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Influence of study population definition on the effect of age on outcomes after blunt head trauma

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Abstract

Objectives: The purpose of this study was to assess whether study population definition influences the effect of age on outcomes after blunt head trauma. We hypothesized that examining ‘all comers’ receiving head computerized tomography after blunt head trauma, fewer older individuals would meet Veterans Administration and Department of Defense (VA/DoD) criteria for traumatic brain injury (TBI), and would, therefore, display better outcomes than younger cohorts. However, restricting to participants meeting VA/ DoD criteria for TBI, we hypothesized that older individuals would have worse outcomes.

Methods: Data from a recently completed prospective cohort study were analysed with age dichotomized at 65 years. Logistic regression modelling, controlled for potential confounders including head trauma severity, was estimated to measure the effect of age on functional recovery, post-concussion symptoms (PCS), and depressive symptoms at 1-month post-TBI.

Results: Fewer older than younger individuals met VA/DoD criteria for TBI. Older individuals had better functional, PCS, and depressive outcomes at 1 month. Restricting to those meeting

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Declaration of interest

The authors report no declarations of interest relevant to this manuscript.

VA/DoD criteria for TBI, older individuals continued to have better functional and PCS outcomes but had outcomes comparable to younger on depressive symptoms.

Conclusions: Contrary to our hypothesis, there was a tendency for older adults to have better outcomes than younger, independent of the diagnostic criteria applied.

Keywords

Traumatic brain injury; TBI; blunt head trauma; outcomes research; age differences

Introduction

It has been reported since the 1970s that older age is a risk factor for worse prognosis after severe traumatic brain injury (TBI) (1), a pattern seen in older individuals suffering most any form of trauma (2). The research on whether this pattern extends to mild and moderate TBI is less clear with significant variability in the literature (2–5). While some studies clearly show worse outcomes after new TBI of any severity in older adults, there is growing evidence of a subset of older individuals with outcomes similar to their younger counterparts after TBI occurrence (3). Some have commented that this variability can be explained by important demographic and clinical differences between these two age groups (4,5). Here, we examine another potential cause of the observed variability, namely study population definition.

The occurrence of TBI across the lifespan is best described as trimodal with clustering of peak occurrence in very young children (0–4 years), older adolescents (15–19 years), and older adults (65 years or older), with the highest occurrence of TBI-related hospitalization or death in those 75 years of age (6). The mechanism of injury also shows age variation with fall-related TBI occurrence highest in very young children (0–4 years) and older adults (65 years or older) and motor vehicle-traffic or assault-related TBI occurrence highest in young adults (20–24 years). The most common point of TBI evaluation for an individual of any age (with the possible exception of the paediatric population (7)) is the emergency department (ED). A recent report from the National Hospital Ambulatory Medical Care Survey (NHAMCS) of ED visits noted that 4.8 million ED visits in the USA every year include evaluation for TBI during the visit (8).

What criteria are used in TBI studies is of paramount importance; here, we focus on two important clinical populations: (1) those who meet criteria to receive head computerized tomography (CT) at ED presentation after blunt head trauma and (2) those meeting established clinical criteria for TBI (a subset of #1). This is an important distinction with the former denoting the occurrence of a concerning blow to the head and the latter that this blow is presumed to have resulted in injury to the brain. In a previous paper (9), we described the high risk of adverse outcomes in individuals presenting with blunt head trauma, but not diagnosed clinically with TBI (Head Injury Brain Injury Debatable), highlighting the importance of considering both groups. Since age is a criterion used to determine whether a blunt head trauma patient receives a head CT scan, we hypothesized that fewer older individuals (> 65 years) versus younger individuals receiving head CT would meet Veterans Administration and Department of Defense (VA/DoD) criteria (10) for TBI and, therefore,

when looking at all comers receiving head CT after blunt head trauma (first clinical population), older individuals would have better 1-month outcomes. However, restricting to participants meeting the VA/DoD criteria for TBI and adjusting for head injury severity (second clinical population, a subset of first), we hypothesized that older individuals would have worse outcomes. A secondary objective was to examine differences in demographic and clinical characteristics between younger and older individuals evaluated for TBI in the ED.

Methods

Sampling, screening, and procedure

The present analyses utilized data from the Head Injury Serum Markers for Assessing Response to Trauma study (HeadSMART), a prospective cohort study examining the utility of blood-based biomarkers for diagnosing TBI and for early prediction of TBI outcome. Details of the HeadSMART design have been described (11). Of relevance to this analysis, HeadSMART enrolled participants 18 years of age or older who presented to the EDs of the Johns Hopkins Hospital or Johns Hopkins Bayview Medical Center within 24 h of injury and met American College of Emergency Physician (ACEP) criteria (12) for evaluation with a non-contrast head CT scan in the setting of blunt head trauma (Supplemental Table 1, *please note that older age is a criterion for imaging*). Written informed consent was obtained from all participants and/or legally authorized representatives under the approval and oversight of a Johns Hopkins Institutional Review Board.

Head injury severity was determined using the head Abbreviated Injury Scale (head AIS) (13). The AIS provides a universal injury language that can be used in any body region with injuries rated from '1 – minor' to '6 – maximal'. Due to few participants having severe, critical, and maximal injuries (values of 4, 5, and 6 on the head AIS, respectively), these injury severities were combined in the analyses. As mentioned above, the VA/DoD criteria (10) for diagnosing TBI were utilized. The VA/DoD criteria were chosen over the other widely accepted criteria developed by the Demographics and Clinical Assessment Working Group of the International and Interagency Initiative towards Common Data Elements for Research on Traumatic Brain Injury and Psychological Health (known as the ACRM criteria) (14) because the ACRM criteria are focused on mild TBI only. Individuals meeting ACEP criteria for CT scan, but not VA/DoD criteria for TBI, remained in the study.

Collection of demographic and clinical information occurred at the enrolment visit in the ED based on recommendations provided by the National Institute of Neurological Disorders and Stroke common data elements for TBI (CDE v.2) (15). Head CT images were read by a single board-certified neuroradiologist. The Galveston Orientation and Amnesia Test (GOAT) (16), a measure of attention and orientation developed for use during the subacute stage of recovery from closed head injury, was collected at the baseline visit.

Assessment of outcomes

Outcome data were collected 1 month after enrolment via telephone interview or in-person assessment. Return to daily life activities, such as working, community activities, and social

activities (functional recovery), was ascertained using the Extended Glasgow Outcome Scale (GOSE) (17), which characterizes recovery on a scale of 1 (dead) to 8 (upper good recovery). Incomplete functional recovery was defined as GOSE <8. By *ICD-10* criteria, participants were deemed to have post-concussion symptoms (PCS) if they reported at least mild/moderate/severe problems in two or more of the following symptom domains reported on the Rivermead Post-Concussion Questionnaire (18): (1) headaches, dizziness, general malaise, excessive fatigue, or noise intolerance; (2) irritability, emotional lability depression, or anxiety; (3) subjective complaints of concentration or memory difficulty; (4) insomnia; (5) reduced tolerance to alcohol; (6) preoccupation with these symptoms and fear of permanent brain damage. The Patient Health Questionnaire 9 (PHQ9) (19) was used to define depressive symptoms using a score of ≥ 5 (at least mild depressive symptoms). For depressive symptoms, the analysis was run a second time using the PHQ9 criteria for depression in TBI originally articulated by Fann et al. (20). These criteria define depression in TBI as the presence of five or more depressive symptoms for at least several days over the last 2 weeks (score of ≥ 1 on the PHQ9) with at least one symptom being a cardinal symptom (anhedonia or depressed mood).

Analysis

These analyses were carried out using STATA(SE) version 13.0 (StataCorp LP, College Station, TX, USA). Participants were dichotomized as <65 (younger) or ≥ 65 (older) based on age at enrolment. Age 65 years was chosen as it is used in the ACEP criteria for head CT after blunt head trauma and it is the age traditionally used in aging literature. Demographic and injury descriptors between the two groups were compared on descriptive variables applying the Fisher's exact test (pro-portions) and Kruskal-Wallis test (continuous variables) to assess for statistical significance. Demographic and clinical information were compared between those who did and did not follow-up for each age group. Logistic regression models were estimated to evaluate determinants of 1-month out-comes. First, an unadjusted model of the association between age (dichotomized as <65 years and ≥ 65 years) and TBI outcome was constructed for each of the three dichotomized outcomes. Next, multivariable models adjusted for confounders of at least one of the outcomes were constructed. Last, a model adjusting for these same confounders, as well as head AIS score, was constructed. To determine how criteria for defining study population influences estimates of the effect of age on TBI recovery, we investigated the association between age and TBI outcome separately for all blunt head trauma participants (first clinical population) and for participants meeting VA/DoD criteria for TBI only (second clinical population, a subset of first). All TBI severities were included. A significance level of $p = 0.05$ was used.

Results

Between April 2014 and May 2016, 4452 patients evaluated in the ED for TBI were screened for study eligibility, 1374 were eligible for enrolment, and 500 were enrolled (Figure 1). Of those enrolled, 78% (391/500) were <65 years old and 22% (109/500) were ≥ 65 . Compared to the younger, older individuals with blunt head trauma were more likely to be female (60% vs. 36%, $p < 0.001$), white (82% vs. 44%, $p < 0.001$), married (41% vs. 27%, $p = 0.007$), and less likely to be employed (15% vs. 60%, $p < 0.001$) or have a prior

history of concussion (22% vs. 32%, $p = 0.045$) (Table 1). When restricting the population to those meeting VA/DoD criteria for TBI, the same findings were noted with the exception that prior concussion no longer was different statistically between the age groups (see Supplemental Table 2).

In all comers with blunt head trauma, there was a difference ($p < 0.001$) in mechanism of injury with older persons most commonly injured by falls (70%) or motor vehicle-traffic (19%) versus the younger by motor vehicle-traffic (27%), falls (26%), or assaults (21%) (Table 2). The older group was less likely to be intoxicated on drugs or alcohol at time of injury (11% vs. 24%, $p = 0.002$) or to have a headache (70% vs. 84%, $p = 0.002$). Similar results were noted when restricting the population to those meeting VA/DoD criteria for TBI (see Supplemental Table 3). A smaller percentage of older participants met VA/DoD criteria for a diagnosis of TBI compared to younger (58% vs. 77%, $p = < 0.001$). Looking at all comers with blunt head trauma, no difference was seen in head AIS score with the majority of injuries classified as minor. Restricting to those meeting VA/DoD TBI criteria, there were significant age differences in head AIS scores with older adults, compared to younger participants ($p = 0.016$), less likely to have suffered minor (65% vs. 77%) versus severe/critical/maximal (29% vs. 13%) injuries.

The difference in percentage of participants with complete 1-month follow-up was not significantly different between older (86%, 94/109) and younger (72%, 282/391) participants. In the older group, those who completed 1-month follow-up, compared to those who did not, were more likely to be married (46% vs. 13%, $p = 0.023$) and less likely to have a history of depression (32% vs. 67%, $p = 0.010$). In the younger age group, those who completed 1-month follow-up, compared to those who did not, were more likely to be married (30% vs. 20%, $p = 0.048$) or employed (65% vs. 49%, $p = 0.006$), and less likely to be intoxicated on substances at time of injury (19% vs. 32%, $p = 0.007$).

One-month outcomes are in Table 3, by age group, for all comers (blunt head trauma) and for the subset of participants meeting VA/DoD criteria for TBI (subset diagnosed clinically with TBI). Identified potential confounders were mechanism of injury, intoxication at time of injury, marital status, and unemployment. These variables were added to the adjusted logistic regression modelling. Results of logistic regression models are in Table 4. Looking at all comers (blunt head trauma), older adults had superior outcomes to younger on all three measures and in all models, including the model adjusted both for potential confounders and head AIS score. When restricting to those meeting VA/DoD criteria for TBI (subset diagnosed clinically with TBI), older adults had superior functional recovery and PCS to younger in all models analysed, including the model adjusted for both potential confounders and head AIS score. In this subset, older adults had similar depressive symptoms to younger once potential confounders were adjusted for. For depressive symptoms, the outcome was unchanged when using the Fann et al. criteria (19) for depression in TBI (data not shown).

Discussion

Historically, it was accepted that at all severities of TBI, when compared to younger, older individuals were more likely to be hospitalized, recover more slowly, and exhibit worse

outcomes (21). With the increasing focus on individualized medicine, these blanket statements are being questioned and studies have begun to focus on establishing profiles for predicting outcome at the level of the individual. The primary objective of this analysis was to determine how the criteria for defining the study population influence estimates of the effect of age on TBI recovery. To do this, we compared two important groups: (1) individuals with blunt head trauma meeting ACEP criteria for head CT in the ED and (2) the subset diagnosed clinically with TBI by VA/DoD criteria. From a clinical standpoint, both groups are important as patients might report to outpatient providers that they received a head CT for blunt head trauma, but not whether a formal diagnosis of TBI was made.

As hypothesized, the cohort of older individuals with blunt head trauma receiving head CT was less likely to meet criteria for TBI since older age is a criterion leading to a head CT in the ACEP guidelines. As hypothesized, when looking at all individuals with blunt head trauma, older individuals had better functional outcomes, fewer PCS, and fewer depressive symptoms at 1 month. We predicted this outcome given that ACEP guidelines are more cautious in the older population and therefore a smaller percentage of individuals in the older group have 'true' TBI. This was evident even after adjustment for potential confounders and head injury severity scores.

The results when restricting to those diagnosed clinically with TBI using VA/DoD criteria were unexpected. For functional recovery and PCS, older adults showed superior outcome to younger cohorts, even after adjusting for confounders and head injury severity. Older adults showed similar rates of depressive symptoms to younger once adjusting for potential confounders. Overall, these findings run contrary to our hypothesis that the criteria for defining the study population would influence estimates of the effect of age on TBI recovery.

Looking at generalizability, our older participants have similar demographic and injury characteristics to previously described cohorts with one difference being a higher percentage of individuals being on anti-coagulation (39%, 43/109) compared to about 20% described nationally (5). We would expect this to lead to worse, not better, outcomes in our older cohort. Compared to participants of all ages in the NHAMCS (22), our younger cohort had a higher percentage of black participants (48% vs. 39%) and a higher percentage of intoxication on drugs/alcohol at time of presentation (24% vs. 6%). Race was not found to be a potential confounder and intoxication at time of presentation was adjusted for in the out-come analyses.

Perhaps the most interesting finding is that when focused on individuals meeting VA/DoD criteria for TBI, older adults showed at least equal outcomes to younger, with older adults showing superior 1-month outcome for functional recovery and PCS. At present, we do not have a biological explanation for this and thus we must look at potential biases and limitations in our sample.

Limitations

Our findings and conclusions must be interpreted in the context of limitations. First, we only look here at 1-month outcomes with some differences observed between those who

completed 1-month follow-up and those who did not. Second, the study was not powered to look at age differences. Although the sample size in each age group is respectable, the younger group makes up four-fifth of our sample. Also, as described in a recent review (23), there is no consensus on the appropriate ‘critical threshold’ at which risk profile after TBI changes due to age, with studies citing anywhere between 35 and 75 years old. Two of our outcome measures, the GOSE and PHQ9, are not TBI-specific. In addition, the PHQ9 allows us to comment on depressive symptoms, but not on a diagnosis of major depressive disorder. It is also possible that older individuals with blunt head trauma are more likely to come to the ED than younger persons, meaning that less symptomatic individuals in the younger age group who did not come to the ED were not part of our study (selection bias). Although we can adjust, a direct comparison of younger and older participants matched by key (demographic or injury) characteristics, including similar mechanisms of injury, would better allow us to comment on the impact of age on outcomes. Last, we did not evaluate for cognition here, which may impact symptom reporting, and may differ between the younger and older individuals.

Conclusions/implications

There is growing support for the hypothesis that a subset of older individuals has outcomes after TBI comparable to younger persons. Our data support this hypothesis even for patients meeting rather stringent criteria for TBI, and after adjustments for head injury severity. Further studies on the influence of age at time of TBI occurrence will have important implications for establishing profiles of older individuals warranting more aggressive treatment than the current standard. Given the aging of the population, this field of study will only become more important.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

This figure describes participant sampling and how the study population was derived from the source population. VA/DoD: Veterans Administration and Department of Defense.

Table 1.

Baseline demographic comparison of older vs. younger individuals with blunt head trauma.

Characteristics ^a	Younger: age <65 (n = 391)	Older: age ≥ 65 (n = 109)	Statistic ^b	p-Value
Age, median in years (IQR)	37 (26–51)	75 (70–81)	255.204	<0.001
Sex				
Male	252 (64.5)	44 (40.4)	20.4681	<0.001
Female	139 (35.5)	65 (59.6)		
Race				
Black	187 (47.8)	17 (15.6)	49.0981	<0.001
White	171 (43.7)	89 (81.7)		
Other	33 (8.5)	3 (2.7)		
Highest level of education				
Less than high school	70 (17.9)	24 (22.0)	2.5191	0.276
High school graduate	234 (59.8)	56 (51.4)		
College graduate	87 (22.3)	29 (26.6)		
Married	107 (27.4)	45 (41.3)	7.8045	0.007
Employed	234 (59.8)	16 (14.7)	69.5582	<0.001
Prior concussion	125 (32.0)	24 (22.0)	4.0347	0.045
Mood disorder	112 (28.6)	40 (36.7)	2.8437	0.296
Non-mood psychiatric disorder	81 (20.7)	18 (16.5)	1.2508	0.488

^aNo. (%) unless listed otherwise;^bFisher's exact for proportions and Kruskal-Wallis for continuous variables.

Table 2.

Injury descriptor comparison of older vs. younger individuals with blunt head trauma.

Characteristics ^a	Younger: age <65 (n = 391)	Older: age ≥ 65 (n = 109)	Statistic ^b	p-Value
Mechanism of injury				
Pedestrian struck	46 (11.8)	4 (3.7)	79.4018	<0.001
Motor vehicle-traffic	105 (26.9)	21 (19.3)		
Fall	100 (25.6)	76 (69.7)		
Assault	83 (21.3)	3 (2.8)		
Struck by/against	21 (5.2)	3 (2.8)		
Pedal cycle	36 (9.2)	2 (1.7)		
Intoxicated on drugs/alcohol	94 (24.0)	12 (11.0)	8.6652	0.002
Abnormal CT findings	65 (16.6)	27 (24.8)	3.7677	0.068
Symptoms at time of presentation				
GCS < 15 at presentation	61 (15.6)	12 (11.0)	1.4414	0.283
Post-traumatic amnesia	221 (56.5)	52 (47.7)	3.0436	0.226
Deficits in short-term memory	54 (13.8)	14 (12.8)	0.9925	0.511
Focal neurological deficits	33 (8.4)	5 (4.6)	2.0996	0.392
Headache	329 (84.1)	76 (69.7)	12.1865	0.002
Vomiting since injury	43 (11.0)	9 (8.3)	0.6870	0.481
GOAT total score, median (IQR)	99 (94–100)	99 (92–100)	0.109	0.7408
Met VA/DoD criteria	302 (77.2)	63 (57.8)	16.3428	<0.001
Head AIS score				
Minor	311 (79.5)	79 (72.5)	3.9128	0.267
Moderate	13 (3.3)	4 (3.7)		
Serious	20 (5.1)	5 (4.6)		
Severe, critical, or maximal	47 (12.1)	21 (19.2)		

^aNo. (%) unless listed otherwise;^bFisher's exact for proportions and Kruskal-Wallis for continuous variables; GCS: Glasgow Coma Scale; GOAT: Galveston Orientation and Amnesia Test; VA/DoD: Veterans Administration/Department of Defense; AIS: Abbreviated Injury Scale.

Table 3.

One-month outcomes in older vs. younger participants with blunt head trauma and diagnosed clinically with TBI (a subset of those with blunt head trauma).

Outcome	Blunt head trauma		Subset diagnosed clinically with TBI	
	Younger: age <65	Older: age 65	Younger: age <65	Older: age 65
Incomplete functional recovery, No. (%) ^a	182/282 (64.5%)	39/94 (41.5%)	155/222 (69.8%)	26/56 (46.4%)
Post-concussive symptoms ^b	145/282 (51.4%)	24/91 (26.4%)	121/222 (54.5%)	16/54 (29.6%)
Depressive symptoms ^c	121/280 (43.2%)	22/90 (24.4%)	102/220 (46.4%)	14/53 (26.4%)

^aIncomplete functional recovery defined as Glasgow Outcome Scale Extended Score of <8;

^bPost-concussive symptoms defined as endorsing at least two symptom categories on the Rivermead Post-Concussion Questionnaire;

^cDepressive symptoms defined a score of 5 on the Patient Health Questionnaire-9.

Table 4.

Ordered logistic regression (models adjusted as described below^{d,e}) of 1-month outcomes in older vs. younger participants with blunt head trauma and diagnosed clinically with TBI (a subset of those with blunt head trauma).

Models by outcome	Blunt head trauma		Subset diagnosed clinically with TBI	
	Odds ratio	p-Value	Odds ratio	p-Value
Incomplete functional recovery^a				
Unadjusted model	0.39	<0.001	0.37	0.001
Model adjusted for potential confounders ^d	0.39	0.001	0.41	0.010
Model adjusted for potential confounders and head AIS ^e	0.26	<0.001	0.24	<0.001
Post-concussive symptoms^b				
Unadjusted model	0.34	<0.001	0.35	0.001
Model adjusted for potential confounders ^d	0.37	0.001	0.42	0.017
Model adjusted for potential confounders and head AIS ^e	0.30	<0.001	0.32	0.003
Depressive symptoms^c				
Unadjusted model	0.43	0.002	0.42	0.010
Model adjusted for potential confounders ^d	0.45	0.008	0.52	0.078
Model adjusted for potential confounders and head AIS ^e	0.42	0.004	0.51	0.079

^aIncomplete functional recovery defined as Glasgow Outcome Scale Extended Score of <8;

^bPost-concussive symptoms defined as endorsing at least two symptom categories on the Rivermead Post-Concussion Questionnaire;

^cDepressive symptoms defined a score of ≥ 5 on the Patient Health Questionnaire-9;

^dAdjusted for mechanism of injury, intoxication at time of injury, marital status, and unemployment;

^eAdjusted for #4 plus head Abbreviated Injury Scale.