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Long-Term Survival After Traumatic Brain Injury: A Population-Based Analysis Controlled for Nonhead Trauma

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Abstract

Objective—To examine the contribution of cooccurring nonhead injuries to hazard of death after traumatic brain injury (TBI).

Participants—A random sample of Olmsted County, Minnesota, residents with confirmed TBI from 1987 through 1999 was identified.

Design—Each case was assigned an age- and sex-matched, non-TBI “regular control” from the population. For “special cases” with accompanying nonhead injuries, 2 matched “special controls” with nonhead injuries of similar severity were assigned.

Measures—Vital status was followed from baseline (ie, injury date for cases, comparable dates for controls) through 2008. Cases were compared first with regular controls and second with regular or special controls, depending on case type.

Results—In total, 1257 cases were identified (including 221 special cases). For both cases versus regular controls and cases versus regular or special controls, the hazard ratio was increased from baseline to 6 months (10.82 [2.86–40.89] and 7.13 [3.10–16.39], respectively) and from baseline through study end (2.92 [1.74–4.91] and 1.48 [1.09–2.02], respectively). Among 6-month survivors, the hazard ratio was increased for cases versus regular controls (1.43 [1.06–2.15]) but not for cases versus regular or special controls (1.05 [0.80–1.38]).

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Conclusions—Among 6-month survivors, accounting for nonhead injuries resulted in a nonsignificant effect of TBI on long-term

Keywords

epidemiology; mortality; rehabilitation; risk

Injuries cause an estimated 165 600 (7%) of deaths annually in the United States[1] and impose an economic burden of greater than $400 billion from medical treatment and lost productivity.[2] Of these injury-related deaths, 26% are reportedly caused by traumatic brain injury (TBI).[1] Survival and life expectancy, usually reported as standardized mortality ratios, are significantly decreased for patients with TBI compared with noninjured populations.[3–9] These estimates are obtained by compiling information from national surveys, administrative data from individual clinical practices or prospectively acquired data sets, and death certificates; such approaches have several recognized limitations. Case ascertainment that is limited to hospital or emergency department (ED) discharge diagnosis codes, hospital or other clinical registries, and death certificates provides incomplete estimates because the proportion of TBI events diagnosed and managed in the outpatient setting is substantial and growing.[2,10] This markedly biases the estimates against mild cases, even though mild cases account for an estimated 90% of all TBI events.[11–13]

Accurate estimates of the risk of death associated with TBI require that the sample is population based and representative of the full spectrum of disease (ie, from mild to fatal events).[14] Investigators must have access to data for both sexes, all age groups, all mechanisms of injury, and all encounters (inpatient and outpatient). In addition, population-based samples must be controlled for potential confounders, which is particularly important for injuries involving multiple organ systems that may account for death beyond that attributable to TBI.

For this study, we used the records-linkage resources of the Rochester Epidemiology Project (REP).[15] The REP is a unique resource in the United States that is capable of providing data for population-based studies of disease risk factors, incidence, and outcomes. The REP, which collects healthcare data from residents of Olmsted County, Minnesota, was used to identify the first lifetime event of clinically recognized TBI by searching across all healthcare delivery settings and the full range of disease severity; it also allowed long-term follow-up of individuals for vital status information. Rochester Epidemiology Project resources identified unaffected ageand sex-matched controls from the same population, seen within the same calendar year, and statistically controlled for potential confounding due to accompanying nonhead injuries. The goal of this analysis was to determine whether nonhead trauma contributed to the hazard for death after TBI by comparing survival after TBI with matched controls.

METHODS

This study was approved by the Mayo Clinic and Olmsted Medical Center institutional review boards.

Study setting

Olmsted County, Minnesota (2010 census population, 144 248), provides a rare opportunity to investigate the natural history of TBI.[11–13,16–19] Rochester, the Olmsted County Seat, is home to Mayo Clinic, one of the largest private medical practices in the world. Medical care is provided to nearly all county residents by Mayo Clinic and its 2 hospitals in Rochester or by Olmsted Medical Center, the only other group practice and hospital in Olmsted County.

Since the early 1900s, every Mayo Clinic patient has been assigned a unique identifier. This identifier links each patient to all his or her medical information (eg, medical histories and physical examinations from the clinic, hospital admission and dismissal documents, consultations, diagnostic or surgical procedures, laboratory results, correspondence, death certificates, autopsy reports) and from any setting (eg, clinic, hospital, ED, nursing home). Diagnoses assigned at each visit are coded and entered into continuously updated files.[15] The coding system was developed for clinical, not billing, purposes and uses an 8-digit modification of the Hospital Adaptation of the International Classification of Diseases (1973), which affords high sensitivity and specificity. This system allows identification of the broad range of TBI severity, including less-severe injuries identified in the medical office setting as previously reported.[13,20] The diagnostic index and the medical records-linkage system of the REP include Olmsted Medical Center and the very few private practitioners in the area.

Case identification

As previously described,[12] TBI was defined as a traumatically induced injury that contributed to physiological disruption of brain function. Evidence of physiological disruption included documentation of any of the following: concussion with loss of consciousness, post-traumatic amnesia, neurological signs of brain injury, and/or evidence of intracerebral, subdural, or epidural hematoma, cerebral or hemorrhagic contusion, or brain stem injury; penetrating brain injury; skull fracture; or postconcussive symptoms (dizziness, confusion, blurred vision, double vision, headache, nausea, or vomiting that lasted greater than 30 minutes and that were not attributable to preexisting or comorbid conditions). Individuals who did not seek medical attention specifically for either the event or for sequelae (ie, injuries identified as part of the medical history) were excluded as cases.

We identified all Olmsted County residents in the REP diagnostic index with a potential TBI. All settings were included (eg, hospital inpatient, hospital outpatient, ED, office visit, or nursing home). Confirmed cases were defined as patients with no documentation of a prior TBI, who had their first TBI event occur from January 1, 1985, through December 31, 1999. Date of incident TBI was defined as the baseline date for cases. All incident TBI events were further characterized by mechanism of injury; classification was made according to methods developed by the National Center for Injury Prevention and Control, Division of Injury Disability, Outcomes, and Programs (part of the Centers for Disease Control and Prevention).[21] Incident events were assigned to one of the TBI classification categories detailed in Table 1, using the classification system developed by Malec et al,[19] which emphasizes positive evidence of brain injury, obtained by reviewing clinical information contained within REP provider-linked medical records.

In total, 46 114 unique Olmsted County residents were assigned a TBI-related code. We excluded 323 patients who refused authorization to disclose medical records for research at all REP providers where seen. Because of the labor-intensive effort needed to confirm and characterize each case in the medical record, a 20% random sample originally was identified for manual review; however, budget and time constraints further limited the review to 7175 records (16%), of which 1429 were confirmed as TBI cases. Trained abstractors completed medical-record abstraction, as directed by a board-certified physiatrist (A.W.B) and neuropsycholo-gist (J.F.M).

Selection of controls

The list of potential Olmsted County resident controls that was provided by the REP records-linkage system has been shown to be complete when compared with census data.[15] To investigate how estimates of TBI-associated hazard for death is affected by controlling for severity of accompanying nonhead injuries, we used 2 approaches for selecting controls as described in a previous report of this cohort.[20] For the first approach, each TBI case was matched to an individual of same sex and similar birth year (±1) who was registered by a REP provider as an Olmsted County resident in the year (±1) of the case's TBI. The REP diagnostic index was then used to obtain all diagnosis codes assigned to each potential control by any REP provider. Individuals assigned any code associated with head injury from the date first seen through the date of the cases' TBI were excluded as a potential control for that case and another was selected. This first set of controls is subsequently termed “regular controls.”

The second approach to control selection was intended to reduce potential confounding due to accompanying nonhead injuries. Control selection for this purpose was limited to the subset of “special cases,” that is, individuals who had presented to the ED or hospital at the time of their TBI and were assigned a diagnosis code for that encounter that indicated an accompanying nonhead injury. For each accompanying nonhead injury, we first assigned a diagnosis code-based empiric measure of severity and then applied the Trauma Mortality Prediction Model to assign an overall measure of nonhead-injury severity to each individual.[22] For each special case, we randomly selected 2 controls from the list of all Olmsted County residents who were of same sex and birth year (±2) as the case and who had no diagnosis code associated with head injury within or before the year of the case's event. We also required that these patients were admitted to the ED or hospital in the year of the case's event and that the control patients' injuries contributed to an overall measure of nonhead-injury severity similar to that of the case's accompanying nonhead injuries.[22] These controls are subsequently termed “special controls.” The baseline date for regular controls was the relevant REP registration date. The baseline date for special controls was the date of ED or hospital admission. Because information on ED and hospital admissions needed to identify special cases and their controls was first available electronically in 1987, the entire study was limited to patients with baseline dates after January 1, 1987 (N = 1257) (see Supplemental Digital Content 1, available at http://links.lww.com/JHTR/A67, which outlines the cohort identification procedure).

Outcomes

All cases and both types of controls were followed for vital status from baseline through December 31, 2008, the end of the study period. Vital status was obtained by reviewing medical records, obituary notices, Olmsted County death certificates, and electronic death certificates for all Minnesota residents, obtained from the State of Minnesota Department of Vital Health Statistics.

Statistical analysis

The hazard ratio (HR) for death was analyzed for 3 follow-up periods: (1) from baseline through study end, (2) from baseline to 6 months after TBI, and (3) from 6 months after TBI through study end. The HR for death was analyzed by each TBI classification category (definite, probable, and possible, as listed in Table 1) and all categories combined.

For each follow-up period and TBI classification category, 2 analyses were conducted that considered hazard of death for all cases relative to their assigned controls. In the first analysis, each case (regardless of whether it was a regular or special case) was assigned a regular control. In the second analysis, regular cases were assigned a regular control and special cases were assigned 2 special controls (except for 1 special case for which only 1 special control could be identified).

Cox proportional hazard regression analyses that accounted for case-to-control matching and adjusted for age and sex were performed for the follow-up periods baseline through study end and baseline to 6 months. Analysis of data from 6-month survivors (ie, 6 months through study end) was performed using Cox proportional hazards regression that adjusted only for age and sex; analyses did not account for matching because matching was lost if either a case or a control died within the first 6 months. Assessment of proportional hazards assumption was based on a plot of Schoenfeld residuals versus survival time. A plot showing a random scatter was considered to indicate that this assumption was met.[23,24] Associations were reported as HRs and 95% CIs.

RESULTS

We identified 1257 individuals with a definite, probable, or possible TBI from January 1, 1987, through 12 December, 1999. Case characteristics and mechanism of TBI injury are shown in Table 2. The median age for the entire sample was 21 years (range, 0-102 years) and 56% were men. There were 1477 controls (regular and special). The number of deaths among cases and controls, stratified by TBI classification, is reported in Table 3. The mean (SD) follow-up for all subjects was 10.5 (5.98) years.

Hazard of death for all cases versus regular controls

Table 4 shows HRs for death when comparing all cases only with regular controls. Subjects were stratified by follow-up period and TBI classification category.

Over the full period from baseline to study end, we observed statistically significant HRs overall (all TBI classification categories combined) and for cases with definite TBI (HR = 2.92 and 9.73, respectively). During the first 6 months after injury, the HR for death for cases (all classification categories combined) was markedly increased compared with that for regular controls (HR = 10.82), but interpretation of results for each classification category was limited by small sample sizes or few deaths (or both). For persons surviving at least 6 months after injury, the HR for death for cases remained significantly greater both overall (all TBI classifications categories combined) and for those with possible TBI (HR = 1.43 and 2.10, respectively).

Hazard of death for regular and special cases versus their respective regular and special controls

Table 5 shows HRs for death when comparing all cases and controls. However, for this analysis, each regular case was assigned his or her regular control and each special case was assigned their 2 special controls. Subjects were stratified by follow-up period and TBI classification category.

Over the full period from baseline to study end, we observed statistically significant HRs overall (all TBI classification categories combined) and for cases with definite TBI (HR = 1.48 and 4.29, respectively). During the first 6 months after injury, the HR was significantly increased for cases (all TBI classification categories combined, HR = 7.13) and was dramatically increased for cases with definite TBI (HR 67.42; 95% CI, 4.10– 1107). For persons surviving at=least 6 months after injury, the HRs were not significantly different from that of controls (CIs included the value 1.0) for each TBI classification category and when all classification categories were combined.

Table 6 shows that the HRs for death during all follow-up periods when all TBI classification categories are combined were markedly reduced when using population-based special controls for special cases compared with using regular controls for all cases. However, it is important to note that the associated CIs for each comparison were overlapping.

Appreciating that TBI-associated mortality differs also as a function of age at TBI,[12,25,26] we additionally conducted analyses stratified by age group, which magnified the issue of sample size (see Supplemental Digital Content 2, available at http://links.lww.com/JHTR/A68, which shows the HRs for death for all 1257 cases versus 1257 regular controls by age group and follow-up period, and see Supplemental Digital Content 3, available at http://links.lww.com/JHTR/A69, which shows the HRs for death for all 1257 cases versus 1477 controls [1036 regular cases and their 1036 regular controls plus 221 special cases and their 441 special controls] by age group and follow-up period).

DISCUSSION

These analyses highlight the differences in survival observed during a mean 10.5-year follow-up in a population-based cohort of individuals with TBI when 2 different control populations are used for comparison. When individuals in the cohort with injuries in addition to TBI were similarly matched with individuals who experienced traumatic nonhead injuries of the same severity (special controls), the HRs were substantially reduced compared with that observed when using regular controls when all TBI classification categories are combined, as shown in Table 6. This suggests that non-head injury may be accounting for this difference in hazard of death between control groups and further showed that there is no increased hazard of death for 6-month survivors when compared with the control sample that included special controls.

A previous report of the Olmsted County TBI population stratifying injury severity in a similar manner (although not including the injury category of "possible TBI") used the Kaplan-Meier estimator of survival and reported a risk ratio of death over the entire follow-up period after moderate or severe (definite) injury of 5.29 (95% CI, 4.11–6.71; $P < .001$).[11] For individuals with moderate or severe injury in that cohort who survived more than 6 months, the risk ratio was 1.10 (95% CI, 0.60–1.85; $P = .72$). The relative hazard for death was 1.04 (95% CI, 0.57–1.88; $P = .91$) when comparing in dividuals surviving more than 6 months after moderate or severe injury with those suffering mild injury. The results of the present analysis are consistent with this previous report, showing a large increase in mortality during the entire period after definite injury compared with that in individuals without head injury, as well as no significant difference in survival among those who survived 6 months after injury of any severity.

In a recent analysis, 3-year survival of adults after traumatic injury in the Washington State Trauma Registry was reported as an overall adjusted HR of 1.20 for trauma cases dismissed alive with the maximum head injury Abbreviated Injury Scale score when compared with the general noninjured Washington State population.[25] The substantial difference in HR between this subset from a state trauma registry (HR = 1.20) and the HR for definite injury over the entire study period when considering regular controls (HR = 9.73) and special controls (HR = 4.29) reported here is likely because of the difference in samples (a trauma registry versus a population-based record review sample), injury classification (Abbreviated Injury Scale score versus clinical classification through medical-record review), and the comparison populations (age- and sex-adjusted noninjured adults in Washington State versus population-based controls that included pediatric age groups).

Many investigators have reported mortality for cohorts of adults with TBI who were admitted for hospital-based rehabilitation (generally with moderate or severe injuries), comparing survival with matched individuals who had no history of traumatic injury.[3–7]

Other authors have reported mortality in population-or state-based hospital discharge data sets.[8,9,27] Because these analyses all report standardized mortality ratios, they cannot be directly compared with the results reported here.

This unique report is a population-based record review study of TBI mortality over the full spectrum of injury severity and age. To our knowledge, it is the first time that mortality attributable to TBI has been estimated by selecting matched population-based controls for multiple-injury cases to adjust for nonhead-injury severity. These results suggest that TBI is associated with high levels of mortality during the first 6 months after injury. The lack of significantly increased HRs for any injury classification category among 6-month survivors reinforces the concept that aging with the sequelae of TBI represents a chronic medical condition.[28] This has particularly important implications for older adults who are at high risk for fall-related TBI. Medical and rehabilitation management of impairment related to both head and nonhead injury after TBI in older adults can be expected to increase during the coming decade, along with socioeconomic support, as the percentage of the US population that is older adults grows. In addition, reporting mortality in a population-based sample that includes the spectrum of injury severity shows how the least-severe injuries dominate its epidemiology, as they do when studying TBI incidence[13] and cost.[20] This has implications related to public education and prevention of concussive and other mild brain injuries.

Study limitations

Our study has a number of limitations. The numbers of deaths in some age and injury-severity categories were too few to make meaningful statements regarding hazard of death, which limited the estimation of some HRs or resulted in wider CIs (or both); it also made comparisons with other published mortality rates difficult. Also, differences between the analyses (incorporating only regular controls versus regular and special controls) with respect to statistical significance, that is, whether the 95% CI included the value 1.0, likely reflect the greater number of controls and thus larger sample sizes in analyses that considered regular and special controls. While this analysis did adjust for nonhead injuries that were concomitant to TBI for special cases, other preexisting comorbidities of cases were not considered when selecting controls. This may have affected our results.

The population of Olmsted County in 2000 was 90% white, with age and sex distribution similar to that for Minnesota, the upper mid-west, and the US white population. However, residents of Olmsted County have a higher median income and education level than those from these regions.[15] The underrepresentation of minorities in this population (US population was 75% white in 2000) and the fact that the population's medical care is provided by 2 group practices limits how these findings can be generalized to other communities. Cases were identified by retrospective medical-record analysis and included only those individuals who sought medical attention for injuries; others have reported that up to 42% of nonfatal, self-reported cases of TBI are not medically attended.[29,30] This study compared mortality rates and hazard of death across TBI classification categories, using a novel classification system that differed in some ways from others reported in the literature.[13,14,31] We included possible-injury cases, for which the only medical-record evidence of brain dysfunction was postconcussive symptoms, and the extent to which the number of these cases may have been inflated (by an individual's attribution of symptoms not associated with recent head trauma[32]) cannot be determined. Another potential limitation was that the overall measure of nonhead-injury severity[22] was designed to predict only acute outcome, which may limit the accuracy of our results.

CONCLUSION

We used population-based matched controls that included patients who experienced a traumatic nonhead injury (matched to the severity of a case with TBI and other traumatic injuries) to determine that the hazard of death after TBI in Olmsted County was 1.48 for all TBI injury classification categories combined during the entire follow-up period. Hazard of death was highest within the first 6 months after injury. Among 6-month survivors for any classification category or when all categories are combined, no significant difference in hazard of death was seen compared with controls after adjusting for nonhead-injury severity. Hazard ratios were consistently lower for all follow-up periods and all injury classification categories when the special cases in the sample were compared with special controls; however, the point estimates for HRs need to be interpreted with caution given the fact that 95% CIs overlap for these comparisons. These results raise questions about whether the underlying causes of increased long-term mortality after TBI that were reported elsewhere relate to brain injury specifically, to traumatic nonhead injuries, or to other factors. Prospective, longitudinal, population-based research is needed to better understand these interactions. The preserved life expectancy after TBI among 6-month survivors in this population should be considered when predicting their need for rehabilitation and other medical services because a proportion of this group will age with injury-related impairment and activity limitations that may affect their quality of life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Mayo TBI Severity Classification System[a]

A. Classify as “Definite TBI” (moderate-severe TBI) if 1 or more of the following criteria apply:

1. Death due to this TBI.
2. Loss of consciousness of ≥30 min.
3. Posttraumatic anterograde amnesia of ≥24 h.
4. Worst Glasgow Coma Scale full score <13 in first 24 h (unless invalidated upon review, eg, attributable to intoxication, sedation, systemic shock).
5. One or more of the following present:
    - Intracerebral hematoma.
    - Subdural hematoma.
    - Epidural hematoma.
    - Cerebral contusion.
    - Hemorrhagic contusion.
    - Penetrating TBI (dura penetrated).
    - Subarachnoid hemorrhage.

B. If none of criteria A apply, classify as “Probable TBI” (mild TBI) if 1 or more of the following criteria apply:

1. Loss of consciousness that is momentary or lasts <30 min.
2. Posttraumatic anterograde amnesia that is momentary or lasts <24 h.
3. Depressed, basilar or linear skull fracture (dura intact).

C. If none of criteria A or B apply, classify as “Possible TBI” (symptomatic TBI) if 1 or more of the following symptoms are present:

- Blurred vision.
- Confusion (mental-state changes).
- Dazed.
- Dizziness.
- Focal neurologic symptoms.
- Headache.
- Nausea.

Abbreviation: TBI, traumatic brain injury.

[a] Adapted with permission from Leibson et al.[20]

TABLE 2

Characteristics of patients with TBI

Characteristic	**Age, <16 y (*n* = 446)**	**Age, 16-64 y (*n* = 698)**	**Age, >64 (*n* = 113)**
Male, *n* (%)	286 (64)	371 (54)	41 (36)
TBI classification category, *n* (%)			
Definite (moderate/severe)	20 (5)	58 (8)	27 (24)
Probable (mild)	153 (34)	286 (41)	44 (39)
Possible (symptomatic)	273 (61)	354 (51)	42 (37)
TBI mechanism of injury, *n* (%)			
Fall	146 (33)	123 (18)	83 (73)
Motor-vehicle accident	27 (6)	296 (42)	19 (17)
Hit by object	15 (3)	56 (8)	3 (3)
Assault or gunshot	17 (4)	63 (9)	2 (2)
Sports or recreation	198 (44)	111 (16)	1 (1)
Other	43 (10)	49 (7)	5 (4)

Abbreviation: TBI, traumatic brain injury.

TABLE 3

Proportion of deaths among cases and controls

TBI Classification Category	**Cases, *n* (%)**		**Controls, *n* (%)**		
	Regular	**Special**	**Regular**	**Special**	**Total, *n*(%)**
Possible	32/593 (5)	8/76 (11)	31/669 (5)	17/152 (11)	88/1414 (6)
Probable	37/365 (10)	12/118 (10)	42/483 (9)	30/235 (13)	121/1083 (11)
Definite	38/78 (49)	12/27 (44)	25/105 (24)	13/54 (24)	88/237 (37)
Total	107/1036 (10)	32/221 (14)	98/1257 (8)	60/441 (14)	297/2955 (10)

Abbreviation: TBI, traumatic brain injury.

TABLE 4

Hazard ratio for death for all cases (N = 1257) versus regular controls (N = 1257)

TBI Classification Category	**Hazard Ratio (95% CI)[a]**		
	Baseline to Study End	**Baseline to 6 mo[b]**	**6 mo to Study End**
Possible	1.71 (0.68-4.35)	...	2.10 (1.23-3.58)
Probable	2.11 (0.96-4.67)	3.00 (0.31-28.84)	1.14 (0.73-1.79)
Definite	9.73 (2.72-34.84)	...	1.05 (0.51-2.15)
Total	2.92 (1.74-4.91)	10.82 (2.86-40.89)	1.43 (1.06-1.93)

Abbreviation: TBI, traumatic brain injury.

[a] Baseline was defined as injury date for cases and comparable dates for controls. Study end was December 31, 2008.

[b] Hazard ratios could not be calculated for some groups because of very few or 0 deaths in the group.

TABLE 5

Hazard ratio for death for all cases versus regular and special controls[a]

TBI Classification Category	Hazard Ratio (95% CI)[b]		
	Baseline to Study End	**Baseline to 6 m**	**6 mo to Study End**
Possible	0.85 (0.45-1.60)	0.35 (0.04-3.29)	1.29 (0.81-2.05)
Probable	1.09 (0.68-1.74)	3.23 (0.67-15.54)	0.93 (0.62-1.40)
Definite	4.29 (2.14-8.59)	67.42 (4.10-1107.60)	0.88 (0.45-1.73)
Total	1.48 (1.09-2.02)	7.13 (3.10-16.39)	1.05 (0.80-1.38)

Abbreviation: TBI, traumatic brain injury.

[a] The analysis examined 1036 regular cases and their 1036 regular controls combined with 221 special cases and their 441 specia controls. For 1 special case, only 1 special control was identified.

[b] Baseline was defined as injury date for cases and comparable dates for controls. Study end was December 31, 2008.

TABLE 6

Risk of death calculated using regular versus special controls[a]

	Hazard Ratio (95% CI)	
Follow-Up Period	**Regular Control**	**Special Control**
Baseline to study end	2.92 (1.74-4.91)	1.48 (1.09-2.02)
Baseline to 6 mo	10.82 (2.86-40.89)	7.13 (3.10-16.39)
6 mo to study end	1.43 (1.06-2.15)	1.05 (0.80-1.38)

[a] Analysis combined all traumatic brain injury classification categories.