Clustering identifies endotypes of traumatic brain injury in an intensive care cohort: a CENTER-TBI study

Cecilia A. I. Åkerlund1,2*, Anders Holst2, Nino Stocchetti3, Ewout W. Steyerberg4, David K. Menon5, Ari Ercole5,6, David W. Nelson1 and the CENTER-TBI Participants and Investigators

Abstract

Background: While the Glasgow coma scale (GCS) is one of the strongest outcome predictors, the current classification of traumatic brain injury (TBI) as ‘mild’, ‘moderate’ or ‘severe’ based on this fails to capture enormous heterogeneity in pathophysiology and treatment response. We hypothesized that data-driven characterization of TBI could identify distinct endotypes and give mechanistic insights.

Methods: We developed an unsupervised statistical clustering model based on a mixture of probabilistic graphs for presentation (< 24 h) demographic, clinical, physiological, laboratory and imaging data to identify subgroups of TBI patients admitted to the intensive care unit in the CENTER-TBI dataset (N = 1,728). A cluster similarity index was used for robust determination of optimal cluster number. Mutual information was used to quantify feature importance and for cluster interpretation.

Results: Six stable endotypes were identified with distinct GCS and composite systemic metabolic stress profiles, distinguished by GCS, blood lactate, oxygen saturation, serum creatinine, glucose, base excess, pH, arterial partial pressure of carbon dioxide, and body temperature. Notably, a cluster with ‘moderate’ TBI (by traditional classification) and deranged metabolic profile, had a worse outcome than a cluster with ‘severe’ GCS and a normal metabolic profile. Addition of cluster labels significantly improved the prognostic precision of the IMPACT (International Mission for Prognosis and Analysis of Clinical trials in TBI) extended model, for prediction of both unfavourable outcome and mortality (both p < 0.001).

Conclusions: Six stable and clinically distinct TBI endotypes were identified by probabilistic unsupervised clustering. In addition to presenting neurology, a profile of biochemical derangement was found to be an important distinguishing feature that was both biologically plausible and associated with outcome. Our work motivates refining current TBI classifications with factors describing metabolic stress. Such data-driven clusters suggest TBI endotypes that merit investigation to identify bespoke treatment strategies to improve care.

Trial registration

The core study was registered with ClinicalTrials.gov, number NCT02210221, registered on August 06, 2014, with Resource Identification Portal (RRID: SCR_015582).

*Correspondence: cecilia.akerlund@ki.se

1 School of Electrical Engineering and Computer Science, KTH Royal Institute of Technology, Stockholm, Sweden

© The Author(s) 2022. Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated in a credit line to the data.
**Background**

Traumatic brain injury (TBI) is a heterogeneous disease with a wide variety of injury mechanisms and tissue pathologies, affecting people at all stages of life. It is one of the leading causes of mortality and morbidity in young individuals globally, with a leading global cause being road traffic incidents (RTI) [1]. Additionally, the incidence of TBI in older patients is increasing as this multi-morbid and fall-prone population increases in prevalence [2].

Although mortality from TBI has decreased over the last 30 years, the proportion of patients with favourable outcomes have remained relatively unchanged [2–4], despite developments such as intracranial pressure (ICP) monitoring [5]. A recent report identified large variation in TBI management in a European multi-centre cohort, without a corresponding variation in outcomes [6]. While it is possible that these management variations truly had no impact on outcome, this result could also be due to a substantial heterogeneity of the disease masking treatment effect in relevant subgroups. Due to lack of high-quality evidence, variations in treatment strategies are based largely on local strategies rather than mechanistically aligned to injury types [7–9]. A better characterization of patients could allow discrimination into more specific and biologically relevant sub-groups based on clinical, biomarker, pathoanatomic, and physiological features.

This approach could provide a basis for determining whether specific treatments and interventions might be more effective in some of these sub-groups [7, 9–11]. However, implementation of such individualized treatment strategies relies on the identification of robust and relevant endotypes. Endotypes are subtypes of a clinical condition or syndrome, which can be characterized by distinct pathophysiology, and have an implicit likelihood of variation in response to therapies. This approach was first used to describe subgroups in asthma [12], but has now been used in other conditions [13]. Recently, unsupervised machine learning methods have been successful in discovering subgroups and endotypes with specific treatment-responses in diseases such as acute respiratory distress syndrome (ARDS) and sepsis in the intensive care unit (ICU) [14, 15].

The current classification of TBI simply as ‘mild’, ‘moderate’ and ‘severe’ is based on the level of consciousness at presentation, assessed using the Glasgow coma scale (GCS). While this is well known to be an important predictor of outcome and easy to operationalize, it is also clearly an overly simplistic description of such a complex disease and unlikely to be aligned with underlying pathobiology. As such, this simple classification provides a poor substrate from which to individualise care. Furthermore, it limits research into personalised medicine as populations stratified in this way retain biological heterogeneity and therefore are likely to be diverse in terms of their treatment response.

Instead, we hypothesize the existence of distinct clinically and/or physiologically determinate endotypes in patients with TBI requiring ICU treatment and that these may be described not only by canonical measures of injury severity, such as Glasgow Coma Scale (GCS), but also by pathophysiology. We further hypothesize that these parameters might present complex or nonlinear relationships to disease course and outcome, so that unsupervised/machine learning methods may be required to reveal underlying relationships between parameters. The aim of this study is not primarily to describe endotypes associated with outcome, but to describe endotypes that could motivate tailored treatments in the future, and potentially lead to improved outcome in patients with TBI.

**Methods**

**Patient and feature selection**

All patients over 18 years old enrolled in the multinational study Collaborative European Neuro Trauma Effectiveness Research in TBI (CENTER-TBI) ICU cohort (N = 2006) were included in the study, between 2014 and 2018 [4, 10], Additional file 1: Fig S1. All patients met the general inclusion criteria for CENTER-TBI (clinical diagnosis of TBI, presentation at hospital within 24 h from injury, and a clinical need for a CT scan) and were admitted to the ICU immediately after hospital admission. More than 2000 parameters were collected for each patient. Of these, a total of 35 early features were selected, including those in the core IMPACT prediction model for TBI [16] and features identified to be of clinical interest. The data and variables in the CENTER-TBI database were based on the synthesis of current knowledge of TBI in concert with much of European and Northern American expertise. The variables chosen for this analysis were early features with known or plausible relations with outcome, or deranged physiology (Table 1) as judged by clinicians with extensive neurointensive
Table 1 Features included in the model

| Age* | Hypotension | Sodium |
|------|-------------|--------|
| Sex  | MAP         | Platelet count |
| ASA-PS classification | Heart rate         | Creatinine |
| Anticoagulant or anti-platelet treatment pre-injury | Body temperature          | Haemoglobin |
| BMI at arrival | SpiO₂         | Rotterdam CT score |
| Type of injury | pH             | Fisher classification |
| Cause of injury | Base excess     | Midline shift (mm) |
| Pupillary reactivity* | PaO₂         | TAI |
| GCS motor score* | PaCO₂         | EDH |
| GCS total score | Lactate         | aSDH |
| Hypoxia | Glucose       | Contusion |

All values were collected at admission

ASA-PS American society of anesthesiologists physical status classification; BMI body mass index; GCS Glasgow coma scale; MAP mean arterial pressure; SpO₂ oxygen saturation; PaO₂ arterial partial pressure of oxygen; PaCO₂ arterial partial pressure of carbon dioxide; TAI traumatic axonal injury; EDH epidural hematoma; aSDH acute subdural hematoma

*Feature included in the IMPACT core model

care experience. CT characteristics were extracted from a central imaging review. All selected features were recorded at presentation, i.e., either prehospital, during emergency room (ER) admission or early within the ICU, but no later than 24 h post-injury. Both GCS total and motor sub-score were included, as the total score is of clinical interest and the motor sub-score have shown prediction ability in the IMPACT model. Outcome was represented by the eight-point Glasgow outcome scale extended, (GOS-E) score, where GOS-E 1 = dead and GOS-E 8 = full recovery.

Version 3.0 of the CENTER-TBI dataset was used for this work. Models were created using proprietary low-level code in C++ and all other analyses were performed using R version 1.1.453 [17].

The clustering model

We used a mixture of probabilistic graph models to construct an unsupervised classifier suitable for dealing with the mix of discrete and continuous features with missingness. The univariate probability distributions for all features were modelled as a product model, and compensating factors for each pair of strongly correlated features were included.

To first determine which features were correlated and therefore would need to be considered jointly, linear correlations between features were examined graphically using the R package corrplot (version 0.84), Fig. 1 [18]. Pairs of strongly correlated features (pH and base excess, pH and arterial partial pressure of carbon dioxide (PaCO₂), GCS motor and total score, Rotterdam CT score and midline shift, Rotterdam CT score and Fisher classification, GCS motor score and pupil response, age and ASA PS-class (American Society of Anesthesiologists physical status classification), and age and anticoagulants at baseline) were modelled as bivariate joint Gaussian distributions. Complete data is presented in, Additional file 2: Table S1.

To estimate the parameters and cluster membership probabilities in our graph mixture model, we used an expectation maximisation (EM) algorithm [19, 20]. This is a generalization of the maximum likelihood estimation of incomplete data and offers a principled, probabilistic approach to the unsupervised clustering of large multivariable datasets without the need for imputation when missingness is present [20]. Conceptually, the EM algorithm is a two-step iterative algorithm: in the expectation (E) step, the probability distribution over all clusters for each patient is calculated from the given parameters of the features in the cluster (i.e., the probability for cluster membership for each patient), and the maximization (M) step is the re-estimation of parameter distributions in all clusters. These steps are repeated until convergence, giving the most probable separation of clusters given the chosen number of clusters and predictor features. Further mathematical details are described in Additional file 3.

Determination of number of clusters

We used a cluster stability to robustly determine the most appropriate number of clusters to choose [21]. Numbers from three to fifteen clusters were evaluated for stability. This selection was a clinical trade off – too many clusters might not be clinically relevant, despite the risk that they may represent potentially important separation of phenotypes. However, within this range a methodologically principled optimum may be identified.

For each number of clusters considered, we created ten different models, using different random seeds. The log-likelihood for each model was calculated, and the model with the highest log-likelihood was selected. This process was repeated twenty times (Fig. 2) and cluster similarity was quantified using a cluster similarity index (CSI) defined as the fraction of patients who were assigned to the same cluster in two models [21]. CSI was calculated between all pairs of the models of the same number of clusters, and median and interquartile range (IQR) was calculated. As the CSI, when numbers of clusters << number of patients, by nature is higher for lower number of clusters, a penalty for the number of clusters was added by subtracting 1/n clusters from all median CSI. The optimal clustering was defined as number of clusters with the highest median CSI.
(representing the most stable number of clusters). When describing the clusters, the model of the optimal number of clusters with the highest log-likelihood was chosen to represent our model.

**Evaluation of the clusters**

To investigate the importance of each feature for the model, the mutual information (MI) was calculated between each feature and the cluster labels. The MI represents how well the cluster label is determined by a feature, with respect to how the distributions differ between the clusters. Features were considered to be of value if the MI > 0.1. A descriptive analysis of the clusters using these features was undertaken. Univariable logistic regression analysis was performed to determine the pseudo-explained variance between cluster label and...
outcome, and a multivariable regression analysis was performed to investigate if the cluster label could improve predicted outcome over the “International Mission for Prognosis and Analysis of Clinical Trials in TBI” (IMPACT) variables which have been well characterised as predictors in TBI [16]. For the outcome prediction (but not the clustering), missing values were imputed using the multiple imputation with chained equations (MICE) algorithm in \( R \) [22]. The observed mortality and unfavourable outcome (defined as GOS-E < 5) frequencies in all clusters was compared to the IMPACT predicted outcome.

Results

Patient characteristics

278 patients were excluded due to missing Glasgow outcome scale extended (GOS-E) score at 6 months, leaving 1728 patients for the analysis. The mean age was 50.4 years (SD 19.3) and 1269 (73.4%) were male. The most common causes of injury were RTIs (46.5%) and falls (43.7%). The overall mortality in the cohort was 22%, and 45% had unfavourable outcomes (defined as Upper Severe Disability or worse according to the GOS-E outcome scale) 6 months post-injury. Based on the IMPACT core model, the overall analysis cohort had a predicted mortality of 31%, and a predicted unfavourable outcome of 51%.

Optimal number of clusters

Applying a penalty of \( 1/n \) from the median CSI of each number of clusters revealed a peak in median CSI, indicating the highest cluster stability, for 6 clusters, Fig. 3. Cluster assignments in twenty randomly generated models of 6 clusters are presented in Fig. 4, demonstrating the robust reproducibility of our model. The number of patients in the clusters was 48, 262, 360, 343, 218, and 497, respectively.

Importance of features included in the model

GCS motor score, GCS total score, lactate, oxygen saturation (\( \text{SpO}_2 \)), creatinine, glucose, base excess, pH, PaCO\(_2\) and body temperature were identified as the most important features in our model with respect to MI. Median values in all clusters are presented in Fig. 5, Table 2, and a full list of MI and cluster medians for all features is provided in, Additional file 4: Table S2. A description of cluster characteristics is given in Fig. 6 and Table 3. The results were interpreted by the authors with extensive academic and clinical neurointensive care experience. The six clusters may generally be described by combinations of GCS score and degrees or patterns of deranged metabolism. Outcome predictions and parameters, as well as injury severity and treatment features which were not used in the clustering, are presented in Table 4.

Relation of clusters to outcome

Outcome information was not included in the clustering process. In all clusters except Clusters B and C, the IMPACT model overestimated mortality with overestimation ranging from 4 to 7%, but underestimated functional outcome in four of the six clusters, with an underestimation ranging from –2 to –15%. By adding the cluster label to the IMPACT extended model variables (age, GCS motor score, pupil reactivity, Rotterdam CT score, presence of traumatic subarachnoid haemorrhage, intraventricular haemorrhage, epidural hematoma, hypoxia, and hypotension), predictions for mortality as well as unfavourable outcome were improved with a small but statistically significant increase.
of Nagelkerke pseudo-$R^2$ from 0.42 to 0.44 and from 0.36 to 0.38, respectively ($p=0.001$ and $p=2.9 \times 10^{-5}$, respectively). The improvement in explained variance was comparable to that achieved by the addition of laboratory values within the original IMPACT model for mortality prediction (Nagelkerke pseudo-$R^2$ of 0.42 to 0.44, $p=3.6 \times 10^{-5}$), and prediction of unfavourable outcome (Nagelkerke pseudo-$R^2$ of 0.36 to 0.37, $p=2.1 \times 10^{-4}$). These clusters, therefore, appear to represent groups with outcomes that differ in both directions from current prediction models. The relationships of clusters to outcomes and IMPACT predicted outcomes are seen in Table 4.

**Discussion**

We have used an EM clustering approach, based on early clinical and laboratory data, that identified six distinct potential clusters of TBI patients admitted to the ICU. These clusters exhibited distinct systemic metabolic profiles defined by combinations of plasma lactate, SpO$_2$, creatinine, glucose, base excess, pH, PaCO$_2$, and body temperature, which in combination with GCS, characterizes 6 clinically distinct patient endotypes. Profiles of metabolic derangement may be readily recognized clinically, and arguably contribute to our impression of severity state in TBI patients in the ICU. However, except for blood glucose, the identified features are not incorporated into current formal
definitions of TBI severity or outcome prediction models, although earlier publications have reported improved accuracy adding physiology-based prediction scores, such as APACHE II score (Acute Physiology and Chronic Health Evaluation II) [23, 24].

We hypothesize there to be several diverging mechanisms leading to deranged metabolism in TBI patients that are not fully captured by conventional ICU disease severity metrics, such as APACHE II scores. These may include interplay of secondary and extracranial injury, and concurrent comorbidities. This is the rationale for defining metabolic profiles using several features highly correlated to pH– base excess, \( \text{PaCO}_2 \), and lactate that may reflect several intrinsic mechanisms. In Cluster C, a deranged metabolic picture appears to reflect a general stress response, with high lactate and high blood glucose in more elderly patients prone to insulin resistance. In contrast, Cluster E is representative of younger patients displaying tachycardia and relative hypotension, in whom the cause of metabolic compromise is more likely to reflect a state of systemic shock, which is more likely to be related to extracranial injury. It must be noted that the endotype with a general stress response is a relatively small subset of patients \( (N=48) \) but may nevertheless be of clinical importance as it seems likely to result from a distinct pathology. These two metabolic pictures may easily be distinguished clinically and likely benefit from different treatment approaches allowing for articulation of broad strategies of care and overall management in endotypic groups.

Although GCS has been shown to be one of the most principal factors in classification of TBI [16], the weakness of GCS alone as a classifier of TBI severity becomes apparent in this study. In Cluster A, comprising 28% \( (N=497) \) of the total number of patients TBI severity would be classified as ‘mild’ based on GCS. This group was in general characterized by patients who were older with comorbidities and receiving anticoagulant or antiplatelet treatments pre-injury and the cause of ICU admission did not seem to be explained by extracranial injuries, Table 4, but may rather have been motivated by a need for clinical observation, something which was highlighted in a previous CENTER-TBI sub-study [6]. However, the morbidity and treatment burden in this group is substantial: 45% of patients in this cluster were intubated, 15% had ICP monitoring, and 7% died within 6 months post-injury. In addition, Cluster C, the cluster with deranged metabolism, had the largest deviation in outcome prediction in comparison with the IMPACT
Table 2  Cluster medians and mutual information (MI) for features with MI > 0.1

| Cluster       | All patients | A   | B   | C   | D   | E   | F   | MI  |
|---------------|--------------|-----|-----|-----|-----|-----|-----|-----|
| N patients    | 1728         | 497 | 262 | 48  | 343 | 360 | 218 |     |
| GCS motor Score | 5 (1–6)     | 6 (6–6) | 5 (2.5–5) | 5 (3.5–5) | 4 (2–5) | 1 (1–1) | 4 (1–5) | 1.44 |
| GCS total Score | 9 (4–14)   | 15 (14–15) | 9 (6–12) | 9 (6.75–13) | 7.5 (6–10) | 3 (3–3) | 7 (4–10) | 1.29 |
| Lactate [mmol/L] | 2.2 (1.4–3.4) | 2.0 (1.2–2.7) | 2.3 (1.4–3.4) | 4.9 (2.3–8.1) | 1.7 (1.2–2.4) | 2.2 (1.4–3.4) | 5.3 (2.9–10) | 0.88 |
| SpO₂ [%]      | 99 (96–100) | 98 (96–100) | 98 (96–100) | 98 (95–100) | 100 (99–100) | 99 (97–100) | 95 (85–98) | 0.69 |
| Creatinine [µmol/L] | 75 (62–89) | 76 (64–88) | 70 (58–86) | 106 (64–257) | 71 (60–83) | 74 (59–91) | 83 (71–101) | 0.63 |
| Glucose [mmol/L] | 7.7 (6.5–9.4) | 7.2 (6.3–8.4) | 8.0 (6.7–9.3) | 8.5 (6.9–14.3) | 7.3 (6.3–8.6) | 8.1 (6.8–10.5) | 9.1 (6.9–11.8) | 0.25 |
| Base Excess [mmol/L] | –2.9 (–5.7–0.9) | –1.7 (–3.7 to −1.1) | –3.15 (–5.3 to −1.1) | –3.9 (–12.1–0.6) | –2.3 (–4 to −1) | –3.6 (–6.6 to −1) | –5 (–7.9 to −2) | 0.23 |
| pH            | 7.35 (7.28–7.39) | 7.37 (7.32–7.41) | 7.35 (7.31–7.4) | 7.27 (7.09–7.4) | 7.36 (7.32–7.39) | 7.32 (7.25–7.39) | 7.29 (7.20–7.36) | 0.23 |
| PaCO₂ [kPa]   | 5.5 (4.8–6.2) | 5.3 (4.8–6.3) | 5.3 (4.7–6) | 5.3 (4.4–5.8) | 5.4 (5–6) | 5.6 (4.8–6.7) | 5.9 (5–7.2) | 0.14 |
| Body temperature [°C] | 36.0 (35.4–36.7) | 36.5 (35.9–36.9) | 36.2 (35.5–36.7) | 35.7 (34.3–36.6) | 36 (35.4–36.6) | 35.9 (35.0–36.6) | 35.8 (34.8–36.4) | 0.12 |

Data presented as median (interquartile range)

GCS, Glasgow coma scale; SpO₂, oxygen saturation; PaCO₂, arterial partial pressure of carbon dioxide; MI, mutual information
model. When compared to Cluster D (which comprises patients with severe TBI but without such metabolic derangement), Cluster C had a worse outcome, which further supports the impact of assessing the metabolic profile in TBI patients, beyond derangements that are simply explained by extracranial injuries. It may also reflect an increased vulnerability of the brain in older patients which is not captured in other factors associated with severity of brain damage, such as GCS. Although they did not have as complete a description of biochemical derangements in their dataset, Folweiler et al. elegantly showed TBI clustering that did not relate well to 'mild,' 'moderate' or 'severe' descriptions of TBI [25]. In our study again, although GCS is here shown to be an important component of endotypes in an ICU cohort, metabolic profiles may add additional, clinically
important, information as descriptors of TBI severity, and perhaps identify patient groups in which treatment should be individualized.

Surprisingly, neither our model nor earlier endotypic multidimensional descriptions of TBI patients generated by unsupervised machine learning methods have identified the type of intracranial injuries and CT characteristics as relevant for describing endotypes [25, 26]. However, a recent study could identify clusters based solely on CT characteristics [27], supporting that these factors may play an essential role in understanding the type of injury and determining the need for intracranial surgery, and prediction models using CT findings such as the Marshall, Rotterdam, Helsinki and Stockholm CT scores do discriminate outcome [28–31]. These findings are less evident in multivariable analyses when including GCS and other IMPACT variables as covariates, then contributing approximately only 5% additional pseudo-variance toward outcome [31, 32]. This covariance may be a possible explanation as to why we could not identify CT characteristics as one of the most important discriminative factors between the clusters.

Unsupervised learning is appealing from the point of view of objectivity, but cannot be performed entirely without making certain choices, and requires subsequent interpretation. The number of clusters is a trade-off between not being overwhelmed by multitudes of clusters with small sizes that cannot be interpreted, and very few clusters inherently containing little discriminant information. The identification of six clusters of TBI patients was supported by both the maximal and stable reproducibility represented by a CSI of 80%, as well as a suggestion of clinical relevance. Most clusters were relatively stable across different random initializations of the clustering, with the exception of cluster B and C, both representing patients with intermediate GCS, Fig. 4. By nature, more extreme patient characteristics and their corresponding clusters tend to be more stable while the intermediate level characteristics and clusters are less stable. Most patients were clearly assigned to a stable cluster, as seen in, Additional file 1: Fig. S2.

### Table 4 Injury severity, outcome and predicted outcome with the IMPACT lab model

|                  | All patients | A       | B       | C       | D       | E       | F       |
|------------------|--------------|---------|---------|---------|---------|---------|---------|
| Age              | 52 (33–67)   | 53 (36–67) | 56.5 (42–69) | 58 (48–74.5) | 52 (29–67) | 47.5 (32–62) | 44 (29–62) |
| Male sex         | 1269 (73.4)  | 370 (74.4) | 177 (67.6) | 40 (83.3) | 241 (70.3) | 277 (76.9) | 164 (75.2) |
| Decompressive Craniectomy | 216 (12.5) | 22 (4.4) | 48 (18.3) | 7 (14.6) | 40 (11.7) | 73 (20.3) | 26 (11.9) |
| ISS              | 29 (25–41)   | 25 (16–34) | 26 (25–38) | 29.5 (25–41.5) | 29 (25–41) | 38 (25–52.5) | 38 (25–50) |
| Head ISS         | 25 (16–25)   | 16 (9–16) | 25 (16–25) | 25 (16–25) | 25 (16–25) | 25 (16–25) | 25 (16–25) |
| Highest extracranial ISS | 9 (0–16) | 4 (0–16) | 4 (0–9) | 9 (0–10.75) | 9 (0–16) | 9 (0–16) | 9 (0.25–16) |
| Intubation       | 1334 (78.9)  | 218 (45.7) | 224 (85.8) | 39 (84.8) | 314 (93.2) | 347 (97.5) | 192 (89.7) |
| ICP monitoring   | 757 (44.2)   | 76 (15.6) | 153 (58.4) | 19 (40.4) | 177 (51.8) | 225 (62.7) | 107 (49.5) |
| Median daily TIL | 2 (0–5.5)    | 0.5 (0–1.5) | 3.5 (0.5–8) | 2 (0–3.25) | 3 (1–5) | 4.5 (2–8.5) | 3 (1–5.625) |
| GOS-E at 6 months|              |         |         |         |         |         |         |
| 1                | 388 (22.5)   | 34 (6.8) | 77 (29.4) | 19 (39.6) | 62 (18.1) | 135 (37.5) | 61 (28) |
| 2 or 3           | 268 (15.5)   | 40 (8) | 50 (19.1) | 5 (10.4) | 70 (20.4) | 68 (18.9) | 35 (16.1) |
| 4                | 123 (7.1)    | 31 (6.2) | 19 (7.3) | 6 (12.5) | 27 (7.9) | 21 (5.8) | 19 (8.7) |
| 5                | 241 (13.9)   | 71 (14.3) | 34 (13) | 5 (10.4) | 49 (14.3) | 47 (13.1) | 35 (16.1) |
| 6                | 214 (12.4)   | 70 (14.1) | 31 (11.8) | 5 (10.4) | 51 (14.9) | 29 (8.1) | 28 (12.8) |
| 7                | 229 (13.3)   | 107 (21.5) | 24 (9.2) | 2 (4.2) | 40 (11.7) | 37 (10.3) | 19 (8.7) |
| 8                | 265 (15.3)   | 144 (29) | 27 (10.3) | 6 (12.5) | 44 (12.8) | 23 (6.4) | 21 (9.6) |
| Mortality, %     | 22           | 7       | 29       | 40       | 18       | 38       | 28       |
| Unfavourable outcome, % | 45 | 21 | 56 | 63 | 46 | 62 | 53 |
| IMPACT predicted mortality, mean (SD) | 27 | 13 (8) | 27 (18) | 30 (23) | 24 (16) | 45 (18) | 32 (22) |
| IMPACT predicted unfavourable outcome, mean (SD) | 45 | 26 (15) | 46 (24) | 48 (27) | 43 (22) | 70 (18) | 51 (26) |
| Difference between predicted and observed mortality, % | 5 | 6 | -2 | -10 | 6 | 7 | 4 |
| Difference between predicted and observed unfavourable outcome, % | 0 | 5 | -10 | -15 | -3 | 8 | -2 |

Data presented as median (IQR) or N (%) if not else is stated

ISS injury severity score; ICP intracranial pressure; TIL therapy intensity level; GOS-E glasgow outcome scale extended; IMPACT international mission on prognosis and clinical trial design in TBI
unrealistic to expect perfectly stable cluster assignment in heterogeneous real world data with any method, particularly with random assignment to initial clusters. We believe our evaluation of model robustness to be an important and generalisable strength of our work.

In this study we are naturally limited by the variables collected. These represent nevertheless the compound experience and knowledge of a large cohort of leading TBI researchers and clinicians during the planning of the study. However, additional variables such as future biomarkers and genetic profiles may be needed to sufficiently describe patient heterogeneity in TBI. Furthermore, despite that the object of clustering is to identify reproducible compound and complex patterns, it does not weigh variables toward severity as would for example an experienced clinician and represents a general limitation of unsupervised leaning.

The aim of this study was not primarily to create clusters of TBI patients toward outcome prediction, but to identify clinically relevant and distinct endotypes of patients, which could potentially infer personalization of future treatment strategies. Current TBI therapy is based on limited high-level evidence, leading to between-centre treatment variability beyond that of case mix [7, 9, 33]. Further discrimination of patient heterogeneity has been identified as necessary to further the field [7, 9]. Prediction of both mortality and functional outcome using the IMPACT extended model was significantly improved by adding cluster labels. That the metabolic cluster profiles identified in this study are significantly associated with outcome, despite an unsupervised clustering method (not including outcome), supports a biological underpinning and motivates further investigation. A natural progression will be to investigate if the clusters described in this study exhibit a different temporal trajectories in the ICU or, in analogy with work within the field of ARDS [14] respond differently to treatments in earlier RCTs.

Conclusions

While GCS is a strong predictor of TBI outcome, an admission metabolic profile incorporating hypothermia, lactatemia, blood glucose, SpO₂, PaCO₂, pH, base excess and creatinine allows for a more holistic description of patients with TBI who require ICU care. Synthesis of these data using an unsupervised clustering method reveals six distinct and stable subgroups of TBI patients. Although not a key objective of the analysis, we found that clusters contain information that can provide a significantly better explanation of outcome beyond that provided by variables used in current outcome prediction models. The addition of biomarkers and genetics may improve this endotypic classification further. Future studies should address replication and validation of this approach, but our work provides an important starting point from which to devise and prospectively investigate therapeutic strategies individualised to more biologically relevant groups or TBI patients.

Abbreviations

APACHE II score: Acute physiology and chronic health evaluation II score; ARDS: Acute respiratory distress syndrome; ASA-PS class: American society of anesthesiologists physical status classification; aSDH: Acute subdural hematoma; BMI: Body mass index; CENTER-TBI: Collaborative European neuro trauma effectiveness research in TBI; CSI: Cluster similarity index; DC: Decompressive craniectomy; EDH: Epidural hematoma; EM: Expectation maximization; GCS: Glasgow coma scale; GOS-E: Glasgow outcome scale extended; ICU: Intensive care unit; ICP: Intracranial pressure; IMPACT: International mission for prognosis and analysis of clinical trials in TBI; IQR: Interquartile range; ISS: Injury severity score; MAP: Mean arterial pressure; MI: Mutual Information; MICE: Multiple imputation with chained equations; PaCO₂: Arterial partial pressure of carbon dioxide; PaO₂: Arterial partial pressure of oxygen; RTC: Road traffic collision; RTI: Road traffic incident; SpO₂: Oxygen saturation; TAI: Traumatic axonal injury; TBI: Traumatic brain injury; TIL: Therapy intensity level; TSAH: Traumatic subarachnoid haemorrhage.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-022-04079-w.

Acknowledgements

Data for the CENTER-TBI study was collected through Quesgen e-CRF (Quesgen Systems Inc, USA), hosted on the INCF Neurobot tool (INCF, Sweden). Version 3.0 of the CENTER-TBI dataset was used in this manuscript. The authors would like to thank the patients for their participation in the CENTER-TBI study, and all CENTER-TBI Participants and Investigators for taking part in the collection and sharing their valuable expertise: Cecilia Åkerlund, Kristzina Amrein, Nada Andelic, Lasse Andreassen, Audny Anke, Anna Antoni, Gérard Audibert, Philippe Azouvi, Maria Luisa Azzolini, Ronald Bartels, Jāi Barzō, Remoulad Beauvais, Ronny Beer, Bo-Michael Bellander, Antonio Belli, Habib Benali, Maurizio Berardinì, Luigi Beretta, Morten Blaabjerg, Peter Bragge, Alexandra Brazinovà, Vibeke Brinck, Joanne Brooker, Camilla Brosson, Andreas Buki, Monika Bullingier, Manuel Cabaleira, Alessio Caccioppola, Emíliana Calippi, Maria Rosa Calvi, Peter Cameron, Guillermo CarbayoLozano, Marco Carbonara, Simona Cavallo, Giorgio Chevallard, Arturo Chieregato, Giuseppe Citerio, Hans Clusmann, Mark Coburn, Jonathan Coles, Jamie D’Cooper, Marta Corneia, Anna CVid, Nicola Curry, Endre Cretei, Marek Czyszka, Cléa DahiyoTifiseler, Paul Dark, Helen Dawes, Véronique DeKeyser, Vincent Degos, Francesco DellaCorte, Hugo denBoogert, Bart Depreitere, Dula Dilvesi, Abishhek Dixit, Emma Dongoghue, Jens Dreier, GuyLoup Dulièvre, Ari Ercol, Patrick Esser, Erzsébet Ezer, Martin Fabricius, Valery FEFi, Kelly Folds, Shirin Frisvold, Alex Furmanow, Pablo Gagliardi, Damien Galraud, Dashiel Gantner, Guoyi Gao, Pradeep George, Alexandre Ghysen, Leide Giga, Ben Glocker, Jago’s Golubovic, Pedro A. Gomez, Jochen Gratza, Benjamin Gravesteijn, Francesco Grossi, Russell L. Grueni, Deepak Gupta, Juanita A Haagsma, Iain Haisma, Raimund Helbok, Erik Im.
UK11Department of Neurology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands112Neurointensive Care, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK113Saltacon Royal Hospital NHS Foundation Trust, Acute Research Delivery Team, Salford, UK114Department of Intensive Care and Department of Ethics and Philosophy of Medicine, Erasmus Medical Center, Rotterdam, The Netherlands115Department of Clinical Neuroscience, Neurosurgery, Umeå University, Umeå, Sweden116Hungarian Brain Research Program – Grant No. KTIA_13_NAP-A-II/6, University of Pécs, Pécs, Hungary117Department of Anaesthesiology, University Hospital of Aachen, Aachen, Germany118Cyclotron Research Center, University of Liège, Liège, Belgium119Department of Emergency and Critical Care Research (CURE), Health Services Research Section, School of Health and Related Research (SCHARR), University of Sheffield, Sheffield, UK110Emergency Department, Saarland Royal Hospital, Saarbrücken, Germany111Institute of Research in Operative Medicine (IFOM), Witten/Herdecke University, Cologne, Germany119VIP Global Project Management CNS, ICON, Paris, France114Department of Anaesthesiology-Intensive Care, Lille University Hospital, Lille, France112Department of Neurosurgery, Rambam Medical Center, Haifa, Israel118Department of Anaesthesiology and Intensive Care, University Hospitals Southhampton NHS Trust, Southampton, UK116Department of Traumatology, Cologne-Merheim Medical Center (CMMC), Orthopedic Surgery and Sportmedicine, Witten/Herdecke University, Cologne, Germany115Intensive Care Unit, Southmead Hospital, Bristol, Bristol, UK111Department of Neurological Surgery, University of California, San Francisco, CA, USA113Department of Anesthesiology, Bufalini Hospital, Cesena, Italy117Department of Neurosurgery, University Hospital Heidelberg, Heidelberg, Germany115Department of Neurosurgery, The Walton centre NHS Foundation Trust, Liverpool, UK110Department of Medical Genetics, University of Pécs, Pécs, Hungary114Department of Neurosurgery, Emergency County Hospital Timisoara, Timisoara, Romania118School of Medical Sciences, Örebro University, Örebro, Sweden118Institute for Molecular Medicine Finland, University of Helsinki, Helsinki, Finland119Analytic and Translational Genetic Unit, Department of Medicine, Psychiatric and Neurodevelopmental Genetics Unit, Department of Psychiatry, Department of Neurology, Massachusetts General Hospital, Boston, MA, USA117Program in Medical and Population Genetics, The Stanley Center for Psychiatric Research, The Broad Institute of MIT and Harvard, Cambridge, MA, USA113Department of Radiology, University of Antwerp, Edegem, Belgium113Department of Anaesthesiology and Intensive Care, University Hospital of Grenoble, Grenoble, France118Department of Anesthesia and Intensive Care, Azienda Ospedaliero Universitaria di Padova, Padua, Italy115Department of Neurosurgery, Leiden University Medical Center, Leiden, The Netherlands117Department of Neurosurgery, Medical Center Haaglanden, The Hague, The Netherlands117Department of Neurosurgery, Helsinki University Central Hospital, Helsinki, Finland116Division of Clinical Neurosciences, Department of Neurosurgery and Turku Brain Injury Centre, Turku University Hospital, University of Turku, Turku, Finland116Department of Anaesthesiology and Critical Care, Pitie-Salpetriere Teaching Hospital, Assistance Publique, Hôpitaux de Paris and University Pernette Marie Curie, Paris, France117Neurotraumatology Research Group, Neurosurgical Unit (UNINNI), Vall d’Hebron Research Institute, Barcelona, Spain118Department of Neurosurgery, Kaunas University of Technology and Wminius University, Vilnius, Lithuania116Department of Neurosurgery, Rezekne Hospital, Rezekne, Latvia118Department of Anaesthesia, Critical Care and Pain Medicine NTH Liothian, University of Edinburgh, Edinburgh, UK119MRB Biostatistics Unit, Cambridge Institute of Public Health, Cambridge, UK118Department of Physical Medicine and Rehabilitation, Oslo University Hospital, University of Oslo, Oslo, Norway118Division of Orthopedics, Oslo University Hospital, Oslo, Norway118Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway118Broad Institute, Massachusetts General Hospital, Cambridge, MA, Harvard Medical School, Boston MA, USA115National Trauma Research Institute, The Alfred Hospital, Monash University, Melbourne, Australia117Australias119Department of Neurosurgery, Odense University Hospital, Odense, Denmark118International Neurotrauma Research Organisation, Vienna, Austria115Klinikk für Neurochirurgie, Klinikum Ludwigshurg, Ludwigshurg, Germany115Division of Biostatistics and Epidemiology, Department of Preventive Medicine, University of Debrecen, Debrecen, Hungary118Department of Health and Prevention, University of Greifswald, Greifswald, Germany117Department of Anaesthesiology and Intensive Care, AUVA Trauma Hospital, Salzburg, Austria118Department of Neurology, Elisabeth-Tweesteden Ziekenhuis, Tilburg, The Netherlands118Department of Neuroanesthesia and Neurointensive Care, Odense University Hospital, Odense, Denmark118Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, NTNU, Trondheim, Norway118Department of Physical Medicine and Rehabilitation, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway118Department of Neurosurgery, University of Pécs, Pécs, Hungary118Division of Neuroscience Critical Care, John Hopkins University School of Medicine, Baltimore, USA118Department of Neuropathology, Queen Elizabeth University Hospital and University of Glasgow, Glasgow, UK118Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands118Department of Pathophysiology and Transplantation, NeuroscienceCU, Fondazione IRCCS Ca Granda Ospedale Maggiore Policlinico, Milan University, Milan, Italy118Department of Radiation Sciences, Biomedical Engineering, Umeå University, Umeå, Sweden118Intensive Care Medicine and Pain Management, Perioperative Services, Turku University Hospital, University of Turku, Turku, Finland118Department of Neurosurgery, Kaunas University of Health Sciences, Kaunas, Lithuania118Department of Intensive Care and Department of Pediatric Surgery, Erasmus Medical Center, Sophia Children’s Hospital, Rotterdam, The Netherlands118Department of Neurosurgery, Kings College London, London, UK118Neurologie Neurochirurgie und Psychiatrie, Charité – Universitätsmedizin Berlin, Berlin, Germany118Department of Intensive Care Adults, Erasmus MC – University Medical Center Rotterdam, Rotterdam, The Netherlands118Komedrivex NL, Louvain, Belgium118Psychology, Department, Antwerp University Hospital, Edegem, Belgium118Director of Neurocritical Care, University of California, Los Angeles, USA118Department of Neurosurgery, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway117Department of Emergency Medicine, University of Florida, Gainesville, FL, USA118Department of Neurosurgery, Berlin Institute of Health, Charité – Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität Zu Berlin, Berlin, Germany118VTT Technical Research Centre, Tampere, Finland119Section of Neurosurgery, Department of Surgery, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada

Author contributions
AH, AE and DN undertook the primary supervision of the project. NS, ES, DM, DT took part in funding acquisition. CA, AE and DN were involved in data curation. CA, AH, AE and DN prepared the draft manuscript. CA and AH did the analyses and prepared the script used for the analyses. All authors read and approved the final manuscript.

Funding
Open access funding provided by Karolinska Institute. CENTER-TBI was supported by the European Union’s 7th Framework program (EC grant 602150). Additional funding was obtained from the Hannelore Kohl Stiftung (Germany), from OneMind (USA) and from Integra LifeSciences Corporation (USA). The funders had no role in study design, data collection and analysis; decision to publish, or preparation of the manuscript.

Availability of data and materials
CENTER-TBI encourages data sharing, and there is a data sharing statement published. Data will be made available to researchers who provide a study proposal that is approved by the management committee to achieve the aims in the approved proposal. Proposals can be submitted online at https://www.center-tbi.eu/data-sharing. A data access agreement is required, and all access must comply with regulatory restrictions imposed on the original study.

Declarations
Ethics approval and consent to participate
This sub-study was approved by the CENTER-TBI management committee. The CENTER-TBI study was conducted in accordance with all relevant laws of the country where the Recruiting sites were located, including but not limited to, the relevant privacy and data protection laws and regulations (the "Privacy Law"), the relevant laws and regulations on the use of human materials, and all relevant guidance relating to clinical studies from time to time in force including, but not limited to, the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) ("ICH GCP") and the World Medical Association Declaration of Helsinki. Informed Consent by the patients or next of kin was obtained, according to the local legislations, for all patients recruited in the Core Dataset of CENTER-TBI and documented in the electronic case report form. Ethical approval for CENTER-TBI was obtained at...
References

1. Rubiano AM, Carney N, Chensue S, Puyana JC. Global neurotrauma research challenges and opportunities. Nature. 2015;527(7578):5193–7.
2. Roozenbeek B, Maas AIR, Menon DK. Changing patterns in the epidemiology of traumatic brain injury. Nat Rev Neurol. 2013;9(4):231–6.
3. Bragg P, Snydoot A, Maas AI, Menon DK, Cooper DJ, Rosenfeld JV, et al. A state-of-the-science overview of randomized controlled trials evaluating acute management of moderate-to-severe traumatic brain injury. J Neurotrauma. 2016;33(16):1461–78.
4. Steyerberg EW, Wiegens E, Sewalt C, Buki A, Citerio G, De Keyser V, et al. Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI: a European prospective, multicentre, longitudinal, cohort study. Lancet Neurol. 2019;18(10):923–34.
5. Chensue RM, Temkin N, Carney N, Nikmen S, Rendina C, Videtta W, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. N Engl J Med. 2012;367(26):2471–81.
6. Huijben JA, Wiegens EA, Lingsma HF, Citerio G, Maas AIR, Menon DK, et al. Changing care pathways and between-center practice variations in intensive care for traumatic brain injury across Europe: a CENTER-TBI analysis. Intensive Care Med. 2020;46(5):995–1004.
7. Carney N, Totten AM, D’Reilly C, Ullman JS, Hawrylyuk GW, Bell MJ, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. Neurosurgery [Internet]. 2016 [cited 2017 Oct 26]. Available from: www.neurosurgery-online.com
8. Newcombe VF, Chow A. The features of the typical traumatic brain injury patient in the ICU are changing: what will this mean for the intensivist? Curr Opin Crit Care. 2021;27:80.
9. Maas AIR, Menon DK, Adelson PD, Anselc N, Bell MJ, Belli A, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. Lancet Neurol. 2017;16(12):987–1048.
10. Maas AIR, Menon DK, Steyerberg EW, Citerio G, Lechey F, Manley GT, et al. Collaborative European neurotrauma effectiveness research in traumatic brain injury (CENTER-TBI): a prospective longitudinal observational study. Neurosurgery. 2015;76:67–80.
11. Tenevou O, Diaz-Arrastia R, Goldstein LE, Sharp DJ, van der Naalt J, Jasler ND. Assessing the severity of traumatic brain injury—time for a change? J Clin Med. 2021;10(1):148.
12. Kuruvilla ME, Lee FEH, Lee GB. Understanding asthma phenotypes, endotypes, and mechanisms of disease. Clin Rev Allergy Immunol. 2019;56(2):219–33.
13. Prescott HC, Calfee CS, Taylor Thompson B, Angus DC, Liu VX. Toward smarter lumping and smarter splitting: rethinking strategies for sepsis and acute respiratory distress syndrome clinical trial design. Am J Respir Crit Care Med. 2016;194(2):147–55.
14. Calfee CS, Delucchi K, Parsons PE, Thompson BT, Ware LB, Matthy MA, et al. Latent class analysis of ARDS subphenotypes: analysis of data from two randomized controlled trials. Lancet Respir Med. 2014;2:611–20.
15. Antcliffe DB, Burnham KL, Al-Bedh F, Santhakumar S, Brett SJ, Hinds CJ, et al. Transcriptomic signatures in sepsis and a differential response to steroids. From the VANISH randomized trial. Am J Respir Crit Care Med. 2019;199(8):980–6.
16. Steyerberg EW, Muskudiani N, Perel P, Butcher I, Lu J, McHugh GS, et al. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. 2008 [cited 2018 May 24]. Available from: http://journals.plos.org/plosmedicine/article/file?id=doi:10.1371/journal.pmed.0050165&type=printable
17. R Core Team. R: A language and environment for statistical computing [Internet]. Vienna, Austria: R Foundation for Statistical Computing; 2018. Available from: https://www.r-project.org/
18. Wei T, Simko V, Levy M, Xie Y, Jin Y, Zemla J. R package ’comrpt’: visualization of a correlation matrix. Statistician. 2017;56:316–24.
19. Dempster AP, Laird NM, Rubin DB. Maximum likelihood from incomplete data via the EM algorithm. J Roy Stat Soc Ser B (Methodol). 1977;39(1):1–22.
20. Holst A. The use of a bayesian neural network model for classification tasks. [Internet]. 1997 p. 172. Available from: oai:DIVA.org:61748
21. Lange T, Roth V, Braun ML, Buhmann JM. Stability-based validation of clustering solutions. Neurocomput. 2004;16(6):1299–323.
22. van Buuren S, Groothuis-Oudshoorn K. MICE: multivariate imputation by chained equations in R. J Stat Softw. 2011;45(3):1–67.
23. Hyam JA, Welch CA, Harrison DA, Menon DK. Case mix, outcomes and comparison of risk prediction models for admissions to adult, general and specialist critical care units for head injury: a secondary analysis of the ICNARC case mix programme database. Crit Care. 2006;10(Suppl 2):S2.
24. Raj R, Skrifvars MB, Bendel S, Selander T, Kivisaari R, Sironen J, et al. Predicting six-month mortality of patients with traumatic brain injury: usefulness of common intensive care severity scores. Crit Care. 2014;18(2):1–9.
25. Folwiler KA, Sandmark DK, Diaz-Arrastia R, Cohen AS, Masino AJ. Unsupervised machine learning reveals novel traumatic brain injury patient phenotypes with distinct acute injury profiles and long-term outcomes. J Neurotrauma. 2020;144:1431–44.
26. Gravesteijn BY, Sewalt CA, Ercole A, Akerlund G, Nelson D, Maas AIR, et al. Toward a new multi-dimensional classification of traumatic brain injury: a collaborative European neurotrauma effectiveness research for traumatic brain injury study. J Neurotrauma. 2020;37(7):1002–10.
27. Yuh EL, Jain S, Sun X, Piscia D, Harris MH, Taylor SR, et al. Pathological computed tomography features associated with adverse outcomes after mild traumatic brain injury: A TRACK-TBI study with external validation in CENTER-TBI. JAMA Neurol. 2021;78(9):1137–48.
28. Maas AIR, Hukkelhoven CWP, Marshall LF, Steyerberg EW. Prediction of outcome in traumatic brain injury with computed tomographic classification: a comparison between the computed tomographic classification and combinations of computed tomographic predictors. Neurosurgery. 2005;57(6):1173–81.
29. Thelin EP, Nelson DW, Vehvilainen J, Nyström H, Kivisaari R, Sironen J, et al. Evaluation of novel computerized tomography scoring systems in human traumatic brain injury: an observational, multicenter study. PLoS Med. 2017;14(8):1–19.
30. Raj R, Sironen J, Skrifvars MB, Hernesniemi J, Kivisaari R. Predicting outcome in traumatic brain injury: development of a novel computerized tomography classification system (Helsinki Computerized Tomography Score). Neurosurgery. 2014;75(6):632–46.
31. Nelson DW, Nyström H, MacCallum RM, Thornquist B, Lilja A, Bellander BM, et al. Extended analysis of early computed tomography scans of traumatic brain injured patients and relations to outcome. J Neurotraum. 2010;27(1):51–64.
32. Lingsma HF, Roozenbeek B, Steyerberg EW, Murray GD, Maas AI. Early prognosis in traumatic brain injury: from prophecies to predictions. Lancet Neurol. 2010;9(5):543–54.
33. Hawryluk GWJ, Aguilera S, Buki A, Bulger E, Citerio G, Cooper DJ, et al. A management algorithm for patients with intracranial pressure monitoring: the seattle international severe traumatic brain injury consensus conference (SIBICC). Intensive Care Med. 2019;45(12):1783–94.

34. CENTER-TBI. CENTER-TBI Ethical approval [Internet]. Available from: https://www.center-tbi.eu/project/ethical-approval

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.