# Toward a New Multi-Dimensional Classification of Traumatic Brain Injury

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# Toward a New Multi-Dimensional Classification of Traumatic Brain Injury: A Collaborative European NeuroTrauma Effectiveness Research for Traumatic Brain Injury Study

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## Abstract

Traumatic brain injury (TBI) is currently classified as mild, moderate, or severe TBI by trichotomizing the Glasgow Coma Scale (GCS). We aimed to explore directions for a more refined multidimensional classification system. For that purpose, we performed a hypothesis-free cluster analysis in the Collaborative European NeuroTrauma Effectiveness Research for TBI (CENTER-TBI) database: a European all-severity TBI cohort ($n = 4509$). The first building block consisted of key imaging characteristics, summarized using principal component analysis from 12 imaging characteristics. The other building blocks were demographics, clinical severity, secondary insults, and cause of injury. With these building blocks, the patients were clustered into four groups. We applied bootstrap resampling with replacement to study the stability of cluster allocation. The characteristics that predominantly defined the clusters were injury cause, major extracranial injury, and GCS. The clusters consisted of 1451, 1534, 1006, and 518 patients, respectively. The clustering method was quite stable: the proportion of patients staying in one cluster after resampling and reclustering was 97.4% (95% confidence interval [CI]: 85.6–99.9%). These clusters characterized groups of patients with different functional outcomes: from mild to severe, 12%, 19%, 36%, and 58% of patients had unfavorable 6 month outcome. Compared with the mild and the upper intermediate cluster, the lower intermediate and the severe cluster received more key interventions. To conclude, four types of TBI patients may be defined by injury mechanism, presence of major extracranial injury and GCS. Describing patients according to these three characteristics could potentially capture differences in etiology and care pathways better than with GCS only.

**Keywords:** classification; clustering; GCS; prospective

## Background

The global burden of traumatic brain injury (TBI) is high: it is a leading cause of injury-related death and disability.[1] Although the rates vary among countries, TBI is estimated to be responsible for ~300 hospital admissions and 12 deaths per 100,000 persons per year in Europe.[2] TBI is currently classified using the baseline Glasgow Coma Scale (GCS).[3] Although there is variation,[4] TBI is usually divided according to GCS scores 3–8 (severe), 9–12 (moderate), and 13–15 (mild).

The current classification, based on only GCS, does not fully capture the multidimensionality of TBI.[5,6] TBI is defined as an alteration in brain function, or other brain pathology, following an external force.[7] However, the manifestation of TBI is heterogeneous: a variety of pathoanatomical lesions can be present as the result of a multitude of trauma mechanisms.[5] A novel multidimensional classification of TBI could potentially be used for improving the efficiency of care pathways. Additionally, the classification could increase understanding of the divergent clinical courses of TBI patients.

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This study aimed to explore directions for a more refined multidimensional classification system, capturing the heterogeneity throughout the entire spectrum of TBI severity. For that purpose, a hypothesis-free cluster analysis was performed.

## Methods

### *Study population*

Data from the Collaborative European NeuroTrauma Effectiveness Research for TBI (CENTER-TBI) was used for this analysis. This prospective cohort study comprised 4509 patients with all-severity TBI. The patients were included in 59 centers from 18 countries across Europe. Inclusion criteria were a clinical diagnosis of TBI, presentation within 24 h, and clinical indication for computed tomographic (CT) scanning. The exclusion criterion of CENTER TBI was pre-existing neurological disease. For this study, the total CENTER TBI cohort was used. The study design was previously published.[8] Version 1.0 of the database was used.

### *Variable selection*

The cluster analysis was hypothesis free, as we did not assume any relationship, weights, or importance among the variables, or a role such as exposure, confounder, or outcome. However, to arrive at a set of variables to be used by the algorithm, a starting point was that the classification should be implementable, including characteristics that are generally available at any emergency department. Additionally, we wanted to use prognostically relevant characteristics: the characteristics of which the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) and Corticosteroid Randomization After Significant Head Injury (CRASH) prediction models are composed.[9,10] Finally, we included variables describing the mechanism of injury.

The prognostic and mechanistic relevant variables were aggregated in ''building blocks'': groups of variables describing similar information of a patient. The building blocks that were used for the exploratory clustering were: (1) demographics: age; (2) clinical severity: baseline GCS score, baseline pupil score, and major extracranial injury (defined as an abbreviated injury scale [AIS] >3 in a body region other than neck and head); (3) second insults: hypoxia and hypotension in the emergency department; (4) cause of injury: road traffic incident (RTI), all falls, violence, or suicide, or other; and (5) imaging characteristics: all imaging characteristics available in the database, which are the presence of epidural hematoma, subdural mixed density collection, skull fracture, subacute subdural hematoma, midline shift (> 5 mm), traumatic subarachnoid haemorrhage, any mass lesion, intraventricular hemorrhage, subdural hematoma, or cisternal compression. Imaging characteristics were obtained through a central reviewing process.[11]

### *Clustering*

First, the key imaging characteristics were extracted. The imaging characteristics comprised 12 binary variables, which are not easily handled by a clustering algorithm. Therefore, to increase efficiency of the clustering algorithm, we described all those binary variables using principal components: the primary principal component is a continuous variable capturing the most information across the included variables. The second principal component captures somewhat less, and subsequent principal components capture progressively less. The *PCAmixdata* package was used, because this version of a PCA can handle non-continuous data.[12] Consecutively, the first four principal components (dimensions) were included in the clustering algorithm. We included four principal components, because these described the majority (> 70%) of the variability in the imaging characteristics. Although principal components themselves are not clinically applicable, they can be easily calculated from all binary imaging variables.

The selected clinical and injury severity variables ($n = 8$), together with the four imaging dimensions were included in a clustering algorithm. The *cluster* package was used. First, the metric on which the data are grouped is calculated. Because we are using both categorical and numerical data, the Gower's distance was calculated with the *daisy* function.[13] Using this distance metric, four clusters in the data were identified using the partition around medoids *(pam)* function.

Table 1. Baseline Characteristics Used for the Clustering, as Well as the Six Month Outcome

| *In k-mode clustering* | n = *4509* | *Missing* |
|---|---|---|
| Age (median [IQR]) | 50 [30, 66] | 0.0 |
| Injury cause (%) | | 3.7 |
| RTI | 1682 (38.7) | |
| Fall | 2024 (46.6) | |
| Other | 343 (7.9) | |
| Violence/suicide | 293 (6.7) | |
| GCS Motor (median [IQR]) | 6.0 [5.0, 6.0] | 2.5 |
| GCS Score (median [IQR]) | 15.0 [10.0, 15.0] | 4.0 |
| Pupils (%) | | 5.8 |
| Both reactive | 3802 (89.5) | |
| One reactive | 164 (3.9) | |
| None reactive | 281 (6.6) | |
| ED hypoxia (%) | 299 (7.0) | 5.6 |
| ED hypotension (%) | 297 (6.9) | 4.7 |
| Major extracranial injury[a] (%) | 668 (14.8) | 0.0 |
| *PCA before clustering* | | |
| Axonal injury (%) | 324 (9.4) | 23.2 |
| Contusion (%) | 1087 (31.4) | 23.2 |
| Subdural hematoma subacute chronic (%) | 17 (0.5) | 23.2 |
| Traumatic subarachnoid hemorrhage (%) | 1531 (44.2) | 23.2 |
| Epidural hematoma (%) | 373 (10.8) | 23.2 |
| Subdural hematoma acute (%) | 943 (27.2) | 23.2 |
| Skull fracture (%) | 1266 (36.6) | 23.2 |
| Subdural collection mixed density (%) | 82 (2.4) | 23.2 |
| Cisternal compression (%) | 494 (14.3) | 23.2 |
| Midline shift (%) | 380 (11.0) | 23.2 |
| Mass lesion (%) | 579 (16.7) | 23.2 |
| Intraventricular hemorrhage (%) | 453 (13.1) | 23.2 |
| Stratum (%) | | 0.0 |
| ER | 848 (18.8) | |
| Admission | 1523 (33.8) | |
| ICU | 2138 (47.4) | |
| *6 month outcome* | | |
| GOSE (%) | | 15.7 |
| 1 | 475 (12.5) | |
| 2[b] | 370 (9.7) | |
| 4 | 110 (2.9) | |
| 5 | 198 (5.2) | |
| 6 | 401 (10.6) | |
| 7 | 725 (19.1) | |
| 8 | 1520 (40.0) | |

[a]Defined as non-head Abbreviated Injury Scale (AIS) ≥3.
[b]GOS-E 2 and 3 are combined into 2.

IQR, interquartile range; RTI, road traffic incident; GCS, Glasgow Coma Scale; ED, emergency department; PCA, principal component analysis; ER, emergency room; ICU, intensive care unit; GOS-E, Glasgow Outcome Scale–Extended

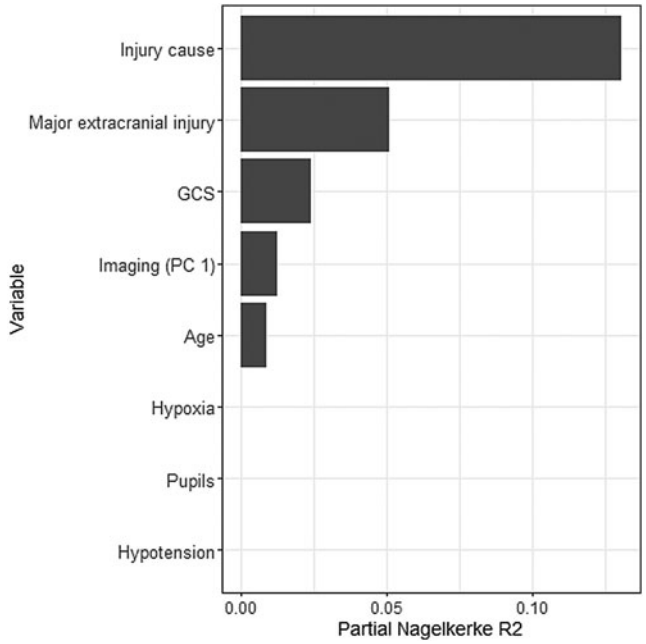


**FIG. 1.** The importance of the variables to identify the four clusters, quantified by the partial Nagelkerke $R^2$ value of the multinomial model predicting class. The $R^2$ is a measure for the proportion of the variation in outcome (class) explained by the predictors (the clustering variables). Imaging is displayed, which is the first principal component (PC 1) of the imaging characteristics.

Clustering studies with mixed data may optimize the silhouette value to arrive at an optimal number of clusters.[14] It is a measure of the similarity to its own cluster (cohesion), compared with other clusters (separation).

Stability of the clustering was assessed using the same variables and a bootstrapping procedure to repeatedly resample with replacement and recluster the patients. The proportion of patients who stayed in a cluster after resampling was calculated per repetition. The median and 95% credibility interval, defined by the 2.5th to the 97.5th percentile, was calculated with 999 repetitions.

To assess the importance of the clustering variables, we used multinomial regression. The independent variables of this regression were the four clusters, and the dependent variables were the clustering variables. We assumed linear effects, and we did not allow for any statistical interaction. The partial Nagelkerke $R^2$ was calculated for each variable by comparing the Nagelkerke $R^2$ of the model without the variable to the Nagelkerke $R^2$ of the model with the variable.

### *Cluster description*

The clusters were described based on the clustering variables. Additionally, gender, motor GCS score, as well as clinical course characteristics (receiving intracranical pressure [ICP] monitoring, intracranial or extracranial surgery, length of intensive care unit [ICU] stay) were described across the clusters. We then examined the outcome of the patients within the clusters.

First, the 6 months Glasgow Outcome Scale – Extended (GOS-E) was used to describe the functional outcome. The GOS-E score was imputed exactly at 180 days, using a multi-state model. Subsequently, outcomes among the clusters were compared, and used to rank the clusters based on the proportion of favorable outcomes in the following order: ''mild,'' ''upper intermediate,'' ''lower intermediate,'' or ''severe.'' This order resembles the GOS-E, in which ''lower'' refers to the more severe category (e.g.: ''lower severe disability'' vs. ''upper severe disability''). The clusters were named accordingly to enable easier interpretation of

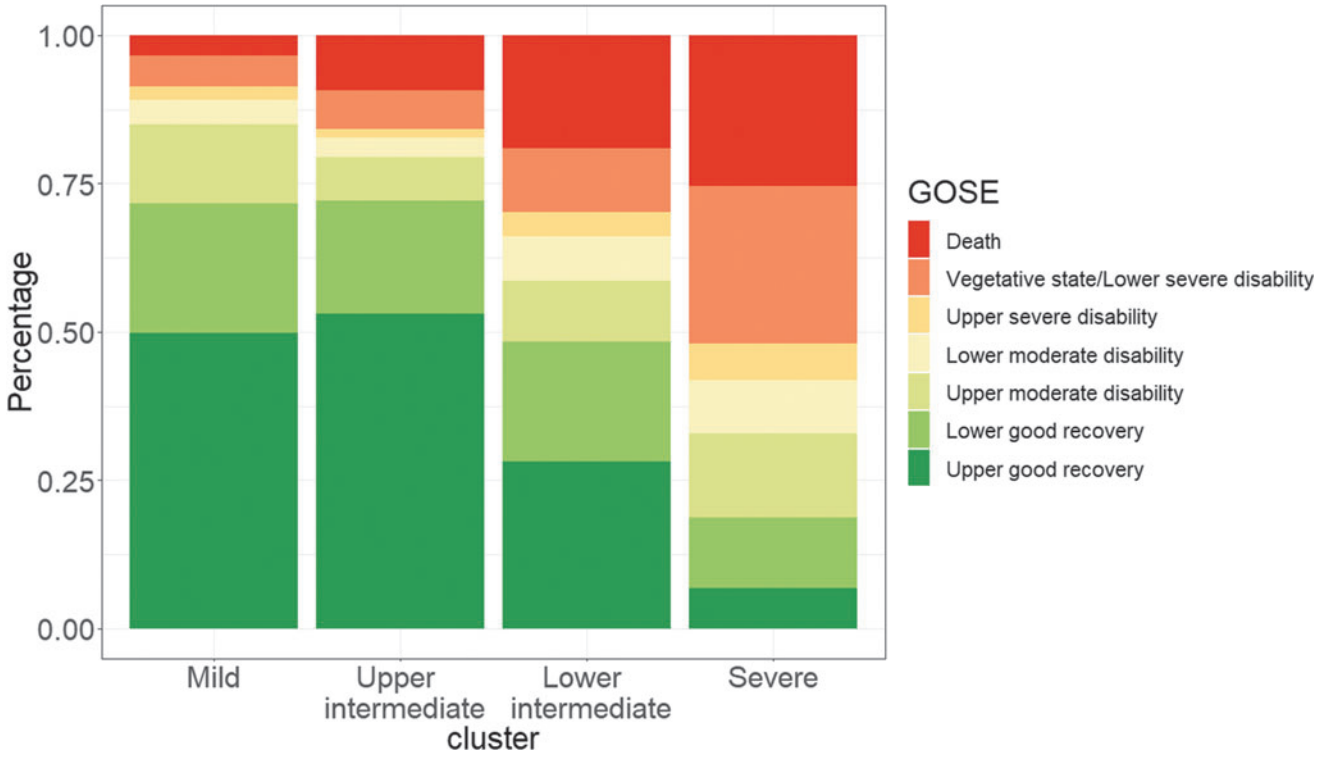


**FIG. 2.** Outcome of the four clusters. The stacked bar chart shows the distributions of Glasgow Outcome Scale – Extended (GOS-E) in the four identified clusters. Color image is available online.

the characteristics of clusters. Second, using all baseline characteristics in a logistical regression model, the predicted probability of 6 months unfavorable outcome (GOS-E < 5) was calculated. The observed and predicted probabilities were compared to assess the calibration of the model within the four clusters.

Further, the most important classification strategies, as defined by the partial $R^2$, were used to describe the patients. The GOS of all combinations of possible characteristics was visually assessed.

Finally, we assessed whether the baseline characteristics included in the clustering algorithm were prognostically relevant. Ordinal logistical regression with GOS-E as outcome variable was used. The area under the receiver operating characteristic (ROC) curve was used to describe the discrimination of the models. The following models were compared:

1. GCS
2. GCS + most important clustering variables (defined by the partial $R^2$)
3. GCS + pupils + age (core version of the IMPACT model[15])

All analyses were performed using R (R Core Team (2013). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing: Vienna, Austria). The published code can be found on https://github.com/ErasmusCMB/CENTER-TBI/blob/master/code_classification_TBI.R.

## Results

The 4509 patients in the CENTER-TBI study were on average 50 (interquartile range [IQR]: 30–66) years old, and predominantly male (67%). The most important causes of injury were road traffic incident (RTI) (39%) and incidental falls (47%). The majority of patients were classified as having mild TBI: the median GCS in the cohort was 15 (IQR: 10–15) (Table 1).

### *Imaging characteristics*

The first four dimensions of the principal component analysis (PCA) explained 68% of the variation in all imaging



Table 2. The Characteristics of the Four Clusters

| *Cluster* n = | *Mild* *1451* | *Upper intermediate* *1534* | *Lower intermediate* *1006* | *Severe* *518* |
|---|---|---|---|---|
| Age (median [IQR]) | 38 [24, 53] | 61 [42, 73] | 57 [42, 70] | 40 [25, 57] |
| Male (%) | 1000 (68.9) | 909 (59.3) | 708 (70.4) | 405 (78.2) |
| Injury cause (%) | | | | |
| RTI | 1095 (78.2) | 0 (0.0) | 194 (20.2) | 393 (79.1) |
| Fall | 0 (0.0) | 1354 (91.3) | 617 (64.2) | 53 (10.7) |
| Other | 138 (9.9) | 90 (6.1) | 91 (9.5) | 24 (4.8) |
| Violence/suicide | 168 (12.0) | 39 (2.6) | 59 (6.1) | 27 (5.4) |
| GCS Motor (median [IQR]) | 6 [6, 6] | 6 [6.0, 6.0] | 6 [4.0, 6.0] | 1 [1, 4] |
| GCS Score(median [IQR]) | 15 [14, 15] | 15 [14, 15] | 13 [8, 15] | 3 [3,7] |
| Pupils (%) | | | | |
| Both reactive | 1298 (94.7) | 1339 (93.1) | 829 (87.8) | 336 (67.9) |
| One reactive | 30 (2.2) | 45 (3.1) | 38 (4.0) | 51 (10.3) |
| None reactive | 42 (3.1) | 54 (3.8) | 77 (8.2) | 108 (21.8) |
| ED hypoxia (%) | 60 (4.4) | 59 (4.0) | 57 (6.1) | 123 (25.4) |
| ED hypotension (%) | 76 (5.4) | 51 (3.5) | 45 (4.8) | 125 (25.8) |
| Major extracranial injury (%) | 145 (10.0) | 87 (5.7) | 52 (5.2) | 384 (74.1) |
| Subdural hematoma Subacute chronic (%) | 2 (0.2) | 9 (0.8) | 6 (0.8) | 0 (0.0) |
| Traumatic subarachnoid hemorrhage (%) | 269 (24.0) | 302 (25.7) | 640 (83.6) | 320 (80.4) |
| Epidural hematoma (%) | 77 (6.9) | 55 (4.7) | 169 (22.1) | 72 (18.1) |
| Subdural hematoma acute (%) | 130 (11.6) | 206 (17.5) | 428 (55.9) | 179 (45.0) |
| Skull fracture (%) | 232 (20.7) | 216 (18.4) | 584 (76.2) | 234 (58.8) |
| Subdural collection mixed density (%) | 8 (0.7) | 30 (2.5) | 34 (4.4) | 10 (2.5) |
| Cisternal compression (%) | 39 (3.5) | 92 (7.8) | 220 (28.7) | 143 (35.9) |
| Midline shift (%) | 28 (2.5) | 94 (8.0) | 180 (23.5) | 78 (19.6) |
| Mass lesion (%) | 34 (3.0) | 113 (9.6) | 328 (42.8) | 104 (26.1) |
| Intraventricular hemorrhage (%) | 66 (5.9) | 64 (5.4) | 150 (19.6) | 173 (43.5) |
| Axonal injury (%) | 77 (6.9) | 51 (4.3) | 78 (10.2) | 118 (29.6) |
| Contusion (%) | 49 (4.4) | 0 (0.0) | 765 (99.9) | 273 (68.6) |
| ICP monitoring (%) | 99 (6.9) | 92 (6.0) | 245 (24.5) | 308 (59.9) |
| Intracranial surgery (%) | 75 (5.2) | 116 (7.6) | 214 (21.4) | 116 (22.4) |
| Extracranial surgery (%) | 129 (9.0) | 49 (3.2) | 37 (3.7) | 134 (25.9) |
| LOS (median [IQR]) | 5 [2, 12] | 4 [2, 10] | 11 [6, 23] | 31 [18, 47] |
| LOICUS (median [IQR]) | 0 [0, 2] | 0 [0, 1] | 3 [0, 10] | 15 [7, 24] |
| Stratum (%) | | | | |
| ED | 361 (24.9) | 440 (28.7) | 46 (4.6) | 1 (0.2) |
| Admission | 603 (41.6) | 660 (43.0) | 258 (25.6) | 2 (0.4) |
| ICU | 487 (33.6) | 434 (28.3) | 702 (69.8) | 515 (99.4) |

IQR, interquartile range; RTI, road traffic incident; GCS, Glasgow Coma Scale; ED, emergency department; ICP, intracranial pressure; LOS, length of stay; LOICUS, length of ICU stay; ICU, intensive care unit.

characteristics. In the first dimension, the dimension explaining most of the variability in all imaging characteristics (34%), the most important imaging characteristics were the absence or presence of traumatic axonal injury, midline shift, and subdural mixed density (Fig. S1).

### *Clustering analysis*

We restricted the number of clusters to four for easy interpretation, and thereby used a silhouette value similar to the maximum silhouette value (0.21 with 3, 0.24 with 4, and 0.25 with 5). The most important building blocks of the clusters were injury cause, major extracranial injury, and GCS, respectively: the partial $R^2$, indicating relative importance in the clusters, were 13%, 5%, and 2%, respectively. The key imaging characteristics and age also were relatively important clustering characteristics (Fig. 1).

The clustering method was quite stable: the proportion of patients staying in one cluster after resampling and reclustering was 97% (95% CI: 86–100%). Four examples of resampling and recluster iterations are shown in Figure S2.

From mild to severe, 12%, 19%, 36%, and 58% of patients had unfavorable outcome in the four clusters (Fig. 2). The same pattern was seen for mortality, where 1%, 4%, 8%, and 17% mortality rates were observed. Based on the model with the IMPACT variables fitted on the data, the severe cluster had 1.5 times worse functional outcome than expected (calibration intercept: 0.4, 95% CI: 0.2–0.6; observed to expected ratio 1.5; Fig. S3). From mild to severe, the four clusters consisted of 1451, 1534, 1006, and 518 patients respectively (Table 2).

The mild and the severe cluster consisted of younger patients (median of 38 [24–53] and 40 [25–57] years old, compared with 61 [42–73] in the upper intermediate cluster and 57 [42–70] in the lower intermediate cluster). In these younger patients, the trauma was predominantly caused by road traffic incidents, instead of incidental falls. The lower intermediate and the severe cluster consisted of patients with a median GCS <15, and more unreactive pupils.

The different clusters were also characteriezd by different care pathways and disease evolutions. In the severe cluster, 515 (99%) patients were admitted to the ICU, whereas only 702 (70%) of the patients in the lower intermediate cluster were admitted to the ICU. Compared with the mild and the upper intermediate cluster, the lower intermediate and the severe cluster received more key interventions, such as ICP monitoring, intracranial surgery, and extracranial surgery. However, the severe cluster consisted of more patients requiring extracranial surgery: 134 (26%) versus 37 (3.7%) in the lower intermediate cluster. Although the length of (ICU) stay was longer in the lower intermediate and severe cluster, the length of (ICU) stay was longest in the severe cluster: the median length of ICU stay was 15 (IQR: 7– 24) days in the severe cluster, whereas in the lower intermediate cluster, the median was 3 (IQR: 0–10); the length of hospital stay was on average 30.5 (IQR: 18–47) days in the severe cluster, compared with a median length of hospital stay of 11 (IQR: 6–23) days in the lower intermediate cluster. Although some of the patients in the upper intermediate and the mild cluster were admitted to the ICU, the median ICU length was 0 (IQR 0–2 for the mild cluster, and 0–1 for the upper intermediate cluster).

All these characteristics are also presented for the current classification based on GCS in Table S1. In comparison to the four clusters, the groups based on GCS scaled less well with demographic differences and cause of injury: the median age was 46 (IQR: 25–64) in the severe group, 53 (IQR: 34–69) in the moderate group, and 51 (IQR 31–67) in the mild group. The proportions of road traffic accidents were 47%, 36%, and 35% in the three groups, respectively. The treatment intensity and presence of imaging abnormalities differed across the three groups.

Based on the most important clustering variables, the patients were described again on outcome (Fig. 3). The distribution of GOS-E scores was mainly different for patients with lower GCS scores.

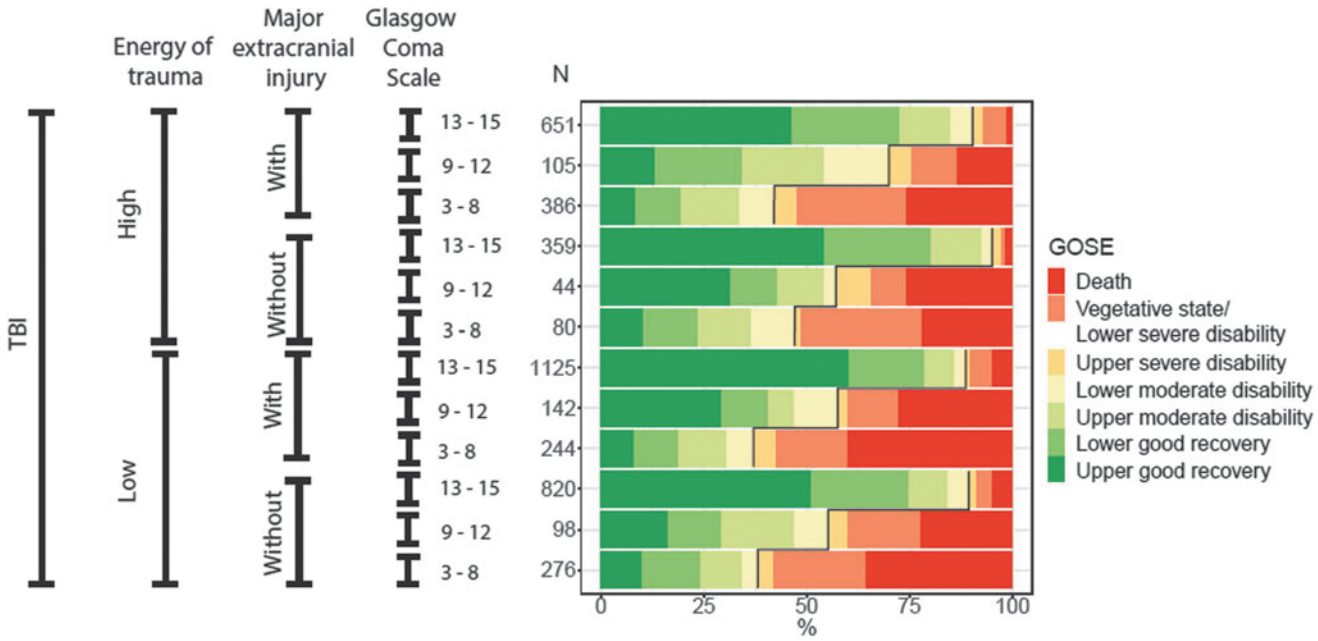


**FIG. 3.** The proposed classification system for traumatic brain injury (TBI) and their observed Glasgow Outcome Scale – Extended (GOS-E) scores. The classification is based on the characteristics that mostly defined the clustering algorithm. The black line in the stacked bar chart indicates the border of unfavorable and favorable. Color image is available online.

The largest group consisted of low energy (no road traffic incident), mild (GCS 13–15) TBI with major extracranial injury (1125 [25%]). The smallest groups were high energy moderate (GCS 9–12) and severe (GCS <9) TBI without major extracranial injury: 44 (1%) and 80 (2%) patients, respectively.

For the prediction of functional outcome, the model with only GCS had an area under the ROC curve of 0.72 (95% CI 0.71–0.72). Adding major extracranial injury and cause of injury (as most relevant clustering variables), did not improve the discrimination of the model. In contrast, adding age and pupils did increase the area under the ROC curve to 0.75 (95% CI 0.74–0.75).

## Discussion

This study was a hypothesis-free exploration of cluster analysis in TBI to inform development of a new, multidimensional classification for TBI. We clustered TBI patients into four groups. The most defining building blocks of the clustered groups were injury cause, major extracranial injury, and GCS. With these three most defining characteristics, patients could be classified into 12 groups, ranging from high energy mild TBI with major extracranial injury, to low energy severe TBI without major extracranial injury.



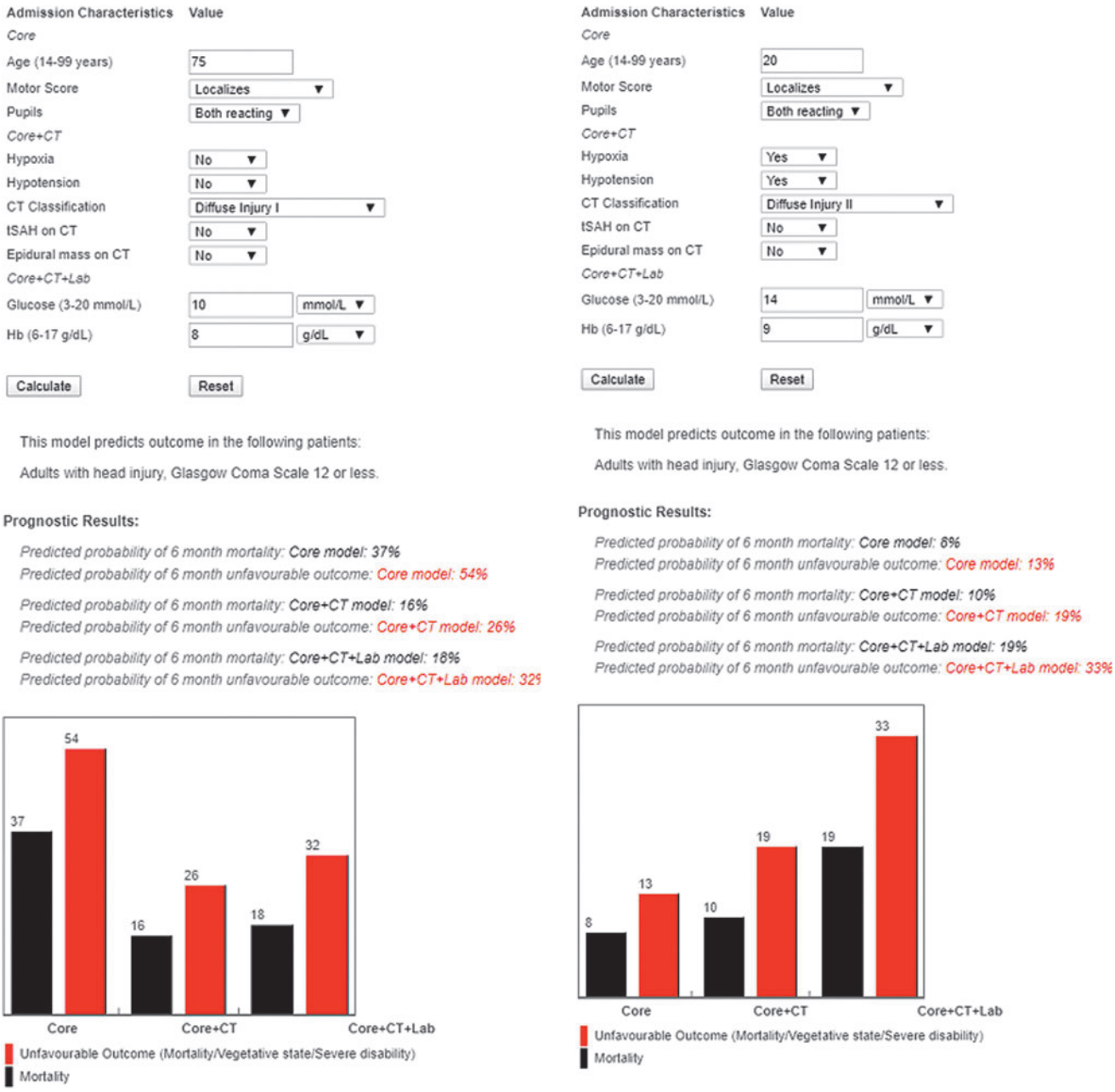


**FIG. 4.** Two exemplary patients: an elderly patient who fell, and a younger patient who was in a road traffic accident. Their predicted risk of 6 month mortality and 6 month unfavorable outcome is similar in both cases. These figures are made from: http://www.tbi-impact.org/?p=impact/calc. Color image is available online.

Our proposed classification might capture differences in required treatment approaches, irrespective of differences in prognosis. Patients with similar risk of outcome could still require different treatment approaches.[16] As an illustration, an elderly patient with multiple comorbidities who fell at home might, according to the IMPACT model, be at equal risk of dying and unfavorable outcome within 6 months compared with a younger patient with TBI caused by a road traffic incident (Fig. 4).[15] Even though their risk would be equal, they would need different approaches of care: our study suggests that the first patient would more likely require intracranial surgery and would have a relatively short ICU stay, and the latter would require extracranial surgery and ICP monitoring with a long ICU stay.

Additionally, the characteristics identified by our study relate to care pathways. This is because they are already used to hand over trauma patients. This is the experience in our hospitals. A possible reason is that the widely used format for handovers, the Situation, Background, Assessment, Recap/Rx (S-BAR),[17] dictates including background information: this is typically described by the mechanism of injury, and whether the patient has major extracranial injury. Clinical experience has led to the description of these characteristics, because they apparently impact care pathways.

Describing TBI patients based on energy of trauma and major extracranial injury potentially may capture etiological differences and could possibly improve the development of new treatments and subsequent clinical trials in the TBI field. It has been suggested that the traditional classification of TBI is one of the causes of a history of negative trials in TBI.[5,18] A classification that better integrates the pathological differences in the heterogeneous TBI patient population could enable more focused, and therefore potentially more positive, trials.

It could be argued that imaging characteristics, which we included in our analysis, are not always available at the emergency department: only selected TBI patients should be scanned, to avoid unnecessary oncogenic risk of radiation, costs, and productivity loss.[19] However, in contrast to novel biomarkers, or characteristics visible on magnetic resonance imaging (MRI) scan, CT characteristics are usually available. Moreover, imaging characteristics are key to discerning different TBI pathologies, such as epidural versus subdural hematoma. Our aim was to explore a classification that better describes the variation in TBI pathologies. Therefore, it was considered essential to include this type of information.

The fact that this study has applied hypothesis-free analyses in a large TBI database is both a limitation and a strength. On the one hand, a data-driven approach to clustering could lead to poor generalizability. Moreover, critique on clustering algorithms often involves low interpretability of the clusters, because they are not based on pre-existing subject knowledge.[20] In our case, the clustering approach revitalized the importance of describing patients using major extracranial injury and mechanism of injury. This is in contrast with previous research, which mainly has focused on a prognostic, instead of a mechanistic, description of TBI patients.[1]

Another limitation is that we did not take biomarker profiles into account. Currently, there is not enough knowledge about longitudinal biomarker profiles. Implementing these profiles could improve the classification, and more research is necessary to know what precisely should be included in such a classification.

Finally, another limitation of our study is that the current analysis is biased toward classifying more severe injuries. The majority of the used variables are known to be prognostically relevant for moderate to severe TBI.[9] Further, ICU patients were preferentially included in the core CENTER-TBI database. This resulted in a somewhat selected TBI sample. However, 2310 (51%) of the patients in our sample were non-ICU patients. Moreover, most heterogeneity is to be expected among those patients with severe TBI.[5] Therefore, it can be argued that analyzing a cohort with an overrepresentation of the most heterogeneous subgroup can assist in better characterizing the disease. However, we recognize that other variables might be more appropriate for clustering milder TBI patients.

## Conclusion

After unsupervised, hypothesis-free clustering, four clusters were identified, which were mainly defined by injury mechanism, presence of major extracranial injury, and GCS. Describing patients with these three characteristics could potentially capture more differences in etiological and care pathway aspects than based on GCS alone. Our proposed classification should be validated and extended upon; in particular, we feel that biomarkers could play an important role.

## CENTER-TBI Participants and Investigators

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## Supplementary Material

Supplementary Figure S1
Supplementary Figure S2
Supplementary Figure S3
Supplementary Table S1

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