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Acute Clinical Predictors of Symptom Recovery in Emergency Department Patients with Uncomplicated Mild Traumatic Brain Injury or Non-Traumatic Brain Injuries

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Abstract

There is a subset of patients with mild traumatic brain injury (mTBI) who report persistent symptoms that impair their functioning and quality of life. Being able to predict which patients will experience prolonged symptom recovery would help clinicians target resources for clinical follow-up to those most in need, and would facilitate research to develop precision medicine treatments for mTBI. The purpose of this study was to investigate the predictors of symptom recovery in a prospective sample of emergency department trauma patients with either mTBI or non-mTBI injuries. Subjects were examined at several time points from within 72 h to 45 days post-injury. We quantified and compared the value of a variety of demographic, injury, and clinical assessment (symptom, neurocognitive) variables for predicting self-reported symptom duration in both mTBI ($n = 89$) and trauma control ($n = 73$) patients. Several injury-related and neuropsychological variables assessed acutely (< 72 h) post-injury predicted symptom duration, particularly loss of consciousness (mTBI group), acute somatic symptom burden (both groups), and acute reaction time (both groups), with reasonably good model fit when including all of these variables (area under the receiver operating characteristic curve [AUC] = 0.76). Incorporating self-reported litigation involvement modestly increased prediction further (AUC = 0.80). The results highlight the multifactorial nature of mTBI recovery, and injury recovery more generally, and the need to incorporate a variety of variables to achieve adequate prediction. Further research to improve this model and validate it in new and more diverse trauma samples will be useful to build a neurobiopsychosocial model of recovery that informs treatment development.

Keywords: computerized testing; concussion; reaction time; recovery; somatic symptoms

Introduction

In the United States, an estimated 1,400,000 emergency department (ED) visits each year involve traumatic brain injury (TBI), with >80% of TBIs classified as ''mild'' based on traditional acute injury characteristics.[1,2] Contrary to what is implied by the ''mild'' label, a sizeable minority of ED patients with mTBI experience chronic symptoms post-injury, with prevalence estimates ranging from ~20%[3,4] to upwards of 50%.[5–7] Because of the persistent effects of mTBI on some patients' functioning and quality of life,[8–10] along with the lack of validated treatments, there is increasing momentum toward developing algorithms to predict which patients are at highest risk for prolonged symptoms. The ability to accurately stratify patients by risk status would help clinicians and researchers alike. Clinicians could focus resources for follow-up on those at greatest risk, while researchers could employ enrichment study designs to accelerate the development of empirically supported, precision medicine treatments for mTBI.

To date, findings from outcome prediction research have been insufficient to realize these objectives. A recent review of this literature concluded that prediction studies were of variable quality, with only a minority employing ideal research methods such as prospective enrollment, direct statistical comparison of multiple predictors, and reporting of overall model fit.[11] Beyond needs to standardize and tighten methodology and statistical reporting is a more fundamental issue about how to operationalize recovery,

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given that many of the lingering symptoms attributed to mTBI also occur frequently in healthy adults[12–14] and non-mTBI patient populations.[15–22] The nonspecificity of mTBI symptoms is further supported by findings that mTBI itself (vs. other injuries) does not predict scores on standard ''mTBI'' symptom checklists;[16–18,23] rather, mTBI symptoms are more strongly predicted by premorbid psychosocial factors such as anxiety,[17,23–25] depression,[26–28] and somatization.[29–31] Although such findings are often used to conclude that persistent mTBI symptoms are explained by psychological factors,[30–35] it is possible that correlations between psychiatric and mTBI symptoms are inflated artificially because of the design and properties of the questionnaire instruments used to assess them.[36,37] In order to tease apart the role of such measurement issues from bona fide psychological risk factors, it would be valuable to explore such predictive relationships using outcome measures of recovery assessed through different modalities, such as through interviews of injury recovery.

Notwithstanding issues with outcome measurement, there is consensus that traditional markers of injury severity that are important for patients with moderate-to-severe TBI are less relevant to mTBI recovery.[11,38,39] Instead, mTBI recovery appears to be affected by a variety of other factors, especially demographic (e.g., gender, age)[24,40,41] and various pre- and post-injury clinical neuropsychological variables.[11,18,23–25,39,42–47] Although single variables and variables readily extracted from medical records have yielded insufficient predictive power,[40,41] prediction has sometimes approached acceptable levels with additional clinical assessment (e.g., symptom, neurocognitive) measures.[16,25,43,44,47] These findings suggest that a multidimensional approach to outcome prediction is needed.[48] In addition to optimizing model accuracy through such a neurobiopsychosocial approach, it will be helpful to maximize the ease with which predictor variables can be obtained, in order to deploy prognostic procedures on a large scale. Therefore, brief, cost-effective clinical assessments that can be administered with minimal direct patient interaction or expertise should be prioritized over measures that are more burdensome to obtain.

This prospective study stems from a comprehensive research program designed to improve mTBI outcome prediction within a neurobiopsychosocial framework. In particular, we aimed to quantify and compare the predictive value of a host of demographic, injury, and clinical neuropsychological variables assessed in ED-recruited trauma patients acutely (< 72 h) post-injury. The study protocol emphasized assessments that can be performed without special neuropsychological training (i.e., self-report symptom checklists, computerized neurocognitive tests) and an outcome measure that is readily assessed and intuitively associated with injury recovery (number of days of self-reported injury symptoms). Our objectives were to (1) identify the key demographic and clinical variables that predict symptom duration after uncomplicated mTBI (as well as non-mTBI injury) and (2) estimate the accuracy of prediction using models of increasing complexity, starting with readily available demographic and acute injury variables and adding, sequentially, the questionnaire and neurocognitive performance measures that require more intensive patient assessment. We hypothesized that (1) multiple demographic/injury and neuropsychological factors would independently predict symptom duration; (2) the factors associated with risk versus resilience would largely generalize across mTBI and trauma control groups; and (3) prediction accuracy would improve with the addition of clinical assessment variables (over and above the prediction achieved with demographic and injury variables).

Methods

Participants

The sample was derived from participants in Project Head to Head, which enrolled patients from the ED at a tertiary care hospital that also serves as southeastern Wisconsin's only level I trauma center. Participants were enrolled from September 2012 to May 2014. They completed informed consent prior to their first evaluation and were paid $210 for their time and effort in completing the assessments. All testing procedures were approved by the Institutional Review Board at the Medical College of Wisconsin.

In order to identify eligible research subjects, we conducted a prospective chart review of every patient treated and released from the ED. Patients in the age range of interest (see Inclusion Criteria) who were exposed to a common cause of mTBI[2] were screened in real time. Eligible causes of injury included falls, motor vehicle-traffic (MVT) crashes, assaults, and being struck by/against an object. Using 4579 charts that were screened in real time based on age and chief complaint, 2670 patients appeared eligible based on the electronic medical record review, 1058 were approached in the ED, 331 consented to be contacted with further study information, and 181 provided informed consent to participate in the study (98 of whom met criteria for mTBI, and 83 who were enrolled as trauma controls). Of these, one subject did not complete any assessment procedures, two were withdrawn after the first assessment when it was discovered that they met exclusion criteria (neurological disorder and positive head CT), and 12 were excluded because of evidence of poor effort on neurocognitive testing (see Data Analyses), yielding a final sample for analysis of 162 (89 mTBI, 73 controls). The study sample was similar in demographics to the larger population of eligible ED patients screened for inclusion in the study. In particular, the eligible patient population was 53.6% female with a mean age 29.49 years, and was distributed by cause of injury in the following manner: 73.1% MVT, 16.0% fall, 6.8% assault, and 4.1% struck by/against an object; the enrolled sample was 54.9% female with a mean age of 29.64 years, and was distributed by injury cause as follows: 63.0% MVT, 28.4% fall, 2.5% assault, and 6.2% struck/by against an object.

Inclusion and exclusion criteria

Inclusion criteria for participation were age 18–45 (the age range of interest to the study sponsor), initial Glasgow Coma Scale score 13–15, loss of consciousness (LOC) <30 min, post-traumatic amnesia <24 h, absence of acute intracranial findings on brain imaging (if performed), proficiency in English, and the ability to present to the initial assessment within 72 h of injury. Subjects were excluded if they had an injury that precluded participation in the study protocol (e.g., hand injury that prevented use of a computer mouse), current diagnosis of a psychotic disorder, history or clinical suspicion of other conditions (e.g., epilepsy, stroke, dementia) known to cause cognitive dysfunction, or a history of moderate or severe TBI. Early in the study, we also excluded individuals with a current diagnosis of a mood or anxiety disorder and required subjects to present to the initial assessment within 24 h of injury. These criteria were relaxed in September 2013, because of suboptimal enrollment. In particular, individuals with a mood or anxiety disorder were allowed to enroll if they reported having been stable on any treatment (e.g., medication) for at least 3 months.

Subjects assigned to the mTBI group were required to meet the definition of mTBI specified by the study sponsor, the United States Department of Defense: ''mTBI is defined as an injury to the brain resulting from an external force and/or acceleration/deceleration mechanism from an event such as a blast, fall, direct impact, or motor vehicle accident which causes an alteration in mental status typically resulting in the temporally related onset of symptoms such as headache, nausea, vomiting, dizziness/balance problems, fatigue, insomnia/sleep disturbances, drowsiness, sensitivity to light/

noise, blurred vision, difficulty remembering, and/or difficulty concentrating.''[49] Subjects assigned to the control group had injuries other than mTBI and were excluded if they reported having had a concussion within the last 6 months.

Assessment protocol

Participants were assessed within 72 h of injury and at ~8, 15, and 45 d post-injury. Mean (SD) time from injury to follow-up was 39.03 (21.62) h, 7.94 (1.16) d, 14.63 (1.54) d, and 43.94 (3.93) d for the 72 h and the 8-, 15-, and 45-day time points, respectively. Tests were individually proctored by a research assistant in a quiet setting, nearly always with only one participant being examined at a time. The first assessment began with a one-on-one interview of contact information, demographics, and health history information followed by a neuropsychological assessment battery. Follow-up assessments began with an interview about subjects' recoveries followed by the same neuropsychological assessment battery. In order to reduce the burden on participants to travel to assessments, day 8 follow-up appointments were completed via phone and only involved assessment of recovery and Sport Concussion Assessment Tool, 3rd edition (SCAT3) symptom ratings.

The neuropsychological assessment battery consisted of, in order: Wechsler Test of Adult Reading (WTAR) (first assessment only);[50] a computerized neurocognitive test (CNT); Standardized Assessment of Concussion (SAC)[51] SCAT3 symptom checklist;[52] a second CNT, Green's Medical Symptom Validity Test (MSVT);[53] Satisfaction With Life Scale (SWLS);[54] Brief Symptom Inventory-18 (BSI-18);[55] and the Balance Error Scoring System (BESS).[56] Each subject took two of three CNTs: Automatic Neuropsychological Assessment Metrics (ANAM v. 4.3; Vista Life Sciences), Defense Automated Neurobehavioral Assessment (DANA) (United States Navy Bureau of Medicine and Surgery [BUMED]), and Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT, Online version; ImPACT Applications Inc.). CNT pairs were filled sequentially during the course of the study with order of administration counterbalanced across participants. These measures are described in prior publications from this study.[57–60]

Statistical analysis

The primary outcome measure of interest was self-reported duration of post-concussive symptoms (in days). Potential predictors of symptom duration were extracted from the measures collected at the first (72 h) assessment. Twelve subjects with suspect effort (determined by failure of one or more indices of the MSVT at this visit) were excluded from analyses, resulting in 162 subjects included in analyses. Self-reported symptom measures (SCAT3, BSI-18, SWLS, PTSD Checklist – Civilian Version [PCL-C]) and performance variables (WTAR, SAC, ANAM, DANA, and ImPACT measures) were standardized to facilitate comparisons of recovery hazards.

Time to recovery was evaluated using a Cox proportional hazards model. Categories with low frequencies (''other'' race category, ''other/unknown'' insurance type, learning disability, psychiatric disorder, non-migraine headache history, assault and struck by/against mechanisms of injury) were excluded from analysis. Most subjects (88.3%) could not complete the foam-surface trials of the BESS examination because of polytrauma or symptom severity; 53.1% ($n=86$) completed the firm-surface trials (i.e., modified BESS, [mBESS]). Therefore, only mBESS score was entered as a predictor. For all models, we verified that the proportional hazards assumption was met (the mBESS score needed to be dichotomized at its median to meet this assumption). Because self-reported litigation status violated the assumption, stratified (on litigation) proportional hazard models were applied to account for nonproportionality of hazards associated with litigation.

Initial analyses revealed distinct patterns of findings for two subsets of mTBI subjects: those with and without LOC. For this reason, the analyses presented here used a variable injury group with three levels (mTBI with LOC, mTBI without LOC, and trauma control). Because of the large number of models being estimated, α was set to 0.01 to reduce the chances of false discoveries. Initial analyses explored single-predictor (unadjusted) models, after which multi-predictor models were fitted with any predictor with $p<0.10$ in an unadjusted model considered for each multi-predictor model. To maximize statistical power for all inferences and because the n available for each CNT was lower than the total sample size, multivariate analyses examined the effect of each CNT (ANAM, DANA, ImPACT) variable through interactions with having taken that CNT. However, in order to verify the stability of inferences across methods, complete case analysis was also performed on the smaller data set where data from each CNT were available. Finally, as described subsequently, a set of logistic regression analyses were conducted on the major predictors identified in the Cox models to explore the predictive value of litigation status and to provide intuitive metrics of model accuracy.

Results

Sample characteristics

The demographic makeup and acute injury characteristics of the sample are presented in Table 1. The mTBI and trauma control groups were closely matched on age, sex, race, insurance type, estimated verbal intellectual ability (WTAR score), and socioeconomic status. Within the mTBI group, 36.8% reported having LOC, 15.8% reported having post-traumatic amnesia, and 6.3% reported having retrograde amnesia. Because cases of LOC were self-reported, they could have included cases of post-traumatic amnesia. Participants reported or displayed injuries to a variety of bodily regions, most commonly neck (48.9% overall), upper extremity (43.1%), and back injuries (48.2%), with back injuries present more frequently in the trauma control than the mTBI group (59.0% vs. 39.5%, $p=0.011$). Observable signs of head trauma were present in a minority of cases but were more common in the mTBI than in the control group (38.2% vs. 16.4%, $p=0.004$).

Descriptive statistics for the outcome (symptom duration) and clinical assessment (neuropsychological) variables are provided in Table 2. The mTBI group was divided into two groups (with vs. without LOC) based on findings of distinct recovery trajectories between these groups. (Median number of days to reach self-reported symptom recovery = 26.5 for mTBI participants with LOC vs. 13 for mTBI participants without LOC; controls had a median symptom duration of 25 days). The percentage of all subjects who reported symptom recovery by 1 week, 1 month, and 45 days post-injury was 21.6%, 50.0%, and 54.9%, respectively. Approximately one third (35.2%) of the sample was still symptomatic at the final 45 day visit, and 9.9% of subjects were symptomatic at an earlier visit but did not complete later visits.

Single-predictor (i.e., unadjusted) models of symptom duration

Results of single-predictor regression models for symptom duration are presented in Table 3. Across subjects, mTBI subjects without LOC had better (faster) recoveries than both mTBI subjects with LOC (hazard ratio [HR] = 2.68, $p=0.003$) and trauma controls (HR = 1.96, $p=0.004$), with equivalent hazards of recovery for the LOC+ mTBI group and trauma control group (HR = 0.77, $p=0.427$). Further, there was a trend for participants who had taken opioid medications after injuries ($n=35$) to experience more prolonged recoveries than non-

Table 1. Sample Characteristics

	mTBI n = *89*	*Trauma control* n = *73*	
	Mean (SD) or %	*Mean (SD) or %*	p
Female gender	60.7%	47.9%	0.105
Age (years)	28.87 (7.38)	30.59 (7.83)	0.152
Race			0.362
Black	49.4%	53.4%	
White	42.7%	43.8%	
Other	7.9%	2.7%	
WTAR standard score	94.78 (16.88)	96.64 (16.68)	0.482
Household SES	41.49 (11.90)	43.11 (10.68)	0.411
Health insurance type			0.831
Commercial	48.3%	50.7%	
Government	32.6%	31.0%	
None	18.0%	18.3%	
Other/unknown	1.1%	0.0%	
ADHD	12.5%	6.8%	0.233
Learning disability	3.4%	6.8%	0.309
Psychiatric diagnosis	9.0%	1.4%	0.035
Migraine history	20.2%	15.3%	0.417
Non-migraine headache history	7.9%	2.8%	0.162
Prior concussion(s)	34.8%	30.6%	0.566
Mechanism of injury			0.028
Motor vehicle-traffic	59.6%	67.1%	
Fall	25.8%	31.5%	
Assault	4.5%	0.0%	
Struck by/against an object	10.1%	1.4%	
Litigation related to injury	26.5%	26.8%	0.972
Worker's compensation injury	16.9%	9.9%	0.206
Acute injury characteristics			
Loss of consciousness	39.0%	-	
Posttraumatic amnesia	17.2%	-	
Retrograde amnesia	6.8%	-	
Head CT			
Ordered and normal	42.7%	-	
Not ordered	57.3%	-	
Medications used after injury			
Opioids	13.2%	41.0%	0.001
Non-opioid	66.1%	66.7%	0.987
Injury locations (self-report)[a]			
Head/face	34.8%	15.1%	0.004
Neck	51.7%	49.3%	0.764
Upper extremity	40.4%	45.2%	0.542
Back	41.6%	61.6%	0.011
Trunk	18.0%	20.5%	0.679
Lower extremity	30.3%	41.1%	0.154

[a]The intention of the head/face injury variable was to document observable signs of injury (e.g., bruise, laceration) that might be present irrespective of clinical signs of concussion. Non-mTBI control participants who checked off this item reported or demonstrated signs of head trauma without meeting other clinical criteria for mTBI (i.e., altered mental status, mTBI symptoms). Other bodily injuries were coded as positive in the presence of either observable signs of injury (e.g., bruise, laceration, fracture) or subjective signs of injury (e.g., new-onset back pain).

ADHD, attention-deficit/hyperactivity disorder; mTBI, mild traumatic brain injury; SES, Hollingshead socioeconomic status score; TBI, traumatic brain injury; WTAR, Wechsler Test of Adult Reading.

users ($n = 102$;[*] HR = 0.50, $p = 0.016$; with a median symptom duration of 40 days for opioid users vs. 12.5 days for non-users), whereas use of non-opioid medications was unrelated to symptom duration ($p = 0.305$). Opioid use was more common in control than mTBI participants (see Table 1) and appeared to partially explain the longer recovery time of trauma controls versus mTBI participants without LOC (e.g., in a model including both injury group and opioid predictor variables, the Control vs. mTBI LOC- recovery time diminished somewhat but remained marginally significant, going from HR = 0.49, $p = 0.004$ in the single-predictor model to HR = 0.59, $p = 0$ .046 in this two-predictor model; opioid use HR = 0.57, $p = 0.067$ in this model).

Among acute clinical measures captured within 72 h of injury, several self-report and performance measures significantly predicted symptom recovery in the expected direction (i.e., more symptoms or poorer neurocognitive performance being acutely predictive of lower hazards of recovery, akin to slower recovery). These included BSI-18 somatization score (HR = 0.68, $p = 0.002$), SCAT3 post-concussive symptom severity (HR = 0.69, $p = 0.008$), ANAM simple reaction time 2 (HR = 1.90, $p = 0.003$), and DANA simple reaction time 1, simple reaction time 2, and procedural reaction time (HR = 1.78, 1.56, and 1.43, respectively, p's ≤ 0.008).

Because a surprising percentage of the sample (46.9%) was unable to complete the balance (mBESS) examination acutely (due to polytrauma or symptom severity), an exploratory analysis was undertaken to investigate whether *completion* of the mBESS predicted recovery. Completion of the mBESS was a strong univariate predictor of recovery (mBESS incomplete HR = 0.53, $p = 0.004$) and appeared to be most associated with having a lower extremity injury,[†] although neither mBESS completion nor lower extremity injury status added incrementally to outcome prediction in the multivariate models described subsequently.

Multivariate (i.e., adjusted) prediction of symptom duration

Multi-predictor models (presented in more detail in Tables S1–S4) were developed in a stepwise fashion (see online supplementary material at http://www.liebertpub.com). Our objective was to both build a maximally predictive parsimonious model while prioritizing variables that are most readily obtained. First, we developed a model using only demographic, history, and injury information (demographics model). Second, we evaluated whether the addition of variables assessed through symptom questionnaires yielded improved outcome prediction beyond the demographics

[*]Twenty-five patients who took unknown prescription medications were excluded from analyses of medication usage.

[†]The rationale for investigating mBESS completion as a predictor was that it may suggest a role of vestibular symptoms, lower extremity injuries, or other factors not already assessed on recovery. As stated, inability to complete the mBESS was associated with a lower hazards of recovery (mBESS incomplete HR = 0.53, $p = 0.004$). Exploration of measurable factors that were associated with an incomplete mBESS examination revealed that having a lower extremity injury was most associated with an incomplete mBESS (51.3% of those without an mBESS score had a lower extremity injury, versus 20.9% of those who completed the mBESS, χ^2 [1] = 16.33, $p < 0.001$; whereas SCAT3 symptom severity, report of dizziness on the SCAT3, or other symptom variables were not significantly associated with mBESS completion). Having a lower extremity injury was somewhat more closely associated with symptom recovery than mBESS completion (lower extremity injury HR = 0.49, $p = 0.004$), whereas having an injury to other bodily locations (e.g., head/neck, upper extremity, back, trunk) was not significantly predictive of symptom duration (ps = .038–0.835). However, neither mBESS completion nor the presence of a lower extremity injury contributed significantly to any multivariate model.

Table 2. Descriptive Statistics for the Outcome and Clinical Assessment Variables

	Mean (SD)		
	mTBI without LOC	*mTBI with LOC*	*Trauma control*
Outcome			
Symptom duration (days)	18.42 (15.94)	26.13 (16.84)	26.27 (17.59)
Median	13	26.5	30
Clinical assessments	($n=50$)	($n=32$)	($n=73$)
SCAT3 symptom severity	28.74 (20.53)	33.81 (29.07)	15.63 (14.82)
BSI-18 somatization SS	111.02 (13.38)	112.09 (16.72)	103.71 (11.24)
BSI-18 depression SS	101.12 (14.99)	103.75 (17.55)	93.92 (10.86)
BSI-18 anxiety SS	98.86 (14.82)	107.50 (17.98)	94.95 (12.26)
BSI-18 GSI SS	104.96 (14.63)	109.63 (17.54)	97.48 (12.24)
SWLS total	22.34 (7.54)	20.38 (7.15)	22.84 (7.13)
PCL-C total	30.00 (13.36)	32.77 (17.93)	28.78 (12.92)
mBESS total score[a]	5.79 (3.86)	6.05 (3.58)	4.29 (3.38)
SAC total score	25.68 (2.38)	25.59 (2.24)	25.93 (2.63)
ANAM	($n=27$)	($n=19$)	($n=33$)
Composite score	–0.71 (1.63)	–0.94 (1.39)	–0.55 (1.57)
Simple reaction time	213.44 (52.69)	211.26 (54.75)	200.88 (67.58)
Code substitution learning	46.93 (10.20)	46.47 (15.61)	48.52 (13.47)
Procedural reaction time	94.15 (22.34)	89.68 (24.71)	96.36 (22.98)
Math processing	18.44 (7.70)	18.79 (6.50)	22.00 (6.61)
Matching two sample	0.05 (0.86)	–0.04 (0.91)	0.22 (1.16)
Code substitution-delayed	44.15 (24.09)	41.11 (18.62)	39.64 (18.31)
Simple reaction time 2	206.15 (47.4)	188.58 (47.79)	209.67 (50.02)
Go/no-go	3.15 (1.41)	3.00 (1.29)	3.58 (1.52)
DANA	($n=44$)	($n=28$)	($n=63$)
Simple reaction time	137.18 (33.97)	127.45 (39.38)	134.76 (28.20)
Code substitution learning	41.78 (8.26)	41.30 (10.98)	40.44 (9.99)
Procedural reaction time	94.71 (17.44)	83.8 (17.58)	90.89 (16.39)
Spatial processing	29.10 (7.77)	28.03 (6.50)	27.56 (7.09)
Go/no-go	81.36 (30.53)	73.96 (34.6)	78.58 (31.91)
Code substitution-delayed	47.83 (11.90)	51.34 (15.84)	47.38 (14.19)
Matching to sample	27.31 (8.75)	26.20 (11.43)	26.14 (9.89)
Memory search	57.90 (17.04)	54.36 (20.98)	56.64 (19.16)
Simple reaction time 2	138.97 (28.20)	125.71 (39.83)	139.76 (29.20)
ImPACT	($n=29$)	($n=17$)	($n=50$)
Verbal memory composite	78.00 (12.63)	76.53 (13.22)	78.78 (14.68)
Visual memory composite	64.21 (16.01)	65.41 (14.24)	62.40 (14.87)
Visual motor speed composite	33.29 (6.05)	31.06 (8.72)	33.06 (7.49)
Reaction time composite	0.66 (0.11)	0.68 (0.13)	0.68 (0.12)

[a]Modified BESS $n=29$ (mTBI without LOC), $n=20$ (mTBI with LOC), and $n=34$ (trauma control).

ANAM, Automated Neuropsychological Assessment Metrics; BESS, Balance Error Scoring System; BSI-18, 18-item Brief Symptom Inventory; DANA, Defense Automated Neurobehavioral Assessment; GSI, Global Severity Index; ImPACT, Immediate Postconcussion Assessment and Cognitive Testing; LOC, loss of consciousness; mTBI, mild traumatic brain injury; PCL-C, Post-traumatic Stress Disorder (PTSD) Checklist – Civilian; SAC, Standardized Assessment of Concussion; SS, Standard Score (mean = 100, SD = 15); SCAT3, Sport Concussion Assessment Tool Symptom Checklist; SWLS, Satisfaction with Life Scale. ANAM and DANA scores are all throughput scores except for Go/no-go d-prime.

model (symptom model). Finally, we tested the incremental contribution of performance (e.g., neurocognitive, balance) variables to the symptom model (performance model). Two-way interactions between the variables in each multivariate model were tested and found to be nonsignificant.

Demographics model. The demographics model consisted of only one significant predictor: Injury Group ($p=0.003$).

Symptom model. The symptom model added to the demographics model one additional predictor, BSI-18 somatization score (HR = 0.61, $p<0.001$), with the effect of injury group in this model significant at $p<0.001$ (mTBI LOC- vs. Control HR = 2.68, $p<0.001$; mTBI LOC+ vs. Control HR = 1.08, $p=0.812$).

Performance model. The best parsimonious model produced from all available variables added DANA reaction time to the symptom model. In particular, the effects of each predictor in this model were as follows: injury group ($p<0.001$; mTBI LOC- vs. Control HR = 2.53, $p<0.001$; mTBI LOC+ vs. Control HR = 1.08, $p=0.830$); BSI-18 somatization (HR = 0.63, $p=0.001$); DANA reaction time (HR = 1.70, $p<0.001$). A similarly strong model could also be derived substituting DANA reaction time with ANAM simple reaction time 2 (Akaike information criterion [AIC] for performance model with DANA vs.

Table 3. Cox Regression Results Predicting Symptom Duration from Single Predictors ($N = 162$)

	HR	*95% CI*	p		*HR*	*95% CI*	p
Demographics and injury				*Performance measures*			
Female gender	0.84	(.55, 1.28)	0.422	mBESS incomplete	0.53	(0.34, 0.82)	**0.004**
Age (years)	0.98	(.96, 1.01)	0.262	mBESS total score	0.86	(0.66, 1.12)	0.273
Race (black v. white)	0.77	(.49, 1.21)	0.252	SAC total score	1.05	(0.84, 1.32)	0.648
WTAR standard score	1.01	(.81, 1.26)	0.924	ANAM ($n = 83$)			
House SES (Hollingshead)	1.01	(.99, 1.03)	0.654	Composite	1.49	(1.08, 2.06)	0.016
Health insurance			0.497	SRT	1.48	(1.02, 2.16)	0.039
None (v. Govt.)	1.21	(.64, 2.30)	0.554	CDS	1.31	(0.98, 1.76)	0.065
Commercial (v. Govt.)	1.34	(.82, 2.19)	0.237	PRT	1.40	(0.98, 2.01)	0.068
ADHD	1.20	(.55, 2.60)	0.651	MTH	1.11	(0.82, 1.49)	0.514
Migraine history	0.68	(.38, 1.24)	0.209	M2S	1.27	(0.96, 1.68)	0.093
Prior concussion(s)	1.34	(.87, 2.08)	0.185	CSD	1.36	(1.05, 1.75)	0.019
MVT vs. fall	0.56	(.34, .93)	0.024	SR2	1.90	(1.25, 2.88)	**0.003**
Injury Group			**0.003**[a,b,c]	GNG	1.00	(0.75, 1.34)	0.993
mTBI LOC- vs. LOC+	2.56	(1.32, 4.90)	**0.005**	DANA ($n = 141$)			
mTBI LOC- vs. control	1.96	(1.24, 3.10)	**0.004**	SRT	1.78	(1.36, 2.34)	**<0.001**[c]
mTBI LOC+ vs. control	0.77	(0.40, 1.47)	0.427	CDS	1.27	(1.00, 1.60)	0.048
Worker's Compensation	0.96	(0.52, 1.77)	0.896	PRO	1.43	(1.10 1.86)	**0.008**
Loss of consciousness[d]	0.37	(0.19, 0.72)	**0.003**	SP	1.30	(1.04, 1.62)	0.023
Posttraumatic amnesia[d]	0.48	(0.20, 1.12)	0.091	GNG	1.36	(1.04, 1.79)	0.027
Retrograde amnesia[a]	1.53	(0.61, 3.86)	0.367	CDD	1.09	(0.86, 1.38)	0.457
Head CT ordered[a]	0.62	(0.35, 1.10)	0.099	M2S	1.00	(0.80, 1.24)	0.974
Medication after injury				MS	1.16	(0.92, 1.45)	0.217
Opioid	0.50	(0.28, 0.88)	0.016	SR2	1.56	(1.20, 2.03)	**0.001**
Non-opioid	0.77	(0.46, 1.27)	0.305	ImPACT ($n = 100$)			
Self-reported symptoms				Verbal memory	1.37	(0.98, 1.93)	0.067
SCAT3 symptom severity	0.69	(0.52, 0.91)	**0.008**	Visual memory	1.40	(1.04, 1.87)	0.024
BSI-18 somatization	0.68	(0.53, 0.87)	**0.002**[b,c]	Visual motor speed	1.22	(0.90, 1.66)	0.197
BSI-18 depression	0.88	(0.70, 1.10)	0.248	Reaction time	0.90	(0.67, 1.21)	0.484
BSI-18 anxiety	0.82	(0.65, 1.03)	0.084				
BSI-18 global severity	0.76	(0.60, 0.97)	0.024				
SWLS total	1.02	(0.84, 1.25)	0.835				
PCL-C total	0.88	(0.69, 1.11)	0.265				

[a]Predictor in the demographics multivariate model. [b]Predictors in the demographic+symptoms multivariate model. [c]Predictors in the best-fitting demographic+symptoms+performance multivariate model. [d]Recorded for mTBI group only.

Bold indicates $p < .01$.

An alternate model with similar fit was found when swapping DANA SRT with ANAM SR2. WTAR, symptom, and performance measures were standardized to facilitate comparisons of hazard ratios (HR). ADHD, attention-deficit/hyperactivity disorder; ANAM, Automated Neuropsychological Assessment Metrics; BSI-18, 18-item Brief Symptom Inventory; CDD, code substitution-delayed; CDS, code substitution learning; CSD, code substation delayed; DANA, Defense Automated Neurobehavioral Assessment; Govt., government; GNG, go/no-go; ImPACT, Immediate Postconcussion Assessment and Cognitive Testing; LOC, loss of consciousness; M2S, matching to sample; mBESS, Modified Balance Error Scoring System; MS, memory search; mTBI, mild traumatic brain injury; MTH, mathematical processing; MVT, motor vehicle-traffic accident; PCL-C, Post-traumatic Stress Disorder (PTSD) Checklist – Civilian; PRO, procedural reaction time; PRT, procedural reaction time; SAC, Standardized Assessment of Concussion; SCAT3, Sport Concussion Assessment Tool Symptom Checklist; SES, Hollingshead socioeconomic status score; SP, spatial processing; SRT, simple reaction time; SR2, simple reaction time 2; SWLS, Satisfaction with Life Scale. WTAR, Wechsler Test of Adult Reading; ANAM and DANA scores are all throughput scores except for Go/no-go d-prime.

ANAM = 674.52 vs. 678.51, respectively). No ImPACT composite scores added incrementally to prediction of symptom recovery over and above the variables of the symptom model.

Logistic regression models to explore the predictive value of litigation status

The models described were stratified on self-reported involvement in litigation (because of the nonproportional hazards of this variable) which precluded quantification of the predictive value of litigation status. However, a log-rank test confirmed an association between litigation status and hazards of symptom recovery ($p = 0.003$). To evaluate whether litigation status added incremental predictive value beyond the other predictors identified, we computed logistic regression models to predict symptom duration, dichotomized as ≥30 versus <30 days, from the major predictors identified in the multivariate Cox models. Although dichotomizing the outcome variable was expected to reduce statistical power,[61,62] this approach was considered advantageous, because logistic regression introduces less restrictive model assumptions than Cox regression. First, we verified that the three multivariate models identified through Cox regression remained robust in a logistic model (see Table S5) (see online supplementary material at http://www.liebertpub.com). This largely held true, with the major predictive variables identified previously (injury group, BSI-18 somatization score, ANAM reaction time 2, and DANA reaction time) still significant with p's < 0.05 and most <0.01. As is listed in Table S5, litigation status added significant incremental predictive value to each model, with an effect size ranging from odds ratio (OR) = 3.72–3.84 across models (p's = 0.002–0.005).

Classification accuracy of multivariate models

The logistic regression models were also used to provide more interpretable goodness of fit statistics than those available through

Table 4. Predictive Accuracy of Logistic Regression Models (DV: 30+ vs. >30 Days of Symptoms)

	Without litigation				*With litigation*			
	AUC (95% CI)	*% Correct*	*NPV*	*PPV*	*AUC (95% CI)*	*% Correct*	*NPV*	*PPV*
Model 1: Demographics	0.62 (0.53, 0.72)	60.4	71.1	55.3	0.70 (0.61, 0.79)	64.0	61.8	70.3
Model 2: + Symptoms	0.70 (0.61, 0.79)	66.2	68.5	63.6	0.75 (0.66, 0.83)	67.6	68.4	66.7
Model 3: + Performance	0.76 (0.68, 0.84)	71.9	72.7	71.0	0.80 (0.73, 0.88)	74.1	74.4	73.8

AUC, under the receiver operating characteristic curve; CI, confidence interval; DV, dependent variable; NPV, negative predictive value; PPV, positive predictive value.

Cox regression. Consistent with prediction, the area under the receiver operating characteristic curve (AUC) increased with the complexity of the model. The AUCs of the logistic models using predictors variables of the demographic, symptom, and performance models were 0.62, 0.70, and 0.76, respectively (see Table 4). Adding litigation status to each model raised the AUC values modestly, with the maximum AUC of 0.80 achieved in a model including the variables of the most complex (performance + litigation) model. The percentage of cases correctly classified by this model was 74.1% (vs. the base rate of having ≥30 days of symptoms of 47.3%).

Discussion

This study served as a preliminary step in a comprehensive research program designed to improve outcome prediction for mTBI patients within a neurobiopsychosocial framework. Consistent with our hypotheses, several variables independently predicted symptom duration in this prospective sample of ED patients with mTBI and non-mTBI traumatic injuries. In particular, the most robust acute predictors of more prolonged symptom duration were occurrence of LOC (relevant only for the mTBI group), higher acute somatic symptom burden (both groups), and slower acute reaction time as assessed by a CNT (both groups). These findings support the theory that a multifaceted set of factors, including injury characteristics and neuropsychological assessment variables, contribute to patients' course and duration of symptom recovery after mTBI, lending credence to these types of variables as robust predictors of symptom outcome even when symptom outcome is assessed through a different modality (i.e., interview assessment of symptom duration, vs. more common questionnaire assessment of current symptoms).[11] That predictors relevant to trauma control groups (e.g., acute somatic symptoms, reaction time) were also predictive of symptom recovery in this group implies that these are relevant factors for recovery from trauma in general rather than mTBI specifically. Also as hypothesized, more complex models that included clinical assessment metrics outperformed those using only more readily available demographic, history, and injury variables. Model accuracy improved incrementally with the number and variety of predictor variables included, with AUC values ranging from poor (0.62) to good (0.80) depending on the information included in the model. This corresponded to 60.4–74.1% accuracy, with the best performing model incorporating injury (LOC), symptom (somatization ratings), performance (reaction time), and contextual (litigation status) variables. These findings underscore the complex, multidimensional nature of mTBI/injury recovery and the need to collect a diverse set of variables to adequately predict outcomes.

That somatic symptom burden (i.e., BSI-18 ''somatization'' ratings) was associated with clinical recovery is consistent with prior work on hospital (''civilian'') and athlete mTBI populations.[29,63,64] It is worth noting, however, that although somatization ratings outperformed mTBI symptom scores in this sample, prediction was quite similar between the two (HR = 0.68 vs. 0.69). Further, there was much shared variance between somatization and mTBI symptom variables ($R^2 = 0.49$), both of which were assessed within 72 h of injury. It is possible that the two measures both tap into a similar construct related to physical complaints associated with an injury. On the other hand, the item content between the two questionnaires is largely non-overlapping, and there is compelling evidence from other work that *pre-injury* somatization plays a role in enhancing patients' experience of post-injury symptoms and, consequently, prolongs clinical recovery from injury.[29,63] Therefore, it is unclear to what degree acute somatization and mTBI symptoms measured in this study indexed premorbid tendencies to experience and report such symptoms versus effects of injury. Taken together, however, these findings warrant additional study into the construct of somatization and the mechanisms by which pre- and post-injury levels of somatization and other individual difference dimensions influence injury presentation and recovery.

In comparison to parallel work from the sport-related concussion arm of the current study, neurocognitive variables carried greater predictive power within this ED-recruited sample than within a high school and college athlete sample that underwent highly similar assessment procedures.[29] This could reflect population-specific factors that moderate the role of acute neurocognitive impairment in symptom recovery. Alternatively, this could reflect sampling/measurement issues. For example, given the relative heterogeneity of ED versus athlete subjects,[65–67] it could be the case that the greater variance on neurocognitive performance measures (or higher base rates of neurocognitive impairment) in the ED sample yielded increased statistical power to detect effects of these measures. Similarly, LOC (and other acute injury characteristics), although predictive in this sample, has not consistently predicted clinical outcomes in other studies. It is possible that this reflects variability in power resulting from differences in sample sizes, sample prevalence of LOC, and/or the validity of estimates of this and other acute injury characteristics. For example, occurrences of LOC are likely underestimated when coded from the medical record, and overestimated when defined (as in this study) by patient self-report, because of patients' misattribution of periods of amnesia to unconsciousness. Given variable findings with regard to LOC,[40,47,68–71] it will be important in future studies to consider issues such as mode of assessment and statistical power, and to make efforts to tease apart the role of such issues in reported findings.

In addition to illustrating the predictive power that can be achieved using a multidimensional clinical assessment battery, the findings may have direct relevance to the clinical management of traumatic injuries. Particularly intriguing was the reported association between use of opioid medications after injury and more

prolonged symptom recovery. This effect appeared to partially explain the longer recovery of the trauma control group, who more commonly used opioid medications after injury. That opioid use was unrelated to initial symptom severity (e.g., 72 h SCAT3 symptom severity score for users versus nonusers $p = 0.263$) and that no association was found between recovery and use of other medications, implies that this variable was not simply flagging a group of patients with more pronounced acute symptoms; rather, there could be a detrimental effect of opioids on recovery. This is a viable hypothesis: opioid use has been associated with increased chronic pain in clinical[72,73] and pre-clinical[74–76] studies of injury recovery. Opioid use is associated with paradoxical hyperalgesia,[77,78] and there is substantial evidence that opioids trigger inflammatory responses in the brain and in the periphery.[79,80] Opioid drugs not only bind to opioid receptors, but also to certain pattern recognition receptors that are found on cells of the innate immune system.[81,82] For example, morphine binds to the same myeloid differentiation factor 2/Toll-like 4 receptor (MD-2/TLR4) complex as endotoxin, and engages the NLRP3 inflammasome.[83,84] Importantly, inhibition of the inflammasome during morphine treatment reduces the persistence of neuropathic pain.[83,84] Future studies will be needed to examine the mechanistic effects of opioid analgesics on recovery from mTBI.

It is important to consider what constitutes an adequate model. Although relevant metrics of model fit vary by the type of statistical analyses performed, researchers should routinely report an omnibus measure of model accuracy to facilitate comparisons across studies. Silverberg and colleagues, for example, suggested that a model predicting a binary outcome should have an AUC >0.80 or classification accuracy greater than the base rate of the outcome.[11] In this study, in which the outcome was dichotomized at roughly the median symptom duration for the purpose of obtaining model fit statistics, only our most complex model achieved the recommended AUC of 0.80, whereas all models exceeded the latter criterion. Although such guidelines about model fit are useful heuristics, it is important to remember that fit is a matter of degree and tends to diminish with cross validation using a new sample. Therefore, although we achieved ''good'' overall model accuracy in this study, even our best model is likely insufficient to survive cross-validation or to generalize to more diverse TBI patients. Therefore, identifying additional predictor variables that reliably boost model accuracy is an ongoing goal. Useful variables might include estimates of pre-injury psychological functioning previously demonstrated to be predictive of mTBI outcome, broad personality traits that have consistently predicted diverse health outcomes outside the field of mTBI,[85–88] and biometric (e.g., blood, neuroimaging) measures currently under study.[45,69,70,89]

It is interesting that the same sets of neuropsychological measures (somatic symptoms, reaction time) were broadly associated with reported symptom duration across both mTBI and trauma control groups, suggesting a nonspecific role of these factors in subjective recovery from traumatic injury in general.[‡] An implication of this is that researchers could leverage the power of larger and more diverse samples of trauma patients to identify general risk and resilience factors associated broadly with recovery from injury. On the other hand, that presence versus absence of LOC (relevant only to the mTBI group in this sample) was specifically related to recovery highlights that both generic and population-specific risk factors are important to consider. That generic risk factors exist is not surprising in light of work finding some common psychological resilience factors relevant to numerous other health outcomes.[85–88] Recruiting maximally diverse samples of trauma patients into TBI outcome studies could also provide an evidence base by which to inform the operational definition of mTBI and to partition patients into subgroups in a bottom-up fashion. Importantly, this research strategy would align with the objectives of the TBI Endpoints Development Project,[90] a large federally funded initiative aimed at improving the diagnosis and treatment of TBI.

This study had several limitations that warrant mention. First, the relatively tight definition of mTBI (i.e., restriction to uncomplicated mTBI) and other inclusion/exclusion criteria (e.g., age 18–45, without certain comorbid factors) could limit the applicability of findings to this subset of the injury population. Second, because model fit statistics were derived from the sample used for initial model development, these are considered upper bounds for what can be achieved with these predictors, and model fit would likely diminish in a new sample. Further, because patient follow-up terminated at 45 days post-injury, a large minority of the sample (35.2%) was right censored on the outcome variable, contributing to loss of variance on the outcome and an inability to specifically examine cases of unusually prolonged recovery. Further, loss to follow-up could have contributed to biased estimates in regression models, although the attrition rate in this sample (9.9%) was better than commonly recommended targets for longitudinal research and the typical rates achieved in similar studies.[11,91] Finally, our sample was relatively small given the number of analyses performed. Similarly, we were likely inadequately powered to detect some small effects that could be clinically meaningful (e.g., group interactions, effects of psychiatric history on outcomes) and did not collect information on a host of variables that could prove predictive of recovery and outcome. Consequently, these findings are considered preliminary and in need of cross-validation in larger and more diverse trauma samples.

A purported advantage of this study was that it included a continuous patient-reported outcome measure (symptom duration) that is theoretically more related to injury recovery than the questionnaire-based symptom checklist scores that are more commonly used in this literature. That we saw some consistency between general findings (e.g., a role of somatic symptoms, neurocognitive performance measures) in this versus previous studies speaks to the robustness of these predictors and suggests that a variety of symptom-based outcome measures may be valid. However, more systematic study of how findings are affected by different operational definitions of recovery is warranted before drawing firm conclusions about the degree to which these various outcome measures are interchangeable and whether alternative assessment approaches would improve outcome measurement. Formally quantifying the effects of various assessment approaches would elevate the scientific basis for patient-reported outcome measures and could improve perceptions of ''subjective'' symptom scales.

Conclusion

In sum, this study found that several distinct injury, psychological, and neurocognitive variables independently predicted self-

[‡]Although interactions between injury group and other predictors were not significant, there was a trend interaction between group and mechanism of injury. Cause of injury was also closely associated with litigation status, with subjects involved in motor vehicle-traffic crashes more likely to endorse pursuit of litigation. Exploration of the associations between these variables and recovery outcome suggested that the effects of mechanism of injury and litigation status were stronger in trauma controls than mTBI groups. Replication of this group interaction within a larger sample is needed to test the robustness and nature of this effect.

reported symptom duration after mTBI and non-mTBI traumatic injuries. Although prediction accuracy was reasonable, the expected diminishment of model fit in new samples suggests that it will be necessary to improve on this model before implementing it on a large scale. Ideally, future work would both identify new independent predictors of recovery and investigate and refine the measurement of existing predictor and outcome variables. With continued large-scale, collaborative research to build on existing findings, the field will continue to move toward a comprehensive neurobiopsychosocial model of recovery that better informs treatment development for mTBI.

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Author Disclosure Statement

No competing financial interests exist.

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