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ORIGINAL ARTICLE

Magnetic Resonance Imaging Findings Are Associated with Long-Term Global Neurological Function or Death after Traumatic Brain Injury in Critically Ill Children

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Abstract

The identification of children with traumatic brain injury (TBI) who are at risk of death or poor global neurological functional outcome remains a challenge. Magnetic resonance imaging (MRI) can detect several brain pathologies that are a result of TBI; however, the types and locations of pathology that are the most predictive remain to be determined. Forty-two critically ill children with TBI were recruited prospectively from pediatric intensive care units at five Canadian children's hospitals. Pathologies detected on subacute phase MRIs included cerebral hematoma, herniation, cerebral laceration, cerebral edema, midline shift, and the presence and location of cerebral contusion or diffuse axonal injury (DAI) in 28 regions of interest were assessed. Global functional outcome or death more than 12 months post-injury was assessed using the Pediatric Cerebral Performance Category score. Linear modeling was employed to evaluate the utility of an MRI composite score for predicting long-term global neurological function or death after injury, and nonlinear Random Forest modeling was used to identify which MRI features have the most predictive utility. A linear predictive model of favorable versus unfavorable long-term outcomes was significantly improved when an MRI composite score was added to clinical variables. Nonlinear Random Forest modeling identified five MRI variables as stable predictors of poor outcomes: presence of herniation, DAI in the parietal lobe, DAI in the subcortical white matter, DAI in the posterior corpus callosum, and cerebral contusion in the anterior temporal lobe. Clinical MRI has prognostic value to identify children with TBI at risk of long-term unfavorable outcomes.

Keywords: functional outcomes; magnetic resonance imaging; pediatrics; prediction models; traumatic brain injury

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Introduction

Traumatic brain injury (TBI) is a major cause of death and acquired disability in children and youth.[1,2] These injuries often result in lifelong sequelae including physical disability, memory problems and learning disorders.[3,4] Importantly, there is significant variability in functional neurological outcomes in surviving children. Establishing a reliable prognosis, in the early phases after injury, remains a challenge because clinical and injury-related factors are only moderately predictive of long-term outcomes.[5–7]

The current approach to evaluating TBI, in the early phase after injury, involves a broad clinical assessment and basic neuroimaging studies, typically computed tomography (CT). While CT imaging is sufficient for diagnosis and assessing the need for neurosurgical intervention, it has a low sensitivity to detect many important lesions (e.g., diffuse axonal injury (DAI)) hindering its predictive utility for long-term functional outcomes.[8] Our inability to identify children at risk of poor recovery makes it difficult to make level of care decisions in the pediatric intensive care unit (PICU) and to plan early rehabilitation and educational interventions that have the potential to improve long-term outcomes.[9]

Magnetic resonance imaging (MRI) modalities present an opportunity to detect injuries overlooked by conventional CT imaging, and lesions detected with MRI previously have been reported to be associated with functional outcomes.[8,10,11] The complex neuropathology of TBI consists of interactions among primary and secondary injury mechanisms, involving both focal injuries (e.g., contusions and hemorrhages) and diffuse injuries (e.g., DAI).[7,12] A DAI is initiated by the rapid acceleration or deceleration of the brain inside the skull, disrupting white matter integrity, and has been shown to play a pivotal role in functional outcome.[13–15] Pediatric patients are particularly susceptible to these types of shear injuries, because of the higher water content and reduced amount of myelin in the developing brain.[16,17]

Importantly, MRI modalities such as diffusion weighted imaging (DWI) and T2* weighted gradient echo (T2* GRE) sequence imaging are unique in their sensitivity to these types of injury.[18–20] Therefore, MRI has great potential to improve prognostic models for integration into the clinical care of critically ill children and adolescents with TBI.[21]

A large amount of data is generated from MRI after brain injury, because of its increased sensitivity for detecting multiple pathologies. This makes it challenging to identify MRI features that are most relevant for prognostic models. A number of MRI scoring schemes have been developed to summarize this wealth of MRI data, most notably the depth of lesion model[22]; however, the failure of these models to predict long-term functional outcomes has limited their applicability in clinical settings.[23] It is unclear what type and location of pathology detected with MRI should be included in prognostic models.

We conducted a prospective multi-center study in critically ill children with TBI to evaluate the use of subacute phase MRI data in predictive models of long-term outcome after TBI. First, we developed a prognostic model, using clinical variables and a novel composite MRI score, to predict children at risk of unfavorable functional neurological outcomes or death more than one-year after TBI. We then used the Random Forest (RF) machine learning algorithm[24] to examine all MRI variables to determine objectively the most predictive MRI features and formulate a second prognostic model.

Methods

Subject recruitment and data collection

Consecutive children age 5 to 17 with mild, moderate, and severe TBI were recruited from five PICUs in Canada. The eligibility criteria for the Attention and Traumatic Brain Injury study have been published previously[25–28] and are included in the Supplementary Appendix. Demographic information, data relevant to the trauma and clinical prognostic factors (e.g., Glasgow Coma Scale [GCS] score) were collected during the admission to the PICU. The prospective study protocol included collecting MRIs to determine whether findings on MRI had value as a prognostic biomarker. This study was approved by ethics review boards at all five participating hospitals. Parent or guardian consent was obtained before data collection.

MRI

The MRI acquisition sequences were acquired as part of the study protocol on clinical 1.5T scanners and included a T1-weighted, T2-weighted, diffusion weighted, fluid attenuated inversion recovery (FLAIR), and T2* weighted gradient echo sequence. The goal was to perform MRIs within two weeks of injury, and MRIs were timed based on clinical indications and/or clinical stability. Sedation and anesthesia were used, if necessary, during the MRI.

In this study, DAI was radiologically defined using FLAIR, DWI, and T2* GRE. The diagnosis of DAI was based on a combination of FLAIR hyperintensity, diffusion restriction, and susceptibility on T2* GRE. An MRI assessment tool and scoring procedure was developed by an expert panel (see Supplementary Appendix). A board certified pediatric neuroradiologist (EW) coded each MRI for the presence of 62 injury variables: cerebral hematoma, transtentorial and/or foramen magnum herniation, cerebral laceration, cerebral edema, midline shift, and the presence and location of cerebral contusion or

DAI in 28 regions of interest (ROI, see Supplementary Appendix). From these data, a composite score was derived for each subject's MRI (see Supplementary Appendix). The MRI score ranged from 0 to 37 with 0 representing no pathology and 37 representing the worst pathology and/or highest number of ROIs with DAI.

Global functional neurological and mortality outcome measure

The functional outcome or death of each child was assessed using the pediatric cerebral performance category (PCPC), a measure of neurological function and death developed and validated for patients admitted to the PICU.[29] The PCPC score ranges from 1, corresponding to normal functioning, to 6, corresponding to death. The ''pre-injury'' score was collected within a week of the injury, to provide an assessment of pre-injury neurological function. The long-term PCPC score was collected by telephone interview of a parent at 12 or more months after injury. If we were unable to reach the parent by phone, the PCPC was collected from physician medical records of neurological assessments from follow-up clinics.

Functional status or death was defined as a binary outcome based on the reduction in PCPC score at the long-term assessment compared with pre-injury functioning. Unfavorable outcomes were defined as ΔPCPC >1, and favourable outcomes were defined as ΔPCPC $\leq$1.

Statistical analysis

The association between demographic and clinical prognostic factors, the MRI composite score, and unfavorable outcome were analyzed using multi-variable regression models (area under the receiver operating characteristic [ROC] curves). Two regression models were examined: (1) a linear model composed of three clinical factors previously validated as the most predictive independent variables, as suggested by Haghbayan and associates[9] (age at injury, GCS score, and pupillary reactivity), and (2) a linear model composed of those same clinical factors and the composite MRI score. The rationale for the small number of prognostic factors entered into our multivariable models was based on our small sample size. Comparison of the two linear models was performed using the Delong test for two correlated ROC curves.

To overcome the limited number of prognostic factors than can be incorporated into linear multi-variable models and identify the MRI features that account for the predictive utility of the MRI composite score, nonlinear regression analysis was employed to generate regression models that included all 62 variables from the MRI dataset. The RF is a machine learning algorithm that assesses each variable's predictiveness using the Breiman-Cutler variable importance measure (VIMP), such that larger VIMP values represent the most predictive variables.[24] In accordance with the procedure from Oyefiade and colleagues,[30] modifications were made from the standard RF approach (see Supplementary Appendix for full description), including variable selection in a two-step process by generating three predictive models.

The first model included all the MRI variables. The second model included a reduced number of MRI variables with positive VIMP measures from the previous model. The third model included the fewest and most predictive MRI variables, only selecting variables that remained predictive through both previous RF models. The predictive value of each RF model was assessed using ROC curves, percent error rate, and percent variance explained; overfitting was minimized by limiting the number of trees and depth within each model. All analyses were performed using R v3.5.2 of the RF SRC package v2.9.1.[31]

Results

Patients were recruited to the Attention and Traumatic Brain Injury (ATBI) study prospectively between 2009 and 2012; the long-term follow-up of the last recruited patient was completed in 2013. We have previously reported more detailed patient and injury characteristics for the ATBI study.[25–28] Fifty-eight of 129 (45%) patients who met eligibility criteria for the study were enrolled in the study. The reasons for nonenrollment are shown in Figure 1.

The research ethics boards, at the study sites, did not allow us to collect data on patients without informed consent, which would have allowed us to compare enrolled to nonenrolled eligible patients. Forty-two of 58 (72%) children and adolescents completed MRI and full PCPC measurements (Fig. 1). The main reason for not obtaining an MRI was that the attending physician judged that sedation or anesthesia to obtain the research MRI would pose undue risk for the patient. Another reason was that the patient was discharged from the hospital before obtaining an MRI and was unwilling to come back to the hospital for the MRI.

Thirty-eight of 42 (90%) patients had MRIs performed within two weeks of injury (range 1–11 days), and the remaining four patients had MRIs performed at 18, 29, 65, and 91 days post-injury, respectively. The MRIs were performed at a median of 3.86 days after injury (interquartile range [IQR] = 5.08 days).

In Table 1, we compare the patient characteristics, including study site, sex, age, GCS score, pupillary reactivity, PCPC outcome, and death in the 42 patients enrolled in the MRI study with the 16 patients with missing MRI and/or outcome data that could not be included in the MRI study. A summary of the cerebral pathologies identified using MRI is shown in Table 2.

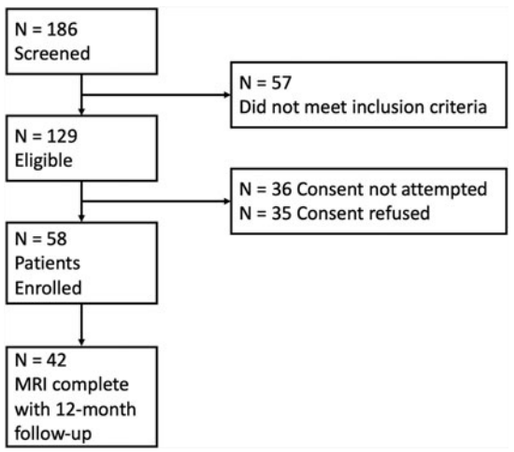

FIG. 1. Attention and Traumatic Brain Injury study enrollment. Children and adolescents ($n = 186$), admitted to five pediatric intensive care units with a diagnosis of traumatic brain injury (TBI) were screened for eligibility for the study. After obtaining informed consent, we enrolled 58 patients into the study. Forty-two of these 58 (72%) patients had both acute phase magnetic resonance imaging (MRI) scans and Pediatric Cerebral Performance Category scores collected at 12 or more months post-TBI.

Table 1. Demographic and Clinical Data of Attention and Traumatic Brain Injury Study Participants

	Included (n = 42)	*Excluded (n = 16)*
Study site		
CHEO	3 (7.1%)	2 (13%)
HHSC	4 (9.5%)	0
HSJ	2 (4.8%)	0
LHSC	11 (26%)	5 (31%)
SK	22 (52%)	9 (56%)
Sex		
Female	11 (26%)	6 (37%)
Male	31 (74%)	10 (63%)
Age at injury (mean ± SD)	12.6 ± 3.3	12.2 ± 4.3
Glasgow Coma Scale score		
Mild (13-15)	5 (12%)	2 (13%)
Moderate (9-12)	2 (4.9%)	3 (20%)
Severe (<9)	34 (83%)	10 (67%)
Pupillary reactivity		
Reactive	37 (88%)	15 (94%)
One Fixed	1 (2.4%)	0 (0%)
Both Fixed	4 (9.5%)	1 (6%)
Functional outcome		
Favorable (ΔPCPC ≤1)	35 (83%)	13 (93%)
Unfavorable (ΔPCPC >1)	7 (17%)	1 (7%)
Mortality		
Yes	2 (4.8%)	0 (0%)
No	40 (95%)	16 (100%)

Of the 58 participants enrolled in the Attention and Traumatic Brain Injury cohort, 16 (28%) were excluded because of the absence of patient magnetic resonance imaging (14), incomplete pediatric cerebral performance category (PCPC) follow-up (1), or both (1). CHEO denotes Children's Hospital of Eastern Ontario, HHSC denotes Hamilton Health Sciences Centre, HSJ denotes Hospitalier Sainte-Justine, LHSC denotes London Health Sciences Centre, and SK denotes SickKids Hospital. ΔPCPC denotes the difference between the pre-injury pediatric performance category score and the PCPC score obtained at 12 or more months after injury. SD, standard deviation.

Long-term outcomes

Twenty-six of 42 (62%) patients had their PCPC scored using parental interview. The time of interview ranged from 11.8 to 18.8 months (mean 12.6 ± 1.51 months) after injury. Sixteen of 42 (38%) patients had their PCPC scored from medical records. Follow-up visits ranged from 12.0 to 53.3 months (mean 31.1 ± 12.5 months) post-injury.

Linear modeling

The composite MRI scores were used to generate a linear predictive model of long-term unfavorable global functional outcome or death (Fig. 2). Three clinical variables previously established as independent predictive variables (age at injury, GCS score, and pupillary reactivity) showed modest prediction of unfavorable functional outcome or death (area under the curve [AUC] = 0.613). Inclusion of the MRI composite score to the predictive model, in addition to these clinical variables, significantly improved prediction of functional outcome or death (AUC = 0.752; $p = 0.03$).

Nonlinear modeling – RF

The RF analysis was used subsequently to assess the predictive value of all of the specific features of MRI lesions coded by the neuroradiologist (see Supplementary Appendix table). We identified 13 MRI variables with positive VIMP measures and included these in the second model. Five of these 13 (38%) variables remained predictive of unfavorable outcome or death through both these previous RF models. These five most prognostic MRI variables are listed from the most predictive to the least

Table 2. Summary of Cerebral Pathology of 42 Study Participants

Cerebral pathology coded on MRI	*Number of patients (%)*	*Number of regions of interest per patient with lesion (mean ± SD)*
Cerebral hematoma	8 (19%)	NA
Cerebral laceration	1 (2.4%)	NA
Cerebral edema	7 (17%)	NA
Midline shift	3 (7.1%)	NA
Transtentorial herniation	2 (4.8%)	NA
Cerebral contusion	33 (79%)	2.9 ± 2.2
Diffuse axonal injury	32 (76%)	3.8 ± 3.7

The number of patients with each injury type is shown. Accordingly, for injury variables measured in each of the 28 regions of interest (cerebral contusion and diffuse axonal injury), the mean number of lesions corresponding to that injury type is shown. MRI, magnetic resonance imaging; SD, standard deviation.

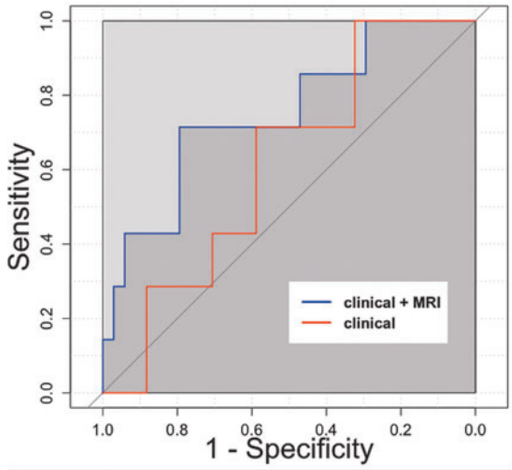

FIG. 2. Linear predictive modeling of unfavorable global neurological outcome or death. The receiver operating characteristic (ROC) curves are shown for the three demographic and clinical prognostic variables of age, Glasgow Coma Scale score, and pupillary reactivity alone denoted as "clinical data" and shown in red, and for the combination of clinical data and the magnetic resonance imaging (MRI) composite score, shown in blue. The predictive model, including the MRI score, had an area under the ROC curve (AUC) of 0.752 and was significantly better than the model that included clinical data alone (AUC = 0.613; $p = 0.03$). Color image is available online.

predictive: DAI in the parietal lobe, DAI in the posterior corpus callosum, DAI in the subcortical white matter, the presence of transtentorial herniation, and cortical contusion in the anterior temporal lobe (Fig. 3).

We compared the predictive utility of these three nonlinear models. The first model, consisting of all variables from the MRI dataset, had an AUC of 0.755. The second model, consisting of the 13 MRI variables, had an AUC of 0.849. The third model, including the five most predictive MRI variables, had an AUC of 0.845. Adding the three predictive clinical variables of age at injury, GCS score, and pupillary reactivity to these five MRI variables did not improve the final model (AUC = 0.800). Along with the AUC, error rate and percent variance explained were used to further characterize the predictive value of each MRI predictive model (Fig. 4). With an overall error rate of 7.14% and 39.3% variance explained, a measure of data variance accounted for by variables in the model, the third model outperformed all linear and nonlinear models generated.

MR images, clinical and outcome features

Examples of DAI and other pathologies seen on MRI and the clinical and outcome features of four patients enrolled in this study are shown in Figures 5, 6, 7, and 8 and described in the figure legends. The two patients shown in Figure 5 and Figure 7 both had an admission GCS score of 3 and a PCPC score of 3 (moderate disability) assessed at 12 months after injury. The MRI scores were 12 for the patient in Figure 5 and 20 for the patient in Figure 7. Comparing the pathologies visible on these two MRIs illustrates the challenges faced by investigators and clinicians when using MRIs to prognosticate. The patient in Figure 5 appears to have less pathology compared with the patient in Figure 7, yet the 12-month global functional outcome scores were the same in both patients.

Discussion

Using data from a prospective multi-center study of 42 critically ill children with TBI, we showed that a multivariable model that included a composite MRI score and clinical predictive variables was associated with unfavorable global neurological function or death at 12-months after injury. This prognostic model showed significant improvement compared with the multi-variable model that included the basic clinical predictive variables alone (age, GCS score, and pupillary reactivity). The importance of these clinical variables is highlighted by a recent meta-analysis by Haghbayan and coworkers[9] that identified a failure of studies assessing the predictive value of imaging to adequately control for established, independent prognostic variables.

We then examined our MRI data using a RF analysis, a nonlinear, machine learning approach, to identify the neuroimaging findings most closely associated with unfavorable functional outcome. Only five pathologies, detected using MRI, were retained in the final prognostic model: DAI in the parietal lobe, DAI in the posterior corpus callosum, DAI in the subcortical white matter, the presence of herniation, and cortical contusion in the anterior temporal lobe. Interestingly, this model consisting only of five MRI features showed superior prediction when compared with all linear and nonlinear prognostic models, including those incorporating clinical variables.

Other investigators have previously published approaches to MRI scoring for prognosis in TBI. Previous scoring procedures for moderate and severe TBI, including the Firsching Score[32] and Adams-Gentry Classification[33] (a method radiologically adapted from classifying histological brain lesions), principally rely on staging determined by the most caudal brain region affected. While evidence exists showing risk of unfavorable outcome as maximal depth of lesions increases,[9] these methods largely ignore lesion load and nonbrainstem lesions, which have been shown to be important prognostic factors for TBI functional recovery.[34]

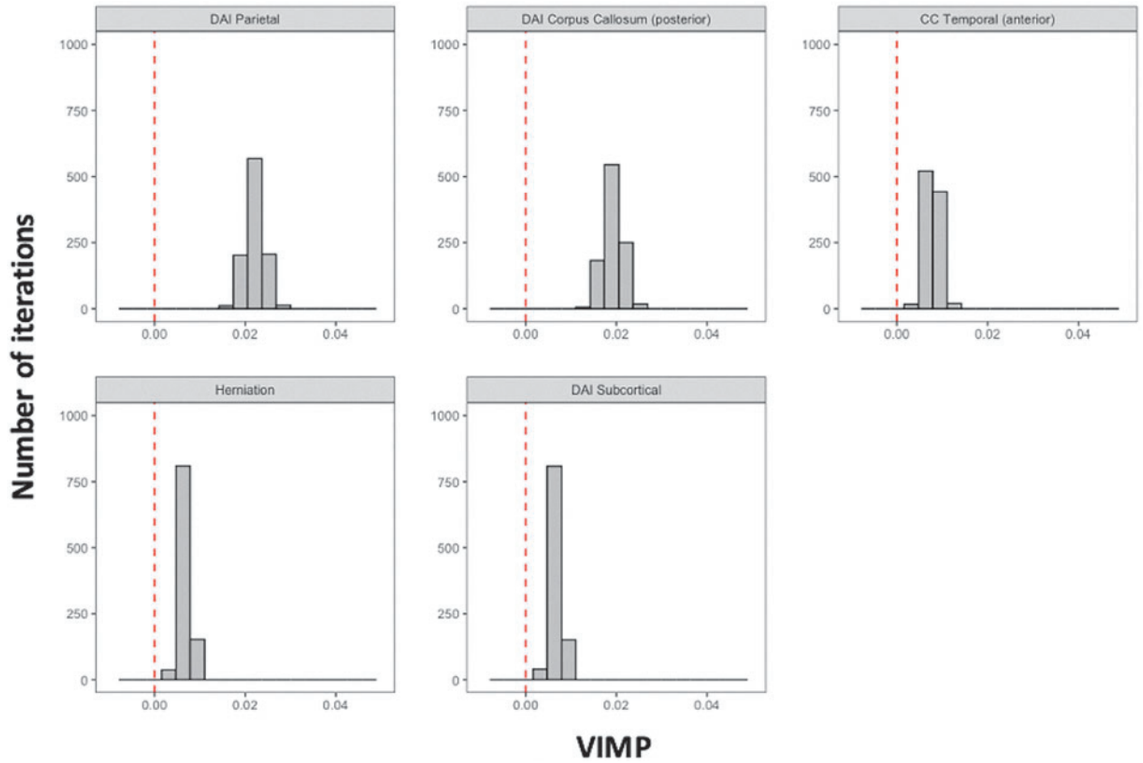

FIG. 3. Random Forest (RF) predictive magnetic resonance imaging (MRI) variables. Density plots of Breiman-Cutler variable importance (VIMP) measure for important predictors identified by the selection RF model. The number of iterations of the RF algorithm is provided on the y-axis, while the VIMP measure associated with each iteration is provided on the x-axis. Diffuse axonal injury (DAI) Parietal, DAI Corpus Callosum (posterior), Cerebral Contusion (CC) Temporal (anterior), Herniation, and DAI Subcortical provided positive VIMP measures across all iterations of the selection RF algorithm. Color image is available online.

Our MRI scoring approach aims to overcome this limitation, and has added relevance in clinical settings because the scoring procedure relies on MRI information available from clinically requested scans. Our findings also build on work by Smitherman and associates[35] who showed that injury volume in specific brain regions, determined from FLAIR sequences, is predictive of long-term functional outcomes in children with TBI. Importantly, our radiological determination of injuries relied in part on diffusion changes in DWI, along with FLAIR and T2* GRE, which builds on previous work highlighting the functional significance of DWI and its ability to discriminate cytotoxic and vasogenic injury after TBI.[36]

A strength of our approach is the application of a nonlinear methodology to overcome conventional limitations to the number of independent variables examined using multi-variable predictive models. The RF algorithm, through its recursive generation of randomly generated decision trees, presents a unique alternative to traditional approaches and enabled the examination of our entire MRI dataset. To our knowledge, this is the first application of RF to predict functional outcome after pediatric TBI using neuroimaging-based datasets, and it presents an opportunity to examine the wealth of MRI data generated for each patient.

All RF predictive models outperformed linear predictive models, with improved error rate and variance explained measures when the model was refined by removing candidate variables with negative VIMP measures from the model. Interestingly, the final MRI prediction model consisting of only five MRI variables showed greater predictive ability without the addition of the validated clinical prognostic variables. This finding may indicate that predictive models containing MRI features alone may be superior to those that rely on basic clinical variables, at least in the context of nonlinear modeling.

Beyond the generation of a nonlinear predictive model that supported the value of MRI, the RF analysis also identified the five key variables that contributed to its predictive value. Along with the presence of herniation, and

cortical contusions within the anterior temporal lobe, the most highly predictive variables were DAI lesions in three regions, emphasizing the impact of DAI on the long-term recovery of neurological function after TBI. The relevance of injury to these specific brain regions is supported by previous studies in patients with TBI.[37–40] A series of representative MRIs (Fig. 5–7) also highlight these specific injuries patterns.

Importantly, some brain regions previously implicated as important predictors of recovery after TBI were not ultimately identified by RF analysis, including injury to the frontal lobe, brainstem, and thalamus. This may be because our strict selection criteria for predictive variables, because injuries to the frontal lobe and brainstem were included in the first RF model but did not remain predictive after the second screening in the second RF model (see Supplementary Appendix). In addition, RF analysis may have removed lesser, but still predictive, variables that have biological importance because it identified more strongly predictive variables to model our dataset.

While this analysis does not demonstrate causal relationships or elucidate the underlying mechanisms that explain the association between pathology and decline in functional status or death, injury to white matter, contusions of the anterior temporal lobe, and herniation detected using MRI may have long lasting effects on brain function essential for learning and independent function.

Despite our promising findings, we recognize several limitations of the current study. We were unable to compare demographic and injury characteristics of patients who met eligibility criteria for this study, but were not enrolled, with patients enrolled in our study. We acknowledge that this may have introduced bias into our study. It will be important to request that research ethics boards allow collection of this type of data in future prognostic studies. Prospective studies with larger sample sizes, which include a larger number of clinical and demographic prognostic variables in the predictive models, are needed to validate our findings through multi-variable regression. We also acknowledge the exploratory nature of incorporating RF, a machine learning methodology, for the identification of prognostic MRI variables. These preliminary results should be further explored using other machine learning techniques and should aim to incorporate more detailed measures of neurobehavioral outcome.

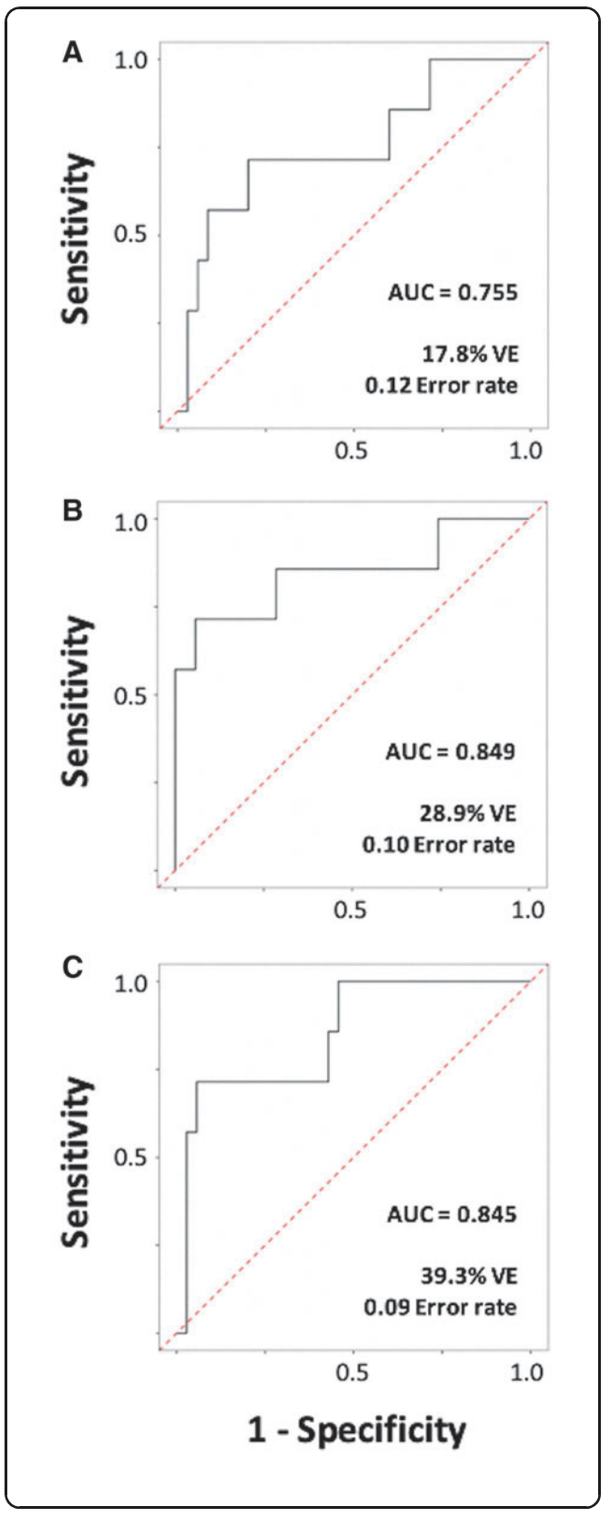

FIG. 4. Nonlinear predictive modeling of global unfavorable neurological outcome or death. The area under the receiver operating characteristic curves (AUC) is represented for each of the Random Forest (RF) prediction models: (**A**) The first prediction model included all 62 magnetic resonance imaging (MRI) variables; (**B**) the second "selection" model included 13 MRI variables; (**C**) the final model included only five MRI variables. The model accuracy is shown using AUC, percent variance explained (VE), and the Error rate. Color image is available online.

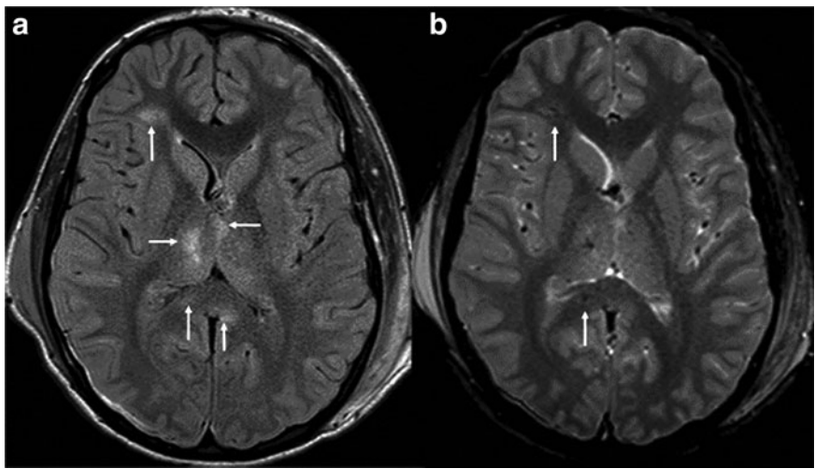

FIG. 5. Brain magnetic resonance image of a 15-year-old male taken at seven days after a motor vehicle collision. The admission Glagow Coma Scale score was 3, the pre-injury Pediatric Cerebral Performance Category (PCPC) score was 2 (mild disability), and the PCPC measured at 12 months after injury was 3 (moderate disability). (**a**) Axial fluid attenuated inversion recovery (FLAIR) and (**b**) axial T2* gradient echo showing high FLAIR signal associated with susceptibility in the bilateral thalami (arrows), splenium of corpus callosum (arrows), and right frontal white matter (arrows), in keeping with diffuse axonal injury.

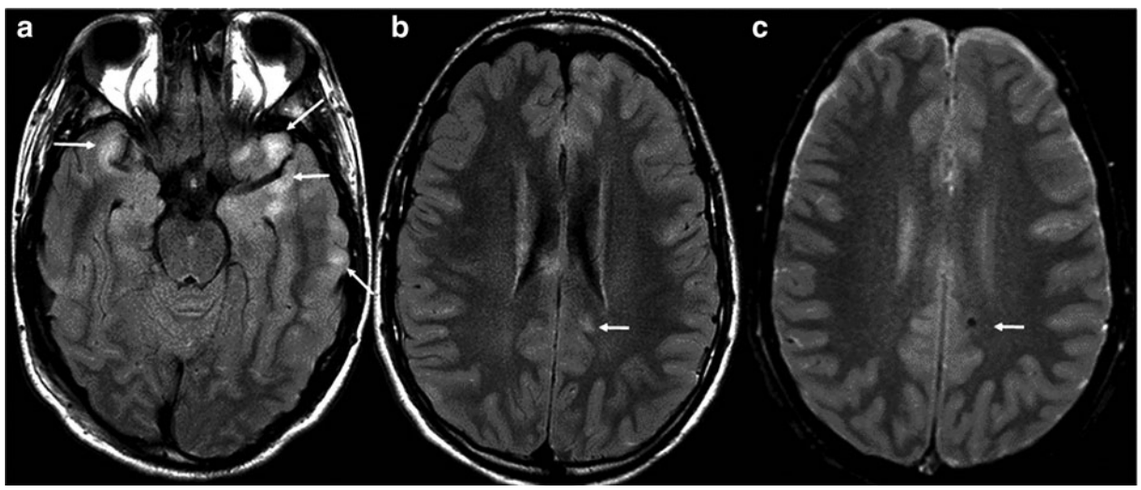

FIG. 6. Brain magnetic resonance image of a 15-year-old male taken at two days after a motor vehicle collision. The Glasgow Coma Scale score on admission was 6, the pre-injury Pediatric Cerebral Performance Category (PCPC) score was 2 (mild disability), and the PCPC score measured at 53 months after injury had returned to the pre-injury score of 2. (**a**) Axial fluid attenuated inversion recovery (FLAIR) showing contusion in the bilateral temporal lobes and left inferior frontal lobe (arrows). (**b**) Axial FLAIR and (**c**) () axial T2* hyperintensity showing a focus of FLAIR hyperintensity associated with susceptibility in the left mesial parietal lobe.

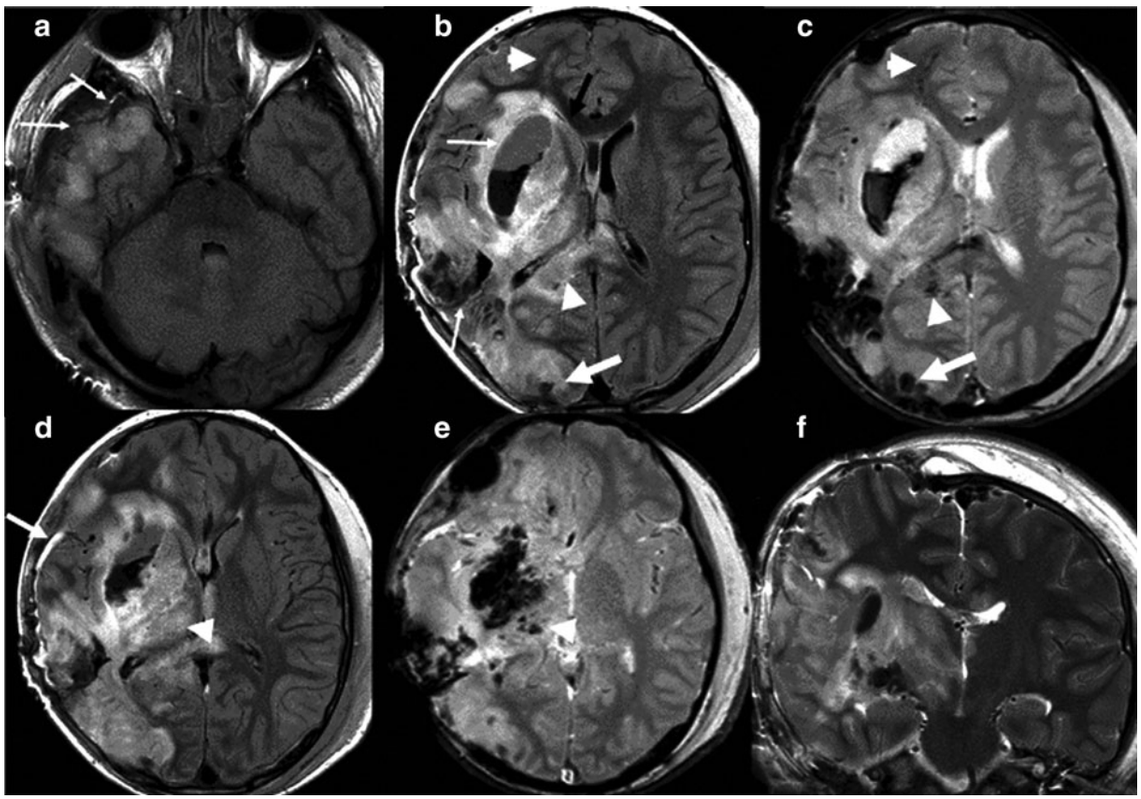

FIG. 7. Brain magnetic resonance image of an 11-year-old male taken at four days after injury from an all terrain vehicle collision and after a right-sided decompressive craniectomy. The admission Glasgow Coma Scale score was 3, the pre-injury Pediatric Cerebral Performance Category (PCPC) score was 1 (normal neurological function), and the PCPC score measured at 12 months after injury was 3 (moderate disability). (**a**) Axial fluid attenuated inversion recovery (FLAIR) showing right temporal contusion (white arrows). (**b**) Axial FLAIR showing hematoma with fluid level in the right lentiform nucleus (white arrow) with surrounding edema and effacement of the right lateral ventricle (black arrow). Another hematoma is seen in the right posterior temporal lobe (white arrow). There is high FLAIR signal associated with susceptibility on the T2* gradient echo in the (**b** and **c**) splenium of corpus callosum (arrowhead) and right frontal white matter (arrowhead), as well as in the (**d** and **e**) bilateral thalami (right more than left) (arrowhead), in keeping with diffuse axonal injury. Hemorrhagic contusion is seen in the right occipital lobe (**b** and **c**) (thick arrow). (**d**) A small subdural collection is seen overlying the right frontal and temporal lobes (white arrowhead). (**f**) The right frontal and temporal lobe herniate through the right craniectomy.

Accordingly, these prognostic models should capture outcomes at greater than one year after injury to capture the impact of disrupted neurodevelopmental processes and the development of neural plasticity. Future prognostic studies should aim to standardize the timing of post-injury MRI as changes in the MRI signals, particularly in the DW MRI and measures of edema, are dynamic over the first 7–10 days after injury.

In the current study, we used clinically available and conventional MRI sequences, with clinical utility in mind. We and others are currently studying the utility of other novel MRI sequences and approaches that may further improve prognostic models. Prognostic models with clinically useful sensitivity and specificity will likely be based on a more multi-model approach combining clinical predictors with neuroimaging, blood biomarkers, and electrophysiological and physiological biomarkers in children with TBI.[25,41,42]

In this study, strong predictive models of unfavorable global outcome or death at 12-months after injury were developed, using both linear and nonlinear methods, by supplementing previously validated independent clinical prognostic variables with MRI data. The use of nonlinear methods, specifically the RF machine learning algorithm,

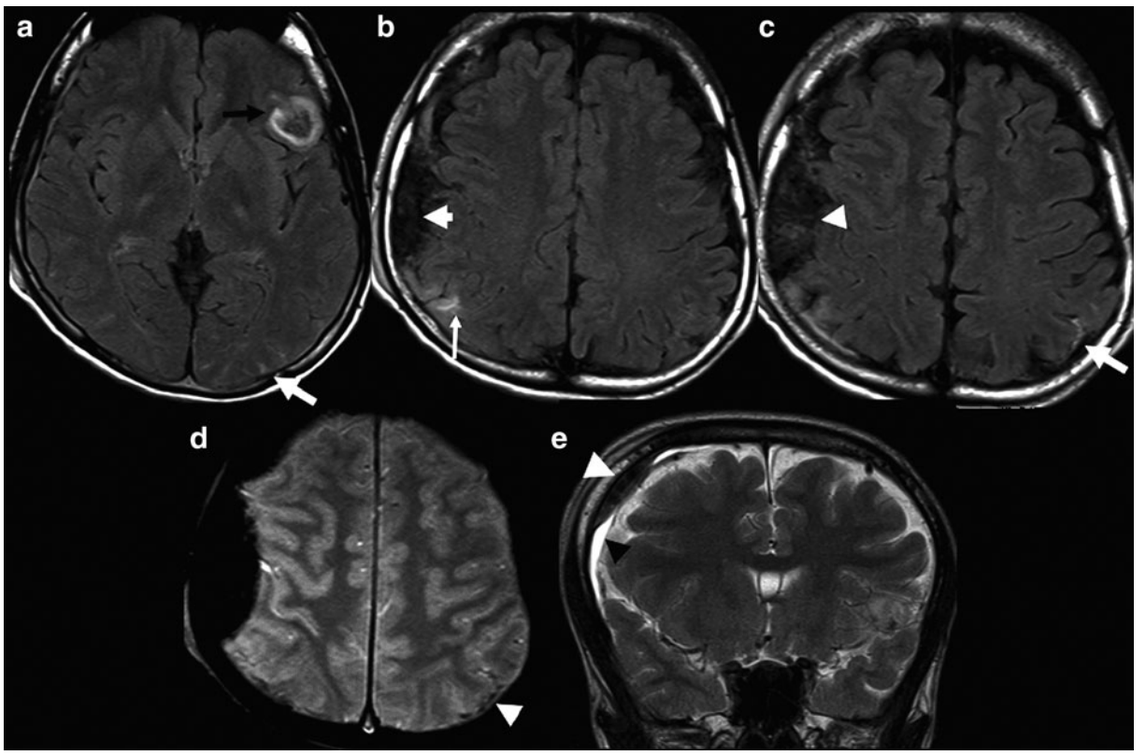

FIG. 8. Brain magnetic resonance image of a 15-year-old male taken at two days after a fall. The admission Glasgow Coma Scale score was 15, the pre-injury Pediatric Cerebral Performance Category (PCPC) score was 1, and the PCPC score assessed at 12 months after injury was again 1. (**a**) Axial fluid attenuated inversion recovery (FLAIR) demonstrating left inferior frontal hematoma (black arrow) and left occipital subarachnoid hemorrhage (large arrow). (**b**) Axial FLAIR showing right parietal lobe contusion (white arrow) and right frontoparietal epidural hematoma (white arrowhead). (**c**) Curvilinear FLAIR hyperintensity (large arrow) associated with (**d**) susceptibility (large arrowhead), in keeping with subarachnoid hemorrhage. (**e**) Coronal T2 showing right convexity subdural collection (black arrowhead) and right epidural hematoma (white arrowhead).

to analyze MRI data significantly improved the accuracy of predictive models of unfavorable outcomes in critically ill children with TBI. If validated in future studies, these early predictive models could support an accurate prognosis, improve clinical decision making in the subacute phase of injury, and help to risk stratify patients for early psychological therapies and rehabilitation and randomized controlled therapeutic trials.

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Supplementary Material

Supplementary Appendix

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