Clinical descriptors of disease trajectories in patients with traumatic brain injury in the intensive care unit (CENTER-TBI): a multicentre observational cohort study

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Summary

Background Patients with traumatic brain injury are a heterogeneous population, and the most severely injured individuals are often treated in an intensive care unit (ICU). The primary injury at impact, and the harmful secondary events that can occur during the first week of the ICU stay, will affect outcome in this vulnerable group of patients. We aimed to identify clinical variables that might distinguish disease trajectories among patients with traumatic brain injury admitted to the ICU.

Methods We used data from the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) prospective observational cohort study. We included patients aged 18 years or older with traumatic brain injury who were admitted to the ICU at one of the 65 CENTER-TBI participating centres, which range from large academic hospitals to small rural hospitals. For every patient, we obtained pre-injury data and injury features, clinical characteristics on admission, demographics, physiological parameters, laboratory features, brain biomarkers (ubiquitin carboxy-terminal hydrolase L1 [UCH-L1], S100 calcium-binding protein B [S100B], tau, neurofilament light [NFL], glial fibrillary acidic protein [GFAP], and neuron-specific enolase [NSE]), and information about intracranial pressure lowering treatments during the first 7 days of ICU stay. To identify clinical variables that might distinguish disease trajectories, we applied a novel clustering method to these data, which was based on a mixture of probabilistic graph models with a Markov chain extension. The relation of clusters to the extended Glasgow Outcome Scale (GOS-E) was investigated.

Findings Between Dec 19, 2014, and Dec 17, 2017, 4509 patients with traumatic brain injury were recruited into the CENTER-TBI core dataset, of whom 1728 were eligible for this analysis. Glucose variation (defined as the difference between daily maximum and minimum glucose concentrations) and brain biomarkers (S100B, NSE, NFL, tau, UCH-L1, and GFAP) were consistently found to be the main clinical descriptors of disease trajectories (ie, the leading variables contributing to the distinguishing clusters) in patients with traumatic brain injury in the ICU. The disease trajectory cluster to which a patient was assigned in a model was analysed as a predictor together with variables from the IMPACT model, and prediction of both mortality and unfavourable outcome (dichotomised GOS-E ≤4) was improved.

Interpretation First-day ICU admission data are not the only clinical descriptors of disease trajectories in patients with traumatic brain injury. By analysing temporal variables in our study, variation of glucose was identified as the most important clinical descriptor that might distinguish disease trajectories in the ICU, which should direct further research. Biomarkers of brain injury (S100B, NSE, NFL, tau, UCH-L1, and GFAP) were also top clinical descriptors over time, suggesting they might be important in future clinical practice.

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See Comment page 7

*A full list of investigators and participating centres is provided in the appendix

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Introduction

Patients with traumatic brain injury who are treated in an intensive care unit (ICU) are extensively monitored to minimise the risk of harmful secondary events. However, between 30% and 40% of patients with severe traumatic brain injury will deteriorate within 10 days of the injury.[1] Therefore, a fundamental question in neurointensive care is how to monitor, identify, and avoid harmful secondary events and further brain injury. Unfortunately, patients with traumatic brain injury are a highly heterogeneous group with respect to their initial presentation and subsequent clinical trajectory. In a 2021 review,[2] two studies were identified in which subgroups of patients with severe traumatic brain injury in the acute phase were classified, based on pre-injury variables and admission data, but it is unclear how these clinical descriptors can be implemented into clinical practice.

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Research in context

Evidence before this study

We searched PubMed in English with the keywords "traumatic brain injury" AND ("clustering" OR "trajectory"), from database inception to July 17, 2023, to identify relevant studies. Several cross-sectional studies had aimed to identify patients with a traumatic brain injury who might benefit from different treatment approaches. Few studies have focused on the temporal evolution of traumatic brain injury during the first days after injury. We identified 14 studies describing disease trajectories in acute traumatic brain injury. Most focused on single trajectories of intracranial pressure, biomarkers, proteomics, or neuroinflammation, and only one previous multivariate time-series study assessed composite patterns. We identified one report that described pathophysiological trajectories in acute traumatic brain injury in the multicentre Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) observational cohort study. In the TRACK-TBI study, three longitudinal disease trajectories were found by grouping patients according to many clinical features, including baseline demographics and time-series features. These trajectories were associated with different clinical and outcome profiles. However, the TRACK-TBI study did not include brain injury biomarkers.

Added value of this study

To the best of our knowledge, our study is the first to describe pathophysiological trajectories in patients with traumatic brain injury requiring intensive care. We obtained patient data from the large multicentre Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) cohort study.

Implications of all the available evidence

Longitudinal changes in physiological parameters add valuable information to admission data alone, and provide insight into disease trajectories. We identified glucose variation and a panel of brain biomarkers (ubiquitin carboxy-terminal hydrolase L1, S100 calcium-binding protein B, tau, neurofilament light, glial fibrillary acidic protein, and neuron-specific enolase) as key clinical descriptors of disease trajectories in traumatic brain injury in the intensive care unit (ICU). Although glucose levels are known to be associated with traumatic brain injury outcomes, glucose variability has been less investigated. Future study of glucose variation is warranted, to understand pathophysiological mechanisms and potential treatment targets. Together with previous findings, our study highlights the potential utility of serial brain biomarker measurements in traumatic brain injury and suggests incorporation of these measures in clinical care. The characterisation of disease trajectories in traumatic brain injury could be an important step towards future targeted therapeutic approaches.

In a previous study,[3] we identified six distinct pathophysiological subgroups—often referred to as endotypes—of patients with traumatic brain injury in the ICU by applying unsupervised clustering methods on data obtained from the first day after the injury. These subgroups of patients had differences in composite metabolic responses, particularly in relation to lactate and glucose. However, this work did not address the more complex problem of how to distinguish subsequent disease trajectories of traumatic brain injury during the ICU stay.

Previous studies in general ICU patients have shown that clear pathophysiological patterns can emerge during the first weeks in the ICU, with different disease trajectories related to changes in Sequential Organ Failure Assessment (SOFA) score.[4] In patients with traumatic brain injury, variability in intracranial pressure has been described and shown to correlate with the expression of an oedema-regulating gene, *ABCC8*.[5] Other studies have shown that traumatic brain injury is associated with extracranial complications, such as acute respiratory distress syndrome (ARDS), acute kidney injury, myocardial injury, and coagulopathy.[6–8] This work has led us to hypothesise that a multidimensional analysis of physiological, laboratory, and demographic variables during the ICU stay might describe composite longitudinal disease trajectories after traumatic brain injury. A complete description must also include treatment factors, such as those described in the Therapy Intensity Level scale,[9] which otherwise could confound physiological measurements. Multidimensional factors related to the trajectory of traumatic brain injury have received relatively little attention to date, although Ghaderi and colleagues[10] identified three multivariable clusters of time-series data in patients with traumatic brain injury, showing differences in physiological and haematological factors, thereby suggesting that different clinical presentations might have distinct disease trajectories.

We aimed to identify clinical variables that might distinguish disease trajectories in patients with traumatic brain injury admitted to the ICU. Objectives were to better understand disease progression and to identify distinct trajectory-based subgroups of patients with traumatic brain injury, which could form the basis for targeted therapies in the future.

Methods

Patients

We obtained patient data from the core dataset of the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) prospective observational cohort study.[11] All patients

enrolled in CENTER-TBI meet general inclusion criteria—ie, a clinical diagnosis of traumatic brain injury, presentation at hospital within 24 h from injury, and clinical need for a CT scan. In our analysis, we included all patients aged 18 years or older who were admitted to the ICU at hospital admission. Version 3.0 of the CENTER-TBI core dataset was used in this study.

This study was approved by the CENTER-TBI management committee. Ethics approval was obtained at every recruiting site. The list of participating sites and details of ethics approvals are available online.[12] Written or oral informed consent was obtained from patients or their next of kin, according to local legislation, for all patients recruited in the core dataset of CENTER-TBI. This information was documented in an electronic case report form (e-CRF). In the case of oral consent, written confirmation was requested.[12]

Procedures

Data were collected through the Quesgen e-CRF (Quesgen Systems, Burlingame CA, USA), which is hosted on the International Neuroinformatics Coordinating Facility (INCF) platform. Information about 59 candidate admission features and daily measures, comprising brain protein biomarkers and interventions during the first 7 days of ICU stay was extracted from the CENTER-TBI dataset via the INCF Neurobot tool (INCF, Stockholm, Sweden); these variables cover major aspects of neurological ICU monitoring and care (appendix pp 6–7). We did not extract data for pairs of features that are known to be highly covariate. CT characteristics were based on central imaging review in CENTER-TBI. The brain biomarker panel consisted of ubiquitin carboxy-terminal hydrolase L1 (UCH-L1), S100 calcium-binding protein B (S100B), tau, neurofilament light (NFL), glial fibrillary acidic protein (GFAP), and neuron-specific enolase (NSE), as these were available in the CENTER-TBI dataset and have shown potential for neurological evaluation and prognostication.[13,14] Blood samples were centrifuged within 60 min of collection, stored at –80°C at each centre, and analysed in one round at two sites using the same batch of reagents. See the appendix (p 2) for further details.

Missing longitudinal data were imputed either by interpolation, set to 0, or by last observation carried forward (appendix pp 8–14). If a patient was discharged or died during the first week post-injury, all features on the following days were represented as not available. Continuous features were characterised by daily means or by the daily difference between maximum and minimum values if repeated measures of a feature occurred on one day.

The clustering model

Full details of the modelling process are in the appendix (pp 3–5). In brief, to identify disease trajectories during the first week of ICU stay, we used a clustering method based on a mixture of probabilistic graph models to group patients based on baseline and longitudinal clinical variables. Each graph comprised the univariate probability distributions for all clinical variables on each day, and joint distributions for pairs of variables that are directly correlated. Each cluster represents a similar disease trajectory or course. To estimate cluster membership probabilities and parameter values within the clusters, we used the iterative expectation maximisation algorithm,[15,16] which calculates a probability for each patient's membership of each cluster and estimates cluster means and variances for continuous features and the relative frequency of categorical features.

We used an incremental clustering approach, starting with two clusters (which each represented a disease trajectory) then adding one cluster at a time to a maximum of 12 clusters (figure 1). For each step, 100 patients were randomly assigned to each disease trajectory cluster, then the model with the highest log likelihood was used as a so-called seed to create the next model with one additional cluster. This process was repeated 25 times until 25 models had been picked for each cluster count from two to 12. To assess cluster stability, we calculated a cluster similarity index (CSI),[17] which was defined as the proportion of patients with cluster assignment agreement between all possible pairs

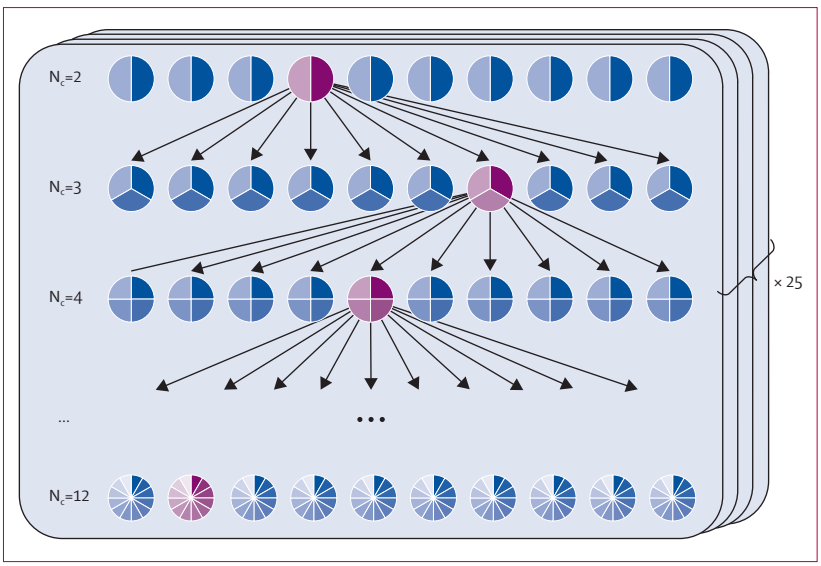

Figure 1: **The modelling process**
Our modelling approach used an incremental clustering method, with a cluster representing a similar disease trajectory after traumatic brain injury. Models (represented as blue circles) were created in which patients were grouped into between two and 12 trajectories (represented as segments of each blue circle). To converge on the best model for every number of clusters, we initially created ten models of two clusters (top row), with 100 patients randomly assigned to each of the two clusters. The model with the highest log likelihood (represented by a purple circle) was then used as a seed to create models of three clusters; as for the previous step, 100 patients were randomly selected in every cluster, with an additional 100 randomly selected patients assigned to the incremental cluster. This optimisation process was repeated until we had 12 clusters per model (bottom row). To assess model stability, all steps were repeated 25 times, and stability was assessed using a cluster similarity index for every number of clusters. Importance of clinical variables was assessed by averaging mutual information over the 25 selected models for each number of clusters (N_c).

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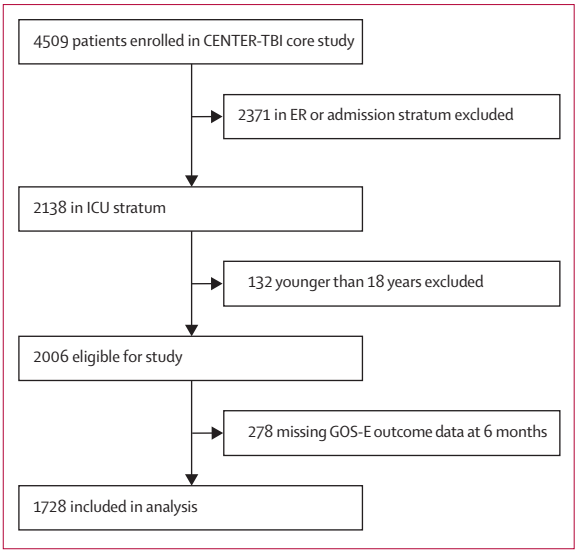

Figure 2: **Patient selection**
CENTER-TBI=Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury. ER=emergency room. ICU=intensive care unit. GOS-E=extended Glasgow Outcome Scale.

of the 25 models for each number of clusters, with a higher CSI indicating more stable clustering.

To investigate the importance of each clinical variable in the model, we calculated mutual information—ie, a measure of how much the distribution of the value of a particular clinical feature differs between clusters.[15,18] The average mutual information over all 25 models for each number of clusters was calculated. Additionally, the average daily mutual information was calculated for each clinical variable to assess the overall most important features. We then did a qualitative analysis of disease trajectories with respect to the clinical features with the highest average mutual information.

To ascertain whether membership of a particular cluster by a patient was related to late functional outcome, we analysed scores at 6 months on the extended Glasgow Outcome Scale (GOS-E). Scores on GOS-E range from 1 (dead) to 8 (good recovery), with an unfavourable outcome defined as a GOS-E score of 4 or lower. If GOS-E was missing at 6 months, but available at one or more of the other assessment timepoints (ie, at 2 weeks or 3 or 12 months post-injury), the value was imputed centrally in the CENTER-TBI dataset.[11,19] Moreover, we evaluated the improvement in outcome predictions for mortality and unfavourable outcome beyond the International Mission for Prognosis and Clinical Trials (IMPACT) model[20] by addition of trajectory assignments using logistic regression. The improvement of predictions was evaluated by calculating Nagelkerke's R^2. Uncertainty in predictions was estimated by bootstrap sampling with replacement 1000 times, and the results were bias-adjusted to correct for adding features in the model. To assess whether disease trajectory was site-dependent, mutual information was calculated between site and cluster label in a post-hoc analysis.

In a previous study, we identified six distinct pathophysiological subgroups (also referred to as endotypes) in the CENTER-TBI ICU stratum cohort, using only data from the first 24 h post-admission.[3] These admission endotypes can be described as a composite of Glasgow Coma Scale (GCS) and systemic metabolic profiles—ie, high GCS and normal metabolism (A); intermediate GCS and normal metabolism (B); intermediate GCS and abnormal metabolism (C); low GCS and normal metabolism (D); low GCS and abnormal metabolism with a higher incidence of intracranial pathology (E); and low GCS and abnormal metabolism with a higher incidence of systemic shock (F). To investigate if the disease trajectories in this study could be predicted by the endotypes described at admission, probabilities of following each disease trajectory were calculated for all admission clusters.

The models were created using open-source code developed in C++ by AH and CAIÅ. All subsequent analyses were performed using R version 4.0.5.

CENTER-TBI is registered with ClinicalTrials.gov, NCT02210221.

Role of the funding source

The funding sources had no role in data collection, analysis, interpretation, writing of the manuscript, or the decision to submit for publication.

Results

Between Dec 19, 2014, and Dec 17, 2017, 4509 patients were enrolled to the CENTER-TBI core dataset from 65 centres across 18 European countries. 2006 patients were initially eligible for our study, but 1728 patients were included in the final analysis after excluding 278 individuals due to missing GOS-E data at 6 months (figure 2). These patients were from 54 of the 65 recruiting sites in CENTER-TBI. The median GCS score at admission was 9 (IQR 4–14). 388 (22·5%) patients died, and 779 (45·1%) had unfavourable outcomes (defined as upper severe disability or worse, GOS-E ≤4). The median age was 52 years (IQR 33–67); 1269 (73·4%) patients were male and 459 (26·6%) were female (table 1, details in appendix pp 16–22).

Disease trajectory clusters were derived from patients' baseline data and from adding information for clinical variables obtained over time. No distinct peak was identified when comparing the median CSI between different numbers of clusters (appendix p 27), which indicated that no specific number of clusters generated a more stable model. Sensitivity analyses were done to evaluate the stability of the mutual information of the clinical variables that were included in the clusters (table 2; appendix p 28). The progress of cluster assignments for increasing the number of clusters from two to 12 is illustrated in the appendix (p 29). Because

there was no optimal number of clusters, six were chosen to compare differences between clusters; these disease trajectory clusters were labelled α, β, γ, δ, ε, and ζ. Of the 1728 patients who were included in the final analysis, 438 were assigned to disease trajectory α, 506 to β, 119 to γ, 202 to δ, 257 to ε, and 206 to ζ; most patients were assigned to their final disease trajectory with high probability of being assigned to that disease trajectory versus any of the others (appendix pp 16, 30, 23).

The clinical variables that contributed to and distinguished disease trajectories during the first week of ICU stay in patients with traumatic brain injury were glycaemic variation, brain biomarkers (tau, UCH-L1, GFAP, S100B, NSE, and NFL), serum creatinine, and oxygen saturation (figure 3, table 2). A daily analysis revealed that these clinical variables were important on all days of ICU stay, whereas mean intracranial pressure and sodium variation showed greater importance on the first days, 3 versus 2 respectively (appendix p 24). The results were consistent across our models from two to 12 clusters, irrespective of the number of clusters in each model. Distributions of these clinical variables on each day are presented in the appendix (p 31). Glucose variability and brain biomarkers were consistently the main clinical descriptors of disease trajectory in patients with traumatic brain injury in the ICU.

To evaluate whether CENTER-TBI participating site had an effect on disease trajectory, mutual information of cluster membership and site was calculated in a post-hoc analysis. Findings indicated a mutual information value on par with the ninth most important clustering variable, indicating a low impact of site effect on trajectory.

Ordering the six disease trajectory clusters from α to ζ showed progressively decreasing GOS-E, increasing amounts of brain biomarkers, and increasing glucose variability, suggesting the disease trajectory clusters could be associated with functional outcome. Although the primary aim was not to identify subgroups with different functional outcomes, the different disease trajectory clusters differed substantially in 6-month mortality and GOS-E score. The α cluster had the most benign disease trajectory, with 6-month mortality of 4% (16 of 438) and 6-month unfavourable outcome of 18% (78 of 438). The most pathological cluster was ζ, which was associated with 65% mortality (134 of 206) and 84% unfavourable outcome (174 of 206) (figure 4). 42% of patients assigned to disease trajectory ζ died within 7 days post-injury, whereas most patients assigned to disease trajectory α were discharged at 7 days (377 [86%] of 438). Trajectory ε had the largest proportion of patients still in ICU 7 days post-injury (180 [70%] of 257). Similar patterns were seen in models of all numbers of clusters (appendix p 28). Moreover, disease trajectory assignments were seen to add substantial ability to discriminate both mortality and unfavourable outcome in logistic regression models, including IMPACT prediction variables (appendix p 26). The addition of cluster assignments for 12 clusters was associated with the highest increase in bias-adjusted Nagelkerke's pseudo-R^2, from 0·44 to 0·53 (bootstrap SE 0·02) for mortality, and from 0·36 to 0·45 (0·02) for unfavourable outcome—showing that unsupervised clustering discriminated disease trajectories that were related to outcome.

Relations of clusters (disease trajectories) to previously identified admission endotypes were explored (appendix p 32, 25). Endotype A (ie, patients presenting with the highest GCS and normal metabolism) had the highest probability (57·1%) of following a specific disease trajectory, and this trajectory was the cluster associated with best functional outcome (α; GOS-E 7 [IQR 5–8] at 6 months). Endotype C (moderate traumatic brain injury and abnormal metabolic profile) comprised a substantially larger proportion of patients who followed

	All patients (n=1728)
Age, years	52 (33–67)
Sex	
Female	459 (26·6%)
Male	1269 (73·4%)
ICU length of stay, days	7 (2–16)
Total ISS	29 (25–41)
GCS total score at arrival	9 (4–14)
Pupil reactivity	
Both reacting	1403 (81·2%)
One reacting	114 (6·6%)
Both unreactive	211 (12·2%)
ICP monitoring	749 (43·3%)
Intubated	1366 (79·1%)
Creatinine, max (µg/L)	77 (64·5–94·0)
Glucose, mean first day (mmol/L)*	7·7 (6·5–9·2)
ICP, mean (mm Hg)*	11·7 (8·2–15·3)
SpO_2, arrival [%]	99% (96–100)
Sodium, mean (mmol/L)*	141 (139–144)
Rotterdam CT score	3 (3–4)
Daily TIL, max	4 (1–10)
GOS-E at 6 months	5 (3–7)
1	388 (22·5%)
2 or 3†	268 (15·5%)
4	123 (7·1%)
5	241 (13·9%)
6	214 (12·4%)
7	229 (13·3%)
8	265 (15·3%)
IMPACT predicted mortality, %	22·1% (10·7–40·2)

Data are median (IQR) or n (%) unless otherwise stated. ICU=intensive care unit. ISS=injury severity score. GCS=Glasgow coma scale. ICP=intracranial pressure. SpO_2=oxygen saturation. TIL=therapy intensity level. GOS-E=extended Glasgow outcome scale. IMPACT=International Mission for Prognosis and Analysis of Clinical trials in Traumatic Brain Injury. *Data are group medians and patient daily means. †GOS-E 2 and 3 were combined in the CENTER-TBI data due to the low incidence of GOS-E 2. This was done centrally and is valid for all CENTER-TBI studies.

Table 1: **Patient characteristics**

	2 clusters	3 clusters	4 clusters	5 clusters	6 clusters	7 clusters	8 clusters	9 clusters	10 clusters	11 clusters	12 clusters
1	Δ Glucose	Δ Glucose	Δ Glucose	Δ Glucose	Δ Glucose	Δ Glucose	Δ Glucose	Δ Glucose	Δ Glucose	Δ Glucose	Δ Glucose
2	Creatinine	Creatinine	Tau	Tau	Tau	Tau	Tau	Tau	Tau	Tau	Tau
3	Δ SpO_2	Tau	Creatinine	UCH-L1	UCH-L1	UCH-L1	UCH-L1	UCH-L1	GFAP	GFAP	GFAP
4	Tau	UCH-L1	UCH-L1	GFAP	GFAP	GFAP	GFAP	GFAP	UCH-L1	UCH-L1	UCH-L1
5	SpO_2 mean	Δ SpO_2	GFAP	Creatinine	NFL	NFL	NFL	S100B	NFL	S100B	NFL
6	S100B	GFAP	Δ SpO_2	NFL	S100B	Creatinine	S100B	NFL	S100B	NFL	S100B
7	NFL	NFL	NFL	S100B	Creatinine	S100B	Creatinine	Creatinine	Creatinine	Creatinine	Creatinine
8	UCH-L1	Δ pH	S100B	Δ SpO_2	Δ SpO_2	Δ SpO_2	Δ SpO_2	Δ SpO_2	Δ SpO_2	NSE	Δ SpO_2
9	Δ pH	S100B	NSE	NSE	NSE	NSE	NSE	NSE	NSE	Δ SpO_2	NSE
10	GFAP	SpO_2 mean	SpO_2 mean	SpO_2 mean	SpO_2 mean	SpO_2 mean	SpO_2 mean	SpO_2 mean	SpO_2 mean	Lactate	Lactate

Feature importance was assessed with MI. Features or descriptors of trajectories are ranked in falling order of MI values, with a value of 1 being most important to 10 being least important. The top ten features are shown for models ranging from two to twelve clusters. Glycemic variation, the brain biomarkers Tau, UCH-L1, GFAP, S100B, NSE and NFL, creatinine, and oxygen saturation are seen to have the highest overall average information content in describing trajectories during the first week of ICU stay in patients with TBI. The main parameters were largely consistent for models of two to twelve clusters and can be seen to additionally stabilise with an increasing number of clusters, with creatinine and oxygen saturation losing importance with an increasing number of clusters. MI=mutual information. Δ=change in. SpO_2=oxygen saturation. NFL=neurofilament light. NSE=neuron-specific enolase. S100B=S100 calcium-binding protein B. GFAP=glial fibrillary acidic protein. UCH-L1=ubiquitin carboxy-terminal hydrolase L1.

Table 2: **The ten most important features describing trajectories in models of two to twelve clusters**

the ζ disease trajectory (associated with 65·0% mortality) than endotype D (severe traumatic brain injury and normal metabolic profile). In general, endotypes B–F had more variable relations to disease trajectory than did admission endotype A (appendix p 32), suggesting that disease trajectory is affected by multiple biological processes and clinical factors during the ICU stay.

Discussion

By applying an unsupervised temporal clustering method to a large cohort of patients with traumatic brain injury who were treated in the ICU, we were able to investigate clinical descriptors (ie, baseline and longitudinal patient characteristics and clinical variables) of disease trajectories. Glucose variation and brain biomarkers (ie, tau, UCH-L1, GFAP, S100B, NSE, and NFL) were consistently the best performing clinical descriptors of disease trajectories in the ICU. Furthermore, mean intracranial pressure, CSF drainage volume, creatinine, sodium variation, and oxygen saturation were important clinical descriptors of disease trajectories in the first 3 days of the ICU stay. These findings have possible implications for clinical practice, since these variables have received relatively little attention to date.

The importance of glycaemic variability, rather than absolute values, has received scant attention to date. In previous work, glycaemic variability has been shown to correlate with worse outcomes in general ICU cohorts as well as traumatic brain injury ICU cohorts.[21–23] However, the mechanistic and causal relations between glycaemic variation and outcome are little understood. Possible mechanistic explanations might be multifactorial, representing several processes and including biological toxicity due to oxidative stress triggered by changing glucose levels, neuronal and mitochondrial damage, modulation of haemostasis, a direct association with greater sympathetic stimulation (a metabolic biomarker of injury severity), or simply a reflection of less attentive care in general.[22,23] Our study suggests that glucose variation, rather than absolute values, is a key variable to distinguish ICU disease trajectories. An extensive and targeted investigation in the future is warranted, to better understand patients' metabolic profiles and the causes and effects of glucose variability.

Brain biomarkers (ie, tau, UCH-L1, GFAP, S100B, NSE, and NFL) have been associated with both outcome and secondary events in patients with traumatic brain injury,[13,24–27] but implementation into clinical practice has not yet taken place. Our study suggests a surprisingly high effect of brain biomarkers as clinical descriptors of disease trajectories. Biomarker levels can be assumed to represent ongoing processes of brain injury, indicating that both neuronal or glial release (depending on the biomarker), alone or in combination,[28] could reflect disease evolution, treatment effects, or both. The levels and trajectories of biomarkers should be further explored as surrogate outcome measures in traumatic brain injury. The dynamic evolution of protein biomarkers could provide an important first step towards targeted care in traumatic brain injury, recognising that the predictive value of serial biomarkers needs to be evaluated in external datasets.

Our finding that sodium variation was an important clinical descriptor of early ICU stay could be a biological effect, but it more probably reflects aggressive use of hypertonic saline boluses to treat increased intracranial pressure. Harrois and colleagues identified an association between sodium variability and mortality,[29] and rapid changes in sodium levels can induce osmotic neuronal injury. We postulate that—as an important clinical descriptor of disease trajectories in patients with traumatic brain injury in the ICU—sodium variation is more highly

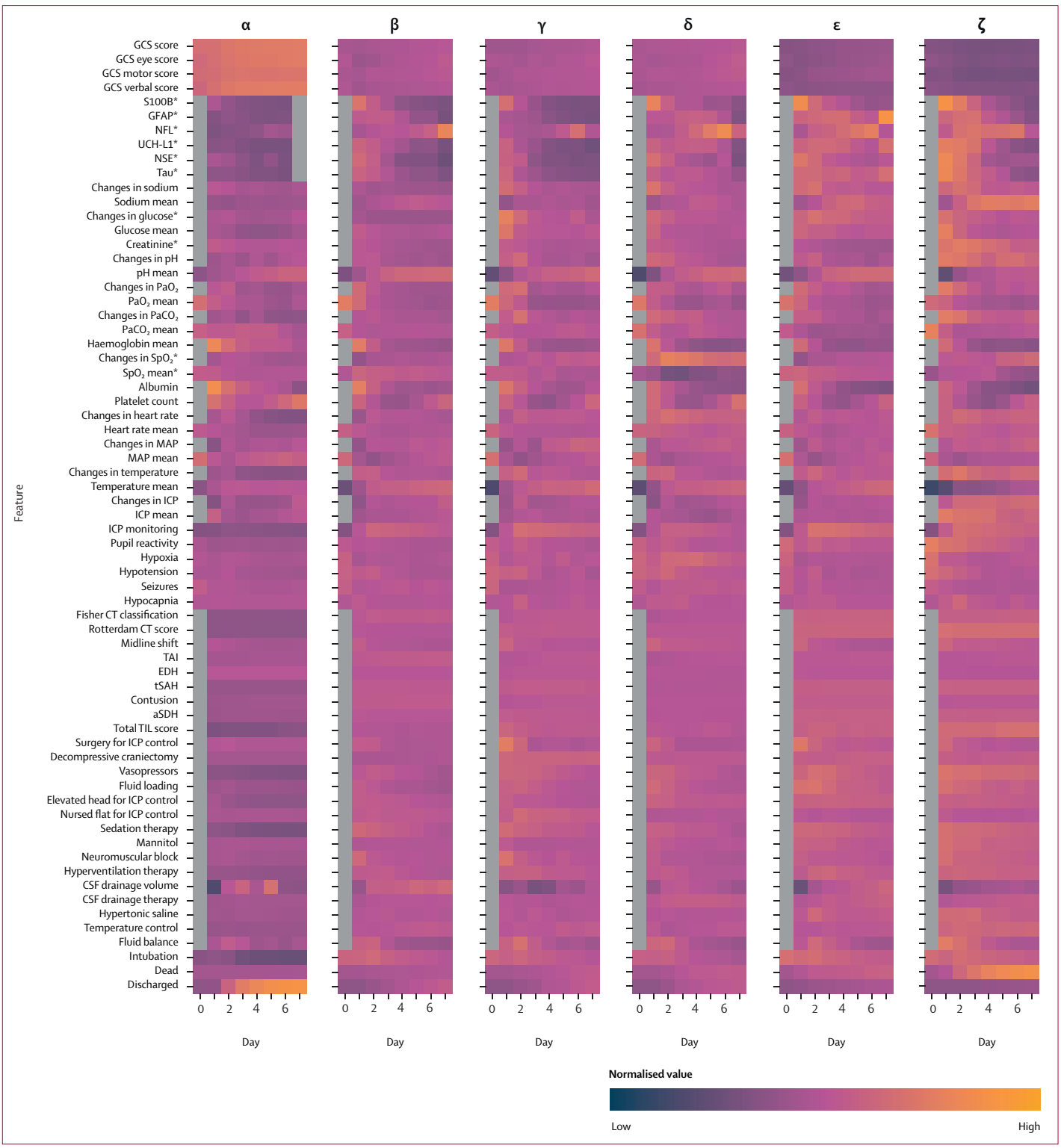

Figure 3: **Distribution of features stratified by trajectory cluster and day**

The features GCS score, dead, and discharged were not included in the clustering but are shown here for reference. All values (x) are normalised to (x-mean[x])/SD, where SD is standard deviation. GCS=Glasgow coma scale. S100B=S100 calcium-binding protein B. GFAP=glial fibrillary acidic protein. NFL=neurofilament light. UCH-L1=ubiquitin carboxy-terminal hydrolase L1. NSE=neuron-specific enolase. PaO_2=arterial partial pressure of oxygen. $PaCO_2$=arterial partial pressure of carbon dioxide. SpO_2=oxygen saturation. MAP=mean arterial pressure. ICP=intracranial pressure. TAI=traumatic axonal injury. EDH=epidural haematoma. tSAH=traumatic subarachnoid haemorrhage. aSDH=acute subdural haematoma. TIL=therapy intensity level. *Indicates the ten features with highest mutual information.

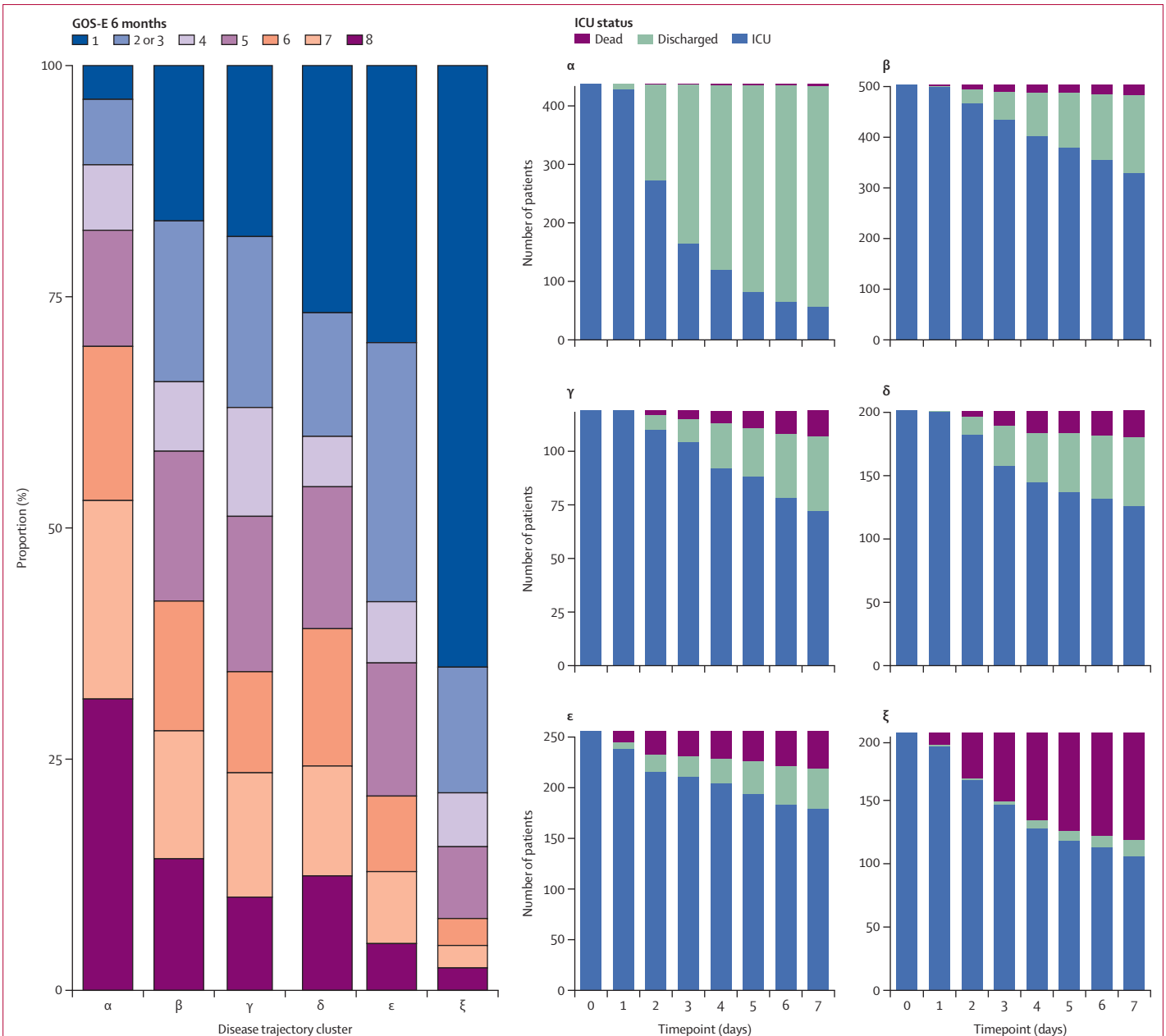

Figure 4: **Distribution of outcomes by disease trajectory cluster**
(A) The bar chart shows the proportion of patients who were assigned to each disease trajectory cluster (α, β, γ, δ, ε, and ζ) according to functional outcome on GOS-E (unfavourable outcome was defined as GOS-E ≤4). Cluster α had the most benign disease trajectory and cluster ζ the most pathological. (B) Plots show, for each disease trajectory cluster, the numbers of patients who were dead, discharged, or still in ICU for the first 7 days after traumatic brain injury. The numbers of patients assigned to each disease trajectory cluster differed. GOS-E=extended Glasgow Outcome Scale. ICU=intensive care unit. (B) In trajectory α, most patients were discharged during the first week of ICU stay. Trajectory ζ had very few patients being discharged alive during the first week, but 42% died during the same period. Trajectory cluster ε had the largest proportion of patients still in ICU 7 days post-injury.

related to treatment intensity than to biological effects. This will require further study to elucidate.

In our clustering model, we did not by design include 6-month outcome as a variable, as it is not defined during the ICU stay and we aimed to explore an unbiased relation of clusters towards outcome. Considering the six disease trajectory clusters that were identified for between-cluster analysis, the most benign disease trajectory (α) had very low mortality, whereas the most severe disease trajectory (ζ) showed high mortality. The cluster indices also greatly improved outcome prediction using canonical IMPACT variables. Thus, our findings suggest that disease trajectory during the first week in ICU is an independent marker

of long-term outcome. This finding is important because early events post-admission are more readily modifiable by therapy and present more tractable targets to improve outcome.

Our clustering model did not definitively specify an optimal number of clusters (disease trajectories). In clustering in general, there is never a guarantee of an optimal number of clusters to exist. For example, in many situations a hierarchy of clusters can be found, whereby each cluster can be further subdivided into smaller clusters, and it is subjective when to stop. Rather than the absolute number of disease trajectories, the most important insights provided by our study relate to the clinical variables that appear to be of importance when describing disease trajectories during the first week of ICU stay in a cohort of patients with traumatic brain injury.

We did a post-hoc analysis to investigate if the CENTER-TBI recruiting site had any effect on patients' assignment to disease trajectory clusters. Cluster and site shared some information, with the mutual information on par with the ninth most important cluster variable, indicating a low impact of site effect on trajectory. The estimate of the mutual information is probably inflated, because there were 54 recruiting centres. Moreover, a site effect would not exclude a biological meaning of the cluster variables. Further explorations by site could form the basis for future comparative effectiveness research and targeted therapeutic approaches.

Our study has several limitations. First, a large proportion of data were missing for several of the clinical descriptors that were included in the analysis (appendix pp 8–14), and it is impossible to be certain that missing data did not bias our results. Data were obtained from the CENTER-TBI observational study and reflect clinical practice. For example, brain biomarkers were more frequently analysed in patients with severe head injury, which is a subgroup of patients with typically longer ICU stays. Moreover, follow-up CT scans were not systematically reported in the version of the CENTER-TBI dataset that we used, and the strategy of last observation carried forward imputation might have underestimated dynamic intracranial pathologies identifiable on CT scans.

A second limitation of our study is that, although our aim was to identify clinical descriptors of disease trajectories during the first week of ICU stay, we included patients with shorter durations of ICU stay (ie, <7 days). This inclusion might have biased the analyses, because patients in the cohort with short stays in the ICU (≤72 h) receive less monitoring of intracranial pressure and less mechanical ventilation.[30] However, as we did not include information on patient discharge into the model—ie, information about why a patient was discharged (dead or discharged to a ward, either as a consequence of being stable enough to not need intensive care or owing to withdrawal of care)—we believe the effect of ICU length of stay is limited. Our analysis strategy provides important information about the behaviour of patients being discharged within 1 week of ICU admission.

Acknowledging these limitations, with our clustering method we identified dynamic disease trajectories in traumatic brain injury during the first week of ICU stay. Although the optimal number of clusters could not be identified, the main clinical descriptors of disease trajectories in this large ICU cohort were highly consistent over a range of cluster numbers. This finding suggests that disease trajectories of traumatic brain injury can, to some extent, be categorised. Importantly, glucose variation and longitudinal brain biomarker profiles were the main clinical descriptors of disease trajectories for traumatic brain injury in the ICU. Membership of a particular disease trajectory cluster was associated with patient outcome, which suggests biological relevance of these parameters. Our results suggest the need for a detailed investigation of the magnitude and mechanisms by which glucose values and variation might affect outcome in traumatic brain injury. Furthermore, serial brain biomarker measurements had substantial discriminating power above other measured variables in this study, indicating that use of serial biomarker measurements could become part of future monitoring plans for patients with traumatic brain injury in the ICU. To prove clinical feasibility, our results need to be validated in external cohorts, and prospective studies are needed to show whether the identified disease trajectories can indicate areas for clinical action. Nevertheless, our findings are a first step towards identification of clinical descriptors of disease trajectories for traumatic brain injury in the ICU, with which future targeted medicine approaches could be identified for this vulnerable patient group and complex disease.

Contributors

All authors verify that they have participated in the concept, design, analysis, writing, or revision of the manuscript, and approved the final manuscript. AH, AE, and DWN were responsible for the primary supervision of the project. NS, DKM, ES, and DWN took part in funding acquisition. NS, ES, PS, AE, DKM, and DWN took part in data collection. CAIÅ, AE, and DWN performed data curation and accessed and verified the underlying data. CAIÅ performed all analyses and prepared the figures and tables. SB took part in figure preparation. AH and CAIÅ wrote the open-source C++ code used for analysis. All authors contributed to interpretation of results and critical review and revision of the manuscript.

Declaration of interests

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Data sharing

CENTER-TBI encourages data sharing, and there is a data sharing statement published online at https://www.center-tbi.eu/data. Researchers can request access to the data by providing a study proposal to CENTER-TBI management committee, which can be submitted online at https://www.center-tbi.eu/data/sharing. Code as used for the

statistical analysis is available at https://git.center-tbi.eu/cecilia/tbi-trajectory-clustering.

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