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Derivation of a clinical decision rule for emergency department head CT scanning in older adults who have fallen: study protocol.

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ABSTRACT

Introduction

Falling on level ground is now the most common cause of traumatic intracranial bleeding world-wide. Older adults frequently present to the emergency department after falling. It can be challenging for clinicians to determine who requires brain imaging to rule out traumatic intracranial bleeding, and often head injury decision rules do not apply to older adults who fall. The goal of our study is to derive a clinical decision rule which will identify older adults who present to the emergency department after a fall who do not have clinically important intracranial bleeding.

Methods and analysis

This is a prospective cohort study enrolling patients aged 65 years or older, who present to the emergency department of 11 hospitals in Canada and the United States within 48 hours of having a fall. Patients are included if they fall on level ground, off a chair, toilet seat or out of bed. The primary outcome is the diagnosis of clinically relevant intracranial bleeding within 42 days of the index emergency department visit. An independent adjudication committee will determine the primary outcome, blinded to all other data. We are collecting data on 17 potential predictor variables. The treating physician completes a study data form at the time of initial assessment, prior to brain imaging. Data extraction is supplemented by an independently structured electronic medical record review. We will perform binary recursive partitioning using Classification and Regression Trees to derive a clinical decision rule.

Ethics and dissemination

The study has been approved by the research ethics boards governing all participating sites. We will disseminate our results by journal publication, presentation at international meetings and social media.

Registration details ClinicalTrials.gov NCT03745755

ARTICLE SUMMARY

Strengths and limitations of this study

- It can be challenging to determine which older adults have intracranial bleeding after a fall and there is little evidence to guide practice.
- This study will derive a clinical decision rule to determine which older emergency department patients who present after a fall do not require head CT imaging.
- Our clinical decision rule will be composed of routine clinical bedside and laboratory findings.
- The main threat to our study is that not all patients will have head CT imaging at their initial emergency department visit and we will not know if a patient dies of undiagnosed intracranial bleeding during 42-day follow up.

INTRODUCTION

In contrast to the younger population, the incidence of traumatic intracranial bleeding in older adults is rising[1] and has a worse prognosis.[2,3] Older adults are at higher risk of traumatic intracranial bleeding because there can be loss of the elastic integrity of the cerebral bridging veins and brain atrophy, allowing rapid movements of the brain within the cerebral spinal fluid with trauma. Older adults may be less able to withstand intracranial bleeding because of pre-existing comorbidity, frailty and polypharmacy.

Falling on level ground is now the most common cause of traumatic intracranial bleeding world-wide, accounting for up to 80% of cases.[4-8] Fall-associated intracranial bleeding in older adults is increasing in incidence.[9,10] The mortality rate for fall-associated intracranial bleeding is 15%[7,11] (accounting for half of all fall-associated deaths[12,13]). Rather than seeing a decrease in these deaths, this mortality rate is rising.[10] Emergency departments (EDs) are managing an increasing number of older adults who have fallen[14] and ED visits for fall-related head injuries in older adults have increased year after year.[9,13,15-17] There is a paucity of evidence to guide neuroimaging for intracranial bleeding in older adults.

The Canadian CT Head Rule can determine the need for head computed tomography (CT) in head-injured patients who experienced loss of consciousness, disorientation or amnesia after their injury.[18] However, older ED patients who present after a fall cannot always give a history of what happened, falls are frequently unwitnessed and many older adults who fall do not sustain a head injury. Ordering a head CT scan on every older adult who has fallen would be an inefficient and costly way to diagnose intracranial bleeding when only approximately 5% have intracranial bleeding.[19] Patients awaiting a CT scan will typically occupy an ED bed. CT overuse in this population not only causes prolonged ED visits, but it also contributes to ED overcrowding, which may result in worse outcomes for other patients.[20] Older adults are at greater risk of developing delirium the longer they stay in the ED.[21] There is a need for a simple bedside tool which can rapidly stratify the risk of intracranial bleeding in older ED patients who present after falling. Our aim is to derive a clinical decision rule which will identify older adults who present to the ED after a fall who do not have clinically important intracranial bleeding and therefore do not require a head CT.

METHODS AND ANALYSIS

Study design

This is a prospective cohort study designed to develop a unique clinical decision rule for ED physicians evaluating older adults who have fallen. Clinical decision rules are a commonly applied method of standardized clinical diagnostic decision-making in the ED. The rules incorporate the standardized collection and interpretation of multiple predictor variables from the patient's history, physical examination and test results to optimize evidence-based clinical decision-making. For example, clinical decision rules are used to determine which patients should have cervical spine imaging in trauma,[22] thoracic imaging for pulmonary embolism[23] and admission after syncope.[24] Our study follows the methodological standards for clinical decision rules in emergency medicine.[25]

Patient and public involvement

Prior to the protocol development, we conducted a qualitative study with older adults who were waiting in the ED for head CT after a fall. We found that diagnosing intracranial bleeding was important to the participants, that they valued testing tailored to their personal risk and shorter ED visits. This protocol was designed with feedback and input from our patient partners.

Study population

This study is conducted at 11 hospitals in Canada and the United States and enrolls patients aged 65 years or older who present to the ED within 48 hours of having a fall. Patients are eligible if they fall on level ground (either inside or outside), off a chair or toilet seat or out of bed. Patients are included regardless of whether they hit their head. Patients are excluded if they fell down steps, fell from a height, were knocked down by a car/bike/pedestrian or other mechanism of injury. Patients who live outside of the hospital catchment area, who have previously been enrolled in this study, who are transferred from another hospital and who leave the ED prior to completion of their medical assessment are also excluded. Recruitment commenced on January 30, 2019. Patients are recruited 24 hours a day, seven days a week.

Patient assessment

Each patient is assessed at their index ED visit by an emergency physician who decides on the need for head CT based on clinical history and examination. It would be impractical to perform a head CT on all older adults who have fallen, for example, after a simple trip, because there is not always an indication for CT, hospitals have limited resources and ordering a CT delays discharge home. However, if participants return to the ED within 42 days of enrolment with new confusion, headache, loss of balance, repeat falls, change in behaviour, reduced Glasgow Coma Score (GCS) or other neurological symptoms, they will undergo head CT.

Outcome definition and measurement

The primary outcome is '***clinically important intracranial bleeding***' diagnosed within 42 days of the index ED presentation. Our definition was derived after surveying specialists (including neurosurgeons, neurologists, trauma physicians, geriatricians, thrombosis and emergency physicians) who determined that symptoms from intracranial bleeding might develop as late as six weeks after a fall. 'Clinically important intracranial bleeding' is defined as bleeding within the cranial vault (including subdural, intracerebral, intraventricular, subarachnoid, epidural blood and cerebral contusion), which requires medical or surgical treatment. Medical treatment is defined as any of the following: temporary or permanent discontinuation of anticoagulant or antiplatelet medication; administration of an antifibrinolytic drug; reversal of anticoagulation; or admission to hospital for neurological observation. Clinically important intracranial bleeding will be determined by independent adjudication of head CT scans by the centralized outcome adjudication committee consisting of a study neurologist, neurosurgeon, trauma surgeon and radiologist. The adjudicators will be blinded to all ED baseline data. Secondary outcomes relate to the 'severity' of the intracranial bleeding: 1) neurosurgical intervention; 2) intensive care admission; 3) hospital length of stay; 4) in-hospital death as determined by medical record review.

We found poor sensitivity (37%, 95% confidence interval: 21 to 56%) for patient-reported diagnosis of intracranial bleeding.[26] Furthermore, our experience of personal follow up in this population[27] is that it is frequently not feasible because of residence in nursing homes or baseline cognitive impairment. Therefore, the current study follow up is restricted to systematic medical record review with independent validation and enrollment is restricted to patients who reside within the hospital catchment area.

Predictor variables

Demographic and predictor variables are collected in two ways: 1) the treating physician completes a standardized data collection form at the time of initial patient assessment, and before the results of the

170 head CT are available (therefore blinded to outcome); 2) data is collected by trained on-site research assistants using standardized medical record review protocols, following detailed data definitions and instructions for systematic medical record review. We follow standardized validation procedures for all medical record review data points: de-identified source documentation is uploaded for validation by the coordinating centre. A query is sent to the site research assistant to resolve each discrepancy. The study site investigator resolves discrepancies which persist after research assistant review. Table 1 details the demographic and predictor variables collected.

Table 1: Description of collected demographic and predictor variables

	Data collected by treating physician at initial assessment	Data collected by systematic medical record review by research assistant
Predictor variables		
Age		x
Sex		x
Head injury (as reported by patient or carer)	x	
Loss of consciousness	x	
New amnesia about events of fall	x	
History of previous major bleed[28]		x
Cirrhosis		x
Previous diagnosis of ischemic stroke		x
Chronic renal impairment	x	x
Reduced Glasgow Comma Score from normal	x	
Bruise or laceration on the head	x	
New abnormality on neurological examination	x	
Haemoglobin		x
Platelet count		x
Anticoagulation medication	x	x
Antiplatelet medication	x	x
Clinical Frailty Score[29]	x	

Descriptive variables		
Living circumstances		x
Diabetes		x
Hypertension		x
Active cancer within past 2 years		x
Dementia		x
History of frequent falls		x
Congestive heart failure		x
Mechanism of injury		x
Weight		x
GCS at time of physician assessment	x	
Vomiting (once / more than once)	x	
Signs of basal skull fracture	x	
Suspected open or depressed skull fracture	x	
Retrograde amnesia for >30 minutes	x	
Creatinine		x
International normalized ratio (INR)		x

We initially identified potential predictor variables by a systematic review of prior evidence. We then assessed the frequency among our population and the association between predictor and intracranial bleeding in a study of 1753 older ED patients who had fallen.[27] We selected 17 candidate predictor variables, which are considered to be biologically plausible and related to the outcome of intracranial bleeding, and are routinely collected in the ED: age; sex; head injury; loss of consciousness; amnesia; history of previous major bleed (International Society of Thrombosis and Haemostasis criteria[28]); cirrhosis; prior ischemic stroke; chronic renal impairment; GCS reduced from baseline; bruise or laceration on the head; abnormal neurological examination; haemoglobin, platelet count; anticoagulant therapy; antiplatelet therapy; and, Clinical Frailty Score.[29] We did not include potential predictors such as suspected open or depressed skull fractures or retrograde amnesia because these features were extremely rare among our prior study.[27]

Analysis

Variables with large amounts of missing data will be excluded from the models as they would be missing in clinical practice. Likewise, continuous variables whose distributions are too narrow will also be excluded. We will perform binary recursive partitioning using Classification and Regression Trees to develop a decision rule. A clinical decision rule for a life-threatening event like intracranial bleeding requires very high sensitivity. The model with a sensitivity of > 99% and the highest specificity will be selected. We will assess the derived decision rule by comparing the classification of each patient with his or her actual status for the primary outcomes. In addition, 1000 bootstrap iterations will be performed to assess the internal classification performance and overfitting of the selected decision rule.

We will also develop a predictive risk model using multivariable logistic regression. Continuous variables may be transformed and will be fit using restricted cubic splines to relax the linearity assumption. First, a full model with all variables will be fit. To further reduce the model, backward selection without model re-fitting with p <0.5, which has shown to have valid inference will be performed.[30,31] Clinically and biologically plausible interactions will be tested within the model. Internal validation to obtain unbiased and optimism corrected estimation of model performance will be done using 1000 bootstrap samples. Model discrimination will be reported using the C-statistic and a calibration plot of observed versus predicted probabilities.

Sample size

The current guidelines suggest that we would require at least 10 events per included variable.[32,33] We expect that 5% of patients will be diagnosed with clinically important intracranial bleeding,[19] and we assume that our initial model will consist of 17 candidate variables. Based on this assumption, a sample size of 4000 should include 200 cases of intracranial bleeding (12 events per variable).

Sources of bias

Intracranial bleeding will be adjudicated blind to all baseline and predictor data. Predictor data is collected before the primary outcome data is collected. However, it is possible that we do not identify every case of intracranial bleeding during the 42-day follow up period. In our prior study, only 60% of patients had a head CT during the index ED visit.[27] Although patients are advised to return if they develop neurological symptoms, it is possible that a patient may die of an intracranial bleed before being diagnosed. Furthermore, 42-day follow-up involves institutional electronic medical record review.

If a patient attended an unrelated hospital during follow up and was diagnosed with an intracranial bleed, we might miss this diagnosis. To reduce the chance of this happening, we are restricting study enrollment to patients who reside within the hospital catchment area and most sites have access to records from regional neurosurgical centres. In our prior study where we performed in-person follow up, no patient was diagnosed with an intracranial bleed at another hospital.

Study oversight

The coordinating centre is McMaster University. Electronic data and de-identified source documents are uploaded to a Research Electronic Data Capture (REDCap) database[34,35] and stored on a secure server at McMaster University. The coordinating centre validates all data and supervises the adjudication committee activities. The study steering committee consists of the site investigators.

Ethics and dissemination

Research ethics approval has been obtained from each enrolling site local research ethics board. In our previous study on the same population,[27] we obtained patient consent. An interim analysis showed a number of patients were confused (144/890, 16%) or died before a researcher could ask for their consent (39/890, 4%). Family were often not available in the ED. In all, we were unable to obtain consent from 204/890 (23%) patients. To address this problem, we obtained research ethics board approval to include patients who were unable to give informed consent. It is essential we include patients who cannot consent since they are often the most frail patients who are challenging to evaluate in the ED and frequently excluded from studies. Excluding these patients could limit the generalizability of our clinical decision rule. The current study has research ethics approval at all sites to include patients without obtaining informed consent.

The study results will be submitted for publication in a peer reviewed journal and presented at national and international emergency medicine meetings.

AUTHORS' CONTRIBUTIONS

The study was conceived by KdW, MM, CK, SS and AW. The protocol was designed with input from all authors and has been endorsed by the Network of Canadian Emergency Researchers. The study is being conducted by KdW, NC, EM, CV, DE, DB, RJ and JM. YK, AS, SS and PE are the study adjudicators. SP will oversee the analysis.

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ABSTRACT

Introduction

Falling on level ground is now the most common cause of traumatic intracranial bleeding world-wide. Older adults frequently present to the emergency department after falling. It can be challenging for clinicians to determine who requires brain imaging to rule out traumatic intracranial bleeding, and often head injury decision rules do not apply to older adults who fall. The goal of our study is to derive a clinical decision rule which will identify older adults who present to the emergency department after a fall who do not have clinically important intracranial bleeding.

Methods and analysis

This is a prospective cohort study enrolling patients aged 65 years or older, who present to the emergency department of 11 hospitals in Canada and the United States within 48 hours of having a fall. Patients are included if they fall on level ground, off a chair, toilet seat or out of bed. The primary outcome is the diagnosis of clinically relevant intracranial bleeding within 42 days of the index emergency department visit. An independent adjudication committee will determine the primary outcome, blinded to all other data. We are collecting data on 17 potential predictor variables. The treating physician completes a study data form at the time of initial assessment, prior to brain imaging. Data extraction is supplemented by an independent, structured electronic medical record review. We will perform binary recursive partitioning using Classification and Regression Trees to derive a clinical decision rule.

Ethics and dissemination

The study was initially approved by Hamilton Integrated Research Ethics Committee and subsequently approved by the research ethics boards governing all participating sites. We will disseminate our results by journal publication, presentation at international meetings and social media.

Registration details ClinicalTrials.gov NCT03745755

ARTICLE SUMMARY

Strengths and limitations of this study

- This cohort study aims to derive a clinical decision rule which identifies older adults at risk of intracranial bleeding after a fall.
- This is a large study enrolling patients from 11 hospitals in two countries.
- Potential predictor variables are recorded by emergency physicians prior to CT scanning.
- The primary outcome, clinically important intracranial bleeding, is determined by an independent adjudication committee.
- The main limitation is that not all patients will have head CT imaging at their initial emergency department visit.

INTRODUCTION

In contrast to the younger population, the incidence of traumatic intracranial bleeding in older adults is rising[1] and has a worse prognosis.[2,3] Older adults are at higher risk of traumatic intracranial bleeding because there can be loss of the elastic integrity of the cerebral bridging veins and brain atrophy, allowing rapid movements of the brain within the cerebral spinal fluid with trauma. Older adults may be less able to withstand intracranial bleeding because of pre-existing comorbidity, frailty and polypharmacy.

Falling on level ground is now the most common cause of traumatic intracranial bleeding world-wide, accounting for up to 80% of cases.[4-8] Fall-associated intracranial bleeding in older adults is increasing in incidence.[9,10] The mortality rate for fall-associated intracranial bleeding is 15%[7,11] (accounting for half of all fall-associated deaths[12,13]). Rather than seeing a decrease in these deaths, this mortality rate is rising.[10] Emergency departments (EDs) are managing an increasing number of older adults who have fallen[14] and ED visits for fall-related head injuries in older adults have increased year after year.[9,13,15-17] There is a paucity of evidence to guide neuroimaging for intracranial bleeding in older adults.

The Canadian CT Head Rule can determine the need for head computed tomography (CT) in head-injured patients who experienced loss of consciousness, disorientation or amnesia after their injury.[18] However, older ED patients who present after a fall cannot always give a history of what happened, falls are frequently unwitnessed and many older adults who fall do not sustain a head injury. Ordering a head CT scan on every older adult who has fallen would be an inefficient and costly way to diagnose intracranial bleeding when only approximately 5% have intracranial bleeding.[19] Patients awaiting a CT scan will typically occupy an ED bed. CT overuse in this population not only causes prolonged ED visits, but it also contributes to ED overcrowding, which may result in worse outcomes for other patients.[20] Older adults are at greater risk of developing delirium the longer they stay in the ED.[21] There is a need for a simple bedside tool which can rapidly stratify the risk of intracranial bleeding in older ED patients who present after falling. Our aim is to derive a clinical decision rule which will identify older adults who present to the ED after a fall who do not have clinically important intracranial bleeding and therefore do not require a head CT.

METHODS AND ANALYSIS

Study design

This is a prospective cohort study designed to develop a unique clinical decision rule for ED physicians evaluating older adults who have fallen. Clinical decision rules are a commonly applied method of standardized clinical diagnostic decision-making in the ED. The rules incorporate the standardized collection and interpretation of multiple predictor variables from the patient's history, physical examination and test results to optimize evidence-based clinical decision-making. For example, clinical decision rules are used to determine which patients should have cervical spine imaging in trauma,[22] thoracic imaging for pulmonary embolism[23] and admission after syncope.[24] Our study follows the methodological standards for clinical decision rules in emergency medicine[25] and the Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines.[26]

Patient and public involvement

Prior to the protocol development, we conducted a qualitative study with older adults who were waiting in the ED for head CT after a fall. We found that diagnosing intracranial bleeding was important to the participants, that they valued testing tailored to their personal risk and shorter ED visits. This protocol was designed with feedback and input from our patient partners.

Study population

This study is conducted at 11 hospitals in Canada and the United States and enrolls patients aged 65 years or older who present to the ED within 48 hours of having a fall. Patients are eligible if they fall on level ground (either inside or outside), off a chair, toilet seat or out of bed. Patients are included regardless of whether they hit their head. Patients are excluded if they fell down steps, fell from a height, were knocked down by a car/bike/pedestrian or other mechanism of injury. Patients who live outside of the hospital catchment area, who have previously been enrolled in this study, who are transferred from another hospital and who leave the ED prior to completion of their medical assessment are also excluded. Recruitment commenced on January 30, 2019. Patients are recruited 24 hours a day, seven days a week.

Patient assessment

Each patient is assessed at their index ED visit by an emergency physician who decides on the need for head CT based on clinical history and examination. It would be impractical to perform a head CT on all older adults who have fallen, for example, after a simple trip, because there is not always an indication for CT, hospitals have limited resources and ordering a CT delays discharge home. However, if participants return to the ED within 42 days of enrolment with new confusion, headache, loss of balance, repeat falls, change in behaviour, reduced Glasgow Coma Score (GCS) or other neurological symptoms, they will undergo head CT.

Outcome definition and measurement

The primary outcome is '***clinically important intracranial bleeding***' diagnosed within 42 days of the index ED presentation. Our definition was derived after surveying specialists (including neurosurgeons, neurologists, trauma physicians, geriatricians, thrombosis and emergency physicians) who determined that symptoms from intracranial bleeding might develop as late as six weeks after a fall. 'Clinically important intracranial bleeding' is defined as bleeding within the cranial vault (including subdural, intracerebral, intraventricular, subarachnoid, epidural blood and cerebral contusion), which requires medical or surgical treatment. Medical treatment is defined as any of the following: temporary or permanent discontinuation of anticoagulant or antiplatelet medication; administration of an antifibrinolytic drug; reversal of anticoagulation; or admission to hospital for neurological observation. Clinically important intracranial bleeding will be determined by independent adjudication of head CT scans by the centralized outcome adjudication committee consisting of a study neurologist, neurosurgeon, trauma surgeon and radiologist. The adjudicators will be blinded to all ED baseline data. Secondary outcomes relate to the 'severity' of the intracranial bleeding: 1) neurosurgical intervention; 2) intensive care admission; 3) hospital length of stay; 4) in-hospital death as determined by medical record review.

We found poor sensitivity (37%, 95% confidence interval: 21 to 56%) for patient-reported diagnosis of intracranial bleeding.[27] Furthermore, our experience of personal follow up in this population[28] is that it is frequently not feasible because of residence in nursing homes or baseline cognitive impairment. Therefore, the current study follow up is restricted to systematic medical record review with independent validation and enrollment is restricted to patients who reside within the hospital catchment area.

Predictor variables

Demographic and predictor variables are collected in two ways: 1) the treating physician completes a standardized data collection form at the time of initial patient assessment, and before the results of the head CT are available (therefore blinded to outcome); 2) data is collected by trained on-site research assistants using standardized medical record review protocols, following detailed data definitions and instructions for systematic medical record review. We follow standardized validation procedures for all medical record review data points: de-identified source documentation is uploaded for validation by the coordinating centre. A query is sent to the site research assistant to resolve each discrepancy. The study site investigator resolves discrepancies which persist after research assistant review. Table 1 details the demographic and predictor variables collected.

Table 1: Description of collected demographic and predictor variables

	Data collected by treating physician at initial assessment	Data collected by medical record review	Comment on predictor choice for rule derivation
Predictor variables			
Age		x	No association found* but will be included
Sex		x	Trend towards association with male sex*
Head injury (as reported by patient or carer)	x		Plausible higher risk
Loss of consciousness	x		Marker for head injury severity
New amnesia about events of fall	x		Marker for head injury severity
History of previous major bleed[28]		x	Trend towards association* and biologically plausible
Cirrhosis		x	Biologically plausible
Previous diagnosis of ischemic stroke		x	Biologically plausible
Chronic renal impairment	x	x	Association demonstrated*
Reduced Glasgow Coma Score from normal (as indicated by caregiver or family)	x		Association demonstrated*

Bruise or laceration on the head (any size)	x		Association demonstrated*
New abnormality on neurological examination	x		Association demonstrated *
Haemoglobin		x	Biologically plausible
Platelet count		x	Biologically plausible
Anticoagulation medication	x	x	Commonly held dogma
Antiplatelet medication	x	x	Commonly held dogma
Clinical Frailty Score[30]	x		Biologically plausible
Descriptive variables			
Living circumstances		x	No association found*
Diabetes		x	No association found*
Hypertension		x	No association found*
Active cancer within past 2 years		x	No association found*
Dementia		x	No association found*
History of frequent falls		x	Not previously assessed*
Congestive heart failure		x	No association found*
Mechanism of injury		x	No association found*
Weight		x	No association found*
Glasgow coma score at time of physician assessment	x		Reduced Glasgow Coma Score from normal has a stronger association*
Vomiting (once / more than once)	x		No association found*
Signs of basal skull fracture	x		Too rare to assess*
Suspected open or depressed skull fracture	x		Too rare to assess*
Retrograde amnesia for >30 minutes	x		Not previously assessed*

Creatinine		x	No association found*
International normalized ratio (INR)		x	Anticipated missing data

* According to the results of our prior study,[28] N=1753

We initially identified potential predictor variables by a systematic review of prior evidence. We then assessed the frequency among our population and the association between predictor and intracranial bleeding in a study of 1753 older ED patients who had fallen.[28] We selected 17 candidate predictor variables, which are considered to be biologically plausible and related to the outcome of intracranial bleeding, and are routinely collected in the ED: age; sex; head injury; loss of consciousness; amnesia; history of previous major bleed (International Society of Thrombosis and Haemostasis criteria[29]); cirrhosis; prior ischemic stroke; chronic renal impairment; GCS reduced from baseline; bruise or laceration on the head; abnormal neurological examination; haemoglobin, platelet count; anticoagulant therapy; antiplatelet therapy; and, Clinical Frailty Score.[30]

Analysis

Variables with large amounts of missing data will be excluded from the models as they would be missing in clinical practice. Likewise, continuous variables whose distributions are too narrow will also be excluded. We will perform binary recursive partitioning using Classification and Regression Trees to develop a decision rule. A clinical decision rule for a life-threatening event like intracranial bleeding requires very high sensitivity. The model with a sensitivity of > 99% and the highest specificity will be selected. We will assess the derived decision rule by comparing the classification of each patient with his or her actual status for the primary outcomes. In addition, 1000 bootstrap iterations will be performed to assess the internal classification performance and overfitting of the selected decision rule.

We will also develop a predictive risk model using multivariable logistic regression. Continuous variables may be transformed and will be fit using restricted cubic splines to relax the linearity assumption. First, a full model with all variables will be fit. To further reduce the model, we will perform backward elimination without model re-fitting with p <0.5, which has shown to have valid inference.[31,32] Clinically and biologically plausible interactions will be tested within the model. Internal validation to obtain unbiased and optimism corrected estimation of model performance will be done using 1000 bootstrap samples. Model discrimination will be reported using the C-statistic and a calibration plot of observed versus predicted probabilities.

Sample size

The current guidelines suggest that we would require at least 10 events per included variable.[33,34] We expect that 5% of patients will be diagnosed with clinically important intracranial bleeding,[20] and we assume that our initial model will consist of 17 candidate variables. Based on this assumption, a sample size of 4000 should include 200 cases of intracranial bleeding (12 events per variable).

Sources of bias

Intracranial bleeding will be adjudicated blind to all baseline and predictor data. Predictor data is collected before the primary outcome data is collected. However, it is possible that we do not identify every case of intracranial bleeding during the 42-day follow up period. In our prior study, only 60% of patients had a head CT during the index ED visit.[28] Although patients are advised to return if they develop neurological symptoms, it is possible that a patient may die of an intracranial bleed before being diagnosed. Furthermore, 42-day follow-up involves institutional electronic medical record review. If a patient attended an unrelated hospital during follow up and was diagnosed with an intracranial bleed, we might miss this diagnosis. To reduce the chance of this happening, we are restricting study enrollment to patients who reside within the hospital catchment area and most sites have access to records from regional neurosurgical centres. In our prior study where we performed in-person follow up, no patient was diagnosed with an intracranial bleed at another hospital.

Study oversight

The coordinating centre is McMaster University. Electronic data and de-identified source documents are uploaded to a Research Electronic Data Capture (REDCap) database[35,36] and stored on a secure server at McMaster University. The coordinating centre validates all data and supervises the adjudication committee activities. The study steering committee consists of the site investigators.

Ethics and dissemination

Research ethics approval has been obtained from each enrolling site local research ethics board. In our previous study on the same population,[28] we obtained patient consent. An interim analysis showed a number of patients were confused (144/890, 16%) or died before a researcher could ask for their consent (39/890, 4%). Family were often not available in the ED. In all, we were unable to obtain consent from 204/890 (23%) patients. To address this problem, we obtained research ethics board approval to include patients who were unable to give informed consent. It is essential we include patients who cannot consent since they are often the most frail patients who are challenging to evaluate in the ED and frequently excluded from studies. Excluding these patients could limit the generalizability of our clinical decision rule. The current study has research ethics approval at all sites to include patients without obtaining informed consent.

The study results will be submitted for publication in a peer reviewed journal and presented at national and international emergency medicine meetings.

AUTHORS' CONTRIBUTIONS

The study was conceived by KdW, MM, CK, SP and AW. The protocol was designed with input from all authors (KdW, MM, CK, SP, AW, NC, EM, ME, IS, DE, DB, RJ, JM, CV, SM, AP, YK, AS, SS and PE) has been endorsed by the Network of Canadian Emergency Researchers. The study is being conducted by KdW, NC, EM, CV, DE, DB, RJ and JM. YK, AS, SS and PE are the study adjudicators. SP will oversee the analysis.

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BMJ Open

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INTRODUCTION

In contrast to the younger population, the incidence of traumatic intracranial bleeding in older adults is rising[1] and has a worse prognosis.[2,3] Older adults are at higher risk of traumatic intracranial bleeding because there can be loss of the elastic integrity of the cerebral bridging veins and brain atrophy, allowing rapid movements of the brain within the cerebral spinal fluid with trauma. Older adults may be less able to withstand intracranial bleeding because of pre-existing comorbidity, frailty and polypharmacy.

Falling on level ground is now the most common cause of traumatic intracranial bleeding world-wide, accounting for up to 80% of cases.[4-8] Fall-associated intracranial bleeding in older adults is increasing in incidence.[9,10] The mortality rate for fall-associated intracranial bleeding is 15%[7,11] (accounting for half of all fall-associated deaths[12,13]). Rather than seeing a decrease in these deaths, this mortality rate is rising.[10] Emergency departments (EDs) are managing an increasing number of older adults who have fallen[14] and ED visits for fall-related head injuries in older adults have increased year after year.[9,13,15-17] There is a paucity of evidence to guide neuroimaging for intracranial bleeding in older adults.

The Canadian CT Head Rule can determine the need for head computed tomography (CT) in head-injured patients who experienced loss of consciousness, disorientation or amnesia after their injury.[18] However, older ED patients who present after a fall cannot always give a history of what happened, falls are frequently unwitnessed and many older adults who fall do not sustain a head injury. Ordering a head CT scan on every older adult who has fallen would be an inefficient and costly way to diagnose intracranial bleeding when only approximately 5% have intracranial bleeding.[19] Patients awaiting a CT scan will typically occupy an ED bed. CT overuse in this population not only causes prolonged ED visits, but it also contributes to ED overcrowding, which may result in worse outcomes for other patients.[20] Older adults are at greater risk of developing delirium the longer they stay in the ED.[21] There is a need for a simple bedside tool which can rapidly stratify the risk of intracranial bleeding in older ED patients who present after falling. Our aim is to derive a clinical decision rule which will identify older adults who present to the ED after a fall who do not have clinically important intracranial bleeding and therefore do not require a head CT.

METHODS AND ANALYSIS

Study design

This is a prospective cohort study designed to develop a unique clinical decision rule for ED physicians evaluating older adults who have fallen. Clinical decision rules are a commonly applied method of standardized clinical diagnostic decision-making in the ED. The rules incorporate the standardized collection and interpretation of multiple predictor variables from the patient's history, physical examination and test results to optimize evidence-based clinical decision-making. For example, clinical decision rules are used to determine which patients should have cervical spine imaging in trauma,[22] thoracic imaging for pulmonary embolism[23] and admission after syncope.[24] Our study follows the methodological standards for clinical decision rules in emergency medicine[25] and the Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines.[26]

Patient and public involvement

Prior to the protocol development, we conducted a qualitative study with older adults who were waiting in the ED for head CT after a fall. We found that diagnosing intracranial bleeding was important to the participants, that they valued testing tailored to their personal risk and shorter ED visits. This protocol was designed with feedback and input from our patient partners.

Study population

This study is conducted at 11 hospitals in Canada and the United States and enrolls patients aged 65 years or older who present to the ED within 48 hours of having a fall. Patients are eligible if they fall on level ground (either inside or outside), off a chair, toilet seat or out of bed. Patients are included regardless of whether they hit their head. Patients are excluded if they fell down steps, fell from a height, were knocked down by a car/bike/pedestrian or other mechanism of injury. Patients who live outside of the hospital catchment area, who have previously been enrolled in this study, who are transferred from another hospital and who leave the ED prior to completion of their medical assessment are also excluded. Recruitment commenced on January 30, 2019. Patients are recruited 24 hours a day, seven days a week.

Patient assessment

Each patient is assessed at their index ED visit by an emergency physician who decides on the need for head CT based on clinical history and examination. It would be impractical to perform a head CT on all older adults who have fallen, for example, after a simple trip, because there is not always an indication for CT, hospitals have limited resources and ordering a CT delays discharge home. However, if participants return to the ED within 42 days of enrolment with new confusion, headache, loss of balance, repeat falls, change in behaviour, reduced Glasgow Coma Score (GCS) or other neurological symptoms, they will undergo head CT.

Outcome definition and measurement

The primary outcome is '***clinically important intracranial bleeding***' diagnosed within 42 days of the index ED presentation. Our definition was derived after surveying specialists (including neurosurgeons, neurologists, trauma physicians, geriatricians, thrombosis and emergency physicians) who determined that symptoms from intracranial bleeding might develop as late as six weeks after a fall. 'Clinically important intracranial bleeding' is defined as bleeding within the cranial vault (including subdural, intracerebral, intraventricular, subarachnoid, epidural blood and cerebral contusion), which requires medical or surgical treatment. Medical treatment is defined as any of the following: temporary or permanent discontinuation of anticoagulant or antiplatelet medication; administration of an antifibrinolytic drug; reversal of anticoagulation; or admission to hospital for neurological observation. Clinically important intracranial bleeding will be determined by independent adjudication of head CT scans by the centralized outcome adjudication committee consisting of a study neurologist, neurosurgeon, trauma surgeon and radiologist. The adjudicators will be blinded to all ED baseline data. Secondary outcomes relate to the 'severity' of the intracranial bleeding: 1) neurosurgical intervention; 2) intensive care admission; 3) hospital length of stay; 4) in-hospital death as determined by medical record review.

We found poor sensitivity (37%, 95% confidence interval: 21 to 56%) for patient-reported diagnosis of intracranial bleeding.[27] Furthermore, our experience of personal follow up in this population[28] is that it is frequently not feasible because of residence in nursing homes or baseline cognitive impairment. Therefore, the current study follow up is restricted to systematic medical record review with independent validation and enrollment is restricted to patients who reside within the hospital catchment area.

171 **Predictor variables**

172 Demographic and predictor variables are collected in two ways: 1) the treating physician completes a standardized data collection form at the time of initial patient assessment, and before the results of the head CT are available (therefore blinded to outcome); 2) data is collected by trained on-site research assistants using standardized medical record review protocols, following detailed data definitions and instructions for systematic medical record review. We follow standardized validation procedures for all medical record review data points: de-identified source documentation is uploaded for validation by the coordinating centre. A query is sent to the site research assistant to resolve each discrepancy. The study site investigator resolves discrepancies which persist after research assistant review. Table 1 details the demographic and predictor variables collected.

Table 1: Description of collected demographic and predictor variables

	Data collected by treating physician at initial assessment	Data collected by medical record review	Comment on predictor choice for rule derivation
Predictor variables			
Age		x	No association found* but will be included
Sex		x	Trend towards association with male sex*
Head injury (as reported by patient or carer)	x		Plausible higher risk
Loss of consciousness	x		Marker for head injury severity
New amnesia about events of fall	x		Marker for head injury severity
History of previous major bleed[28]		x	Trend towards association* and biologically plausible
Cirrhosis		x	Biologically plausible
Previous diagnosis of ischemic stroke		x	Biologically plausible
Chronic renal impairment	x	x	Association demonstrated*
Reduced Glasgow Coma Score from normal (as indicated by caregiver or family)	x		Association demonstrated*

Bruise or laceration on the head (any size)	x		Association demonstrated*
New abnormality on neurological examination	x		Association demonstrated *
Haemoglobin		x	Biologically plausible
Platelet count		x	Biologically plausible
Anticoagulation medication	x	x	Commonly held dogma
Antiplatelet medication	x	x	Commonly held dogma
Clinical Frailty Score[30]	x		Biologically plausible
Descriptive variables			
Living circumstances		x	No association found*
Diabetes		x	No association found*
Hypertension		x	No association found*
Active cancer within past 2 years		x	No association found*
Dementia		x	No association found*
History of frequent falls		x	Not previously assessed*
Congestive heart failure		x	No association found*
Mechanism of injury		x	No association found*
Weight		x	No association found*
Glasgow coma score at time of physician assessment	x		Reduced Glasgow Coma Score from normal has a stronger association*
Vomiting (once / more than once)	x		No association found*
Signs of basal skull fracture	x		Too rare to assess*
Suspected open or depressed skull fracture	x		Too rare to assess*
Retrograde amnesia for >30 minutes	x		Not previously assessed*

Creatinine		x	No association found*
International normalized ratio (INR)		x	Anticipated missing data

* According to the results of our prior study,[28] N=1753

We initially identified potential predictor variables by a systematic review of prior evidence. We then assessed the frequency among our population and the association between predictor and intracranial bleeding in a study of 1753 older ED patients who had fallen.[28] We selected 17 candidate predictor variables, which are considered to be biologically plausible and related to the outcome of intracranial bleeding, and are routinely collected in the ED: age; sex; head injury; loss of consciousness; amnesia; history of previous major bleed (International Society of Thrombosis and Haemostasis criteria[29]); cirrhosis; prior ischemic stroke; chronic renal impairment; GCS reduced from baseline; bruise or laceration on the head; abnormal neurological examination; haemoglobin, platelet count; anticoagulant therapy; antiplatelet therapy; and, Clinical Frailty Score.[30]

Analysis

Variables with large amounts of missing data will be excluded from the models as they would be missing in clinical practice. Likewise, continuous variables whose distributions are too narrow will also be excluded. We will perform binary recursive partitioning using Classification and Regression Trees to develop a decision rule. A clinical decision rule for a life-threatening event like intracranial bleeding requires very high sensitivity. The model with a sensitivity of > 99% and the highest specificity will be selected. We will assess the derived decision rule by comparing the classification of each patient with his or her actual status for the primary outcomes. In addition, 1000 bootstrap iterations will be performed to assess the internal classification performance and overfitting of the selected decision rule.

We will also develop a predictive risk model using multivariable logistic regression. Continuous variables may be transformed and will be fit using restricted cubic splines to relax the linearity assumption. First, a full model with all variables will be fit. To further reduce the model, we will perform backward elimination without model re-fitting with p <0.5, which has shown to have valid inference.[31,32] Clinically and biologically plausible interactions will be tested within the model. Internal validation to obtain unbiased and optimism corrected estimation of model performance will be done using 1000 bootstrap samples. Model discrimination will be reported using the C-statistic and a calibration plot of observed versus predicted probabilities.

Sample size

The current guidelines suggest that we would require at least 10 events per included variable.[33,34] We expect that 5% of patients will be diagnosed with clinically important intracranial bleeding,[20] and we assume that our initial model will consist of 17 candidate variables. Based on this assumption, a sample size of 4000 should include 200 cases of intracranial bleeding (12 events per variable).

Sources of bias

Intracranial bleeding will be adjudicated blind to all baseline and predictor data. Predictor data is collected before the primary outcome data is collected. However, it is possible that we do not identify every case of intracranial bleeding during the 42-day follow up period. In our prior study, only 60% of patients had a head CT during the index ED visit.[28] Although patients are advised to return if they develop neurological symptoms, it is possible that a patient may die of an intracranial bleed before being diagnosed. Furthermore, 42-day follow-up involves institutional electronic medical record review. If a patient attended an unrelated hospital during follow up and was diagnosed with an intracranial bleed, we might miss this diagnosis. To reduce the chance of this happening, we are restricting study enrollment to patients who reside within the hospital catchment area and most sites have access to records from regional neurosurgical centres. In our prior study where we performed in-person follow up, no patient was diagnosed with an intracranial bleed at another hospital.

Study oversight

The coordinating centre is McMaster University. Electronic data and de-identified source documents are uploaded to a Research Electronic Data Capture (REDCap) database[35,36] and stored on a secure server at McMaster University. The coordinating centre validates all data and supervises the adjudication committee activities. The study steering committee consists of the site investigators.

Ethics and dissemination

Research ethics approval has been obtained from each enrolling site local research ethics board. In our previous study on the same population,[28] we obtained patient consent. An interim analysis showed a number of patients were confused (144/890, 16%) or died before a researcher could ask for their consent (39/890, 4%). Family were often not available in the ED. In all, we were unable to obtain consent from 204/890 (23%) patients. To address this problem, we obtained research ethics board approval to include patients who were unable to give informed consent. It is essential we include patients who cannot consent since they are often the most frail patients who are challenging to evaluate in the ED and frequently excluded from studies. Excluding these patients could limit the generalizability of our clinical decision rule. The current study has research ethics approval at all sites to include patients without obtaining informed consent.

The study results will be submitted for publication in a peer reviewed journal and presented at national and international emergency medicine meetings.

AUTHORS' CONTRIBUTIONS

The study was conceived by KdW, MM, CK, SP and AW. The protocol was designed with input from all authors (KdW, MM, CK, SP, AW, NC, EM, ME, IS, DE, DB, RJ, JM, CV, SM, AP, YK, AS, SS and PE) has been endorsed by the Network of Canadian Emergency Researchers. The study is being conducted by KdW, NC, EM, CV, DE, DB, RJ and JM. YK, AS, SS and PE are the study adjudicators. SP will oversee the analysis.

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Which older emergency patients are at risk of intracranial bleeding after a fall? A protocol to derive a clinical decision rule for the emergency department.

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ABSTRACT

Introduction

Falling on level ground is now the most common cause of traumatic intracranial bleeding world-wide. Older adults frequently present to the emergency department after falling. It can be challenging for clinicians to determine who requires brain imaging to rule out traumatic intracranial bleeding, and often head injury decision rules do not apply to older adults who fall. The goal of our study is to derive a clinical decision rule which will identify older adults who present to the emergency department after a fall who do not have clinically important intracranial bleeding.

Methods and analysis

This is a prospective cohort study enrolling patients aged 65 years or older, who present to the emergency department of 11 hospitals in Canada and the United States within 48 hours of having a fall. Patients are included if they fall on level ground, off a chair, toilet seat or out of bed. The primary outcome is the diagnosis of clinically relevant intracranial bleeding within 42 days of the index emergency department visit. An independent adjudication committee will determine the primary outcome, blinded to all other data. We are collecting data on 17 potential predictor variables. The treating physician completes a study data form at the time of initial assessment, prior to brain imaging. Data extraction is supplemented by an independent, structured electronic medical record review. We will perform binary recursive partitioning using Classification and Regression Trees to derive a clinical decision rule.

Ethics and dissemination

The study was initially approved by Hamilton Integrated Research Ethics Committee and subsequently approved by the research ethics boards governing all participating sites. We will disseminate our results by journal publication, presentation at international meetings and social media.

Registration details ClinicalTrials.gov NCT03745755

ARTICLE SUMMARY

Strengths and limitations of this study

- This cohort study aims to derive a clinical decision rule which identifies older adults at risk of intracranial bleeding after a fall.
- This is a large study enrolling patients from 11 hospitals in two countries.
- Potential predictor variables are recorded by emergency physicians prior to CT scanning.
- The primary outcome, clinically important intracranial bleeding, is determined by an independent adjudication committee.
- The main limitation is that not all patients will have head CT imaging at their initial emergency department visit.

INTRODUCTION

In contrast to the younger population, the incidence of traumatic intracranial bleeding in older adults is rising[1] and has a worse prognosis.[2,3] Older adults are at higher risk of traumatic intracranial bleeding because there can be loss of the elastic integrity of the cerebral bridging veins and brain atrophy, allowing rapid movements of the brain within the cerebral spinal fluid with trauma. Older adults may be less able to withstand intracranial bleeding because of pre-existing comorbidity, frailty and polypharmacy.

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Study design

This is a prospective cohort study designed to develop a unique clinical decision rule for ED physicians evaluating older adults who have fallen. Clinical decision rules are a commonly applied method of standardized clinical diagnostic decision-making in the ED. The rules incorporate the standardized collection and interpretation of multiple predictor variables from the patient's history, physical examination and test results to optimize evidence-based clinical decision-making. For example, clinical decision rules are used to determine which patients should have cervical spine imaging in trauma,[22] thoracic imaging for pulmonary embolism[23] and admission after syncope.[24] Our study follows the methodological standards for clinical decision rules in emergency medicine[25] and the Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines.[26]

The study was approved by the Hamilton Integrated Research Ethics Board, Ottawa Health Science Network Research Ethics Board, Mount Sinai Hospital Research Ethics Board, Comité d'éthique du CHU de Québec-Université Laval, Providence Health Care Research Ethics Board and the Institutional Review Board of St. Luke's University Health Network.

Patient and public involvement

Prior to the protocol development, we conducted a qualitative study with older adults who were waiting in the ED for head CT after a fall. We found that diagnosing intracranial bleeding was important to the participants, that they valued testing tailored to their personal risk and shorter ED visits. This protocol was designed with feedback and input from our patient partners.

Study population

This study is conducted at 11 hospitals in Canada and the United States and enrolls patients aged 65 years or older who present to the ED within 48 hours of having a fall. Patients are eligible if they fall on level ground (either inside or outside), off a chair, toilet seat or out of bed. Patients are included regardless of whether they hit their head. Patients are excluded if they fell down steps, fell from a height, were knocked down by a car/bike/pedestrian or other mechanism of injury. Patients who live outside of the hospital catchment area, who have previously been enrolled in this study, who are transferred from another hospital and who leave the ED prior to completion of their medical assessment are also excluded. Recruitment commenced on January 30, 2019. Patients are recruited 24 hours a day, seven days a week.

Patient assessment

Each patient is assessed at their index ED visit by an emergency physician who decides on the need for head CT based on clinical history and examination. It would be impractical to perform a head CT on all older adults who have fallen, for example, after a simple trip, because there is not always an indication for CT, hospitals have limited resources and ordering a CT delays discharge home. However, if participants return to the ED within 42 days of enrolment with new confusion, headache, loss of balance, repeat falls, change in behaviour, reduced Glasgow Coma Score (GCS) or other neurological symptoms, they will undergo head CT.

Outcome definition and measurement

The primary outcome is '***clinically important intracranial bleeding***' diagnosed within 42 days of the index ED presentation. Our definition was derived after surveying specialists (including neurosurgeons, neurologists, trauma physicians, geriatricians, thrombosis and emergency physicians) who determined that symptoms from intracranial bleeding might develop as late as six weeks after a fall. 'Clinically important intracranial bleeding' is defined as bleeding within the cranial vault (including subdural, intracerebral, intraventricular, subarachnoid, epidural blood and cerebral contusion), which requires medical or surgical treatment. Medical treatment is defined as any of the following: temporary or permanent discontinuation of anticoagulant or antiplatelet medication; administration of an antifibrinolytic drug; reversal of anticoagulation; or admission to hospital for neurological observation. Clinically important intracranial bleeding will be determined by independent adjudication of head CT scans by the centralized outcome adjudication committee consisting of a study neurologist, neurosurgeon, trauma surgeon and radiologist. The adjudicators will be blinded to all ED baseline data. Each scan will be adjudicated independently by two reviewers. In the case of a disagreement, a third adjudicator, blinded to the prior reviews, will determine the classification. Agreement between the adjudicators will be reported. Secondary outcomes relate to the 'severity' of the intracranial bleeding: 1) neurosurgical intervention; 2) intensive care admission; 3) hospital length of stay; 4) in-hospital death as determined by medical record review.

We found poor sensitivity (37%, 95% confidence interval: 21 to 56%) for patient-reported diagnosis of intracranial bleeding.[27] Furthermore, our experience of personal follow up in this population[28] is that it is frequently not feasible because of residence in nursing homes or baseline cognitive impairment. Therefore, the current study follow up is restricted to systematic medical record review with independent validation and enrollment is restricted to patients who reside within the hospital catchment area.

Predictor variables

Demographic and predictor variables are collected in two ways: 1) the treating physician completes a standardized data collection form at the time of initial patient assessment, and before the results of the head CT are available (therefore blinded to outcome); 2) data is collected by trained on-site research assistants using standardized medical record review protocols, following detailed data definitions and instructions for systematic medical record review. We follow standardized validation procedures for all medical record review data points: de-identified source documentation is uploaded for validation by the coordinating centre. A query is sent to the site research assistant to resolve each discrepancy. The study site investigator resolves discrepancies which persist after research assistant review. Table 1 details the demographic and predictor variables collected.

We initially identified potential predictor variables by a systematic review of prior evidence. We then assessed the frequency among our population and the association between predictor and intracranial bleeding in a study of 1753 older ED patients who had fallen.[28] We selected 17 candidate predictor variables, which are considered to be biologically plausible and related to the outcome of intracranial bleeding, and are routinely collected in the ED: age; sex; head injury; loss of consciousness; amnesia; history of previous major bleed (International Society of Thrombosis and Haemostasis criteria[29]); cirrhosis; prior ischemic stroke; chronic renal impairment; GCS reduced from baseline; bruise or laceration on the head; abnormal neurological examination; haemoglobin, platelet count; anticoagulant therapy; antiplatelet therapy; and, Clinical Frailty Score.[30]

Analysis

Variables with large amounts of missing data will be excluded from the models as they would be missing in clinical practice. Likewise, continuous variables whose distributions are too narrow will also be excluded. We will perform binary recursive partitioning using Classification and Regression Trees to develop a decision rule. A clinical decision rule for a life-threatening event like intracranial bleeding requires very high sensitivity. The model with a sensitivity of > 99% and the highest specificity will be selected. We will assess the derived decision rule by comparing the classification of each patient with his or her actual status for the primary outcomes. In addition, 1000 bootstrap iterations will be performed to assess the internal classification performance and overfitting of the selected decision rule.

We will also develop a predictive risk model using multivariable logistic regression. Continuous variables may be transformed and will be fit using restricted cubic splines to relax the linearity assumption. First, a full model with all variables will be fit. To further reduce the model, we will perform backward elimination without model re-fitting with p <0.5, which has shown to have valid inference.[31,32] Clinically and biologically plausible interactions will be tested within the model. Internal validation to obtain unbiased and optimism corrected estimation of model performance will be done using 1000 bootstrap samples. Model discrimination will be reported using the C-statistic and a calibration plot of observed versus predicted probabilities.

<u>Sample size</u>

The current guidelines suggest that we would require at least 10 events per included variable.[33,34] We expect that 5% of patients will be diagnosed with clinically important intracranial bleeding,[20] and we assume that our initial model will consist of 17 candidate variables. Based on this assumption, a sample size of 4000 should include 200 cases of intracranial bleeding (12 events per variable).

<u>Sources of bias</u>

Intracranial bleeding will be adjudicated blind to all baseline and predictor data. Predictor data is collected before the primary outcome data is collected. However, it is possible that we do not identify every case of intracranial bleeding during the 42-day follow up period. In our prior study, only 60% of patients had a head CT during the index ED visit and 6/738 participants without a head CT (0.8%) were subsequently diagnosed with intracranial bleeding within 42 days.[28] In comparison, 6/939 (0.6%) with a negative head CT were diagnosed with intracranial bleeding within 42 days, suggesting emergency physicians may correctly identify lower risk patients who do not require a scan. However, this evidence is indirect and hypothesis generating only. Given that not all participants in this study will have a head CT scan at baseline, we may underdiagnose intracranial bleeding in this subpopulation which will comprise around 40% of the cohort. Although patients are advised to return if they develop neurological symptoms, it is possible that a patient may die of an intracranial bleed or else fully recover without testing for intracranial bleeding. Furthermore, 42-day follow-up involves institutional electronic medical record review. If a patient attended an unrelated hospital during follow up and was diagnosed with an intracranial bleed, we might miss this diagnosis. To reduce the chance of this happening, we are restricting study enrollment to patients who reside within the hospital catchment area and most sites have access to records from regional neurosurgical centres. In our prior study where we performed in-person follow up, no patient was diagnosed with an intracranial bleed at another hospital. The imperfect reference standard bias introduced with differential testing depending on the emergency physician CT request, might inflate the strength of association between predictor variables which are commonly utilized to determine the need for head CT in this population (such as a history of loss of consciousness and anticoagulation use).

Study oversight

The coordinating centre is McMaster University. Electronic data and de-identified source documents are uploaded to a Research Electronic Data Capture (REDCap) database[35,36] and stored on a secure server at McMaster University. The coordinating centre validates all data and supervises the adjudication committee activities. The study steering committee consists of the site investigators.

Ethics and dissemination

Research ethics approval has been obtained from each enrolling site local research ethics board. In our previous study on the same population,[28] we obtained patient consent. An interim analysis showed a number of patients were confused (144/890, 16%) or died before a researcher could ask for their consent (39/890, 4%). Family were often not available in the ED. In all, we were unable to obtain consent from 204/890 (23%) patients. To address this problem, we obtained research ethics board approval to include patients who were unable to give informed consent. It is essential we include patients who cannot consent since they are often the most frail patients who are challenging to evaluate in the ED and frequently excluded from studies. Excluding these patients could limit the generalizability of our clinical decision rule. The current study has research ethics approval at all sites to include patients without obtaining informed consent.

The study results will be submitted for publication in a peer reviewed journal and presented at national and international emergency medicine meetings.

AUTHORS' CONTRIBUTIONS

The study was conceived by KdW, MM, CK, SP and AW. The protocol was designed with input from all authors (KdW, MM, CK, SP, AW, NC, EM, ME, IS, DE, DB, RJ, JM, CV, SM, AP, YK, AS, SS and PE) has been endorsed by the Network of Canadian Emergency Researchers. The study is being conducted by KdW, NC, EM, CV, DE, DB, RJ and JM. YK, AS, SS and PE are the study adjudicators. SP will oversee the analysis.

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Table 1: Description of collected demographic and predictor variables

	Data collected by treating physician at initial assessment	Data collected by medical record review	Comment on predictor choice for rule derivation
Predictor variables			
Age		x	No association found* but will be included
Sex		x	Trend towards association with male sex*
Head injury (as reported by patient or carer)	x		Plausible higher risk
Loss of consciousness	x		Marker for head injury severity
New amnesia about events of fall	x		Marker for head injury severity
History of previous major bleed[28]		x	Trend towards association* and biologically plausible
Cirrhosis		x	Biologically plausible
Previous diagnosis of ischemic stroke		x	Biologically plausible
Chronic renal impairment	x	x	Association demonstrated*
Reduced Glasgow Coma Score from normal (as indicated by caregiver or family)	x		Association demonstrated*
Bruise or laceration on the head (any size)	x		Association demonstrated*
New abnormality on neurological examination	x		Association demonstrated *
Haemoglobin		x	Biologically plausible
Platelet count		x	Biologically plausible
Anticoagulation medication	x	x	Commonly held dogma
Antiplatelet medication	x	x	Commonly held dogma
Clinical Frailty Score[30]	x		Biologically plausible

Descriptive variables			
Living circumstances		x	No association found*
Diabetes		x	No association found*
Hypertension		x	No association found*
Active cancer within past 2 years		x	No association found*
Dementia		x	No association found*
History of frequent falls		x	Not previously assessed*
Congestive heart failure		x	No association found*
Mechanism of injury		x	No association found*
Weight		x	No association found*
Glasgow coma score at time of physician assessment	x		Reduced Glasgow Coma Score from normal has a stronger association*
Vomiting (once / more than once)	x		No association found*
Signs of basal skull fracture	x		Too rare to assess*
Suspected open or depressed skull fracture	x		Too rare to assess*
Retrograde amnesia for >30 minutes	x		Not previously assessed*
Creatinine		x	No association found*
International normalized ratio (INR)		x	Anticipated missing data

* According to the results of our prior study,[28] N=1753