Performance of mortality prediction models in older adults with TBI

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Abstract

Traumatic brain injury (TBI) is a rising cause of disability and death in older adults. However, this population has been understudied in this context and current TBI mortality prediction models were developed and validated on younger cohorts. This study tested the accuracy of TBI mortality prediction models on a cohort of real-world older adults who sustained a TBI, and explored mortality predictors in this population.

TRACK-Geriatrics TBI (TRACK-GERI) is a two-center prospective observational study of adults 65+ years old who presented to the emergency department (ED) 72 hours after a TBI. This study's cohort (n=90) included participants who had a CT positive for intracranial trauma and excluded participants who died due to causes unrelated to their TBI.

The accuracy of 6-month mortality prediction models Marshall's CT score, Rotterdam score and IMPACT models was evaluated, and individual CT, clinical and lab predictors were tested for their association with mortality. Subgroup analysis of participants who died and were misclassified by the models was carried out. Survivors' functional status was assessed at 6 months using Glasgow Coma Outcome Scale extended (GOSE).

6-month mortality rate was 13% (n=12). Marshall's CT score had a sensitivity of 67% (AUC = 0.81, 95% CI: 0.67-0.96), Rotterdam Score had a sensitivity of 58% (AUC=0.78, 95% CI: 0.60-0.96), IMPACT Lab model had a sensitivity of 75% and specificity of 87% (AUC=0.81, 95% CI: 0.65-0.97). IMPACT Extended achieved an AUC of 0.76 (95% CI: 0.60-0.91) and IMPACT core model performed poorly (AUC=0.45, 95% CI: 0.28-0.71) in our cohort.

CT findings basal cisterns effacement and midline shift showed a statistically significant correlation to 6-month mortality (p-value<0.001), but epidural, subarachnoid and intraventricular hematoma (which are used in the Rotterdam score and IMPACT model) did not. Non-hemorrhagic findings such as contusion, edema and shear were correlated to 6-month mortality (p-value=0.004, 0.002, 0.009). Clinical features motor GCS, pupil reactivity, hypoxia and hypotension (used in IMPACT core and extended models) were not significantly correlated to the outcome, same as hemoglobin (used in IMPACT lab model). ED Blood glucose levels were higher in those who died (mean 160 mg/dL vs. 130 mg/dL, p-value=0.004), and ED hyperglycemia (>200 mg/dL) was correlated to mortality (p-value=0.006).

Of 63 participants who were assessed at 6 months, 35 (45%) achieved good recovery (GOSE=7 or 8) while 17 participants (12%) sustained severe disability (GOSE=3).

In conclusion, current 6-month mortality prediction models showed low sensitivity (54%-75%) in our cohort of older adults, and IMPACT core model proved to be inadequate. Many predictors used in current outcome prediction models were not

significantly correlated to mortality in our cohort. Other predictors such as non-hemorrhagic CT pathologies and ED glucose levels may be used to improve outcome prediction in older adults.

Introduction

Traumatic brain injury (TBI) is a significant cause of disability and mortality, with over 2.87 million emergency department (ED) visits per year in the US [1]. Older adults have the highest incidence of TBI cases and TBI-related hospitalizations [2]. TBI-related death rate was highest in persons aged ≥75 (76.7 per 100,000), followed by those aged 65-74 years old (24.5 per 100,000) [3].

These mortality rates may be an underestimate as most studies exclude persons who died before reaching a hospital or those who did not seek medical attention. While TBI incidence, hospitalizations and deaths due to MVA decrease over time in high-income countries [2], rates of TBI due to falls in older adults are continually on the rise [2,4–7].

TBI in older adults has different characteristics compared to younger age groups. Although the majority of TBIs in older adults are considered mild (Glasgow Coma scale-GCS 15-13), TBI mortality rates are higher compared to younger age groups, with 19% in-hospital mortality for persons 65+ years old compared to 6% among persons 16-64 years old [8]. It is well established that the most common injury mechanism in older adults is falls [2,3,9,10], compared to motor vehicle accidents and suicide in younger age groups[3]. Pre-injury cognitive impairment may bias clinical assessment in older adults with TBI [10]. Frailty [11], comorbidities [10] and use of anticoagulants[12] may contribute to complications and worse outcomes.

Mortality prediction models can identify high-risk patients and aid in clinical decision making. Prediction models can detect risk factors that may be preventable or modifiable. They can also reveal associations and interactions between predictors that can lead to a better understanding of TBI pathophysiology and epidemiology.

Despite the rising rates and numbers, TBI in older adults has been understudied. Current TBI mortality prediction models were developed and validated on predominantly young cohorts. The median age in the cohort used for establishing Marshall's CT score[13,14] was 26 years (Inter Quartile Range IQR: 21-40), the mean age in the cohorts used for Rotterdam's score[15,16] and the International Mission for Prognosis and Clinical Trial Design in Traumatic Brain Injury (IMPACT) models[17] was 34 years and 30 years, respectively. Rotterdam's score, which is used clinically, was developed on a cohort that excluded patients who are older than 65 years [15]. In addition, all of these models included patients with moderate (Glasgow Comma Scale= GCS 12-9) or severe (GCS 8-3) TBI. This inclusion criterion will have excluded the majority of CT-positive TBI cases in older adults, as older adults are more likely to present with a high GCS even in the setting of substantial intracranial traumatic pathology [18]. Rotterdam score and IMPACT models were developed mostly on data from clinical trials, which do not necessarily represent the real-life TBI population.

A few studies validated these models in small cohorts of older adults. One study[19] tested the performance of IMPACT models in 202 older adults (age 65+) and found adequate discrimination (ROC AUC=0.75 compared to 0.81 in a younger cohort) and poor calibration, with a substantial under-prediction of mortality for older adults. Another study[20] used a cohort of 104 older adults who sustained an MVA-related moderate or severe TBI and found a ROC AUC of 0.95-0.98 for the IMPACT models.

In summary, there is a need for validation of current TBI mortality prediction models in a real-world cohort of older adults, and identify predictors that are relevant for mortality prediction in this population.

The aim of this study was to begin to fill this gap in knowledge by testing the accuracy of current TBI mortality prediction models on a cohort of older adults who presented to the emergency department with a TBI, and explored possible mortality predictors in this population.

Methods

Participants

Transforming Research And Clinical Knowledge in Geriatric Traumatic Brain Injury -Geriatrics TBI (TRACK-GERI) is a two-center prospective observational study of adults 65+ years old who presented to the emergency department within 72 hours of head trauma who received CT. Participant and study partner dyads were followed-up for 12 months.

This study included only those participants who had a CT positive for acute intracranial trauma (regardless of their GCS) and had 6-month mortality data available. Participants who died due to reasons unrelated to their TBI (N=2; see Figure XX) were excluded, to diminish the confounding effects of competing mortality risks such as comorbidity and frailty, for which there already exists many validated mortality prediction models [21–23]. The final analytic cohort included N=90 participants with CT-positive TBI. The study was approved by the institutional review board of each participating center and informed consent was obtained from the participant or legally authorized representative.

Data

Data on participants' demographics, pre-injury clinical characteristics, injury characteristics, mortality, cognitive and functional outcomes at 2 weeks, 3 months and 6 months were collected from participants, their study partners, and electronic medical records. TBI CDEs [24] were coded from ED CT images by a neuroradiologist blinded to all clinical data except age. Our outcome was death by 6 months due to study TBI. Participants' characteristics were compared by mortality outcome.

Models' implementation

Marshall's CT score: Marshall[13] defined 6 categories of head injury based on CT findings. In order to convert this 6-level score to a binary score we used the cut-off used in IMPACT models: diffuse injuries (categories I and II) were assigned a score of 0 and all other categories (swelling, midline shift, evacuated and non-evacuated mass) were assigned a score of 1.

Rotterdam's score: Similarly to Marshall's score, Rotterdam score was developed based on CT findings. It includes midline shift and basal cisterns effacement, the presence of Epidural hematoma (EDH), Subarachnoid hematoma (SAH) and Intraventricular hematoma (IVH). Rotterdam score ranges between 1 and 6 and was calculated for each participant according to Rotterdam's score chart[15].

IMPACT models: Steyerberg et al. developed 3 models, which included the following predictors:

1. IMPACT Core model- age, GCS motor score and pupils' reaction to light in ED.

2. IMPACT Extended model- Core model + CT findings (Marshall score, traumatic SAH, EDH), hypoxia and hypotension at arrival to ED.

3. IMPACT Lab model - extended model + blood glucose and blood hemoglobin in ED.

Models were implemented using the model coefficients published by the authors[17] for 6-month mortality and a final score was calculated for each model.

Statistical Analysis

Clinical characteristics and CT characteristics of the cohort were compared between those who survived and those who died by 6 months, using Wilcoxon rank-sum test and Fisher's exact test.

Accuracy of each model's final score to predict 6-month mortality in the cohort was tested using logistic regression models. Models were assessed using the Area Under Curve of the Receiver Operating Characteristic curve (AUC). Models' sensitivity and specificity were calculated using the optimal threshold obtained from the ROC curve using Youden's J statistic (maximal distance from the diagonal line, maximizing both sensitivity and specificity). Sensitivity and specificity of Marshall's CT score were calculated based on a threshold of injury category > II, as used in the IMAPCT models. To test for differences between models' performance, pairwise comparisons of AUCs of the 3 models were performed using DeLong's test for two correlated ROC curves.
All predictors included in Marshall's classification, Rotterdam score and IMPACT model were tested for their association with 6-month mortality using Wilcoxon rank-sum test and Fisher's exact test. The variables tested were age, GCS motor, pupil reactivity, ED hypoxia, ED hypotension, ED hemoglobin and ED glucose.

Odds ratios and their 95% confidence intervals were derived using logistic regression models for each predictor. Additional TBI Common Data Element CT findings [24] were

tested for their correlation to the outcome using the same methods: shear, edema, contusion, skull fracture and number of CT findings indicating intracranial trauma.

Models' error analysis was performed using confusion matrices for Marshall's CT score, Rotterdam score and IMPACT lab model. A descriptive subgroup analysis of participants who died was carried out, to identify characteristics of participants who died but were predicted to survive by mortality prediction models (false negatives).
Functional status of survivors at 6 months was evaluated and described using Glasgow Coma Scale Extended (GOSE). GOSE describes functional ability and participation post TBI and ranges between 1 (dead) and 8 (full recovery).

Data analysis was performed in R 4.2.2 [25]. Statistical significance was assessed at $p<0.05$.

Results

Clinical characteristics are shown in Table 1. There's an overall higher proportion of females who sustain a TBI (but a larger proportion of males who died). Most TBIs were caused by falls: the injury mechanism in 60% of TBI cases was a ground level fall, and another 19% were caused by a fall from height. 90% of participants presented with GCS 13-15.

6-month mortality rate was 13% overall, 12% among those presenting with GCS 13-15, and 33% among those presenting with GCS <13.

Overall, twelve participants died. 6 died in the hospital, of whom, 5 died within 2 weeks and one died within 3 months. 6 died after discharge, of whom,3 died within 2 weeks and 3 died within 3 months. No additional deaths occurred between 3 months and 6 months.

TBI severity was worse in those who died, with 25% severe TBI vs. 7.7% in those who survived. It should be noted that 6 out of 9 participants who sustained a moderate-severe TBI survived.

Table 1. Demographic, injury and clinical characteristics

	Overall (N=90)	**Died (N=12)**	**Survived (N=78)**	**P-value**
Age				0.412
Mean (SD)	77 (± 7.5)	75 (± 7.6)	77 (± 7.5)	
Sex female	49 (54.4%)	5 (41.7%)	44 (56.4%)	0.369
Race white	78 (86.7%)	11 (91.7%)	67 (85.9%)	1

Table 1. Demographic, injury and clinical characteristics

	Overall (N=90)	Died (N=12)	Survived (N=78)	P-value
Injury mechanism				0.514
Ground level fall	54 (60.0%)	6 (50.0%)	48 (61.5%)	
Fall from height	17 (18.9%)	3 (25.0%)	14 (17.9%)	
Motor vehicle accident	11 (12.2%)	1 (8.3%)	10 (12.8%)	
Assault	3 (3.3%)	1 (8.3%)	2 (2.6%)	
Other	5 (5.6%)	1 (8.3%)	4 (5.1%)	
Glasgow Coma Scale (GCS)				0.019
15	51 (56.7%)	3 (25.0%)	48 (61.5%)	
14	24 (26.7%)	6 (50.0%)	18 (23.1%)	
13	6 (6.7%)	0 (0%)	6 (7.7%)	
<13	9 (10.0%)	3 (25.0%)	6 (7.7%)	
TBI severity by GCS				0.009
Mild	81 (90.0%)	9 (75.0%)	72 (92.3%)	
Moderate	5 (5.6%)	0 (0%)	5 (6.4%)	
Severe	4 (4.4%)	3 (25.0%)	1 (1.3%)	
Time from injury to first CT scan (hours)				0.71
Mean (SD)	5.1 (± 11)	6.6 (± 14)	4.8 (± 11)	
Missing	5 (5.6%)	0 (0%)	5 (6.4%)	
LOC - Loss of Consciousness				0.765
No	41 (45.6%)	5 (41.7%)	36 (46.2%)	
Yes	47 (52.2%)	7 (58.3%)	40 (51.3%)	
Missing	2 (2.2%)	0 (0%)	2 (2.6%)	
PTA - Post-traumatic Amnesia				0.535

Table 1. Demographic, injury and clinical characteristics

	Overall (N=90)	Died (N=12)	Survived (N=78)	P-value
No	40 (44.4%)	4 (33.3%)	36 (46.2%)	
Yes	48 (53.3%)	8 (66.7%)	40 (51.3%)	
Missing	2 (2.2%)	0 (0%)	2 (2.6%)	
ED disposition				0.153
Hospital admit no ICU	39 (43.3%)	3 (25.0%)	36 (46.2%)	
Hospital admit with ICU	39 (43.3%)	9 (75.0%)	30 (38.5%)	
ED Discharge	2 (2.2%)	0 (0%)	2 (2.6%)	
Missing	10 (11.1%)	0 (0%)	10 (12.8%)	
Discharge disposition				<0.001
Home	33 (36.7%)	2 (16.7%)	31 (39.7%)	
Rehabilitation	4 (4.4%)	0 (0%)	4 (5.1%)	
Nursing facility	8 (8.9%)	0 (0%)	8 (10.3%)	
Died before discharge	6 (6.7%)	6 (50.0%)	0 (0%)	
Missing	39 (43.3%)	4 (33.3%)	35 (44.9%)	
Charlson Comorbidity Index (range 2-37 (worst))				0.352
Mean (SD)	4.2 (± 1.5)	4.6 (± 1.4)	4.1 (± 1.5)	
Missing	14 (15.6%)	4 (33.3%)	10 (12.8%)	
Number of pre-injury medications				0.883
Mean (SD)	12 (± 6.5)	12 (± 7.8)	12 (± 6.4)	
Missing	9 (10.0%)	0 (0%)	9 (11.5%)	
Frailty status (Groningen Frailty Index)				0.707
Frail (>4 total score)	22 (24.4%)	3 (25.0%)	19 (24.4%)	
Not frail (<4)	46 (51.1%)	5 (41.7%)	41 (52.6%)	

Table 1. Demographic, injury and clinical characteristics

	Overall (N=90)	Died (N=12)	Survived (N=78)	P-value
Missing	22 (24.4%)	4 (33.3%)	18 (23.1%)	
Pre-injury cognitive status				0.348
Mild Cognitive Impairment/dementia	39 (43.3%)	7 (58.3%)	32 (41.0%)	
Normal	40 (44.4%)	4 (33.3%)	36 (46.2%)	
Missing	11 (12.2%)	1 (8.3%)	10 (12.8%)	
Alcohol Use Disorder Identification Test (range 0-12 (worst))				0.486
Mean (SD)	1.5 (± 1.9)	2.2 (± 2.7)	1.4 (± 1.8)	0.412
Missing	5 (5.6%)	0 (0%)	5 (6.4%)	
Anticoagulants	19 (21.1%)	3 (25.0%)	16 (20.5%)	0.369
Platelet aggregation inhibitors	24 (26.7%)	3 (25.0%)	21 (26.9%)	1

Models' performance comparison

Models' performance metrics are summarized in table 2.

Marshall's score had an AUC of 0.81 (95% CI: 0.67-0.96), Rotterdam score had an AUC of 0.78 (95% CI: 0.60-0.96) and IMPACT lab model had an AUC of 0.81 (CI: 0.65-0.97).

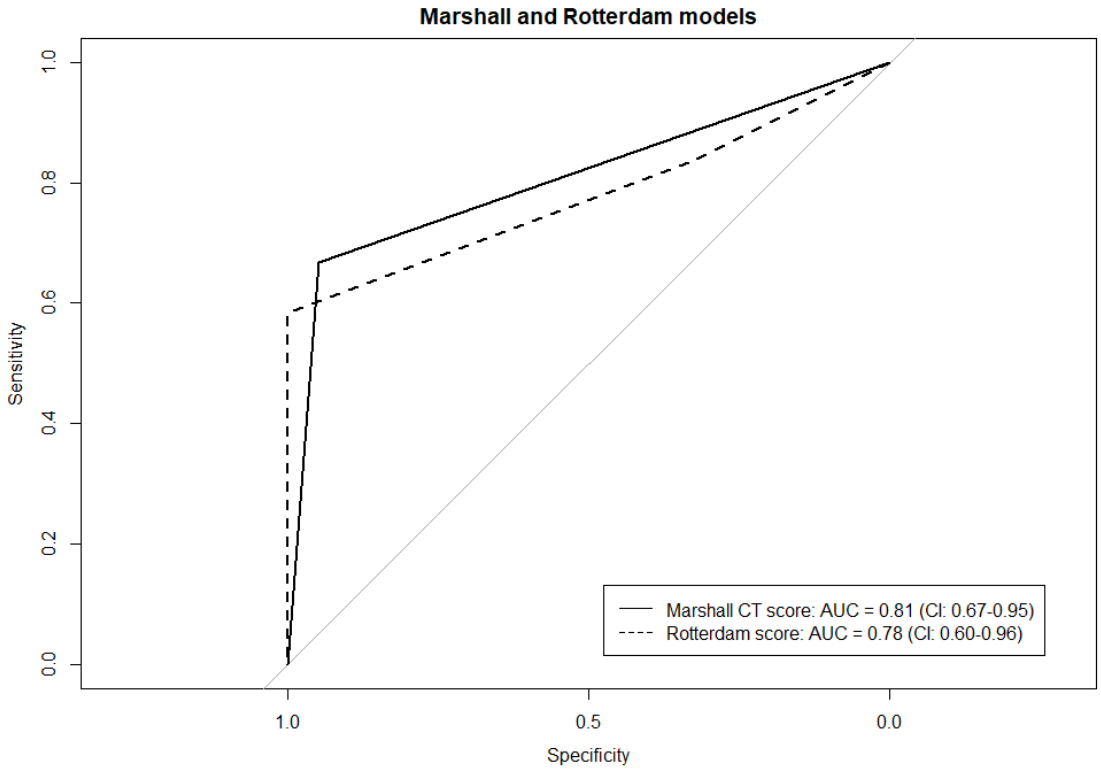
No statistically significant differences were found between models' AUCs, except for IMPACT core model which was significantly worse than IMPACT lab (p-value=0.023), Marshall's CT score (p-value=0.01) and Rotterdam's score (p-value=0.046). In addition, the IMPACT Core model score had no statistically significant correlation to 6-month mortality (p-value=0.415).

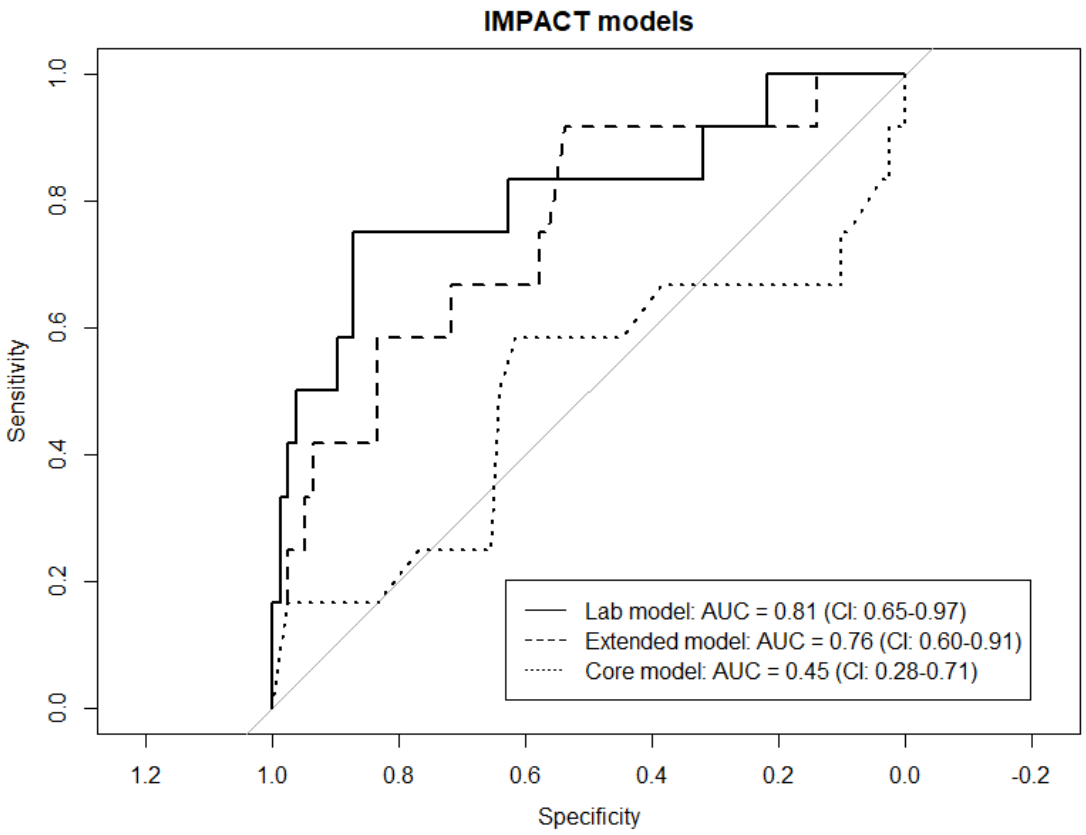
Table 2 shows sensitivity and specificity of each model for correctly predicting 6-month mortality in the TRACK-GERI cohort using the referenced cut-offs.

Table 2.

Performance metric	Marshall's CT score	Rotterdam's score	IMPACT Core model	IMPACT Extended model	IMPACT Lab model
AUC	0.81	0.78	0.45	0.76	0.81
95% CI	0.67-0.96	0.60-0.96	0.28-0.71	0.60-0.91	0.65-0.97
Sensitivity	67%	58%	58%	54%	75%
Specificity	95%	100%	62%	92%	87%
Threshold	Injury category > II *	ROC optimal threshold	ROC optimal threshold	ROC optimal threshold	ROC optimal threshold

(*) As in IMPACT models [17]





6-month mortality predictors

CT findings (table XX) are the basis for Marshall's CT score, Rotterdam score and IMPACT Extended and Lab models.

While both lesion mass size greater than 25 cc and hematoma evacuation are significant predictors of 6-month mortality (p-value=0.016, 0.007), they were quite rare in our cohort.

When tested for their correlation to 6-month mortality, it appears that basal cisterns effacement (partial or full) and a midline shift greater than 5 mm are significant predictors of mortality (p-value=0.016 and 0.007). Shear, edema and contusion were also significantly correlated to 6-month mortality (p-value=0.009, 0.002, 0.004 and 0.05). Skull fracture is not an intracranial injury, but it is a statistically significant predictor of mortality in our cohort (p-value=0.003).

Epidural hematoma, Subarachnoid hematoma and Intraventricular hematoma are hemorrhagic findings that are used in most prediction models. These pathologies did

not show a statistically significant correlation to 6-month mortality in our cohort (p-value=0.13, 0.206 and 0.068).

	Overall (N=90)	Died (N=12)	Survived (N=78)	P-value
Lesion size > 25cc	2 (2.2%)	2 (16.7%)	0 (0%)	0.016
Evacuated hematoma	4 (4.4%)	3 (25.0%)	1 (1.3%)	0.007
Basal cisterns effacement (partial or full)	8 (8.9%)	6 (50.0%)	2 (2.6%)	<0.001
Midline shift > 5mm	9 (10.0%)	7 (58.3%)	2 (2.6%)	<0.001
Shear	17 (18.9%)	6 (50.0%)	11 (14.1%)	0.009
Edema	6 (6.7%)	4 (33.3%)	2 (2.6%)	0.002
Contusion	26 (28.9%)	8 (66.7%)	18 (23.1%)	0.004
Skull fracture	19 (21.1%)	7 (58.3%)	12 (15.4%)	0.003
Subdural hematoma	57 (63.3%)	11 (91.7%)	46 (59.0%)	0.05
Epidural hematoma	5 (5.6%)	2 (16.7%)	3 (3.8%)	0.13
Subarachnoid hematoma	59 (65.6%)	10 (83.3%)	49 (62.8%)	0.206
Intraventricular hematoma	13 (14.4%)	4 (33.3%)	9 (11.5%)	0.068
Number of CT findings				<0.001
Mean (SD)	2.0 (± 1.4)	4.2 (± 2.0)	1.6 (± 0.95)	

SDH = Subdural hematoma, EDH = Epidural hematoma, SAH = Subarachnoid hematoma, IVH = Intraventricular hematoma

Clinical and lab characteristics used by IMPACT models are summarized in table XX.

No statistically significant correlation was found between age, GCS motor, pupil reactivity, ED hypotension or ED hemoglobin to 6-months mortality in our cohort (p-value=0.412, 0.166, 0.126, 1, 0.69).

Those who died had significantly higher levels of glucose on arrival to the ED, 160 mg/dL (SD=51 mg/dL) vs. 130 mg/dL (SD=31 mg/dL), with a p-value of 0.042. Hyperglycemia (ED glucose level > 200 mg/dL) was more prevalent among those who died (33% vs. 4%) and the correlation to mortality was statistically significant (p-value=0.006).

	Died (N=12)	Survived (N=76)	P-value
Age			0.355
Mean (SD)	75 (± 7.6)	77 (± 7.6)	
ED GCS motor			0.175
1-No Response	1 (8.3%)	1 (1.3%)	
4-Flexion Withdrawal	1 (8.3%)	3 (3.9%)	
5-Localizes to Pain	1 (8.3%)	4 (5.3%)	
6-Obeys Commands	9 (75.0%)	68 (89.5%)	
ED pupil reactivity			0.101
Bilateral	6 (50.0%)	62 (81.6%)	
Unilateral	1 (8.3%)	0 (0%)	
Missing	5 (41.7%)	14 (18.4%)	
ED arrival hypotension			1
No	10 (83.3%)	68 (89.5%)	
Yes	0 (0%)	3 (3.9%)	
Missing	2 (16.7%)	5 (6.6%)	
ED arrival hypoxia			0.127
No	9 (75.0%)	69 (90.8%)	
Yes	1 (8.3%)	0 (0%)	
Missing	2 (16.7%)	7 (9.2%)	
ED glucose (mg/dL)			0.004
Mean (SD)	160 (± 51)	130 (± 31)	
Missing	0 (0%)	2 (2.6%)	
ED Hyperglycemia			0.006
≤200 mg/dl	8 (66.7%)	71 (93.4%)	
>200 mg/dl	4 (33.3%)	3 (3.9%)	
Missing	0 (0%)	2 (2.6%)	
ED Hemoglobin (mg/dL)			0.538
Mean (SD)	13 (± 1.9)	13 (± 1.7)	
Missing	0 (0%)	1 (1.3%)	

The predictors' unadjusted odds ratios are illustrated in figure XX. The number of cases on which the ORs are calculated is limited, and therefore these findings should be

regarded as a possible trend that should be further investigated and not as conclusive results.

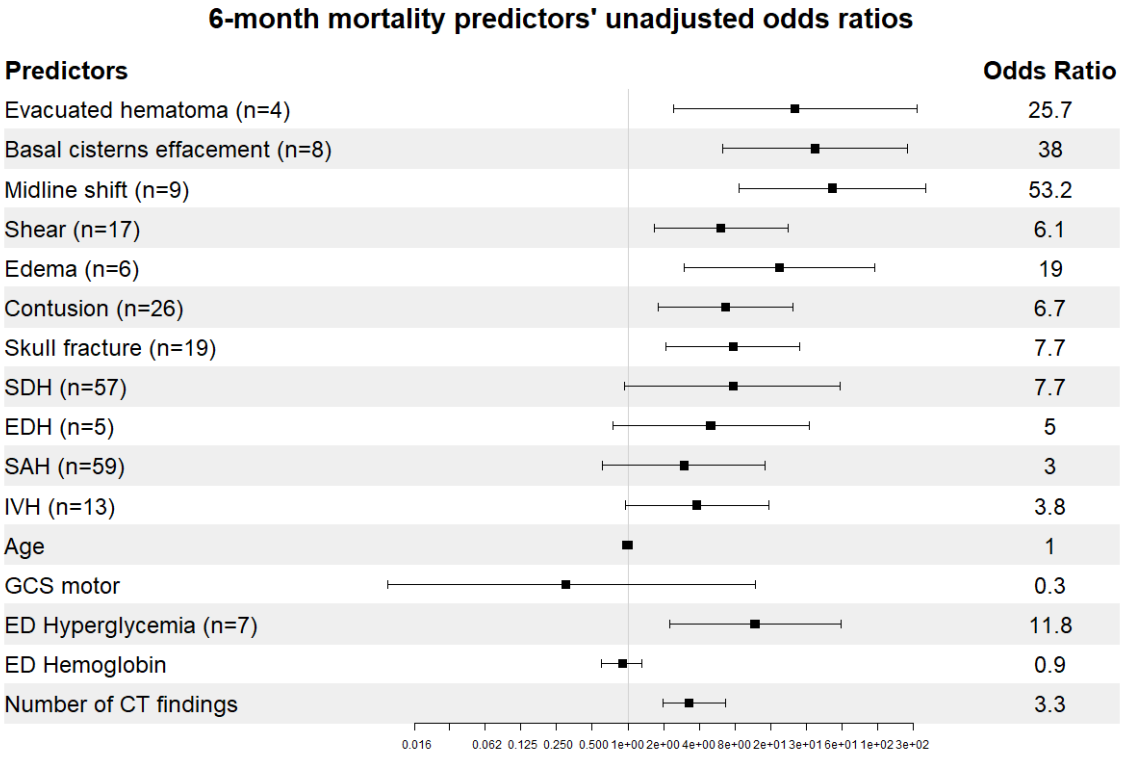


Fig. XX: The odds ratios are represented by a black box. The farther it is from the vertical line, the stronger the correlation between the predictor and outcome. Confidence intervals that include the number 1 (whiskers cross the vertical line) indicate that the association between the predictor and the outcome is not statistically significant in our cohort. The x-axis is in log scale.

We can see that the strongest predictors (top 3 rows) are related to massive lesions: evacuated hematoma, basal cisterns effacement and midline shift. These findings have a low prevalence in our cohort (4%-10%). Shear, edema, contusion and skull fracture are CT predictors that have not been used before in TBI mortality prediction, but are significantly correlated to 6-month mortality in our cohort and are also more prevalent (7%-29%). Hemorrhagic findings used in current predictions models (SDH, EDH, SAH, IVH) showed no statistically significant correlation to mortality in our cohort, but a larger cohort will have more power to determine their association to mortality in older adults. Age, GCS motor and ED hemoglobin are not statistically significant predictors in our cohort. The number of CT findings indicative of intracranial trauma had an odds ratio of 3.3 (CI: 1.96-6.67), which means that the odd of mortality at 6 months increases 3.3 times with each additional CT finding.

The distribution and intersections of CT findings in our cohort (fig. XX) shows that the most common injuries are isolated SAH (n=22) and isolated SDH (n=21), a combination of SAH and SDH with contusion (n=5) or without (n=6).

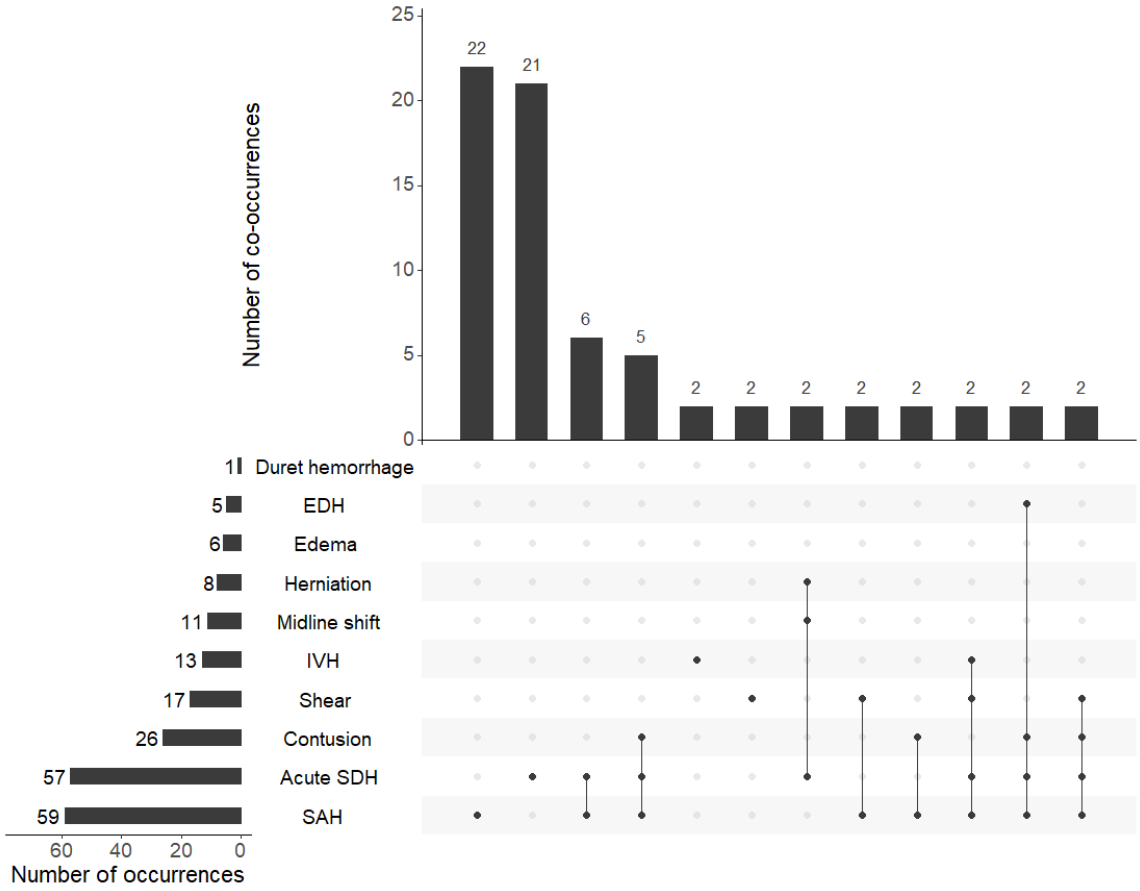


Figure XX: Distribution and intersections of CT findings indicative of intracranial trauma. The 12 most common intersections are displayed.

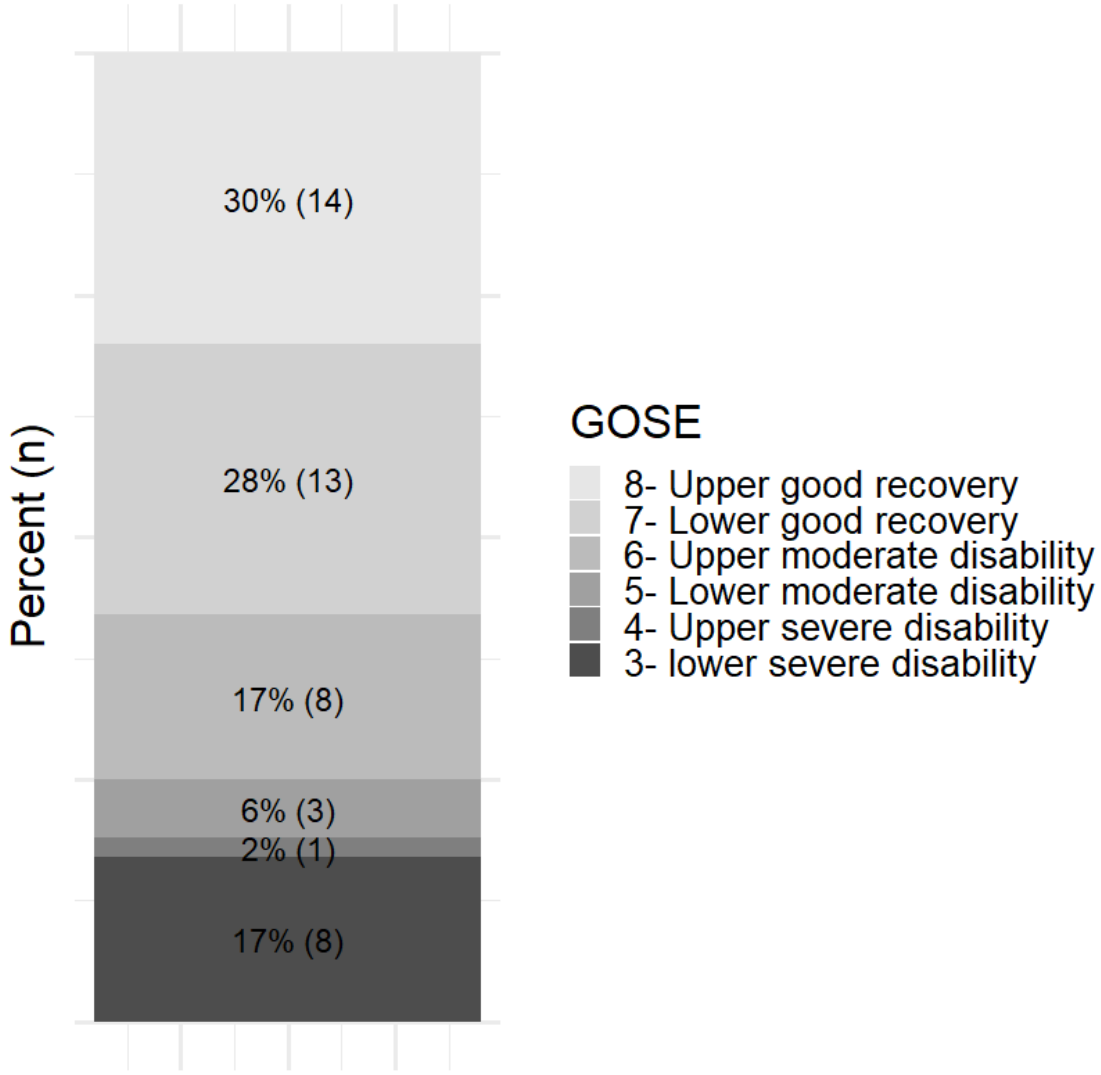
Mortality prediction models' error analysis

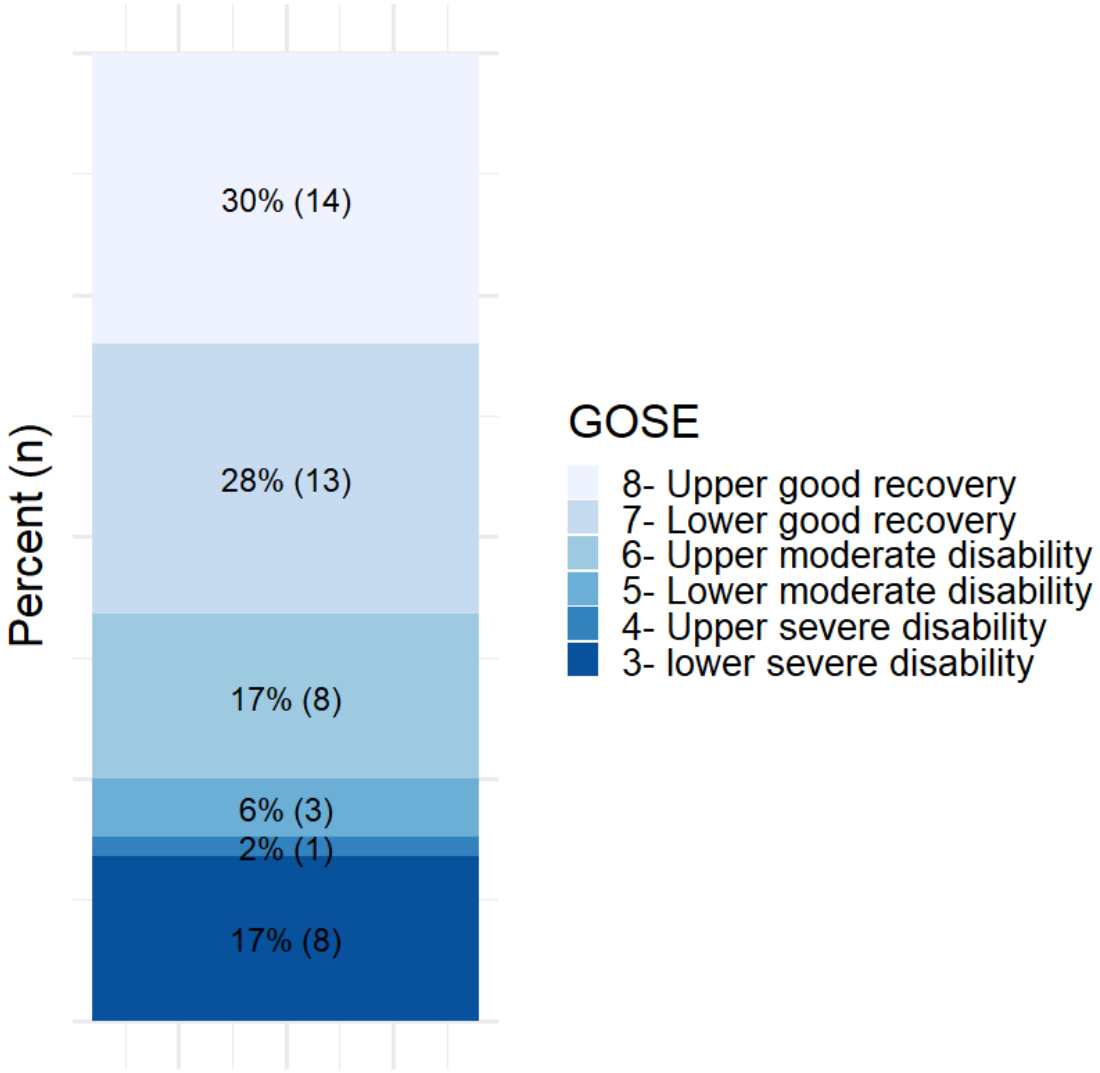
Out of 12 participants who died, 5 were misclassified and were predicted to survive. A comparison of those who were correctly and incorrectly classified by the models can be found in the supplements. The sample sizes are very small, but some trends emerge. Those who were misclassified seem to be more characteristic of the geriatric TBI population: injury mechanism is fall, GCS indicates mild TBI, higher number of pre-injury medications and a higher proportion of frailty and cognitive impairment. Those who were correctly classified by the models had a much longer time from injury to first CT- 10 hours (SD=17 hours) vs. 1.2 hours (SD=1.1 hours) in those who were misclassified. They also had higher alcohol consumption (AUIDT-C of 3.3. vs. 0.6).

Survivors' functional outcomes

Of the 78 survivors at 6 months, data regarding GOSE score was available for 63 participants (81%). Good recovery (GOSE=7 or 8) was achieved at 6 months by 45% of participants (n=35) and full recovery was achieved by 22% (n=17). The lowest GOSE among survivors was 3 (severe disability), and occurred in 12 participants (15%).

The distribution of GOSE scores are depicted in the figure below.





Discussion

This study of 90 older adults who presented to the ED after a TBI has found population characteristics similar to those previously described. Fifty-four percent were female, 90% of participants sustained a mild TBI, most common injury mechanism was ground level fall (60%) and overall mortality rate 13% [7,18,26].

Current mortality prediction models or scores had low sensitivity in our cohort, ranging between 54% (IMPACT Extended model) to 67% (Marshall's CT score). The best sensitivity was achieved by IMPACT lab model (75%), but at the cost of lower specificity (87%) and using 10 predictors (CT, clinical and lab).

Age, frailty, comorbidities, use of anticoagulants and pre-injury cognitive impairment were suggested as contributing factors to adverse outcomes of TBI in older adults, but none of them had a statistically significant correlation to mortality in our cohort. Age is

an important predictor of TBI mortality in the general population with steeply increasing mortality rates in older adults, but when focusing on people 65+ years old the age distribution of those who survived and those who died is the same. A study comparing young-old (65-74 years), middle-old (75-84 years) and oldest-old (85+ years) patients post TBI found no statistically significant difference in mortality rates between groups with either mild or moderate-severe TBI [26]. The role of other contributing factors should be examined in a larger cohort with a higher proportion of severe or moderate TBI cases, that may help determine if such correlations exist in this population.

Predictors of mortality should be further studied for the development of evidence based tools for mortality prediction, to help guide acute care decisions and follow-up care.

GCS vs. CT evidence of intracranial injury

GCS is a simple and widely used assessment tool, which is synonymous with TBI severity. However, it's validity in assessment of injury severity in older adults should be considered. Intracranial hemorrhages may have a lesser clinical effect in older adults due to normal age-related brain atrophy, and GCS may underestimate the severity of their injury. A recent study found that older patients with TBI had a higher mean GCS compared to younger patients with the same Rotterdam score[5]. Another study found that adults over 60 years old with a GCS of 15 (normal exam) after TBI had a 17% chance of a positive CT scan, vs. 7% in the general TBI population[27]. A mild TBI (GCS 13-15) in older adults was found to be 20 times more likely to result in an unfavorable outcome compared to a younger age group, whereas the odds ratio for having an unfavorable outcome with a moderate or severe TBI were lower (11 and 2) [5]. In addition, a recent meta-analysis found that in older adults, mortality rates following moderate or severe TBI are similar and GCS may not be predictive of mortality as it is in younger age groups[18]. In summary, despite its many advantages, GCS may not be the optimal tool for injury severity assessment and mortality prediction in older adults, especially in mild TBI.

Current mortality prediction models

Although they were developed based on younger cohorts with worse injuries, when applied to a cohort of older adults, current mortality prediction models' achieved AUCs similar to those previously published (with the exception of IMPACT core model).

However, a closer look at the predictors used for these models reveals that no statistically significant correlation was found between some of them and mortality in our cohort.

Marshall's CT score items lesion > 25cc, evacuated hematoma, basal cisterns effacement and midline shift are strong predictors of 6-mortality as they indicate severe injury.

However, a model based solely on these predictors may fail to identify high-risk patients with milder injuries, or injuries that are not related to a space occupying lesion.

The prominence of these predictors is also evident in Rotterdam's score. This model is based mostly on basal cisterns effacement and midline shift, while its other predictors EDH, IVH and SAH are not correlated to mortality in our cohort. Anatomical and physiological age-related changes to the brain may explain this discrepancy. Age-related brain atrophy may mitigate the adverse effects of intracranial hemorrhage. In addition, epidural hematomas are less prevalent in older adults as the dura adheres more firmly to the skull [28,29]; its prevalence in individuals 65+ who sustained TBI is estimated at 2.4% [26]. The Rotterdam score adds 1 point if an EDH is not present, because the model found an inverse correlation between mortality and EDH. The mechanism behind this finding are unknown, but age may be a mediating factor. As a consequence, older adults are more likely to get a higher score on the Rotterdam scale due to EDH's low prevalence in this population. These findings imply that the Rotterdam model may under-predict mortality in mild TBI cases in older adults, and may also over-predict mortality when EDH is not present.

IMPACT models uses clinical and lab predictors whose relevance in older adults should be further investigated. GCS motor and pupil reactivity may have low sensitivity for detecting trauma severity in older adults since intracranial hemorrhage may not manifest in a clinical exam due to brain atrophy. In our cohort, 89 out of 90 participants had a normal pupil reactivity to light. However, a larger study with a higher proportion of moderate-severe TBI found a 6.5% prevalence of unilateral or bilateral abnormal pupil reactivity in older adults [26]. Conversely, ED glucose and ED Hyperglycemia (>200 mg/dL) were statistically significant predictors in our cohort. Hyperglycemia after TBI is involved in a few mechanisms that lead to poor outcome in severe TBI [30], and stress-induced hyperglycemia was found to predict worse outcome in older adults who sustained a trauma [31].

In summary, entering uncorrelated or poorly correlated predictors introduces noise and bias into prediction models. These predictors should be tested in a multivariable model in a larger and diverse cohort to determine their significance in this population.

TBI outcomes at 6 months

Despite the small cohort, it should be noted that 6 out of 9 participants aged 65+ years who had a moderate-severe TBI survived. (Two out of 8 participants who had a partial/full basal cisterns effacement survived, and 2 out of 9 participants who had a midline shift greater than 5mm survived). Of those who survived, almost half had good recovery and severe disability rates were low.

Study limitations

The main limitation of our study is the small sample size (n=90). The sample's small size may have limited our ability to assess and compare the performance of mortality prediction models and detect significant correlations between existing or new predictors of 6-month mortality in older adults. A larger sample size would have also enabled multivariable analyses, combining multiple predictors and testing interactions. In addition, calibration of models was not evaluated as at least 100 events are required [32].

Our cohort had a limited proportion of moderate and severe injuries (10%), compared to a proportion of 16.7% of moderate-severe TBI cases in older adults that was found in a recent larger epidemiological study [26]. A larger proportion of moderate-severe injuries could have improved our estimation of CT findings' correlation to 6-month mortality.

External injury[33] is a possible predictor that could not be tested for its correlation to mortality due to a large proportion of missing data.

Recommendations for further research

Future studies of TBI in older adults should consider using CT evidence of intracranial trauma as an inclusion criterion rather than GCS, to better represent this population.

A meta-analysis of TBI in older adults found that the pooled mortality rate for mild TBI is 12.3% (CI=6.1-23.3%) [18], which is similar to the 11% mortality rate for mild TBI in our cohort. These findings stress the importance of identifying high-risk patients with CT-positive mild TBI, and developing an appropriate mortality prediction model and interventions.

Hemorrhagic findings were prevalent but did not show a statistically significant correlation to mortality. A possible direction is considering the size of the hemorrhage, as the effect of intracranial hemorrhage on older adults may be more size-dependent.

Non-hemorrhagic CT findings such as shear, edema, contusion and skull fracture demonstrated a statistically significant correlation to 6-month mortality and may be useful predictors in mortality prediction models.

Other predictors that relevant for this population such as comorbidity and frailty should also be considered.

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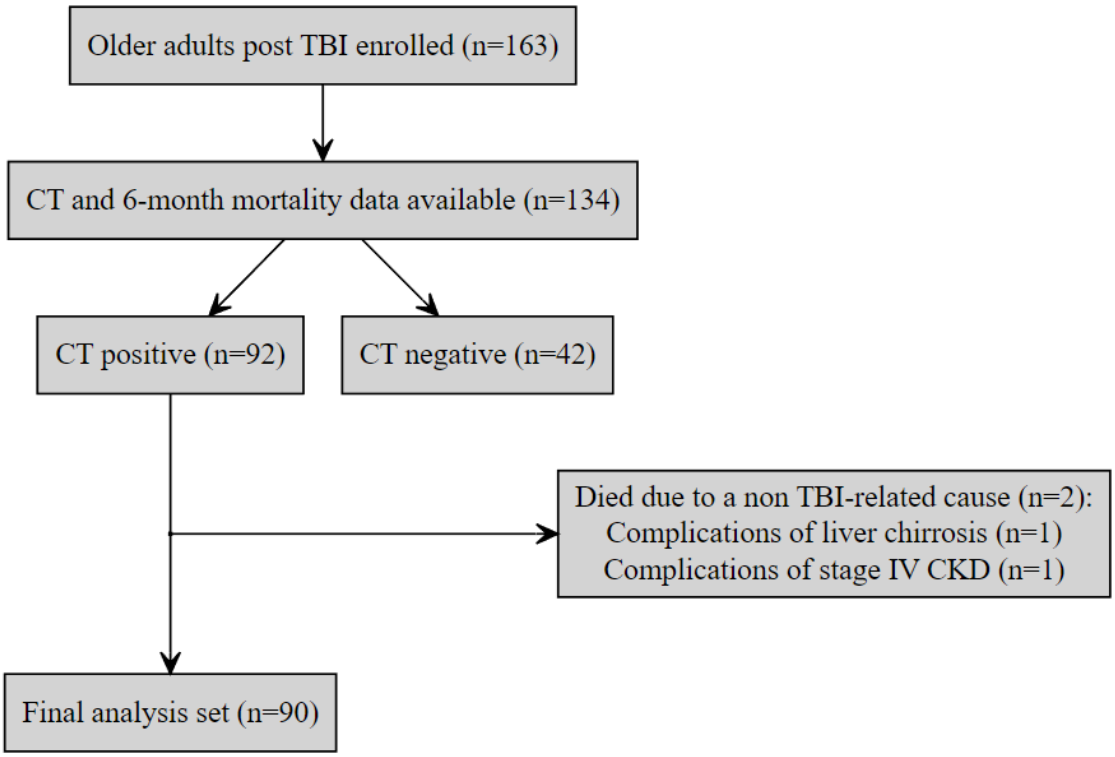
Flowchart



Supplements

- Tables of Marshall, Rotterdam and IMPACT score charts

Confusion matrices

Prognosis by Marshall's score vs. Actual outcome

	Died	Survived
Predicted survival	4	74
Predicted death	8	4

[a] Balanced accuracy: 81%, Sensitivity: 67%, Specificity: 95%

Prognosis by Rotterdam score >3 vs. Actual outcome

	Died	Survived
≤3	5	78
>3	7	0

[a] Balanced accuracy: 79%, Sensitivity: 58%, Specificity: 100%

Prognosis by IMPACT Lab model vs. Actual outcome

	Died	Survived
Predicted survival	7	71
Predicted death	7	7

The best threshold found by the ROC curve of the IMPACT lab model was used as a cut-off for mortality prediction at 6 months.

Subgroup analysis of participants who died by model classification

This analysis was carried out to identify characteristics of participants who died but were predicted to survive by outcome prediction models (false negatives). The sample sizes are very small, but some trends emerge. Those who were misclassified seem to be more characteristic of the geriatric TBI population: injury mechanism is fall, GCS indicates mild TBI, higher number of pre-injury medications and a higher proportion of frailty and cognitive impairment.

Those who were correctly classified by the models had a much longer time from injury to first CT- 10 hours (SD=17 hours) vs. 1.2 hours (SD=1.1 hours) in those who were misclassified. They also had higher alcohol consumption (AUIDT-C of 3.3. vs. 0.6).

Supplemental Table X.

	Correctly classified (N=7)	Misclassified (N=5)	Overall (N=12)
Age			

	Correctly classified (N=7)	Misclassified (N=5)	Overall (N=12)
Mean (SD)	75 (± 5.9)	75 (± 10)	75 (± 7.6)
Sex female	3 (42.9%)	2 (40.0%)	5 (41.7%)
Race white	7 (100%)	4 (80.0%)	11 (91.7%)
Injury mechanism			
Ground level fall	2 (28.6%)	4 (80.0%)	6 (50.0%)
Fall from height	2 (28.6%)	1 (20.0%)	3 (25.0%)
Motor vehicle accident	1 (14.3%)	0 (0%)	1 (8.3%)
Assault	1 (14.3%)	0 (0%)	1 (8.3%)
Other	1 (14.3%)	0 (0%)	1 (8.3%)
Glasgow Comma Scale (GCS)			
15	2 (28.6%)	1 (20.0%)	3 (25.0%)
14	2 (28.6%)	4 (80.0%)	6 (50.0%)
13	0 (0%)	0 (0%)	0 (0%)
<13	3 (42.9%)	0 (0%)	3 (25.0%)
TBI severity by GCS			
Mild	4 (57.1%)	5 (100%)	9 (75.0%)
Moderate	0 (0%)	0 (0%)	0 (0%)
Severe	3 (42.9%)	0 (0%)	3 (25.0%)
Time from injury to first CT scan (hours)			
Mean (SD)	10 (± 17)	1.2 (± 1.1)	6.6 (± 14)
LOC - Loss of Consciousness			
No	3 (42.9%)	2 (40.0%)	5 (41.7%)
Yes	4 (57.1%)	3 (60.0%)	7 (58.3%)
PTA - Post-traumatic Amnesia			
No	4 (57.1%)	0 (0%)	4 (33.3%)
Yes	3 (42.9%)	5 (100%)	8 (66.7%)
ED disposition			
Hospital admit no ICU	2 (28.6%)	1 (20.0%)	3 (25.0%)
Hospital admit with ICU	5 (71.4%)	4 (80.0%)	9 (75.0%)
Discharge disposition			
Home	1 (14.3%)	1 (20.0%)	2 (16.7%)
Rehabilitation	0 (0%)	0 (0%)	0 (0%)

	Correctly classified (N=7)	Misclassified (N=5)	Overall (N=12)
Nursing facility	0 (0%)	0 (0%)	0 (0%)
Died	4 (57.1%)	2 (40.0%)	6 (50.0%)
Missing	2 (28.6%)	2 (40.0%)	4 (33.3%)
Charlson Comorbidity Index (range 2-37 (worst))			
Mean (SD)	4.5 (± 1.7)	4.8 (± 1.3)	4.6 (± 1.4)
Missing	3 (42.9%)	1 (20.0%)	4 (33.3%)
Number of pre-injury medications			
Mean (SD)	8.0 (± 7.2)	17 (± 5.9)	12 (± 7.8)
Frailty status (GFI)			
Frail (>4 total score)	1 (14.3%)	2 (40.0%)	3 (25.0%)
Not frail (<4)	3 (42.9%)	2 (40.0%)	5 (41.7%)
Missing	3 (42.9%)	1 (20.0%)	4 (33.3%)
Pre-injury cognitive status			
MCI/dementia	4 (57.1%)	3 (60.0%)	7 (58.3%)
Normal	3 (42.9%)	1 (20.0%)	4 (33.3%)
Missing	0 (0%)	1 (20.0%)	1 (8.3%)
Alcohol Use Disorder Identification Test (range 0-12 (worst))			
Mean (SD)	3.3 (± 3.1)	0.60 (± 0.89)	2.2 (± 2.7)