Predicting Outcome after Pediatric Traumatic Brain Injury by Early Magnetic Resonance Imaging Lesion Location and Volume

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Abstract

Brain lesions after traumatic brain injury (TBI) are heterogeneous, rendering outcome prognostication difficult. The aim of this study is to investigate whether early magnetic resonance imaging (MRI) of lesion location and lesion volume within discrete brain anatomical zones can accurately predict long-term neurological outcome in children post-TBI. Fluid-attenuated inversion recovery (FLAIR) MRI hyperintense lesions in 63 children obtained 6.2±5.6 days postinjury were correlated with the Glasgow Outcome Scale Extended-Pediatrics (GOS-E Peds) score at 13.5±8.6 months. FLAIR lesion volume was expressed as hyperintensity lesion volume index (HLVI)=(hyperintensity lesion volume / whole brain volume)×100 measured within three brain zones: zone A (cortical structures); zone B (basal ganglia, corpus callosum, internal capsule, and thalamus); and zone C (brainstem). HLVI-total and HLVI-zone C predicted good and poor outcome groups ($p<0.05$). GOS-E Peds correlated with HLVI-total ($r=0.39$; $p=0.002$) and HLVI in all three zones: zone A ($r=0.31$; $p<0.02$); zone B ($r=0.35$; $p=0.004$); and zone C ($r=0.37$; $p=0.003$). In adolescents ages 13–17 years, HLVI-total correlated best with outcome ($r=0.5$; $p=0.007$), whereas in younger children under the age of 13, HLVI-zone B correlated best ($r=0.52$; $p=0.001$). Compared to patients with lesions in zone A alone or in zones A and B, patients with lesions in all three zones had a significantly higher odds ratio (4.38; 95% confidence interval, 1.19–16.0) for developing an unfavorable outcome.

Key words: biomarkers; cognitive function; MRI; outcome measures; pediatric brain injury

Introduction

IN THE UNITED STATES ALONE, traumatic brain injury (TBI) affects over 0.5 million children and adolescents annually, including 630,000 emergency department (ED) visits, 60,000 hospitalizations, and over 6100 deaths.¹ Although guidelines were published in 2003 for severe TBI (sTBI),² mortality and poor outcomes remain significant, ranging from 21% to 30% and 40% to 50% respectively.^{3–5} Establishing rigorous, reliable prediction models of neurological outcome and accurate assessments of neurological injury are necessary for 1) clinical management, 2) stratification in clinical trials, 3) counseling families regarding long-term expectations and potential life withholding decisions, and 4) providing valuable data for investigative research.^{6–8} Whereas clinical-based injury scoring systems, such as the Glas-

gow Coma Scale (GCS), are appropriate for assessing neurological injury severity in the initial triage evaluation, they are less accurate when evaluating long-term neurological function. A lower GCS score is frequently associated with a higher risk of morbidity; however, up to 40% of children classified as having an sTBI with a GCS ≤5 will still experience a favorable outcome.^{9,10} Assessing the neurological status of a child in the acute setting can be difficult owing to developmental immaturity, traumatic unconsciousness, presence of an endotracheal tube, and sedative or paralytic medications. Inaccurate evaluation of neurological severity is associated with intubation and pharmacological sedation and 89–98% of children with sTBI will present to the tertiary trauma center with an endotracheal tube in place having received sedative medications.^{11–13} Extended traumatic coma can further obscure outcome prognostication in the initial injury period given that 30–70% of

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children with prolonged disturbances in traumatic consciousness may recover with acceptable outcomes at 1 year.^{14–16} Novel therapies from clinical, translational, and basic science advances in pediatric TBI will require clinical trial testing, emphasizing the need for reliable early neuroimaging biomarkers of outcome.

Computed tomography (CT) is the most appropriate neuroimaging method in the initial evaluation of intracranial injury; yet, CT underestimates the extent of parenchymal brain injury, diffuse axonal injury (DAI), nonhemorrhagic contusions, and brainstem pathology, identifying only 30–60% of lesions, compared with magnetic resonance imaging (MRI).^{17–22} Pediatric studies report associations of individual CT morphologies, such as diffuse swelling, cistern effacement, subarachnoid hemorrhage, subdural hemorrhage, and DAI, with increased mortality and morbidity; nonetheless, a normal head CT can be found in 40% of children with a poor outcome post-TBI.^{11,12,23,24} Since the first report in 1986 by Jenkins and colleagues detailing the improved diagnostic accuracy of MRI in identifying brain lesions post-trauma, MRI-based techniques have been intensely studied as imaging biomarkers to predict mortality and functional outcomes in children and adults post-TBI.^{22,24–34} Despite the more routine use of brain MRI to assess neuropathological injuries after pediatric TBI, there remains no clear consensus among clinicians who care for children with TBI on the significance of early MRI lesions on long-term functional outcome.

In pioneering studies in primates, Ommaya and Generalli proposed that the depth of parenchymal brain lesions paralleled the forces transmitted to the brain, where the location of the brain lesions determined the level of neurological impairment.³⁵ Examining this model relative to outcome prediction revealed that children with subcortical or brainstem lesions, present greater than 3 months postinjury on MRI, sustained significantly worse impairment as measured by disability rating scales, global outcome scores, and tests of psychosocial and cognitive function than those with cortical lesions alone.^{36–38} These findings endorsed the concept that the lesion location and, notably, increasing depth of lesion can influence long-term outcome. Data on lesions detected early postinjury by MRI is less substantiated given that by 3 months up to 45% of patients will have lesions disappear that were present on the initial MRI.³⁹

The high spatial resolution, high signal-to-noise ratio, and generated tissue contrasts enable MRI to be an ideal image-based biomarker. Quantitative lesion analysis has the ability to further probe the relationship between the injury volume in distinct brain regions and neurocognitive and functional outcome.^{24,26,40} Early MRI-based injury prognostication has been reported in children post-TBI; however, we are unaware of any studies examining quantitative fluid-attenuated inversion recovery (FLAIR) injury volume in specific brain regions for long-term functional outcome prediction. A summary of literature investigating early MRI in predicting neurological outcome after pediatric TBI is presented in Table 1. The aim of this study is to determine whether FLAIR hyperintensity lesions (FHLs) on early MRI can predict long-term neurological outcome in children after moderate and sTBI. To investigate the outcome of acute FLAIR lesions within individual brain regions, we compared the Glasgow Outcome Scale Extended-Pediatrics (GOS-E Peds) functional outcome score and intelligent quotient (IQ) score to quantitative FHLs from total, superficial, deep, and brainstem brain zones. We also sought to determine whether the correlation of injury volumes within distinct brain zones with outcome would differ depending on the age of the child; thus, we also analyzed children ≤12 years and adolescents ages 13–17 years separately.

Methods

Patient selection and data collection

Deidentified demographic, clinical, and radiological data were analyzed retrospectively from prospectively collected data from longitudinal studies of acute, moderate, and sTBI at Parkland Memorial Hospital (PMH) and Children Medical Center Dallas (CMCD) in Dallas, Texas, from 2005 to 2012. Patients were ages 0–17 years, with accidental TBI and a GCS of ≤12 on presentation or after deterioration; thus, some patients had higher initial GCS on admission, but declined within the first 24 h. Patients were excluded if they had suspected abusive head injury, had penetrating brain injury, or were not expected to survive. At UT Southwestern (UTSW) Medical Center, children with traumatic injury ages 0–13 years are admitted to CMCD and adolescents ages 14–17 years to PMH. Management of TBI is in accord with published guidelines.² All subjects were enrolled according to UTSW standards for human research with institutional review board approval with written and informed parental consent. We excluded patients with MRI evidence of hypoxic-ischemic injury (HII) given that TBI patients with coexisting HII may confer a worse prognosis, but recorded their outcomes.⁴¹ We defined HII as diffusion abnormalities on apparent diffusion coefficient (ADC) and diffusion-weighted imaging (DWI) sequences in bilateral parietooccipital cortical watershed areas and/or bilateral basal ganglia ± bilateral thalamic regions. Brain MRI FLAIR images from 63 (CMCD, $n=45$; PMH, $n=18$) patients were analyzed. We considered MRI early if obtained within 0–21 days from the injury date. In 1 patient, the MRI was obtained at 28 days.

Fluid-attenuated inversion recovery image processing and hyperintensity lesion volume measurements

Conventional MRI and FLAIR sequences were collected on a Philips Intera 1.5T (Philips Healthcare, Andover, MA): field of view, (FOV) 220 mm; matrix size, 512×512; and 8000–1000/2300/120 repetition time (TR)/inversion time (TI)/echo time (TE) at CMCD; and GE Genesis Signa 1.5T scanner (General Electric Medical, Milwaukee, WI); FOV, 200 mm; matrix size, 256×256; and 8800/2200/130 TR/TI/TE at PMH. Three subjects from CMCD and 4 from PMH were imaged on a 3T scanner. Images were acquired in the axial plane with 5-mm slice thickness and interslice gap of 0.5–1.0 mm. Blinded to outcome assessment, FLAIR DICOM images were converted to ANALYZE format using MRICro⁴² and processed in a semiautomatic quantitative fashion for total and regional lesion volume analysis using MATLAB software (Mathworks, Inc., Natick, MA); the detailed steps were described previously by our group.²⁶ Inter-rater reliability for this method of volumetric analysis was shown to be excellent and consistent (0.956; $p<0.001$). This tool uses signal thresholding and morphological erosion, in combination with human knowledge to segment and quantify hyperintensity lesion volume and whole-brain volume (WBV), illustrated in Figure 1. We measured all hyperintense hemorrhagic and nonhemorrhagic lesions abnormalities that met threshold excluding postsurgical or intracranial device tracks. All postprocessed FHLs were cross-referenced with the neuroradiology report; any disagreement was resolved by a blinded pediatric neuroradiologist (M.M.) interpretation. For data analysis, we analyzed hyperintensity lesion volume (HLV) as an index relative to WBV. $HLV \text{ index (HLVI)} = \text{hyperintensity lesion volume} / \text{WBV} \times 100$.²⁶

Regional brain injury zone measurements

The brain was divided into three major anatomic zones for analysis: zone A=superficial (frontal, parietal, temporal, and occipital cortical gray [GM] and subcortical white matter [WM]); zone B=deep (genu and splenium of the corpus callosum [CC],

TABLE 1. SUMMARY OF STUDIES ASSESSING EARLY MRI (<21 DAYS) IN LONG-TERM FUNCTIONAL OUTCOME PREDICTION AFTER PEDIATRIC TBI

Reference	Patients and age	Injury to MRI time	MRI analysis	Outcome and time from injury	Results
Woischneck (2002) ²⁸	N = 30; severe TBI (age, 12.1 ± 5.9 years)	3.5 days (range, 10 hours–8 days)	Presence of T1- and T2-weighted lesions	Glasgow Outcome Score (GOS); 3 months–2 years postinjury	Presence of BS lesions correlated significantly with GOS; however, supratentorial lesion did not. Five of 18 (22%) with BS lesions, except bilateral pons (which was fatal by 2 months), had favorable outcomes.
Tong (2004) ³¹	N = 40; mild, moderate, and severe TBI (age range, 1.5–18 years)	7 ± 4 days (range, 1–16 days)	SWI global and brain regional lesion volume and number	PCPCS; 6–12 months postinjury	The presence of SWI lesions in multiple brain regions was highly associated with outcome. The number of SWI lesions in total, superficial, deep, and posterior fossa brain zones were greater in poor outcome groups. SWI lesion volume was increased in deep and posterior fossa zones in poor outcomes.
Babikian (2005) ²⁹	N = 18; mild, moderate, and severe TBI (age, 12 ± 5.6 years)	6 ± 4 days	SWI and MR spectroscopic (MRS) imaging total and regional lesion volume and number	Neuropsychological composite index of eight functional domains and IQ; 2.1 ± 0.5 years postinjury	Total, BG, TH, and BS SWI lesion number and volume were associated with worse individual neuropsychological domains, IQ, and composite index scores. Mean total <i>N</i> -acetyl aspartate/creatine and total SWI lesion volume were the best predictors of neuropsychological index score and IQ.
Sigmund (2007) ²⁴	N = 40; mild, moderate, and severe TBI (age range, 1.5–18 years)	7 ± 4 days (range, 1–16 days)	Compared T2-weighted, FLAIR, and SWI global lesion volume and number	PCPCS; 6–12 months postinjury	All MRI sequences were able to distinguish between normal (PCSCP 1) and poor (PSCPS 3–6) groups and between mild (PCPCS 2) and poor outcome groups by MRI lesion count and volume. SWI detected > number of lesions while FLAIR/T2 detected > volume. CT was unable to differentiate outcome groups, and 40% of the poor outcome group had a negative CT.
Galloway (2008) ⁵⁶	N = 37; mild, moderate, and severe TBI (age, 10.6 ± 5.8 years)	7 ± 4 days (range, 1–16 days)	DWI, ADC maps of total and regional values	PCPCS; 6–12 months postinjury	DWI detected different abnormalities than T2 or FLAIR. Mean ADC values in frontal white matter, temporal gray and white matter, and BG were lower in poor outcome groups with severe TBI. Average total brain ADC values had the greatest ability to correctly predict outcome.
Babikian (2009) ⁷⁰	N = 17; mild, moderate, and severe TBI (age, 12 ± 5.8 years)	6 ± 4 days	DWI, ADC maps of total and regional values	Neuropsychological composite index and IQ; 25.5 ± 6.4 months postinjury	ADC values from peripheral gray and white matter regions inversely correlated with IQ and neuropsychological index, whereas total, posterior fossa, and deep gray and white matter ADC values did not.

MRI, magnetic resonance imaging; TBI, traumatic brain injury; ADC, apparent diffusion coefficient; BS, brainstem; IQ, intelligent quotient; BG, basal ganglia; TH, thalamus; SWI, susceptibility-weighted imaging; FLAIR, fluid-attenuated inversion recovery; CT, computed tomography; DWI, diffusion-weighted imaging; PCPCS, Pediatric Cerebral Performance Category Scale.

FIG. 1. Representation of injury patterns based on anatomical zones of injury and quantitative analysis. Computed tomography (CT) (A, D, and G) and fluid-attenuated inversion recovery (FLAIR) images (B, E, and H) from comparable axial sections. A only (B), superficial zone (parietal lobe, arrow); A + B (E), superficial (insulate gyrus, arrow), and deep zone (putamen and globus pallidus, arrowhead); A + B + C (H), superficial (inferior frontal and medial temporal lobes, arrow), deep (not shown), and brainstem (pons/midbrain, double arrow head). (C), (F), and (I) illustrate postprocessed image with areas in red representing quantitative FLAIR hyperintensity lesion volume after thresholding. HLV, hyperintensity lesion volume. Color image is available online at www.liebertpub.com/neu

internal and external capsule, basal ganglia [BG], and thalamus [TH]); and zone C = brain stem (mid-brain, pons, and medulla); lesions in the cerebellum were excluded (Fig. 1). Lesions were grouped into specific brain zones based upon known neuroanatomical structures readily identified on MRI. Lesion volumes within specific brain zones were calculated by manual delineation using the region of interest function, followed by sequential image lesion extraction by each zone. This function allowed the operator, while referencing the processed FLAIR image, to circumscribe the lesion and extract the lesion volume of each zone separately when lesions crossed borders of zones on the same slice.

Functional outcome measure

Functional outcome was performed approximately 12 months postinjury using the GOS-E Peds, a structured interview that assesses functional abilities in multiple domains post-TBI.^{3,43} A neuropsychologist or a trained neuropsychology technician by a face-to-face or phone interview administered the GOS-E Peds with caregivers. Patients who were enrolled early in the study and from PMH were administered the Glasgow Outcome Scale-Extended (GOS-E), an adult instrument with known validity used to measure functional outcome in adults and used to predict outcome in children before the availability of the GOS-E Peds.⁴⁴ The GOS-E Peds is a downward extension of the GOS-E and a valid measure of outcome in children.⁴³ All GOS-E scores were converted to GOS-E

Peds scores for analysis. From the principal study, functional outcome assessments were made in 81 of 113 (72%) subjects from PMH and in 136 of 172 (79%) children from CMCD. The GOS-E Peds score ranges from 1 to 8, with lower scores associated with a better outcome. The 8-point GOS-E Peds is divided into the following categories: 1) upper good recovery: performs all age-appropriate activities as before; 2) lower good recovery: normal activities with mild impairment in social activities or family relationships; 3) upper moderate disability: reduced capacity for school work and moderate impairment in social activities and family relationships; 4) lower moderate disability: requires sheltered work or school environment or unable to attend school and unable to participate in social activities or daily severe disruptions in family relationships; 5) upper severe disability: assistance of another person at home is essential for most, but not all, activities of everyday living or child's ability to interact outside the home is impaired as expected for age; 6) lower severe disability: assistance of another person at home is essential for all activities of everyday living as expected for age; 7) vegetative state: unable to follow simple commands or interact beyond reflexes; and 8) death.

Cognitive outcome: Measure

General cognitive function (i.e., IQ) was assessed by either the Mullen Scales of Early Development, the Wechsler Preschool and Primary Scale of Intelligence-Third Edition, or the Wechsler

Intelligence Scale for Children-Forth Edition according to patient age.⁴⁵⁻⁴⁷ IQ has been shown to have a dose-related relationship with severity of TBI, with increasing effects demonstrated as time elapses.^{48,49}

Statistical analysis

Descriptive analyses of the continuous and categorical data were performed using proportions, frequency distributions, means, and confidence intervals (CIs). Spearman's correlation test was used to investigate the association between two ranked variables. Wilcoxon's rank-sum test was used to test the difference in medians between two samples. Statistical analyses were performed with SAS software (9.3; SAS Institute Inc., Cary, NC).

Results

Demographic, clinical, and outcome data

In all patients ($n=63$), mean age at injury was 9.9 ± 5.7 years, in the ≤ 12 years age group ($n=36$) average age was 5.5 ± 3.7 years, and for ages 13–17 years ($n=27$) average was 15.5 ± 2.1 years. Mean Injury Severity Score (ISS) and Emergency Department Glasgow Coma Score (ED GCS) were 28.7 ± 10.5 and 5.6 ± 3.9 , respectively; mechanism of injury, ED GCS, ISS, and GOS-E Peds outcome did not differ significantly between the two age groups. Mean time

postinjury to MRI was 6.2 ± 5.6 days (range, 0–28), similar to intervals reported in other studies studying early MRI for outcome prediction.^{24,28,31,50} Mean time postinjury to GOS-E Peds assessment was 13.5 ± 8.6 months (range, 1–50), and mean GOS-E Peds score was 3.1 ± 1.9 . Demographic, clinical, and outcome data for all patients, and for ages ≤ 12 years and >12 years, are presented in Table 2. Overall mortality was low (2 of 63; 3%); 1 died in the hospital and 1 after hospital discharge. The low mortality rate was expected given patients with a low likelihood of survival were not enrolled.

Fluid-attenuated inversion recovery lesion location and injury pattern

Brainstem lesions were present in 15 of 63 (24%) subjects, similar to reports in adults and children with sTBI, ranging from 20% to 30%.^{21,50,51} Hyperintense FLAIR lesions were present in 58 of 63 (92%) patients; 5 of 63 (8%) had no abnormalities on FLAIR. Craniotomy surgery with hematoma evacuation was significantly associated with FLAIR lesion volume from the superficial zone for children ≤ 12 years ($p < 0.0001$), but not for children >12 years ($p = 0.23$). Regression method showed that surgically evacuated lesions were not associated with outcome for all patients or age groups.

We observed three distinct injury patterns classified by brain zone: A: lesions restricted to the superficial zone; A + B: injuries

TABLE 2. PATIENT DEMOGRAPHICS, INJURY DATA, AND FUNCTIONAL OUTCOME

	All patients (n=63)	Age ≤ 12 years (n=36)	Age >12 years (n=27)
Age (years), mean $\pm$ SD	9.9 ± 5.7	5.5 ± 3.7	15.5 ± 2.1
Gender, no. (%)			
Male	44 (70)	27 (75)	17 (63)
Female	19 (30)	9 (25)	10 (37)
Mechanism, no. (%)			
MVC	37 (59)	21 (59)	16 (59)
MPC	13 (20)	7 (19)	6 (22)
Fall	9 (14)	5 (14)	4 (15)
Falling object	3 (5)	2 (5)	1 (4)
Other	1 (2)	1 (3)	
ISS, mean $\pm$ SD	28.7 ± 10.5	28.1 ± 9.5	29.6 ± 11.8
ED GCS, mean $\pm$ SD	5.6 ± 3.9	5.9 ± 3.6	5.3 ± 4.3
ED GCS, no. (%)			
3–5	39 (62)	19 (53)	20 (74)
6–9	13 (21)	10 (28)	3 (11)
10–12	4 (6)	4 (11)	
13–15	7 (11)	3 (8)	4 (15)
Surgically evacuated lesions, no. (%)	7 (11)	4 (11)	3 (11)
Injury to MRI (days), mean $\pm$ SD	6.2 ± 5.6	5.1 ± 4.6	7.8 ± 6.5
Discharge disposition, no. (%)			
Home	20 (32)	11 (31)	9 (33)
Rehab facility	42 (66)	24 (66)	18 (67)
Morgue	1 (2)	1 (3)	
Injury to GOS-E Peds (months), mean $\pm$ SD	13.5 ± 8.6	16.0 ± 9.0	7.6 ± 2.4
GOS-E Peds, mean $\pm$ SD	3.1 ± 1.9	3.2 ± 1.9	3.0 ± 2.0
GOS-E Peds, no. (%)			
1–2	27 (43)	16 (44)	11 (41)
3–4	20 (32)	10 (28)	10 (37)
5–6	12 (19)	8 (22)	4 (15)
7–8	4 (6)	2 (6)	2 (7)
Hospital LOS (days), mean $\pm$ SD	17.4 ± 10.7	15.9 ± 7.7	19.3 ± 13.8

For GOSE-Peds, 8-point scale where 1–2=normal or mild disability, 3–4=upper and lower moderate disability, 5–6=upper and lower severe disability, 7=vegetative state, and 8=death.

MVC, motor vehicle collision; MPC, motor pedestrian collision; ISS, Injury Severity Score; ED GCS, Emergency Department Glasgow Coma Score; LOS, length of stay; GOSE-Peds, Glasgow Outcome Scale Extended-Pediatrics; SD, standard deviation.

TABLE 3. FUNCTIONAL OUTCOME BASED ON FLAIR ANATOMIC BRAIN INJURY ZONES AND VOLUME

<i>Injury pattern lesions in zone(s)</i>	<i>No. (%)</i>	<i>GOS-E P, favorable no. (%)</i>	<i>GOS-E P, unfavorable no. (%)</i>	<i>GOSE-P, mean $\pm$ SD</i>	<i>HLVI, mean $\pm$ SD</i>
All patients ^a					
A only	19 (33)	16 (84)	3 (16)	2.47 $\pm$ 1.84	1.18 $\pm$ 1.15
A + B	24 (42)	19 (79)	5 (21)	3.00 $\pm$ 1.62	1.70 $\pm$ 2.12
A + B + C	14 (25)	7 (50)	7 (50)	4.50 $\pm$ 2.10	3.24 $\pm$ 5.45
Total ^a	57	42 (74)	15 (26)		
Age $\leq$ 12 years					
A only	11 (35)	9 (82)	2 (18)	2.36 $\pm$ 1.69	1.00 $\pm$ 0.85
A + B	12 (39)	9 (75)	3 (25)	3.33 $\pm$ 1.44	1.58 $\pm$ 2.18
A + B + C	7 (23)	3 (43)	4 (57)	4.86 $\pm$ 2.27	3.80 $\pm$ 7.22
Total	30	21 (70)	9 (30)		
Age 13–17 years					
A only	8 (30)	7 (87.5)	1 (12.5)	2.63 $\pm$ 2.13	1.43 $\pm$ 1.49
A + B	12 (44)	10 (83)	2 (17)	2.67 $\pm$ 1.78	1.81 $\pm$ 2.14
A + B + C	7 (26)	4 (57)	3 (43)	4.14 $\pm$ 2.04	2.68 $\pm$ 3.39
Total	27	21 (78)	6 (22)		

For GOS-E P: favorable=scores of 1–4; unfavorable=scores of 5–8). Zone A=superficial (cortical gray and subcortical white matter); zone B=deep (basal ganglia, thalamus, corpus callosum, and external and internal capsule); and zone C=brainstem (mid-brain, pons, and medulla).

^aExcludes the one patient with lesion in zone C only and five with no FLAIR hyperintensity lesions.

FLAIR, fluid-attenuated inversion recovery; GOS-E P, Glasgow Outcome Score Extended-Pediatrics; HLVI, hyperintensity lesion volume index; SD, standard deviation.

present in both superficial and deep zones; and A + B + C: lesions present in all three zones, which were evenly distributed among age groups (Fig. 1; Table 3). As predicted in the Ommaya-Generalli model, lesions in deep or brainstem zones were almost universally associated with injury to other regions of the brain. Brainstem lesions were associated with lesions in both A and B zones in 14 of 15 (93%) patients and deep zones lesions were associated with superficial zone injuries in 24 of 24 (100%). In those with detectable FHLs, 19 of 58 (32.8%) were in zone A only, 24 of 58 (41.4%) in zones A and B, and 14 of 58 (24.1%) in zones A, B, and C. One patient (1.7%) had an isolated zone C lesion. After excluding the 5 patients without FHLs and 1 with zone C lesion, we analyzed the injury pattern by dichotomized favorable (GOS-E Peds, 1–4) and unfavorable (GOS-E Peds, 5–8) outcome (Table 3). Overall, 42 of 57 (74%) had favorable and 15 of 57 (26%) unfavorable outcomes. Favorable outcomes were observed in 16 of 19 (84%) of children with zone A lesions, 19 of 24 (79%) with zone A + B lesions, and 7 of 14 (50%) if all three zones (A + B + C) were involved. Children sustained higher GOS-E Peds scores (worse outcome) with addition of injury zones stratified by depth of lesion across injury pattern types, mean GOS-E Peds score, A (2.47 $\pm$ 1.84), A + B (3.00 $\pm$ 1.62), and A + B + C (4.50 $\pm$ 2.10). We found a statistically significant association of increasing probability for developing an unfavorable outcome with increasing number of regions involved by depth of lesion (Cochran-Armitage's trend test, $p=0.047$; Fig. 2). We did not find a significant difference in distribution of injury patterns or outcomes of specific injury zones between younger children and adolescents. Although we did not measure FHLs in children with TBI and MRI findings of HII, their outcomes were universally poor: 6 of 6 (100%) sustained an unfavorable outcome; 2 of 6 (33%) died; and 4 of 6 (67%) survived, with lower severe disability (GOS-E Peds, 6). In logistic regression testing of all injury patterns (A, A + B, and A + B + C), only A + B + C injury pattern was significantly predictive of outcome, with an odds ratio of 4.38 (95% CI, 1.19–16.0) for unfavorable outcome ($p=0.03$), compared to those with lesions in either A alone or A + B regions.

Quantitative fluid-attenuated inversion recovery regional lesion volume analysis

There were wide ranges in lesion volume across injury patterns; although mean HLVI values suggested that a larger lesion burden was associated with injury to increasing number of zones (Table 3), we did not find a statistically significant association between HLVI and injury pattern. HLVI-total (global lesion burden) and HLVI from the three brain regions—superficial zone (HLVI-A), deep zone (HLVI-B), and brainstem zone (HLVI-C)—were measured from all patients ($n=63$) and analyzed against the GOS-E Peds. In our study, patients did not sustain injuries in more inferior brain

FIG. 2. Percentage of patients with unfavorable outcome increase with superior to inferior depth of lesion injury zone pattern ($n=57$). Outcome dichotomized by Glasgow Outcome Scale Extended-Pediatrics score (favorable=scores of 1–4; unfavorable=scores of 5–8). Brain zone of injury: A only, superficial; A + B, superficial and deep; A + B + C, superficial and deep and brainstem.

FIG. 3. Wilcoxon's rank-sum analysis for all patients ($n=63$) of total brain hyperintensity lesion volume index (HLVI) and HLVI from brain zones A (superficial), B (deep), and C (brainstem) with dichotomized Glasgow Outcome Scale Extended-Pediatrics (GOS-E Peds) score (favorable=scores of 1–4; unfavorable=scores of 5–8). The line inside the box represents median (50% percentile). The triangle represents mean. The lower edge of the box represents the first quartile (25% percentile), whereas the upper edge of the box represents the third quartile (75% percentile). The endpoint of the upper whisker shows the maximum, and the endpoint of the lower whisker shows the minimum values.

zone in isolation; thus, it is important to consider that regional HLVI analysis represented some patients with injuries in other brain regions. For example, HLVI-A represented the FHL volumes from zone A irrespective of the lesion type (A, A+B, or A+B+C). Wilcoxon's rank-sum analysis for all patients found HLVI-total ($p=0.02$; Fig. 3D) and HLVI-C ($p=0.024$; Fig. 3C) significantly distinguished favorable and unfavorable outcome groups, whereas HLVI-A ($p=0.07$; Fig. 3A) and HLVI-B ($p=0.06$; Fig. 3B) approached significance. Spearman's nonparametric correlation

analysis was then performed to determine the linear relationship between the 8-point GOS-E Peds score and the total lesion volume index and the lesion volume index within individual brain zones (Table 4). In all patients, there was a moderate, but statistically significant, correlation between outcome and HLVI-total ($r=0.39$; $p=0.002$) and in all brain zones—HLVI-A ($r=0.31$; $p=0.01$), HLVI-B ($r=0.35$; $p=0.004$), and HLVI-C ($r=0.37$; $p=0.003$)—such that a greater amount of lesion volume coincided with a worse functional outcome score (Fig. 4). We found significant distinctions

TABLE 4. CORRELATION OF GOS-E PEDS WITH FLAIR LESION VOLUME INDEX IN INDIVIDUAL BRAIN ZONES IN YOUNGER CHILDREN AND ADOLESCENT AGE GROUPS

	All patients ($n=63$)		Age ≤ 12 years ($n=36$)		Age 13–17 years ($n=27$)	
	ρ	p value	ρ	p value	ρ	p value
HLVI-total	0.39	0.002	0.34	0.040	0.5	0.007
HLVI-zone A	0.31	0.013	0.22	0.198	0.45	0.018
HLVI-zone B	0.35	0.004	0.52	0.001	0.22	0.274
HLVI-zone C	0.37	0.003	0.41	0.013	0.35	0.075

Zone A=superficial; zone B=deep; and zone C=brainstem.

GOS-E Peds, Glasgow Outcome Scale Extended-Pediatrics; FLAIR, fluid-attenuated inversion recovery; HLVI, hyperintensity lesion volume index.

FIG. 4. Spearman's nonparametric correlation and scatter plot analysis in all patients ($n=63$) of total hyperintensity lesion volume index (HLVI) and HLVI in distinct brain zones A (superficial), B (deep), and C (brainstem) with 8-point Glasgow Outcome Scale Extended-Pediatrics (GOS-E Peds) score (1=upper good recovery; 2=lower good recovery; 3=upper moderate disability; 4=lower moderate disability; 5=upper severe disability; 6=lower severe disability; 7=vegetative state; 8=death).

in the correlations of lesion volume within specific brain zones with outcome, depending on the age at which the injury occurred. In younger children ages ≤ 12 years, FLAIR volumes from total, HLVI-total ($r=0.34$; $p=0.048$), deep, HLVI-B ($r=0.52$; $p=0.004$), and brainstem, HLVI-C ($r=0.41$; $p=0.01$) zones, but not superficial regions, were correlated with outcome. Whereas in the 13- to 17-year age group, FHL volumes from total, HLVI-total ($r=0.5$; $p=0.007$) and superficial, HLVI-A ($r=0.45$; $p=0.02$) zones, but not deep or brainstem areas, had significant correlations (Table 4). The most

robust correlation with functional outcome for all patients and adolescents was with HLVI-total and for children ≤ 12 years, HLVI-B.

We next performed Spearman's correlation testing using IQ scores collected between 6 and 24 months postinjury to investigate FLAIR injury volume correlations within individual brain zones with cognitive function. IQ scores were available for 30 children (ages ≤ 12 , $n=28$; age >12 , $n=2$). Total lesion volume, HLVI-total ($r=-0.47$; $p=0.009$) and superficial zone volume, HLVI-A ($r=-0.44$; $p=0.014$) were negatively correlated with IQ, but deep and brainstem regions were not (Table 5).

To model *injury location* (injury pattern) and *injury volume* (HLVI) relationships, we analyzed the GOS-E Peds score with seven variables (HLVI-total, HLVI-A, HLVI-B, and HLVI-C) and injury patterns A, A + B, and A + B + C using forward step-wise and backward step-wise multiple regression. In this model, the two significant predictors of GOS-E Peds outcome were HLVI-total ($p<0.0001$) and injury pattern A + B + C ($p=0.020$). In addition, when compared to patients with A or A + B injury patterns, patients with lesion in all the three zones had significantly worse GOS-E Peds scores despite similar total lesion volumes ($p=0.02$).

Discussion

Our major findings investigating early quantitative FLAIR MRI in specific brain zones as a pediatric TBI imaging biomarker are the

TABLE 5. CORRELATION OF IQ WITH FLAIR LESION VOLUME INDEX IN INDIVIDUAL BRAIN ZONES^a

	Rho	p value
HLVI-total	-0.47	0.009
HLVI-zone A	-0.44	0.014
HLVI-zone B	-0.12	0.515
HLVI-zone C	-0.12	0.528

Zone A=superficial; zone B=deep; and zone C=brainstem.

^aIQ was available for 30 children ($n=28$ for ages ≤ 12 years and $n=2$ for ages >12 years).

IQ, intelligent quotient; FLAIR, fluid-attenuated inversion recovery; HLVI, hyperintensity lesion volume index.

following: 1) Injury to specific brain regions in the superficial, deep, and brainstem structures act in an additive and descending fashion to increase the risk for developing an unfavorable outcome; 2) FLAIR total lesion volume and the volume of brainstem lesions were able to significantly discriminate favorable and unfavorable outcome groups; 3) total, superficial, deep, and brainstem FLAIR lesion volumes correlated with GOS-E Peds outcome, which was affected by age—the most robust correlation was in deep brain structures for children ≤ 12 years and total lesion volume in adolescents 13–17 years; 4) long-term cognitive outcome appeared to be more dependent on total injury volume and injury volume within cortical brain structures than deep or brainstem zones; and 5) in multivariate analysis, the two significant predictors of functional outcome were total FLAIR lesion volume and FLAIR lesions occurring in all three brain zones.

Magnetic resonance imaging techniques in outcome prediction

Advanced neuroimaging techniques have advanced our understanding of the complexity and heterogeneity of injury that occurs post-TBI. As an emerging, more commonly utilized facet of TBI care, MRI has the potential to predict individual patient outcomes, design targeted therapies, facilitate early neurocognitive intervention, and guide appropriate neurological injury stratification for clinical trials. Clinical MRI scanning protocols typically include T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), FLAIR, as well as sequences that are sensitive to magnetic susceptibility effects, such as T2*-gradient-recalled echo (T2*GRE) and susceptibility-weighted imaging (SWI) sequences. The preferred MRI technique for neurological injury prognostication post-TBI is unknown and the threshold at which lesions begin to influence outcome is also uncertain.

In contrasting MRI sequences, T2*GRE and SWI are superior for detection of small hemorrhagic lesions associated with axonal shear injury, whereas FLAIR and T2WI have greater sensitivity for nonhemorrhagic lesions, contusions, and vasogenic edema detected in the brainstem and deep brain structures.^{21,50,52,53} FLAIR may be a more sensitive sequence than T2WI for detection of DAI and cortical contusions owing to suppression of the high signal from cerebrospinal fluid (CSF) observed on T2WI, which can conceal hyperintense lesions adjacent to CSF.⁵⁴ Although SWI and T2*GRE generally identify a greater number of traumatic lesions, lesion volume may be significantly higher when measured by FLAIR or T2WI.^{18,24,27,55} Moen and colleagues measured quantitative traumatic axonal lesion load 8 days postinjury in 128 adolescents and adults with moderate and sTBI. After adjustment for age, GCS, and pupil dilation, they found that FLAIR, but not T2*GRE, predicted outcome using whole brain, CC, brainstem, and thalamic lesion volume, which was most pronounced in the sTBI population.⁵⁰ Severity of brain injury may therefore also have a role in which particular MRI sequence is most specific for outcome prognostication. In a study by Yuh and colleagues of 135 adults from the prospective TBI-TRACK study with mild TBI (GSC, 13–15) and a brain MRI 12 ± 3.9 days postinjury, patients with one or more brain contusions or >4 foci of axonal hemorrhagic injury on MRI were 4.5 times more likely to have some element of neurological dysfunction at 3 months after controlling for socioeconomic, clinical, and CT features.³⁴ The increased sensitivity to detect subtle abnormalities by either T2*GRE, SWI, DWI, or DTI may make these MRI techniques particularly useful in predicting neurological sequelae with milder injury phenotypes.

Early FLAIR volumetric analysis has not been previously reported in discrete brain zones; however, Tong and colleagues studied SWI lesions early after pediatric TBI in specific brain zones and found children with poor outcomes had significantly higher SWI lesion volume and numbers in total, deep, and brainstem regions.³¹ Additionally, DWI and ADC mapping can identify lesions not apparent on either FLAIR, T2WI, or SWI sequences and has been reported to correlate with outcome using total lesion burden and within specific brain regions in adults and in children.^{50,56} We did not directly compare CT to FLAIR in our study, but others have found that CT lesion burden does not accurately predict outcome in children or adults, compared with MRI.^{24,27} By only using FLAIR to detect brain abnormalities, we likely underestimated the extent of smaller hemorrhagic lesions detected by SWI or T2*GRE sequences; however, the specificity for outcome prediction may have increased by identifying more clinically significant abnormalities. Chastain and colleagues compared zonal and volumetric lesions from T2WI, FLAIR, and SWI MRI sequences in 38 adults 5.6 days after acute mild, moderate, and sTBI and found that, although SWI detected a significantly greater number of lesions, T2WI and FLAIR total lesion volume and lesion volume in deep and brainstem regions demonstrated a superior ability to distinguish between good and poor outcome groups.²⁷ In a study of 40 TBI children, Sigmund and colleagues found quantitative analysis of T2WI, FLAIR, and SWI total lesion volumes all performed comparably in distinguishing between normal and poor outcome groups.²⁴ There exists considerable variation in the literature assessing the validity of early MRI for neurological outcome determination in MRI timing, MRI sequence, neurological severity, age, outcome measure, and analytical method. Advances in the field are likely to continue as newer techniques, such as functional MRI, DWI, DTI, and MR spectroscopy, are probed.^{57–59} We believe FLAIR imaging, used in this study, is an ideal MRI technique for early injury prognostication because it is a commonly acquired MRI sequence, has excellent inter-rater reliability for quantification, is accurate for early and chronic quantitative and qualitative outcome analysis within specific brain regions, and has excellent tissue injury discrimination and diagnostic sensitivity for traumatic injuries.^{24,26,27,39,40,54,55}

Brain zone and depth of lesion injury pattern

We separated FLAIR lesions into three distinct brain zones similar to the categorization proposed by Tong and colleagues and Chastain and colleagues: *superficial* (frontal, parietal, temporal, and occipital lobes); *deep* (genu, body, and splenium of the CC, BG, TH, and external and internal capsule); and *brainstem* (mid-brain, pons, and medulla). By identifying and separating lesions into anatomic zones, we were able to demonstrate a significant increase in unfavorable outcomes in groups stratified by the three injury patterns, suggesting that acquisition of injury in each additional zone had a prognostic effect on outcome (Fig. 2). We believe this zone-based classification scheme may provide a simple, yet practical, anatomic categorization that renders lesions into easily partitioned areas for accurate volumetric analysis and clinical application. Adult prospective studies using early MRI report a highly significant relationship between mortality and poor neurological function in subjects with pons and mid-brain brainstem injuries versus those with supratentorial lesions only.^{25,51} Fifty percent of children with brainstem lesions in our study sustained an unfavorable outcome. Brainstem lesions were always found in association with injury to deep and superficial zones; thus, an independent attribution of brainstem lesions to outcome was not readily

determinable. The only patient with an isolated brainstem lesion in our study had an upper moderate disability (GOS-E Peds, 3). Edgar and colleagues, in a retrospective study of 20 comatose TBI children, reported unfavorable GOS outcomes in 47% of those with traumatic brainstem lesions on either CT or MRI.²² Patrick and colleagues, in a study of 32 children, examined 11 brain areas in the neuroaxis and found that injury to brainstem regions, but not cortical areas, were significantly associated with prolonged low response states and injury to BG and thalamic regions approached significance ($p=0.07$).⁶⁰ Our results disagree somewhat with findings by Blackman and colleagues, who reported that injury of decreasing-level (cortical to brainstem) injuries did not predict Functional Independence Measure for Children scores post-discharge from inpatient rehabilitation.⁶¹ In this study, however, one third of the subjects had CT imaging alone and MRIs were obtained up to 2 months postinjury, which may account for differences from our results. Woischneck and colleagues performed MRI 8 days postinjury in 30 consecutive comatose children and found brainstem lesions in 60% of subjects, which correlated highly with GOS, but found no qualitative relationship with supratentorial lesions and outcome.²⁸ Tong and colleagues also reported that patients with poor outcomes had significantly more brain regions affected with SWI lesions (8.4, compared to 6.1; $p=0.003$).³¹ Our findings lend support to previous studies in demonstrating that early FLAIR MRI lesions in multiple brain zones are associated with a significant increase in poor outcomes post-TBI. Moreover, patients with lesions in all three zones experienced a trend toward worse GOS-E Peds scores and a 438% higher risk for developing an unfavorable outcome, compared to those with superficial lesions only or superficial and deep zone lesions.

Quantitative injury zone analysis and age-related effect

We assessed the ability of FLAIR injury volumes in total, superficial, deep, and brainstem regions to distinguish between favorable and unfavorable outcome groups. We found significant differences in the total lesion volume and the lesion volume in the brainstem zone between those with favorable and unfavorable outcomes, whereas superficial zone ($p=0.07$) and deep zone ($p=0.058$) approached significance. Notably, given that mortality was low (3%), unfavorable outcomes represented survivors with significant neurological disabilities. Our findings support results by Sigmund and colleagues, who found that total FLAIR lesion volume on early MRI in children was significantly higher in poor outcome groups, and with Moen and colleagues, who found that nonhemorrhagic lesion volumes measured by FLAIR in specific brain zones in the brainstem, CC, and TH (corresponding to our deep regions) in adults were predictors of dichotomous GOS-E outcome.^{24,50} Using a different MRI technique, Tong and colleagues divided the brain into three zones analogous to our anatomical distinctions and found similar significant increases in global SWI lesion volume and SWI volume in deep and posterior fossa regions in poor outcome groups.³¹

Testing the linear correlation of GOS-E Peds and regional FLAIR lesion volumes provided another method to examine the relationship of injury with specific brain regions. We found significant, but moderate, correlations in the total, superficial, deep, and brainstem zones with outcome ($r=0.31$ – 0.39). Marquez de la Plata and colleagues found slightly higher correlations between DAI lesion volume index and GOS-E measured by FLAIR in global ($r=-0.453$; $p=0.034$) and in internal/external capsule ($r=-0.484$) regions in adults. When examining the two age groups separately, we found

that the strength of correlation relationship of HLVI within specific brain zones was impacted by the age at which the injury occurred; this effect seemed to be independent of the distribution of injury pattern, mean functional outcome scores, or lesion burden owing to the fact that these were very similar in both age groups (Table 3). In the ≤ 12 years age group (mean, 5.5 ± 3.7 years), the best correlation of outcome was with deep brain zone volume ($r=0.52$). In contrast, in the adolescent age group, ages 13–17 years (mean, 15.5 ± 2.1 years), the best correlation was with total lesion volume ($r=0.50$), and deep zones did not show a significant relationship at all. This suggests that within the pediatric age range, there may exist developmental and maturational factors that may influence recovery that differ in specific brain locations contingent on the age at which the injury occurs.

The neural plasticity and maturation mechanisms inherent in a young child's brain are believed to confer a greater capacity for self-repair, compared to adults. However, these paradigms are largely based on the observation of enhanced re-establishment of neural connections and recovery of function in focal brain disruption models.⁶² It is unclear whether a more diffuse brain injury that occurs with significant translational and rotational forces affecting many brain regions, for example, after a high speed motor vehicle collision (MVC), affords the same plasticity potential. The importance of injury to immature and developing neural progenitor populations in recovery pathways is increasingly recognized; evidence points toward increased vulnerability and susceptibility of early progenitor populations to various forms of cellular injury in the developing brain.⁶³ Recent animal experiments have shown that ablation of these immature precursors can interfere with recovery from brain injury and impair restoration of spatial learning and memory as well as cognitive and motor function.^{64–67} Because myelination, synaptogenesis, and neural organization occur throughout childhood, it is plausible that neural self-repair and adaptive potential is, in part, determined by the consequence of traumatic interruption of immature neural networks. Hence, injury to deep brain structures, which are immature and evolving in younger children, resulted in a greater influence on functional recovery, whereas in adolescents organizing and developing cortical regions exert a more dominant impact. Teasing out the specific association of injury within individual brain zones with outcome is challenging owing to the interconnectivity of the brain and potential for multiple brain regions to be involved post-TBI. In multiple regression modeling of injury location and injury volume variables, we found that the two significant predictors of outcome were total HLVI ($p<0.0001$) and injury pattern A + B + C ($p=0.02$). One explanation for the A + B + C injury pattern being an important predictor of outcome is that this pattern is reflective of a greater energy imparted to the brain at impact, as outlined by the Ommaya-Generalli model.³⁵ Undoubtedly, total or global MRI lesion burden is an important early prognostic variable because it consistently predicts outcome in children and adult studies across multiple MRI techniques and was significant for all patients, both age groups, and in our multivariate analysis.^{24,26,27,31,40,50,52,56,68,69} Our results would add that in addition to considering global lesion volume, one must take into account the effect that the specific lesion location burden and the child's age have in the long-term recovery process and on neurocognitive and functional outcomes.

Cognitive outcome

We found total FLAIR lesion volume (HLVI-total) and superficial zone volume (HLVI-A) were inversely correlated with IQ score, but not deep (HLVI-B) or brainstem volumes (HLVI-C).

This was somewhat unexpected given that HLVI-A was not correlated with GOS-E Peds and HLVI-B demonstrated the best correlation with GOS-E Peds in ages ≤ 12 years and the majority (28 of 30) of those with IQ testing was in the young age group, although they were slightly older at 7.6 ± 4.6 (IQ) versus 5.5 ± 3.7 years (GOS-E Peds). Intelligence tests and GOS-E Peds assessments, however, measure different aspects of outcome that may, in turn, be affected by injury to a particular part of the brain that is important for that function. Although GOS-E Peds has been found to have a strong association with intelligence 6 months postinjury, little is known of its association with IQ longer term (i.e., 12, 24, or 36 months postinjury).⁴³ It is important to consider that GOS-E Peds is a test of *overall* functional ability of a child, involving performance of daily living activities, social functions, and academic success. Measures of intelligence assess specific cognitive domains based on the age of the child, which may, in turn, affect functional outcome capacity, particularly in areas where a premium is placed on cognition, such as academic and vocational functioning; but other areas of daily performance, such as social and emotional functioning, may be less dependent on IQ. For example, a child with average IQ may still be rated as moderately disabled owing to frequent disruption of family or friendships as a result of psychological, behavioral, or academic performance problems. There are scarce reports on the association of early MRI findings in specific brain zones with neurocognitive or neuropsychological outcomes after pediatric TBI. Babikian and colleagues, in comparing DWI ADC values from peripheral and deep brain regions, found that only peripheral regions (corresponding to our superficial zone) were negatively correlated with neurocognitive and -psychological domains.⁷⁰ In a separate report of 18 patients (mean age, 14 ± 5.6 years) assessed 2 years postinjury, they found that total SWI lesion volume was a stronger predictor than SWI lesion number and negatively correlated with Full Scale IQ ($r = -0.57$; $p = 0.01$). They also found strong associations between SWI lesion volume in deep brain regions, such as the BG, TH, and brainstem regions, with nearly all domains of intellectual and neuropsychological functioning.²⁹ We only analyzed general cognitive functioning (i.e., IQ), so it is possible that deep or brainstem FLAIR lesion volumes would be significantly associated with other neuropsychological domains distinct from those measured by IQ. In addition, IQ testing was done in a younger age group of children in our study and was not available for adolescents enrolled from PMH, making age-related comparisons of FLAIR lesions specific to long-term cognition limited. Cognitive IQ testing has been argued to be insensitive to the impact of childhood brain injury; however, recent research has demonstrated that IQ is impacted by moderate-to-severe TBI, and that the impact increases as time elapses.^{48,49} We used Full Scale IQ for our analysis; separate analysis of Performance IQ might serve to strengthen the association with neurocognitive function given that Performance IQ is more sensitive to changes over time than Verbal IQ. These findings, however, illustrate the important contribution MRI may have on long-term recovery assessment. Future analysis with specific neurocognitive domain indices may help identify more focal associations.

Study limitations

There were several limitations in the study design and analysis. The primary limitations were in the retrospective design and variation in patient selection and timing of MRI. Although the MRI was ordered at the medical team's discretion, patients who did not undergo MRI had similar neurological injury severity and outcomes:

ages ≤ 12 years ($n = 82$): mean age (5.7 ± 3.7 years); GCS (6.3 ± 3.0); and GOS-E Peds (3.2 ± 2.2); and ages 13–17 ($n = 54$): mean age (16.1 ± 1.2 years); GCS (5.9 ± 3.6); and GOS-E Peds (3.35 ± 2.1), compared to study patients (Table 2). In the principal prospective studies, patients were not included owing to patient/parent refusal, being lost to follow-up, and if expectation of survival was low. We also did not control for other common prognostic variables known to affect outcome. In Spearman's testing, we did not find a significant correlation between GCS and GOS-E Peds outcome ($p = 0.08$); nor did regression analysis find a significant association between GCS and outcome; thus, GCS was not included in multivariate analysis. Future modeling with injury, clinical, and neuroimaging variables in addition to family, psychosocial factors, and preinjury functioning may help contribute to improved outcome prediction models after childhood TBI.^{48,71–73}

In 15 of 63 subjects, the MRI was obtained within 1 day postinjury, which may have led to an underestimation of the presence and/or volume of lesions, given that vasogenic and interstitial edema may continue to develop for several days after the initial insult on FLAIR sequence. Also, acute hemorrhage can appear iso- or hypointense on FLAIR in the first 1–3 days, contributing to lower volume measurements of hemorrhagic lesions.⁷⁴ Patients ≤ 13 years were treated at CMCD and ages 14–17 years were treated at PMH under UTSW Medical Center; thus, hospital variations in practice could have influenced our age-group analysis. In addition, interrater reliability of the GOS-E Peds score was not assessed between the two institutions. Study sample size limited center stratification of data; however, both centers followed pediatric sTBI guidelines introduced in 2003 and are large academic level 1 trauma centers providing a level of internal adjustment. Functional outcome scores were also remarkably similar from the two institutions; CMCD (GOS-E Peds, 3.1 ± 1.7), PMH (GOS-E Peds, 3.2 ± 2.3) with equivalent admission GCS scores (5.5 ± 3.4 and 5.9 ± 4.7 , respectively). Although we could not exclude a potential difference in practice between institutions, this suggests that the age-related outcome differences observed in our study were more likely dependent on the actual developmental stage of the child rather than center variation. Although FLAIR images were obtained from different MRI scanners and image acquisition methods at two sites over 8 years, FLAIR sequences produce highly reproducible images, which have been used to quantitatively measure lesion burden in multicenter studies for the past two decades.^{75,76} Interscanner agreement for quantitative assessments of FLAIR lesion volumes, using quantitative semiautomated thresholding techniques similar to those employed in our study, was 96.7% (95% CI, 95–97.5) for scanners operating at 1.5T field strength and 91.1% (95% CI, 90.2–94.1) for scanners of different field strengths.⁷⁷ The effect of such variances on cross-sectional studies such as the one presented here is likely to be small. Every effort was made to assure unbiased measurements; however, lesion thresholds were set manually to detect the subtlest lesion present; thus, there is some subjective interpretations inherent in the thresholding method used for quantification. Although our study is the largest pediatric study to date examining early MRI and long-term functional outcome, a prospective study design approach to MRI sequence, timing, patient selection, and outcome assessment would serve to strengthen our results.

Summary and Conclusion

MRI will likely not soon replace CT in the initial evaluation of TBI; CT is rapid, has excellent evaluation of bone and hemorrhagic

injury, and quickly assesses the need for neurosurgical intervention. The higher cost, longer acquisition time, requirement for sedation, and difficulty with monitoring potentially unstable patients are drawbacks to MRI. Early brain MRI may not alter clinical management, such as craniotomy, intracranial pressure (ICP) monitoring, or ICP therapy⁷⁸; however, it provides superior anatomical and pathological detection of primary and secondary brain injuries and is increasingly utilized for long-term prognostic information. In our study, children with TBI and MRI evidence of severe diffuse HII were excluded from FLAIR analysis; however, their outcomes were uniformly poor (death or lower severe disability). Additionally, in the 5 children without FLAIR abnormalities, 4 had favorable outcomes: 2 with GOS-E Peds 1 and 2 with GOS-E Peds 2. In the single patient without FLAIR lesions who sustained an unfavorable outcome (GOS-E Peds 5), imaging was obtained less than 8 h postadmission; thus, FLAIR abnormalities may not have yet been apparent owing to hyperacute timing of this MRI.

A recent National Institutes of Health workshop organized to develop reliable, efficient, and valid classification systems of TBI report widespread agreement that “patient selection based on the pathoanatomic features of an individual’s brain injury should be the cornerstone for a new TBI classification approach to clinical trials.”⁸ Our data add to the validity of early MRI-based methods as an imaging biomarker to classify and predict long-term outcome after pediatric TBI based on neuroanatomical injury distribution. There are multiple factors contributing to individual patient outcomes post-TBI, and MRI by itself may not be sufficient. We observed moderate correlations of FLAIR total lesion volume and volumes within specific brain regions with outcome, suggesting that other factors, such as cellular dysfunction, secondary injury, endogenous repair mechanisms, and environmental and social structure, also affect recovery potential post-TBI. Therefore, there currently exists important limitations in our ability to designate neurological outcome categories based solely on early MRI findings, and further research and refinement of neuroimaging-based methods is needed. Nevertheless, outcome prognostication presently is often a “wait and see” approach, given that many patients experience significant recovery in the first 6 months to 1 year post-TBI. This assessment should be improved by increasing our knowledge and understanding of how outcome is influenced by age and pathoanatomical injury burden in specific brain regions. Combining neuroimaging with outcome predictors, such as age, genetic profile, GCS, clinical severity score, and neural-specific biomarkers, might contribute to an early biological profile of injury risk for better outcome prediction and stratification into clinical trials.^{4,12,79–83} Large, multi-center, prospective pediatric studies designed with standardized MRI protocols and techniques investigating neuropsychological and -cognitive function will assist in further elucidating the role of early MRI in pediatric TBI outcome assessment.

In conclusion, this study demonstrated that, in children and adolescents with moderate and sTBI, lesions in multiple zones, total FLAIR lesion volume, and lesion volumes within specific brain zones correlated with long-term functional outcome, which was, in part, dependent on the age of the child at the time of injury. Further, in younger children ≤ 12 years, cognitive impairment appeared to be correlated with injury to superficial brain structures, whereas functional disabilities were more dependent on injury volume in deep brain regions. To our knowledge, this is the first study investigating quantitative early FLAIR MRI in discrete anatomical brain zones and age categories on long-term outcome after pediatric TBI. These findings may further advance our ability to predict

specific risks for neurocognitive dysfunction in children across age ranges post-TBI, enabling earlier, more targeted neurological therapies.

Acknowledgments

The authors thank Dr. Michael Morriss for his assistance in the interpretation of neuroradiology results and Evin Shirley for her research coordinator support. This article was made possible through generous funding that supported the Perot Brain and Nerve Injury Center at Children’s Medical Center Dallas.

Author Disclosure Statement

No competing financial interests exist.

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