Identification and Validation of Prognostic Criteria for Persistence of Mild Traumatic Brain Injury–Related Impairment in the Pediatric Patient

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Objectives: This study aimed to develop and validate prognostic criteria to identify children at risk for persistence of mild traumatic brain injury (MTBI) impairment.

Methods: A prospective cohort study was conducted among 11- to 17-year-old emergency department (ED) patients admitted for MTBI. The Immediate Postconcussion Assessment and Cognitive Testing neurocognitive test was administered during hospitalization and at routine clinic follow-up (ImPACT©). Logistic regression and receiver operating characteristic (ROC) analyses were used to develop prognostic criteria for MTBI-related impairment in 1 group and validate the criteria in a second group. Mild traumatic brain injury–related impairment was defined as any impairment (symptom score >8 or <25th percentile on at least 1 of 4 neurocognitive composite domains) or severe impairment (symptom score >12 or <25th percentile on at least 2 of 4 neurocognitive composite domains) present on follow-up.

Results: The derivation and validation cohorts were 42 and 21 patients (median age, 14 years; 71.4% male). Using the mean of the validation cohort patients' 4 neurocognitive deficit composite percentiles at baseline, a cut point of less than 39 percentile had high sensitivity (0.89) and specificity (0.80) and an area under the ROC curve of 0.85 in predicting the presence of any impairment at follow-up; it discriminated equally well in the validation cohort. A cut point of less than 27 percentile had good sensitivity (0.67) and specificity (0.67) and area under the ROC curve of 0.67 in predicting the presence of severe impairment in the derivation cohort at follow-up; it discriminated equally well in the validation cohort.

Conclusions: This is the first study demonstrating prognostic criteria that may greatly help physicians identify patients who would benefit from structured follow-up care after MTBI.

Key Words: concussion, mild traumatic brain injury, prognostic, cohort study

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Head injuries are a frequent source of morbidity and the most common source of mortality in the pediatric patient population with trauma.[1] An estimated 500,000 emergency department (ED) visits, 95,000 hospital admissions, and 7000 deaths occur among children in the United States due to head injuries each year.[1] Although most head injuries (75%) are classified as mild (ie, "concussion"),[2] their consequences can be serious. A National Institutes of Health consensus panel recognized that the sheer volume of mild traumatic brain injury (MTBI), as well as the potential for enduring neurologic sequelae, makes MTBI a significant public health problem.[3]

For most patients, the symptoms of MTBI wane in a matter of days to weeks. However, premature return to exertional activities or contact sports may be detrimental and prolong recovery.[4–6] Athletes returning to play before adequate recovery are more susceptible to a second concussion. This second concussion is typically associated with greater symptoms and longer duration of symptoms. Also, younger athletes are slower to recover (ie, should refrain from exertional activities longer) than college athletes.[7] In the most dramatic cases, children returning to contact sports in a still-vulnerable state have been reported to experience "second impact syndrome," with associated profound neurobehavioral sequelae including death.[8,9] In 15% or so of children with MTBI, symptoms may persist for weeks or months leading to difficulty performing schoolwork, school absence, and difficulty returning to a normal active life.[10] The burden of MTBI extends to parents and caregivers, who must alter their routines to care for their children with MTBI during the phases of recovery when the child's capacities are diminished and their activities must be limited. Currently, the recommendations for return to exertional activities for children with MTBI (whether evaluated in an ED or inpatient setting) are variable and frequently lacking. Thus, many children are potentially at risk for adverse neurobehavioral sequelae due to a lack of knowledge and resources in the health care community.

Several critical barriers have prevented advancements in how this large group of patients with MTBI is managed in the ED. There is lack of consensus in the health care community regarding the definition of MTBI, a lack of consensus over the ideal assessment modality for the injured child, a lack of consensus over recommendations for return to activity after a brain injury, a lack of resources in the community for follow-up care, and a lack of appreciation for the potential consequences of these injuries by patients, their families, and even some health care providers. Further still, there is tremendous variability in the time to full recovery exhibited by children with brain injury, which makes generic treatment guidelines naive.[11] Identification of potential predictive criteria for persistent MTBI symptoms would allow clinicians to better triage follow-up care (eg, who would benefit from structured care, who can be seen on an "as-needed" basis, who should be admitted to the hospital) at the ED level.

METHODS

Participants

The study was conducted at The Children's Hospital of Philadelphia, an academic tertiary care center. During a 2-year period, 11- to 17-year-old patients who presented to the ED with MTBI and hospitalized were prospectively enrolled. All patients were evaluated using neurocognitive testing at the time of their initial hospitalization and again at the time of their routine clinic

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follow-up (typically 2 weeks after discharge). Mild traumatic brain injury was determined with a Glasgow Coma Scale (GCS) score of 14 to 15 on arrival in the ED, a mechanism of injury consistent with a head injury and symptoms of a head injury (eg, loss of consciousness, confusion, amnesia). Patients were eligible for inclusion regardless of abnormalities on head computed tomographic scans. Patients with a penetrating mechanism of injury or discharged home from the ED were excluded. The patient sample was split randomly, assigning two thirds of the patients to a cohort from which to derive predictive criteria and assigning one third of the patients to a cohort in which to validate the predictive criteria. This larger assignment to the derivation cohort was used to enhance the precision the estimates. We excluded 53 patients who were evaluated in the hospital during the study period and did not return for follow-up examination or testing. Patients who returned for follow-up did not differ significantly from patients who did not return in sex, mechanism of injury, median age, Injury Severity Score (ISS), MTBI symptoms, or neurocognitive deficits. This study was approved by the institutional review board of The Children's Hospital of Philadelphia.

Bedside Risk Scoring System

Patients were evaluated for the presence and severity of symptoms and neurocognitive deficits associated with MTBI with the Immediate Postconcussion Assessment and Cognitive Testing (ImPACT), a validated, interactive software application that was administered at the bedside with a laptop computer.[7,12] Evaluation included information on concussive history, injury characteristics, symptom assessment, and neurocognitive testing. The symptom assessment component involves a series of 22 symptom-related questions (eg, headache, vomiting, nausea) with responses measured on a 7-point Likert scale (0 = no symptom, 6 = severe symptom). The neurocognitive testing component involves multiple task-based exercises:

- Word discrimination: evaluates attentional processes/verbal recognition memory via a word discrimination paradigm.
- Design memory: evaluates attentional processes and visual recognition memory through recall of designs.
- Xs and Os: measures visual working memory and processing speed through a visual memory paradigm with a distracter task.
- Symbol matching: evaluates visual processing speed, learning, and memory.
- Color matching: measures choice reaction time and impulse control/response inhibition.
- Three letters: measures working memory and visual-motor response speed.

The patient's performance on these neurocognitive components is summarized in 4 primary composite domains: verbal memory, visual memory, reaction time, and visual motor processing speed. The severity of neurocognitive deficits are reported in age- and sex-specific percentiles for the 4 primary composite domains. The results are available immediately on completion of the evaluation and presented in percentiles relative to age- and sex-specific norms.

Each patient was evaluated using ImPACT during his/her inpatient hospital stay and at the time of his/her scheduled clinic follow-up after discharge.

Definition of Outcome

We defined 2 outcomes of interest—any impairment and severe impairment—based on previously established criteria for neurocognitive impairment with false-positive rates from 4% to 8%.[13] The presence of any impairment at either baseline or 2-week follow-up was defined as having a total symptom score (ie, sum of the 22 Likert-based ImPACT symptoms items) higher than 8 (possible range, 0–132; normal, 0–8) or scoring less than the 25th percentile on at least 1 of the 4 neurocognitive deficit composite domains at baseline. Presence of severe impairment at baseline or during the 2-week follow-up was defined as having a total symptom score higher than 12 or scoring less than the 25th percentile on at least 2 of the 4 neurocognitive deficit composite domains at baseline. Two weeks was used as it was the standard follow-up interval for patients with trauma after hospital discharge.

Criteria Derivation

Stata version 11 (StataCorp, College Station, Tex) was used for analysis. Logistic regression was applied to the derivation cohort to separately regress the 2 outcome variables of interest against variables characterizing the patients at baseline including symptoms and neurocognitive deficits, clinical characteristics, and demographics. Forward stepwise regression was used to retain the variables statistically associated with either outcome at a level of $P < 0.10$. Each of the 2 final models was used to generate a variable in both the derivation and the validation cohorts that represented the probability each patient would have the outcome on a 2-week follow-up test. The 2 sets of predicted values were then analyzed using receiver operating characteristic (ROC) curves as described in the next paragraphs.

In addition to analyzing the 2 sets of predicted values from logistic regression in ROC analyses, ROC analyses were also applied directly to 3 variables that were derived from the ImPACT test at baseline: patients' total symptom score at baseline and the mean and median of patients' percentile scores on the 4 composite neurocognitive domains at baseline. In this way, each of these variables was evaluated on its own to determine whether it served as a criterion that predicted patients' outcome status at 2 weeks.

Each of the total of 5 potentially predictive criteria was used in its own ROC analysis. First, we generated an ROC curve in the derivation cohort, with the patient's score on the given criterion at baseline used as the classification variable and the presence of either any impairment at follow-up or severe impairment at follow-up used as the reference variable (ie, outcome). The results of that analysis were examined to identify the percentile cut point that served to maximize the true-positive rate (ie, sensitivity) and true-negative rate (ie, specificity) in the derivation cohort. A second ROC analysis was then performed in the derivation cohort with a dichotomous variable as the predictor variable, with patients classified as having a criterion score at or beyond cut point coded 1 and other patients coded 0. The area under the curve (AUC) for this analysis and 95% confidence interval (CI) were used as measures of the discriminatory power of this test.

Patients in the validation cohort were then classified according to whether their percentiles fell above or below the same cut point, and the discriminatory power of this dichotomous classification variable was evaluated in the validation cohort by conducting an ROC analysis and determining the AUC and positive and negative predictive values. The performance of this predictive criterion in the validation cohort relative to the derivation cohort was evaluated by comparing the 2 AUCs with a nonparametric test of equality.[14]

Last, the diagt command was used estimate how the predictive criterion would perform, in positive and negative predictive values, if it were applied to a patient population where the prevalence of lasting impairment could be expected to be lower

than observed in the present study (eg, patients who are evaluated in the ED and discharged).

RESULTS

Characteristics of Participants

A total of 63 patients with MTBI were evaluated using ImPACT at the time of hospitalization and again at the 2-week follow-up. Characteristics of the patients, divided into a derivation cohort of 42 patients and a validation cohort of 21 patients, are shown in Table 1. The characteristics of the derivation and validation cohorts did not differ substantively across categories and levels of any variables.

Presence of Impairment

In the derivation cohort, 100.0% of patients had any impairment and 78.6% of patients had severe impairment at initial testing. At follow-up, 88.1% of patients had any impairment and 71.4% of patients had severe impairment. In the validation cohort at the initial testing, 95.2% of patients had any impairment and 52.4% of patients had severe impairment; during follow-up, 95.2% of patients had any impairment and 81.0% of patients had severe impairment. This overall increase in the prevalence of severe impairment in the validation cohort between baseline and follow-up occurred because of the 10 of the 11 patients with severe impairment at baseline still had severe impairment on follow-up, and of the 10 patients who did not have severe impairment at baseline, 7 did have severe impairment at follow-up. Importantly, 2 of the 11 patients with severe impairment at baseline were symptom free at baseline.

Prognostic Testing Results

Of the 5 types of variables evaluated for their ability to predict the presence of any impairment or severe impairment at follow-up (2 composed of predicted values generated by logistic regression and 3 composed of performance results derived directly from the ImPACT test at baseline), 1 variable emerged as having the ability to discriminate patients according to outcome status effectively: the mean of patients' 4 neurocognitive domain scores at baseline.

The ROC analysis in the derivation cohort that predicted the presence of any impairment at follow-up from the mean of patients' neurocognitive domain scores at baseline produced an AUC of 0.88 (Fig. 1). The percentile cut point that served to best discriminate between derivation cohort patients who did versus those who did not have any impairment at the 2-week follow-up was a mean domain score percentile of 38 or lower, where lower percentiles are associated with a higher probability of abnormality at follow-up. This cut point had an AUC of 0.85 and served to correctly classify the follow-up status of 88.1% of the 42 derivation cohort patients. When applied to the validation cohort, this same cut point correctly classified the outcome status of 76.2% of the 21 validation cohort patients (AUC = 0.88) and had a positive predictive value of 1.00 and negative predictive value of 0.17 (Table 2).

The ROC analysis in the derivation cohort that predicted the presence of severe impairment at follow-up from the mean of patients' neurocognitive domain scores at baseline produced an AUC of 0.70 (Fig. 1). The cut point that served to best discriminate between derivation cohort patients who did versus those who did not have severe impairment at the 2-week follow-up was a mean percentile of 26 or lower. This cut point had an AUC of 0.67 and served to correctly classify the follow-up status of 66.7% of the 42 derivation cohort patients. When applied to the validation cohort, this same cut point correctly classified

TABLE 1. Characteristics of Patients in Derivation and Validation Cohorts

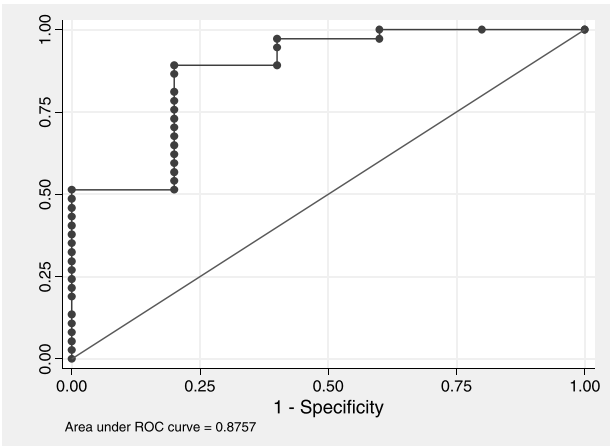
Characteristic	Derivation (n = 42)	Validation (n = 21)	P*
Baseline			
Age, n (%), y			
11–13	9 (21.4)	7 (33.3)	0.27
14–15	23 (54.8)	7 (33.3)	
16–17	10 (23.8)	3 (33.3)	
Age, median (25%–75%)	14 (13–15)	14 (12–16)	0.92
Male, n (%)	30 (71.4)	6 (71.4)	1.00
Injury mechanism, n (%)			
Motor vehicle crash	7 (16.7)	8 (38.1)	0.30
Fall	12 (28.6)	5 (23.8)	
Sports	5 (11.9)	2 (9.5)	
Other	18 (42.9)	6 (28.6)	
ISS ≥ 17, n (%)	7 (16.7)	2 (9.5)	0.71
Loss of consciousness, n (%)	29 (69.1)	17 (81.0)	0.32
Length of hospital stay >7 d, n (%)	2 (4.8)	2 (9.5)	0.47
Length of ICU stay ≥1 d, n (%)	17 (40.5)	8 (38.1)	0.86
Symptoms, median (25%–75%)			
Symptom score	26 (15–41)	18 (10–32)	0.16
Neurocognitive deficits, median (25%–75%)			
Verbal domain score	26 (5–46)	14 (1–52)	0.32
Visual domain score	8 (4–31)	24 (2–60)	0.20
Motor domain score	12 (4–32)	18 (4–41)	0.45
Reaction domain score	5 (1–16)	18 (3–44)	0.07
Median of 4 domain scores (25%–75%)	12 (5–28)	16 (6–41)	0.35
Mean of 4 domain scores (SD)	15 (8–34)	27 (13–40)	0.24
Any impairment present, n (%)†	42 (100.0)	20 (95.2)	0.33
Severe impairment present, n (%)‡	33 (78.6)	11 (52.4)	0.03
Follow-up			
Symptoms, median (25%–75%)			
Symptom score	3 (1–12)	7 (1–22)	0.36
Neurocognitive deficits, median (25%–75%)			
Verbal domain score	37 (13–70)	24 (7–48)	0.25
Visual domain score	39 (14–62)	34 (12–55)	0.55
Motor domain score	23 (9–51)	21 (5–51)	0.84
Reaction domain score	12 (4–37)	34 (13–50)	0.19
Any impairment present, n (%)	37 (88.1)	20 (95.2)	0.65
Severe impairment present, n (%)	30 (71.4)	17 (81.0)	0.54

*Computed with χ^2 and Fisher exact tests for categorical data and nonparametric tests for median data.

†Symptom score greater than 8 on the sum of Likert-based items or less than the 25th percentile on at least 1 of 4 composite domains.

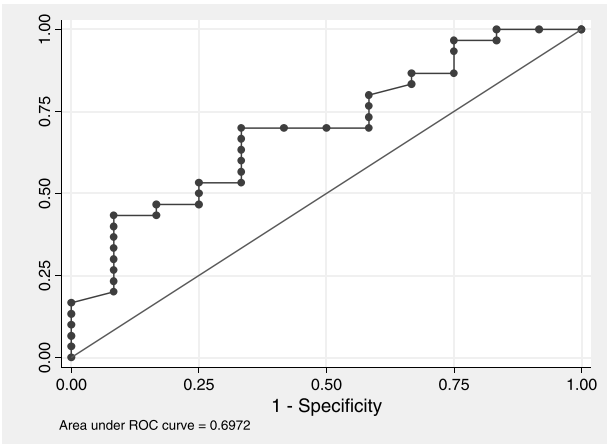
‡Symptom score greater than 12 on the sum of Likert-based items or less than the 25th percentile on at least 2 of 4 composite domains.

A



Any impairment two weeks after discharge

B



Severe impairment two weeks after discharge

FIGURE 1. Receiver operating characteristic curves for derivation cohort predicting presence of any impairment (A) or severe impairment (B) 2 weeks after hospital discharge from patients' mean ImPACT neurocognitive deficit score at baseline.

the outcome status of 61.9% of the 21 validation cohort patients (AUC = 0.67) and had a positive predictive value of 0.91 and negative predictive value of 0.30.

We estimated that if applied in a population with lower prevalence of any (33%) and severe impairment (20%) (eg, ED-based population), the same criteria would yield positive and negative predictive values of 0.69 and 0.94 for any impairment and 0.33 and 0.89 for severe impairment. As such, this test holds great potential to help ED physicians determine optimal follow-up for those children evaluated and subsequently discharged from the ED.

A notable negative finding was that patients' symptoms scores at baseline, measured as the sum of the 22 Likert-based symptom items administered through ImPACT, did not predict whether impairment would be present 2 weeks after hospital discharge. When patients' baseline symptom scores were used as the predictive criterion in ROC analyses, the AUC for predicting any impairment at follow-up was 0.52 (95% CI, 0.28–0.75) and the AUC for predicting severe impairment at follow-up was 0.59 (95% CI, 0.39–0.79). That is, baseline symptom scores performed no better than a coin toss. Although the predictive variables generated through logistic regression analysis did not have discriminatory ability overall, 2 variables were associated with the outcomes in the analyses in the derivation cohort: injury severity score and mechanism of injury. Specifically, having a baseline injury severity score of 17 or higher was associated with a lower odds of having any impairment at follow-up (odds ratio = 0.07, $P = 0.073$) after adjusting for patients' mean score on the 4 neurocognitive domains. Having an injury from a motor vehicle crash was associated with a lower odds of having severe impairment at follow-up (odds ratio = 0.17, $P = 0.056$) after adjusting for patients' mean score on the 4 neurocognitive domains.

DISCUSSION

We have identified prognostic criteria that hold promise for use in stratifying pediatric MTBI inpatients based on risk of persistence of any impairment or severe impairment after hospital discharge. Such criteria would provide a much-needed tool for managing a condition that is highly prevalent but has a disease course that is also highly variable. Although tested in an MTBI population that was hospitalized, we estimated that these

TABLE 2. Sensitivity, Specificity, and AUC Values for Derivation and Validation Cohorts for Predicting Presence of Neurocognitive Deficits and Symptoms 2 Weeks After Hospital Discharge

	n	Cut Point	SE	SP	PPV	NPV	TP	FN	TN	FP	Correctly Classified, %	AUC (95% CI)	*P**
Any condition present[†]													
Derivation	42	≤38	0.89	0.80	0.97	0.50	33/37	4/37	4/5	1/5	88.1	0.85 (0.64–1.00)	0.74
Validation	21	≤38	0.75	1.00	1.00	0.17	15/20	5/20	1/1	0/1	76.2	0.88 (0.60–1.00)	
Severe condition present[‡]													
Derivation	42	≤26	0.67	0.67	0.83	0.44	20/30	10/30	8/12	4/12	66.7	0.67 (0.51–0.83)	0.99
Validation	21	≤26	0.59	0.75	0.91	0.30	10/17	7/17	3/4	1/4	61.9	0.67 (0.40–0.94)	

Cut points are set along the mean of patients' scores on 4 composite domains.

**P* was calculated from nonparametric test of equality of area under 2 curves.

[†]Symptom score greater than 8 on the sum of Likert-based items or less than the 25th percentile on at least 1 of 4 composite domains.

[‡]Symptom score greater than 12 on the sum of Likert-based items or less than the 25th percentile on at least 2 of 4 composite domains.

FN indicates diseased patients but with negative test result; FP, no disease but positive test result; NPV, negative predictive value; PPV, positive predictive value; SE, sensitivity; SP, specificity; TN, no disease and correct negative test; TP, diseased patients with correct positive test.

criteria would also perform well in an acute ED-based child and adolescent population. The test used is Web based and can be administered at the bedside with a standard computer and mouse. Distinguishing those patients evaluated in the ED that are likely to have persistent symptoms is of paramount importance in determining the optimal care (ie, who would benefit from structured medical follow-up) and allocation of limited resources.

It was notable to have instances of patients classified as symptom free at baseline who demonstrated impairment 2 weeks after discharge. This highlights the variable clinical course of MTBI and challenges to standardizing treatment algorithms. Persistent symptoms, whether present at initial testing or not, warrant appropriate follow-up with a health care provider knowledgeable of the management of MTBI. Formal neurocognitive testing, which can be performed in the ED setting, will aid the clinician in identifying these challenging patients in need of structured medical follow-up.

The population tested in this study sustained MTBI through a variety of mechanisms typically encountered in an ED setting (eg, sports, motor vehicle crash), yet the goals are the same as with sports-related injuries: When is it safe and/or appropriate to return to exertional activities and contact sports? Our study suggests that the criteria outlined would also be suitable for the majority of patients with MTBI evaluated in the ED who sustain injuries by sports as well as non–sports-related mechanisms.

We found that the straightforward approach of using just a single indicator of the patient's condition at baseline—mean score on the 4 neurocognitive composite domains derived at the bedside using ImPACT—had a high prognostic value. This testing was practical and easy to use at the bedside. Moreover, we found no prognostic value in using patients' symptom scores alone, and yet at present, typical recommendations regarding the need for structured follow-up are based on patient symptoms (eg, nausea, dizziness). Although the use of logistic regression did not serve to derive scoring criteria that had prognostic value, this may have been due to working with a derivation cohort composed of relatively few patients.

However, logistic regression did identify that higher ISS was associated with lower odds of any impairment at follow-up after controlling for average baseline neurocognitive deficit score. This may stem from that fact that the decision to admit some patients may be based on the severity or complexity of their anatomic injury regardless of their symptoms associated with MTBI. Our recommendations for next steps are reinforced by this issue and are in response to limitations of the present study. Our study was based on only those ED patients who required hospitalization for their injuries and was based on a relatively small patient sample. A study in a larger sample with both ED-treated only and admitted patients is needed. It will be important to evaluate whether the 2 criteria we identified have portability and the ability to identify cut points that minimize false negatives in both population types. Also, it will be important to evaluate whether the use of logistic regression in that larger, heterogeneous population can serve to identify even better predictive criteria, and whether the prognosis for more severely injured children can be predicted in the longer term. Other research we have underway involves enrolling patients with MTBI in the ED and administering ImPACT in the ED to establish its feasibility in this setting, but we believe the study presented here is the first of its kind in aiming to predict the prognoses of patients with MTBI. Given these promising first results, the high incidence of MTBI, and the great benefit that would come from a tool to inform patient management decisions, additional studies are warranted.

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