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Prognosis of Diffuse Axonal Injury with Traumatic Brain Injury

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Abstract

BACKGROUND—Determine the prognostic impact of MRI-defined DAI after TBI on functional outcomes, quality of life, and 3-year mortality.

METHODS—This retrospective single center cohort included adult trauma patients (age>17y) admitted from 2006-2012 with TBI. Inclusion criteria were positive head CT with brain MRI within 2 weeks of admission. Exclusion criteria included penetrating TBI or prior neurologic condition. Separate ordinal logistic models assessed DAI's prognostic value for following scores: 1)hospital-discharge Functional Independence Measure (FIM); 2)long-term Glasgow Outcome Scale-Extended (GOSE); and 3)long-term Quality of Life after Brain Injury-Overall Scale (QOLIBRI-OS). Cox proportional hazards modeling assessed DAI's prognostic value for 3-year survival. Covariates included age, sex, race, insurance status, Injury Severity Score (ISS), admission Glasgow Coma Scale Score, Marshall Head CT Class, clinical DAI on MRI (Y/N), research-level anatomic DAI Grades I-III (I:cortical, II:corpus callosum, III:brainstem), ventilator days, time to follow commands, and time to long-term follow up (for logistic models).

RESULTS—Eligibility criteria was met by 311 patients, who had a median age=40y (IQR: 23-57), ISS=29 (IQR:22-38), ICU stay=6d (IQR:2-11), and follow-up=5y (IQR:3-6y). Clinical DAI was present on 47% of MRIs. Among 300 readable MRIs, 56% of MRIs had anatomic DAI (25% Grade I, 18% Grade II, 13% Grade III). On regression, only clinical (not anatomic) DAI was predictive of a lower FIM score (OR=2.5 [95% CI:1.28-4.76], P=0.007). Neither clinical nor anatomic DAI were related to survival, GOSE, or QOLIBRI scores.

CONCLUSIONS—In this longitudinal cohort, clinical evidence of DAI on MRI may only be useful for predicting short-term in-hospital functional outcome. Given no association of DAI and long-term TBI outcomes, providers should be cautious in attributing DAI to future neurologic function, quality of life, and/or survival.

LEVEL OF EVIDENCE—III

STUDY TYPE—Retrospective cohort study

Keywords

Traumatic Brain Injury; Axonal Injury; Magnetic Resonance Imaging; Outcomes; Neurocritical Care

BACKGROUND

Diffuse axonal injury (DAI), also known as shear injury or traumatic axonal injury, refers to intracranial injury caused by rapid and sustained deceleration or acceleration of the brain. When damage is extensive as evidenced by a positive head CT for intracranial hemorrhage, DAI can be identified. Most often, however, DAI is diagnosed by MRI and represents a common radiographic diagnosis in up to 50% of traumatic brain injuries (TBIs) requiring hospital admission in the United States (1). It is believed that DAI is present in nearly all of those who sustain loss of consciousness due to a motor vehicle crash (1), and DAI appears associated with coma following TBI (2).

With rapidly improving MRI technology, evidence suggests there may be a relationship between the presence and/or severity of DAI and worse outcomes after TBI (3–9). This previous work has sometimes employed precise mapping and volume quantification of DAI (i.e., research MRI interpretations) lesions in order to evaluate their effect on solely neurologic outcomes. These are laudable efforts, but these studies do not account for other aspects of polytrauma, and these findings may not have clear clinical utility, as trauma surgeons, intensivists, neurosurgeons, and radiologists do not necessarily share the same expertise when reviewing a clinical MRI. Furthermore, providers and/or families of TBI patients often equate the presence of DAI in a clinical MRI with a devastating or mortal outcome.

The objective of this single center, retrospective cohort study is to examine the relationship of radiographic evidence of diffuse axonal injury on clinical MRI in patients with TBI with three-year mortality, functional status, and quality of life. We hypothesize that in patients with CT evidence of intracranial hemorrhage, the presence of MRI evidence of diffuse axonal injury is associated with worse functional status at discharge, long-term functional status, long-term quality of life, and decreased long-term survival at three-years.

METHODS

The patient population for this IRB approved, single-center, retrospective cohort study consisted of adults greater than or equal to age 18 years, who sustained a blunt TBI from 2006 to 2012 and were admitted to Vanderbilt University Medical Center. Inclusion criteria were an initial head CT read as positive for acute intracranial injury, as well as a MRI of the brain obtained within two weeks of injury. We excluded patients with a penetrating brain injury, history of epilepsy, history of a serious psychiatric condition evidenced by prior admission to a psychiatric hospital, previous hospital admission due to TBI, congenital neurological disorder, admission for condition other than blunt TBI, and patients who did not speak English. Our data sources included our local Trauma Registry of the American College of Surgeons and the electronic medical health record.

We obtained the following in-hospital data: age, sex, race, insurance status, injury severity score (ISS), emergency department Glasgow Coma Scale (GCS) score, Marshall Head CT Classification (10), presence of cerebral subarachnoid hemorrhage on head CT, presence of cerebral extra/epidural mass on head CT, ventilator days, ICU length of stay, hospital length of stay, time to follow commands, the presence or absence of DAI or “shear injury” on clinical MRI interpretation (i.e., clinical DAI yes or no), and in-hospital mortality. One of three neuro-radiologists analyzed each MRI and recorded the following: adequacy of clinical MRI for research interpretation, presence or absence of DAI, number of DAI lesions noted, and a grade of the DAI based on location (grade I: cortical, grade II: corpus callosum, or grade III: brainstem) if present (11). For clarity, the clinical MRI interpretation will be referred to as clinical MRI and the research interpretation of the same clinical MRI images will be referred to as research MRI.

We obtained a registry score of functional status at discharge, a modified Functional Independence Measure (FIM). This modified FIM score is a total of the self-feeding,

locomotion, and expression scores (each of which is on a scale of 1-4 ranging from dependence to independence, score range from 3-12), which are obtained as part of the discharge assessment. Then, using contact information present in the medical record or found using IRB-approved Internet search tools, we sent a letter to each eligible participant informing them about the study. At least one week following the mailed information, we attempted contact by telephone. We made at least 3 telephone contact attempts for each study participant. Upon contact, interested patients were administered the Orientation Log assessment (12), the Extended Glasgow Outcome Scale score (GOSE, eight point scale) (13), and the Quality of Life after Brain Injury-Overall Scale (QOLIBRI-OS, 0-100 points) (14). For reference, higher GOSE and QOLIBRI-OS scores correlate with better neurologic function and quality of life, respectively. Mortality data were obtained from the medical record, the Social Security Death Index, and/or based on follow-up phone calls. All data were maintained using REDCap, a secure database hosted at Vanderbilt University (15).

Statistical Methods

Separate ordinal logistic models assessed the prognostic value of DAI on clinical MRI (i.e., independent variable) in the following outcome scores: FIM, GOSE, and QOLIBRI-OS. Cox proportional hazards modeling assessed the prognostic value of clinical DAI for 3-year mortality. Model covariates included age, sex, race, insurance status, Injury Severity Score (ISS), admission Glasgow Coma Scale Score, Marshall Head CT class, DAI grade on research MRI, ventilator days, time to follow commands through hospitalization, and time interval post-injury (for GOSE and QOLIBRI logistic models). We found the clinical MRI had an unclear reading in six cases and the research MRI was inadequate for DAI grading in eleven cases. Given these were randomly missing in a very small number of cases (5%), and to limit bias and power loss, we employed a multiple imputation strategy (i.e. as opposed to a complete case analysis or arbitrary value assignment) for these select instances. In order to impute either the clinical or MRI read for each of the 4 models, we did not include any outcomes, and used the variables listed in Tables 2–5.

RESULTS

Using our inclusion criteria, we identified 395 eligible study participants. After applying exclusion criteria, eligibility criteria were met by 311 patients. Our cohort had a median age of 40 years, ISS of 29, ICU length of stay of 6 days, and time interval post-injury of 5 years. Among all clinical MRIs obtained, 47% (n=147) had DAI documented in the clinical interpretation. Among research MRIs, 56% (n = 168) had anatomic DAI (25% Grade I, 18% Grade II, 13% Grade III). A summary of demographic information and injury characteristics for our study population is presented in Table 1.

Functional status at discharge was obtained for 240 patients with a median FIM score of 10 (IQR: 6-11). When controlling for covariates, DAI was predictive of a lower FIM score (OR=2.5 [95% CI: 1.28 – 4.76]. In other words, the presence of DAI on clinical MRI was associated with worse discharge functional status (OR=0.4 [95% CI: 0.21 – 0.78]). The overall results of our ordinal regression model for discharge functional status are listed in Table 2.

Neurologic function was assessed only for the 118 patients who survived and who could be contacted for a follow-up interview with a median GOSE score of 6 (IQR: 5-8). After adjusting for covariates, GOSE scores did not differ based on the presence or absence of clinical MRI DAI. Increasing age was also associated with lower GOSE scores on follow-up (0.38 [0.18 – 0.81]). When compared to private insurance, other insurance (0.21 [0.08 – 0.59]) and public insurance (0.27 [0.11 – 0.65]) were associated with a lower GOSE at follow-up. The overall results of our ordinal logistic regression model for GOSE at follow up are summarized in Table 3.

Quality of life was assessed only for 118 patients who survived and who could be contacted for follow up with a QOLIBRI-OS median score of 62 (IQR: 34-83). After adjusting for covariates, higher QOLIBRI scores were not associated with the presence or absence of DAI on clinical or research MRI. Increasing ventilator days was associated with lower QOLIBRI-OS score at follow up (OR=0.52 [95% CI: 0.27 – 0.99]). When compared to private insurance, other insurance (0.19 [0.07 – 0.53]) and public insurance (0.23 [0.09 – 0.56]) were associated with lower QOLIBRI-OS scores at follow up. The overall results of our ordinal logistic regression model for QOLIBRI-OS at follow up are summarized in Table 4.

We obtained three-year survival information for all 311 patients in our cohort, of which 25% (78) died. Adjusting for covariates, the presence or absence of DAI on clinical MRI was not associated with 3-year mortality. Higher age (HR=2.56 [95% CI: 1.63 – 4.03]), higher ISS (1.74 [1.30 - 2.34]), not following commands (5.98 [3.04 – 11.77]), and higher Marshall Head CT Class (2.83 [1.09 – 7.36]) were all independently associated with 3-year mortality. The overall results of our Cox proportional hazards model for 3-year survival are summarized in Table 5.

DISCUSSION

This study represents the largest cohort of TBI patients with DAI to ever undergo long-term follow-up assessment with multiple outcome measures. In our study, the presence of DAI on acute MRI within 2 weeks of injury was associated with worse functional status at the time of discharge. Our models did not demonstrate a relationship between the early diagnosis of DAI and long-term functional outcome or quality of life status.

These data suggest that the presence or anatomic grade of DAI as evidenced by in-hospital MRI early during recovery may not accurately predict long-term survival and functional status. Our study contrasts the work of Cicuendez et. al., who in a study of 178 patients with “traumatic axonal injury” found an association between axonal injury located in the corpus callosum and worse long-term functional outcomes as measured by GOSE at 1 year (8). However, this work focused on imaging in the subacute phase (up to 60 days post-injury), as compared to our two-week acute MRI window, and thus may not be directly comparable. The authors also note that while the presence and extent of injury in the corpus callosum was associated with worsening prognosis, up to 1/3 of patients with this pathology can expect good recovery. Additionally, in a study of 128 patients with moderate to severe TBI, Moen and colleagues found that DAI lesion volume and location could be used as a prognostic tool to predict functional outcome at 12 months (7). However, in our practice, lesion volume is

rarely used or reported on a clinical MRI interpretation. Our study evaluated whether the clinical finding of DAI predicted outcomes controlling for baseline, critical illness, polytrauma, socioeconomic indices, and DAI on research MRI interpretation.

The current study has important strengths. It examines a unique population, those with other traumatic brain pathology on CT scan but who also received an MRI very early during their hospital stay. We also included both clinical MRI data as well as a research interpretation using a known radiograph DAI grading scale. We screened a very large pool of patients for inclusion in the study. To our knowledge, our study provides the longest follow-up to date of patients with diffuse axonal injury using two measures of long-term outcome (GOSE and QOLIBRI). Our statistical modelling was thorough and controlled for important typical demographic variables as well as insurance status, which may serve as a surrogate for other more difficult to quantify lifestyle and socioeconomic factors(16, 17).

Our study has several limitations. As with all retrospective cohort studies, we are limited by the quality of the data recorded at the time it was obtained. We were unable to include any time-dependent variables in our model. We did not include specific data on other brain injury patterns (e.g. subdural/epidural hemorrhage, ischemia) in order to maximize the statistical power of our model, however the Marshall classification of the head CT does account for the extent of other brain injury in a structured manner. The study at hand was performed at a single trauma center. Also, we do not know the clinical reasoning behind the decision to obtain an MRI during initial hospitalization. Some of these MRIs may have been obtained for reasons unrelated to suspicion for DAI, including evaluation of venous thrombosis or a search for a non-traumatic etiology of the patient's injury. When an MRI was obtained, it was not always obtained using the same protocol or identical magnet strength. It is possible that the reasoning was based on confounding factors that we did not adequately control in our models. The patients included in our study may not accurately represent the injury patterns of all patients presenting to a trauma center with DAI. We were unable to account for lifestyle factors that may have influenced outcome, such as pre-injury functional status, family and social support, access to rehabilitation, and individual financial resources. Insurance status may serve as a rough surrogate for access to long-term rehabilitation, therapy, social support and/or financial well-being, however this status may change over time during the hospitalization and even afterwards. Our models may not have been adequately powered for our long-term outcome measures, the GOSE and QOLIBRI, and this work is therefore at risk of a Type II error. This is in spite of the large patient population we initially screened for inclusion and the minimization of covariates in our models. Also, it is possible that the group of patients who we were unable to contact for long-term follow-up differed significantly from those successfully located. Variable length to follow-up could have further confounded the data.

Based on this large longitudinal cohort, clinical evidence of DAI on MRI may only be useful for predicting short-term in-hospital functional outcome and helpful in disposition planning, but not helpful for long-term prognostication. It is possible that a clinical rating scale could be developed based on the number, location, and volume of lesion location that would provide more useful information to physicians, patients and their families when making difficult care decisions in the days and weeks following traumatic brain injury.

CONCLUSIONS

Given no association of DAI and long-term TBI outcomes, healthcare providers and patient family members should be cautious when using DAI on early MRI to predict prognosis (e.g., future neurologic function, quality of life, and/or survival). Recovery following traumatic brain injury is variable and, at this time, difficult to predict. Physicians, patients and their families would benefit from useful in-hospital predictors of survival and long-term functional status, but despite rapid advances in quality of imaging, its clinical value in this domain has not been well established. Future work should include prospective trials in order to determine whether MRI or other testing modalities may predict long-term outcomes in patients with TBI. Hopefully, this work will lead to simple and shared nomenclature, as well as better diagnostic tools that will allow patient, providers, and family members better utilize MRI results to direct care and prognosis.

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Table 1

Demographic Characteristics of cohort with Magnetic Resonance Injury data within 2 weeks of Traumatic Brain Injury with CT evidence of Intracranial Hemorrhage^a

Characteristic	n=311
Age	40 (IQR: 23 – 57)
Sex, No. (%)	
Male	221 (71)
Female	90 (29)
Race, No. (%)	
White	276 (89)
Other	35 (11)
Insurance Status, No. (%)	
Private	137 (44)
Public	110 (35)
Other (none, self pay, workers comp)	64 (21)
Injury Severity Score	29 (IQR: 22 – 38)
ED Glasgow Coma Scale	3 (IQR: 3 – 14)
Marshall Head CT class	2 (IQR: 2 – 2)
Ventilator days	5 (IQR: 1 – 11)
ICU length of stay	6 (IQR: 2 – 11)
Hospital length of stay	11 (IQR: 5 – 21)
Cerebral subarachnoid hemorrhage, No. (%)	146 (47)
Cerebral extra/epidural mass, No. (%)	12 (4)
DAI on clinical MRI, No. (%)	147 (47)
Grade of DAI on research MRI, No. (%)	
No DAI	132 (44)
Grade I: Cortical	75 (25)
Grade II: Corpus	53 (18)
Grade III: Brainstem	40 (13)

Abbreviations: ED, Emergency Department; ICU, Intensive Care Unit; DAI, Diffuse Axonal Injury

^aMedian (interquartile range) unless noted.

Table 2

Ordinal logistic regression for modified Functional Independence Measure score of cohort (n=240) with Magnetic Resonance Injury data within 2 weeks of Traumatic Brain Injury with CT evidence of Intracranial Hemorrhage

Independent Variable	OR	P-value
DAI on Clinical MRI (yes:no)	0.4 (0.21, 0.78)	0.007
Covariates	OR	P-value
Age	0.47 (0.3, 0.74)	0.001
Injury Severity Score	0.56 (0.39, 0.82)	0.003
Ventilator Days	0.39 (0.26, 0.6)	<0.001
Emergency Department Glasgow Coma Scale	1.82 (1.29, 2.57)	<0.001
Marshall Head CT class	0.14 (0.03, 0.57)	0.006
Did not follow commands	0.25 (0.11, 0.55)	<0.001
Time to follow commands	1.01 (0.96, 1.07)	0.58
Grade I DAI on Research MRI (cortical:no DAI)	1.92 (0.95, 3.86)	0.101
Grade II DAI on Research MRI (corpus:no DAI)	0.81 (0.33, 1.96)	0.101
Grade III DAI on Research MRI (brainstem:no DAI)	0.84 (0.35, 2.04)	0.101
Insurance status (public:private)	0.69 (0.39, 1.22)	0.048
Insurance (other:private)	1.67 (0.88, 3.18)	0.048
Sex (female:male)	0.92 (0.54, 1.59)	0.774
Race (non-white:white)	0.59 (0.29, 1.23)	0.162

Abbreviations: DAI, Diffuse Axonal Injury; MRI, Magnetic Resonance Imaging

Table 3

Ordinal logistic regression for Extended Glasgow Outcome Scale of cohort (n=118) with Magnetic Resonance Injury data within 2 weeks of Traumatic Brain Injury with CT evidence of Intracranial Hemorrhage

Independent Variable	Odds Ratio (95% CI)	P-value
DAI on Clinical MRI (yes:no)	0.71 (0.29, 1.75)	0.459
Covariates	Odds Ratio (95% CI)	P-value
Age	0.38 (0.18, 0.81)	0.012
Injury Severity Score	0.87 (0.5, 1.52)	0.622
Ventilator Days	0.95 (0.49, 1.85)	0.878
Emergency Department Glasgow Coma Scale	0.90 (0.35, 2.32)	0.835
Marshall Head CT class	0.55 (0.03, 8.67)	0.670
Time Interval post-injury	0.90 (0.52, 1.56)	0.718
Did not follow commands	0.23 (0.05, 1.04)	0.056
Time to follow commands	0.98 (0.90, 1.07)	0.636
Grade I DAI on Research MRI (cortical:no DAI)	0.69 (0.27, 1.74)	0.225
Grade II DAI on Research MRI (corpus:no DAI)	0.41 (0.1, 1.6)	0.225
Grade III DAI on Research MRI (brainstem:no DAI)	0.22 (0.05, 0.96)	0.225
Insurance status (public:private)	0.27 (0.11, 0.65)	0.002
Insurance (other:private)	0.21 (0.08, 0.59)	0.002
Sex (female:male)	0.53 (0.24, 1.2)	0.129
Race (non-white:white)	0.35 (0.08, 1.51)	0.161

Abbreviations: DAI, Diffuse Axonal Injury; MRI, Magnetic Resonance Imaging

Table 4

Ordinal logistic regression for Quality of Life after Brain Injury-Overall Scale of cohort (n=118) with Magnetic Resonance Injury data within 2 weeks of Traumatic Brain Injury with CT evidence of Intracranial Hemorrhage

Independent Variable	Odds Ratio (95% CI)	P-value
DAI on Clinical MRI (yes:no)	0.85 (0.35, 2.05)	0.713
Covariates	Odds Ratio (95% CI)	P-value
Age	0.57 (0.28, 1.16)	0.122
Injury Severity Score	1.19 (0.70, 2.05)	0.521
Ventilator Days	0.52 (0.27, 0.99)	0.047
Emergency Department Glasgow Coma Scale	0.86 (0.35, 2.12)	0.745
Marshall Head CT class	0.65 (0.05, 9.12)	0.752
Time Interval post-injury	0.84 (0.49, 1.46)	0.543
Did not follow commands	1.20 (0.29, 5.02)	0.799
Time to follow commands	1.03 (0.94, 1.12)	0.563
Grade I DAI on Research MRI (cortical:no DAI)	1.09 (0.45, 2.62)	0.084
Grade II DAI on Research MRI (corpus:no DAI)	0.35 (0.10, 1.23)	0.084
Grade III DAI on Research MRI (brainstem:no DAI)	0.30 (0.08, 1.05)	0.084
Insurance status (public:private)	0.23 (0.09, 0.56)	<0.001
Insurance (other:private)	0.19 (0.07, 0.53)	<0.001
Sex (female:male)	0.64 (0.30, 1.39)	0.261
Race (non-white:white)	0.30 (0.07, 1.22)	0.093

Abbreviations: DAI, Diffuse Axonal Injury; MRI, Magnetic Resonance Imaging

Table 5

Cox proportional hazards model for 3-year Mortality of cohort (n=311) with Magnetic Resonance Injury data within 2 weeks of Traumatic Brain Injury with CT evidence of Intracranial Hemorrhage

Independent Variable	Hazard Ratio (95% CI)	P-value
DAI on Clinical MRI (yes:no)	0.9 (0.49, 1.64)	0.724
Covariates	Hazard Ratio (95% CI)	P-value
Age	2.56 (1.63, 4.03)	<0.001
Injury Severity Score	1.74 (1.3, 2.34)	<0.001
Ventilator Days	0.53 (0.32, 0.89)	0.016
Emergency Department Glasgow Coma Scale	0.98 (0.74, 1.29)	0.881
Marshall Head CT class	2.83 (1.09, 7.36)	0.033
Did not follow commands	5.98 (3.04, 11.77)	<0.001
Time to follow commands	0.92 (0.8, 1.07)	0.279
Grade I DAI on Research MRI (cortical:no DAI)	0.70 (0.34, 1.6)	0.431
Grade II DAI on Research MRI (corpus:no DAI)	0.74 (0.34, 1.42)	0.431
Grade III DAI on Research MRI (brainstem:no DAI)	1.25 (0.58, 2.69)	0.431
Insurance status (public:private)	1.32 (0.76, 2.29)	0.451
Insurance (other:private)	0.88 (0.4, 1.95)	0.451
Sex (female:male)	0.61 (0.53, 1.07)	0.086
Race (non-white:white)	0.88 (0.4, 1.95)	0.754

Abbreviations: DAI, Diffuse Axonal Injury; MRI, Magnetic Resonance Imaging