 20–45) and 52% (IQR 35–76), respectively. As expected, patients with unfavorable outcomes were more likely to have a lower GCS (5 vs. 8, P = 0.001), at least 1 pupil nonreactive to light (50% vs. 8%, P = 0.004), an effaced basal cistern on CT brain scan (31% vs. 8%, P = 0.039), and a higher IMPACT and CRASH model predicted risk of unfavorable outcome (71% vs. 34%, P = 0.001) (Table 1). Petechial hemorrhage on the CT brain scan was also more common in patients with unfavorable outcome, but this difference was not statistically significant (97% vs. 83%, P = 0.079).

The presence of DAI on the MRI scan (32%) was significantly associated with a higher risk of unfavorable outcome 18 months after surgery (44% vs. 17%, P = 0.032), especially when the brainstem was involved (25% vs. 4%, P = 0.036) (Table 2). The increasing number of brain regions with DAI was also associated with an increased risk of unfavorable outcome (P = 0.032); however, the grading of the DAI was not significantly different between patients with favorable and unfavorable outcome at 18 months (P = 0.178).

The grading of DAI (AUROC = 0.625, 95% confidence interval [CI] 0.481–0.754) and the number of brain regions with DAI on the MRI scan (AUROC = 0.621 (95% CI 0.477–0.751) both had a weak and statistically insignificant ability to discriminate between patients with and without unfavorable outcome in comparison with the IMPACT predicted risks (AUROC = 0.918, 95% CI 0.809–0.976). The IMPACT predicted risk was significantly better

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Table 3. Ability of Different Magnetic Resonance Imaging Parameters to Predict Unfavorable Outcome 18 Months After Decompressive Craniectomy While Adjusting for the IMPACT Model Predicted Risk of Unfavorable Outcome

Variable	Odds Ratio (OR) (95% Confidence Interval)	*P* Value
Model 1		
Grading of DAI (OR per grade increment)	1.278 (0.681–2.398)	0.445
IMPACT predicted risk (OR per 10% increment in risk)	3.155 (1.681–5.923)	0.001
Model 2		
Number of brain regions with DAI (OR per region increment)	1.086 (0.649–1.815)	0.754
IMPACT predicted risk (OR per 10% increment in risk)	3.247 (1.713–6.152)	0.001
Model 3		
Brainstem with DAI	3.237 (0.274–38.2)	0.351
IMPACT predicted risk (OR per 10% increment in risk)	3.166 (1.687–5.941)	0.001
Model 4		
Substantia nigra or mesencephalic region with DAI	1.056 (0.07–16.4)	0.969
IMPACT predicted risk (OR per 10% increment in risk)	3.305 (1.744–6.264)	0.001

Grading of DAI: 0, no DAI; I, Cerebral hemispheres; II, Corpus callosum; III, Brainstem; IV, Substantia nigra or mesencephalic region.
DAI, diffuse axonal injury on Susceptibility-weighted imaging sequence; IMPACT, International Mission for Prognosis and Analysis of Clinical Trials.

than the grading of DAI (difference in AUROC = 0.293, 95% CI 0.156–0.431; $P < 0.001$) or the number of brain regions with DAI (difference in AUROC = 0.297, 95% CI 0.159–0.435; $P < 0.001$) in differentiating between patients with and without unfavorable outcome 18 months after decompressive craniectomy (Figure 3).

In the multivariate analysis, 1) the grading of DAI, 2) the number of brain regions with DAI, and 3) also the presence of DAI in brainstem, 4) substantia nigra, or mesencephalic tegmentum were all not significantly associated with unfavorable outcome at 18 months while adjusting for the IMPACT predicted risk of unfavorable outcome (Table 3).

There was no significant association between the timing of the MRI scan (median time for all patients 24 days, interquartile range 14–42) after decompression, and the presence or absence of DAI being detected on the scans ($P = 0.852$) (Figure 4). In the restricted analysis of the patients with the MRI scan done within 2 weeks of severe TBI (n = 19), the discriminative ability of the grading of DAI (AUROC 0.694, 95% CI 0.452–0.937; $P = 0.153$), and number of regions with DAI (AUROC 0.711, 95% CI 0.474–0.949; $P = 0.121$) both appeared to improve slightly, but their performance remained inferior to the IMPACT model (AUROC 0.950, 95% CI 0.856–0.999). Similarly, in patients with a MRI scan within 2 weeks of severe TBI, none of the DAI parameters was significantly associated with an unfavorable outcome after adjustment for the IMPACT predicted risks. Including any of the MRI findings into the IMPACT prognostic model also did not improve the multivariate models' calibration and overall explanatory power based on the Hosmer-Lemeshow χ^2 and Nagelkerke's R^2 criteria, respectively.

DISCUSSION

This study confirms that the presence of DAI on MRI scan was associated with a significant increase in unfavorable outcome at 18 months in patients with severe TBI requiring decompressive craniectomy. This was especially the case when the brainstem was involved. However, the grading of DAI and the total number of brain regions with DAI were not as accurate as the IMPACT models in discriminating between patients with and without unfavorable outcome. The presence of DAI in the brainstem, substantia nigra, or mesencephalic region also did not add prognostic significance to the IMPACT prognostic risks in predicting unfavorable outcome at 18 months in this group of patients. These results have some clinical significance and require further discussion.

First, DAI on MRI scan was a common finding (32%) in this group of patients, and its presence was important in predicting long-term neurologic outcome 18 months after surgery. The finding that brainstem DAI was associated with an increased risk of unfavorable neurologic outcome is consistent with previous studies.[12-14] Nevertheless, similar to previous reports, we demonstrated that not all patients with DAI, including those with brainstem DAI, have an unfavorable outcome.[12,17,18] About 17% (95% CI 9–45) and 11% (95% CI 2–43) of our patients who had DAI in any brain regions and brainstem DAI, respectively, indeed turned out to have a favorable outcome at 18 months. As such, our results suggest that clinicians should be prudent not to rely on the presence of DAI or brainstem DAI alone to prognosticate the outcome in their patients with severe TBI.

Second, our results are different from some previous reports in which the presence of DAI on the MRI scan is more important than some clinical and CT brain features in determining long-term patient outcome.[13,14] There are a few possible reasons for this difference. In the first instance, the IMPACT prognostic model has incorporated a wide range of clinical, laboratory, and CT brain features, —including GCS, pupillary reactivity to light, cerebral petechial haemorrhage, and effacement of basal cistern—that may have captured, at least in part, the prognostic consequences of DAI. This explanation is supported by the fact that the significant association between DAI and outcome in the univariate analysis no longer existed after adjustment for the IMPACT predicted risks (Table 3). It is also possible that DAI is a "confounder" in relation to outcome; any association between DAI and poor outcome might have been, in part, apparent only through its associations with other important prognostic information that is already captured by the IMPACT prognostic model.

The question remains whether an early MRI scan would have provided more accurate prognostic information, given that some

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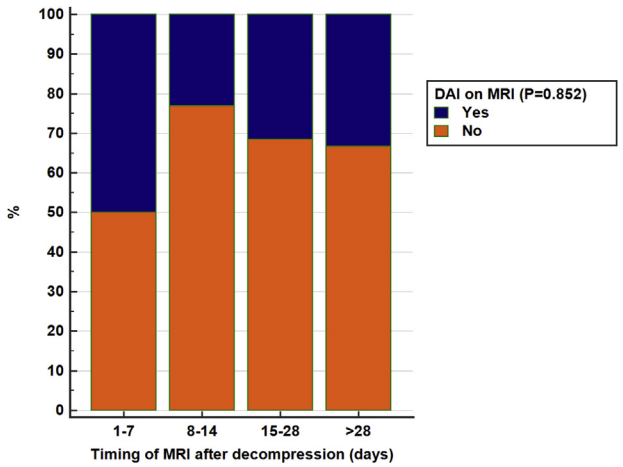


Figure 4. Proportion of patients with diffuse axonal injury (DAI) on the magnetic resonance imaging (MRI) scans after decompressive craniectomy.

of the early microhemorrhagic lesions might have disappeared with time.[12-14] In this study, all our patients had a Codman intraparenchymal pressure monitor in situ within their first week of decompressive craniectomy. The concern about heating up the intraparenchymal metallic probe and severe extracranial injuries had precluded early MRI scans for these patients. In addition, 55% of our patients had severe unilateral brain injury requiring unilateral decompressive craniectomy, mostly as a primary decompression after evacuation of a mass lesion. It is likely that DAI on the MRI scan will have a better prognostic value in patients with diffuse brain injury than in those with predominantly focal lesions.

Finally, we need to acknowledge our limitations. The study cohort was a highly selected group of patients with severe TBI requiring decompressive craniectomy. We also did not include any patients younger than 16 years old in this study. Hence, our results are not generalizable to pediatric patients with TBI or those with only mild to moderate TBI not requiring decompressive craniectomy. The sample size of this study was small, and the MRI scan was not performed within a standardized time frame. Both of these features might have limited the statistical power to detect a small prognostic effect of DAI when combined with the IMPACT predicted risks. A large prospective multicenter cohort will be essential to confirm whether DAI on MRI scan would provide prognostic significance over and beyond the IMPACT predicted risks. If yes, the information about when and for whom the MRI scan would be most appropriate is extremely useful to both clinicians and families of patients with severe TBI. If a delay in performing the MRI scan after TBI is going to substantially reduce its prognostic utility, a risk-to-benefit assessment must be made in the decision whether an external ventricular drain as an intracranial pressure monitor would be preferable to a metallic intraparenchymal probe despite a higher risk of complications, to allow an early MRI scan for prognostic purposes.

In summary, DAI on MRI scan was a common finding in patients with severe TBI, and this was associated with an increased risk of unfavorable neurologic outcome 18 months after TBI. The presence of DAI, even when the brainstem was involved, was not invariably associated with an unfavorable long-term neurologic outcome. The grading of DAI, number of brain regions with DAI, and brainstem or substantia nigra DAI, did not add prognostic significance to the IMPACT model predicted risk. A prospective multicenter trial is needed to confirm whether early MRI scan after severe TBI is useful in addition to the IMPACT prognostic model in predicting long-term outcome in patients with severe TBI.

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