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# Identification of Factors in Moderate-Severe TBI Related to a Functional Decline in Cognition Decades After Injury

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## Abstract

**Objective:** To investigate whether a functional decline in cognitive activities decades after moderate-to-severe traumatic brain injury (m-sTBI) might relate to injury features and/or lifetime health factors, some of which may emerge as consequences of the injury.

**Design:** Secondary analysis of the TBI Model Systems National Database, a prospective, multi-center, longitudinal study of patients with m-sTBI.

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**Setting:** TBI Model Systems Centers

**Participants:** Included were 732 participants rated on the cognitive subscale of the Functional Independence Measure (FIM Cognitive), a metric for everyday cognitive skills, across three time points out to 20 years (visits at 2-, 10-, and 20-year follow ups).

**Interventions:** Not applicable

**Main Outcome Measure(s):** FIM Cognitive Scale. Injury characteristics such as timing and features pertaining to severity and health-related factors (e.g., alcohol use, socioeconomic status) were examined to discriminate stable from declining participants on the FIM Cognitive Scale using logistic regression.

**Results:** At 20 years post-injury, there was a low base rate of FIM Cognitive decline (11%, n=78), with the majority being stable or having meaningful improvement (89%, n=654). Older age at injury, longer duration of post-traumatic amnesia, and presence of repetitive seizures were significant predictors of FIM Cognitive decline in the final model (AUC=0.75), while multiple health-related factors that can represent independent co-morbidities or possible consequences of injury were not.

**Conclusion(s):** The strongest contributors to reported functional decline in cognitive activities later-in-life were related to acute characteristics of m-sTBI and experiencing post-traumatic seizures. Future studies are needed integrating functional with performance-based cognitive assessments to affirm conclusions and identify the timeline and trajectory of cognitive decline.

## Keywords

Traumatic Brain Injury; Cognition; Dementia; Amnesia

Across the globe, there is interest in understanding what places individuals sustaining a moderate-to-severe traumatic brain injury (m-sTBI) at risk for future functional decline. While most improve or remain stable following recovery from a m-sTBI, a small proportion experience cognitive decline later-in-life that impacts their everyday functioning.[1] There is general consensus that m-sTBI is associated with an increased risk for developing a neurodegenerative disorder;[2,3] however, it remains unclear how or why. Post-mortem studies have revealed an accumulation of neuropathologic features (e.g., Aβ plaques, tau tangles) after m-sTBI, which are also hallmark features of neurodegenerative conditions.[4,5] Although post-mortem studies were limited to small samples, neuropathologic features were only found in up to a third of individuals with long survival durations after m-sTBI (between 1 and 40+ years). Given such, it is posited that TBI-related neurobehavioral decline is complex and occurs in a proportion of susceptible individuals for reasons that require further investigation.[6]

Injury characteristics, including severity and age at injury, appear to impact likelihood of developing cognitive decline later-in-life.[7] Notably, m-sTBI was associated with an increased risk for dementia at least one year after m-sTBI across age groups (55–85+) in a retrospective analysis of a health database, relative to orthopedic controls, whereas an increased risk for those with mild injuries was seen only for individuals at least age 65 at time of injury.[8] Although the risk of dementia for individuals with m-sTBI has been the

focus of much research, most studies relied on diagnostic codes within health databases for identifying the injury as well as dementia. This approach yields limited knowledge as to the factors that may underlie the association, as many injury characteristics cannot be studied using this method. Also, it is important to look beyond risk for dementia diagnosis and examine whether and how m-sTBI can be associated with changes in functional abilities and everyday cognitive functioning during aging. Clinically, a functional decline in cognition embodies a significant change in the ability to execute complex everyday activities that require cognitive processes. Because functional decline is one of the essential features in diagnosing dementia syndromes, indices of everyday cognitive skills such as the cognitive subscale of the Functional Independence Measure (FIM), can provide meaningful insight into dementia risk. As such, investigating whether m-sTBI might be associated with a decline on functional indices of cognition over decades, and identifying the factors related, can build upon earlier findings to better understand how m-sTBI relates to later-in-life cognitive decline.

Other health factors not directly related to neurotrauma may also contribute to cognitive and functional decline during aging among individuals with m-sTBI. For example, vascular conditions such as hypertension and myocardial infarction—which may represent independent comorbidities or downstream complications of TBI — were shown to increase the risk of dementia in population-based studies.[9,10] m-sTBI is also associated with later developing poor health behaviors, including heavy alcohol consumption and drug use,[11] which are known risk factors for cognitive changes and functional decline. Additionally, mounting evidence suggests that social determinants of health (SDOH), including various adverse economic and environmental conditions, may contribute to onset of dementia,[12–14] and although some may pre-date a TBI, others may emerge following (and consequent to) serious TBI (e.g., behavioral problems leading to changes in marital status). Thus, the factors that increase the risk of (or protect against) cognitive or functional decline long after m-sTBI remain unclear and may comprise both injury-related and other health-related contributors. The current study aims to elucidate whether acute injury factors and/or lifetime health-related comorbidities are associated with a functional decline in cognitive skills up to 20 years following m-sTBI. To accomplish this, we leveraged prospectively collected longitudinal data since 1987 from the Traumatic Brain Injury Model Systems (TBIMS) National Database (https://www.tbindsc.org).[15] The TBIMS National Database is the largest dataset in the world on long-term functional outcomes in m-sTBI, and can yield insights into the factors that may contribute to a functional decline in cognitive skills among individuals with m-sTBI.

## METHODS

The TBIMS program is a multicenter project involving 16 centers in the US that follows participants with m-sTBI requiring hospitalization and inpatient rehabilitation. Data from TBIMS is de-identified within the meaning of the Health Insurance Portability and Accountability Act (HIPAA) and its implementing regulations. All procedures were approved by local institutional review boards and conform to the Helsinki Declaration. TBIMS centers enroll participants who are at least 16 years old at time of injury and have a TBI involving either loss of consciousness more than 30 minutes, PTA more than 24 hours,

Glasgow Coma Scale (GCS) score of 12 or less at hospital admission, or an intracranial abnormality on neuroimaging and later receive acute inpatient rehabilitation. The TBIMS program collects injury, medical, sociodemographic, and functional outcomes data from individuals with m-sTBI or their significant other at the time of inpatient rehabilitation and then 1, 2, and every 5 years thereafter, primarily through phone follow-up visits. All TBIMS participants who had follow-up data on the primary outcome (functional measure of cognition) at 2-, 10-, and 20-year visits were included for this study.

The primary outcome was the FIM,[16] which is a widely used structured interview that includes 5 items rating functional cognition in the domains of memory, problem-solving, comprehension, expression, and social interaction.[17] Each item is rated between 1 and 7, with 1 reflecting total dependence and 7 reflecting full independence. A total FIM Cognitive score was computed by summing ratings for all 5 domains. Changes in the FIM Cognitive score between the 2, 10, and 20 year post-injury time intervals were calculated for each participant. A Reliable Change Index was used according to established procedures [17,18] and data [19] to classify individuals as having stable, meaningful improvement, significant variability, or a meaningful decline on the FIM Cognitive score over time (see Table 1). Only participants classified as being stable or having a significant decline were selected for subsequent analyses.

## TBI Characteristics

Age at injury along with several characteristics regarding injury severity are recorded in TBIMS. The GCS at the time of hospital admission is one of the most common instruments used to grade TBI severity. Since it is not uncommon for patients to be intubated early after a m-sTBI, which prohibits a person from completing one of the GCS requirements (i.e., verbal responses) to obtain a total score, a full GCS score was estimated for those who were intubated (without sedation). Based on a validated formula,[20] a verbal score was derived from the other two score requirements [−0.3756 + (Motor Score x 0.5713) + (Eye Score x 0.4233)]. Duration of PTA was also used to characterize injury severity, and is the number of days from injury to when PTA resolves, characterized by showing adequate orientation for two consecutive days (i.e., Galveston Orientation and Amnesia Test score >75, Orientation Log score >24, or full orientation recorded in medical record). For participants still having PTA at the time of discharge from rehabilitation, one day was added to the length of stay for acute hospitalization and rehabilitation to reflect duration of PTA as is consistent with prior work.[21,22] Time to follow commands is another severity characteristic and is the number days from injury until a participant is able to follow commands. Last, major neurologic insults often accompany the initial TBI, and we computed a composite score to represent severity of secondary injury(s) that would be associated with the TBI. The number of the following intracranial complications that were documented during the first 7 days of injury were totaled for a maximum score of 9: brain compression, brain hemorrhage (intracranial, punctate, subarachnoid, and/or intraventricular), intracranial hypertension, fragments within brain, and craniotomy as well as craniectomy procedures (when recorded as separate procedures).

### Health and Lifestyle Factors

Ten lifetime health-related factors were examined alongside TBI severity features. The selection of variables was guided by well-documented associations of cognitive changes with repetitive post-traumatic seizures, chronic health conditions, health behaviors, and SDOH,[11,23–25] and all were derived from information recorded at the 20-year visit. We defined the presence of repetitive post-traumatic seizures as experiencing at least 3 reported seizures in the past year during the 20-year visit. Chronic health conditions were characterized as a history of hypertension, diabetes, stroke, and/or heart attack, as well as the presence of obesity (measured with body mass index). Poorer health behaviors included heavy alcohol use (average number of alcoholic drinks during consumption, number of days in past month 5+ drinks were consumed) and drug use (use of illicit substances). Because SDOH can evolve over a lifetime, and a downturn in some economic and social environments can emerge with m-sTBI, we focused on 3 domains related to education access, economic stability, and social context from the Healthy People 2030 framework to account for important lifelong effects.[26] These were level of educational attainment (high school graduate or less vs college education), household income (<$25,000 vs ≥$25,000), minority racial/ethnic background (Black vs other racial identities, Hispanic vs non-Hispanic), and marital status (married versus single, divorced, separated, and widowed).

### Statistical Analysis

Univariate logistic regression models were used to inform variable selection for entry into the multivariable analysis to determine predictors of a functional decline in cognitive activities (versus remaining stable). Factors with $p < 0.25$ were retained for the multivariable logistic regression model. Multicollinearity among the candidate predictors were examined using a correlation coefficient cutoff of > 0.70, and no variables required removal. Predictors remained in the multivariable model if $p < 0.15$. This was to include variables associated with a functional decline in cognition, but to eliminate ones that reduced the model fit, in which an acceptable fit was defined as $p > 0.05$ and a good fit as $p > 0.40$ using the Hosmer-Lemeshow statistic.[27] The DeLong test was used to compare the areas under the curve (AUC) from Receiver operating characteristic (ROC) analyses using the predicted scores from the multivariable models, serially adding different factors until all were included. This method was used to determine whether the addition of predictors significantly improved classification accuracy for a functional decline in cognition vs stable. Because only a subset of participants had data for a self-report depression symptom scale (Patient Health Questionnaire-9), and depression can relate to a reported functional decline in cognitive activities,[28] a sensitivity analysis was then performed to examine if significant predictors from the multivariable model remained important after accounting for depression severity measured at the 20-year visit. Analyses were conducted using IBM© SPSS Statistics V22 (IBM Corp, SPSS Statistics V22, Armonk, NY, 2013) and MedCalc Windows Version 20.112 (MedCalc Software, Ostend, Belgium).

## RESULTS

A total of 732 participants had complete FIM Cognitive scale data at 2, 10, and 20 years after injury (see Figure 1). Over this timeframe, 67% of participants (N=487) showed

stable scores using the Reliable Change Index, while 14% had meaningful improvement (N=106) and 8% demonstrated significant variability (N=61). There were 78 participants (11%) who had a meaningful decline on the FIM Cognitive score, and among these, most (N=52) showed the decline between the 10- and 20-year follow-up. Only 1 subject showed a significant decline at both the 10- and 20-year time intervals. Characteristics for the groups being *stable* and having a *decline* on FIM Cognitive scores can be seen in Table 2.

Four TBI characteristics and four long-term health-related effects were significant predictors of having a functional decline in cognition in *univariate* analyses and retained for modelling. These included Black race, age at injury, PTA duration, time to follow commands, presence of repetitive post-traumatic seizures, average number of alcoholic drinks during consumption, low household income, and high educational attainment. However, only older age at injury, more days of PTA, and presence of repetitive post-traumatic seizures were significant predictors in the *multivariable logistic regression model* (See Figure 2), while more alcohol use (average number of drinks), low household income, and a high level of educational attainment were non-significant predictors. Time to follow commands (OR=1.00) and Black race (OR=0.72) were removed as predictors from the model due to the degree of non-significance (p's >0.15). The Hosmer-Lemeshow statistic indicated that the final full multivariable model was an acceptable fit to the data (p=0.09). ROC results showed that the full model discriminated participants having a functional decline in cognition from those being stable decades later with an AUC of 0.75 (95% CI=0.71–0.79). However, DeLong test results revealed that a combination of two TBI characteristics, age at injury and duration of PTA, significantly improved prediction (AUC=0.68, 95% CI=0.63–0.72; p=0.006) compared to age at injury alone (AUC=0.58, 95% CI=0.54–0.63). The addition of repetitive post-traumatic seizures, very low household income, and high level of educational attainment (separately or in combination) did not significantly improve prediction beyond those two factors (p >0.05), indicating that age at injury and duration of PTA were the two essential predictors for having a functional decline in cognition. A sensitivity analysis with the subset of participants having data on a depression symptom scale (Stable n=362; Decline n=42) showed that depression symptom severity (OR=1.14; p<0.001) was an additional significant predictor as expected and the model had a good fit to the data (Hosmer-Lemeshow p=0.80). However, age at injury and repetitive post-traumatic seizures became non-significant predictors when combined in the model (p >0.05), while only duration of PTA remained a significant predictor (OR=1.01; p=0.03).

## DISCUSSION

Only 11% of m-sTBI survivors showed a functional decline in cognitive skills over 20 years, similar to prior work reporting outcomes 10–15 years after m-s TBI [21,29] as well as incidence rates for dementia up to 30 years post-injury.[1,30] To our knowledge, this study is the first to evaluate which features (injury and health-related factors) are most associated with a functional decline in cognition decades later following a m-sTBI. Only older age at injury, more days of PTA, and presence of repetitive post-traumatic seizures significantly predicted a decline, despite examining multiple health-related factors that have been associated with a functional decline out to 5 years after m-sTBI and recognized as independent risk factors for dementia.[11,31] While both groups were in the early to

mid-30s at time of injury, it is important to note that aging is the largest risk factor for a functional decline in cognitive skills, and thus, it is possible that the odds for experiencing decline might relate to the influence of being older across the study's intervals (i.e., aging effect) rather than being older at timing of injury. When depression symptom severity was accounted for, duration of PTA was the only significant factor retained, suggesting length of PTA appears to be an essential feature of m-sTBI relating to future risk for functional decline. To illustrate how the risk changes with varying durations of PTA, we calculated the odds for 30 (1.14), 60 (1.24), and 90 (1.47) days of PTA, which corresponds to a 14%, 24%, and 47% increase in odds for having a functional decline in cognition. However, the links with injury age and seizures should not be disregarded, as there were limited cases with available depression data (Declined N = 78 vs 42) that may have weakened the associations, as opposed to depression symptoms attenuating them entirely. To build upon earlier work, the current findings inform that injury-related factors are linked to a functional decline in cognitive skills decades after a m-sTBI, whereas other possible health-related contributors do not seem to have a significant role.

Because post-traumatic seizures did not significantly add to the classification accuracy for a functional decline in cognitive skills, such a finding points to age at injury and duration of PTA having the most associations with a functional decline in cognitive skills. It does not suggest that post-traumatic seizures is unimportant, however. It is not surprising that the report of post-traumatic seizures was a predictor for functional decline in cognitive activities, as it has long been established that seizures are risk factors for functional decline.[32] There are a number of reasons for this, including the propensity of post-traumatic seizures to lead to more seizures that may be refractory to medication,[33] potentially causing further neuronal degeneration and more cognitive difficulties with age. However, those with cognitive decline are also at increased risk for seizures.[34] In our current study, the findings may be bidirectional and/or due to reverse causation, as the precise timing of seizures or the specific reasons individuals were having post-traumatic seizures are unknown. It is possible that those with more cognitive impairment may have more difficulties with antiepileptic medication adherence, increasing the risk of experiencing post-traumatic seizures decades after injury. In addition, while post-traumatic seizures were more frequent in those with functional decline (~14%) than those without (~4%), it was a low frequency phenomenon and the confidence interval of the significant finding was wide. Future research will need to elucidate whether post-traumatic seizures, or reverse causality instead truly underlies the association.

## STUDY LIMITATIONS

This study has some important methodological limitations that warrant consideration. First, the duration of PTA is unknown for approximately 11% of individuals in this sample (Stable N=48; Decline N=16), as their PTA did not resolve before discharge. Knowing the duration of PTA in these more extreme cases conceivably could have altered the significance of findings, though this is less likely in our analyses (logistic regression vs multiple linear regression). Another limitation is that only persons seen in one of 16 acute inpatient rehabilitation centers enroll in TBIMS. While attrition is a common limitation of all longitudinal studies, it is possible that individuals who drop out of the TBIMS

study may differ from those who remain in for decades. Prior work comparing TBIMS participants with nationwide data for individuals in the US receiving inpatient rehabilitation after TBI demonstrated there were minimal differences in representativeness of the TBIMS cohort,[35] but nonetheless, a limitation is the possibility of selection bias (i.e., those not able to access rehabilitation, survival) that could limit generalizability of findings. Along these lines, although Hispanic individuals were overrepresented relative to national data for persons receiving inpatient rehabilitation, the available samples in the current study were predominantly White; thus, further studies in more diverse populations are needed.

## CONCLUSIONS

In summary, over a 20-year period, only 11% of individuals who received inpatient rehabilitation for m-sTBI experienced a functional decline in cognition. Altogether, this study informs that characteristics reflective of injury severity and acute recovery course, more so than health comorbidities downstream of injury, were most strongly associated with a functional decline in cognitive skills over time after m-sTBI. However, the directionality and implications of the associations with age at injury and seizures is unknown. Future research will need to investigate these factors further, and would ideally incorporate both standardized neuropsychological assessments with indices of functional cognition. By collectively examining performance on formal neuropsychological tests that precisely measure various skills in conjunction with the FIM, investigations could maximize sensitivity of cognitive assessments. As a result, the scientific field would be positioned to begin identifying what effects m-sTBI characteristics (e.g., PTA duration, etc.) might have on the timing and rate of decline in specific cognitive abilities and subtle cognitive impairment that may eventually lead to a significant loss of everyday function.[7]

## Abbreviations

| | |
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| **AUC** | Area under curve |
| **CI** | Confidence interval |
| **FIM** | Functional Independence Measure |
| **GCS** | Glasgow Coma Scale |
| **m-sTBI** | Moderate-to-severe traumatic brain injury |
| **OR** | Odds ratio |
| **PTA** | Posttraumatic amnesia |
| **ROC** | Receiver operating characteristic |
| **SDOH** | Social determinants of health |
| **TBI** | Traumatic brain injury |
| **TBIMS** | Traumatic Brain Injury Model Systems |

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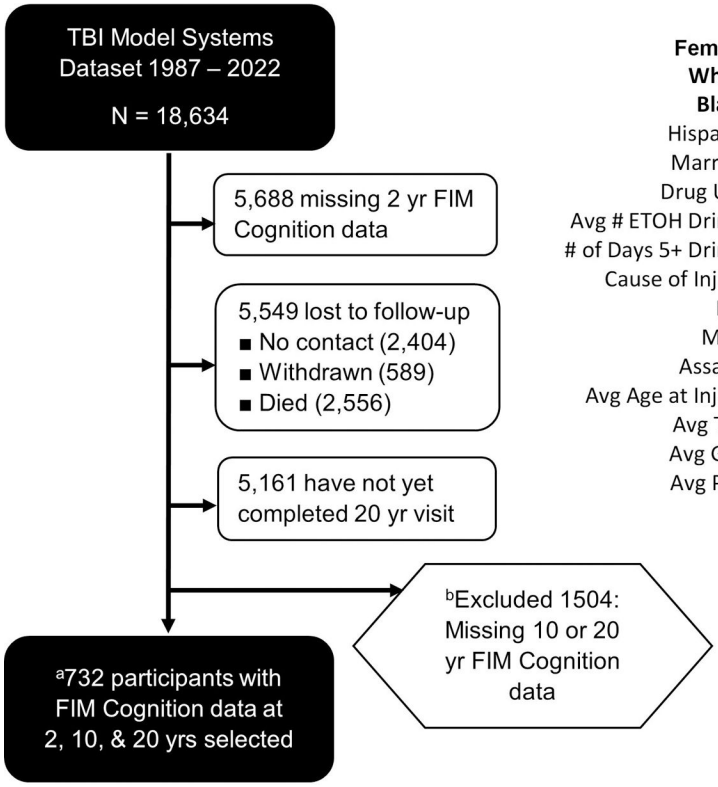


| | [a]Selected | vs [b]Excluded | vs [c]US TBI |
|---|---|---|---|
| **Female** | 28% | 24% | 35% |
| **White** | 69% | 54% | 78% |
| **Black** | 23% | 31% | 9% |
| Hispanic | 5% | 10% | 7% |
| Married | 35% | 32% | 40% |
| Drug Use | 16% | 12% | |
| Avg # ETOH Drinks | 1.35 | 1.37 | |
| # of Days 5+ Drinks | 0.97 | 0.91 | |
| Cause of Injury | | | |
| Fall | 10% | 13% | |
| MVA | 50% | 48% | |
| Assault | 14% | 10% | |
| Avg Age at Injury | 31.33 | 33.19 | |
| Avg TFC | 8.70 | 8.97 | |
| Avg GCS | 8.93 | 9.10 | |
| Avg PTA | 33.86 | 36.20 | |

Bold variables have difference of > 5%.

*Minimal differences between study cohort and the excluded TBI Model Systems participants followed for 20 yrs. Study cohort has fewer females but more representative of persons from a minority background than US adults admitted for rehabilitation for TBI.

**Figure 1.**

Flowchart of Study Cohort Selection

Note. Avg = average. Yr = year(s). TBI = traumatic brain injury. ETOH = alcohol. MVA = motor vehicle accident. TFC = time to follow commands. GCS = Glasgow Coma Scale score. PTA = duration of post-traumatic amnesia in days

[c]Characteristics of US adults admitted for rehabilitation for TBI derived from study of the Uniform Data System for Medical Rehabilitation and the American Medical Rehabilitation Providers Association dataset [35]

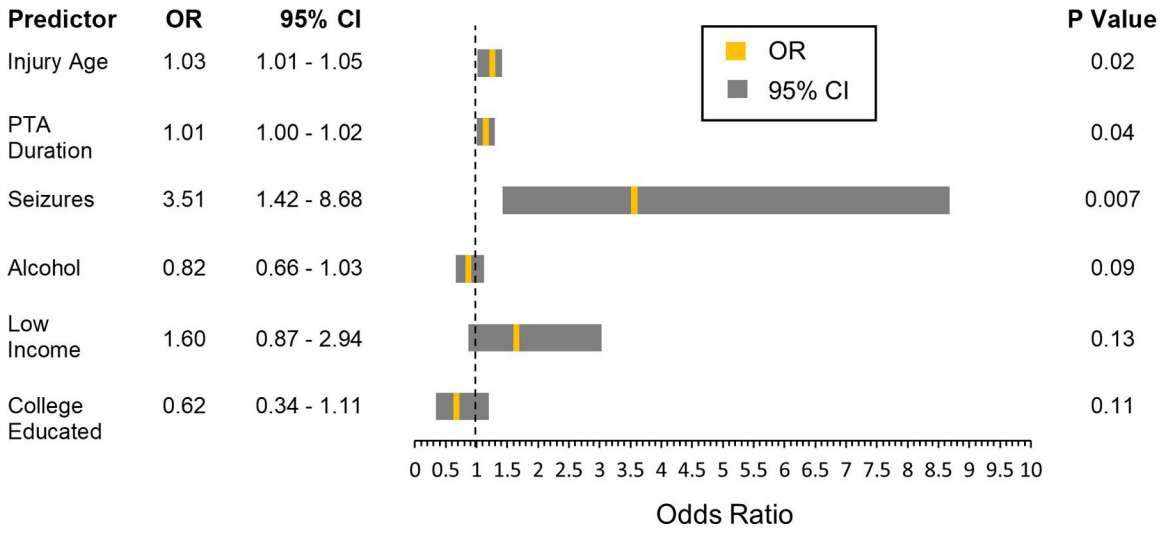


**Figure 2.**
Model Results for Predicting a Functional Decline in Cognitive Skills

**Table 1.**

Reliable Change Index Equation and Definitions for Course Classification

| | | | | |
|---|---|---|---|---|
| Equation | 1.96 X SD √2(1 – *r* for FIM Cognitive scale) | *SD* = 5.63 | *r* = 0.95 | *RCI* = 3.63 |

| **Course Classifications*** | |
|---|---|
| *Stable* | No change ± 4 points on FIM Cognition scores across time |
| *Meaningful Decline* | A decrease of 4 or more points at 10 or 20 years |
| *Meaningful Improvement* | An improvement of 4 or more points at 10 or 20 years |
| *Significant Variability* | At least + 4 points at 10 and − 4 points at 20 years (or vice versa) |

Note. *SD* = standard deviation for overall sample at 2 years post-injury. *r* = test-retest reliability coefficient derived from published work.[23] *RCI* = reliable change index. FIM = Functional Independence Measure.

* RCI was rounded to 4 given FIM Cognition score changes are integers only.

**Table 2.**

Characteristics of the Groups Being Stable and Having a Decline

| Characteristic | No. of Subjects (%) | |
|---|---|---|
| | Stable (n = 487) | Decline (n = 78) |
| Sex, Female | 145 (30) | 24 (31) |
| Race | | |
| Black | 99 (20) | 17 (22) |
| Asian | 15 (3) | 3 (4) |
| White | 352 (72) | 52 (67) |
| Other | 21 (5) | 6 (7) |
| Hispanic Ethnicity | 23 (5) | 5 (7) |
| Education – Beyond High School | 316 (65) | 37 (47) |
| Marital Status – Married | 189 (39) | 25 (32) |
| Household Income < $25,000 | 137 (28) | 34 (44) |
| Mechanism of Injury | | |
| Fall | 47 (10) | 9 (12) |
| Motor Vehicle Accident | 298 (61) | 44 (56) |
| Assault | 41 (8) | 7 (9) |
| Other | 100 (21) | 18 (23) |
| Age at Injury, M (SD) | 30.43 (12.01) | 35.24 (15.06) |
| GCS at Hospital Admission, M (SD) | 9.12 (4.21) | 9.06 (4.16) |
| PTA Duration, days, M (SD) | 29.34 (27.62) | 42.61 (33.70) |
| TFC, days, M (SD) | 7.15 (12.57) | 13.00 (19.46) |
| # of Intracranial Conditions[a], M (SD) | 2.23 (1.57) Median = 2 | 2.63 (1.47) Median = 3 |
| Repetitive post-traumatic seizures | 19 (4) | 11 (14) |
| Other Health Conditions/Behaviors | | |
| Avg # Alcoholic Drinks, M (SD) | 1.48 (1.88) | 0.70 (1.22) |
| # of days had 5+ Drinks, M (SD) | 0.98 (3.46) Median = 0 | 0.46 (2.51) Median = 0 |
| Drug Use | 81 (17) | 9 (12) |
| Body Mass Index | 28.10 (5.78) | 28.27 (7.46) |
| Lifetime Hypertension | 151 (31) | 36 (46) |
| Lifetime Diabetes | 46 (9) | 7 (9) |
| Lifetime Stroke | 33 (7) | 7 (9) |
| Lifetime Myocardial Infarction | 22 (5) | 4 (5) |

Note. *GCS* = Glasgow Coma Scale score. *PTA* = post-traumatic amnesia. *TFC* = time to follow commands.

[a]Total number of the intracranial conditions recorded in first 7 days of hospitalization, involving brain compression, brain hemorrhage (intracranial, punctate, subarachnoid, and/or intraventricular), intracranial hypertension, fragments within brain, and craniotomy and craniectomy procedures (when recorded as separate procedures).