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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.

Carl Marincowitz¹ NIHR Clinical Lecturer Emergency Medicine, MB BChir, PhD, MSc, BA (Hons), MRCEM

B.Y. Gravesteijn² MSc, PhD Candidate

Trevor A. Sheldon³ Professor, MSc, MSc, DSc, FMedSci

Ewout W. Steyerberg⁴ Professor, MSc, PhD

Fiona E. Lecky^{1,5} Professor, Honorary Emergency Medicine Consultant, MB ChB, FRCS, DA, MSc, PhD, FRCEM

1. **Corresponding Author.** Centre for Urgent and Emergency Care Research (CURE), Health Services Research School of Health and Related Research, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA, UK, Fax: +44 (0)114 222 0749 Tel: (+44) (0)114 222 4345,

Email: C.Marincowitz@Sheffield.ac.uk

2. Department of Public Health, Erasmus Medical Centre, P.O. Box 2040, 3000 CA, Rotterdam, The Netherlands. Email: b.gravesteijn@erasmusmc.nl

3. Institute of Population Health Sciences, Barts and The London School of Medicine and Dentistry, Queen Mary University London, Yvonne Carter Building, 58 Turner Street, London E1 2AB, Email: t.sheldon@qmul.ac.uk

4. Department of Biomedical Data Sciences, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, Tel: +31 71 526 9700, Email: e.w.steyerberg@lumc.nl

5. Emergency Department, Salford Royal Hospital, Salford, UK. Email: F.E.Lecky@Sheffield.ac.uk

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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}

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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 inpatient care, e.g closed fracture humerus)	
Intoxication		Not intoxicated
Hb	Not included in risk score	

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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

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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: 17% 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: 98.8% 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% (98.8-100%) 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%)

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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 be admitted under non-specialist teams the BIG criteria recommended discharge of 26% of patients with brain

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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 injuries 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

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

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28 In the CENTER TBI cohort, 20% of patients underwent neurosurgery, died, or were intubated
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30 compared to 13.1% in our development cohort and had a higher prevalence of deterioration
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32 than reported in a previous systematic review.⁴ This may reflect recruitment of more
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34 severely injured patients to the CENTER-TBI study.
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39 The BIG criteria for discharging patients from the ED achieved a lower sensitivity (94.6%)
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41 and higher specificity (13.3%) than when applied to our development cohort (sensitivity
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43 99.5% and specificity 4.8%). Application of the BIG criteria would have allowed 11.4% of
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45 patients to be discharged from the ED which is similar to the 10% of patients estimated in
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47 studies conducted where the BIG criteria was developed in the USA and 15% reported in an
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49 external validation study.^{6 21 23} The derivation and validation studies reported by the team
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51 that developed the BIG criteria and available external validation studies report no adverse
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53 outcomes in patients recommended for discharge by the BIG criteria.^{6 21-23 26} In the CENTER-
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55 TBI cohort, patients recommended for discharge had a 11.4% (95% CI: 6.7 % to 18.9%), risk
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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-DR⁷ 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.

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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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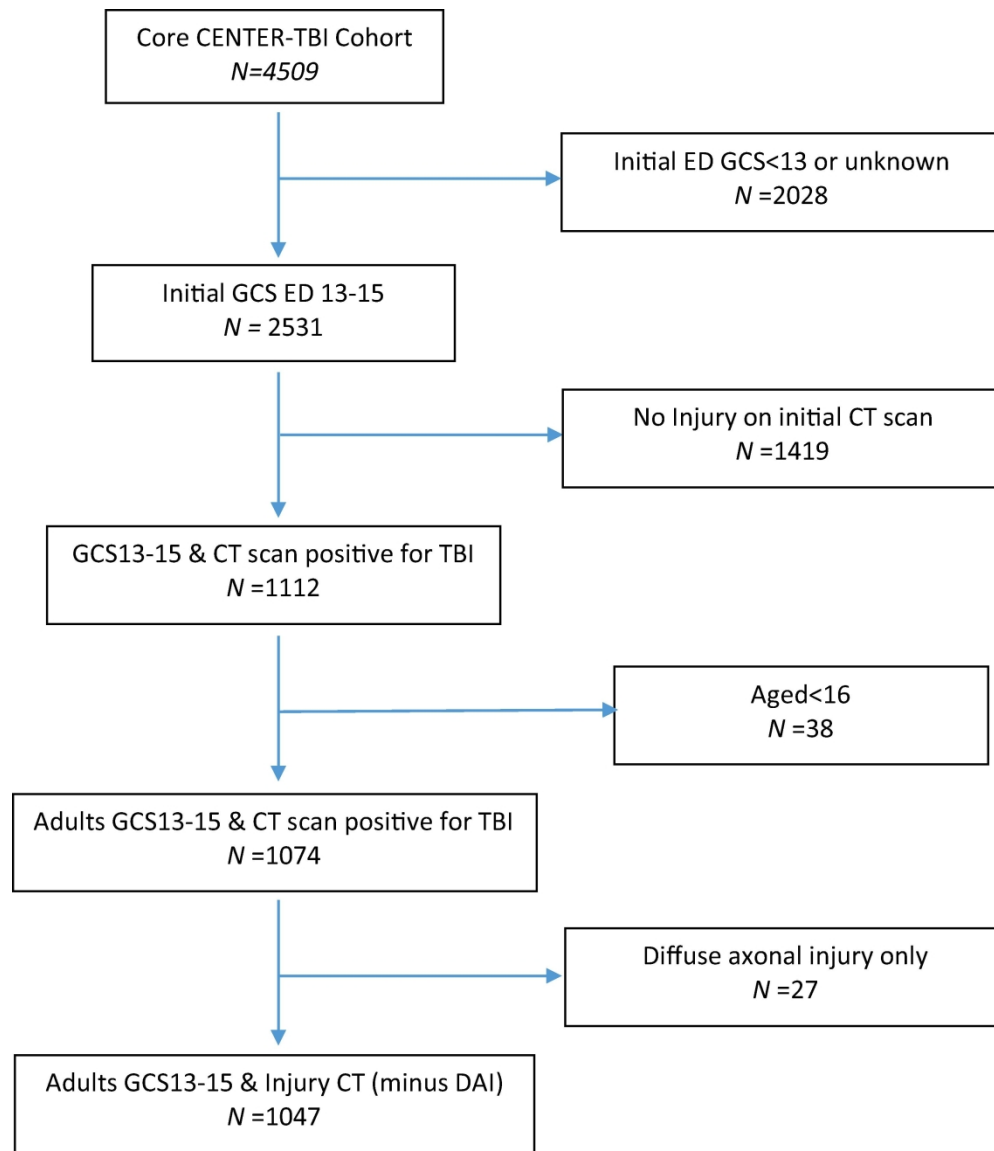


Figure 1: STROBE flow diagram of selection of study population

139x160mm (600 x 600 DPI)

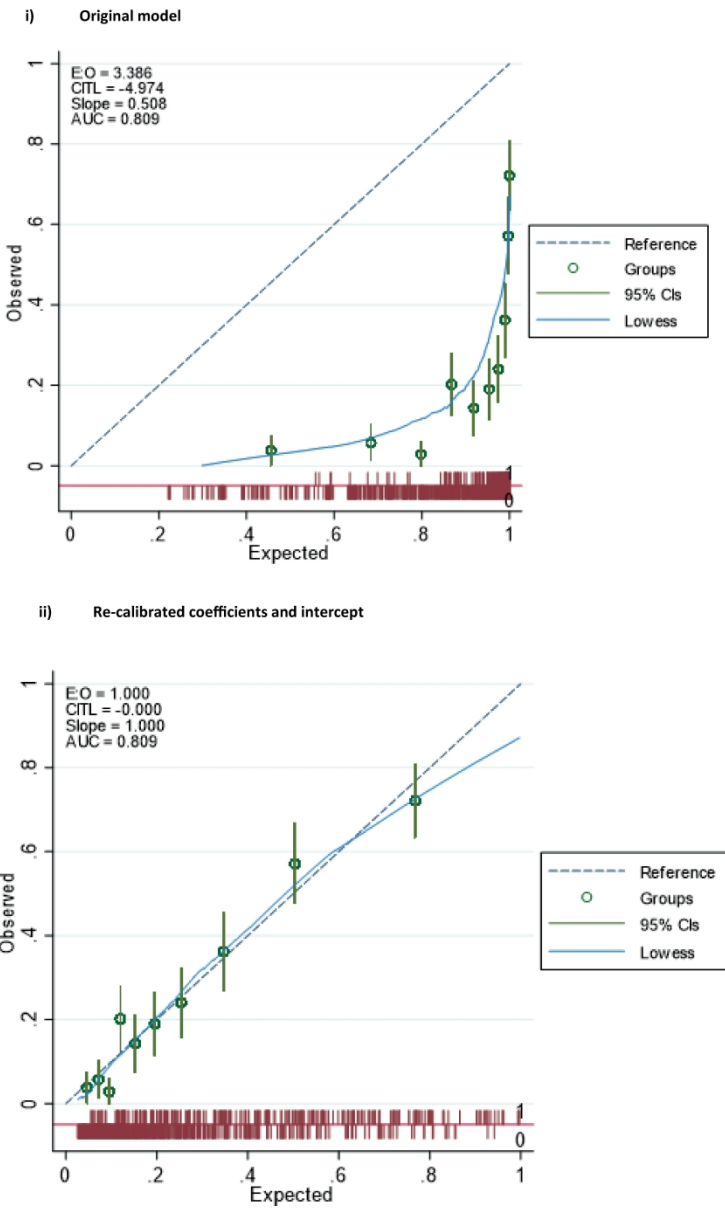
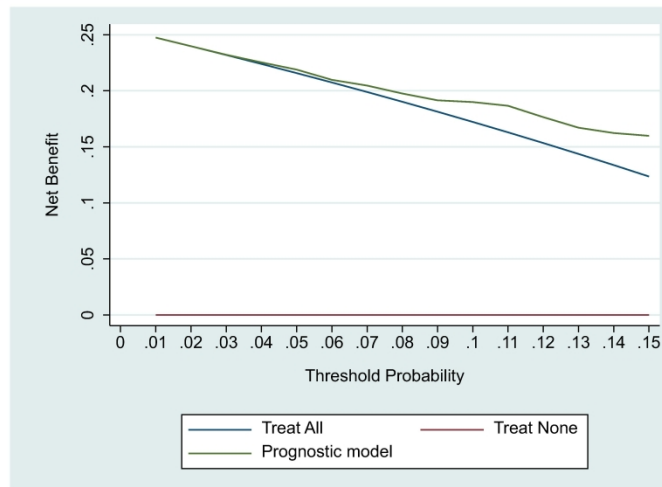


Figure 2: Calibration slope of original and re-calibration prognostic model

176x280mm (600 x 600 DPI)

i) Use of prognostic model



ii) Use of the BIG criteria

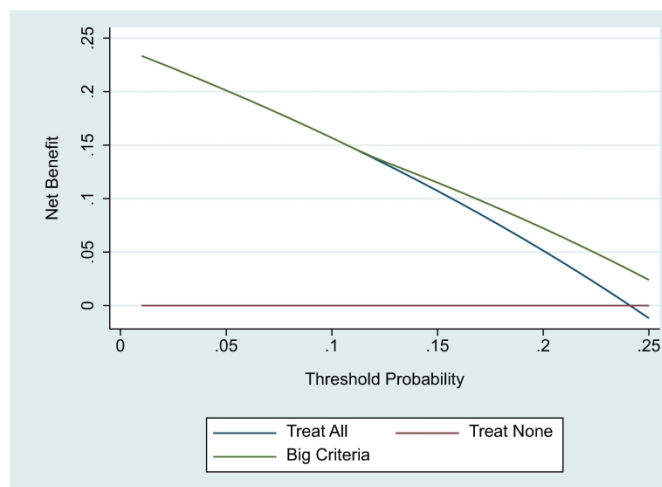


Figure 3: Decision Curve analysis

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	0 (Vs)	GCS 15 0
14	0.4	GCS 14 1
13	0.7	GCS 13 2
Normal first Neurological Examination	0.45	Abnormal 1.5
Number of Injuries on CT		
1	0 (Vs)	1 0
2	0.25	2 1
3	0.4	3 1
4	0.8	4 3
5	0.9	5 3
Diffuse	0.3	Diffuse 1
Injury severity on CT		
1 simple skull fracture	0 (Vs)	1 0
2 complex Skull Fracture	0.3	2 1
3 Marshall IIa 1-2 bleeds < 5mm (total)	0.08	3 0
4 Marshall IIb bleeds ≥ 5mm	0.7	4 2
5 Marshall III/IV	1.7	5 5
6 Marshall VI	2.7	6 9
7 Brain stem/Cerebellar	1.7	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	12	93	
Composite deterioration			
Neurosurg/Death/intubation	6	99	
BIG 2 (non-specialist admission)			
N=921	Deteriorated	Didn't deteriorate	
N=82	10	72	
Composite deterioration			
Neurosurg/Death/intubation	8	74	
BIG 3 (Neurosurgical Admission, repeat CT imaging)			
N=921	Deteriorated	Didn't deteriorate	
N=734	200	534	
Composite deterioration			
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	75 (71.4%)	34 (100%)
	14	24 (22.9%)	
	13	6 (5.7%)	
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

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

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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:

Cecilia Åkerlund¹, Krisztina Amrein², Nada Andelic³, Lasse Andreassen⁴, Audny Anke⁵, Anna Antoni⁶, Gérard Audibert⁷, Philippe Azouvi⁸, Maria Luisa Azzolini⁹, Ronald Bartels¹⁰, Pál Barzó¹¹, Romuald Beauvais¹², Ronny Beer¹³, Bo-Michael Bellander¹⁴, Antonio Belli¹⁵, Habib Benali¹⁶, Maurizio Berardino¹⁷, Luigi Beretta⁹, Morten Blaabjerg¹⁸, Peter Bragge¹⁹, Alexandra Brazinova²⁰, Vibeke Brinck²¹, Joanne Brooker²², Camilla Brorsson²³, Andras Buki²⁴, Monika Bullinger²⁵, Manuel Cabeleira²⁶, Alessio Caccioppola²⁷, Emiliana Calappi²⁷, Maria Rosa Calvi⁹, Peter Cameron²⁸, Guillermo Carbayo Lozano²⁹, Marco Carbonara²⁷, Simona Cavallo¹⁷, Giorgio Chevallard³⁰, Arturo Chierogato³⁰, Giuseppe Citerio^{31, 32}, Hans Clusmann³³, Mark Coburn³⁴, Jonathan Coles³⁵, Jamie D. Cooper³⁶, Marta Correia³⁷, Amra Čović³⁸, Nicola Curry³⁹, Endre Czeiter²⁴, Marek Czosnyka²⁶, Claire Dahyot-Fizelier⁴⁰, Paul Dark⁴¹, Helen Dawes⁴², Véronique De Keyser⁴³, Vincent Degos¹⁶, Francesco Della Corte⁴⁴, Hugo den Boogert¹⁰, Bart Depreitere⁴⁵, Đula Đilvesi⁴⁶, Abhishek Dixit⁴⁷, Emma Donoghue²², Jens Dreier⁴⁸, Guy-Loup Dulière⁴⁹, Ari Ercole⁴⁷, Patrick Esser⁴², Erzsébet Ezer⁵⁰, Martin Fabricius⁵¹, Valery L. Feigin⁵², Kelly Foks⁵³, Shirin Frisvold⁵⁴, Alex Furmanov⁵⁵, Pablo Gagliardo⁵⁶, Damien Galanaud¹⁶, Dashiell Gantner²⁸, Guoyi Gao⁵⁷, Pradeep George⁵⁸, Alexandre Ghuysen⁵⁹, Lelde Giga⁶⁰, Ben Glocker⁶¹, Jagoš Golubovic⁴⁶, Pedro A. Gomez⁶², Johannes Gratz⁶³, Benjamin Gravesteijn⁶⁴, Francesca Grossi⁴⁴, Russell L. Gruen⁶⁵, Deepak Gupta⁶⁶, Juanita A. Haagsma⁶⁴, Iain Haitsma⁶⁷, Raimund Helbok¹³, Eirik Helseth⁶⁸, Lindsay Horton⁶⁹, Jilske Huijben⁶⁴, Peter J. Hutchinson⁷⁰, Bram Jacobs⁷¹, Stefan Jankowski⁷², Mike Jarrett²¹, Ji-yao Jiang⁵⁸, Faye Johnson⁷³, Kelly Jones⁵², Mladen Karan⁴⁶, Angelos G. Kolias⁷⁰, Erwin Kompanje⁷⁴, Daniel Kondziella⁵¹, Evgenios Kornaropoulos⁴⁷, Lars-Owe Koskinen⁷⁵, Noémi Kovács⁷⁶, Ana Kowark⁷⁷, Alfonso Lagares⁶², Linda Lanyon⁵⁸, Steven Laureys⁷⁸, Fiona Lecky^{79, 80}, Didier Ledoux⁷⁸, Rolf Lefering⁸¹, Valerie Legrand⁸², Aurelie Lejeune⁸³, Leon Levi⁸⁴, Roger Lightfoot⁸⁵, Hester Lingsma⁶⁴, Andrew I.R. Maas⁴³, Ana M. Castaño-León⁶², Marc Maegele⁸⁶, Marek Majdan²⁰, Alex Manara⁸⁷, Geoffrey Manley⁸⁸, Costanza Martino⁸⁹, Hugues Maréchal⁴⁹, Julia Mattern⁹⁰, Catherine McMahon⁹¹, Béla Meleghe⁹², David Menon⁴⁷, Tomas Menovsky⁴³, Ana Mikolic⁶⁴, Benoit Misset⁷⁸, Visakh Muraleedharan⁵⁸, Lynnette Murray²⁸, Ancuta Negru⁹³, David Nelson¹, Virginia Newcombe⁴⁷, Daan Nieboer⁶⁴, József Nyirádi², Otesile Olubukola⁷⁹, Matej Oresic⁹⁴, Fabrizio Ortolano²⁷, Aarno Palotie^{95, 96, 97}, Paul M. Parizel⁹⁸, Jean-François Payen⁹⁹, Natascha Perera¹², Vincent Perlberg¹⁶, Paolo Persona¹⁰⁰, Wilco Peul¹⁰¹, Anna Piippo-Karjalainen¹⁰², Matti Pirinen⁹⁵, Horia Ples⁹³, Suzanne Polinder⁶⁴, Inigo Pomposo²⁹, Jussi P. Posti¹⁰³, Louis Puybasset¹⁰⁴, Andreea Radoi¹⁰⁵, Arminas Ragauskas¹⁰⁶, Rahul Raj¹⁰², Malinka Rambadagalla¹⁰⁷, Jonathan Rhodes¹⁰⁸, Sylvia Richardson¹⁰⁹, Sophie Richter⁴⁷, Samuli Ripatti⁹⁵, Saulius Rocka¹⁰⁶, Cecilie Roe¹¹⁰, Olav Roise^{111, 112}, Jonathan Rosand¹¹³, Jeffrey V. Rosenfeld¹¹⁴, Christina Rosenlund¹¹⁵, Guy Rosenthal⁵⁵, Rolf Rossaint⁷⁷, Sandra Rossi¹⁰⁰, Daniel Rueckert⁶¹, Martin Rusnák¹¹⁶, Juan Sahuquillo¹⁰⁵, Oliver Sakowitz^{90, 117}, Renan Sanchez-Porras¹¹⁷, Janos Sandor¹¹⁸, Nadine Schäfer⁸¹, Silke Schmidt¹¹⁹, Herbert Schoechl¹²⁰, Guus Schoonman¹²¹, Rico Frederik Schou¹²², Elisabeth Schwendenwein⁶, Charlie Sewalt⁶⁴, Toril Skandsen^{123, 124}, Peter Smielewski²⁶, Abayomi Sorinola¹²⁵, Emmanuel Stamatakis⁴⁷, Simon Stanworth³⁹, Robert Stevens¹²⁶, William Stewart¹²⁷, Ewout W. Steyerberg^{64, 128}, Nino Stocchetti¹²⁹, Nina Sundström¹³⁰, Riikka Takala¹³¹, Viktória Tamás¹²⁵, Tomas Tamosuitis¹³², Mark Steven Taylor²⁰, Braden Te Ao⁵², Olli

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43
44
45
46
47
48
49
50
51
52
53
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60

Tenovuo¹⁰³, Alice Theadom⁵², Matt Thomas⁸⁷, Dick Tibboel¹³³, Marjolein Timmers⁷⁴,
Christos Toliás¹³⁴, Tony Trapani²⁸, Cristina Maria Tudora⁹³, Andreas Unterberg⁹⁰, Peter
Vajkoczy¹³⁵, Shirley Vallance²⁸, Egils Valeinis⁶⁰, Zoltán Vámos⁵⁰, Mathieu van der Jagt¹³⁶,
Gregory Van der Steen⁴³, Joukje van der Naalt⁷¹, Jeroen T.J.M. van Dijck¹⁰¹,
Thomas A. van Essen¹⁰¹, Wim Van Hecke¹³⁷, Caroline van Heugten¹³⁸,
Dominique Van Praag¹³⁹, Thijs Vande Vyvere¹³⁷, Roel P. J. van Wijk¹⁰¹, Alessia Vargiolu³²,
Emmanuel Vega⁸³, Kimberley Velt⁶⁴, Jan Verheyden¹³⁷, Paul M. Vespa¹⁴⁰, Anne Vik^{123, 141},
Rimantas Vilcinis¹³², Victor Volovici⁶⁷, Nicole von Steinbüchel³⁸, Daphne Voormolen⁶⁴,
Petar Vulekovic⁴⁶, Kevin K.W. Wang¹⁴², Eveline Wiegers⁶⁴, Guy Williams⁴⁷, Lindsay Wilson⁶⁹,
Stefan Winzeck⁴⁷, Stefan Wolf¹⁴³, Zhihui Yang¹¹³, Peter Ylén¹⁴⁴, Alexander Younsi⁹⁰, Frederick
A. Zeiler^{47,145}, Veronika Zelinkova²⁰, Agate Ziverte⁶⁰, Tommaso Zoerle²⁷

- 1
- 2
- 3
- 4 ¹ Department of Physiology and Pharmacology, Section of Perioperative Medicine and Intensive
- 5 Care, Karolinska Institutet, Stockholm, Sweden
- 6 ² János Szentágothai Research Centre, University of Pécs, Pécs, Hungary
- 7 ³ Division of Surgery and Clinical Neuroscience, Department of Physical Medicine and
- 8 Rehabilitation, Oslo University Hospital and University of Oslo, Oslo, Norway
- 9 ⁴ Department of Neurosurgery, University Hospital Northern Norway, Tromsø, Norway
- 10 ⁵ Department of Physical Medicine and Rehabilitation, University Hospital Northern Norway,
- 11 Tromsø, Norway
- 12 ⁶ Trauma Surgery, Medical University Vienna, Vienna, Austria
- 13 ⁷ Department of Anesthesiology & Intensive Care, University Hospital Nancy, Nancy, France
- 14 ⁸ Raymond Poincaré hospital, Assistance Publique – Hopitaux de Paris, Paris, France
- 15 ⁹ Department of Anesthesiology & Intensive Care, S Raffaele University Hospital, Milan, Italy
- 16 ¹⁰ Department of Neurosurgery, Radboud University Medical Center, Nijmegen, The
- 17 Netherlands
- 18 ¹¹ Department of Neurosurgery, University of Szeged, Szeged, Hungary
- 19 ¹² International Projects Management, ARTTIC, Munchen, Germany
- 20 ¹³ Department of Neurology, Neurological Intensive Care Unit, Medical University of
- 21 Innsbruck, Innsbruck, Austria
- 22 ¹⁴ Department of Neurosurgery & Anesthesia & intensive care medicine, Karolinska
- 23 University Hospital, Stockholm, Sweden
- 24 ¹⁵ NIHR Surgical Reconstruction and Microbiology Research Centre, Birmingham, UK
- 25 ¹⁶ Anesthésie-Réanimation, Assistance Publique – Hopitaux de Paris, Paris, France
- 26 ¹⁷ Department of Anesthesia & ICU, AOU Città della Salute e della Scienza di Torino -
- 27 Orthopedic and Trauma Center, Torino, Italy
- 28 ¹⁸ Department of Neurology, Odense University Hospital, Odense, Denmark
- 29 ¹⁹ BehaviourWorks Australia, Monash Sustainability Institute, Monash University, Victoria,
- 30 Australia
- 31 ²⁰ Department of Public Health, Faculty of Health Sciences and Social Work, Trnava
- 32 University, Trnava, Slovakia
- 33 ²¹ Quesgen Systems Inc., Burlingame, California, USA
- 34 ²² Australian & New Zealand Intensive Care Research Centre, Department of Epidemiology
- 35 and Preventive Medicine, School of Public Health and Preventive Medicine, Monash
- 36 University, Melbourne, Australia
- 37 ²³ Department of Surgery and Perioperative Science, Umeå University, Umeå, Sweden
- 38 ²⁴ Department of Neurosurgery, Medical School, University of Pécs, Hungary and
- 39 Neurotrauma Research Group, János Szentágothai Research Centre, University of Pécs,
- 40 Hungary
- 41 ²⁵ Department of Medical Psychology, Universitätsklinikum Hamburg-Eppendorf, Hamburg,
- 42 Germany
- 43 ²⁶ Brain Physics Lab, Division of Neurosurgery, Dept of Clinical Neurosciences, University of
- 44 Cambridge, Addenbrooke's Hospital, Cambridge, UK
- 45 ²⁷ Neuro ICU, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy
- 46 ²⁸ ANZIC Research Centre, Monash University, Department of Epidemiology and Preventive
- 47 Medicine, Melbourne, Victoria, Australia
- 48 ²⁹ Department of Neurosurgery, Hospital of Cruces, Bilbao, Spain
- 49 ³⁰ NeuroIntensive Care, Niguarda Hospital, Milan, Italy
- 50 ³¹ School of Medicine and Surgery, Università Milano Bicocca, Milano, Italy
- 51
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60

- ³² NeuroIntensive Care, ASST di Monza, Monza, Italy
- ³³ Department of Neurosurgery, Medical Faculty RWTH Aachen University, Aachen, Germany
- ³⁴ Department of Anesthesiology and Intensive Care Medicine, University Hospital Bonn, Bonn, Germany
- ³⁵ Department of Anesthesia & Neurointensive Care, Cambridge University Hospital NHS Foundation Trust, Cambridge, UK
- ³⁶ School of Public Health & PM, Monash University and The Alfred Hospital, Melbourne, Victoria, Australia
- ³⁷ Radiology/MRI department, MRC Cognition and Brain Sciences Unit, Cambridge, UK
- ³⁸ Institute of Medical Psychology and Medical Sociology, Universitätsmedizin Göttingen, Göttingen, Germany
- ³⁹ Oxford University Hospitals NHS Trust, Oxford, UK
- ⁴⁰ Intensive Care Unit, CHU Poitiers, Poitiers, France
- ⁴¹ University of Manchester NIHR Biomedical Research Centre, Critical Care Directorate, Salford Royal Hospital NHS Foundation Trust, Salford, UK
- ⁴² Movement Science Group, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford, UK
- ⁴³ Department of Neurosurgery, Antwerp University Hospital and University of Antwerp, Edegem, Belgium
- ⁴⁴ Department of Anesthesia & Intensive Care, Maggiore Della Carità Hospital, Novara, Italy
- ⁴⁵ Department of Neurosurgery, University Hospitals Leuven, Leuven, Belgium
- ⁴⁶ Department of Neurosurgery, Clinical centre of Vojvodina, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia
- ⁴⁷ Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK
- ⁴⁸ Center for Stroke Research Berlin, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany
- ⁴⁹ Intensive Care Unit, CHR Citadelle, Liège, Belgium
- ⁵⁰ Department of Anaesthesiology and Intensive Therapy, University of Pécs, Pécs, Hungary
- ⁵¹ Departments of Neurology, Clinical Neurophysiology and Neuroanesthesiology, Region Hovedstaden Rigshospitalet, Copenhagen, Denmark
- ⁵² National Institute for Stroke and Applied Neurosciences, Faculty of Health and Environmental Studies, Auckland University of Technology, Auckland, New Zealand
- ⁵³ Department of Neurology, Erasmus MC, Rotterdam, the Netherlands
- ⁵⁴ Department of Anesthesiology and Intensive care, University Hospital Northern Norway, Tromsø, Norway
- ⁵⁵ Department of Neurosurgery, Hadassah-hebrew University Medical center, Jerusalem, Israel
- ⁵⁶ Fundación Instituto Valenciano de Neurorehabilitación (FIVAN), Valencia, Spain
- ⁵⁷ Department of Neurosurgery, Shanghai Renji hospital, Shanghai Jiaotong University/school of medicine, Shanghai, China
- ⁵⁸ Karolinska Institutet, INCF International Neuroinformatics Coordinating Facility, Stockholm, Sweden
- ⁵⁹ Emergency Department, CHU, Liège, Belgium
- ⁶⁰ Neurosurgery clinic, Pauls Stradins Clinical University Hospital, Riga, Latvia
- ⁶¹ Department of Computing, Imperial College London, London, UK
- ⁶² Department of Neurosurgery, Hospital Universitario 12 de Octubre, Madrid, Spain

- 63 Department of Anesthesia, Critical Care and Pain Medicine, Medical University of Vienna, Austria
- 64 Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, The Netherlands
- 65 College of Health and Medicine, Australian National University, Canberra, Australia
- 66 Department of Neurosurgery, Neurosciences Centre & JPN Apex trauma centre, All India Institute of Medical Sciences, New Delhi-110029, India
- 67 Department of Neurosurgery, Erasmus MC, Rotterdam, the Netherlands
- 68 Department of Neurosurgery, Oslo University Hospital, Oslo, Norway
- 69 Division of Psychology, University of Stirling, Stirling, UK
- 70 Division of Neurosurgery, Department of Clinical Neurosciences, Addenbrooke's Hospital & University of Cambridge, Cambridge, UK
- 71 Department of Neurology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands
- 72 Neurointensive Care , Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK
- 73 Salford Royal Hospital NHS Foundation Trust Acute Research Delivery Team, Salford, UK
- 74 Department of Intensive Care and Department of Ethics and Philosophy of Medicine, Erasmus Medical Center, Rotterdam, The Netherlands
- 75 Department of Clinical Neuroscience, Neurosurgery, Umeå University, Umeå, Sweden
- 76 Hungarian Brain Research Program - Grant No. KTIA_13_NAP-A-II/8, University of Pécs, Pécs, Hungary
- 77 Department of Anaesthesiology, University Hospital of Aachen, Aachen, Germany
- 78 Cyclotron Research Center , University of Liège, Liège, Belgium
- 79 Centre for Urgent and Emergency Care Research (CURE), Health Services Research Section, School of Health and Related Research (SchARR), University of Sheffield, Sheffield, UK
- 80 Emergency Department, Salford Royal Hospital, Salford UK
- 81 Institute of Research in Operative Medicine (IFOM), Witten/Herdecke University, Cologne, Germany
- 82 VP Global Project Management CNS, ICON, Paris, France
- 83 Department of Anesthesiology-Intensive Care, Lille University Hospital, Lille, France
- 84 Department of Neurosurgery, Rambam Medical Center, Haifa, Israel
- 85 Department of Anesthesiology & Intensive Care, University Hospitals Southampton NHS Trust, Southampton, UK
- 86 Cologne-Merheim Medical Center (CMMC), Department of Traumatology, Orthopedic Surgery and Sportmedicine, Witten/Herdecke University, Cologne, Germany
- 87 Intensive Care Unit, Southmead Hospital, Bristol, Bristol, UK
- 88 Department of Neurological Surgery, University of California, San Francisco, California, USA
- 89 Department of Anesthesia & Intensive Care, M. Bufalini Hospital, Cesena, Italy
- 90 Department of Neurosurgery, University Hospital Heidelberg, Heidelberg, Germany
- 91 Department of Neurosurgery, The Walton centre NHS Foundation Trust, Liverpool, UK
- 92 Department of Medical Genetics, University of Pécs, Pécs, Hungary
- 93 Department of Neurosurgery, Emergency County Hospital Timisoara , Timisoara, Romania
- 94 School of Medical Sciences, Örebro University, Örebro, Sweden
- 95 Institute for Molecular Medicine Finland, University of Helsinki, Helsinki, Finland

- ⁹⁶ Analytic and Translational Genetics Unit, Department of Medicine; Psychiatric & Neurodevelopmental Genetics Unit, Department of Psychiatry; Department of Neurology, Massachusetts General Hospital, Boston, MA, USA
- ⁹⁷ Program in Medical and Population Genetics; The Stanley Center for Psychiatric Research, The Broad Institute of MIT and Harvard, Cambridge, MA, USA
- ⁹⁸ Department of Radiology, University of Antwerp, Edegem, Belgium
- ⁹⁹ Department of Anesthesiology & Intensive Care, University Hospital of Grenoble, Grenoble, France
- ¹⁰⁰ Department of Anesthesia & Intensive Care, Azienda Ospedaliera Università di Padova, Padova, Italy
- ¹⁰¹ Dept. of Neurosurgery, Leiden University Medical Center, Leiden, The Netherlands and Dept. of Neurosurgery, Medical Center Haaglanden, The Hague, The Netherlands
- ¹⁰² Department of Neurosurgery, Helsinki University Central Hospital
- ¹⁰³ Division of Clinical Neurosciences, Department of Neurosurgery and Turku Brain Injury Centre, Turku University Hospital and University of Turku, Turku, Finland
- ¹⁰⁴ Department of Anesthesiology and Critical Care, Pitié -Salpêtrière Teaching Hospital, Assistance Publique, Hôpitaux de Paris and University Pierre et Marie Curie, Paris, France
- ¹⁰⁵ Neurotraumatology and Neurosurgery Research Unit (UNINN), Vall d'Hebron Research Institute, Barcelona, Spain
- ¹⁰⁶ Department of Neurosurgery, Kaunas University of technology and Vilnius University, Vilnius, Lithuania
- ¹⁰⁷ Department of Neurosurgery, Rezekne Hospital, Latvia
- ¹⁰⁸ Department of Anaesthesia, Critical Care & Pain Medicine NHS Lothian & University of Edinburgh, Edinburgh, UK
- ¹⁰⁹ Director, MRC Biostatistics Unit, Cambridge Institute of Public Health, Cambridge, UK
- ¹¹⁰ Department of Physical Medicine and Rehabilitation, Oslo University Hospital/University of Oslo, Oslo, Norway
- ¹¹¹ Division of Orthopedics, Oslo University Hospital, Oslo, Norway
- ¹¹² Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway
- ¹¹³ Broad Institute, Cambridge MA Harvard Medical School, Boston MA, Massachusetts General Hospital, Boston MA, USA
- ¹¹⁴ National Trauma Research Institute, The Alfred Hospital, Monash University, Melbourne, Victoria, Australia
- ¹¹⁵ Department of Neurosurgery, Odense University Hospital, Odense, Denmark
- ¹¹⁶ International Neurotrauma Research Organisation, Vienna, Austria
- ¹¹⁷ Klinik für Neurochirurgie, Klinikum Ludwigsburg, Ludwigsburg, Germany
- ¹¹⁸ Division of Biostatistics and Epidemiology, Department of Preventive Medicine, University of Debrecen, Debrecen, Hungary
- ¹¹⁹ Department Health and Prevention, University Greifswald, Greifswald, Germany
- ¹²⁰ Department of Anaesthesiology and Intensive Care, AUVA Trauma Hospital, Salzburg, Austria
- ¹²¹ Department of Neurology, Elisabeth-TweeSteden Ziekenhuis, Tilburg, the Netherlands
- ¹²² Department of Neuroanesthesia and Neurointensive Care, Odense University Hospital, Odense, Denmark
- ¹²³ Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, NTNU, Trondheim, Norway

- 124 Department of Physical Medicine and Rehabilitation, St.Olavs Hospital, Trondheim University Hospital, Trondheim, Norway
- 125 Department of Neurosurgery, University of Pécs, Pécs, Hungary
- 126 Division of Neuroscience Critical Care, John Hopkins University School of Medicine, Baltimore, USA
- 127 Department of Neuropathology, Queen Elizabeth University Hospital and University of Glasgow, Glasgow, UK
- 128 Dept. of Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands
- 129 Department of Pathophysiology and Transplantation, Milan University, and Neuroscience ICU, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Italy
- 130 Department of Radiation Sciences, Biomedical Engineering, Umeå University, Umeå, Sweden
- 131 Perioperative Services, Intensive Care Medicine and Pain Management, Turku University Hospital and University of Turku, Turku, Finland
- 132 Department of Neurosurgery, Kaunas University of Health Sciences, Kaunas, Lithuania
- 133 Intensive Care and Department of Pediatric Surgery, Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands
- 134 Department of Neurosurgery, Kings college London, London, UK
- 135 Neurologie, Neurochirurgie und Psychiatrie, Charité – Universitätsmedizin Berlin, Berlin, Germany
- 136 Department of Intensive Care Adults, Erasmus MC– University Medical Center Rotterdam, Rotterdam, the Netherlands
- 137 icoMetrix NV, Leuven, Belgium
- 138 Movement Science Group, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford, UK
- 139 Psychology Department, Antwerp University Hospital, Edegem, Belgium
- 140 Director of Neurocritical Care, University of California, Los Angeles, USA
- 141 Department of Neurosurgery, St.Olavs Hospital, Trondheim University Hospital, Trondheim, Norway
- 142 Department of Emergency Medicine, University of Florida, Gainesville, Florida, USA
- 143 Department of Neurosurgery, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany
- 144 VTT Technical Research Centre, Tampere, Finland
- 145 Section of Neurosurgery, Department of Surgery, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada

Åkerlund	Cecilia	cecilia.ai.akerlund@gmail.com
Amrein	Krisztina	tina.amrein84@gmail.com
Andelic	Nada	NADAND@ous-hf.no
Andreassen	Lasse	Lasse.Andreassen@unn.no
Anke	Audny	Audny.anke@unn.no
Antoni	Anna	anna.antoni@meduniwien.ac.at
Audibert	Gérard	g.audibert@chu-nancy.fr

1			
2			
3	Azouvi	Philippe	philippe.azouvi@rpc.aphp.fr
4	Azzolini	Maria Luisa	azzolini.marialuisa@hsr.it
5	Bartels	Ronald	Ronald.Bartels@radboudumc.nl
6	Barzó	Pál	pbarzo@gmail.com
7	Beauvais	Romuald	beauvais@arttic.eu
8	Beer	Ronny	ronny.beer@i-med.ac.at
9	Bellander	Bo-Michael	bo-michael.bellander@karolinska.se
10	Belli	Antonio	a.belli@bham.ac.uk
11	Benali	Habib	habib.benali@gmail.com
12	Berardino	Maurizio	maurizio_berardino@fastwebnet.it
13	Beretta	Luigi	beretta.luigi@hsr.it
14	Blaabjerg	Morten	morten.blaabjerg1@rsyd.dk
15	Bragge	Peter	peter.bragge@monash.edu
16	Brazinova	Alexandra	alexandra.brazinova@gmail.com
17	Brinck	Vibeke	vibeke.brinck@quesgen.com
18	Brooker	Joanne	Joanne.Brooker@monash.edu
19	Brorsson	Camilla	Camilla.Brorsson@umu.se
20	Buki	Andras	2saturn@gmail.com
21	Bullinger	Monika	bullinger@uke.de
22	Cabeleira	Manuel	mc916@cam.ac.uk
23	Caccioppola	Alessio	alessio.caccioppola@gmail.com
24	Calappi	Emiliana	calemy02@yahoo.it
25	Calvi	Maria Rosa	calvi.mariarosa@hsr.it
26	Cameron	Peter	peter.cameron@med.monash.edu.au
27	Carbayo Lozano	Guillermo	guillermobilbo@gmail.com
28	Carbonara	Marco	marco.carbonara@gmail.com
29	Castañó-León	Ana M.	ana.maria.castano.leon@gmail.com
30	Cavallo	Simona	cavallosimona1@gmail.com
31	Chevallard	Giorgio	giorgio.chevallard@ospedaleniguarda.it
32	Chieriegato	Arturo	arturo.chieriegato@ospedaleniguarda.it
33	Citerio	Giuseppe	giuseppe.citerio@unimib.it
34	Clusmann	Hans	hclusmann@ukaachen.de
35	Coburn	Mark Steven	mark.coburn@ukbonn.de
36	Coles	Jonathan	jpc44@wbic.cam.ac.uk
37	Cooper	Jamie D.	jamie.cooper@monash.edu
38	Correia	Marta	Marta.Correia@mrc-cbu.cam.ac.uk
39	Čović	Amra	amra.covic@med.uni-goettingen.de
40	Curry	Nicola	nicola.curry@ouh.nhs.uk
41	Czeiter	Endre	endre.czeiter@gmail.com
42	Czosnyka	Marek	mc141@medschl.cam.ac.uk
43	Dahyot-Fizelier	Claire	c.dahyot-fizelier@chu-poitiers.fr
44	Dark	Paul	paul.m.dark@manchester.ac.uk
45	Dawes	Helen	hdawes@brookes.ac.uk
46	De Keyser	Véronique	veronique.dekeyser@uza.be
47	Degos	Vincent	vincent.degoss@aphp.fr
48	Della Corte	Francesco	dellacorte.f@gmail.com
49			
50			
51			
52			
53			
54			
55			
56			
57			
58			
59			
60			

den Boogert	Hugo	Hugo.denBoogert@radboudumc.nl
Depreitere	Bart	bart.depreitere@uzleuven.be
Đilvesi	Đula	djuladjilvesi@gmail.com
Dixit	Abhishek	ad825@cam.ac.uk
Donoghue	Emma	emma.donoghue@monash.edu
Dreier	Jens	jens.dreier@charite.de
Dulière	Guy-Loup	glduliere@gmail.com
Ercole	Ari	ae105@cam.ac.uk
Esser	Patrick	pesser@brookes.ac.uk
Ezer	Erzsébet	ezererzsebet@yahoo.com
Fabricius	Martin	fabricius@dadlnet.dk
Feigin	Valery L.	valery.feigin@aut.ac.nz
Foks	Kelly	k.foks@erasmusmc.nl
Frisvold	Shirin	Shirin.Kordasti@unn.no
Furmanov	Alex	alexpuil@yahoo.com
Gagliardo	Pablo	pablog@fivan.org
Galanaud	Damien	galanaud@gmail.com
Gantner	Dashiell	dashiell.gantner@monash.edu
Gao	Guoyi	gao3@sina.com
George	Pradeep	george@incf.org
Ghuysen	Alexandre	A.Ghuysen@chu.ulg.ac.be
Giga	Lelde	lelde.giga@inbox.lv
Glocker	Ben	b.glocker@imperial.ac.uk
Golubović	Jagoš	jagosgolubovic@gmail.com
Gomez	Pedro A.	pagolopez@gmail.com
Gratz	Johannes	johannes.gratz@meduniwien.ac.at
Gravesteijn	Benjamin	b.gravesteijn@erasmusmc.nl
Grossi	Francesca	francesca.grossi@libero.it
Gruen	Russell L.	russell.gruen@anu.edu.au
Gupta	Deepak	drdeepakgupta@gmail.com
Haagsma	Juanita A.	j.haagsma@erasmusmc.nl
Haitsma	Iain	i.haitsma@erasmusmc.nl
Helbok	Raimund	Raimund.Helbok@tirol-kliniken.at
Helseth	Eirik	EHELSETH@ous-hf.no
Horton	Lindsay	lindsay.horton@stir.ac.uk
Huijben	Jilske	j.a.huijben@erasmusmc.nl
Hutchinson	Peter J.	pjah2@cam.ac.uk
Jacobs	Bram	b.jacobs@umcg.nl
Jankowski	Stefan	Stefan.Jankowski@sth.nhs.uk
Jarrett	Mike	mike.jarrett@quesgen.com
Jiang	Ji-yao	jiyaojiang@126.com
Johnson	Faye	faye.johnson@live.co.uk
Jones	Kelly	kejones@aut.ac.nz
Karan	Mladen	mladjokaran@gmail.com
Kolias	Angelos G.	angeloskolias@gmail.com
Kompanje	Erwin	erwinkompanje@me.com

1			
2			
3	Kondziella	Daniel	Daniel.Kondziella@regionh.dk
4	Kornaropoulos	Evgenios	ek481@cam.ac.uk
5	Koskinen	Lars-Owe	Lars-Owe.Koskinen@umu.se
6	Kovács	Noémi	kovacs.noemi@pte.hu
7	Lagares	Alfonso	algadoc@yahoo.com
8	Lanyon	Linda	lindal@incf.org
9	Laureys	Steven	steven.laureys@ulg.ac.be
10	Lecky	Fiona	f.e.lecky@sheffield.ac.uk
11	Ledoux	Didier	dledoux@chu.ulg.ac.be
12	Lefering	Rolf	Rolf.Lefering@uni-wh.de
13	Legrand	Valerie	Valerie.Legrand@iconplc.com
14	Lejeune	Aurelie	aurelie.lejeune@chru-lille.fr
15	Levi	Leon	llevi@rambam.health.gov.il
16	Lightfoot	Roger	Roger.Lightfoot@uhs.nhs.uk
17	Lingsma	Hester	h.lingsma@erasmusmc.nl
18	Maas	Andrew I.R.	andrew.maas@uza.be
19	Maegele	Marc	Marc.Maegele@t-online.de
20	Majdan	Marek	mmajdan@truni.sk
21	Manara	Alex	Alex.Manara@nbt.nhs.uk
22	Manley	Geoffrey	ManleyG@ucsf.edu
23	Maréchal	Hugues	Hugues.Marechal@chrcitadelle.be
24	Martino	Costanza	costmartino74@gmail.com
25	Mattern	Julia	Julia.Mattern@med.uni-heidelberg.de
26	McMahon	Catherine	Catherine.McMahon@thewaltoncentre.nhs.uk
27	Melegh	Béla	bela.melegh@aok.pte.hu
28	Menon	David	dkm13@cam.ac.uk
29	Menovsky	Tomas	tomas.menovsky@uza.be
30	Mikolic	Ana	a.mikolic@erasmusmc.nl
31	Misset	Benoit	Benoit.Misset@chuliege.be
32	Muraleedharan	Visakh	visakh@incf.org
33	Murray	Lynnette	lynnette.murray@monash.edu
34	Nair	Nandesh	nandesh.nair@uza.be
35	Negru	Ancuta	negruancu@gmail.com
36	Nelson	David	david.nelson@karolinska.se
37	Newcombe	Virginia	vfjn2@cam.ac.uk
38	Nieboer	Daan	d.nieboer@erasmusmc.nl
39	Nyirádi	József	nyiradi.jozsef@pte.hu
40	Oresic	Matej	matej.oresic@oru.se
41	Ortolano	Fabrizio	lupeda@gmail.com
42	Otesile	Olubukola	o.otesile@sheffield.ac.uk
43	Palotie	Aarno	aarno.palotie@helsinki.fi
44	Parizel	Paul M.	paul.parizel@uantwerpen.be
45	Payen	Jean-François	Jean-Francois.Payen@ujf-grenoble.fr
46	Perera	Natascha	perera@arttic.eu
47	Perlberg	Vincent	vincent.perlberg@gmail.com
48	Persona	Paolo	ppersona75@gmail.com
49			
50			
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57			
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60			

1	Peul	Wilco	W.C.Peul@lumc.nl
2			
3	Piippo-Karjalainen	Anna	anna.piippo@hus.fi
4	Pirinen	Matti	matti.pirinen@helsinki.fi
5	Ples	Horia	horia.ples@neuromed.ro
6	Polinder	Suzanne	s.polinder@erasmusmc.nl
7	Pomposo	Inigo	inigo.pomposo@osakidetza.net
8	Posti	Jussi P.	jussi.posti@tyks.fi
9	Puybasset	Louis	louis.puybasset@aphp.fr
10	Rădoi	Andreea	aradoi@neurotrauma.net
11	Ragauskas	Arminas	telematics@ktu.lt
12	Raj	Rahul	rahul.raj@hus.fi
13	Rambadagalla	Malinka	malinka.rambadagalla@gmail.com
14	Rehorčíková	Veronika	rehorcikova@gmail.com
15	Rhodes	Jonathan	jrhodes1@staffmail.ed.ac.uk
16	Richardson	Sylvia	sylvia.richardson@mrc-bsu.cam.ac.uk
17	Richter	Sophie	sr773@cam.ac.uk
18	Ripatti	Samuli	samuli.ripatti@helsinki.fi
19	Rocka	Saulius	saulius.rocka@mf.vu.lt
20	Roe	Cecilie	e.c.t.roe@medisin.uio.no
21	Roise	Olav	olav.roise@medisin.uio.no
22	Rosand	Jonathan	jrosand@partners.org
23	Rosenfeld	Jeffrey	J.Rosenfeld@alfred.org.au
24	Rosenlund	Christina	chrisstenrose@gmail.com
25	Rosenthal	Guy	rosenthalg@hadassah.org.il
26	Rossaint	Rolf	RRossaint@ukaachen.de
27	Rossi	Sandra	sandrarossi0@gmail.com
28	Rueckert	Daniel	d.rueckert@imperial.ac.uk
29	Rusnák	Martin	mrusnak@igeh.org
30	Sahuquillo	Juan	sahuquillo@neurotrauma.net
31	Sakowitz	Oliver	oliver.sakowitz@gmail.com
32	Sanchez-Porras	Renan	renan_md@hotmail.com
33	Sandor	Janos	sandor.janos@sph.unideb.hu
34	Schäfer	Nadine	Nadine.Schaefer@uni-wh.de
35	Schmidt	Silke	silke.schmidt@uni-greifswald.de
36	Schoechl	Herbert	Herbert.Schoechl@auva.at
37	Schoonman	Guus	g.schoonman@tsz.nl
38	Schou	Rico Frederik	rico@mymedic.dk
39	Schwendenwein	Elisabeth	elisabeth.schwendenwein@meduniwien.ac.at
40	Sewalt	Charlie	c.sewalt@erasmusmc.nl
41	Skandsen	Toril	toril.skandsen@ntnu.no
42	Smielewski	Peter	ps10011@cam.ac.uk
43	Sorinola	Abayomi	sorinola_abayomi@hotmail.com
44	Stamatakis	Emmanuel	eas46@cam.ac.uk
45	Stanworth	Simon	simon.stanworth@nhsbt.nhs.uk
46	Kowark	Ana	akowark@ukaachen.de
47	Stevens	Robert	rstevens@jhmi.edu

1			
2			
3	Stewart	William	william.stewart@glasgow.ac.uk
4	Steyerberg	Ewout W.	e.steyerberg@erasmusmc.nl
5	Stocchetti	Nino	stocchet@policlinico.mi.it
6	Sundström	Nina	Nina.Sundstrom@vll.se
7	Takala	Riikka	riikka.takala@tyks.fi
8	Tamás	Viktória	tamas.viktoria@pte.hu
9	Tamosuitis	Tomas	tomas.tamosuitis@kaunoklinikos.lt
10	Taylor	Mark Steven	marktrnava@gmail.com
11	Te Ao	Braden	braden.teao@aut.ac.nz
12	Tenovuo	Olli	olli.tenovuo@tyks.fi
13	Theadom	Alice	alice.theadom@aut.ac.nz
14	Thomas	Matt	Matt.Thomas@nbt.nhs.uk
15	Tibboel	Dick	d.tibboel@erasmusmc.nl
16	Timmers	Marjolijn	mtimmers@hotmail.com
17	Tolias	Christos	christos.tolias@nhs.net
18	Trapani	Tony	tony.trapani@monash.edu
19	Tudora	Cristina Maria	cristina.tudora@neuromed.ro
20	Unterberg	Andreas	Andreas.Unterberg@med.uni-heidelberg.de
21	Vajkoczy	Peter	Peter.Vajkoczy@charite.de
22	Valeinis	Egils	Egils.Valeinis@latnet.lv
23	Vallance	Shirley	S.Vallance@alfred.org.au
24	Vámos	Zoltán	azozoka@gmail.com
25	Van der Jagt	Mathieu	m.vanderjagt@erasmusmc.nl
26	van der Naalt	Joukje	j.van.der.naalt@umcg.nl
27	Van der Steen	Gregory	gregory@webstone.be
28	van Dijck	Jeroen T.J.M.	<u>j.van.dijck@haaglandenmc.nl</u>
29	van Essen	Thomas A.	T.A.van_Essen@lumc.nl
30	Van Hecke	Wim	wim.vanhecke@icomatrix.com
31	van Heugten	Caroline	Caroline.vanheugten@maastrichtuniversity.nl
32	Van Praag	Dominique	dominique.vanpraag@uza.be
33	van Wijk	Roel	roel-van-wijk@ziggo.nl
34	Vande Vyvere	Thijs	thijs.vandevyvere@icomatrix.com
35	Vargiolu	Alessia	neurorianimazione@hsgerardo.org
36	Vega	Emmanuel	emmanuel.vega@chru-lille.fr
37	Velt	Kimberley	k.velt@erasmusmc.nl
38	Verheyden	Jan	jan.verheyden@icomatrix.com
39	Vespa	Paul M.	PVespa@mednet.ucla.edu
40	Vik	Anne	anne.vik@ntnu.no
41	Vilcinis	Rimantas	rimantas.vilcinis@kaunoklinikos.lt
42	Volovici	Victor	v.volovici@erasmusmc.nl
43	von Steinbüchel	Nicole	nvsteinbuechel@med.uni-goettingen.de
44	Voormolen	Daphne	d.voormolen@erasmusmc.nl
45	Vulekovic	Petar	pvulekovic@gmail.com
46	Wang	Kevin K.W.	kawangwang17@gmail.com
47	Wiegers	Eveline	e.wiegers@erasmusmc.nl
48	Williams	Guy	gbw1000@wbic.cam.ac.uk
49			
50			
51			
52			
53			
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55			
56			
57			
58			
59			
60			

Wilson	Lindsay	l.wilson@stir.ac.uk
Winzeck	Stefan	sw742@cam.ac.uk
Wolf	Stefan	stefan.wolf@charite.de
Yang	Zhihui	zhuiyang@ufl.edu
Ylén	Peter	peter.ylen@vtt.fi
Younsi	Alexander	alexander.younsi@med.uni-heidelberg.de
Zeiler	Frederick A.	umzeiler@myumanitoba.ca
Ziverte	Agate	agate.ziverte@inbox.lv
Zoerle	Tommaso	tommaso.zoerle@policlinico.mi.it