
Article:
Marincowitz, C. orcid.org/0000-0003-3043-7564, Gravesteijn, B., Sheldon, T. et al. (2 more authors) (2022) Performance of the Hull Salford Cambridge Decision Rule (HSC DR) for early discharge of patients with findings on CT scan of the brain : a CENTER-TBI validation study. Emergency Medicine Journal, 39 (3). pp. 213-219. ISSN 1472-0205

https://doi.org/10.1136/emermed-2020-210975

Emergency Medicine Journal

Performance of the Hull Salford Cambridge Decision Rule (HSC DR) for Early Discharge of patients with findings on CT brain scan: a CENTER-TBI validation study.

Journal:	*Emergency Medicine Journal*
Manuscript ID	emermed-2020-210975.R2
Article Type:	Original research
Date Submitted by the Author:	n/a
Complete List of Authors:	Marincowitz, Carl; The University of Sheffield, School of Health and Related Research (ScHARR) Gravesteijn, Benjamin; Erasmus Medical Center, Department of Public Health Sheldon, Trevor; Queen Mary University of London Barts and The London School of Medicine and Dentistry, Institute of Population Health Sciences Steyerberg, Ewout; Leiden University Medical Center Department of Biomedical Data Sciences Lecky, Fiona; University of Sheffield and Salford Royal Hospital, School of Health and Related Research. Emergency Department, Salford Royal Hospital
Keywords:	Trauma, head, Trauma, research

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Performance of the Hull Salford Cambridge Decision Rule (HSC DR) for Early Discharge of patients with findings on CT brain scan: a CENTER-TBI validation study.

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Abstract

Background

There is international variation in hospital admission practices for patients with mild traumatic brain injury (TBI) and injuries on CT scan. Only a small proportion of patients require neurosurgical intervention, while many guidelines recommend routine admission of all patients. We aim to validate the Hull Salford Cambridge Decision Rule (HSC DR) and the Brain Injury Guideline (BIG) criteria to select low risk patients for discharge from the Emergency Department.

Method

A cohort from 18 countries of GCS 13-15 patients with injuries on CT imaging was identified from the multi-centre CENTER-TBI study (conducted 2014 - 2017) for secondary analysis. A composite outcome measure encompassing need for ongoing hospital admission was used, including seizure activity, death, intubation, neurosurgical intervention, and neurological deterioration. We assessed the performance of our previously derived prognostic model, the HSC DR and the BIG criteria at predicting deterioration in this validation cohort.

Results

Among 1047 patients meeting the inclusion criteria, 267 (26%) deteriorated. Our prognostic model achieved a C-statistic of 0.81 (95% CI, 0.78 to 0.84). The HSC DR achieved a sensitivity of 100% (95% CI: 97% to 100%) and specificity of only 4.7% (95% CI: 3.3% to 6.5%) for deterioration. Using the BIG criteria for discharge from the ED achieved a higher specificity (13.3%, 95% CI: 10.9% to 16.1%) and lower sensitivity (94.6%, 95% CI: 90.5 % to 97%), with

12/105 patients recommended for discharge subsequently deteriorating, compared to 0/34 with the HSC DR.

Conclusion

Our decision rule would have allowed 3.5% of patients to be discharged, none of whom would have deteriorated. Use of the BIG criteria may result in too high a risk of deterioration in a discharged patient to be used clinically. Further validation and implementation studies are required to support use in clinical practice.

What is already known on this subject

NICE head injury guidelines state that following head injury, patients with "new, clinically significant abnormalities on imaging" should be admitted for observation without defining which injuries are clinically significant. We have previously empirically derived the first prognostic model and decision rule (HSC-DR) to identify low risk patients with injuries on CT who could be safely discharged from the ED.

What this Study adds

We present the first validation study of our prognostic model and the HSC-DR. It shows that application of the HSC-DR may allow a modest but safe reduction in inpatient admissions of selected low risk patients with traumatic brain injuries identified by CT imaging.

Keywords: Mild Traumatic Brain Injury; Prognostic Model; Clinical Decision Rule; Emergency Department; Head Injury

Background

Over 2 million patients are admitted to hospital each year across Europe for traumatic brain injury (TBI; injury to the brain or alteration of brain function due to external force).[1] 95% of patients admitted to hospital and 36% of patients admitted to intensive care units with TBI have an initial Glasgow Coma Scale (GCS) of 13-15 and are defined as having mild injuries.[2] The management of mild TBI patients with injuries identified by CT imaging is controversial.

Around 7% of initial GCS13-15 patients who present with head trauma have intra-cranial injuries or skull fractures identified on CT imaging but only around 1% of patients die or require neurosurgery.[3] Some studies advocate routine admission under specialist neurosurgical care and repeat CT imaging of all mild TBI patients with injuries identified on CT.[4 5] Some North American centres have adopted the consensus derived Brain Injury Guideline (BIG) criteria which advocates the discharge of selected patients from the ED (Supplementary Material 1).[6] In Europe there is variation in clinical practice with patients admitted under a range of specialties and with varying levels of intensity of inpatient care.[2]

We recently developed the first empirically derived prognostic model and decision rule (the Hull Salford Cambridge Decision Rule (HSC DR)) predicting need for hospital admission in this population.[7] We compared the performance of the HSC DR and BIG criteria and found both had high sensitivity to clinical deterioration. The HSC DR maximised sensitivity at a cost of a specificity of 7% at the discharge threshold to ensure clinical safety, but implementation would have recommended fewer than one in ten TBI patients be discharged. [7] However, in the “COVID 19” era - where reducing hospital acquired infections is paramount, and in other resource constrained contexts, even small reductions in unnecessary hospital admissions are valuable. Application of this decision rule could – if externally validated – achieve this.[7]

The aims of this study were:

1. Externally validate and compare the performance of the HCS and BIG criteria decision rules, using an international dataset of patients attending Emergency Departments following traumatic brain injury.
2. Evaluate the performance of the HCS and BIG criteria decision rules for mildly injured patients with TBI.
3. Externally validate the empirically derived prediction model underpinning HSC-DR (recalibrating where required) using the CENTER TBI cohort.

Methods

Study design

An international dataset of patients with CT diagnosed TBI, was used to externally validate the two decision rules (BIG and HSC-DR) by comparing their sensitivity and specificity for predicting which patients required hospital admission for specific treatments.[2 8] The CENTER-TBI dataset was then used to recalibrate the HSC prediction model (which then feeds into the decision rule). The aim of the recalibration was to determine if the HSC decision rule performance could be improved using data from a more diverse population compared to the initial derivation dataset. We followed international guidelines (TRIPOD) for reporting of prognostic model validation.[8] The methods used to derive our prognostic model and the HSC-DR are available in the previously published protocol and derivation studies.[7 9]

Source of data

Data for the core CENTER-TBI study were collected between December 2014 and 2017 at 63 centres across Europe and Israel and 4509 patients of all TBI severity were recruited, stratified by three strata of planned clinical management: ED only, admitted initially as a ward inpatient and admitted initially to intensive care. All patients were initially managed in the Emergency Department. Data were prospectively collected by trained research staff as detailed in the study protocol.[10]. Follow up data were collected at 2-3 weeks, 3 months and 6 months with data collected on 83.4% of patients at 6-months.

Inclusion and exclusion criteria

Patients aged 16 and over with an initial GCS 13-15 recorded in the ED and with either a skull fracture, intra-cranial haemorrhage or cerebral contusion identified on first CT scan - regardless of care pathway stratum were included, reflecting the population used in our derivation study.[7] Patients where initial GCS in the ED was unknown and patients where diffuse axonal injury was the sole injury identified on initial CT scan were excluded.

Outcome

A composite outcome encompassing need for hospital admission was defined, matching the outcome in the model derivation study. This included: seizure as inpatient or at 2 week follow-up, death attributed to TBI within 30 days of first attendance, intubation recorded within 30 days of presentation, admission to ICU for any reason apart from close monitoring, neurosurgical intervention and recorded neurological deterioration (new deficit or drop in GCS of more than 1 point).

Predictors

The original extended prediction model includes seven predictor variables for a composite outcome of deterioration encompassing need for hospital admission in this TBI population (Table 1).[7] The full prediction model is available in Supplementary Material 2. Six of these variables were used in our derivation study to form the simplified HSC DR which could be applied clinically to identify patients who could be safely discharged from the ED (Table 1 and Supplementary Material 2). The BIG criteria use 6 factors to risk stratify patient management (Supplementary Material 1). All factors in the prediction model and BIG criteria were available from data collected in CENTER-TBI.

Table 1: Factors in extended prognostic model and HSC DR

Factors in Extended model	**HSC DR** **Discharge if**	**BIG Criteria** **Discharge after 6 hours if**
Preinjury Anti-coagulation or anti-platelets	No	No
Initial GCS 13-15	GCS 15	13-15
First Neurological Examination	Normal	Normal
Number of Injuries on CT: 1-5 or Diffuse	1	
Injury severity on CT: Simple skull fracture Complex Skull Fracture Marshall IIa 1-2 bleeds < 5mm (total) Marshall IIb bleeds ≥ 5mm Marshall III/IV Marshall VI Brain stem/Cerebellar	Simple Skull fracture or 1-2 bleeds< 5mm total	Subdural ≤ 4mm Extradural ≤ 4mm 1 Intra-cerebral haemorrhage ≤ 4mm Trace Subarachnoid haemorrhage No skull fractures No Intra-ventricular haemorrhage
Injury Severity Score (body regions excluding head)	Up to 2 non-significant extra-cranial injuries(not requiring impatient care, e.g closed fracture humerus)	
Intoxication		Not intoxicated
Hb	Not included in risk score	

Sample Size

A minimum of between 100-200 events and 100-200 non-events per study sample has been recommended for validation studies of logistic regression models.[11 12] The validation cohort contained over 200 events and non-events.

Missing data

To evaluate model performance, missing data were multiply imputed using the ICE STATA package on the assumption they were missing at random (fully described Supplementary Material 3).[13] Performance was averaged across imputed data sets.[14 15]

Decision Rule Performance

All analysis was completed using STATA 16 (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC). Sensitivity, specificity of the HSC DR and of the BIG criteria to the composite outcome of deterioration were calculated in patients with complete data for either criteria. To be recommended for discharge all components of HSC DR or BIG criteria (Table 1) must be fulfilled. The proportion of patients recommended for discharge and accompanying risk of deterioration in a discharged patient (negative predictive value) were compared. In pre-specified exploratory subgroup analysis this was repeated in patients with less severe injuries as indicated by having a brain abbreviated injury score (AIS) or Marshall classification <3.[16] This represents patients without obvious midline shift or severe injuries on CT imaging and the population admitted for observation under ED care in the UK.

Model performance and recalibration

Performance of the prediction model was assessed in the CENTER-TBI cohort using measures of discrimination and calibration. Discrimination indicates how well the model differentiates between patients who deteriorated and those who do not deteriorate and was measured using the C-statistic (equivalent to the area under ROC curve).[17]

Calibration measures how closely predictions made by the model match observed outcomes (i.e. do predicted mean outcomes match observed mean outcomes).[17] Calibration was assessed visually using a calibration plot and with estimates of the "calibration in the large" (the ratio of expected versus observed numbers of events) and slope of the calibration plot (the overall prognostic effects of predictors in the model). To account for differences between the derivation and validation cohort and potential model over-fitting during derivation, the intercept and coefficients of the prediction model were also re-estimated to provide a re-calibrated model.

Clinical usefulness

Decision curve analysis was used to estimate the net benefit of using the prognostic model to select patients for discharge from the ED.[18 19] Net benefit is estimated by the number of true positives minus false positives multiplied by the clinical weight given to correct classification across a range of probabilities of deterioration where discharge could be considered.[19] The net benefit of using the prognostic model was compared visually in curves using the BIG criteria's single decision threshold and reference strategies of discharging no or all patients.[20]

Ethics

Ethics approval was obtained for each recruiting site, full details are available here https://www.center-tbi.eu/project/ethical-approval. .

Patient and Public Involvement

The Hull and East Yorkshire NHS Trust Trans-Humber Consumer Research Panel and Hull branch of the Headway charity helped inform developing the overall research aim of developing a predictive model to identify low risk patients with injuries on CT imaging who could be safely discharged from the ED.

Results

Study population

The cohort (n=1047) was mostly male, with over a third of patients aged over 65 and over 20% with either pre-injury anti-coagulant or anti-platelet use (Figure 1, Table 2). A total of 379 (36%) patients had data missing from at least one predictor variable value (mostly initial haemoglobin) used in the full prognostic model (Table 2). 12.1% patients had data missing in one or more predictor variable used in the HSC DR. Any clinical deterioration was noted among 267 patients (26%; 95% CI: 23% to 28%), including 212 patients (20%; 95% CI: 178% to 23%) who underwent neurosurgery, died, or were intubated and 25 patients had deaths attributable to TBI.

Table 2: Characteristics of the study population (N=1047)

Population Characteristic	Category	Mean (SD), min-max or N (%)	Missing data
Age	Years	54.8 (SD=19.7) 16-96	None
Age	≥65	384 (36.7%)	None
Sex	Male Female	688 (66%) 359 (34%)	None
GCS	15 14 13	677 (64.7%) 359 (24.7%) 111 (10.6%)	None
Stratum	ER Admission ICU	87 (8.3%) 587 (56%) 373 (35.6%)	None
Mechanism of Injury	High Velocity Trauma Blow to head/struck by object Ground level fall Fall from >1m or 5 stairs other	210 (20.1%) 183 (17.5%) 384 (36.7%) 218 (20.8%) 19 (1.8%	33 (3.2%)
Intoxicated	Yes	242 (23.1%)	58 (5.5%)
Preinjury Anti-coagulation or anti-platelets	Anticoagulation use Antiplatelet use Both	72 (6.9%) 134(12.8%) 7 (0.7%)	12 (1.1%)
Abnormal First Neurological Examination	Yes	152 (14.5%)	71 (6.8%)
Haemoglobin	Grams/litre	135 (SD 19.9) 47-23.4	325 (31%)
Number of Injuries on CT	1 2 3 4 5 Multiple diffuse injury/>5	468 (44.7%) 243 (23.2%) 135 (12.9%) 81 (7.7%) 56 (5.4%) 64 (6.1%)	None
Injury severity on CT (Modified Marshall Classification described in detail Supplementary Material 2)	**1)** Simple Skull Fractures **2)** Complex Skull fractures **3)**1-2 bleeds < 5mm (total) **4)** No or minimal mass effect **5)** Significant midline shift **6)** High/mixed-density lesion **7)** Cerebellar/Brain stem injury	19 (1.8%) 67 (6.4%) 426 (40.7%) 324 (31%) 29 (2.8%) 114 (10.9%) 68 (6.5%)	None
ISS	Body regions excluding head	17.3 (SD 20.6) 1-75 (range)	9 (0.9%)

Decision Rule performance

The HCS DR achieved a sensitivity of 100% (95% CI: 988% to 100%), but very low specificity of 4.7% (95% CI: 3.3% to 6.5%) for the composite outcome of deterioration (Table 3). BIG 1 classification missed some events (sensitivity 94.6%, 95% CI: 90.5 % to 97%), but had higher specificity (13.3%, 95% CI: 10.9% to 16.1%). Application of the HSC DR would have recommended discharge of only 3.5% of patients, compared to 11.4% patients recommended by the BIG criteria. However, patients recommended for discharge by the BIG criteria had a 11.4% (95% CI: 6.7 % to 18.9%), risk of subsequent deterioration, compared to 0% (95% CI: 0 % to 10.2%) with the HSC DR.

Table 3: Performance of BIG and HSC Decision Rules *

BIG Criteria Performance			
N=921	**Deteriorated**	**Didn't deteriorate**	
BIG1 (discharge from ED after 6 hours)	12	93	Sensitivity 94.6% (90.5-97%) Negative Predictive Value 88.6% (80.5 - 93.7%)
BIG 2/3 (admit)	210	606	Specificity 13.3% (10.9% - 16.1%) Positive Predictive Value 25.7% (22.8 - 28.9%)

HSC DR			
N=961	**Deteriorated**	**Didn't Deteriorate**	
Risk=0 (discharge)	0	34	Sensitivity 100% (988-100%) Negative Predictive Value 100% (87.4 - 100%)
Risk>0 (admit)	234	693	Specificity 4.7% (3.3-6.5%) Positive Predictive Value 25.2% (22.5 - 28.2%)

*Full performance of the BIG are presented in Supplementary Material 4 and characteristics of patients recommended for discharge in Supplementary Material 5

Sub-group analysis of less severely injured patients

One hundred and forty-six patients had AIS<3 and 800 patients had Marshall Classification <3 injuries. Use of the HSC DR would have facilitated discharge of 23% (34/146) of patients with brain AIS < 3, and 4.25% (34/800) of patients with Marshall Classification <3 injuries.

No patients selected for discharge by the HSC DR deteriorated (risk of deterioration 0%, 95% CI: 0% to 10.2%). Use of BIG criteria would have selected 26% (37/142) of patients with brain AIS < 3 injuries for discharge but with an 8.1% (95% CI: 2.8 % to 21.3%) risk of deterioration and 13.6% (105/770) of patients with Marshall classification < 3 injuries but with an 11.4% (95% CI: 6.7% to 18.9%) risk of deterioration (Table 4 and Supplementary Material 6).

Table 4: Subgroup analysis AIS<3

BIG 1			
N=142	**Deteriorated**	**Didn't deteriorate**	
BIG1 (discharge from ED after 6 hours)	3	34	Sensitivity 75% (42.8-93.3%) Negative Predictive Value 91.9% (77 – 97.9%)
BIG 2/3 (admit)	9	96	Specificity 26.2 (19-34.7%) Positive Predictive Value 8.6% (4.2 – 16.1%)

HSC DR			
N=146	**Deteriorated**	**Didn't deteriorate**	
Risk=0 (discharge)	0	34	Sensitivity 100% (69.99-100%) Negative Predictive Value 100% (87.4 - 100%)
Risk>0 (admit)	12	100	Specificity 25.4% (18.4-33.8%) Positive Predictive Value 10.7% (1075.9 - 18.313%)

Twenty-seven patients were excluded from the cohort as the only injury identified on initial CT imaging were diffuse axonal injury and therefore, they could not be assigned to a BIG criterion. These injuries are equivalent to a Marshall score 4 severity and would be recommend for admission by the HSC DR. Sensitivity analysis including these patients found the HSC DR achieved a sensitivity (100% 95% CI: 98% to 100%) and specificity (4.5% 95% CI: 3.2% to 6.3%) to the composite outcome of deterioration.

Model Performance

The original prognostic model achieved a C-statistic of 0.81 (95% CI, 0.78 to 0.84) in the CENTER-TBI cohort (0.75 in the development cohort) and an estimated slope of the calibration plot of 0.51 in the CENTER-TBI cohort (0.86 in the development cohort) (Figure 2i). The effect of re-calibration of both the intercept and coefficients is presented in Figure 2ii and the recalibrated model is presented in Supplementary Material 7. Measures of calibration improved but the estimated C-statistic of the recalibrated model remained 0.81.

Clinical usefulness, analysis according to clinical tolerance for adverse outcomes

Clinical usefulness depends on tolerance of risk of deterioration in those discharged without observation. Figure 3 presents the decision curves and net benefit analysis for the selection of patients either for a period of inpatient hospital observation or discharge directly from the ED using the recalibrated prognostic model or BIG criteria in the CENTER-TBI cohort. Due to the high risk of harm associated with discharging a patient who subsequently deteriorates, the analysis was limited to those with a low predicted probability of deterioration. Use of our recalibrated model showed potential benefit over an 'admit all'

strategy if the threshold for the predicted probability of deterioration was over 2% (Figure 3), which is potentially an acceptable clinical risk of deterioration in a discharged patient. If 2% is considered too high a risk to discharge a patient, given the harm associated with deterioration in the community, then no net benefit over an "admit all" strategy was demonstrated. The BIG criteria showed benefit over an 'admit all' strategy up to a threshold for predicted probability of deterioration of around 12%.

Discussion

Summary

This study validated the performance of the BIG and HSC decision rules in a large international dataset of patients with TBI, who had an overall deterioration prevalence of 26% (95%CI 23%, 28%). The BIG criteria achieved a sensitivity of 94.6% (95% CI: 90.5 % to 97%) and specificity of 13.3% (95% CI: 10.9% to 16.1%) and would have recommended discharge of 11% of patients with an accompanying risk of subsequent deterioration of 11.4% (95% CI: 6.7 % to 18.9%). The HSC DR achieved a sensitivity of 100% (95% CI: 98% to 100%) and specificity of 4.7% (95% CI: 3.3% to 6.5%), comparable to that reported in the development cohort (99.5% and 4.8% respectively). The HSC DR would have recommended discharge of 3.5% of patients but with a subsequent risk of deterioration of 0% (95% CI: 0 % to 10.2%). The prognostic model that underpins the HSC DR achieved a C-statistic of 0.81 and re-calibration improved accuracy of individual predicted risk of deterioration (calibration).

In the subgroup of patients with less severe injuries who are more likely to admitted under non-specialist teams the BIG criteria recommended discharge of 26% of patients with brain

AIS < 3 injuries for discharge but with an 8.1% (95% CI: 2.8 % to 21.3%) risk of deterioration. The HSC DR recommended discharge of 23% of patients of patient in this group with a risk of subsequent deterioration of 0% (95% CI: 0% to 10.2%).

Strengths

This study is the first external validation of the HSC-DR and, alongside our previous development study, is the largest study to externally validate the BIG criteria and only study to do so in a multi-centre European cohort of patients.[4 21-23] The CENTER-TBI study has good prospective patient follow-up and so significant adverse outcomes in the community were unlikely to have been missed. We have adhered to international guidelines for model validation.[8] We explicitly addressed the potential clinical usefulness of the decision rule and prognostic model according to a range of potential thresholds. This decision curve analysis clarified that if quite low risks were already considered too high, e.g. corresponding to a threshold of 1%, a treat all strategy would dominate. On the other hand, a less risk averse clinical policy, such as accepting risks up to 10% as acceptable, would lead to greater value of our rule or model (Fig 3).

Limitations

Previous studies estimated that around 10% of initial GCS13-15 patients have skull fractures or intra-cranial injures identified on CT imaging, whilst in the CENTER-TBI study around 50% of patients have injuries identified on imaging.[3 24 25] The CENTER-TBI population may be a higher risk group than the clinical population assessed in the ED. There was a relatively high proportion of missing data, especially for haemoglobin values. However, it is likely these data were missing at random, i.e. only related to observed variables, and that imputation

methods we used are valid. Study recruitment for CENTER-TBI occurred at 2 sites (Cambridge and Salford) at which the case note review for derivation of our prognostic model was conducted. These sites only contributed 6.9% of patients to the CENTER-TBI validation cohort and exclusion of these patients did not materially affect our results (Supplementary Material 8). Determining the significance of extra-cranial injuries in the HSC-DR as derived from extra-cranial ISS score (including facial injuries) requires some subjective clinical judgement.

Comparison to previous literature

In the CENTER TBI cohort, 20% of patients underwent neurosurgery, died, or were intubated compared to 13.1% in our development cohort and had a higher prevalence of deterioration than reported in a previous systematic review. [4] This may reflect recruitment of more severely injured patients to the CENTER-TBI study.

The BIG criteria for discharging patients from the ED achieved a lower sensitivity (94.6%) and higher specificity (13.3%) than when applied to our development cohort (sensitivity 99.5% and specificity 4.8%). Application of the BIG criteria would have allowed 11.4% of patients to be discharged from the ED which is similar to the 10% of patients estimated in studies conducted where the BIG criteria was developed in the USA and 15% reported in an external validation study.[6 21 23] The derivation and validation studies reported by the team that developed the BIG criteria and available external validation studies report no adverse outcomes in patients recommended for discharge by the BIG criteria.[6 21-23 26] In the CENTER-TBI cohort, patients recommended for discharge had a 11.4% (95% CI: 6.7 % to 18.9%), risk

of subsequently deteriorating. This may reflect the broader composite outcome measure used in our study and more comprehensive prospective follow-up of patients for deterioration. Some validation studies also modified the BIG criteria so that any patient with an initial GCS <15 was admitted to hospital.[22] The USA TBI population used for these studies also appears to be lower risk with a lower reported average age, anti-coagulant use and neurosurgical intervention rate.[4 23] The risk of deterioration when discharging a patient from the ED that is acceptable to patients and clinicians is subjective. When deriving the HSC-DR[7] we aimed to maximise sensitivity and aimed for a risk of a discharged patient deteriorating of around 1%, as this corresponds to other decision rules for discharging patients from the ED,[25 27] and may be a sufficiently low risk to consider routine discharge. However, significant variation in risk tolerance in clinicians and public representatives has been demonstrated, with some indicating that even a 1% risk of deterioration may be too high.[28 29] *Implications*

There is variation internationally in management and admission practices in this TBI population.[4] In the UK and other European countries guidelines recommend admission of all patients with TBI identified on CT imaging. This validation study shows a recalibrated version of our prognostic model could allow accurate prediction of risk of deterioration, and application of the HSC DR would have allowed a modest but safe reduction in hospital admissions for this group. The application of the BIG criteria would have discharged more patients but with a higher risk of subsequent deterioration in this European population, which may not be clinically acceptable. As indicated by our exploratory sub-group analysis, application of the HSC DR may be more beneficial when applied to lower risk populations more reflective of patients who attend the ED and are admitted for observation under Emergency Medicine or other non-neurosurgical specialities in the UK.

Our net benefit analysis using decision curves (Figure 3) showed use of our prognostic model may show benefit over an 'admit all' strategy if the threshold for the predicted probability of deterioration was over 2% and patients selected for discharge by the HSC DR had a 0% (95% CI: 0 % to 10.2%) risk of deterioration. This may be sufficiently low risk to use routinely. Research is needed to assess clinician and patient risk appetite in this population and assess the clinical impact of implementing the HSC DR where patient circumstances like intoxication or social circumstances may further affect whether a patient can be discharged. Research to improve the accuracy of the prognostic model (e.g. through including biomarkers, other novel prognostic factors, or better classification of injury severity on CT imaging) is also needed. .

Conclusion

Use of the HSC DR would allow a modest but safe reduction in hospital admissions for mild TBI patients with injuries identified on CT. The BIG criteria appear to result in an unacceptably high risk of subsequent deterioration (one in ten) among discharged patients. Future research should further validate our prognostic model and the HSC DR, consider safe implementation into clinical practice and assess whether inclusion of novel prognostic factors could improve the specificity of the model allowing more patients to be safely discharged.

Author Disclosure Statement:

No competing financial interests exist.

Data used in preparation of this manuscript were obtained in the context of CENTER-TBI, a large collaborative project with the support of the European Union 7th Framework program (EC grant602150). Full list of participants and investigators are provided in Supplementary

Material 9. Additional funding was obtained from the Hannelore Kohl Stiftung (Germany), from OneMind (USA) and from Integra LifeSciences Corporation (USA) (Grant Number Not Applicable/NA).

FEL and EWS are supported by the European Union Framework 7 Collaborative European Neurotrauma Effectiveness Research in Traumatic Brain Injury ((EC grant 602150)). FEL is also supported by the NHS Trusts "Trauma Audit and Research Network - www.tarn.ac.uk"(Grant Number Not Applicable/NA).

CM is a National Institute for Health Research (NIHR) Clinical Lecturer in Emergency Medicine (Grant Number Not Applicable/NA). This publication presents independent research funded by the National Institute for Health Research and University of Sheffield. The views expressed are those of the author(s) and not necessarily those of the University of Sheffield, the NHS, the NIHR or the Department of Health and Social Care

Authors' contributions:

The idea for the study was conceived by CM, TAS and FEL. The analysis was completed by CM with specialist statistical advice from BYG and EWS and specialist clinical advice from FEL. All authors contributed to interpretation of results, read and approved the final manuscript.

Figures:

Figure 1: STROBE flow diagram of selection of study population

Figure 2: Slope of the calibration plot of original and re-calibrated prognostic model

Figure 3: Decision Curve analysis

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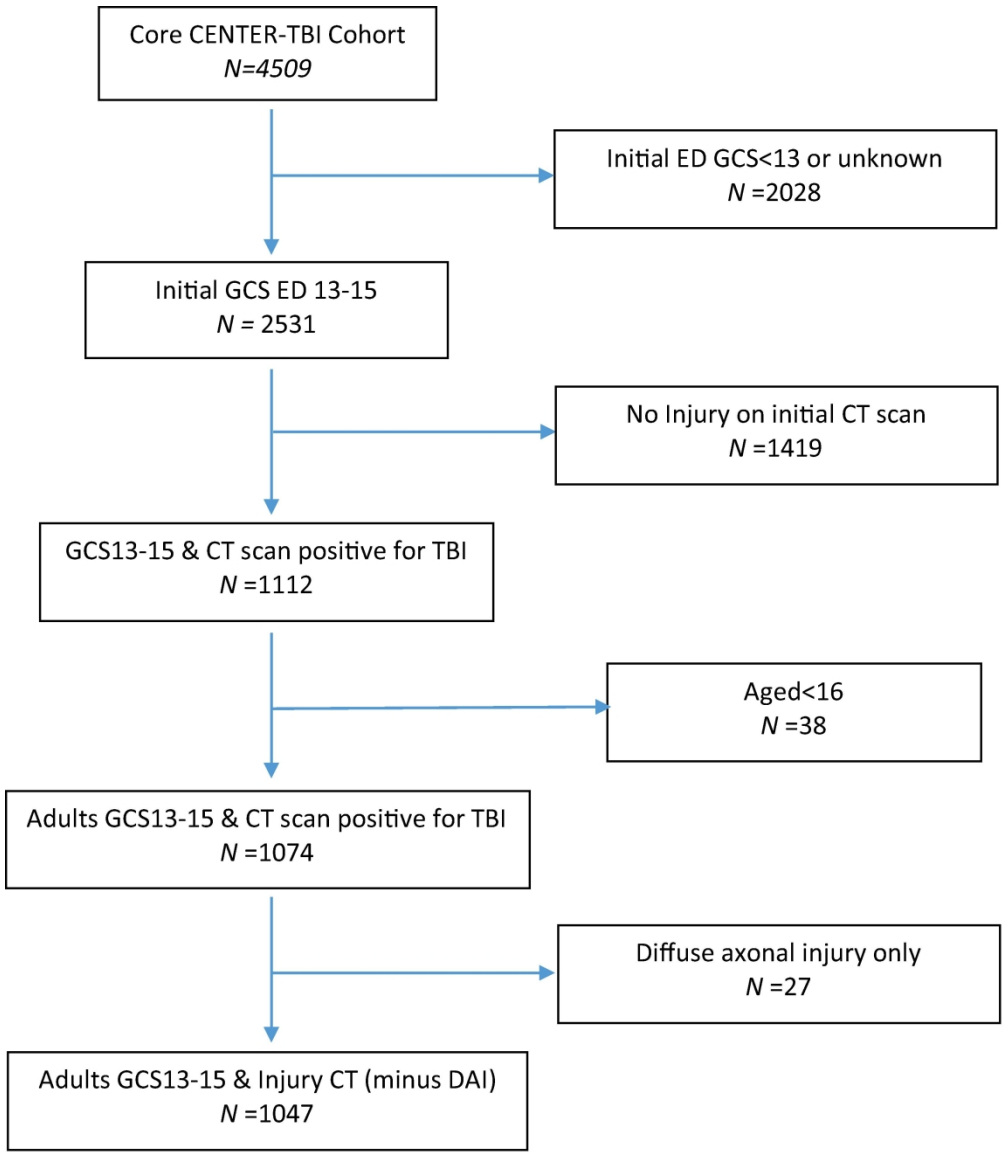

Figure 1: STROBE flow diagram of selection of study population

139x160mm (600 x 600 DPI)

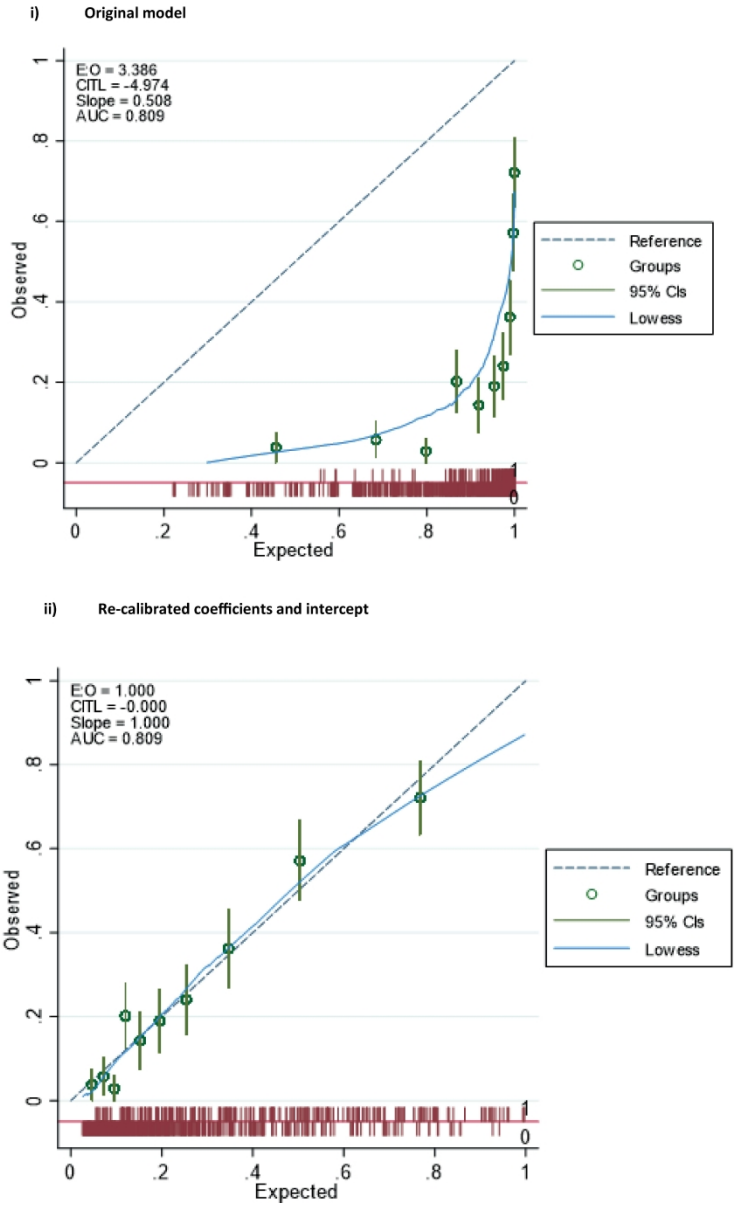

Figure 2: Calibration slope of original and re-calibration prognostic model

176x280mm (600 x 600 DPI)

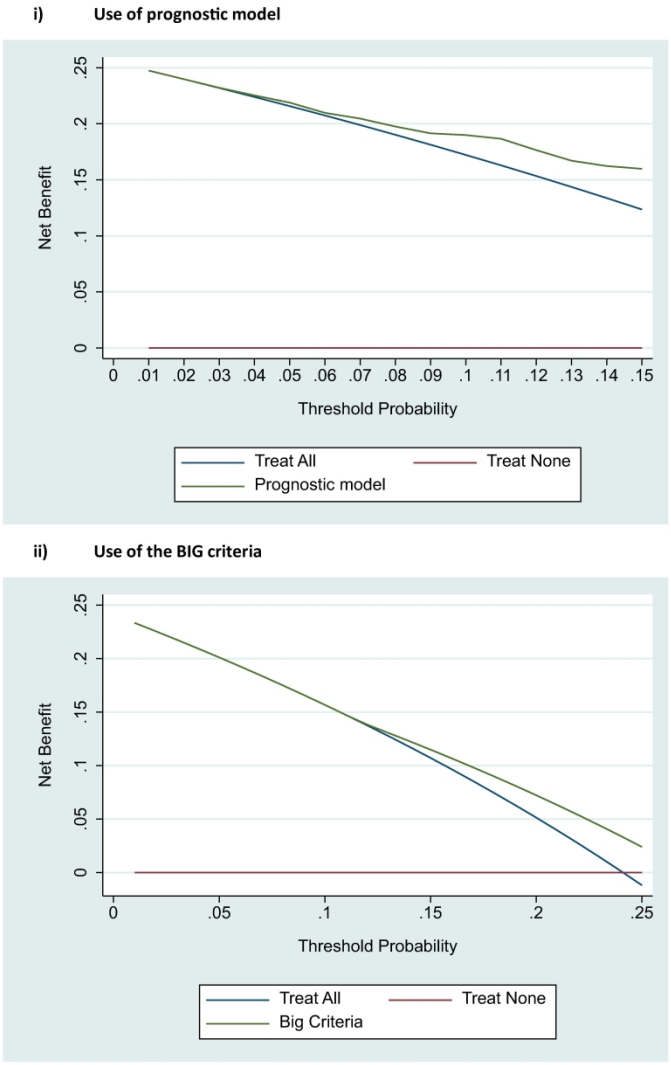

Figure 3: Decision Curve analysis

209x233mm (600 x 600 DPI)

Supplementary Material 1: The Brain Injury Guideline (BIG) criteria:

	BIG1 (Discharge from ED after 6 hours)	BIG2 (Non-specialist hospital admission)	BIG3* (Specialist hospital admission)
Neurological Examination	GCS13-15 Normal pupils No Focal Neurological deficit	GCS13-15 Normal pupils No Focal Neurological deficit	GCS<13 Or Abnormal pupils Or Focal Neurological deficit
Intoxicated	No	No/Yes	No/Yes
Anticoagulants or Anti-platelets	No	No	Yes
Skull Fracture	No	Non-displaced	Displaced
Intracranial Bleed	Subdural Haemorrhage <5mm Or Extradural Haemorrhage <5mm Or 1 Intraparenchymal Haemorrhage <5mm Or Trace Subarachnoid Haemorrhage	Subdural Haemorrhage 5-7mm Or Extradural Haemorrhage 5-7mm Or 1-2 Intraparenchymal Haemorrhages 5-7mm Or Localised Subarachnoid Haemorrhage	All other injuries
Intra-ventricular Haemorrhage	No	No	Yes

*Patients must fulfil all the criteria of BIG1 or BIG2 to be categorised as such and are otherwise automatically in BIG3

Supplementary Material 2: Risk Score

Factor	Coefficient	Risk Score Value
Preinjury Anti-coagulation or anti-platelets	0.3	1
GCS 15 14 13	 0 (Vs) 0.4 0.7	 **GCS 15** 0 **GCS 14** 1 **GCS 13** 2
Normal first Neurological Examination	0.45	**Abnormal** 1.5
Number of Injuries on CT **1** **2** **3** **4** **5** **Diffuse**	 0 (Vs) 0.25 0.4 0.8 0.9 0.3	 **1** 0 **2** 1 **3** 1 **4** 3 **5** 3 **Diffuse** 1
Injury severity on CT **1** simple skull fracture **2** complex Skull Fracture **3** Marshall IIa 1-2 bleeds < 5mm (total) **4** Marshall IIb bleeds ≥ 5mm **5** Marshall III/IV **6** Marshall VI **7** Brain stem/Cerebellar	 0 (Vs) 0.3 0.08 0.7 1.7 2.7 1.7	 **1** 0 **2** 1 **3** 0 **4** 2 **5** 5 **6** 9 **7** 5
ISS (body regions excluding head)	0.2	**Up to 2 non-significant extra-cranial injuries**** 0 **Any significant extra-cranial injury or 3 or more injuries** 2
Hb	-0.01	Not included in risk score
Constant	-1.38	

* Injuries exclude superficial lacerations and abrasions and a significant extra-cranial injury is defined as any injury requiring inpatient care

Supplementary Material 3: Procedure for Multi-imputation of missing data

Missing data was assumed to be missing at random. Thirty-five imputed datasets were created on the basis of the fraction of missing information (around 35% of patients had missing data in at least one predictor variable in the extended prognostic model). The imputation model contained the composite outcome of deterioration, all predictive factors in the prognostic model, and additionally, age and sex. Model performance was averaged across imputed data sets.

Supplementary Material 4: Performance of BIG criteria across all 3 risk stratification categories

BIG Criteria Performance			
BIG 1 (Discharge from ED after 6 hours)			
N=921	**Deteriorated**	**Didn't deteriorate**	
N=105 Composite deterioration	12	93	
Neurosurg/Death/intubation	6	99	
BIG 2 (non-specialist admission)			
N=921	**Deteriorated**	**Didn't deteriorate**	
N=82 Composite deterioration	10	72	
Neurosurg/Death/intubation	8	74	
BIG 3 (Neurosurgical Admission, repeat CT imaging)			
N=921	**Deteriorated**	**Didn't deteriorate**	
N=734 Composite deterioration	200	534	
Neurosurg/Death/intubation	164	570	

Supplementary Material 5: Characteristics of patients recommended for discharge

Population Characteristic	Category Mean (SD), min-max or N (%)	BIG 1 N=105	Recommended Discharge HSC DR N=34
Age	Years	52 (17.5) 17-84	48.4 (18.2) 25-80
Age	≥65	24 (22.9%)	6 (17.7%)
GCS	15 14 13	75 (71.4%) 24 (22.9%) 6 (5.7%)	34 (100%)
Intoxicated	Yes	0 (0%)	7 (20.6%)
Haemoglobin	Grams/litre	137 (SD 17.4) 8.3-16.3	143 (SD12.5) 12.7-15.6
Number of Injuries on CT	1 2 3 4 5 Multiple diffuse injury/>5	105 (100%)	34 (100%)
Injury severity on CT (Modified Marshall Classification described in detail supplementary Material)	**1)** Simple Skull Fractures **3)**1-2 bleeds < 5mm (total)	105 (100%)	1 (2.9%) 33 (97.1%)
ISS	Body regions excluding head	15.4 (12.1) 1-59	4.1 (2) 1-8

Supplementary Material 6: Subgroup analysis Marshall Classification <3

HSC DR			
N=800	**Deteriorated**	**Didn't deteriorate**	
Risk=0	0	34	Sensitivity 100% (96.6-100%)
Risk>0	137	629	Specificity 5.1% (3.6-7.2)

BIG 1 (Discharge after 6 hours)			
N=770	**Deteriorated**	**Didn't deteriorate**	
BIG1	12	93	Sensitivity 90.8% (84.2-95)
BIG 2/3	119	546	Specificity 14.6% (12-17.6)

Supplementary Material 7: Recalibrated prognostic model

Factor	**Coefficient (optimism adjusted)**
Preinjury Anti-coagulation or anti-platelets	0.15
GCS 15 14 13	 0 (Vs) 0.2 0.36
Normal first Neurological Examination	0.23
Number of Injuries on CT **1** **2** **3** **4** **5** **Diffuse**	 0 (Vs) 0.13 0.2 0.41 0.46 0.15
Injury severity on CT* **1** simple skull fracture **2** complex Skull Fracture **3** 1-2 bleeds < 5mm **4** Marshall II **5** Marshall III/IV **6** Marshall VI **7** Brain stem/Cerebellar	 0 (Vs) 0.15 0.04 0.36 0.87 1.38 0.87
ISS (body regions excluding head)	0.1
Hb	-0.005
Constant	-3.68

Supplementary Material 8: Sensitivity analysis with 2 sites used in derivation study excluded

HSC DR			
N=893	**Deteriorated**	**Didn't deteriorate**	
Risk=0	0	31	Sensitivity 100% (98-100)
Risk>0	221	641	Specificity 4.6% (3.2-6.6%)

Supplementary Material 9: The CENTER-TBI participants and investigators:

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