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ORIGINAL WORK

Diffuse Axonal Injury Grade on Early MRI is Associated with Worse Outcome in Children with Moderate-Severe Traumatic Brain Injury

Anna M. Janas[1,5]*, FeiFei Qin[2], Scott Hamilton[1], Bin Jiang[3], Nicole Baier[4], Max Wintermark[3], Zachary Threlkeld[1] and Sarah Lee[1]

Abstract

Background: Traumatic brain injury (TBI) is the leading cause of death and disability in children, but effective tools for predicting outcome remain elusive. Although many pediatric patients receive early magnetic resonance imaging (MRI), data on its utility in prognostication are lacking. Diffuse axonal injury (DAI) is a hallmark of TBI detected on early MRI and was shown previously to improve prognostication in adult patients with TBI. In this exploratory study, we investigated whether DAI grade correlates with functional outcome and improves prognostic accuracy when combined with core clinical variables and computed tomography (CT) biomarkers in pediatric patients with moderate-severe TBI (msTBI).

Methods: Pediatric patients (≤ 19 years) who were admitted to two regional level one trauma centers with a diagnosis of msTBI (Glasgow Coma Scale [GCS] score < 13) between 2011 and 2019 were identified through retrospective chart review. Patients who underwent brain MRI within 30 days of injury and had documented clinical follow-up after discharge were included. Age, pupil reactivity, and initial motor GCS score were collected as part of the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) model. Imaging was reviewed to calculate the Rotterdam score (CT) and DAI grade (MRI) and to evaluate for presence of hypoxic-ischemic injury (MRI). The primary outcome measure was the Pediatric Cerebral Performance Category Scale (PCPCS) score at 6 months after TBI, with favorable outcome defined as PCPCS scores 1–3 and unfavorable outcome defined as PCPCS scores 4–6. The secondary outcome measure was discharge disposition to home versus to an inpatient rehabilitation facility.

Result: Of 55 patients included in the study, 45 (82%) had severe TBI. The most common mechanism of injury was motor vehicle collision (71%). Initial head CT scans showed acute hemorrhage in 84% of patients. MRI was acquired a median of 5 days after injury, and hemorrhagic DAI lesions were detected in 87% of patients. Each 1-point increase in DAI grade increased the odds of unfavorable functional outcome by 2.4-fold. When controlling for core IMPACT clinical variables, neither the DAI grade nor the Rotterdam score was independently correlated with outcome and neither significantly improved outcome prediction over the IMPACT model alone.

Conclusions: A higher DAI grade on early MRI is associated with worse 6-month functional outcome and with discharge to inpatient rehabilitation in children with acute msTBI in a univariate analysis but does not independently correlate with outcome when controlling for the GCS score. Addition of the DAI grade to the core IMPACT model does

*Correspondence: anna.janas@childrenscolorado.org
[5] Present Address: Department of Pediatrics, University of Colorado Anschutz Medical Campus, Aurora, CO, USA
Full list of author information is available at the end of the article

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not significantly improve prediction of poor neurological outcome. Further study is needed to elucidate the utility of early MRI in children with msTBI.

Keywords: Traumatic brain injury, Pediatric neurocritical care, Magnetic resonance imaging, Neuroimaging, Diffuse axonal injury

Introduction

Traumatic brain injury (TBI) is the leading cause of death and disability in children, affecting up to 500,000 children per year in the United States [1]. It is estimated that as many as 62% of children with moderate-severe TBI (msTBI) experience disability, defined as the use of specialized medical and educational services [2]. Although TBI-associated death rates have decreased over the last 2 decades, disabilities for children who survive TBI continue to have significant economic and public health impact on our society [3].

Current treatment guidelines for pediatric patients with TBI are largely adopted from guidelines for adult patients [4]. To improve treatment guidelines and strategies for pediatric TBI, there is an unmet need to understand factors affecting outcome after pediatric TBI. Neuroimaging biomarkers are uniquely well suited because imaging is widely available in most hospitals and provides objective data on the severity of head injury.

Several prognostic models developed in adults incorporate initial head computed tomography (CT) findings (e.g., the International Mission for Prognosis and Analysis of Clinical Trials in TBI [IMPACT] prognostic calculator, Marshall CT classification, Rotterdam CT score, and Helsinki CT score). These models were validated in one pediatric study of more than 300 children with msTBI in Finland [5]. However, CT is insensitive for detection of diffuse axonal injury (DAI), the hallmark pathology in nonpenetrating TBI [6]. Magnetic resonance imaging (MRI) is more sensitive for detection of DAI and may improve prognostic accuracy in adults [7–9].

Increasingly, pediatric patients are undergoing MRI as part of their clinical evaluation of msTBI. MRI may be preferable to CT for pediatric patients because it limits radiation exposure and improves sensitivity for detection of DAI. DAI results from rapid acceleration–deceleration forces that leads to shearing of axons and can be radiographically detected as microhemorrhages in the grey–white junction in the cortex and white matter throughout the brain. Recently published results of a multicenter survey on current imaging practices in pediatric hospitals revealed that MRI is obtained in at least 70% of children hospitalized with severe TBI at most US sites [10]. However, few studies have investigated the prognostic utility of MRI in children with TBI, specifically regarding DAI grade [11–15]. Neuroimaging studies in adult patients with TBI overall support the hypothesis that deeper DAI lesions, particularly in the brainstem, are associated with worse functional outcomes [7–9]. Similarly, pediatric studies found that deeper DAI lesions are associated with worse functional outcome [11, 13–15]; however, these studies are limited by small sample sizes, variable outcome measures, and limited follow-up data. Although these studies report an association between DAI grade and outcome, they do not address whether MRI adds predictive value beyond current prognostic models incorporating core clinical elements and injuries identified on head CT. This retrospective study was aimed to better understand the prognostic value of early MRI, specifically regarding DAI grade. We also aimed to determine whether early MRI improves prognostic accuracy compared with models incorporating early head CT findings and clinical predictors.

Methods

Design, Settings, and Study Population

This exploratory retrospective observational cohort study included pediatric patients aged 1 month to 19 years who were admitted to two tertiary level one trauma centers, Santa Clara Valley Medical Center (SCVMC) and Stanford University Hospital, between January 2011 and July 2019. Although the general cutoff for pediatric patients is less than 18 years, several reports use various age categories and thresholds; for example, the Centers for Disease Control and Prevention reports emergency department visits for TBI in age groupings of 0–4, 5–14 and 15–24, and the American Speech–Language–Hearing Association defines pediatric TBI as <21 years. Our retrospective chart review was a convenience sample of individuals who were admitted to pediatric hospitals (not adult hospitals) with a diagnosis of TBI. Four patients (18–19 years old) included in our study were admitted to the pediatric hospitals and included in the study with the expectation that their mechanism of injury and management received were akin to those of patients <18 years admitted to the same institution. Both hospitals are academic training institutions with pediatric intensive care units and neurosurgical teams. Inclusion criteria were the following: (1) a diagnosis of acute nonpenetrating TBI, defined by *International Classification of Diseases* codes; (2) age less than or equal to 19 years; (3) brain MRI obtained during acute hospitalization within 30 days of injury; and (4) initial

Glasgow Coma Scale (GCS) score of less than 13. We did consider including mild TBI cases (GCS scores 13–15) to improve power; however, ultimately we felt that prognostication is more clinically relevant for patients with msTBI, who often require intensive care unit admission. Limiting our sample to msTBI created a more homogenous cohort in terms of initial assessment of severity. Exclusion criteria were the following: (1) history of prior TBI, (2) penetrating TBI, (3) any prior neurological diagnoses, (4) suspected nonaccidental trauma (NAT), and (5) lack of documented follow-up at 6 months. NAT cases were determined by presence of injuries consistent with NAT (retinal hemorrhages, skeletal injuries, multifocal brain injuries of varying age) without a clear accidental cause. These patients were ultimately given the diagnosis of NAT at discharge. NAT cases were excluded because the pathophysiology is quite different from one-time accidental trauma given the repeated nature of injury in NAT, unclear timing of injury, and frequent delay in presentation [16]. Demographic and clinical data variables were obtained through retrospective chart review. Severity of TBI was defined by the initial postresuscitation GCS score, as assigned by the trauma team in the emergency department. Moderate TBI was defined as GCS scores of 9–12, and severe TBI was defined as GCS scores of 3–8. Additional demographic and clinical variables were extracted through chart review. The Institutional Review Boards of SCVMC and Stanford approved the study protocols and waived patient consent.

Outcomes

The primary outcome was the functional outcome scored with the Pediatric Cerebral Performance Category Scale (PCPCS), which was assessed by chart review of follow-up visits from neurology, neurosurgery, and rehabilitation providers at two time points: approximately 6 months and 1 year after injury. The PCPCS is a qualitative assessment of performance based on the Glasgow Outcome Scale, and scores range from 1 to 6, with 1 being normal and 6 being dead (Supplementary Table S1) [17]. The PCPCS has been validated to quantify cognitive impairments and functional morbidity in children and has been applied to pediatric studies in TBI, cardiac arrest, and general hospitalization [18, 19]. Functional outcome was dichotomized as favorable (PCPCS scores 1–3, normal to moderate disability) or unfavorable (PCPCS scores 4–6, severe disability to death). This dichotomization has been used in prior studies in critically ill pediatric patients, including patients suffering from cardiac arrest and TBI [20–23]. Moderate disability is defined as a child who is able to perform activities of daily living independently but requires special education classes, which we characterized as a favorable outcome. All children included

in the study were assigned a baseline premorbid PCPCS score of 1 after chart review of past medical history. An attending pediatric intensivist (NB) and a pediatric neurology resident (AMJ) scored the PCPCS independently for the SCVMC cohort; an attending pediatric neurologist (SL) and a pediatric neurology resident (AMJ) scored the PCPCS independently for the Stanford cohort. NB and SL were blinded to imaging findings. Adjudication of cases that were assigned different PCPC scores was achieved by discussion of cases.

The secondary outcome measure was hospital discharge disposition either to home or to inpatient rehabilitation. Patients who transferred to another hospital ($n=2$) or died during admission ($n=3$) were excluded from the secondary outcome analysis but included in the primary outcome analysis.

Image Analysis

The first available noncontrast head CT scan and the accompanying radiologist interpretation were reviewed to assess the presence of epidural hematoma (EDH), subdural hematoma, traumatic subarachnoid hemorrhage (tSAH), and intraventricular hemorrhage (IVH). The Rotterdam CT score was assigned as previously described [24]. The Rotterdam score incorporates degree of effacement of basal cisterns, midline shift, presence of EDH, and presence of tSAH/IVH and ranges from 1 (best) to 6 (worst). To minimize potential bias, images from the first available brain MRI were anonymized by BJ, who was blinded to outcomes. Two pediatric neuroradiologists (MW and BJ) and a pediatric neurology resident (AMJ) reviewed the anonymized gradient echo (GRE) or susceptibility-weighted imaging (SWI) sequences to grade hemorrhagic DAI lesions. A senior board-certified neuroradiologist (MW) adjudicated any disagreement. Hemorrhagic DAI lesions were defined as hypointense foci in the white matter and at the grey–white matter junction that were not compatible with vascular, bony, or artifactual structures. DAI grade was assigned on the basis of a previously described system, with grade 0 indicating no lesions, grade 1 indicating lesions in the cortex, grade 2 involving the corpus callosum, and grade 3 involving the brainstem [25]. The original MRI interpretation, diffusion-weighted images, and apparent diffusion coefficient maps were also reviewed for evidence of hypoxic-ischemic injury, defined as unilateral or bilateral restricted diffusion in the cortical grey matter, subcortical white matter, and/or deep grey structures most consistent with ischemia (for sample images, please see Supplementary Fig. S1).

Statistical Analysis

Demographic, clinical, and imaging characteristics of the cohort were summarized by 6-month functional outcome (dichotomized to favorable and unfavorable). The secondary analysis examined a subset of the cohort by discharge outcome (home vs. inpatient rehabilitation). Descriptive statistics are displayed as frequencies and percentages for categorical variables and as medians with interquartile ranges for continuous variables. The χ^2 test or Fisher's exact test was used to compare categorical variables, and the nonparametric Wilcoxon rank-sum test was used to test continuous variables that were not normally distributed.

To evaluate the association between the outcomes of interest and the core IMPACT clinical variables and imaging findings (Rotterdam CT score and DAI grade), we performed a series of univariable and multivariable logistic regression models. Logistic regression was used to fit separate models that included the IMPACT variables (model 1), the Rotterdam CT score (model 2), the DAI grade (model 3), the IMPACT variables and the Rotterdam CT score (model 4), and the IMPACT variables and the DAI grade (model 5). Then to compare the performances of the IMPACT model and CT findings, we assessed the discrimination on the basis of the area under the receiver operating characteristic curve (AUROC). We tested whether the addition of the Rotterdam CT score and/or the DAI grade improved the core IMPACT model by comparing the AUROCs using ROCCONTRAST in SAS (SAS Institute Inc., Cary, NC). This approach exploits the mathematical equivalence of the AUROC to the Mann–Whitney U-statistic, as described by DeLong et al. [26]. Because of the small sample size and limitations to split the cohort into training and testing sets, leave-one-out cross-validation was performed to determine model performance. Additionally, we assessed the positive predictive value for each model and computed the area under the precision recall curve (AUPRC) (see Supplementary Material).

All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc.), and R 4.0.3 (R Core Team, Vienna, Austria). All statistical tests were evaluated at an alpha cutoff of 0.05. There were no missing values for the outcomes or covariates used in the models.

Results

Study Cohort

Retrospective chart review by *International Classification of Diseases* codes for acute brain injury in pediatric patients revealed roughly 9000 possible cases. These were narrowed down by patients who received brain MRI in the acute phase of injury ($n=159$). After excluding patients with prior neurological diagnoses for concern for nonaccidental trauma, a total of 123 pediatric patients with acute TBI were identified. Twelve of the 67 patients classified as msTBI were lost to follow-up after discharge and excluded from the study (Fig. 1). Demographic, clinical, and imaging characteristics are summarized in Table 1. The median age was 13 years, with an IQR of 10 years. Most patients (82%) had severe TBI. The most common mechanism of injury was motor vehicle collision ($n=39$, 71%). Approximately three quarters of patients underwent neurosurgical intervention ($n=42$), with more than half of all patients receiving intracranial pressure monitoring ($n=37$). Thirty-eight patients (69%) were discharged to an inpatient rehabilitation facility, and three patients died in the hospital as a result of their brain injury. The PCPCS score was obtained through chart review for all patients at a median follow-up time of 6 months (range 1–10 months) and 12 months (range 7–16 months) after injury. The interrater agreement for favorable versus unfavorable PCPCS outcomes for the Stanford and SCVMC cohorts was 93% and 85%,
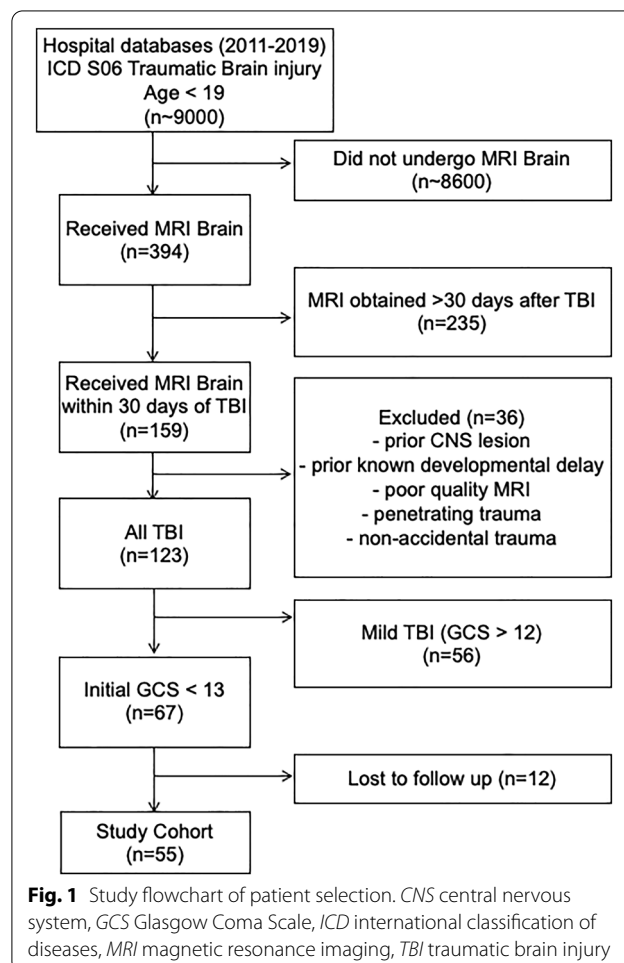

Fig. 1 Study flowchart of patient selection. *CNS* central nervous system, *GCS* Glasgow Coma Scale, *ICD* international classification of diseases, *MRI* magnetic resonance imaging, *TBI* traumatic brain injury

Table 1 Demographic, clinical, and imaging characteristics of patients with moderate and severe TBI patients by (A) functional outcome and (B) discharge disposition

Variable	All (N = 55)	Functional outcome			Discharge disposition		
		Favorable outcome (N = 43)	Unfavorable outcome (N = 12)	*p* value	Discharge to home (N = 11)	Discharge to rehabilitation (N = 38)	*p* value
Age (years), median (Q1, Q3)	13 (6, 16)	13 (6, 16)	12 (6, 15)	0.66	6 (1, 12)	14 (9, 16)	0.0027
Age groups (years)				0.70			0.025
0–5	13 (23.6)	10 (23.3)	3 (25.0)		5 (45.5)	7 (18.4)	
6–12	14 (25.5)	10 (23.3)	4 (33.3)		4 (36.4)	7 (18.4)	
13–19	28 (50.9)	23 (53.5)	5 (41.7)		2 (18.2)	24 (63.2)	
Initial GCS score, median (Q1, Q3)	6 (3, 8)	6 (4, 8)	3 (3, 4.5)	0.001	9 (6, 11)	5 (3, 7)	0.0009
Initial TBI severity							0.0045
Moderate (GCS scores 9–12)	10 (18.2)	10 (23.3)	0 (0.0)	0.096	6 (54.5)	4 (10.5)	
Severe (GCS scores 3–8)	45 (81.8)	33 (76.7)	12 (100.0)		5 (45.5)	34 (89.5)	
Pupil reactivity				0.087			0.47
Both reactive	28 (50.9)	25 (58.1)	3 (25.0)		8 (72.7)	18 (47.4)	
One reactive	12 (21.8)	9 (20.9)	3 (25.0)		1 (9.1)	8 (21.1)	
Neither reactive	15 (27.3)	9 (20.9)	6 (50.0)		2 (18.2)	12 (31.6)	
Mechanism of injury				0.58			0.017
MVC	39 (70.9)	31 (72.1)	8 (66.7)		4 (36.4)	30 (78.9)	
Fall	11 (20.0)	7 (16.3)	4 (33.3)		4 (36.4)	6 (15.8)	
Sports	4 (7.3)	4 (9.3)	0 (0.0)		2 (18.2)	2 (5.3)	
Other	1 (1.8)	1 (2.3)	0 (0.0)		1 (9.1)	0 (0.0)	
Mechanism of MVC (N = 39)				0.84			0.097
Passenger	25 (64.1)	20 (64.5)	5 (62.5)		1 (9.1)	20 (52.6)	
Pedestrian	11 (28.2)	9 (29.0)	2 (25.0)		3 (27.3)	7 (18.4)	
Bike	3 (7.7)	2 (6.5)	1 (12.5)		0 (0.0)	3 (7.9)	
Neurosurgical Intervention							
Any	42 (76.4)	30 (69.8)	12 (100.0)	0.049	7 (63.6)	29 (76.3)	0.45
ICP monitoring	37 (67.3)	25 (58.1)	12 (100.0)	0.0052	5 (45.5)	27 (71.1)	0.16
Craniectomy for bleeding	12 (21.8)	7 (16.3)	5 (41.7)	0.11	2 (18.2)	6 (15.8)	1.00
Craniectomy for ICP	7 (12.7)	5 (11.6)	2 (16.7)	0.64	0 (0.0)	7 (18.4)	0.33
AED/Sseizures							
AED prophylaxis	40 (72.7)	29 (67.4)	11 (91.7)	0.15	8 (72.7)	27 (71.1)	1.00
Post-traumatic seizures	13 (23.6)	11 (25.6)	2 (16.7)	0.71	5 (45.5)	7 (18.4)	0.11
Hospital course, median (Q1, Q3)							
Days on ventilator	11 (3, 20)	10 (2, 17)	29 (9.5, 46)	0.0057	1 (1, 5)	14.5 (7, 25)	0.0005
Days in ICU	15 (8, 26)	14 (8, 22)	23.5 (9.5, 44)	0.085	8 (2, 10)	21 (12, 28)	0.0002
Total days in hospital	23 (11, 33)	21 (11, 29)	28 (10, 45)	0.30	9 (5, 17)	27 (19, 34)	0.0002
Tracheostomy[a]*	14 (26.9)	7 (16.3)	7 (77.8)	0.0007	0 (0.0)	12 (31.6)	0.045
PEG[a]*	24 (46.2)	16 (37.2)	8 (88.9)	0.0078	0 (0.0)	22 (57.9)	0.0005
Acute hemorrhage on CT							
Any	46 (83.6)	34 (79.1)	12 (100.0)	0.18	9 (81.8)	31 (81.6)	1.00
EDH	8 (14.5)	7 (16.3)	1 (8.3)	0.67	4 (36.4)	2 (5.3)	0.018
SDH	32 (58.2)	23 (53.5)	9 (75.0)	0.18	6 (54.5)	23 (60.5)	0.74
tSAH	30 (54.6)	19 (44.2)	11 (91.7)	0.0035	3 (27.3)	22 (57.9)	0.074
IVH	16 (29.1)	14 (32.6)	2 (16.7)	0.47	4 (36.4)	10 (26.3)	0.71
Rotterdam CT score, median (Q1, Q3)	3 (2, 3)	3 (2, 3)	3 (3, 4.5)	0.013	3 (2, 4)	3 (2, 3)	0.69
Rotterdam CT score				0.018			0.51
1	2 (3.6)	2 (4.7)	0 (0.0)		1 (9.1)	1 (2.6)	
2	17 (30.9)	17 (39.5)	0 (0.0)		4 (36.4)	13 (34.2)	

Table 1 (continued)

Variable	All (N=55)	Functional outcome			Discharge disposition		
		Favorable outcome (N=43)	Unfavorable outcome (N=12)	*p* value	Discharge to home (N=11)	Discharge to rehabilitation (N=38)	*p* value
3	23 (41.8)	15 (34.9)	8 (66.7)		3 (27.3)	16 (42.1)	
4	7 (12.7)	6 (14.0)	1 (8.3)		3 (27.3)	4 (10.5)	
5	4 (7.3)	2 (4.7)	2 (16.7)		0 (0.0)	2 (5.3)	
6	2 (3.6)	1 (2.3)	1 (8.3)		0 (0.0)	2 (5.3)	
DAI grade, median (Q1, Q3)	2 (1, 3)	2 (1, 3)	3 (2.5, 3)	0.018	1 (0, 2)	2.5 (2, 3)	0.0092
DAI grade				0.051			0.023
0	7 (12.7)	6 (14.0)	1 (8.3)		3 (27.3)	3 (7.9)	
1	12 (21.8)	12 (27.9)	0 (0.0)		5 (45.5)	6 (15.8)	
2	12 (21.8)	10 (23.3)	2 (16.7)		1 (9.1)	10 (26.3)	
3	24 (43.6)	15 (34.9)	9 (75.0)		2 (18.2)	19 (50.0)	
Evidence of hypoxic-ischemic injury	16 (29.1)	7 (16.3)	9 (75.0)	0.0003	1 (9.1)	11 (28.9)	0.25
Days to MRI, median (Q1, Q3)	5 (1, 13)	4 (1, 14)	8.5 (3.5, 11.5)	0.34	2 (1, 5)	8.5 (2, 14)	0.020
Discharge disposition				0.0017			
Home	11 (20.0)	11 (25.6)	0 (0.0)				
Acute rehabilitation	38 (69.1)	30 (69.8)	8 (66.7)				
Transfer to another hospital	2 (3.6)	2 (4.7)	0 (0.0)				
Transfer to long-term care facility	1 (1.8)	0 (0.0)	1 (8.3)				
Death	3 (5.5)	0 (0.0)	3 (25.0)				
6-month PCPCS score, median (Q1, Q3)	2 (1, 3)	2 (1, 2)	4 (4, 5)	<0.0001	1 (1, 2)	2 (2, 3)	0.0011
Follow-up time (months), median (Q1, Q3)	6 (4, 6.5)	6 (4, 7)	6 (4, 6)	0.95	4 (2, 6)	6 (5, 7)	0.0074
1-year PCPCS, median (Q1, Q3)[b***]	2 (2, 3)	2 (2, 2)	4 (4, 6)	<0.0001	1 (1, 2)	2 (2, 3)	0.046
Follow- up time (months), median (Q1, Q3)	12 (11, 14)	12 (11, 14)	12 (11, 13)	0.97	14 (12, 14)	12 (11, 14)	0.37
Lost to follow-up at 1 year	14	14	0		6	7	

All variables are displayed as N (%), unless specified otherwise

AED antiepileptic drugs, *CT* computed tomography, *DAI* diffuse axonal injury, *EDH* epidural hematoma, *GCS* Glasgow Coma Scale, *ICP* intracranial pressure, *ICU* intensive care unit, *IVH* intraventricular hemorrhage, *MRI* magnetic resonance imaging, *MVC* motor vehicle collision, *PCPCS* Pediatric Cerebral Performance Category Scale, *PEG* percutaneous endoscopic gastrostomy, *SDH* subdural hematoma, *TBI* traumatic brain injury, *tSAH* traumatic subarachnoid hemorrhage

[a] *Tracheostomy/PEG at discharge missing N=3 for patients who died during admission

[b] ***Two patients improved PCPCS score from 4 to 3 at 1-year follow-up. As such, favorable group at 1 year has n=31 and unfavorable group has n=10

respectively. Most patients had a favorable outcome at 6 months (*n*=43, 78%). All patients who presented with moderate TBI had a PCPCS score of 1 or 2 at 6 months. Fourteen patients who were dichotomized to favorable outcome at 6 months were lost to follow-up at 1 year. Two patients who had a PCPCS score of 4 (unfavorable) at 6 months improved to a PCPCS score of 3 (favorable) at 1 year.

Neuroimaging

An initial head CT scan showed acute hemorrhage in 46 of patients (84%). The most common types of hemorrhages were subdural hematoma (*n*=32, 58%) and tSAH (*n*=30, 55%), with EDH and IVH being less common (<30% of patients). Most patients had a Rotterdam CT score of either 2 (*n*=17, 31%) or 3 (*n*=23, 42%). Brain MRI was acquired at a median of 5 days after injury (IQR

12 days). GRE was obtained in 41 patients (75%), whereas SWI was done in 11 patients (20%); three patients (5%) had both sequences. The distribution of DAI grades determined by GRE analysis was not statistically different from that of those determined by SWI analysis (Supplementary Table S2). The interrater agreement on DAI grade was 72%. Hemorrhagic DAI lesions were detected in 87% of all patients, and eight of nine patients without hemorrhage on the initial CT scan were found to have DAI on MRI. Further MRI analysis revealed that 29% of patients had evidence of ischemic injury.

Functional Outcome and Discharge Disposition

There was no difference in age between patients with favorable and unfavorable long-term outcome. Initial GCS scores were lower in the unfavorable outcome group

($p = 0.001$). The incidence of tSAH was significantly higher in the unfavorable outcome group ($p = 0.0035$). Both the Rotterdam CT score and the DAI grade were significantly higher in patients with unfavorable functional outcome ($p = 0.013$ and $p = 0.018$, respectively). Hypoxic-ischemic injury was significantly more likely to occur in patients with unfavorable outcome (75% vs. 16%, $p = 0.0003$) (Table 1). Clinical characteristics obtained at the time of MRI revealed no statistically significant difference in the proportion of patients under mechanical ventilation between the two outcome groups, although significantly more patients with poor outcome had intracranial pressure monitoring at the time of MRI (Supplementary Table S4).

Patients who were discharged to acute rehabilitation ($n = 38$) were more likely to be older, have lower initial GCS scores, and have TBI due to motor vehicle collision ($p = 0.0027$, $p = 0.0009$, and $p = 0.017$, respectively). Presence of EDH was associated with discharge to home ($p = 0.018$). Incidence of tSAH was not significantly different between the groups ($p = 0.074$). DAI grade ($p = 0.023$), but not presence of hypoxic-ischemic injury ($p = 0.25$) or Rotterdam CT score ($p = 0.69$), was significantly higher in patients with unfavorable discharge outcome (Table 1).

Multivariable and Receiver Operating Characteristic Analysis of IMPACT and Imaging Models

Multivariable analysis of the IMPACT core clinical variables (age, initial GCS motor score, and pupil reactivity) showed that a lower initial GCS motor score was significantly correlated with poor functional outcome (odds ratio [OR] 0.34, $p = 0.0061$) but not with discharge disposition (OR 0.53, $p = 0.061$). Older age was correlated with discharge to rehabilitation (OR 1.16, $p = 0.045$) but not with functional outcome ($p = 0.14$). Without controlling for IMPACT core variables, both a higher Rotterdam CT score and a higher DAI grade were associated with worse short- and long-term outcomes. A 1-point increase in the DAI grade increased the odds of unfavorable 6-month functional outcome by 2.4-fold and increased the odds of discharge to inpatient rehabilitation by 2.5-fold (Table 2).

For prediction of unfavorable functional outcome, the IMPACT core model had an AUROC of 0.86 (95% confidence interval [CI] 0.75–0.98), and for prediction of discharge to rehabilitation, the AUROC was 0.86 (95% CI 0.73–0.99). Combining the IMPACT core model with both the Rotterdam CT score and the DAI grade had the best discrimination for the functional outcome (AUROC 0.89; 95% CI 0.78–1.00); however, the improvement over the IMPACT core model was not statistically significant ($p = 0.20$). Furthermore, the addition of neither the Rotterdam CT score nor the DAI grade separately significantly improved the AUROC of the IMPACT core model ($p = 0.58$ for Rotterdam CT score; $p = 0.62$ for DAI grade) (Fig. 2). Leave-one-out validation showed overall good performance of models for functional outcome prediction, with AUROC values lowered by only 0.07–0.15 (Supplementary Table S5). Precision–recall curves were generated given imbalanced outcome groups ($n = 43$ in favorable vs. $n = 12$ in unfavorable) and showed that the AUPRC was much smaller than the AUROC, which was expected given the ratio was 1:3.6 between positive samples (unfavorable outcome) and negative samples (favorable outcome), with a baseline AUPRC of 0.22 for unfavorable outcome (Supplementary Fig. S2). All models scored above baseline, except DAI grade alone.

Discussion

Although CT remains the gold standard for rapid identification of significant traumatic intracranial hemorrhage, the increasing availability of MRI, as well as its superior sensitivity for ischemia and DAI-associated microhemorrhage, has made it a compelling option for diagnosis and prognostication in adult patients with TBI. Several studies in adult patients with TBI showed that cognitive impairment and poor functional outcome were more common in patients with DAI, especially those with deeper brainstem lesions [8, 27, 28]. Pediatric patients with TBI are increasingly undergoing MRI early in their hospitalization, but its utility has not been established, and no prior studies have evaluated performance of an MRI scoring system in pediatric TBI outcome prediction. Although MRI is a noninvasive procedure, it is not entirely without risk; magnetic resonance scan time is typically longer than CT, requiring closer hemodynamic monitoring; in addition, younger or agitated children may require anesthesia, which carries additional risk. It is important, therefore, to understand the utility of early MRI to optimize management strategies for acute TBI and guide prognostication.

DAI grade is a compelling potential early MRI-based biomarker, as it can be easily calculated by an intensive care unit physician (see Supplementary Table S3 for a scoring guide), and microhemorrhages caused by axonal shearing appear early and remain stable for at least 3 months after TBI [29]. The DAI grade has previously been shown in smaller retrospective pediatric studies to correlate with functional outcome [11–15]. In our retrospective cohort study of 55 children admitted with msTBI, we confirmed a significant correlation between the DAI grade and both 6-month functional outcome and discharge disposition. Secondarily, we sought to determine whether incorporating the DAI grade to IMPACT variables would improve prediction over either alone. The core IMPACT model performed well in discriminating

Table 2 IMPACT core predictors and their associated odds ratiosORs in the core model for predicting unfavorable outcome and discharge to inpatient rehabilitation
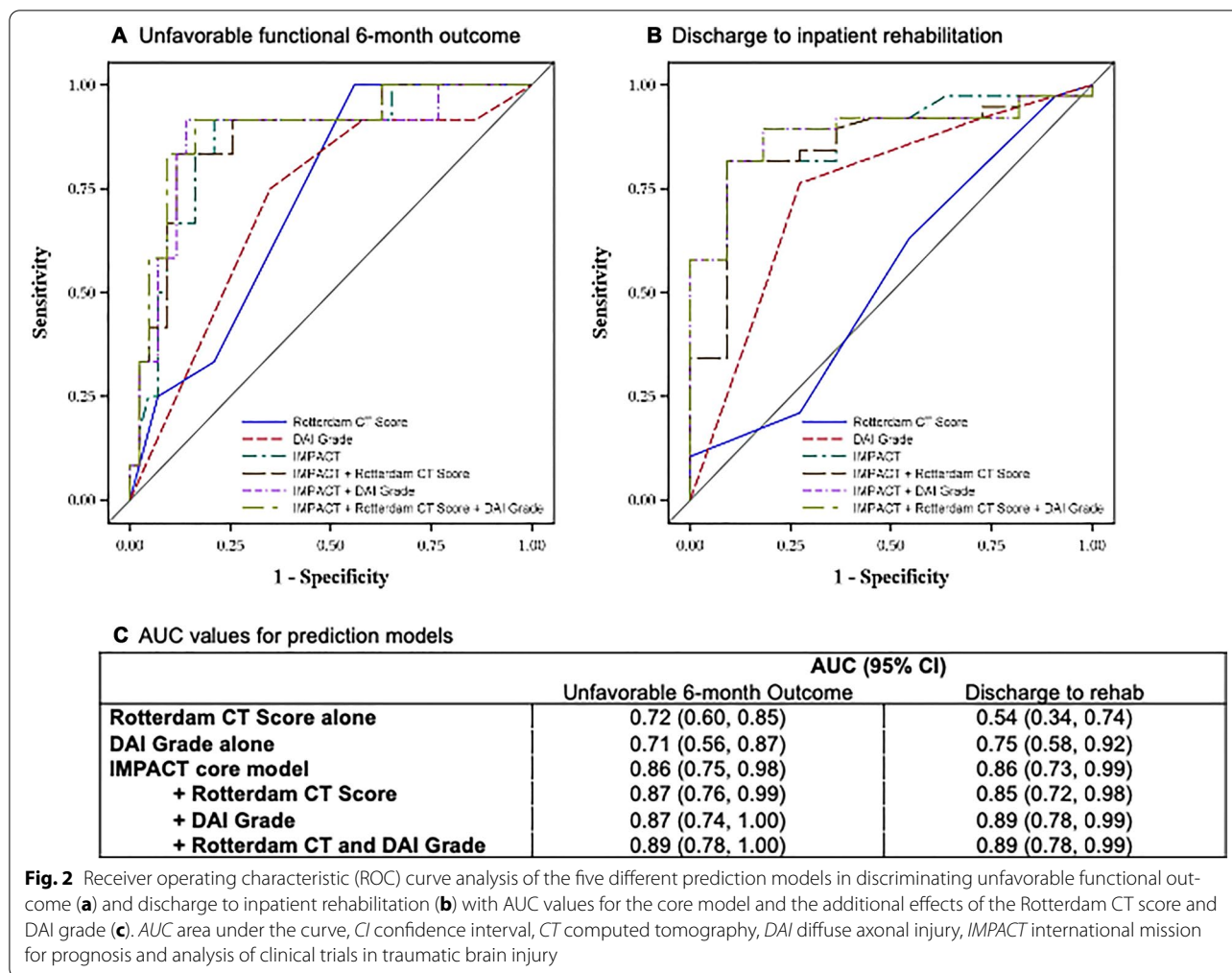
Model	Unfavorable 6-month functional outcome		Discharge to inpatient rehabilitation	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Model 1 (IMPACT variables)				
Age	0.88 (0.74, − 1.04)	0.14	1.16 (1.00, − 1.35)	0.045
GCS initial motor score	0.34 (0.15, − 0.73)	0.0061	0.53 (0.27, − 1.03)	0.061
Pupillary light reactivity				
Both pupils react	Reference	0.31	Reference	0.47
One pupil reacts	1.08 (0.13, − 9.28)		2.69 (0.19, − 38.28)	
Both no reaction	3.68 (0.60, − 22.47)		3.32 (0.39, − 28.30)	
Model 2				
Rotterdam CT score	1.98 (1.09, − 3.61)	0.026	1.25 (0.64, − 2.45)	0.51
Model 3				
DAI grade	2.44 (1.06, − 5.66)	0.037	2.46 (1.23, − 4.95)	0.011
Model 4 (IMPACT + Rotterdam)				
Age	0.84 (0.69, − 1.03)	0.10	1.16 (1.0, − 1.35)	0.055
GCS initial motor score	0.33 (0.14, − 0.76)	0.0093	0.52 (0.27, − 1.03)	0.061
Pupillary light reactivity		0.32		
Both pupils react	Reference		Reference	0.47
One pupil reacts	0.77 (0.083, − 7.14)		2.77 (0.18, − 42.22)	
Both no reaction	3.35 (0.50, − 22.40)		3.35 (0.39, − 28.81)	
Rotterdam CT score	1.76 (0.79, − 3.91)	0.16	0.95 (0.36, − 2.47)	0.91
Model 5 (MPACT + DAI)				
Age	0.89 (0.74, − 1.06)	0.17	1.15 (0.99, − 1.34)	0.060
GCS initial motor score	0.37 (0.17, − 0.85)	0.018	0.62 (0.30, − 1.26)	0.19
Pupillary light reactivity		0.34		0.52
Both pupils react	Reference		Reference	
One pupil reacts	1.16 (0.13, − 10.51)		2.56 (0.17, − 39.50)	
Both no reaction	3.56 (0.58, − 21.90)		3.09 (0.36, − 26.65)	
DAI grade	1.64 (0.56, − 4.81)	0.37	1.61 (0.71, − 3.69)	0.26

CI confidence interval, *CT* computed tomography, *DAI* diffuse axonal injury, *GCS* Glasgow Coma Scale, *IMPACT* international mission for prognosis and analysis of clinical trials in traumatic brain injury, *OR* odds ratio

patients with unfavorable 6-month functional outcome and discharge to inpatient rehabilitation. However, incorporation of the DAI grade to the core IMPACT model did not significantly improve outcome prediction.

In this study, we show that DAI is a common finding on early MRI detected in 87% of our patients, and its grade is associated with neurological outcome. The finding that deeper DAI lesions are associated with an increased risk of unfavorable outcome is consistent with prior studies. These studies remain limited and require further validation. Only one prior study investigated correlation between hemorrhagic DAI lesions detected on early MRI (i.e., within 1 month of injury) and functional outcome in pediatric patients with TBI [13]. Notably, it included all TBI severities and was limited by a small number of patients (*N* = 40, with 30 having severe TBI). A larger study of pediatric patients with msTBI (*N* = 106)

examined the correlation between functional outcome and chronic DAI lesions (MRI at 3 months after injury) [11]. Both studies showed significant correlation between deeper DAI lesions and worse functional outcome at 6–12 months after injury. Our study adds significantly to the existing literature and confirms that the DAI grade may be an important biomarker. It is crucial to point out that not every patient with DAI had unfavorable functional outcome; in our study, 34% of patients with favorable outcome had brainstem DAI lesions, whereas one patient (8%) who had unfavorable outcome did not have any sign of DAI. As such, clinicians should not rely on the presence of DAI alone to prognosticate the outcome in their patients with TBI. This is reflected in our results from cross-validation of models and precision–recall curves in which the DAI grade alone had generally lower AUROC values for unfavorable outcome prediction. This

Fig. 2 Receiver operating characteristic (ROC) curve analysis of the five different prediction models in discriminating unfavorable functional outcome (**a**) and discharge to inpatient rehabilitation (**b**) with AUC values for the core model and the additional effects of the Rotterdam CT score and DAI grade (**c**). *AUC* area under the curve, *CI* confidence interval, *CT* computed tomography, *DAI* diffuse axonal injury, *IMPACT* international mission for prognosis and analysis of clinical trials in traumatic brain injury

is not surprising because a single MRI biomarker would not be expected to predict functional outcome after TBI. Additional early MRI abnormalities, including volume and number of DAI lesions, volume of hypoxic-ischemic injury, and degree of edema on a fluid-attenuated inversion recovery sequence, have been previously proposed as promising MRI biomarkers in pediatric TBI [15, 30–32]. Indeed, in our study, radiographic evidence of ischemic injury was significantly higher in the unfavorable outcome group. Unlike DAI grade, however, these potential biomarkers are dependent on timing of MRI. Further prospective studies incorporating early MRI biomarkers such as DAI grade and degree of ischemia, as quantified by apparent diffusion coefficient values and volume of injury obtained at a specified period, may further augment the prognostic utility of early MRI.

There is no single clinical, laboratory, or imaging characteristic that can accurately predict the chances of favorable outcome after TBI. Hence, several prognostic models have been developed. The IMPACT model

was first described in 2008, and it identified three key clinical variables (the initial GCS motor score, age, and pupillary reactivity) as the core predictors that together significantly discriminate favorable and unfavorable outcome in adult patients with msTBI [33]. The IMPACT model was validated in one study of 341 children with TBI [5]. In accordance with our findings, the authors of this large pediatric study reported an AUROC of 0.83 for the IMPACT core model in pediatric patients with msTBI; furthermore, they reported a lack of significant improvement with the addition of the Rotterdam CT score to the IMPACT model and found that age was not independently correlated with functional outcome [5]. Interestingly, although the study found that pupil reactivity was a significant predictor of outcome, this variable failed to statistically improve outcome prediction in our own cohort. This may be a reflection of a small cohort number in our study and inclusion of more critically ill patients (our study

excluded mild TBI), for whom outcomes are often less certain.

Several neuroimaging models (Rotterdam, Marshall, and Helsinki CT scores) identify early brain injuries on the initial CT scan that are associated with higher risk of mortality in adult patients with TBI. The Rotterdam CT score incorporates the degree of compression of basal cisterns, presence of significant midline shift, and presence of several different types of acute hemorrhagic injury (EDH, IVH, tSAH) and has previously been shown to accurately stratify the risk of mortality [34] as well as correlate with functional outcome [5] in children with TBI. Concordant with prior adult and pediatric TBI literature [33], we found that a higher Rotterdam CT score was associated with unfavorable outcome and that EDH correlated with favorable outcome, whereas tSAH correlated with unfavorable outcome in pediatric patients with TBI. However, when controlling for the core IMPACT variables, only the initial GCS motor score was found to be independently associated with outcome. This is in line with existing pediatric literature: in at least one large retrospective study of 565 children, all three CT scoring systems were inferior to the GCS score in functional outcome prediction [35]. One possible explanation is that head CT may not adequately capture clinically meaningful brain injury in children. In support of this idea, one study of 336 children and 870 adult patients with TBI found that the patterns of intracranial injury on head CT were significantly different between pediatric and adult patients and that the Rotterdam CT score was, on average, lower (less severe) in children [36].

Although brain injuries captured on the initial head CT scan may be used in stratifying risk of mortality in children with TBI, overall, they may not be as helpful in improving prediction of morbidity in surviving children after TBI. This begs the question whether MRI biomarkers may be superior to head CT in improving functional outcome prediction. In our secondary aim we, tested the hypothesis that incorporating the DAI grade to the IMPACT model would improve outcome prediction. Notably, although the extended IMPACT model incorporates radiographic findings on the initial head CT scan, it does not take into consideration early MRI biomarkers. One study in adult patients with severe TBI requiring decompressive craniectomy ($N = 56$) compared the prognostic utility of the DAI grade with that of the extended IMPACT model and showed that the DAI grade was inferior and did not significantly improve discrimination of outcomes over the IMPACT model alone [37]. Of note, in this study, 83% of patients with unfavorable outcome had no sign of DAI on early MRI, and the generalizability of the study is limited by inclusion of only those adult patients with highest severity requiring craniectomy. To

the best of our knowledge, this is the first pediatric study that investigated whether early MRI biomarkers improve the prognostic utility of the IMPACT model. Although our results did not show a statistically significant increase in discrimination of unfavorable outcome with the addition of the DAI grade, further investigations in larger prospective studies are needed.

There are several limitations to our study. First, our cohort may not be fully representative of all pediatric patients with msTBI. For example, potential patients who were too unstable to receive MRI in the first 30 days after injury or who died prior to receiving MRI are not represented. Alternately, children whose clinical examination appears worse than their initial imaging may also prompt MRI, which would skew results in the opposite direction. In addition, our sample is biased against patients who presented with lower GCS scores but made a quicker recovery and did not have a clinical indication for MRI. Although, overall, our results support prior studies that found an association between core clinical and imaging variables and outcome, one notable exception is pupillary reactivity, which we did not find to be significantly different between outcome groups ($p = 0.087$). In our study, 51% of patients had bilaterally reactive pupils, compared to an average of 80% across prior studies [5, 38]. This may represent issue with a smaller sample size or inclusion of more critically ill children because mild TBI cases were excluded. Next, given the retrospective design, we were unable to control the timing, sequence composition, and technical specifications of the MRI scan. That said, we would not expect minor variations in the timing of MRI to have a significant impact given the reported stability of DAI microhemorrhages for several months [29]. A small proportion of patients underwent SWI instead of GRE sequences as part of the institutional MRI protocol. SWI is known to be more sensitive than GRE for detection of microhemorrhages in TBI [39], which suggests our analysis might underrepresent the true incidence of hemorrhagic DAI. However, GRE is an older and more prevalent technology as compared with SWI, and our GRE-predominant results may therefore be more generalizable. In addition, the overall distribution of DAI grade in patients who received GRE was similar to that in those who received SWI, suggesting that depth-of-lesion analysis may be accurately obtained with GRE. Although ours is one of the largest studies published to date on DAI grade on early MRI in children with msTBI, it is possible that improvement in prediction accuracy with the DAI grade could reach statistical significance with a larger sample size. We recognize that many centers lack the considerable resources needed to obtain MRI in acutely ill pediatric patients, and this represents a limitation of generalizability and clinical utility of our

results. Next, the premorbid functional status of our patients is assumed to be normal on the basis of existing chart review, but this is not known with certainty. Patients were excluded from the study only if they had known underlying diagnoses, such as developmental disorders or prior brain injury. Finally, functional morbidity in pediatric patients with TBI may not be accurately captured by the PCPCS at 6 months. PCPCS scores may be falsely elevated in young toddlers who are not attending school and rely more heavily on parental support in general. As such, other functional outcome scales may more accurately capture neurological morbidity in toddlers. In addition to performing more comprehensive neurological outcome measures, the timing of follow-up is important because children are expected to continue improving in the first months to years after TBI. Unfortunately, in our study, 25% of patients were lost to follow-up at 1 year. Interestingly, only two of twelve patients in the unfavorable outcome group at 6 months improved to favorable outcome by 1 year. Longer follow-up time may be required to assess patient's full recovery potential. Further prospective studies are greatly needed to understand if and how early MRI can improve care in pediatric patients with TBI.

Conclusions

A higher DAI grade on early MRI is associated with worse functional 6-month outcome and with discharge to inpatient rehabilitation in children with acute msTBI in a univariate analysis but does not independently correlate with outcome when controlling for the GCS score. Addition of the DAI grade to the core IMPACT model does not significantly improve prediction of poor neurological outcome. Further study is needed to elucidate the utility of early MRI in children with msTBI.

Author details
[1] Department of Neurology and Neurological Sciences, Stanford University, Stanford, CA, USA. [2] Quantitative Science Unit, Department of Medicine, Stanford University, Stanford, CA, USA. [3] Department of Radiology, Stanford University, Stanford, CA, USA. [4] Department of Pediatrics, Santa Clara Valley Medical Center, San Jose, CA, USA. [5] Present Address: Department of Pediatrics, University of Colorado Anschutz Medical Campus, Aurora, CO, USA.

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