Unsupervised Clustering in Neurocritical Care: A Systematic Review

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Supplementary table 1 | PRISMA checklist

Supplementary table 2 | Search strings

Supplementary table 3 | Concise description of unsupervised clustering methods employed in neurocritical care studies

Supplementary table 4 | Brief summary of feature selection, clustering parameters, validation, and distance metrics (N = 18)

Supplementary figure 1 | Example of the k-means algorithm

Section and Topic	ltem #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Titlepage
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Supl. Page 5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	4 Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Methods
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Methods
Data collection process	9	9 Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items 10a List and define all outcomes for which data w were sought (e.g. for all measures, time poin		List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Methods
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Methods
Study risk of bias assessment	11	11 Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	no
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Methods
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Methods
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Methods
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	NA
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Methods

Section and Topic	ltem #	Checklist item		
assessment				
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.		
RESULTS				
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Results	
	16b	b Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.		
Study characteristics	17	Cite each included study and present its characteristics.	Table 2	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Methods	
Results of individual studies	Its of 19 For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.		Table 1	
Results of	20a	a For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.		
syntheses	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Results	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA	
Certainty of evidence	22 Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.		NA	
DISCUSSION				
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion	
	23b	Discuss any limitations of the evidence included in the review.	Discussion	
	23c	Discuss any limitations of the review processes used.	Discussion	
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion	
OTHER INFORMAT	TION			
Registration and	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Methods	
protocol	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Methods	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Methods	
Support	25 Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.		Funding info	
Competing interests	26	Declare any competing interests of review authors.	COI statement	
Availability of	vility of 27 Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included		Suppl. Table	

Section and Topic	ltem #	Checklist item	Location where item is reported
data, code and other materials		studies; data used for all analyses; analytic code; any other materials used in the review.	

ABSTRACT Section and Topic	Item #	Checklist item	Reported
TITLE	m		(103/110)
Title	1	Identify the report as a systematic review.	yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	
Synthesis of results	6	Specify the methods used to present and synthesise results.	yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta- analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	yes
Interpretation	10	Provide a general interpretation of the results and important implications.	yes
OTHER	_		
Funding	11	Specify the primary source of funding for the review.	NA
Registration	12	Provide the register name and registration number.	yes

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: <u>http://www.prisma-statement.org/</u>

Supplemental table 2 Search strings				
	Medline	Elsevier	Clarivate	
Platform	PubMed	Scopus	Web of Science	
Date	13.03.2024	13.03.2024	13.03.2024	
Searches				
Search result	367	566	525	
Filter	Classical Article, Clinical Study, Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Multicenter Study, Observational Study, Randomized Controlled Trial, Humans, English.	LIMIT-TO (SUBJAREA, "NEUR") OR LIMIT- TO (SUBJAREA, "COMP")) AND (LIMIT-TO (DOCTYPE, "ar")) AND (LIMIT-TO (LANGUAGE, "English"))	English (Languages) and Article (Document Types)	
Diseases (traumatic brain injury, subarachnoid hemorrhage, intracerebral hemorrhage, acute ischemic stroke, hypoxic brain injury)	tbi traumatic brain injury[MeSH Terms] OR Traumatic brain injury OR head* OR cranial trauma OR closed head injury OR brain trauma OR acquired brain injury OR skull fracture OR intracranial injury OR cerebral trauma OR neurotrauma OR tbi OR acute stroke[MeSH Terms] OR brain bleeding OR subarachnoid OR sah OR stroke OR subarachnoid hemorrhage[MeSH Terms] OR cerebral haemorrhage OR intracerebral haemorrhage[MeSH Terms] OR intracerebral bleed OR intracerebral haemorrhage OR intracerebral hemorrhage OR ich OR cardiac arrest[MeSH Terms] OR cardiac arrest OR anoxic brain injury OR hypoxic encephalopathy OR hypoxic brain OR cerebral infarction OR ischemic brain damage OR acute cerebral ischemia OR ischemic encephalopathy OR cerebral infarction[MeSH Terms] OR acute ischemic stroke OR neuro* OR cerebral* OR brain*	(TITLE-ABS-KEY ((traumatic AND brain AND injury) OR head* OR (cranial AND trauma) OR (closed AND head AND injury) OR (brain AND trauma) OR (acquired AND brain AND injury) OR (skull AND fracture) OR (intracranial AND injury) OR (cerebral AND trauma) OR neurotrauma OR tbi OR (brain AND bleeding) OR subarachnoid OR sah OR stroke OR (intracerebral AND bleed) OR (intracerebral AND haemorrhage) OR (intracerebral AND hemorrhage) OR ich OR (cardiac AND arrest) OR (anoxic AND brain AND injury) OR (hypoxic AND encephalopathy) OR (hypoxic AND brain) OR (cerebral AND infarction) OR (ischemic AND brain AND damage) OR (acute AND cerebral AND ischemia) OR (ischemic AND encephalopathy) OR (acute AND ischemic AND stroke) OR neuro* OR cerebral* OR brain* OR intracerebral OR hemorrhage))	ALL=(traumatic brain injury[MeSH Terms] OR brain trauma OR acquired brain injury OR neurotrauma OR head trauma OR (subarachnoid hemorrhage [MeSH Terms]) OR subarachnoid OR sah OR acute stroke[MeSH Terms] OR intracerebral haemorrhage[MeSH Terms] OR ich OR (cardiac arrest[MeSH Terms]) OR "Cardiac arrest" OR anoxic brain injury OR hypoxic encephalopathy OR (acute cerebral ischemia [MeSH Terms]) OR "acute cerebral ischemia" OR neuro* OR cerebral* OR brain (All Fields))	
Critical care	Critical care [MeSH Terms] OR ICU OR Intensive care OR Critical care OR Intensive care[MeSH Terms]	(TITLE-ABS-KEY ((critical AND care) OR icu OR (intensive AND care)))	ALL=((Critical care [MeSH Terms] OR ICU OR (Intensive care) OR (Critical care) OR Intensive care[MeSH Terms]))	
Clustering	"cluster analysis"[MeSH Terms] OR ("cluster"[All Fields] AND "analysis"[All Fields]) OR "cluster analysis"[All Fields] OR ("cluster analysis"[MeSH Terms] OR ("cluster"[All Fields] AND "analysis"[All Fields]) OR "cluster analysis"[All Fields] OR "clustering"[All Fields] OR "clusterings"[All Fields] OR "cluster"[All Fields] OR "cluster s"[All Fields] OR "clustered"[All Fields] OR "clusterization"[All Fields] OR "clusters"[All Fields] OR "clusterization"[All Fields] OR "clusters"[All Fields]) OR "cluster analysis"[MeSH Terms]) OR "unsupervised" [All Fields]	(TITLE-ABS-KEY ((cluster AND analysis) OR clustering* OR unsupervised))	ALL=((cluster analysis OR clustering* OR (cluster analysis[MeSH Terms]) OR unsupervised))	
Excluding COVID	COVID [MeSH Terms] OR COVID OR SARS-CoV-2	AND NOT (TITLE-ABS-KEY (covid or "sars-cov-2" OR covid-19))	ALL=((COVID OR "SARS-CoV-2" OR COVID-19))	

Supplementary table 3 | Concise description of unsupervised clustering methods employed in neurocritical care studies. There is a wide range of methodological options for clustering data, with each method having various alternative approaches. Hence, the descriptions in this overview concentrate on their (main) application in the included studies.

Hierarchical	Organizes data in a hierarchical or a 'tree' of clusters from small to high similarity between the clusters. The two main types are agglomerative and divisive clustering. For agglomerative clustering, the clustering starts with all datapoints that combine to different clusters during each iteration, whereas divisive clustering starts with one cluster and iteratively divides into more clusters [1].
K-means	K-means computes the shortest distance from each data point to a centroid, representing the center of a cluster. Through an iterative process, the algorithm updates the centroids, adjusting their positions until each data point is closest to its assigned centroid, minimizing the overall distance within clusters.[2]. A detailed description of the methodology is given in Supplementary figure 1.
MOCAIP	The algorithm was developed to extract meaningful ICP-waveform features and uses also hierarchical clustering in two stages. Firstly, ICP-pulses are clustered and averaged (called dominant ICP-pulse). Subsequently, the dominant pulses are again clustered and compared to a reference library containing ICP-pulses in order to remove artefactual ICP-pulses [3].
GBTM	Clusters individuals according to similar trajectories within a population, such as trajectories determined by age or time. Assessing the significance of these trajectories involves examining noticeable differences between groups in comparison to other clinical variables [4].
Probabilistic graph model (Bayesian approach)	Åkerlund et al. performed analyses using probabilistic graph model Bayesian approaches. This method can handle a mix of data formats (discrete and continuous variables) and dealing with missing values [5]. In 2024, they expanded their approach by incorporating a Markov chain to account for the temporal aspect of the data[6].
Spectral clustering	Clustering occurs through the utilization of a similarity matrix, which assigns weights to individual data points in comparison to others. It applies the graph Laplacian matrices and eigenvectors for spectral embedding (i.e., data reduction), and finally, employs a clustering algorithm such as k-means to group the data points in the set number of clusters. Note, other than with k-means, this method allows the identification of clusters with different data structures [7].
Unsupersived Hidden Markov Models	The method approaches data as composed of various hidden (for example hourly) 'states'. It assumes that the observed data is influenced by an underlying process. To identify the underlying processes, probability functions are applied, and the optimization of these probabilities is carried out using an iterative process such as the EM-algorithm, as demonstrated by [8]. During the iterative optimization process, transition and prediction parameters are adjusted to maximize the likelihood of the different states. Note that each state transition depends only on the current state [9].
Kohonen SOM	In essence, high-dimensional data is transformed through a process of iterative training, wherein each data point is mapped onto a two-dimensional grid of vectors (each vector matched the working dimension). This process involves identifying the datapoint with the closest matching vector, then the vector of the nearest and its neighbors' updates direction, and gradually converging the grid to reveal clusters, ultimately providing a simplified, visual representation for identifying patterns in two dimensions [10].
EM = Expectation MOCAIP = Morph	-Maximization; GBTM = Group-Based Trajectory Modeling; ICP = Intracranial Pressure; ological Clustering and Analysis of Intracranial Pressure; SOM = Self-Organizing Maps.

Supplementary table 4 Brief summary of feature Selection, clustering parameters, validation, and distance metrics (N= 18)		
	Kohonen Self Organizing Maps (SOM)	
Nelson et al, 2004 [10]	 Feature selection: input features defined by the authors. The features are eight MD-markers: glucose, lactate, pyruvate, and glutamate from both penumbral and non-penumbral tissues. Number of nodes: 900; the nodes define the dimension of the map into which the data is projected. Deriving number of nodes: the map size was derived by first allocating the first third period of MD-data to a map with different map sizes. These maps were then trained on data from the last third of the MD-period. The performance was measured by a comparison of both results by evaluating if datapoints were allocated to the same patient in both situations. This is expressed as a percentage correct prediction. The optimal separation is the size for which the percentage of correct prediction not changed by increasing map size. Validation: not explicitly reported. Distance metrics: Euclidean distance. 	
Haqqani et al., 2007 [11]	 K-means, Hierarchical Feature selection: ICAT-based differential protein expression analysis using patient serum compared to pooled reference serum. Number of clusters: 16 proteins with a high pattern similarity to S100β or GCS. Deriving number of clusters: not explicitly reported. Internal validation: assessing different distance metrices. Distance metrics: Euclidean distance; Correlation distance-based method. 	
Sorani et al., 2007 [12]	 Hierarchical Feature selection: input features were defined by the authors. The features were selected based on physiological variables captured through continuous monitoring in an ICU setting. Number of clusters: 3 clusters. Deriving number of clusters: the number of clusters was defined by the authors based on the hierarchical clustering results. Validation: not explicitly reported. Distance metrics: not explicitly reported. 	
Kim et al., 2011 [13]	 Morphological Clustering Analysis of ICP Pulse (MOCAIP) (includes hierarchical clustering) Feature selection: the detection of ICP/CBFV pulses. Hierarchical clustering is used within the MOCAIP-algorithm to detect artifact-free pulses and ensure the quality of signal processing. Number of clusters: not explicitly reported. Deriving number of clusters: the Silhouette criterion is used to determine the optimal number of clusters [3]. Validation: not explicitly reported. Distance metrics: Euclidean distance. 	

	Agglomerative hierarchical
Wainwright et al., 2012 [14]	 Feature selection: inclusion of clinical data present in at least 65% of patients. Number of clusters: not applicable. The study did not define a specific number of clusters but instead used clustering to observe groupings of variables between survivors and non-survivors. Deriving number of clusters: not explicitly reported. Validation: not explicitly reported. Distance metrics: not explicitly reported.
	K-means
Kumar et al., 2016 [15]	 Dimensionality reduction: PCA was applied to reduce the dimensionality of the CSF inflammatory markers before starting the clustering analysis. Number of clusters: 2 clusters. Deriving number of clusters: clustering was initially performed with five clusters. However, two clusters contained only one individual each, and another cluster with only four individuals was combined with a larger cluster due to similar mean principal component scores. This resulted in two final clusters for days 0-3. Validation: the cubic clustering criterion was applied to assess the quality of the cluster groups. Distance metrics: Euclidean distance.
	Group-Based Trajectory Modeling (GBTM)
Jha et al., 2018 [16]	 Feature selection: the input features were predefined by the authors, focusing on longitudinal ICP measurements over a 120-hour period post-TBI, along with adjustments for various risk factors such as age, sex, initial GCS, craniectomy, and primary hemorrhage pattern. Number of clusters: six distinct ICP-trajectories Deriving number of clusters: the number of clusters was determined using the Bayesian Information Criterion. The model selection process involved iteratively eliminating non-significant polynomial terms to achieve the simplest final model where each trajectory group was significant at α=0.05. Validation: not explicitly reported. Distance metrics: not applicable for this method, as GBTM is based on a probabilistic modeling approach rather than distance metrics.
	Hidden Markov Models (HMM)
Asgari et al., 2019 [8]	 Feature selection: input features were defined by the authors and included hourly averaged values of ICP, CPP, RAP, and PRx. Number of clusters: three states (poor, intermediate and good state). Deriving number of clusters: pre-defined by the authors. Internal validation: assessment of the physiological relevance of the derived states such as assessing whether the states were statistically different in terms of the physiological variables, and whether the time spent in these states correlated with patient outcomes. Distance metrics: not applicable for this method, as HMM is a probabilistic model that does not rely on distance metrics.

	Hierarchical			
Eiden et al., 2019 [17]	 Feature selection: the input metabolites were selected based on the authors' criteria and supported by literature. Number of clusters: 2 metabolic states. Deriving number of clusters: the hierarchical tree's first branch divided the data into two clusters, interpreted as two distinct metabolic states. External validation: the findings were validated in a cohort of 12 patients. Distance metrics: not explicitly reported. 			
	Hierarchical			
Gradisek et al., 2021 [18]	 Feature selection/ dimensionality reduction: The LASSO method was used to select proteins associated with TBI-related variables such as the worst mGCS score. From the initial 107 biomarkers, 21 proteins were selected by three LASSO models, and 6 biomarkers (3 glial proteins and 3 cytokines) were ultimately identified as most relevant and used as input for the clustering analysis. Number of clusters: 3 clusters. Deriving number of clusters: not explicitly reported. Validation: not explicitly reported. 			
	Historechical			
Lindblad et al., 2021 [19]	 Feature selection/ dimensionality reduction: the study calculated the CSF/serum ratio and included significant ratios for clustering. Specifically, proteins were included in the clustering analysis if the CSF/serum-ratio was significantly correlated with the albumin quotient, which is a marker of blood-brain barrier integrity. Number of clusters: 3 clusters in CSF; not explicitly reported for serum, but it can be deduced from Figure 3 that the authors found 2 clusters. Deriving number of clusters: selected hierarchical tree's branch as the number of clusters. Validation: validation was performed in a non-matched TBI cohort using serum samples only. Distance metrics: not explicitly reported. 			
	Morphological Clustering and Analysis of ICP (MOCAIP) (includes hierarchical clustering) K-means			
Megjhani et al. 2021 [20]	 Feature selection: hierarchical clustering is used within the MOCAIP-algorithm to detect artifact-free pulses [3]. Number of clusters: k-means identified 20 clusters; hierarchical clustering results were not explicitly reported. Deriving number of clusters: not explicitly reported. Validation: not explicitly reported. Distance metrics: dynamic time warping was used as the distance metric for k-means clustering; Euclidean distance for hierarchical clustering [3]. 			

	Spectral clustering, k-means		
Narula et al., 2021 [21]	 Feature selection: EEG-data was split into 2-second windows, followed by the calculation of a covariance matrix for each window. Number of clusters: 2 clusters were identified, representing "burst" and "suppression". Deriving number of clusters: the authors explicitly defined 2 clusters (burst and suppression). Clustering was applied to each 2-second data window using the similarity matrix to segregate into these 2 clusters. Validation: the algorithm's performance was validated by comparing its results with ground truth annotations (manually labeled bursts and suppressions) and a supervised deep convolutional neural network. Distance metrics: Riemannian distance metric was used for the similarity matrix based on covariance matrices. 		
	Probabilistic Graph Model (Bayesian Approach)		
Åkerlund et al., 2022 [5]	 Feature selection/ dimensionality reduction: input features were defined by the authors. Based on clinical interest and known outcome predictors, particularly those with known or plausible relationships with outcome or deranged physiology. Number of clusters: 6 clusters. Deriving number of clusters: the number of clusters was determined using a stability-based approach [22]. Models with 3 to 15 clusters were created, and the optimal number was identified by evaluating the CSI across multiple iterations. The optimal clustering was defined as the number of clusters with the highest median CSI after adjusting for the number of clusters. Internal validation: internal stability was assessed by repeating the clustering process with different random initializations and evaluating the consistency of cluster assignments. Distance metrics: not applicable. The method used a mixture of probabilistic graph models that account for the relationships between features without relying on traditional distance metrics. 		
	K-means, Divisive/Agglomerative hierarchical		
Boos et al, 2022 [23]	 Feature selection: input features were defined by the authors, based on clinical and radiologic variables that had sufficient interrater reliability (k > 0.6). Number of clusters: 2 clusters. Deriving number of clusters: the optimal number of clusters (2 clusters) was determined using the Silhouette criterion and the gap statistic method for k-means. This number was used as the level in the hierarchical tree Validation: the authors compared the results produced by the three clustering algorithms and with the presence of a clinical "triad" to validate the robustness of the clusters. Distance metrics: Gower's method. 		
	Agglomerative hierarchical		
Rajagopalan et al., 2022 [24]	 Feature selection: input features were defined by the authors. The study included variables such as HR, MAP, ICP, brain tissue oxygenation, and cerebral MD (glucose, lactate, and pyruvate). Number of clusters: 4 clusters. Deriving number of clusters: the number of clusters was derived using the Caliński-Harabasz pseudo-F index. The index was calculated for groupings between 2 to 10 clusters, with the optimal number being 4 clusters. Internal validation: the stability of the clusters was assessed by comparing them with clusters derived using k-means clustering. 		

	Distance metrics: Euclidean distance.				
	K-means				
Satar et al., 2022 [25]	 Feature selection: the study calculated seven spectral features for the analysis: spectral centroid, spectral entropy, spectral flux, energy, energy entropy, zero crossing rate, and spectral roll-off. Number of clusters: 2 clusters. Deriving number of clusters: either hypoxic brain injury or no hypoxic brain injury. Internal validation: the clusters were validated using the Calinski-Harabasz index and the Rand index. Distance metrics: Euclidean distance. 				
-	Probabilistic Graph Model (Bayesian Approach) with a Markov chain extension				
Åkerlund et al. 2024 [6]	 Feature selection: mutual information was computed to determine the importance of each feature in differentiating clusters. The most important features that best explained the differences between the patient groups (clusters) were then selected. Number of clusters: 6 clusters. Deriving number of clusters: the optimal number of clusters was identified using the EM-algorithm in combination with the CSI. Validation: internal stability was assessed by repeating the clustering process with different random initializations and evaluating the consistency of cluster assignments Distance metrics: not applicable for this method, as the method does not rely on a distance metrics. 				
A brief sum defined by before inclu analyzing c methods w between da CBFV = Ce CSI = Clus	imary of (I) study feature selection/dimensionality reduction methods. The feature selection can be the authors, that means that the collected data is not prepared like computing or deriving measures uding the data in the clustering analysis; (II) the number of clusters, which were either configured before or set based on the results; (III) how the number of clusters were determined; (IV) which validation ere applied both internal and/or external; (V) the distance metric, which is used to calculate the distance ata points and cluster centers. This is not required for every methodology. erebral Blood Flow Velocity; CPP = Cerebral Perfusion Pressure; CSF = Cerebrospinal Fluid ter Similarity Index; CT = Computer Tomography; EM-algorithm = Expectation-Maximization Algorithm;				
GCS = Glasgow Coma Scale; GBTM = Group-Based Trajectory Modelling; HMM = Hidden Markov Models; HR = Heart Rate; ICAT-based = Isotope-Coded Affinity Tag ; ICP = Intracranial Pressure; ICU = Intensive Care Unit; LASSO = Least Absolute Shrinkage and Selection Operator ; MAP = Mean Arterial Blood Pressure MD = Microdialysis; MOCAIP = Morphological Clustering and Analysis of Intracranial Pressure; PCA = Principal Component Analysis; PRx = Pressure Reactivity Index; RAP = The correlation coefficient (R) between mean pulse amplitude (A) and mean intracranial pressure (P); SOM = Self-Organizing Maps. TBI = Traumatic Brain Injury.					



Supplementary figure 1 | Example of k-means algorithm. First, the datapoints are projected into an n-dimensional space where n depends on the number of input variables. Centroids (clustering centers) are randomly assigned to the dataset [26]. Datapoints are colored white, as they have not been yet assigned to a cluster (sub-figure I). In the next step, the distance between each datapoint and the centroid is computed. In the current example the Euclidean distance formula is used, but there are alternative distance metrics such as cosine distance, dot product etc.[27]. Once each datapoint has been assigned to a cluster (either cluster 1 or 2 in the current example), the centroids update its position to the average value within that cluster (sub-figure III). Due to the relocation of the centroids, the shortest distance to the nearest centroid changed for some datapoints (sub-figure IV and V). Therefore, the shortest distance between each datapoint and the centroids is computed again, resulting in two datapoints moving from cluster 2 to cluster 1 (sub-figure V). This iteration process (II -V) continues until the distance from each datapoint to a centroid is shortest and the centroids are the center of each cluster. The result is that the datapoints within each cluster are more related to each other than the datapoints between the clusters. This allows the characteristics of the patients within each cluster to be compared. For example, Cluster 1 includes patients with a low mortality and young age and cluster 2 patients with a high mortality and higher age. Various alternative models and parameter settings have been studied. The Figure is adapted from [28]. The methodologies applied in the included studies are briefly described in Supplementary file 1, table 3. The selected parameter settings within the studies are reported in Supplementary file 1, table 4.

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