

ARIC Manuscript Proposal #4309

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1.a. Full Title: Hospital Readmissions after Traumatic Brain Injury (TBI) Hospitalization in Community-Dwelling Adults

b. Abbreviated Title (Length 26 characters): Hospital Readmissions After TBI

2. Writing Group:

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We, the co-first authors, confirm that all the coauthors have given their approval for this manuscript proposal. **RT, HCE**

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3. Timeline:

Data are currently available. We anticipate that analyses will be performed within 12 months of manuscript proposal approval with a goal to submit an abstract to a conference within this time period. We anticipate submitting the manuscript for publication within 2 years of manuscript proposal approval.

4. Rationale:

The annual incidence of traumatic brain injury (TBI) approaches 69 million individuals worldwide.¹ In the United States alone, approximately 2.8 million individuals seek medical care for TBI in emergency departments, resulting in over 282,000 hospitalizations and 56,000 deaths.²⁻⁵ On average, initial TBI hospitalizations are longer in duration, costlier, and carry a higher mortality rate than non-TBI admissions (including both non-trauma admissions and trauma admissions without a TBI diagnosis).³ Older adults have the highest rates TBI, with individuals aged 75 years and older accounting for 32% of all TBI-related hospitalizations.⁴

Among individuals with prior TBI, all-cause hospital readmissions are common, approaching 14% within 1 year⁶ and 20–23% within the first three years after the index injury⁷. Several studies have identified several risk factors for hospital readmission after TBI in the acute post-injury period. Factors associated with increased risk of hospital readmission within 30-days post-injury include male sex, advanced age, history of falls, and public insurance.^{6,8-10} Clinical factors associated with increased risk for hospital re-admission include greater injury severity, intracerebral hemorrhage on imaging (especially subdural hemorrhage),³ diagnosis of acute-symptomatic seizures during index admission,¹¹ and discharge to a skilled nursing facility or against medical advice (AMA)⁹. Few studies have considered longer-term risk for readmission in community-dwelling adults. In a study of Veterans Health Administration (VHA) TBI Model System participants, among active military and Veterans that were discharged to inpatient rehabilitation centers, rehospitalization within 1 year post-injury was associated with occurrence of TBI while on active duty, an important consideration given the high risk of combat-associated TBI¹². However, little is known about time points more remote from injury or about readmission risk among community dwelling older adults. Moreover, prior studies have not compared the rate of readmission following TBI to matched individuals without TBI to fully assess the associated risk.

A better understanding of the sociodemographic and clinical factors associated with hospital readmissions after an index TBI hospitalization could lead to improvements in both inpatient management as well as post-discharge neurorehabilitation approaches. Therefore, building on prior research, the proposed research will examine the long-term risk of all-cause and cause-specific hospital readmission following TBI hospitalization among community-dwelling adults.

5. Main Hypothesis/Study Questions:

We hypothesize that the rates of all-cause hospitalization will be higher among individuals with an index hospitalization TBI as compared with individuals without TBI. We further hypothesize that the rate of hospital readmission will be highest within one month of first TBI but will remain higher among individuals with head injuries within one year, five years, ten years, and more than ten years after TBI as compared with matched participants without TBI.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

In this prospective cohort study, we will examine incidence rates of all-cause hospital admission occurring after an index hospitalization for TBI. We will use propensity score restriction and matching of individuals with TBI based on the recorded date of their index TBI-related hospitalization to those with non-TBI hospitalization. All individuals with TBI-related hospitalization data available and with at least 30 days of follow-up after the index date will be included in the analysis. Follow-up will extend from the date of entry into the cohort on the index date (i.e., the date of TBI hospitalization) until loss to follow-up, withdrawal from the study, death, or administrative censoring on December 31, 2020. We will exclude participants of non-Black and non-White race, and Black participants at the Minnesota and Maryland field centers (due to race-center aliasing). We will exclude individuals with a history of self-reported head injury occurring prior to baseline (ARIC Visit 1) or with missing covariates included in statistical models.

Traumatic Brain Injury

The ARIC study collects data on hospitalizations via annual (through 2011) and semi-annual (starting in 2012) telephone contact with study participants and through active surveillance of hospitalizations occurring in the study community hospitals. We will include subjects that required hospitalization for TBI and will define the index TBI by ICD code in any position with sensitivity analyses performed restricting to the first position. TBI requiring hospital care will be identified using codes from the *International Classification of Diseases, Ninth/Tenth Revisions* (ICD-9/10) according to the Centers for Disease Control and Prevention case definition.¹³⁻¹⁶

ICD-9

- 800.xx = Fracture of vault of skull
- 801.xx = Fracture of base of skull
- 803.xx = Other and unqualified skull fractures
- 804.xx = Multiple fractures involving skull or face with other bones

- 850.xx = Concussion
- 851.xx = Cerebral laceration and contusion
- 852.xx = Subarachnoid subdural and extradural hemorrhage following injury
- 853.xx = Other and unspecified intracranial hemorrhage following injury
- 854.xx = Intracranial injury of other and unspecified nature
- 959.01 = Head injury, unspecified

ICD-10

- S02.0 = Fracture of vault of skull
- S02.1X = Fracture of base of skull
- S02.8 = Fractures of other unspecified skull and facial bones
- S02.91 = Unspecified fracture of skull
- S04.02 = Injury of optic chiasm
- S04.03X = Injury of optic tract and pathways
- S04.04X = Injury of visual cortex
- S06.X = Intracranial injuries, concussion, traumatic cerebral edema, diffuse and focal traumatic brain injury, traumatic epidural, subdural, and subarachnoid hemorrhage
- S07.1 = Crushing injury of skull

Head injuries will be further classified by severity based on the Department of Defense (DOD) head injury severity classification (no head injury; mild head injury; moderate/severe/penetrating injury).¹⁷ In an exploratory analysis, head injuries will be further characterized based on whether they required neurosurgical intervention (yes; no); evidence of intracranial hemorrhage (yes; no, including subarachnoid hemorrhage; subdural hematoma; epidural hematoma; intracerebral hemorrhage); mechanism (motor vehicle crash; assault; fall) and intubation (yes; no) according to the following diagnostic codes:

Neurosurgical Intervention

- ICD-9 01.24 = Craniotomy
- ICD-9 01.25 = Craniectomy
- ICD-9 02.21 = External ventricular drain
- ICD-10 Z48.811 = Post-neurosurgical care

Evidence of Intracranial Hemorrhage

- ICD-9 851.8, 851.9 = Contusion
- ICD-10 S06.330A = Contusion without loss-of-consciousness
- ICD-10 S06.339A = Contusion with loss-of-consciousness
- ICD-9 852, 852.0 = Subarachnoid hemorrhage
- ICD-10 S06.6X0A = Subarachnoid hemorrhage, traumatic, without loss of consciousness
- ICD-10 S06.6X9 = Subarachnoid hemorrhage, traumatic, without loss of consciousness
- ICD-9 852.2, 852.3 = Subdural hematoma
- ICD-10 S06.5X0 = Subdural hematoma, traumatic, without loss of consciousness
- ICD-10 S06.5X9A = Subdural hematoma, traumatic, with loss of consciousness
- ICD-9 852.4, 852.5 = Epidural hematoma
- ICD-10 S06.4 = Epidural hematoma

- ICD-9 853.0 = Intracerebral hemorrhage
- ICD-10 S06.360A = Intracerebral hemorrhage, without loss of consciousness
- ICD-10 S06.369A = Intracerebral hemorrhage, with loss of consciousness

Injury Mechanism

- ICD-9 E810-E819 = Motor vehicle crash
- ICD-10 V89.2 = Motor vehicle crash
- ICD-9 E968.9 = Assault
- ICD-10 Y09 = Assault
- ICD-9 E880-E888 = Fall
- ICD-9 W19.XXXA = Fall

Intubation Requirement

- ICD-9 96.xx = Nonoperative intubation and irrigation
- ICD-10 0BH17EZ = Insertion of airway
- ICD-10 Z99.11 = Dependence on ventilator

All-Cause and Cause-Specific Hospital Readmissions

The main outcome of interest is all-cause hospital readmissions through December 31, 2020. In exploratory secondary analyses, we will investigate cause-specific hospitalization readmissions. We will categorized the primary cause of each hospitalization using the Clinical Classification Software developed by the Agency for Healthcare Research and Quality (<https://www.hcupus.ahrq.gov/toolssoftware/ccs/ccs.jsp>).¹⁸ The primary cause of each hospitalization will be classified into 18 systems-based categories and then subclassified into 285 disease-based categories.¹⁸ In sensitivity analyses, we will recategorize all infection-related ICD code diagnoses to create a more comprehensive infection category, as not all ICD-9 codes that identify infection are classified in the infection category as defined by the Clinical Classification Software (for example, pneumonia is classified under the respiratory system and not the infection category using the Clinical Classification Software).

Sociodemographic Factors and Comorbidities

Covariates included in the analysis will be those ascertained at the closest visit prior to index date (defined below; not including education which will be assessed at Visit 1) and will include age (continuous), sex (male; female), race/center (Maryland White; Minnesota White; North Carolina White; North Carolina Black; Mississippi Black), annual household income (<median; ≥median; not reported), health insurance status (yes; no), marital status (married; divorced; separated; widowed; single), education (<high school; high school/GED/vocational; any college/graduate/professional school), military veteran status (yes; no), alcohol consumption (current; former; never), physical activity (score ranging from 1–5, modified Baecke Physical Activity Questionnaire; continuous), cigarette smoking (current; former; never), hypertension (defined as systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90mmHg, or use of medications), hyperlipidemia (total cholesterol > 200), diabetes (defined as fasting glucose ≥126mg/dL, non-fasting glucose ≥200mg/dL, self-reported physician diagnosis of diabetes, or prescribed medication for diabetes); body mass index (BMI; continuous); psychotropic medication use (anxiolytics, benzodiazepines, antipsychotics, hypnotics/sedatives, opiates, and cholinesterase inhibitors); coronary heart disease (self-reported at visit 1, ongoing adjudicated

event defined based on reported history of myocardial infarction, heart or arterial surgery, coronary artery bypass graft surgery, or angioplasty; or evidence of prior myocardial infarction based on electrocardiogram)¹⁹; and stroke (self-reported at visit 1, ongoing adjudicated definite/probable events).

Statistical Analysis

Our analysis will use propensity score restriction and matching to identify individuals with TBI hospitalization and non-TBI hospitalization who are otherwise comparable in terms of baseline characteristics. The predicted probabilities of TBI hospitalization (i.e., propensity scores)²⁰ will be estimated using the above-described sociodemographic characteristics, comorbidities, and date of the index TBI hospitalization. As has been previously recommended, we will use full matching with replacement.^{21,22}

Propensity scores will be estimated using SuperLearner,²³ an ensemble machine-learning approach that has been previously used to improve propensity score estimation.^{24,25} The SuperLearner package optimally weights multiple machine learning algorithms (e.g., generalized linear models [GLM], Bayesian GLM, multivariate adaptive regression splines, and generalized additive models [GAMs]), to minimize V-fold cross-validated prediction error. The advantage of this approach is reduced reliance on the correct specification of the parametric exposure model for propensity score estimation. To reduce model extrapolation, we will restrict the analytic population to those with propensity scores between the 1st propensity score percentile among those with TBI-related hospitalizations and 99th propensity score percentile among those with non-TBI hospitalization. Quality of the match will be evaluated based on the standardized mean differences between matching variables and via visual inspection of the distribution of propensity scores in the matched TBI and non-TBI groups.^{20,26}

Within our matched analytic sample, we will use Cox regression analysis to examine the risk of all-cause hospital admission among those with and without head injury. We will specify three separate statistical models. First, we will examine the crude association between head injury and hospital admission. Second, we will adjust for sex, age, prior military service, race and center, education, annual household income, health insurance status, physical activity, and alcohol consumption. Third, we will additionally control for an extended set of vascular risk factors that include cigarette smoking, hypertension, diabetes, BMI, coronary heart disease, and stroke. Our analysis will consider the overall rates of all-cause hospital admissions and will further characterize rates of hospital admission based on time elapsed since the index date (within one month; one month–one year; one year–five years; more than five years).

Secondary Analyses

We will conduct secondary analyses within subgroups defined by sex, race, education, income, and age at hospitalization. For all subgroup analyses, we will conduct formal tests of statistical interaction. We will examine rates of hospital readmission by head injury severity and head injury characteristics. In secondary analyses, we will describe cause-specific hospital admissions among those with and without a hospitalized TBI. Among individuals with TBI hospitalization will conduct descriptive secondary analyses in which we explore the frequency and time-to-rehospitalization based on the presence or absence of key characteristics (neurosurgical intervention, evidence of intracranial hemorrhage, mechanism, and intubation).

Sensitivity Analyses and Contingencies

As a sensitivity analysis, we will examine whether rates of all-cause hospital admission differ based on the year of head injury diagnosis (1987–1995; 1996–2005; 2006–2020). Second, we will conduct an analysis restricted to head injuries with a relevant diagnostic code in the first position. Third, we will limit covariates included to estimate propensity scores to key sociodemographic characteristics. Finally, while we plan to exclude participants with missing model covariates, if complete case analysis excludes more than 10% of study participants, we will multiply impute data on covariates using chained equations under the missing at random assumption. Regression models will be estimated for each of 20 imputed datasets with results combined using Rubin’s rule.²⁷

Limitations

The use of ICD codes instead of self-reporting limits certain injury features. While we are able to obtain codable injury characteristics, we do not have certain injury-specific factors including duration of loss of consciousness or post-traumatic amnesia. It is possible that we will not be able to reliably obtain ICD code defined injury characteristics (neurosurgical intervention, intracranial hemorrhage, injury mechanism, intubation). Moreover, inclusion by ICD code limits generalizability to mild TBIs that do not require hospitalization. In addition, co-linearity is anticipated within some variables, for example injury severity with need for neurosurgical intervention, as well as injury mechanism with age given that TBI secondary to falls is more common in older age groups. To address this, we will investigate relationships between injury characteristic covariates and if found to be highly colinear, we will remove the highly correlated variable from our statistical models.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes X No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = “ARIC only” and/or “Not for Profit” ? ____ Yes ____ No

(The file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes X No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 must be used to exclude those with value RES_DNA = “No use/storage DNA”? ____ Yes ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.

ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: <http://www.csc.unc.edu/aric/mantrack/maintain/search/dtSearch.html>

☒ Yes ☐ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

- 4205:** Association of continuity of care with post-acute care among stroke patients discharged to home (Li)
- 4041:** Associations of Prior Head Injury with Physical Functioning, Frailty, and Falls in the Atherosclerosis Risk in Communities (ARIC) Study (Hunzinger)
- 4051:** Associations of Prior Head Injury and Hearing in ARIC-NCS (Schneider)
- 3978:** Associations between Head Injury and Mild Behavioral Impairment (MBI) Domains Across the Cognitive Spectrum (Daneshvari)
- 3958:** Associations of Prior Head Injury with Olfactory Functioning (Schneider)
- 3916:** Associations of Head Injury with Neuropsychiatric Symptoms (NPS) and Mild Behavioral Impairment (MBI) Domains (Schneider)
- 3898:** Post-traumatic Epilepsy (PTE) and Dementia Risk (Schneider)
- 3668:** The risk of post-traumatic epilepsy in the ARIC study (Schneider)
- 3357:** Trends in Heart Failure Hospitalization Before and After Stroke (Zmora)
- 2852:** Hospital readmissions for patients hospitalized with acute decompensated heart failure and preserved vs. reduced ejection fraction
- 2769:** The Association of Head Injury with Risk of Stroke, Cardiovascular Disease, and Mortality in the ARIC Study (Schneider)
- 2768:** The Association of Head Injury and Cognition, Mild Cognitive Impairment, and Dementia in the ARIC Study (Schneider)
- 2598:** Stroke and Risk of Subsequent Hospitalization: The Atherosclerosis Risk in Communities (ARIC) Study (Schneider)
- 1987:** Re-hospitalizations with heart failure: cumulative incidence rates over long term follow up and its prediction (Agarwal)
- 1778:** Predictors of 30-day readmission among heart failure patients (Foraker)
- 1324:** Neighborhood and Individual Socioeconomic Status and Heart Failure Rehospitalization: ARIC Cohort (Foraker)

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ☒ Yes ☐ No

11.b. If yes, is the proposal

- ☐ A. primarily the result of an ancillary study (list number* _____)
- ☒ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* Brain MRI 1999.01)

*ancillary studies are listed by number <https://sites.csc.unc.edu/aric/approved-ancillary-studies>

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

Understood.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from <http://publicaccess.nih.gov/> are posted in <http://www.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

Understood.

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