Interval-censored survival analysis of mild traumatic brain injury with outcome based neuroimaging clinical applications

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Abstract

Objective: The purpose of this study was to assess the relationship between MRI findings and clinical presentation and outcomes in patients following mild traumatic brain injury (mTBI). We hypothesize that imaging findings other than hemorrhages and contusions may be used to predict symptom presentation and longevity following mTBI.

Methods: Patients (n = 250) diagnosed with mTBI and in litigation for brain injury underwent 3T magnetic resonance imaging (MRI). A retrospective chart review was performed to assess symptom presentation and improvement/resolution. To account for variable times of clinical presentation, nonuniform follow-up, and uncertainty in the dates of symptom resolution, a right censored, interval censored statistical analysis was performed. Incidence and resolution of headache, balance, cognitive deficit, fatigue, anxiety, depression, and emotional lability were compared among patients. Image findings analyzed included white matter hyperintensities (WMH), Diffusion Tensor Imaging (DTI) fractional anisotropy (FA) values, MR perfusion, auditory functional MRI (fMRI) activation, hippocampal atrophy (HA) and hippocampal asymmetry as defined by NeuroQuant® volumetric software.

Results: Patients who reported LOC were significantly more likely to present with balance problems (p < 0.001), cognitive deficits (p = 0.010), fatigue (p = 0.025), depression (p = 0.002), and emotional lability (p = 0.002). Patients with LOC also demonstrated significantly slower recovery of cognitive function than those who did not lose consciousness (p = 0.044). Patients over the age of 40 had significantly higher odds of presenting with balance problems (p = 0.006). Additionally, these older patients were slower to recover cognitive function (p = 0.001) and less likely to experience improvement of headaches (p = 0.007). Abnormal MRI did not correlate significantly with symptom presentation, but was a strong indicator of symptom progression, with slower recovery of balance (p = 0.009) and cognitive deficits (p < 0.001).

Conclusion: This analysis demonstrates the utility of clinical data analysis using interval-censored survival statistical technique in head trauma patients. Strong statistical associations between neuroimaging findings and aggregate clinical outcomes were identified in patients with mTBI.

Keywords

Interval-censored survival analysis, advanced neuroimaging, mTBI, clinical outcomes, white matter hyper-intensities, diffusion tensor imaging, post-concussive syndrome

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Introduction

Traumatic Brain Injury (TBI) is a major health challenge around the world, with an estimated burden ranging from 4.6 million cases per year in North America to 18.3 million annual cases in southeast Asia.¹ Severity of a TBI is generally categorized as mild, moderate, or severe. The most common type of TBI is mild, making up approximately 81% of TBIs worldwide.¹ Diagnosis of mTBI is complicated by the fact that individuals with mTBI may not seek immediate medical attention. Additionally, there is currently no definitive set of validated diagnostic tests for mTBI.² Advancements in neuroimaging technology offer great promise in providing objective evidence for diagnosing and predicting the prognosis for patients with mTBI.³⁻⁵

Characterizing the clinical outcomes of patients following mTBI also comes with a unique set of challenges. Symptoms of mTBI are numerous, sometimes nonspecific, and typically rely on self-reporting.⁶⁻⁷ Examples of symptoms frequently associated with mTBI include headache, dizziness, irritability, fatigue, cognitive problems, and poor concentration.⁸ Studies of symptom duration in patients with mTBI report inconsistent patterns; some studies have found that most symptoms of mTBI are transient and resolve within weeks or months, while others report that mTBI patients can retain cognitive, physiological, and clinical symptoms for years.⁹⁻¹² These inconsistencies as well additional pathophysiologic, neuroanatomic, and diagnostic challenges are well described by Bigler in the 2008 publication Neuropsychology and clinical neuroscience of persistent post-concussive syndrome.¹⁰ For example, the terms ‘concussion’ and ‘mild traumatic brain injury’ are often used interchangeably, but exact criteria for both of these terms varies among authors. In general, post-concussive syndrome (PCS) is less explicitly defined and describes symptoms in the acute stages of TBI whereas ‘persistent post-concussive syndrome’ (PPCS) is defined in terms of symptoms lasting more than three months.¹⁰ This study focuses on symptoms commonly described in concussion, mTBI, PCS and PPCS; headache and deficits in balance, emotion, and cognition.

The purpose of this study was to add to the current scientific understanding of mTBI symptomology and prognosis with additional consideration for sex, age, MRI normalcy, and loss of consciousness (LOC). To accurately estimate symptom longevity from our retrospective dataset, this study utilized a statistical method to incorporate the uncertainties associated with irregular time between follow-up visits, irregular time of clinical presentation and patients who either fail to improve or who fail to return for follow-up visits.

Material and methods

Subjects

All subjects were diagnosed with mTBI by a board certified neurologist specializing in head trauma (EF) utilizing standard DSM V diagnostic criteria.¹³ This definition defines mTBI as:

An impact to the head or other mechanisms of rapid movement or displacement of the brain within the skull, with one or more of the following: loss of consciousness, posttraumatic amnesia, disorientation and confusion, neurological signs such as a new onset of seizure, a marked worsening of a preexisting seizure disorder, visual field cuts, anosmia or hemiparesis with neurocognitive complaints that present immediately after the occurrence of the traumatic brain injury or immediately after recovery of consciousness along with associated symptoms such as disturbances in emotional function (irritability, easy frustration, tension and anxiety, affective lability), personality changes (disinhibition, apathy, suspiciousness, aggression), physical disturbances (headache, fatigue, sleep disorders, vertigo or dizziness, tinnitus or hyperacusis, photosensitivity, anosmia, reduced tolerance to psychotropic medications) and in more severe TBI associated neurological symptoms and signs (seizures, hemiparesis, visual field disturbances, cranial nerve deficits) and evidence of orthopedic injuries.¹³

The median time between Date of Injury (DOI) and initial consultation was 70 days (range: 2 to 1,126). All subjects had a single MRI brain exam with advanced imaging, typically obtained after the initial clinical consult. Exclusion criteria were: incomplete records [N = 7], canceled/incomplete MRI [N = 71], >3 years between DOI and consultation [N = 7], demyelinating disease [N = 10], history of a cerebrovascular accident [N = 13], prior head trauma [N = 12], chronic epilepsy [N = 1], prior brain surgery [N = 1], imaging findings of brain contusions [N = 4], hemorrhagic diffuse axonal injury (DAI) [N = 4], sequelae of intracranial hemorrhages [N = 0], cerebral vascular malformations [N = 0], cavernoma [N = 2], or brain tumors [N = 0]. Out of 375 mTBI patients in litigation for brain injury, 250 were included in the study. Of the 250 included patients, documented preexisting conditions were as follows: hypertension [N = 12], diabetes [N = 3], and migraines [N = 6]. Additionally, 32 subjects were prescribed a medication commonly taken for a psychiatric condition and 15 of these had a documented preexisting psychiatric condition (i.e. anxiety and depression). There was no documented evidence of preexisting balance or dizziness, including Meniere’s disease or benign positional vertigo (BPV), in any patients. Since de-identified data were used, no consent was necessary, and this study was determined
exempt from further oversight following an initial review by the Touro University Nevada Institutional Review Board (IRB4-5-17D).

**Measures**

Seven common mTBI symptoms were considered: headache, balance, cognitive deficit, fatigue, anxiety, depression, and emotional lability.\(^8,14\) Cognitive deficit was defined as impairment in attention, learning and memory, as well as frontal executive functions and language and communication.\(^15\) Cognitive symptoms were assessed using a standard written questionnaire as well as assessment by the neurologist. Balance deficits were defined as new onset symptoms including ‘unsteadiness on the feet’, ‘feeling of falling’ and ‘coordination problems’ as assessed by the neurologist as well as confirmatory physical exam such as the Romberg test for balance. Anxiety, depression and emotional lability were diagnosed using standard DSMV diagnostic criteria.\(^15\)

For the chart review, the status of symptoms was noted for each office visit. Clinical symptoms were reported as sustained, improved, or resolved. Rarely, symptoms were reported as worsening, but such cases were combined with the ‘sustained’ category. Gender, LOC, age (<40 or ≥40), and MRI findings (normal or abnormal) were all considered as factors which might mediate the presentation or duration of symptoms.

**MRI acquisition and interpretation**

Patients underwent an MRI protocol with a 3.0 Tesla MR Signa HDxt system (G.E. Healthcare Milwaukee WI) equipped with an 8-channel head coil. Standard sequences included Axial T2 and FLAIR and sagittal FLAIR imaging with in-plane resolutions of 0.45 mm and a slice thickness of 4.0 mm. A gradient echo imaging (GRE) sequence with an in-plane resolution of 0.45 mm × 0.45 mm and a slice thickness of 5.0 mm (TE 6.976 ms, TR 400 ms) or a susceptibility weighted imaging (SWI) sequence with a voxel size of 0.39 mm × 0.39 mm x 1.2 mm (TE 25.024 ms, TR 46.8 ms) was also acquired. A 3D T1-weighted sequence with a voxel size of 0.93 mm × 0.93 mm x 1.2 mm (TE 2.208 ms, TR 5.396 ms) was also performed on each patient. The T1 images were subsequently analyzed with NeuroQuant\(^\text{TM}\) version 3.0 volumetric analysis software.

Single Shell DTI was acquired with an in-plane resolution of 1.0156 mm and a slice thickness of 2.4 mm. Thirty-three directions were sampled with a b-value 1000 s/mm\(^2\) compared against a b0 image. Experienced technologists used an Olea software equipped free-standing workstation to draw six regions of interest across the corpus callosum (total, anterior-inferior, anterior, mid-body, posterior, and posterior-inferior), to calculate FA values.

Dynamic whole brain perfusion imaging was performed with a voxel size of 1.875 mm x 1.875 mm x 4.0 mm (TE 14.0 ms, TR 2000.0 ms, flip angle 90°) with a timed injection of Optimark intravenous contrast. Evaluations of regional cerebral blood volume (rCBV), regional cerebral blood flow (rCBF), mean transit time (MTT), time to peak flow (TPP), and time-to-maximum (Tmax) were performed. Post-processing analysis was completed on the software equipped Olea free-standing workstation with Tmax considered primarily a measure of macrovascular characteristics reflecting a combination of delay, dispersion, and mean transit time.

fMRI was performed utilizing an echo planar imaging sequence with a voxel size of 3.75 mm x 3.75 mm x 4.0 mm (TE 35.0 ms, TR 3000.0 ms, flip angle 90°) and analyzed with BrainWave software to localize the BOLD signal. Separate auditory tasks were performed on the right ear, the left ear, and bilaterally. During each of these three blocks, simple computer-generated nouns (each word repeated 3 times) were presented through headphones for 30 seconds with a 30 second rest period. Each block had 8 cycles, and each cycle contained 4 presentations of the auditory stimulus and 4 rest periods with no auditory stimulus. Audiologic evaluations for hearing abnormalities were not performed.

An abnormal MRI was defined as any one of the following: unusual or atypical white matter hyper-intensities (WMH), hippocampal atrophy (HA) or asymmetry (NeuroQuant\(^\text{TM}\)), abnormal fractional anisotropy (FA) values on Diffusion Tensor Imaging (DTI), abnormalities in MR perfusion, and abnormal auditory functional MRI (fMRI). Abnormal white matter hyper-intensities were defined as white matter foci in subcortical locations without deep or periventricular hyperintensities. WMH patterns consistent with chronic small vessel disease and microvascular changes of aging were not considered abnormal for the purposes of this TBI study or quantified as these are relatively common in older populations. Hippocampal atrophy was defined as either hippocampus <5 percentile in total overall volume as compared to age matched controls and/or in the <5 or >95 percentile asymmetry (NeuroQuant\(^\text{TM}\)). Abnormal DTI was defined as decreased FA values relative to age, determined by radiologists’ combined 10 years of experience with this protocol, spot references to a trauma database from the same scanners, and a large normative database synchronized with human phantom.\(^16,17\)

To qualify as an abnormal DTI, at least one FA value of the 6 regions of the corpus callosum did not conform to age expected values, which was determined subjectively by
the neuroradiologists in a clinical manner. Cutoff values were not utilized as FA values are decreased in children\textsuperscript{18} and then again decrease in the elderly\textsuperscript{19,20} and therefore exact normative values are not well established. The range of the callosal FA values generated using our technique was between 0.45 and 0.65.

Abnormal perfusion was defined as significant asymmetry in the normal expected perfusion color maps. Abnormal fMRI was defined as decreased activation in the temporal cortices or asymmetric activation following auditory word stimulation.

Double blind MRI interpretation were performed by two board certified neuroradiologists with disagreements (which occurred for 21.3\% of readings) reached by consensus.

**Statistical analysis**

The effects of gender, LOC, age, and MRI findings on the occurrence of symptoms and improvement of symptoms were described using odds ratios and 95\% confidence intervals. Comparisons between groups were made using a Fisher’s exact test for each symptom-characteristic pair. The Fisher’s exact test is more robust than a chi-square test for data that have low counts in one cell, and it is valid for all 2×2 table count data. Independence among gender, LOC, age, and MRI findings was also assessed using a Fisher’s exact test.

Symptom longevity was calculated from the date of injury to the time when improvement or resolution (both referred to as ‘improvements’ hereafter) was reported during follow-up visits. Time elapsed between follow-up appointments resulted in non-instantaneous reporting of symptom progression, since improvements could only be reported at scheduled visits. The resulting data are interval-censored, which means that the number of days the symptom persisted after the date of injury are known to be within a time interval but cannot be localized to an exact date. Each patient in the analysis was counted only once for the analysis, and the uncertainty associated with the elapsed time between visits is built into the maximum likelihood estimate of the survival function. To make the situation more complicated, many patients never reported improvement or resolution. In such cases, the data are right-censored, which means that the symptom might improve at some future time, but it had not improved by the date of the last visit to the physician. Data that are both interval-censored and right-censored are relatively common in medical studies, but often statistical methods fail to account for the associated uncertainty.\textsuperscript{21} To estimate longevity of symptoms reported in patients, a Cox proportional hazards model was fit which allowed interval censoring and right censoring. No parametric options provided a satisfactory fit for the observed hazard function, so semi-parametric Cox proportional hazards models were used to estimate and compare treatments.\textsuperscript{22} The analysis assumes that, for an interval of time between two appointments which can be expressed as (L, R], where ‘R’ is the physician visit at which the patient reported improvement and ‘L’ is the physician visit immediately preceding ‘R’, it is equally probable that the symptom abated or resolved across the entire time interval.

Models for groups defined by sex, LOC at the time of injury, age, and MRI findings were estimated separately for each symptom. Standard errors were derived from bootstrapping (1,000 samples), and differences in symptom persistence were tested by using the bootstrapped standard errors to form z-scores. Analyses were conducted in R 3.5.1 software with the ‘icenReg’ package.

**Results**

The sample population had a relatively high percentage (62.4\%) of females, with the primary cause of injury for all patients being motor vehicle collisions (Table 1). Headaches, cognitive disabilities, and balance issues were the most commonly reported symptoms, and they were also the most likely to improve or resolve (Figure 1; Table 2). Anxiety and depression affected approximately half of the patients. Fatigue and emotional lability were both the least commonly noted symptoms and the least likely to improve or resolve (Figure 1; Table 2). On average, patients presented with 4.2 symptoms (presenting for evaluation a median 70 days post injury), with 77.6\% of patients having 3–6 symptoms. Some pairs of symptoms tended to co-occur, most notably anxiety with depression or cognitive problems (Table 3).

Static improvement statistics were complicated by the fact that some patients were followed for over 1,000 days post injury, and others were followed less than three months. The median time between the date of Injury (DOI) and initial consultation was 73 days (range: 0 to 1,536; IQR: 34 to 148); the median number of days between DOI and imaging was 107 (range: 12 to 1,854; IQR: 56 to 196). Each patient had a median of 2 (range: 1 to 9; IQR: 2 to 3) clinical follow-up appointments. The median time between DOI and the last clinical visit was 150 days (range: 0 to 1,175; IQR: 91 to 251).

It would have been insightful to analyze symptom resolution and improvement separately, but few patients reported complete resolution of one or more symptoms (Table 2). Therefore, symptom resolution and improvement were combined for the symptom longevity analysis. Analyses including symptoms which
had very few patients who saw improvement or resolution had lower statistical power and produced less reliable descriptors of actual symptom longevity.

There was no evidence the independent variables of Sex, LOC, Age, or MRI findings tended to co-occur

Table 2. Prevalence of symptoms and symptom resolution by number of patients (percent of patient population for occurrence and percent based on affected patients for percent improved or resolved) in analyzed patient population.

| Symptom     | Occurrence | Improved | Resolved |
|-------------|------------|----------|----------|
| Headache    | 237 (97%)  | 62 (26%) | 11 (5%)  |
| Balance     | 203 (83%)  | 47 (23%) | 9 (4%)   |
| Cognitive   | 221 (90%)  | 59 (27%) | 5 (2%)   |
| Fatigue     | 76 (30%)   | 2 (3%)   | 1 (1%)   |
| Anxiety     | 122 (49%)  | 10 (8%)  | 3 (2%)   |
| Depression  | 112 (46%)  | 10 (9%)  | 2 (2%)   |
| Emotional lability | 59 (24%) | 2 (3%) | 0 (0%)   |

Figure 1. Count of patients who presented symptoms divided into groups based on their characteristics, separated by symptom improvement or resolution during the study. A ‘*’ indicates that the sample size of patients who improved was too small for further analysis.
analyses not shown; Fisher’s exact test between pairs \( p > 0.265 \).

**Effect of sex**

There were no gender-based differences in clinical symptom presentation (Figure 2), nor were there any differences in symptom longevity observed between genders (Table 4, Figure 3(a)).

**Effect of loss of consciousness**

Patients that lost consciousness at the time of injury had higher odds of balance issues, cognitive problems, fatigue, depression, and emotional lability (Figure 2). All patients who lost consciousness had headaches. The only statistically significant difference in recovery time in those with LOC was in cognitive function (Table 4, Figure 3(b)).

**Effect of age (>40)**

Notable differences in symptom presentation and longevity were identified in age dichotomized patient groups. Patients over the age of 40 had significantly higher odds of reporting balance problems at presentation (Figure 2). Patients over the age of 40 were also slower to recover cognitive function and from headaches (Table 4, Figure 3(c) and (d)). Recovery or improvements associated with anxiety and depression were too rare to allow analysis of recovery time.

**Effect of abnormal MRI**

There were no significant differences in symptom presentation based on abnormal MRI findings, although there were trends in depression and anxiety (Figure 2). Patients who had one or more abnormal MRI findings had slower recovery from balance and cognitive deficits (Table 4, Figure 3(f) and (g)). Other symptoms, such as depression, also appeared to show slower recovery in those with abnormal MRI findings (Figure 3(h)), but the sample sizes were not large enough to test statistical significance.

Sixty percent of patients [151] had abnormal MRI findings. Counted independently of other MRI abnormalities, the prevalence of abnormalities in the five categories was: 25% [62] atypical WMH, 15% [38] hippocampal atrophy or asymmetry, 30% [75] abnormal DTI, 6% [16] abnormal perfusion and [87] 35% abnormal auditory fMRI. 57 patients had one abnormal MRI finding, 65 had two abnormal MRI findings, 25 had three abnormal MRI findings and four had four abnormal MRI findings. No patients had all five abnormal MRI findings. The average ages of subjects with a normal MRI versus abnormal MRI was 41.3 and 41.9 years respectively. Examples of imaging findings in each of the 5 categories is shown in supplemental Figures 1 to 6.

**Discussion**

To our knowledge, this is the first study to examine symptom presence and longevity after mTBI within a sizeable civilian patient population using analysis techniques capable of handling retrospective clinical data (even with irregular visit intervals and follow-up). This study is also the largest review of mTBI patients in litigation. A study of 147 severe TBI patients found litigation to be an independent significant predictor of poorer outcomes. A larger meta-analysis found a ‘moderate effect’ of litigation on outcomes in TBI patients. However, other review articles found little effect on cognition and headaches in litigants versus

|                  | Balance | Cognitive | Fatigue | Anxiety | Depression | Emotional lability |
|------------------|---------|-----------|---------|---------|------------|--------------------|
| Headache         | 7.1     | 1.5       | 2.7     | 2.4     | 2.1        | 1.9                |
|                  | 1.2, 5.05 | 0.0, 13.4 | 0.3, 124.8 | 0.4, 26 | 0.3, 22.8 | 0.2, 89.9          |
| Balance          | 4.9     | 2.5       | 1.0, 6.9 | 1.9, 10.8 | 2.5, 19.5 | 1.5, 25.7          |
| Cognitive        | 1.8, 12.8 | *         | 5.8     | 1.9, 23.8 | 3.8, 999.7 | 1.3, 356.1         |
| Fatigue          | 3.5     | 1.9, 6.5  | 1.7, 5.6 | 1.5      | 66.0       | 1.1, 170.8         |
| Anxiety          | 28.4, 170.8 | 2.1       | 60.6     | 2.0      | 1.1, 170.8 | 1.1, 4.1           |
| Depression       | 2.1     |           |         |         |            |                    |

Note: Odds ratios and 95% confidence intervals are reported. Values with Bonferroni-adjusted \( p \)-value \(< 0.05\) are in bold. Note that fatigue always co-occurred with cognitive symptoms, indicated on this table as *.
non litigants\textsuperscript{25} with reported widespread continuation of post-traumatic headaches despite litigation resolution.\textsuperscript{26}

The subjects in this study were more than half female and included a broad age range, from young children to elderly patients. Most studies in the literature have matched controls, whereas this is a retrospective cohort view, which may allow a more representative sample to be included. Many of the disparities between this study and others may be a consequence of the different study populations, study designs and sample sizes.\textsuperscript{27}

Results of this study are generally concordant with already published work. Although there is some limitation in comparison, presenting symptoms of our subjects appear similar to those described in the literature, though we report lower rates of fatigue and higher rates of headache.\textsuperscript{28–30} Some studies have found mTBI patients typically experience a complete recovery and may resume a normal lifestyle in a matter of weeks or occasionally even days.\textsuperscript{31,32} Losoi et al. found that by 6 months nearly 90\% of the mTBI patients had reported “good recovery.”\textsuperscript{33} However, many other studies have found significant deficits and symptoms greater than a year following injury.\textsuperscript{30,34–37} McInnes et al. conducted a large meta review and found a majority of subjects showed cognitive impairment >12 months after injury.\textsuperscript{38} A 2019 meta-analysis found less than half (47.2\%) of patients experienced full recovery in 12 months.\textsuperscript{39} These recent studies are more consistent with our results relative to frequency of symptom presentation and prolonged experience of mTBI symptoms.\textsuperscript{40}

\begin{table}
\centering
\begin{tabular}{cccc}
\hline
Odds without & Odds with & Odds & p-value \\
characteristic & characteristic & ratio & \\
\hline
51.0 & 22.5 & 0.4 & 0.431 \\
4.0 & 7.5 & 1.9 & 0.116 \\
11.0 & 6.8 & 0.6 & 0.281 \\
0.4 & 0.6 & 1.5 & 0.156 \\
1.0 & 0.9 & 0.9 & 0.896 \\
0.8 & 0.9 & 1.2 & 0.602 \\
0.2 & 0.4 & 1.8 & 0.066 \\
\hline
23.9 & All had symptom & Inf & 0.105 \\
3.5 & 24.3 & 7.0 & 0.000 \\
6.6 & 37.0 & 5.6 & 0.010 \\
0.5 & 0.7 & 2.0 & 0.025 \\
0.8 & 1.4 & 1.7 & 0.074 \\
0.6 & 1.5 & 2.4 & 0.002 \\
0.2 & 0.6 & 2.6 & 0.002 \\
\hline
19.5 & 126.0 & 6.4 & 0.063 \\
3.2 & 8.8 & 2.7 & 0.006 \\
6.7 & 13.1 & 2.0 & 0.142 \\
0.4 & 0.5 & 1.2 & 0.583 \\
0.8 & 1.1 & 1.4 & 0.209 \\
0.7 & 1.0 & 1.6 & 0.077 \\
0.3 & 0.4 & 1.4 & 0.305 \\
\hline
52.0 & 36.8 & 1.1 & 1.000 \\
4.5 & 5.5 & 1.2 & 0.750 \\
8.9 & 9.1 & 1.0 & 1.000 \\
0.4 & 0.5 & 1.4 & 0.264 \\
1.3 & 0.8 & 0.6 & 0.053 \\
1.2 & 0.7 & 0.6 & 0.051 \\
0.3 & 0.3 & 1.2 & 0.651 \\
\hline
\end{tabular}
\caption{Odds of presenting symptom based on characteristics, including sex, LOC, age (less than or equal to 40, greater than 40), and abnormal MRI findings. In the tabular data, p-values from the Fisher's exact test are reported, and 'Inf' indicates infinitely large log odds ratio because all individuals with the characteristic had the symptom. In the plot, the log odds and 95\% confidence intervals are provided. The numbers on the far-right side of the plot indicate the upper 95\% confidence limit, which was truncated on the plot for readability.}
\end{table}
Sex associated sequelae of mTBI

TBI is more prevalent in males,\textsuperscript{41,42} likely due to behavioral/risk taking patterns.\textsuperscript{42,43} Evidence for gender differences in TBI symptomology and recovery is more mixed. Several studies have identified female subjects as having diminished recovery and increased severity of symptoms following mTBI.\textsuperscript{42,44,45} This study found no differences between males and females in symptom presence or symptom longevity.

Clinical symptoms after loss of consciousness

The results of this study indicate LOC plays a stronger role in initial symptom presentation and a lesser role in symptom longevity, this is concordant with the results and review of Roy et al, who studied 407 mTBI subjects and found much higher rates of post concussive symptoms in mTBI patients who lost consciousness evaluated one month following head trauma, but no significant associations at a 6 month evaluation.\textsuperscript{46} However, contrary to Roy et al, our subjects who lost consciousness were more likely to present with depression. This study and our study indicate LOC may not be as important for long term outcomes as previously thought. The known dementia risk from mTBI does not require LOC.\textsuperscript{47}

Age as a factor in mTBI outcomes

Age is a well-recognized determinant of outcome after head trauma, with older patients suffering worse outcomes.\textsuperscript{48–51} In this study, older age (\( \geq 40 \)) was adversely related to both symptom presentation and symptom improvement.

MRI abnormalities and mTBI outcomes

Hemorrhagic diffuse axonal injury, cerebral contusions, and intra and extra-axial hemorrhages are well described in the trauma literature as correlating with poorer prognosis; however, the 5 categories comprising our ‘abnormal MRI group’ have been less well studied, particularly in mTBI. This study suggests that the MRI abnormalities studied may be associated with slow recovery of balance and cognition.

Non-hemorrhagic shearing injuries/white matter hyper-intensities secondary to head trauma are well described in the literature.\textsuperscript{52–54} There is a reported 30\% to 50\% resolution of traumatic WMH in the weeks to months following head trauma.\textsuperscript{10} Discerning post traumatic WMH from incidental WMH, changes of aging and microvascular disease, and other etiologies is challenging in clinical practice, particularly in older patients. Incidence of WMH in normative populations is varied, with some reporting low incidence\textsuperscript{55–57} and others higher incidence.\textsuperscript{54,58} Comparing WMH in TBI versus controls, some studies have found no difference, while some have found changes in subcortical predominance of lesions\textsuperscript{59}; others have documented trends approaching significance.\textsuperscript{54} Tate et al., did not find significant differences in WMH between controls and TBI subjects, but did find that TBI patients with WMH had significantly worse cognitive deficits than those without WMH.\textsuperscript{60} 25\% [62] of our subjects has atypical WMH.

### Table 4. Statistics for survival functions comparing symptom retention between patient subgroups.

| Symptom       | Est. effect | Hazard ratio | SE   | z-value | P-value |
|---------------|-------------|--------------|------|---------|---------|
| Sex (Male/female) |             |              |      |         |         |
| Headache      | 0.05        | 1.05         | 0.25 | 0.2     | 0.840   |
| Balance       | -0.17       | 0.84         | 0.30 | -0.6    | 0.570   |
| Cognitive     | -0.36       | 0.70         | 0.29 | -1.2    | 0.214   |
| Anxiety       | 0.14        | 1.15         | 1.06 | 0.1     | 0.896   |
| Depression    | -0.19       | 0.82         | 1.37 | -0.1    | 0.888   |
| Loss of consciousness (with/without) |             |              |      |         |         |
| Headache      | -0.47       | 0.63         | 0.30 | -1.6    | 0.114   |
| Balance       | -0.57       | 0.56         | 0.34 | -1.7    | 0.094   |
| Cognitive     | -0.63       | 0.53         | 0.31 | -2.0    | 0.044   |
| Anxiety       | -0.59       | 0.55         | 1.51 | -0.4    | 0.695   |
| Depression    | -0.46       | 0.63         | 1.52 | -0.3    | 0.760   |
| Age (<40 years/>40 years) |             |              |      |         |         |
| Headache      | -0.68       | 0.51         | 0.26 | -2.7    | 0.007   |
| Balance       | -0.34       | 0.71         | 0.29 | -1.2    | 0.238   |
| Cognitive     | -0.89       | 0.41         | 0.27 | -3.3    | 0.001   |
| MRI status (normal/abnormal) |             |              |      |         |         |
| Headache      | -0.46       | 0.63         | 0.24 | -1.9    | 0.060   |
| Balance       | -0.75       | 0.47         | 0.28 | -2.6    | 0.009   |
| Cognitive     | -0.91       | 0.40         | 0.26 | -3.5    | <0.001  |

Note: The ‘Est Effect’ coefficient indicates the effect size on symptom retention. The hazard ratio (hazard in the group with the characteristic minus hazard in the group without the characteristic), bootstrapped standard errors (SE), z value, and P-value are also reported.
It is well established that brain trauma may result in hippocampal atrophy with the degree of atrophy related to severity of injury. Hippocampal atrophy appears to correlate with clinical outcomes in mTBI. NeuroQuant is an FDA-approved software program for measuring brain MRI volumes and can be used in the clinical setting to assess for hippocampal atrophy following traumatic brain injury and

Figure 3. Estimated symptom longevity based on characteristics, which are denoted in the upper-right key. Statistics are provided in Table 4.
may be more effective than radiologists simply “eyeballing” brain structures.\textsuperscript{55,66} 15\% [38] of our subjects had hippocampal atrophy or asymmetry.

Diffusion Tensor Imaging (DTI) measures the ability of water molecules to move through tissue, with notable directional constraints associated with white matter axons.\textsuperscript{67} DTI is reported to be sensitive to diffuse axonal injury.\textsuperscript{68} Many studies have found differences between mTBI patients and controls.\textsuperscript{16,69,70} Abnormalities in DTI are reported to correlate with clinical outcomes.\textsuperscript{16,71} Wilde et al. found DTI abnormalities associated with LOC in mTBI.\textsuperscript{72} 30\% [75] of our subjects were classified as having an abnormal DTI, with FA values decreased as expected per age by two neuroradiologists with experience interpreting FA values on these scanners.

Perfusion imaging assesses blood flow to regions of the brain. Non-uniform cerebral perfusion has been identified in patients with a variety of brain injuries including head trauma. Reduced cerebral blood flow has been demonstrated following head trauma with improvement in cerebral blood flow correlating with clinical recovery.\textsuperscript{73,74} 6\% [16] of our subjects had abnormal perfusion.

In functional magnetic resonance imaging (fMRI) blood oxygen-level-dependent (BOLD) contrast is altered in response to local blood flow changes associated with increased regional neuronal activity.\textsuperscript{75,76} Auditory fMRI has been studied for over 20 years.\textsuperscript{77–79} Although less well investigated than the other imaging measures, abnormalities in auditory fMRI may correlate with central auditory processing disorder, and a recent study suggested mild differences between mTBI patients and controls in a military population.\textsuperscript{80} Therefore, our auditory fMRI protocol was performed using this same protocol and we found 87 (35\%) of our subjects had an abnormal auditory fMRI.\textsuperscript{80}

To our knowledge, existing literature has addressed outcomes rather than symptom presentation relative to MRI findings in mTBI.

Conclusions and limitations

The study had several limitations. Costs associated with advanced imaging limited us to those patients undergoing litigation cases in a retrospective manner and without a control group. The lack of a control group is the primary limitation of this study. For example, the rates of central auditory processing disorders and abnormal auditory fMRI in a normative population have not been well established. Symptom reporting may be subjective and in part relies on self-reporting. Time between DOI and first presentation and length of follow-up was quite variable, limiting conclusions based only on symptom presentation and improvement without accounting for time. We therefore attempted to restrict our statistical interpretation to differences among groups. ‘Improvement’ in symptoms was not quantified or scaled. Standardized cognitive tests with quantifiable results were not administered. Quantifiable vestibular testing was not performed. Time of loss of consciousness was not quantified. Secondary gain and other factors in the medical legal process have potential to distort data. It is also possible that patients with worse mTBI would be more likely to enter litigation.

Excluding the NeuroQuant\textsuperscript{81} hippocampal volumetric analysis, all the additional imaging findings interpreted by the neuroradiologists contain an element of subjectivity. For example, study design did not include quantified predetermined cutoff DTI FA values or comparison to a normative DTI database with age and sex matched controls and z scores. While unusual in young and middle-aged patients, hearing loss estimates in patients over 65 are 25–40\% and therefore the auditory fMRI results may be less reliable in the older patients.\textsuperscript{81} Resting state fMRI, a component of the auditory fMRI performed, has shown promise in detecting abnormal connectivity in head trauma patients, but this analysis was not performed. We did not assess which abnormal MRI categories played the largest role in the detected adverse clinical outcomes due to limited sample size within categories.

Despite these limitations, our observations agree with existing literature regarding patient age, LOC, and MRI findings.

The purpose of this study was to assess if further investigation of these advanced neuroimaging and white matter findings was warranted using more objective measures and to assert the validity of this statistical technique to analyze the incidence of clinical outcomes. Given the strong association of abnormal advanced imaging and white matter findings with clinical outcomes, further investigation is justified.

A more detailed understanding of symptoms and the prognosis following mTBI has important implications for health care costs and quality.\textsuperscript{82} Interval censored survival statistical analysis appears to be a valid method to assess head trauma cohorts and predict clinical outcomes based on quantitative clinical data. The diagnostics of a mild traumatic brain injury may still rely in part on patient self-reporting and keen clinical assessment; however, this study indicates neuroimaging techniques are likely underutilized in contributing to diagnosis and prognosis of mTBI.

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The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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**Supplemental material**

Supplemental material for this article is available online.

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