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PATHOPHYSIOLOGICAL CHARACTERIZATION OF TRAUMATIC BRAIN INJURY USING NOVEL ANALYTICAL METHODS

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Pathophysiological characterization of traumatic brain injury using novel analytical methods

Thesis for Doctoral Degree (Ph.D.)

By

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To Marcus, Edith and Esther.

Popular science summary of the thesis

Traumatic brain injury (TBI) is one of the leading causes of death and disability worldwide. Historically it has been a young man's disease, acquired often from road traffic incidents. However, as the population is ageing and road traffic safety has improved, injury is increasingly related to falls. The group of patients with TBI is diverse, with differences in age, background, and injury patterns.

The most severely injured patients are treated in highly specialized neurointensive care units, where they are extensively monitored with both brain-specific and general physiological monitoring. Patients receive advanced treatments to avoid insults such as increased intracranial pressure (ICP) and hypoxia, which can worsen the acquired brain injury. Current guidelines advocate avoiding ICP above a fixed threshold of 22 mmHg, but how long a high ICP can be tolerated has not been determined. Treatment recommendations to avoid aggravating the brain injury and improve outcomes in patients with TBI are often consensus-based; it is difficult to study the effects of single treatments when in practice, they are not applied in isolation, and treatments may need to be individualized in this diverse group of patients.

The overall aim of this thesis is to investigate patterns of disease in patients with traumatic brain injury. Therefore, we have studied patients admitted to an intensive care unit (ICU) with TBI. All patients were included in the Collaborative European neurotrauma effectiveness research in TBI (CENTER-TBI) study, the largest observational study in TBI to date, including over 2,000 patients from 19 countries admitted to the ICU with TBI. We applied novel analytical methods of clustering and causal inference.

In **study I**, we investigated the impact of ICP and its duration on outcome. We found a variation in tolerable levels and duration, where lower ICP was tolerated for longer durations than higher ICP. In addition, a higher dose of intracranial hypertension (defined as "pressure time dose") was correlated with worse outcome. Our results suggest that the tolerability of increased ICP is lower if the brain's ability to autoregulate blood flow is impaired. In **study IV**, we investigated the causal relationship of ICP, autoregulation, treatments, and associated factors. We identified a causal relationship between cerebrovascular autoregulation and outcome, and ICP lowering therapies towards outcome. No direct relationship between ICP and outcome was identified.

In **study II and III**, we used an unsupervised clustering method to identify subgroups of patients with TBI in the ICU. In **study II**, six distinct clusters were found. In summary, the clusters could be interpreted by clinical neurological presentation and factors related to metabolism and kidney injury. In **study III** we investigated clinical trajectories during the first week of ICU. We could not identify a distinct best number of trajectories, but the most important distinguishing factors between trajectories were almost identical regardless of number of clusters, with glucose variation and brain injury biomarkers being most prominent. Although no information on outcome was included in the clustering, the clusters and

trajectories all showed different outcome profiles, suggesting that they reflect biological processes associated with traumatic brain injury.

Populärvetenskaplig sammanfattning

Traumatiska hjärnskador (TBI) är en av de ledande orsakerna till död och sjukdomsbörda globalt. Historiskt sett har främst unga män varit drabbade, som skadats i trafikolyckor. I takt med att trafiksäkerheten förbättras och befolkningen åldras skadas allt fler genom fallolyckor. Det har lett till en alltmer blandad grupp av patienter som drabbas av TBI, med skillnader i ålder, bakgrund och skademönster.

De svårast skadade patienterna vårdas på högspecialiserade neurointensivvårdsavdelningar, med noggrann övervakning av till exempel blodtryck, syresättning i blod och i hjärnan, intrakraniellt tryck (ICP) och hjärnans metabolism. Här ges även avancerad behandling för att undvika ytterligare skada på hjärnan av till exempel förhöjt ICP och syrebrist. Enligt nuvarande rekommendationer ska ICP över 22 mmHg undvikas, men hur länge hjärnan tolererar höga tryck har inte studerats lika väl. Behandlingsrekommendationer för TBI är ofta konsensus-baserade: Det är svårt att studera effekten av enskilda behandlingar eftersom de ofta används i kombination med varandra och många studier har varit negativa, kanske på grund av att det är svårt att hitta behandlingar som fungerar lika bra på alla patienter i den heterogena gruppen av TBI-patienter, och en mer individualiserad behandlingsstrategi behövs.

Det övergripande målet med denna avhandling är att beskriva sjukdomsmönster hos patienter med TBI som vårdas på en intensivvårdsavdelning (IVA). Studierna är gjorda på patienter som inkluderats i den största observationella TBI-studien hittills, multicenter-studien ”Collaborative European neurotrauma effectiveness research in TBI” (CENTER-TBI). Över 2000 patienter med TBI och som vårdats vid en intensivvårdsavdelning från 19 europeiska länder har inkluderats. Vi har använt moderna analytiska metoder såsom klustring och kausalitetsmetoder för att studera orsakssamband i observationell data.

I **studie I** undersöktes påverkan på utfall av ICP, både absoluta tryckniåver och durationer. Vi fann en variation av tryckgränser som var associerade med sämre utfall. Lägre tryck tolererades längre perioder än höga tryck. Vi fann även att en högre dos av ICP var korrelerat till sämre utfall, framför allt om hjärnans förmåga till reglering av blodflödet (autoreglering) var nedsatt. I **studie IV** undersökte vi orsakssamband mellan ICP, autoreglering, ICP-sänkande behandlingar och relaterade faktorer, och utfall. Vi fann ett direkt orsakssamband mellan autoreglering och utfall, men inte mellan ICP och utfall. Resultaten tyder på att intrakraniella tryckstegringar tolereras sämre om autoreglering är nedsatt, och att autoregleringen visar ett starkare orsakssamband mot utfall än tryckstegringar i sig.

I **studie II och III** användes en klustringsmetod för att identifiera subgrupper av patienter med TBI på IVA. I **studie II** hittade vi sex distinkta kluster. Dessa kan sammanfattningsvis tolkas utifrån medvetandegrad och faktorer relaterade till metabolismen och njurpåverkan. I **studie III** undersöktes sjukdomsförlopp under första veckan på IVA. Hur många olika förlopp som förekommer kunde vi inte fastställa i analysen, men oavsett antal olika förlopp var glukosvariation och hjärnskademarkörer mätta över tid viktiga faktorer i modellerna, oavsett antal förlopp. Trots att ingen information om utfall inkluderades i modellerna visade klustren

och sjukdomsförloppsbanorna tydliga skillnader i utfall, vilket tyder på att de reflekterar biologiska processer.

Abstract

Severity of traumatic brain injury is usually classified by Glasgow coma scale (GCS) as “mild”, "moderate" or "severe’, which does not capture the heterogeneity of the disease. According to current guidelines, intracranial pressure (ICP) should not exceed 22 mmHg, with no further recommendations concerning individualization or tolerable duration of intracranial hypertension. The aims of this thesis were to identify subgroups of patients beyond characterization using GCS, and to investigate the impact of duration and magnitude of intracranial hypertension on outcome, using data from the observational prospective study Collaborative European neurotrauma effectiveness research in TBI (CENTER-TBI).

To investigate the temporal aspect of tolerable ICP elevations, we examined the correlation between dose of ICP and outcome represented by 6-month Glasgow outcome scale extended (GOSE). ICP dose was represented both by the number of events above thresholds for ICP magnitude and duration and by area under the ICP curve (i.e., “pressure time dose” (PTD)). A variation in tolerable ICP thresholds of 18 mmHg +/- 4 mmHg (2 standard deviations (SD)) for events with duration longer than five minutes was identified using a bootstrapping technique. PTD was correlated to both mortality and unfavorable outcome.

A cerebrovascular autoregulation (CA) dependent ICP tolerability was identified. If CA was impaired, no tolerable ICP magnitude and duration thresholds were identified, while if CA was intact, both 19 mmHg for 5 minutes or longer and 15 mmHg for 50 minutes or longer were correlated to worse outcome. While no significant difference in PTD was seen between favorable and unfavorable outcome if CA was intact, there was a significant difference if CA was impaired. In a multivariable analysis, PTD did not remain a significant predictor of outcome when adjusting for other known predictors in TBI. In a causal inference analysis, both cerebrovascular autoregulation status and ICP-lowering therapies represented by the therapy intensity level (TIL) have a directional relationship with outcome. However, no direct causal relationship of ICP towards outcome was found.

By applying an unsupervised clustering method, we identified six distinct admission clusters defined by GCS, lactate, oxygen saturation (SpO_2), creatinine, glucose, base excess, pH, $PaCO_2$, and body temperature. These clusters can be summarized in clinical presentation and metabolic profile. When clustering longitudinal features during the first week in the intensive care unit (ICU), no optimal number of clusters could be seen. However, glucose variation, a panel of brain biomarkers, and creatinine consistently described trajectories. Although no information on outcome was included in the models, both admission clusters and trajectories showed clear outcome differences, with mortality from 7 to 40% in the admission clusters and 4 to 85% in the trajectories. Adding cluster or trajectory labels to the established outcome prediction IMPACT model significantly improved outcome predictions.

The results in this thesis support the importance of cerebrovascular autoregulation status as it was found that CA status was more informative towards outcome than ICP magnitude and duration. There was a variation in tolerable ICP intensity and duration dependent on whether

CA was intact. Distinct clusters defined by GCS and metabolic profiles related to outcome suggest the importance of an extracranial evaluation in addition to GCS in TBI patients. Longitudinal trajectories of TBI patients in the ICU are highly characterized by glucose variation, brain biomarkers and creatinine.

List of scientific papers

I. **Impact of duration and magnitude of raised intracranial pressure on outcome after severe traumatic brain injury: A CENTER-TBI high-resolution group study.** Åkerlund CA, Donnelly J, Zeiler FA, Helbok R, Holst A, Cabeleira M, Güiza F, Meyfroidt G, Czosnyka M, Smielewski P, Stocchetti N, Ercole A, Nelson DW. *PLoS ONE*. 2020;15(12 December):1-20.

II. **Clustering Identifies Endotypes of Traumatic Brain Injury in an Intensive Care Cohort: A CENTER-TBI Study.** Åkerlund, Cecilia A I, Anders Holst, Nino Stocchetti, Ewout Steyerberg, David K Menon, Ari Ercole, David W Nelson, and CENTER-TBI Participants and investigators. *Critical Care* 26, no. 228 (07 2022): 1–15.

III. **Clinical trajectory subphenotypes of severe traumatic brain injury: The importance of protein biomarkers and glucose variation – a CENTER-TBI study.** Åkerlund CAI, Holst A, Bhattacharyay S, Stocchetti N, Steyerberg EW, Smielewski P, Menon DK, Ercole A, Nelson DW.

Submitted manuscript under revision

IV. **Causal relationships of intracranial pressure, cerebrovascular reactivity, interventions, and outcome in severe traumatic brain injury – a CENTER-TBI high-resolution sub-study.** Åkerlund CAI, Holst A, Beqiri E, Placek M, Smielewski P, Ercole A, Nelson DW.

Manuscript

Contents

List of abbreviations

ABP	Arterial blood pressure
ADH	Antidiuretic hormone
APACHE	Acute Physiologic and Chronic Health Evaluation
BBB	Blood brain barrier
BE	Base Excess
BTF	Brain Trauma Foundation
CA	Cerebrovascular autoregulation
CBF	Cerebral blood flow
CCA	Complete case analysis
CDE	Common data elements
CENTER-TBI	Collaborative European neurotrauma effectiveness research in TBI
CI	Confidence interval
CPP	Cerebral perfusion pressure
CRASH	Corticosteroid Randomization After Significant Head Injury
CRF	Case report form
CT	Computed tomography
DC	Decompressive craniectomy
DCTF	Data curation task force
dHP	Duration of severe hypoperfusion
ECG	Electrocardiography
EDH	Epidural Hematoma
EVD	External ventricular drain
GBTM	Group-based trajectory model
GCS	Glasgow outcome scale
GOSE	Glasgow outcome scale extended
HR	Heart rate
ICP	Intracranial pressure
ICU	Intensive care unit
IMPACT	International Mission on Prognosis And Clinical Trial

IQR	Interquartile range
LLA	Lower limit of autoregulation
LOCF	Last observation carried forward
MAR	Missing at random
MCAR	Missing completely at random
MNAR	Missing not at random
MI	Mutual information
MICE	Multiple imputation by chained equations
OR	Odds ratio
$PaCO_2$	Arterial partial pressure of carbon dioxide
PAM	Partitioning around medoids
PaO_2	Arterial partial pressure of oxygen
PRx	Pressure reactivity index
PTD	Pressure time dose
RCT	Randomized controlled trial
RTI	Road traffic incident
SAH	Subarachnoid hemorrhage
SD	Standard deviation
SDH	Subdural hematoma
SpO_2	Oxygen saturation
TBI	Traumatic brain injury
TCD	Transcranial doppler
TIL	Therapy intensity level
tSAH	Traumatic subarachnoid hemorrhage
ULA	Upper limit of autoregulation
WSS	Within-cluster sum of squares
XGBoost	eXtreme Gradient Boosting

1 Introduction

Traumatic brain injury (TBI) is said to be one of the most complex diseases in the body's most complex organ.[1] With an estimated 82,000 TBI-related deaths and 2.1 million hospital discharges in Europe alone in 2012, TBI is a major contributor to mortality and morbidity world-wide, with large between-countries differences.[2,3] Historically, TBI has been the young man's injury, with road traffic incidents (RTI) as the most common cause. Although men still constitute almost two thirds of the patients and are mostly injured in RTIs, an increasing portion of the patients are older women with fall injuries, likely due to an ageing population.[2,4,5]

The most severely injured patients are treated in highly specialized neurointensive care units, where both brain-specific and general physiologic parameters are extensively monitored to guide treatment as to avoid secondary brain injury. Treatment and monitoring recommendations are mostly supported by consensus recommendations as evidence is generally weak.[3,5,6] In fact, only 23% of the randomized controlled trials (RCTs) in the field have generated positive results, where some interventions even have shown to be harmful.[7,8] A commonly hypothesized reason for this is the lack of a proper sub-classification of TBI patients based on pathoanatomical properties, but on broad symptomatology. Such sub-classifications may have potential to act as inclusion criteria in TBI clinical trials and pave the way to more successful RCTs.[3,9,10]

One such initiative towards a refined classification is the Collaborative European Neurotrauma Effectiveness Research in TBI (CENTER-TBI), a large European multinational prospective observational study including more than 4,500 patients across all severities of TBI.[11] This thesis consists of four sub-studies in CENTER-TBI, with focus on patients in the intensive care unit (ICU) stratum. The aims of the studies are to characterize TBI patients beyond GCS and to investigate the impact of intracranial hypertension and associated physiology towards outcome.

2 Literature review

2.1 TBI classifications and outcome predictions

TBI is broadly defined as "an alteration in brain function, or other evidence of brain pathology, caused by an external force".[12] While TBI is often considered a single type of injury, it encompasses a wide range of injury mechanisms and pathophysiological patterns. More than 100 different TBI prognostic models are available.[13] Which one to use depends on the purpose – outcome prediction, severity stratification or surgical management. Age and Glasgow coma scale (GCS) are consistently identified as the most important predictors for outcome. Classifying TBI by mechanism of injury such as blunt, penetrating, or blast trauma can be valuable when considering whether the patient requires surgery or not, but does not contain much information about the actual injury.[10] Focal or diffuse injury stratification, as seen on computed tomography (CT), might be useful for early clinical management, such as surgery.

Disease severity is commonly classified by GCS, where 13-15 is classified as mild, 9-12 as moderate and 3-8 as severe TBI,[9,14] GCS is a clinical scale introduced almost fifty years ago, where eye opening, motor response and verbal response are scored. It has been criticized for not reflecting the pathoanatomical or physiological component of brain injury and can be confounded by other factors such as intubation, sedation, alcohol, or drug abuse.[15] In addition, there is an increased awareness of a substantial morbidity burden in patients with mild TBI (GCS 13-15), where a significant proportion of patients do not fully recover six months post-injury.[4,5] Despite these limitations, GCS is still one of the strongest predictors of outcome, and has shown a good inter-rater reliability even in relatively inexperienced clinicians.[10,16]

2.1.1 CT classifications

To capture the intracranial pathology in TBI, multiple CT models have been developed during the last thirty years. The first model was the Marshall CT classification, developed in the early 1990's. It classifies diffuse and mass lesions into six classes: Diffuse injury grade I-IV based on degree of cistern compression and magnitude of midline shift and evacuated vs. non-evacuated mass lesion. It is commonly used to describe patients with diffuse brain injuries and has been shown to correlate to intracranial pressure and outcome.[17] Major drawbacks of the Marshall CT include not integrating information about traumatic subarachnoid hemorrhage (tSAH), which is strongly associated with worse prognosis, and not discriminating between different types of intracranial lesions.[10,17] The Rotterdam CT score is a refinement of the Marshall CT classification, where compression of basal cisterns, presence of midline shift, epidural mass lesion and presence of intraventricular blood or subarachnoid hemorrhage are considered.[17,18] The Stockholm CT score developed in 2010 has been shown superior to both Rotterdam and Marshall CT models. It uses information about midline shift in millimeters, subarachnoid hemorrhage/intraventricular hemorrhage, presence of epidural hematoma, diffuse axonal injury and subdural hematoma to predict outcome.[19,20] In 2014, Raj *et al.* developed the Helsinki CT score which, like the Stockholm score, better predicts outcome than

the Marshall and Rotterdam CT models.[21] However, only patients with intracranial lesions on admission CT were included in the development of the model, limiting its generalizability.

2.1.2 Outcome prediction models

Yet another approach to TBI classification is by outcome prognosis. Models such as IMPACT and CRASH have been developed for predictions of mortality and unfavorable outcome.[13,16] The CRASH model uses information about age, GCS, pupillary reactivity, and major extracranial injury to predict outcome in the full spectrum of TBI patients, with an extended model adding characteristics on CT.

The most used outcome prediction model is the IMPACT model. It was developed in 2008 using data from eleven prospective studies of patients with moderate and severe TBI.[16] Patient characteristics available in the first few hours post-injury (including pre-injury features) were considered as predictors and included based on the importance determined by Nagelkerke's R^2 in multivariable analysis. Three models with increasing complexity and prognostic ability were developed: The core, extended and lab models. The three strongest outcome predictors were included in the core model: GCS motor score of 2 (extension at painful stimulus) (odds ratio (OR) 7.2, 95% confidence interval (CI) 6.3-8.3), compared to GCS motor score 5-6 (localizes/obeys pain); absence of pupillary reactivity (OR 5.9, 95% CI 5.3-6.6); and age (OR 2.2, 95% CI 2.0-2.3) in univariate analyses. The additional predictors included in the extended model are the Rotterdam CT score, secondary insults of hypoxia and hypotension, tSAH and epidural hematoma (EDH), with the addition of glucose and hemoglobin in the lab model. The IMPACT model showed good external validity in a sub-population with severe TBI in the CRASH trial mentioned above.

More recently, the IMPACT model has been shown to overestimate the mortality risk,[4,22] but work on updating the model is ongoing (personal communication, E Steyerberg). Nonetheless, it is still regarded gold standard in outcome predictions in TBI and added value of other predictors such as APACHE II, biomarkers and coagulation factors has been evaluated.[23–25] By addition of brain biomarkers to the IMPACT extended model, a relative increase in Nagelkerke's R^2 of 48 to 65% was seen in the CENTER-TBI cohort.[23]

In a recent study, mortality predictions using different methodological approaches were made in the CENTER-TBI China Registry cohort.[26] Performance of models using logistic regression, LASSO regression, support vector machines (SVM), and XGBoost models were developed and validated in the CENTER-TBI European Registry cohort. The machine learning method XGBoost was found to outperform the other models. However, after reducing the number of included features, the difference between the other models was eliminated.

2.2 Intracranial pressure

One of the most central physiologic parameters in neurocritical care is intracranial pressure. According to the Monro-Kellie doctrine, the intracranial compartment space can be seen as a closed volume, where the sum of the volumes of cerebral blood, cerebrospinal fluid (CSF) and the brain is constant. If any of the volumes increase, compensatory mechanisms such as displacement of venous blood or CSF must occur to keep ICP within normal range (0-10 mmHg). When these mechanisms are not sufficient, the ICP will be raised, eventually leading to neuronal injury, herniation and brain death.[27]

The Brain Trauma Foundation (BTF) guidelines state that ICP intensities above 22 mmHg should be treated, a recommendation based on one study,[27,28] and in Europe, most centers employ 20 mmHg as a treatment threshold.[29] Recent work has shown that thresholds might be individualized, and tolerable ICP levels might depend on the duration of the elevation and the cerebrovascular autoregulation status.[30–32] Therefore, ICP should be interpreted in the context of related factors, such as cerebrovascular autoregulation and cerebral perfusion pressure (CPP).

2.2.1 The ICP dose concept

In current guidelines, the temporal aspect of ICP elevations is overlooked. Duration thresholds for ICP elevations have been investigated, and a trend is seen towards a better tolerability of lower pressures for longer durations. However, proposed cutoffs vary between studies: Güiza *et al.* suggested 35 mmHg for 5 minutes or 20 mmHg for 37 minutes in a multi-center study,[30] and Donnelly suggested 20 mmHg for 13 minutes in a single-center study.[33]

Another way of measuring ICP dose is by calculating area under the ICP curve above different thresholds, generating a “pressure time dose” (PTD). The dose above different thresholds has been associated with worse outcome in several studies, both in TBI and in subarachnoid hemorrhage.[34–36]

2.2.2 Cerebrovascular autoregulation

Cerebrovascular autoregulation (CA) is essential for survival. In this thesis we recognize it as the mechanism of maintaining cerebral blood flow (CBF) constant within wide ranges and changes in CPP by rapid regulation of resistance of the cerebral vasculature (Figure 1A). Ranges of CPP outside the lower and upper limits of autoregulation (LLA and ULA) will lead to changes in CBF. CPP below LLA will lead to a sharp decrease in CBF leading to hypoperfusion and ischemia, while CPP above ULA may lead to brain edema and blood brain barrier (BBB) disruption.[37] Although different techniques such as intraparenchymal flow meters and transcranial doppler can measure CBF continuously, their implementation is not always feasible. The state of cerebrovascular autoregulation can be assessed by the pressure reactivity index (PRx), a measure of how much a fluctuation in arterial blood pressure (ABP) leads to changes in ICP. It is calculated as the moving correlation coefficient (ranging from -1 to 1) of ABP and ICP, typically in thirty consecutive 10-second averages.[38,39] Longer time

periods of up to 20 minutes have been suggested as well and shown to correlate to outcome.[40–42] In a healthy brain, the correlation between ABP and ICP is negative, while, in case of brain injury, increases in ABP can lead to increases in ICP, i.e., a positive PRx (Figure 1B). PRx values of +0.2 or +0.3 are commonly used as thresholds for impaired autoregulation, as these have been found to correlate with worse outcome.[28,31,38,39]

Even though PRx is defined, in part, by ICP, the relationship between PRx and ICP is not fully understood. Elevated ICP has been shown to correlate to impaired CA.[38] A retrospective single-center study summarizing data from the past twenty-five years showed a significant decrease in average ICP over time (19 to 12 mmHg), but no change in PRx,[43] suggesting some degree of independence between PRx and ICP. The unresponsiveness to ICP-lowering treatments has been demonstrated,[44,45] and the burden of impaired CA has been shown greater than ICP, CPP and brain tissue oxygen ($PbtO_2$) derangements in moderate/severe TBI.[37] Yet, there are no recognized treatments for impaired CA, and studies have not been able to show relationships between commonly used medications such as sedatives and vasopressors.[46,47]

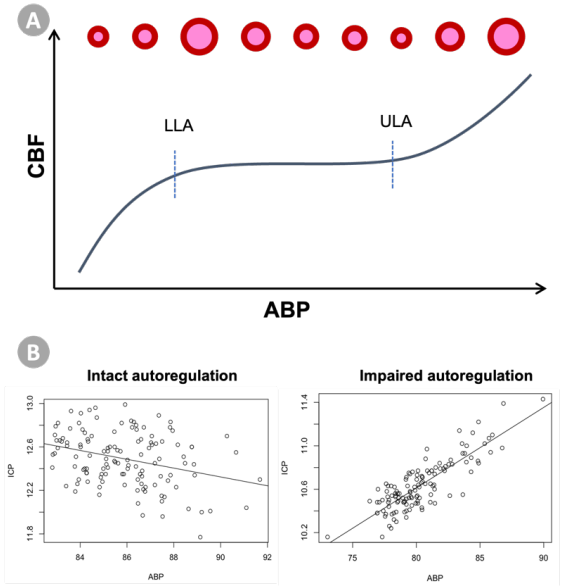

Figure 1: A. Lassen's curve which describes the relationship between mean arterial blood pressure (ABP) and cerebral blood flow (CBF). Between the lower limit of autoregulation (LLA) and upper limit of autoregulation (ULA), the blood flow is approximately constant. Below LLA, CBF decreases, which can lead to hypoperfusion and ischemia, while above ULA CBF increases, which can lead to brain edema and blood barrier disruption. **B. Pressure reactivity index (PRx) representing cerebrovascular reactivity.** In a healthy brain, the correlation between ABP and intracranial pressure (ICP) is negative, maintaining ICP with changes in blood pressure. After brain injury, the reactivity may become impaired and the relationship between ABP and ICP becomes positive.

2.2.3 Cerebral perfusion pressure

While the brain is vulnerable to elevated pressure, which may lead to neuronal damage and herniation, oxygen and metabolite delivery is dependent on CPP, the driving pressure for cerebral blood flow (CBF). CPP is defined as the difference in arterial blood pressure (ABP) and ICP. The relative importance of ICP and cerebral perfusion pressure (CPP) is not clear. Optimal CPP levels seem to vary by individual and can be defined as the CPP where the cerebrovascular autoregulation is maximized (CPPopt). CPPopt as a treatment target has been associated with improved outcomes and COGITATE, a multi-center phase II RCT has shown that CPPopt-guided treatment is safe, even in cases where CPP is above 70 mmHg. However, a larger RCT will be needed to evaluate the benefits of this treatment approach.[48,49] Meanwhile, BTF recommends a CPP target between 60 to 70 mmHg to prevent both ischemia and hyperperfusion.[27]

Historically, there has not been a consensus on the reference level of the arterial blood pressure chosen to compute CPP. Some studies report foramen of Monro as reference level, while others report level of heart or simply do not specify the reference level. Using the heart as zero level can lead to an overestimation of CPP if defined as the driving pressure over the brain. In ICU patients that commonly have a 30-degree head elevation, and an ABP reference level at heart, CPP will be overestimated with approximately 10-13 mmHg. This contributes to difficulties in comparing results from different studies. The latest BTF guidelines do not address this ambiguity and still advocate for arterial pressure dome placement at heart level for the arterial component of CPP calculations.[27] BTF CPP level recommendations must also therefore or be seen in this light. In a recent update of practices for managing severe TBI in the ICU, the foramen of Monro was suggested as the preferable reference level for CPP monitoring,[50] and the COGITATE study adopted this level as well.[48]

2.3 Management of TBI in the ICU

Preventing secondary brain injury is the primary goal in neurointensive care. With multimodal monitoring, ICP-lowering therapies, and optimization of physiological parameters, the goals are to reduce the burden of intracranial hypertension, maintain an adequate CPP and avoid second insults such as hypoxia and hypotension.

2.3.1 Multimodal monitoring in TBI

Patients treated for severe TBI in the ICU are extensively monitored, and large amounts of structured, semi-structured and unstructured data of different types and frequencies are collected from each patient.[51] This advanced multimodal monitoring (MMM) aims to identify neurological deterioration and to guide treatments through both general physiological monitoring (e.g., blood pressure, electrocardiography (ECG), and oxygen saturation) and brain-specific measures (e.g., ICP, $PbtO_2$, cerebral blood flow (CBF) and cerebral metabolism through cerebral microdialysis (CMD)). Knowledge is power, and information retained

through this multifaceted monitoring is believed to improve the quality of and outcome. However, how to present and interpret integrated signals from different monitoring modalities is complex and may be a challenge:[52] Regional measures such as $PbtO_2$ and CMD are sensitive to probe locations in relation to the brain lesion while other measures such as ICP or CPP represent global measures of brain physiology. Suggested targets for separate modalities have been presented,[50,52,53] but trends may be more relevant (Figure 2).[54]

Measuring ICP is recommended for all patients with GCS ≤ 8 and an abnormal CT scan.[27] It is the most commonly used brain-specific monitoring modality, although there are large between-center variations to comply with this recommendation.[29,55] $PbtO_2$ monitoring is becoming increasingly popular as it reflects the balance between brain oxygen consumption and delivery and can identify hypoxic episodes poorly identified by ICP/CPP monitoring. [50,52,56] Brain ischemia is an important contributor to secondary brain injury and has shown correlations with worse outcomes in TBI. Consensus-based treatment algorithms guided by ICP and $PbtO_2$ monitoring have been published,[50,56] and three RCTs are currently investigating the efficacy of $PbtO_2$ monitoring[57–59] which may further add evidence to multimodal monitoring strategies.

2.3.2 ICP monitoring

Monitoring ICP with an external ventricular drain (EVD) is considered gold standard.[60] It has the advantage of allowing for ICP control using CSF drainage and is more accessible for resource-limited settings. However, drainage itself may interfere with autoregulation measurements. An additional method, and the most commonly used monitoring technique, is the placement of an intraparenchymal catheter in brain tissue,[29] allowing for easier monitoring of pressure reactivity and waveform analysis of ICP. Non-invasive monitoring with transcranial doppler (TCD) is increasingly used, although this technique only provides intermittent monitoring of ICP and has not shown to be sufficiently accurate for replacing invasive pressure monitoring techniques.[61] Automated ICP recording is preferable to manual recording of end-hour values as it detects ICP doses more accurately, although the two methods show good agreement of recorded absolute values.[62,63]

In 2012, Chesnut *et al.* published the only RCT on the benefit of ICP monitoring, where no difference in outcome was seen between patients with treatment directed by ICP monitoring or a combination of clinical and imaging examination.[64] Generalization of the results have been questioned, as the study was conducted in South America where the standard mode of monitoring is the clinical and radiological examination, while that of high-income countries is ICP monitoring. Several observational studies have shown increased survival in patients with monitoring, and ICP monitoring is recommended in severe TBI by the Brain Trauma Foundation (BTF) guidelines.[27,65]

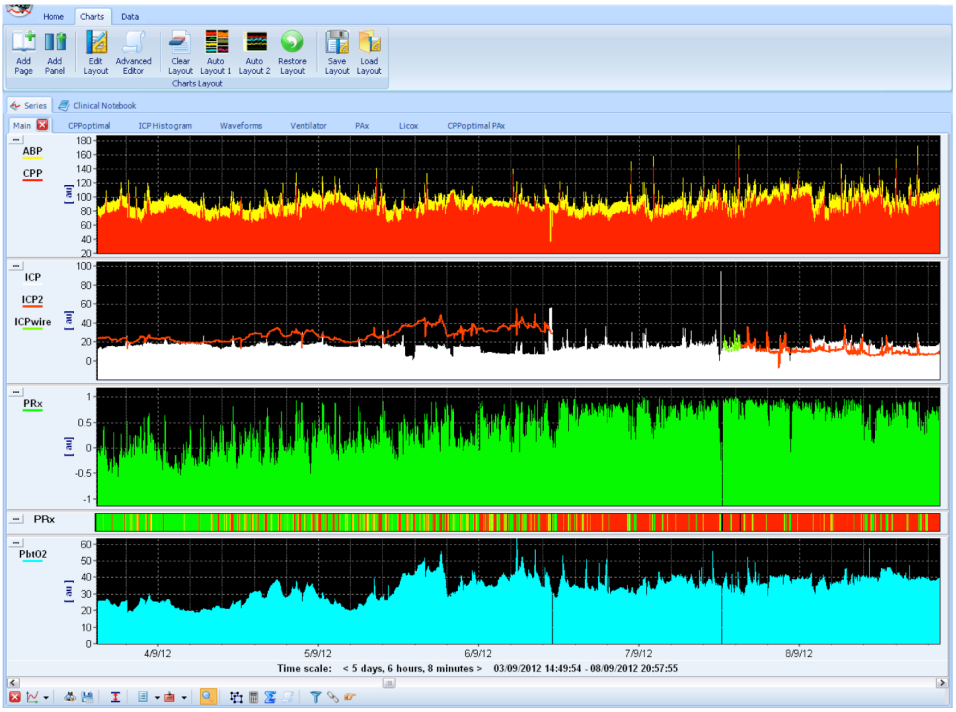

Figure 2: Multimodal monitoring of a patient with traumatic brain injury. Intracranial pressure (ICP), arterial blood pressure (ABP), cerebral perfusion pressure (CPP), cerebrovascular autoregulation (PRx) and brain tissue oxygenation ($PbtO_2$) are continuously monitored. In this figure, the trends of the high-resolution signals are represented. Note the assessment of cerebrovascular autoregulation status, PRx is represented by a color band, corresponding to degree of impairment from green to yellow to red.

2.3.3 ICP-lowering therapies

Clinical interventions used to treat elevated ICP are usually applied in a stepwise manner. The therapy intensity level (TIL) scale can be used to quantify the intensity of applied therapies to gain ICP control. It represents eight categories of ICP lowering therapies: Positioning, sedation and neuromuscular blockade, hyperosmolar therapy, ventilation strategy, CPP management, CSF fluid drainage, and surgery for intracranial hypertension. Therapies associated with higher risks of adverse outcomes – e.g., secondary decompressive craniectomy, metabolic suppression with barbiturates, intensive hyperventilation ($PaCO_2$ < 4 kPa) and hypothermia (< 35 °C) – generate higher sub-scores than those associated with lower risks (i.e., basic care). Although being a consensus-based weighting of therapies, it has been shown to be a reliable measure of therapy intensity.[44] A similar approach to interventions and their associated risks can be seen in a published treatment algorithm for intracranial hypertension.[6] A group of reputable international experts proposed a three-tiered implementation of eighteen ICP lowering therapies and advised against the use of ten therapies. Basic severe-TBI care was expected to be delivered to all patients, including head elevation, intubation and mechanical ventilation,

and avoidance of fever. Non-recommended treatments included scheduled bolus of hyperosmolar infusions, furosemide administration and routine therapeutic hypothermia targeted at below 35 °C. However, in practice, the stepwise escalation in treatment intensity is often lacking.[66]

The first tier includes interventions such as CPP targets of 60 to 70 mmHg (with arterial CPP component likely referenced at heart level), increased sedation, $PaCO_2$ at lower end of normal, intermittent hypertonic saline boluses. The second tier include mild hypocapnia, neuromuscular paralysis and CPP goals titrated by individual cerebrovascular autoregulation evaluation. The third tier includes barbiturate-induced coma, secondary decompressive craniectomy and mild hypothermia (35-36 °C).

The risks associated with the recommendations are increased in each tier. Bolus doses of the hyperosmolar agents hypertonic saline and mannitol are commonly used therapies to reduce ICP. Hypertonic saline has been suggested to be more effective in maintaining its ICP-lowering effect and avoiding hypoperfusion than mannitol boluses.[67,68] Serum sodium levels are normally tightly regulated. Increased variability in sodium has been found to be associated with worse outcomes.[69] Proposed explanations of this mechanism suggest serum sodium to mark either osmotic injury induced by rapid changes, or treatment intensity reflecting injury severity.

Third-tier therapies are recommended to treat refractory intracranial hypertension. Hypothermia is one of the commonly used therapies, although no beneficial effects on 6-month outcome has been shown despite multiple RCTs on the subject. The multi-center Prophylactic Hypothermia Trial to Lessen Traumatic Brain Injury-RCT (POLAR-RCT) study in 2018 showed no benefit on outcome of prophylactic hypothermia targeted at 33 °C compared to normothermia (37 °C) and the European Study of Therapeutic Hypothermia (32-35 °C) for Intracranial Pressure Reduction after Traumatic Brain Injury (Eurotherm3235) investigated the effect of hypothermia to treat ICP > 20 mmHg, finding that the intervention group did worse and was consequently stopped preterm.[70,71] However, prophylactic hypothermia was applied as an early intervention in both studies, and it remains unclear if the results can be generalized to common clinical use, as a late rescue therapy for refractory ICP elevations, as this was not the indication in either the Eurotherm3235 or POLAR study.

Concerning decompressive craniectomy, the multi-center RCT Decompressive Craniectomy (DECRA) studied decompressive craniectomy as a rescue therapy for ICP refractory to first-tier therapies in patients with diffuse severe traumatic brain injury and found a greater risk of unfavorable outcome in the intervention group, with no difference in mortality between the two groups.[72] Hutchinson and colleagues reported lower mortality but higher rates of vegetative state for patients with TBI and refractory ICP > 25 mmHg in the multi-center RCT Randomized Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intracranial Pressure (RESCUEicp).[73] The results in both studies could have been negatively impacted by the use of bifrontal decompressive craniectomy (100% in DECRA and 63% in RESCUEicp), a surgical method which in retrospective studies have been shown to be associated with more complications than the more commonly used unilateral approach.

In summary, hypothermia treatment below 35 °C is associated with worse outcome compared with normothermia treatment and decompressive craniectomy seems to be associated with unfavorable outcome, although it might reduce mortality.

2.4 Non-neurological organ dysfunction in TBI

TBI is commonly associated with extracranial injuries.[4] Severe extracranial trauma may aggravate the brain injury by second insults such as hypotension or hypoxia, which are known predictors for worse long-term outcome in TBI. However, isolated TBI is per se associated with acute extracranial complications not related to polytrauma,[74–80] with reported incidences of 68-89%.[75,80,81]

Sepsis, acute kidney injury,[74,82,83] pulmonary complications such as acute respiratory distress syndrome (ARDS),[84] myocardial injury,[85] and coagulopathy[86–88] are all known complications associated with TBI. Until recently, associations were only known in the acute phase of TBI and extracranial organ injury. In 2022, a single-center study found an association between TBI and chronic complications such as hypertension and diabetes.[89]

Disturbed glucose homeostasis expressed by both hyperglycemia and increased glycemic variability has been found to correlate with worse outcomes in patients with TBI.[90] Suggested mechanisms postulate neuronal and mitochondrial damage due to oxidative stress, a marker of a greater sympathetic stimulation or simply reflecting less attentive care.[90,91]

The etiology of extracranial organ dysfunction is most likely multifactorial, although exact mechanisms still largely remain unclear. Proposed mechanisms include activation of the sympathetic nervous system through the hypothalamic-pituitary-adrenal axis leading to excessive release of catecholamines and glucocorticoids.[75] Induction of immunological response has also been suggested as a pathway towards secondary insults to the brain: A disruption of the blood brain barrier in TBI in combination with neuroinflammation may induce a systemic inflammatory cascade with release of cytokines and chemokines.[75,92] Pharmacological treatments such as norepinephrine used to increase cerebral perfusion pressure and hyperosmolar therapy to treat cerebral edema may also contribute.[74,78,79,93]

Effects of non-neurological dysfunction on outcome remain unclear, as study results are diverging.[80,81]

2.5 Phenotypes and endotypes in critical care

Endotypes are subgroups of a health condition with distinct underlying pathobiological mechanisms. It contrasts to the related concept of phenotypes, where the subgroups are defined by similar characteristics but without the suggested underlying mechanism. The abundant data collected in an ICU is a gold mine for data-driven machine learning approaches to identifying

potential endotypes. Indeed, data-driven unsupervised clustering methods are gaining in popularity and have been used to describe endotypes in the ICU, in both sepsis and ARDS, subgroups which potentially can benefit from different treatment approaches.[94,95]

Machine learning methods have also been applied to temporal ICU data to identify disease trajectories in critical illness, information that might be used to forecast the course of disease and thus allow earlier interventions to avoid clinical deterioration. Peelen *et al.* modeled daily states of multi-organ failure in sepsis patients in the ICU using dynamic Bayesian networks and showed that once an organ failure exists, it takes time to resolve and Eriksson *et al.* identified five longitudinal trajectories of organ dysfunction post trauma using group-based trajectory modeling (GBTM).[96,97] Cohen *et al.* used a hierarchical clustering algorithm on physiological minute data to define ten states in 17 critically ill trauma patients and found associations that could not be identified neither using traditional statistical methods nor by clinical expertise. All patients spent time in more than one of the states, and the states could be related to outcome, such as multiple organ failure, mortality and infection.[98]

2.6 Phenotypes in TBI

A commonly hypothesized reason to the absence of treatment effects in many TBI studies is lack of an individualized treatment approach in a heterogeneous group of patients, where patients traditionally are included based on GCS and not underlying pathophysiology.[3,15,99] During the last decade, several suggestions on phenotypes in TBI have been published.[100] Most studies focus on the milder spectrum of the disease and post-concussion symptoms, which is outside the scope of this thesis, but proposed phenotypes including patients with severe TBI have gained much attention.[99,101]

The two studies identifying phenotypes including patients across all severities in the acute phase are by Folweiler *et al.* and Gravesteijn *et al*.[102,103] Folweiler elegantly identified three sub-phenotypes defined by hematological and coagulation factors (platelet count, hemoglobin, prothrombin time, INR, hematocrit), and glucose. Gravesteijn identified four subphenotypes by cause of injury, major extracranial injury, and GCS.

Although focusing on mild TBI, Yuh *et al.* identified phenotypes based on radiological findings.[104] By hierarchical clustering, three clusters of intracranial lesions were described: (1) Epidural hematoma (EDH) alone, (2) Subdural hematoma (SDH) in combination with contusion and subarachnoid hemorrhage (SAH), and (3) coexisting intracranial hemorrhage (ICH) and petechial hemorrhage. These clusters were externally validated.

By solely focusing on longitudinal intracranial pressure (ICP) trajectories, Jha *et al.* identified six trajectories with different temporal profiles by applying the longitudinal clustering method GBTM. Not only the trajectories with high ICP showed relations with unfavorable outcomes, but also did two trajectories with low ICP levels. Furthermore, the expression of the gene

ABCC8 (coding for the sulfonylurea receptor-1, which regulates edema) was different between the identified groups.

The identified subphenotypes of TBI all go beyond a description by GCS and are pathobiologically plausible. However, where you search, you shall find, which results in the above diverse descriptions of phenotypes – that are largely dependent on which features are included in the specific model. Thus, these phenotypes should presently be regarded as hypotheses until further validation is performed.

None of the above approaches included information on outcome in the models, but nevertheless, all identified clusters showed distinct differences in outcome, indicating important underlying pathophysiological processes.

In summary, there have recently been several novel and seemingly clinically relevant phenotypes presented in the TBI field, possibly reflecting significant pathobiological differences. However, to advance the field of precision medicine in TBI, these need to not only be recognized but also implemented in clinical studies to test efficacy of interventions and treatments.

2.7 Causal inferences in TBI

Randomized controlled trials (RCTs) are considered the gold standard when evaluating cause and effect relationships in medicine and are the cornerstone of evidence-based medicine. Such studies are often time-consuming, expensive and may put patients at risk of interventions with unknown effects. During the last decades, causal inference methods have been developed, used to investigate causal relationships in observational data. These methods can be seen as complementing RCTs, when such studies may not be possible to conduct.

Causal inference methods were first developed in the field of social sciences, where RCTs are inherently difficult to conduct. In 2021, David Card, Joshua Angrist and Guido Imbens were awarded Sveriges Riksbank Prize in Economic Sciences on Memory of Alfred Nobel for their work on causal inference methodology. They used these methods to analyze observational data on the labor market.

At the same time, the use of causal inference methods in medicine is becoming increasingly popular, and within the field of TBI, a few studies have been published during the last few years. In 2017, Gao *et al.* investigated the relationships between mean arterial pressure (MAP), heart rate (HR) and ICP and outcome using Granger causality, which is commonly used to investigate causal relationships among time-series data.[105] A strong interdependence of the features were found, where MAP was identified as driver of ICP and heart rate. The authors not only found this relationship, but also identified a potential physiologic mechanism of impaired vasoreactivity and baroreceptor sensitivity in severe brain injury. The directional relationship of MAP on ICP was confirmed in a later study.[106] This study used data from 47

patients from the CENTER-TBI high-resolution sub-study cohort to analyze relationships between $PbtO_2$, ICP and MAP, but no causal relationship of MAP or ICP on $PbtO_2$ was found.

3 Research aims

The overall aim of this thesis is to apply novel analytical methods to investigate pathophysiological patterns in patients with TBI requiring ICU care. More specifically, the aims are to:

- Evaluate ICP tolerability using and further develop a visualization methodology earlier described by Güiza *et al.*[30] in a multicenter dataset.
- Investigate the uncertainty of ICP tolerability thresholds for duration and intensity.
- Investigate ICP dose and its relationship to outcome.
- Present a pathophysiological characterization of TBI patients using a multi-dimensional unsupervised cluster analysis on admission features.
- Describe pathophysiological trajectories of TBI patients during the first week of ICU stay.
- Investigate causal relationships between ICP, cerebrovascular autoregulation status, ICP targeted therapies and long-term outcome.

4 Materials and methods

4.1 CENTER-TBI

The Collaborative European neurotrauma effectiveness research in TBI (CENTER-TBI) is an international prospective observational cohort study.[11] Its aims are to improve characterization and classification of TBI and identify the most effective treatments in TBI, by using novel analytical methods and comparative effectiveness research. Data has been collected between December 2014 and December 2017 from 4,509 patients admitted to one of the 63 study centers in 19 countries, making it the largest observational study in TBI. All patients met the inclusion criteria:

- Clinical diagnosis of TBI.
- Presenting at a study hospital with a TBI within 24 hours of injury.
- Indication of a head CT scan.

Included patients were stratified by their initial level of care: Emergency room (ER) stratum (*n*=848), where patients were sent home after assessment in the ER; Admission stratum (*n*=1,523), where patients were admitted to a ward, and ICU stratum (*n*=2,138), where patients were admitted to an ICU. At the time of writing, 218 scientific papers have been published with results generated from CENTER-TBI (6 March 2023). These cover a wide range of topics, from descriptive analyses of the cohort to validations of outcome assessment tools and in-depth analysis of physiological high-resolution signals.

4.1.1 Demographics

The median age of included patients were 50 years (interquartile range (IQR) 30-66), and 3,023 (67%) were male. Overall median GCS was 15 (IQR 10-15), and 6-month mortality was 12% (*n*=473). By comparison, the ICU cohort (*n*=2,138) had a median age of 49 (IQR 29-65), *n*=1,562 (73%) were male, median GCS was 9 (IQR 4-14) and 6-month mortality was 21% (*n*=394). A detailed description of the cohort is provided in the publication "Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI".[4] The CENTER-TBI cohort was older, and fall injuries were more common than previously described in other studies.[4]

4.1.2 Data collection

More than 2,500 variables were collected for each patient.[107] These included data on demographics, medical history, injury mechanisms, lab values, CT scan results, physiological parameters such as vital signs and intracranial pathology, given treatments and outcome assessments.[11] Data for the CENTER-TBI study was collected through the Quesgen e-case report form (CRF) (Quesgen Systems Inc, USA), hosted on the INCF platform, and extracted via the INCF Neurobot tool (INCF, Sweden). For patient monitoring and data collection in the High-Resolution repository, the ICM+ platform (University of Cambridge, UK) and/or Moberg Neuromonitoring system (Moberg Research Inc., USA) were used.

4.2 Data curation

Crucial for all research studies is high-quality reliable data. Much time is spent on collecting and registering data, but the process of curating the data is often overlooked. During the course of the CENTER-TBI study, the need for structured data curation was highlighted to ensure high-quality sub-studies. A multidisciplinary data curation task force (DCTF) was established, consisting of expertise with diverse medical, database, statistical and technical domain knowledge. The DCTF continuously, along with ongoing data collection, explored data for inconsistencies. If an issue was found, it could be reported back to the recruiting site, a filter could be applied centrally, or if an issue were judged unresolvable, be described in a data dictionary.

The first step in a data curation process should start before data collection: Making sure relations and syntax in the database are adequate, applying hard limits for acceptable input values, and only making possible combinations of parent/child questions possible to answer (e.g., one can only provide an answer to "type of ICP monitor" if the question "ICP monitoring?" has a positive answer). It is also important with proper instructions on interpretations of questions, such as which measurement each hour should be recorded – maximum, minimum, mean, median, last, or first value. Each recording should be accompanied with a timestamp to avoid different interpretations of how days post injury are defined. The need for a standard regarding definitions and data collection have led to the development of Common Data Elements (CDE) in TBI data collection and research.[108] CDEs are well defined variables suggested to be recorded in clinical TBI studies to increase the ability of pooling data from different studies and make comparative effectiveness research between centers possible. Checklists for standardizing data collection to improve data quality have been developed by the Data Access Quality and Curation for Observational Research Designs (DAQCORD) initiative.[51,109]

High-resolution data collected in the ICU is inherently noisy, with incomplete data and artifacts. This requires special attention from a data curation perspective. To use collected data for analyses, there is a need for detection and removal of artifacts, e.g., apparent outliers or ECG disturbances caused by patient turning or a sternal rub. Data cleaning and dealing with artifacts is usually time-consuming and done manually post-hoc,[51] although methods for automatic detection and removal of artifacts have been proposed, such as the DeepClean algorithm developed by Edinburgh and Ercole.[110,111]

An important conclusion from CENTER-TBI is the importance of allocating resources for data curation – it has been estimated that 15-20% of a large study's budget should be spent on such quality-enhancing activities.[112]

4.2.1 Missing data mechanisms

Clinical data is rarely complete, as observations almost always are missing to some extent. The reasons for missingness may vary and may bias results. It is important to understand the structure of the missingness before deciding how to handle it. Different techniques for imputation exist, while some analytical methods are insensitive to missingness and do not require imputation to perform analyses (such as the probabilistic graph models used in **study II and III**) but may still be affected by structures of missingness.

Missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR) are the important mechanisms for missing data. If MCAR, missing values are randomly distributed over the dataset, e.g., missing oxygen saturation measurements due to accidental displacement of the pulse oximeter. If data is MAR, the missingness is related to other variables in the dataset, such as ICP measurements that are only available for patients with ICP monitoring. In case data is MNAR, the missingness is attributed to the values of the variable itself, as is the case if overweight patients are more reluctant to report their weight in a survey.[113] This structure is difficult to detect and may highly influence the validity of the results.

There are several methods for handling missingness. Some methods, such as the mixture of probabilistic graph models used in **study II and III**, simply leave out the missing value but use all other available data for the analysis. If the analytical method to be used cannot handle missing data, a common approach is imputation. The most recommended method is multiple imputation by chained equations (MICE). This algorithm first creates several imputation sets using regression of all other available data and drawing from a distribution. In analysis, all imputed datasets are pooled to generate a final estimate of the missing features retaining uncertainty of imputation.

How to impute may depend on the type of variable: Longitudinal data may be imputed by linear or higher order interpolation. Single imputation, such as replacing all missings with the overall mean, or by last observation carried forward (LOCF) are other types of imputation. They are usually not recommended as they often lead to a false decrease in standard deviation. However, there are situations when LOCF may be suitable to use, such as in **study III** where CT findings are propagated until a new CT scan is made – absence or presence of pathology is assumed to remain. Another method is the complete-case analysis (CCA), where objects with one or more missing variables are excluded from further analysis. It is usually not recommended to use CCA as it may limit the cohort size, leaving out large amounts of important information.

4.3 Selected clustering algorithms and considerations

Clustering is the task where unlabeled data (i.e., outcome is unknown) is divided into groups with similar characteristics. Machine learning methods for unlabeled data are commonly called unsupervised algorithms. In contrast, classification methods are using labeled data (i.e., known

outcome) to group and sort data, and are examples of supervised algorithms. There is an abundance of clustering methods, all with their own advantages and disadvantages. Clustering algorithms can broadly be classified by four general strategies: Centroid-based, density-based, distribution-based, and hierarchical clustering (Figure 3).

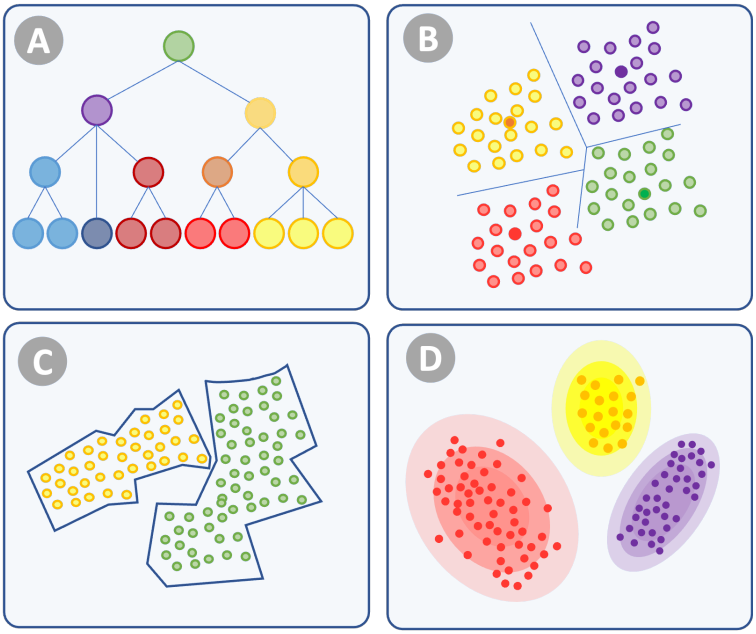

Figure 3: The four clustering strategies. A. Hierarchical clustering is creating a tree-like structure, where objects are grouped stepwise by similarity, until all objects are assigned to one group. **B.** Centroid-based clustering is creating clusters by assigning objects to the cluster where the distance to the cluster mean or medoid is minimized. **C.** Density-based clustering groups objects in areas of high density into clusters, allowing different shapes of the clusters. **D.** Distribution-based clustering is a 'soft' clustering method, where objects are assigned to all clusters, but with different probabilities.

4.3.1 A selection of clustering methods

In **study II and III**, a mixture of probabilistic graph models was used for clustering. This section will briefly explain the used method, as well as a few other clustering methods that have been used in TBI research.

4.3.1.1 Mixture of probabilistic graph models

A mixture of probabilistic graph models is an unsupervised density-based clustering model. One of the most commonly used density-based cluster models is a Gaussian Mixture Model. However, it can only handle continuous variables. In contrast, a mixture of probabilistic graph models can handle a mix of continuous and categorical variables as the distributions for each

feature are simply multiplied together. In addition, it does not require complete data, eliminating the need for imputation of missing data. In a probabilistic graph model, the probability distributions of input features are considered, and the joint probability distribution over all input features is written as a product expansion. The simplest product expansion is when all input features are independent, in which case the joint distribution is the product of the individual feature distributions. In the more general case, for each set of input features that are directly correlated, a compensating factor needs to be included in the product.

A mixture of probabilistic graph models were used for clustering of baseline data in **study II**, and for longitudinal data in **study III**. In **study III**, the method was extended with a Markov model to handle longitudinal data. By including joint distributions of features on two consecutive days, the temporal relation between longitudinal data was considered in the model.

4.3.1.2 The Expectation Maximization (EM) algorithm

The expectation maximization (EM) method is an algorithm which can be used to generate clusters using a density-based cluster model. It is a generalization of the maximum likelihood estimation of incomplete data.[114,115] The EM algorithm was used in **study II and III**.

Conceptually, the EM algorithm is a two-step iterative algorithm: In the E (expectation) step, the cluster membership probabilities for each patient are calculated based on the given parameter values in each cluster. In the M (maximization) step, a re-estimation of parameter distributions is done based on the cluster membership probabilities (i.e., for continuous data, mean and variance, and for categorical data relative frequencies in each category). These steps are repeated until the cluster membership probabilities do not change above a set threshold (indicating stability) or a maximum number of iterations is reached, whichever comes first. In **study II and III**, the probability change threshold was set to 10^{-6}, and maximum number of iterations to 1,000.

The EM method is a so-called "soft" clustering algorithm, that is – each patient is assigned to every cluster by a probability between 0 and 1. However, to make the results easier to interpret, patients in **study II and III** were assigned to the cluster with highest cluster membership probability.

4.3.1.3 Other clustering methods used in TBI research

There is no single method that is unambiguously good to use when analyzing data – which method to use is somewhat a matter of taste, as all methods have their advantages and disadvantages. Some other unsupervised clustering methods that have proven useful in TBI research include partitioning around medoids (PAM) algorithm, hierarchical clustering, and group-based trajectory mean (GBTM) clustering.

Both Gravesteijn *et al.* and Folweiler *et al.* used the clustering method partitioning around medoids (PAM) to identify subgroups of TBI patients.[102,103] PAM is similar to *k*-means, with the distinction that a real object is used as the medoid (compared to the mean of different objects

in the case of *k*-means). The data is split into *k* clusters, and the medoid is defined as the object with the minimal average dissimilarity compared to all other objects in the cluster.

Hierarchical clustering was used by Yuh when describing radiological sub-phenotypes in mild TBI associated with outcome.[104] The method can be implemented bottom-up ("agglomerative") or top-down ("divisive"), and the resulting clustering is presented as a dendrogram (Figure 3A). The most common approach is the bottom-up algorithm: In the first step, each object is treated as separate clusters. The similarity with the other objects (clusters) are determined by some measure, e.g., the Euclidean distance in between. The most similar clusters according to this measure are grouped. In the following step, the similarity of the new clusters are determined, usually by one of the following three approaches: The distance between the clusters are represented by (1) the minimum distance between two objects belonging to different clusters, (2) the maximum distance between two objects belonging to different clusters, or (3) the mean distance between each object in one cluster and all other objects in the other clusters. This algorithm is then repeated until all objects belong to the same cluster.

GBTM is a method for analyzing trajectories – development over time – of subpopulations in a cohort,[116,117] such as ICP trajectories described by Jha *et al*.[118] It is a method based on finite mixture models and maximum likelihood estimations.[116] Each subgroup trajectory can be estimated by a polynomial of degree *k*, described by a set of parameters Ω. The optimal number of trajectories is selected by using the Bayesian information criterion (BIC): If the difference between two models with *n* and *n+1* number of subgroups is greater than a set threshold, a new model is created with *n+1* number of subgroups.[119]

4.3.2 Selecting an appropriate number of clusters

Although different techniques to investigate the optimal number of clusters exist, the number of clusters is set, most commonly, rather arbitrarily. However, there are a few objective measures to use to determine the optimal number. In **study II and III**, the cluster similarity index (CSI) was used, as described in more detail below. Other useful methods include the silhouette and elbow methods, information criterions (AIC/BIC) and gap statistics. A few of them will be described in more detail below.

4.3.2.1 CSI

CSI, or cluster similarity index, is a measure of the reproducibility of a model. It can be calculated as $\frac{\sum_{i=1}^{j} f(x)}{j}$ (Eq 1), where *j*=number of patients, *f(x)*=1 if a patient appears in the same cluster in two compared models. If not, *f(x)*=0. Notably, this index requires that the corresponding clusters are aligned in the compared cluster models. When clusters are randomly generated, models can be similar, but cluster indices may not correspond (cluster 1 in one model may correspond to the cluster called 2 in another model). To overcome this issue, the algorithm we developed translated the cluster indices as to maximize CSI.

In **study II and III**, CSI was calculated for all pairwise combinations of models (i.e., in **study II**, twenty models, and **study III**, twenty-five models), and median and standard deviations were calculated.

A lower number of clusters will naturally generate a higher CSI, as it is more likely to find two patients with cluster assignment agreement in a model with few clusters by chance compared to a model with a higher number of clusters. This is true for a sufficiently small number of clusters. In the case when number of clusters approaches number of patients, the CSI will again rise, to finally reach one when there is one cluster per patient. In **study II and III**, the first case is true, i.e., the number of clusters is small compared to the number of patients. To adjust for this "per chance" higher CSI for fewer clusters, a penalty of 1/number of clusters were subtracted from the CSI when comparing models with different number of clusters.

There are several similar measures to CSI. The most well-known is the Jaccard index, where $J(A,B) = \frac{|A \cap B|}{|A \cup B|}$ (Eq 2), which can be expressed as the number of times a patient appears in the same cluster in model A and B divided by 2 × number of patients in the study. We developed another measure which we called Pairwise similarity index (PSI). This measure can be expressed as Eq 1, but j=number of pairs of patients, and $f(x)$=1 if both patients in a pair appear in the same *or* in different clusters in both models. However, as CSI was more intuitive, we used this measure in our studies.

4.3.2.2 Elbow method

The idea behind the elbow method is to find the number of clusters with the minimum within-cluster sum of squares (WSS). An increasing number of clusters will result in a decrease in WSS. By plotting WSS vs. number of clusters, the optimal number of clusters can be determined by identifying the curve's "elbow", i.e., the point where the curve is flattening out. A major drawback of this method is that if the decrease rate in WSS is constant, which often is the case, no elbow will be found.

4.3.2.3 Silhouette method

In *k*-means (and *k*-medoids) clustering, the Silhouette method is one of the most used methods for finding the optimal number of clusters. Simplified, it is a measure of how similar each datapoint is to other points in its cluster compared to the separation between other clusters. When all objects are clustered, the average Euclidean distance between each point and all other points assigned to the same cluster is calculated. This is compared to the average distance to all other points belonging to other clusters, generating a silhouette index between -1 and 1. The higher the index, the better separation of the clusters. A silhouette coefficient of 0 indicates no separation between clusters, while a negative coefficient indicates that samples are wrongly classified. A major drawback with the silhouette method is that it is computationally time-consuming, especially if the number of samples and features in the model are large.

4.4 Bootstrapping

Bootstrapping is a technique commonly used in machine learning for internal validation in a dataset. It is used in **study I and III**. By bootstrapping with replacement, "new" cohorts, usually of the same sample size as the original cohort, are randomly generated. "With replacement" indicates that a patient in the original cohort may appear more than once in the bootstrapped cohort, to allow for variation from the original cohort. This is a technique used to estimate uncertainty in an analysis, as it allows for calculations of means and confidence interval estimates. Despite its simplicity, bootstrapping is computationally time-consuming as the analysis is repeated commonly 1,000 times.

4.5 Mutual information

In high-dimensional models, it is not uncommon to, at a first stage, remove features that are redundant and do not add information to outcome. A commonly used dimensionality-reduction (feature selection) technique in machine learning is by evaluating the mutual information (MI) for each feature. MI is a measure of the dependency of two features (in the context of this thesis: the dependency between cluster label and features). It can be explained as the reduction of uncertainty (measured by entropy) on values of one feature Y (cluster label) when the other feature X (clinical variable) is known: $I(X;Y) = H(Y) - H(Y|X)$ where H denotes entropy. MI detects both linear relationships and nonlinear dependencies.[120]

4.6 Causal inference

The study of causal relationships in statistics is a relatively new area of research, and it is claimed that the first time it was mathematically described was in the 1920's.[121] The development of the field has accelerated during the last four decades, and a wide range of methods have been implemented. It is beyond the scope of this thesis to describe them all in detail. This section will focus on the PC algorithm used for causal inference analysis in cross-sectional data and Granger-causality used for analysis of temporal data.

4.6.1 The PC algorithm

In **study IV**, the PC algorithm for causal inference is used. It is one of the oldest and most widely used algorithms, and is named after its authors Peter Spirtes and Clark Glymour.[122,123] By testing for conditional independence in cross-sectional data, causal relationships are determined. The result is best presented in a conditional graph for easy interpretation. The relations between included features ("nodes") are investigated in a stepwise approach, where each pair of relations are tested for conditional independence of all other features related to one of the features. The algorithm is described in Figure 4.[123]

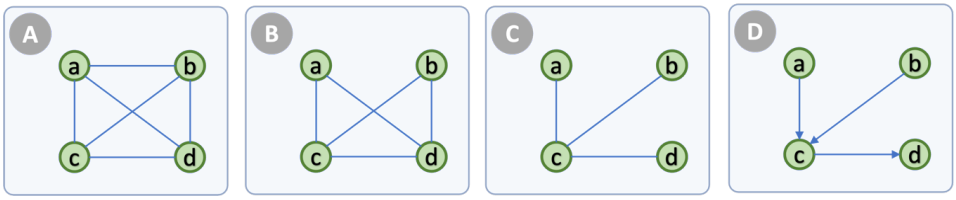

Figure 4: PC algorithm. Correlations between all pairs of features ("nodes") are calculated. If two nodes are independent (not significantly correlated, i.e., $a \perp\!\!\!\perp b$), edges (connections) are removed. In **study IV**, we set the threshold of significance to 0.01. **A.** A fully connected undirectional graph. **B.** Unconditional independence is tested. Edges are removed between independent features. **C.** Pairs of nodes still correlated are tested for independence conditional on one feature ($a \perp\!\!\!\perp b \mid c$) ("*a* is independent of *b*, conditional on *c*"). Conditional independence is tested for all features connected to at least one of the nodes *a* and *b*. If *a* and *b* are conditionally independent on *c*, the edge between *a* and *b* is removed, and *c* is added to the separation set of *a,b*. In this example, ($a \perp\!\!\!\perp b \mid c$) and ($b \perp\!\!\!\perp d \mid c$), removing the edges between *a–b* and *b–d*, and *c* is in the separation sets of *a,b* and *b,d*. Each pair with an edge between them are then tested for pairwise conditional independence on pairs of features that are correlated with at least one of the nodes, e.g., $(a \perp\!\!\!\perp c \mid (b,d))$. This process can be repeated conditioned on triplets of features, and so on, until the number of edges are sufficiently reduced. **D.** When all conditional independencies are removed, we have produced the so-called "skeleton", and causal relationships can be investigated. This is done by analyzing still correlated nodes and their separation set. If *a–b–c* is correlated, but no correlation is found between *a* and *c* directly, and *b* is not in the separation set of (*a,c*), it can be concluded that $a \rightarrow b \leftarrow c$. In the case *b* is present in the separation set of (*a,c*), a causal relationship cannot be determined between *a,b,c* and we can only conclude that there is a correlation between the features.

4.6.2 Granger causality

Clinical monitoring data is usually longitudinal, highlighting the importance of time-series causal inference methods in the ICU setting. One of the most popular methods to investigate causality in time-series data is Granger causality (implemented by Granger in 1969). It can be summarized as "X Granger-causes Y if predicting Y based on past observations of X performs better than predicted Y based on its past only".[124] Granger causality (GC) assumes linear correlations, stationary time-series, and autoregression, assumptions that often are violated in real-world data.[125] Extended Granger causality and nonlinear Granger causality are two extensions of GC suitable for analysis of non-linear data. In a review published in 2021, Edinburgh *et al.* investigated ten different causality indices for time-series data, and concluded that the agreement between the methods were in general high, with nonlinear GC and transfer entropy as the top performing methods.[125]

4.7 Methodological summary of the studies

All studies included the patients in the CENTER-TBI ICU sub-cohort (*n*=2,138). The general exclusion criteria were < 18 years old (*n*=132) and missing GOSE at 6 months post-injury

(*n*=238), leaving *n*=1,728 patients eligible for further analyses. In **study I**, patients with high-resolution monitoring (*n*=273) of ICP for longer than 24 hours and with baseline data recorded were included (*n*=227). **Study II and III** included all 1,728 patients in the analyses. **Study IV** included all patients in the high-resolution sub-cohort who had intraparenchymal ICP monitoring and with monitoring data during first day post-injury (*n*=201).

Outcome was represented by Glasgow outcome scale extended (GOSE) at six months post-injury, a clinical evaluation scale ranging from 1 (dead) to 8 (without any brain injury-related disability) (Table 1).[126] If GOSE was missing at 6 months but available at other timepoints, the score was imputed using assessments at other timepoints. This imputation was done centrally in CENTER-TBI and described elsewhere.[127]

GOSE	Description
1	Dead
2	Vegetative state
3	Lower severe disability
4	Upper severe disability
5	Lower moderate recovery
6	Upper moderate recovery
7	Lower good recovery
8	Upper good recovery

Table 1: Glasgow outcome scale extended (GOSE). GOSE is commonly dichotomized into unfavorable (GOSE 1-4) and favorable (GOSE 5-8) outcome.

4.7.1 Study I

In **study I**, one-minute averages of ICP and arterial blood pressure (ABP) was calculated from 10 s-averages of high-frequency (up to 500 Hz) signals. Pressure reactivity index (PRx) was calculated as the moving Pearson correlation between ICP and ABP.

For each threshold of ICP from 10 to 40 mmHg, and duration of 5 to 360 minutes, the number of events was calculated. An event was defined as an ICP above the set threshold for a duration of longer than the time threshold. In total, 11,036 thresholds were considered. For each threshold, the correlation between the number of events and the outcome represented by GOSE was calculated. A more negative correlation represents a correlation towards a higher number of events and worse outcome, as low GOSE represents worse outcome. The correlation coefficients (from -1 to +1) were then visualized in a grid, where negative correlations were represented as red, and positive correlations as blue.

To investigate the uncertainty of the results, bootstrapping with replacement was performed (*N*=1,000), and correlations of number of events and GOSE were calculated for each threshold

in each sub-cohort. The results were graphically visualized as described above, but with addition of the +-2 standard deviations from the mean transition line.

The mean PRx for each event was calculated. A threshold of +0.3 was set for impaired autoregulation, as previously described.[28,128,129] Sub-analyses as described above were made on data stratified by cerebrovascular autoregulation status.

In addition to the correlation plots described above, "pressure time dose" (PTD) was calculated and related to outcome. PTD was calculated as the area under the ICP curve above different thresholds of ICP (Figure 5), for thresholds of ICP from 0 to 40 mmHg. Total PTD and PTD stratified by intact or impaired cerebrovascular autoregulation were calculated and related to outcome (unfavorable/favorable outcome and mortality at 6 months post-injury). The average PTD for patients with each outcome and above each threshold of ICP was calculated. The distributions were compared using the Kolmogorov-Smirnov non-parametric test, with level of significance set to 0.05. A multivariable logistic regression model adjusting for the IMPACT core features (age, GCS motor score and pupil reactivity) and maximum daily therapy intensity level (TIL) was performed.

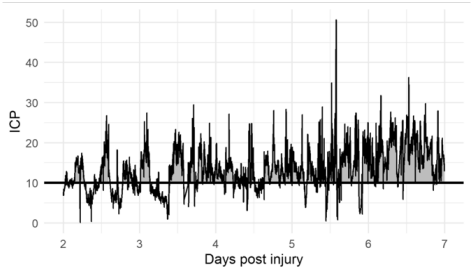

Figure 5: Pressure time dose (PTD) was calculated as area under the curve of the ICP curve above different thresholds of ICP. In this figure, the definition of PTD_{10} is illustrated.

4.7.2 Study II

Thirty-three early features (Table 1) were included in the clustering analysis. These were selected out of clinical interest and experience and were collected within 24 hours post-injury.

The features were clustered using a mixture of probabilistic graph models and the EM algorithm. As some of the included features showed a strong correlation, compensating factors were included in the model to limit the impact of correlation.

To determine the optimal number of clusters, and find the model best fitted to the data the cluster similarity index was calculated. Ten models of each number of clusters, from three to fifteen, were randomly generated. The model with highest log likelihood (indicating best fitted model) for each number of clusters were kept, and the rest were discarded. This was repeated

twenty times, generating in total twenty models of each number of clusters, and median CSI was calculated.

The clusters were evaluated by calculating the mutual information (MI) between each cluster label and feature. All features with MI > 0.1 were used for a qualitative analysis of the clusters. Univariable logistic regression was performed to determine the pseudo-explained variance between cluster index and outcome, and a multivariable logistic regression analysis was performed to investigate if the clusters added explained variance in addition to the IMPACT extended variables.

4.7.3 Study III

A clustering of baseline and longitudinal data from the first week in ICU was performed. A set of features representing baseline characteristics, clinical management, physiological monitoring values, lab values, brain biomarkers and CT characteristics was included in the model. Continuous features measured more than once daily were represented by daily mean and range (difference between maximum and minimum value). Longitudinal features were represented once per day, e.g., "mean glucose day 1", "mean glucose day 2", and so on. Thus, a total of 452 unique representations of fifty-nine features were included in the model.

The method used for clustering in **study II** was used to investigate trajectories during the first week of ICU stay, but with a Markovian extension to handle longitudinal data.

Due to methodological issues when handling longitudinal features, missing longitudinal data was imputed by either interpolation or last value carried forward, as judged most appropriate. In addition, an incremental seed was used when creating the models: First, a model of two clusters were created, with patients randomly assigned at initialization. The cluster memberships in the model with highest log likelihood was then used to initialize a model of three clusters, where a subset of patients in each cluster were assigned to each cluster. In addition, a randomly selected subset of patients were assigned to a third cluster. This process was then repeated for up to twelve clusters, in total twenty-five times.

Cluster stability was assessed as described in **study II**.

To determine the importance of each feature, MI was calculated between the cluster label and each feature. For each number of clusters, average MI for each feature and day, and weekly overall average for each feature was calculated.

Improvement of the IMPACT extended model outcome prediction by addition of trajectory membership was evaluated using a multivariable logistic regression model. The uncertainty in predictions were estimated by bootstrapping with replacement (1,000 times), and the results were adjusted for the bias of adding more features (i.e., the trajectory label) in the model.

4.7.4 Study IV

The relations between the following features were assessed: ICP, PRx, MAP, heart rate, oxygen saturation, arterial partial pressure of carbon dioxide, ICP dose above 20 mmHg, total TIL, and GOSE 6 months post-injury. The features were represented by their weekly averages. A multivariable logistic regression analysis towards outcome was performed. Causal relationships between all features were investigated using the PC algorithm described in section 4.6.1 above.

4.7.5 Software

In **study II and III**, the cluster development, CSI and mutual information calculations were performed using open-source code developed in C++ by Professor Holst. In **study IV**, conditional and unconditional dependencies were calculated using Python version 3.8.15.

All other analyses were performed using the statistical software R (version 3.5.0 In **study I** and version 4.0.5 in **study II-IV**).

4.8 Ethical considerations

CENTER-TBI was approved by local ethical boards at all participating sites (Stockholm dnr: 2014/1473-31/4). The study was conducted in accordance with all relevant laws of the EU and all relevant laws of the country where the participating sites were located. Informed consent was obtained by the patients or legal representative/next of kin for all patients recruited and was documented in the e-CRF. The CENTER-TBI management committee has approved all sub-studies included in this thesis.

Given the observational nature of the studies, participation is not associated with clear risks nor benefits of the individual patient. In large observational datasets, there is always to some extent a risk of identification of individual patients. To minimize this risk, several actions have been taken to increase the anonymization: Patient IDs and admission sites have been masked. All timepoints are made relative to time of injury, which is set to 1970-01-01 for all patients, and free text has been manually gone through and potential identifiers have been removed.

5 Results

5.1 Study I

5.1.1 Number of ICP insults are correlated to outcome

The correlations of number of events above thresholds of ICP (10 to 40 mmHg) and durations (longer than 5 to 360 minutes), vs. outcome represented by 6-month GOSE were calculated for 1,000 bootstrapped populations with the same sample size as the full cohort (*n*=227) (Figure 6B, the non-bootstrapped results are visualized in Figure 6A). A mean threshold of 18 mmHg +/- 4 mmHg (2 standard deviations [SD]) for events with duration longer than five minutes was found (Figure 6B). The transition line can be interpreted as the thresholds above which the number of insults are correlated with a worse outcome. Above the transition line +2 SD (22 mmHg), there is a strong correlation of events to worse outcome.

Area under the ICP curve – pressure time dose (PTD) – above all thresholds of ICP from 0 to 40 mmHg was calculated for each patient and correlated to GOSE (Figure 7A). Patients with unfavorable outcome had significantly higher PTD above ICP 20 and 25 mmHg compared to those with favorable outcome (*p*=0.014) (Figure 7B). Patients who died within 6 months post injury had a significantly higher PTD for all thresholds of ICP 10 mmHg and above (*p*=0.004 for PTD_{20}) (Figure 7C).

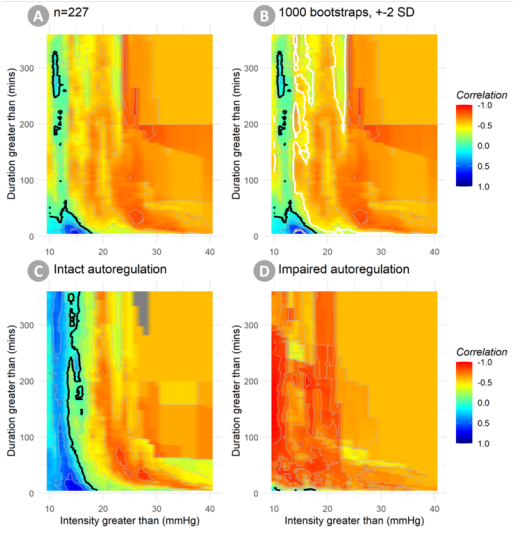

Figure 6: Thresholds of ICP intensity and duration. The color in each pixel corresponds to the correlation between number of events above the threshold of duration and intensity vs outcome represented by 6-month GOSE. **A.** Overall ICP burden. **B.** The analysis was repeated 1,000 times on bootstrapped cohorts. Black line represents mean transition line, white line represent +2 SD, grey line -2 SD. **C.** ICP burden if cerebrovascular autoregulation was intact, and **D.** if autoregulation was impaired.

5.1.2 Cerebrovascular autoregulation correlates with ICP tolerability

24.9% of overall total monitoring time was spent with impaired cerebrovascular autoregulation (defined as PRx > 0.3). If intact autoregulation, 19 mmHg for 5 minutes or longer, or 15 mmHg for 50 minutes or longer were correlated to worse outcome (Figure 6C), while if impaired autoregulation, no ICP intensity and duration thresholds associated with better outcome were identified (Figure 6D).

In periods with intact autoregulation (PRx ≤ 0.3), no significant differences in doses of PTD were seen between patients with favorable and unfavorable outcome (Figure 8A), while a small but statistically significant increase in doses above ICP thresholds of 0 and 20-30 mmHg was seen in patients who died (Figure 8C).

Differences in PTD with impaired autoregulation were remarkably larger between the groups, both when stratified by unfavorable outcome and mortality (Figure 8B,D). These differences were statistically significant above all ICP thresholds for mortality, while only statistically significant above ICP 0 and 20 mmHg for unfavorable outcome. However, in a multivariable analysis, adjusted for the IMPACT core model variables age, GCS motor score and pupillary reactivity, and maximum total therapy intensity level, PTD_{20} was not a significant predictor of unfavorable outcome (OR 1.0, 95% CI 0.99-1.00; p=0.39), but rather of 6-month mortality (OR 1.0, 95% CI 1.00-1.01; p=0.012). Neither PTD_{intact} (OR 1.0, 95% CI 0.99-1.01; p=0.238) nor $PTD_{impaired}$ (OR 1.02, 95% CI 1.00-1.02; p=0.236) above 20 mmHg were significant predictors for outcome when adjusted for the same features.

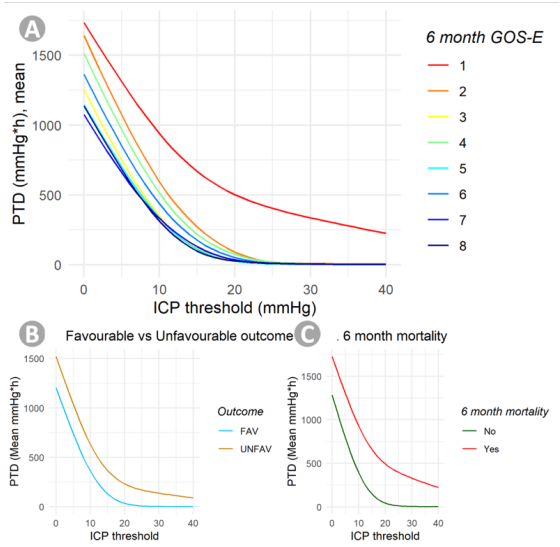

Figure 7: Pressure time dose (PTD) stratified by outcome. A. PTD per GOSE category. **B.** PTD stratified by favorable and unfavorable outcome. **C.** PTD stratified by 6-month mortality. GOSE: Glasgow outcome scale extended.

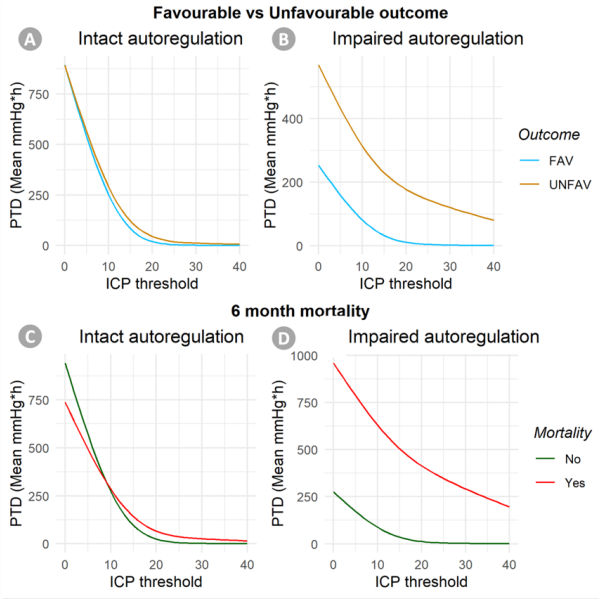

Figure 8: PTD stratified by outcome and cerebrovascular autoregulation status. PTD with impaired autoregulation were higher above all thresholds of ICP for both unfavorable outcome and mortality compared to favorable outcome and survival (**B**, **D**), while no differences in PTD with intact autoregulation were seen (**A**, **C**).

5.2 Study II

5.2.1 Six clusters exhibit distinct patient profiles distinguished by GCS and metabolic state

To determine optimal number of clusters, ten models were created for each number of clusters, and the model with highest log likelihood was chosen as the best model. This was repeated twenty times, generating twenty models for each number of clusters. Cluster similarity index was calculated for each number of clusters: six clusters had the highest median CSI, when a penalty of 1/n(clusters) had been subtracted. The clusters were identified using thirty-three baseline features collected at admission or during the first 24 hours post-injury. Nine of these features were identified as being of most importance to describe the clusters, defined by a mutual information (MI) above 0.1: GCS motor score, GCS total score, lactate, oxygen saturation (SpO_2), creatinine, glucose, base excess, pH, $PaCO_2$, and body temperature (Figure 9).

In aggregate, the clusters could be identified by a combination of GCS and degree of metabolic derangement (Figure 10).

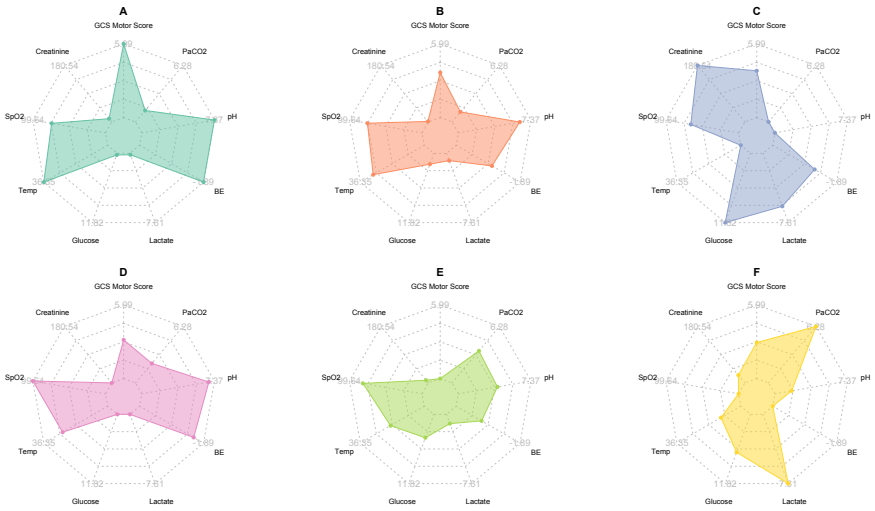

Figure 9: Relative differences in profiles of the identified clusters. Each cluster profile is represented by the most prominent features (defined as mutual information > 0.1). These features were GCS motor score, GCS total score, lactate, oxygen saturation (SpO_2), creatinine, glucose, base excess (BE), pH, arterial partial pressure of carbon dioxide ($PaCO_2$), and body temperature.

5.2.2 Clusters improve current outcome predictions

Information on outcome was not included in the clustering. In all clusters except two (B and C – clusters with moderate TBI according to GCS), the IMPACT extended model overestimated the mortality risk, but underestimated the risk of unfavorable outcome.

By adding the cluster label to the IMPACT extended model, a small but statistically significant increase in Nagelkerke's R^2 were seen both for functional outcome and mortality (0.42 to 0.44; p=0.001, and 0.36 to 0.38; $p=2.9\times10^{-5}$, respectively). This improvement is in the same magnitude as extending the IMPACT core model with the laboratory values (hemoglobin and glucose).

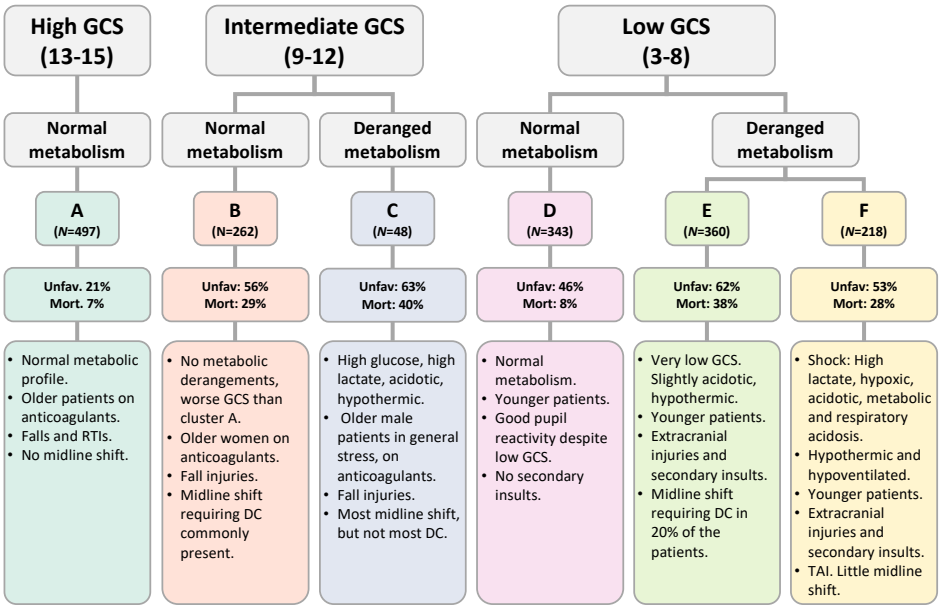

Figure 10: Descriptive analysis of the identified clusters.

5.3 Study III

5.3.1 Glycemic variation and brain biomarkers largely define trajectories during first week in ICU

Using cluster similarity index (CSI) as a measure of robustness could not support a particular number of clusters, as no distinct peak was seen. This suggests that the number of trajectories TBI patients most likely follow in the first week of ICU stay may be a continuum between two and twelve.

Glycemic variation, a panel of serum brain biomarkers (Tau, UCH-L1, GFAP, NFL, and S100B) and serum creatinine were consistently among the most prominent features in describing the clusters from two to twelve clusters, expressed as generating the highest weekly average mutual information. A day-by-day analysis revealed a similar pattern on all individual days. In addition, mean ICP and sodium variation appeared to be more important on early days.

5.3.2 Trajectories are related to previously described admission clusters and improve outcome predictions

Outcome was not considered when generating the clusters. In spite of this, there was a clear difference in outcomes between the trajectories (Figure 11), which, in the case of six clusters, ranged from 3.7% (n=16) to 65% (n=134) mortality and 18% (n=78) to 85% (n=174) unfavorable outcome.

The trajectory assignments in models of three to twelve trajectories added substantial information to outcome prediction beyond that of the IMPACT lab model, with absolute increases in bias-adjusted Nagelkerke's R^2 ranging from 0.02 to 0.09 for mortality and ranging from 0.03 to 0.09 for unfavorable outcome.

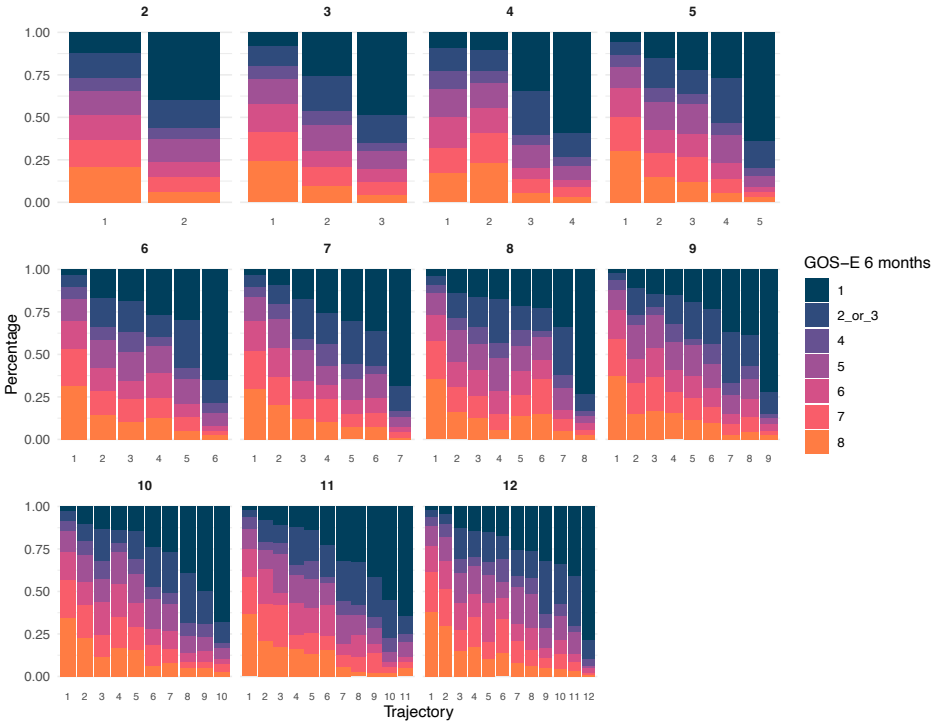

Figure 11: Outcomes in clusters for models of two to twelve number of clusters. Outcome is represented by Glasgow outcome scale extended (GOS-E) where 1 represents "dead" and 8 represents fully recovered.

5.4 Study IV

5.4.1 A directional relationship of pressure reactivity and therapy intensity level on outcome

In a multivariable regression including MAP, PRx, ICP dose above 20 mmHg and TIL towards outcome, PRx (p<0.0001) and TIL (p=0.01) were the only significant predictors of mortality. PRx (p=0.01), TIL (p=0.001), and MAP (p=0.01) were significant predictors for unfavorable outcome defined as GOSE ≤ 4.

The PC algorithm was then used to investigate the causal relationships in a stepwise manner. The results are presented graphically in Figure 12. Correlations still significant when

conditioned on three features were ICP and PTD_{20}; ICP and PRx; heart rate and PRx; $PaCO_2$ and TIL; TIL and GOSE; and PRx and GOSE (Figure 12F). Causal relationships were though only possible to determine for TIL on GOSE and PRx towards GOSE.

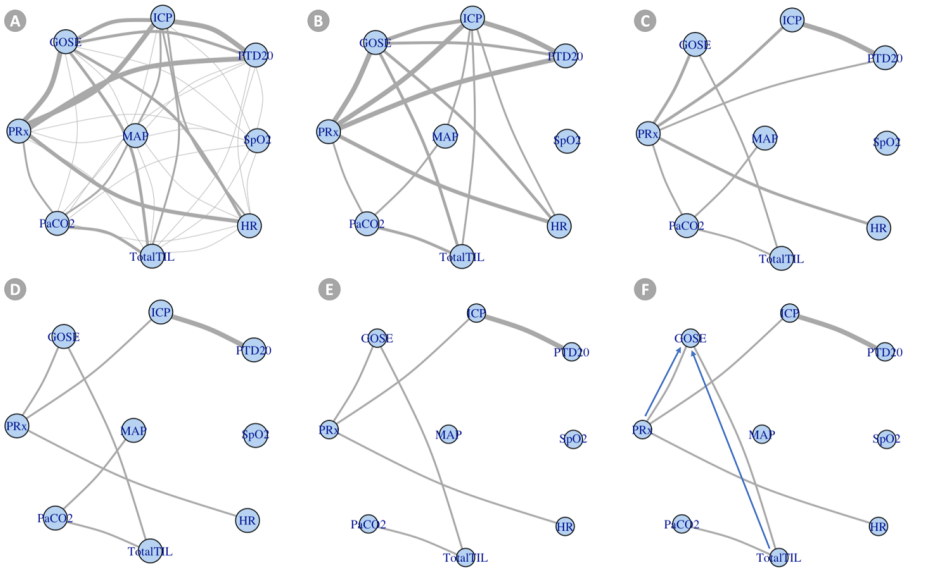

Figure 12: Stepwise implementation of the PC algorithm. A. The complete undirected graph. **B.** In the first step, all unconditional significant correlations are investigated. **C.** In step 2, all correlations are conditionally tested on one feature. **D.** Step 3, all remaining significant correlations are conditionally tested on two features. **E.** Step 4, all remaining significant correlations are conditionally tested on three features. **F.** Directional relationships of the remaining significant correlations are determined.

6 Discussion

This thesis has investigated different aspects of TBI patients admitted to the ICU. Contributions to pathophysiological characterization of this group of patients have here been made by investigation of ICP tolerability in relation to cerebrovascular autoregulation, characterization of patients by admission features using an unsupervised clustering method, and identification of features important in longitudinal assessment during the first week of ICU stay. However, the results need to be interpreted in the context of current evidence, which is the aim of this discussion.

6.1 The ICP dose concept

The concept of ICP dose has indeed been well-studied.[30,32,34–36,62,130–134] Work is ongoing hoping to bring the concept to clinical implementation.[132,133] However, there is not yet a consensus on which threshold of ICP should be used to calculate dose, or a consensus even on how to define it- as number of events of intracranial hypertension, or area under the curve above a certain threshold. In **study I**, we identified an association between dose tolerability and cerebrovascular autoregulation status.[130] In addition, we identified a degree of certainty of tolerable thresholds of ICP intensity and duration: 18 +/- 4 mmHg (2 SD) for five minutes. Thus, even 5-minute long ICP events above 22 mmHg are, with high certainty, correlated with worse outcome.

It is biologically plausible that prolonged periods of intracranial hypertension aggravate injury, although sharp rises with short duration, as those that appear in this study, still have potential of neuronal damage and are thus important to prevent. However, chronic intracranial hypertension may lead to an adaptation to high pressures. In fact, patients have been shown to tolerate pressures as high as 40 mmHg.[31] This may reflect a right-shift in the ICP vs CBF curve, similar to what is seen in chronic systemic hypertension.

The dose concept may be appealing for several physiological processes. In fact, CPP dose has been shown to correlate with outcome, where tolerability was greater when cerebrovascular autoregulation was intact.[135] Dose of intraoperative hypotension has also been investigated, where larger doses were associated with increased risk of myocardial and kidney injury as well as with mortality.[136–138]

Before a consensus is reached on how to define and measure ICP dose, it may be premature to include the concept in current guidelines, even though Meyfroidt *et al.* recommend taking the dose of ICP into consideration in a recent management update.[50] In addition, the introduction of the dose concept will not replace the need of identifying thresholds of absolute values of ICP: dose calculations require computational resources which may not be available in low-resource settings and should rather be seen as a possible additional biomarker in TBI.

6.2 Time for revision of ICP thresholds?

A fixed ICP level has been questioned as a treatment target. During recent years, several studies have indicated that it might not be ICP elevations above a fixed target that are harmful, but the total dose of ICP over time.[34,35] Zeiler and Lazaridis have also shown that individualized thresholds of ICP strengthen the association to outcome and may be lower than guideline thresholds,[31,32] but more studies are needed before it can be implemented in clinical praxis. Results from other studies indicate that ICP tolerability may vary depending on the cerebrovascular autoregulation status, represented by the moving average correlation coefficient between MAP and ICP – the pressure reactivity index (PRx). During episodes of impaired autoregulation, very few tolerable ICP levels have been identified.[30]

Brain Trauma Foundation (BTF) guidelines state 22 mmHg as a threshold of ICP, a recommendation that has not been changed since the last version of the guidelines in 2016.[27] This threshold is based on one single previous study where values above were found to be associated with mortality.[28] Since then, cumulative evidence suggests that tolerable ICP thresholds may be slightly lower than those suggested by guidelines.[30–32,130,134,139]

Common clinical practice in Europe focuses on avoiding values above 20 mmHg.[29] Rather than a treatment threshold, 20-22 mmHg might be regarded a medical emergency, as values above this threshold are associated with increased mortality while thresholds for favorable outcome are lower.

The concept of individual thresholds is appealing, and doses above individualized thresholds have been shown to correlate stronger with outcome than those above generalized thresholds.[31,32] In **study I**, we found a population-dependent and cerebrovascular autoregulation status-dependent variation in threshold.[130] Multiple findings of lower tolerability in older patients further support the use of individualized thresholds.[28,140] ICP thresholds associated with worse outcome have also been shown to be lower over time.[140] The use of an individualized approach is indeed advocated by leading experts in the field of TBI.[50,141,142] However, most TBIs occur in low- and middle-income countries, where resources are limited, and this approach may not be feasible. Fixed thresholds may thus still be needed to guide treatment as to improve outcome.

ICP is not an isolated physiologic parameter and is confounded by ICP management therapies and closely associated with its derived measures CPP and PRx. It should be interpreted in combination with treatments and other brain physiology measures such as $PbtO_2$, cerebral metabolism and blood flow.[50,141,143] In fact, Kim *et al.* have proposed a novel index called duration of severe hypoperfusion (dHP) defined by simultaneous PRx > 0.2, CPP < 70 mmHg, and ICP above 20 or 22 mmHg. A 25-minute duration of dHP was significantly correlated to 6-month mortality.[144]

The variation in suggested ICP targets, and its interplay with other facets of brain physiology (e.g., cerebrovascular autoregulation) and treatments make the "true" tolerable threshold difficult to determine. In addition, thresholds identified in observational studies are most likely

biased by recommendations, where the negative impact of ICP above recommended thresholds simply may reflect refractory ICP.

A new recommendation will most likely be consensus-based. The question remains if it will be lower than today's 22 mmHg threshold or if it will be individualized. However, it is important to remember that the primary aim with an ICP threshold is to avoid second insults which can aggravate the primary injury. A holistic TBI-management approach (as suggested by Chesnut *et al.*) may be a better target than an ICP-focused one in improving outcome after TBI.[142]

6.3 The role of cerebrovascular autoregulation

In **study I**, we found a difference in ICP tolerability depending on cerebrovascular autoregulation. In the visualization plots of duration and magnitude of ICP elevations, no tolerable ICP levels were identified if autoregulation was impaired (PRx ≥ 0.3), while 19 mmHg for 5 minutes or longer, or 15 mmHg for 50 minutes or longer, were correlated with worse outcome if autoregulation was intact. Group differences (i.e., survivors vs. non-survivors and favorable vs. unfavorable outcome) in PTD were also larger in periods of impaired autoregulation than in periods of intact autoregulation. This result raised the question of causality: are ICP and autoregulation causal factors of outcome or rather associations related to injury severity? In **study IV**, we did a follow-up analysis where causal relationships of these parameters in combination with other ICP-related factors and treatments were investigated, and a directional relationship of PRx and TIL on outcome was revealed. When conditioning on other features, no direct causal relationship between ICP and outcome were found. However, the analysis was made on weekly averages of the features, and it is possible that additional causal relationships can be identified on daily sub-analyses.

This result is interesting and raises the question if we should use a PRx-guided treatment approach rather than an ICP-focused one. Indeed, PRx has in multiple studies been shown to correlate to outcome.[28,38,134,145] On the other hand, PRx has been shown to not correlate with therapeutic intensity,[45,146] why may preclude its use as a treatment target in TBI. However, PRx have proven useful in identifying optimal CPP levels[48,147] and individualized ICP thresholds,[31,32] supporting a greater role in TBI management than only being a marker of disease. Incorporating assessment of cerebrovascular autoregulation status by PRx assessment and MAP challenges to assess optimal CPP have been suggested in recent consensus-based management algorithms.[6,50]

6.4 Phenotyping of TBI patients

There has been a strong call to identify TBI endotypes; subgroups of patients which might benefit from different treatment approaches. The hope is also that this may yield important

subgroup analyses in clinical trials to find effective treatments targeted to different groups of patients.[3,9,11]

In **study II**, we included a wide range of clinically interesting and relevant features, both previously identified to be associated with outcome and features judged to be of clinical interest. Six endotypes were identified and could be described by GCS and pattern of metabolic derangement represented by glucose, body core temperature, pH, lactate, base excess, arterial partial pressure of carbon dioxide, oxygen saturation, and creatinine. Notably, two different types of metabolic derangement were observed: in a group with intermediate GCS (mean 9-12), the pattern might be interpreted more as the result of a general stress response, with high glucose and lactate, whereas, in a group with low GCS (<9), the pattern may be presumably related to systemic shock and possibly a different genesis of lactate, associated with extracranial injuries.

Although no information on outcome was included in the model, the described clusters added information towards outcome in addition to previously identified important outcome predictors of the IMPACT model. To our knowledge, this is the most extensive unsupervised clinical endotyping of TBI patients in the ICU. An inflammatory response to TBI is gaining more attention. Unfortunately, inflammatory markers were not available in our dataset, but would be valuable to assess in the clusters. In addition, the biomarker and genetic profiles of the clusters would be interesting to assess, as there is an emerging belief that current classification models of TBI can be significantly improved by including genetic markers and biomarkers. However, to date, no classifications in TBI have incorporated these markers.[4,10]

In **study III**, we described trajectories during the first week of ICU. No fixed number of clusters were found to best distinguish the trajectories, supporting there may rather be a continuum of trajectories. All number of clusters between two and twelve performed similarly with respect to cluster similarity, prediction improvement beyond IMPACT model and outcome distributions. The most important finding was the relatively high contribution of biomarkers of brain injury and homeostasis, which consistently in our analyses showed to be of greatest importance in defining trajectories. The importance of biomarker assessment has been highlighted before: A relationship to intracranial lesions has been described both in the acute phase,[148,149] longitudinally[150,151] and in late functional assessment.[152] Currently, few centers, that we are aware of, use serial brain injury biomarkers as a monitoring modality in clinical practice. Our results further support the incorporation and extension of serial biomarker sampling in clinical TBI management algorithms.

Variations in daily values of glucose and sodium were shown to be of greater importance than absolute values, although daily variations were, in general, low. This does not exclude absolute values of these features from being important. However, the results are supported by previous observational studies,[69,153] although causal relationships are not well-understood. Suggested mechanisms of injury related to glucose variation are oxidative stress triggered by altering glucose levels, an association with sympathetic stimulation and hyperactivation seen in TBI, or simply a marker of less attentive care.[90] Sodium homeostasis is also important and has been

reported to correlate with outcome.[69] There are several possible explanations to the observed variation: sodium may either be a marker of treatment intensity, since hypertonic saline is a commonly used method of ICP management, or a neuroendocrine disturbance of antidiuretic hormone (ADH) secretion. Serum creatinine as a recurrent important factor when describing the clusters and trajectories, predominantly on early days post-injury requires attention. The exact mechanism remains unknown, but pre-injury comorbidities, colloidal ICP lowering treatments, polytrauma and systemic hypotension may possibly be contributing.

Although our proposed endotypes show explainable underlying mechanisms, it is important to stress that the results have not been validated in an external cohort and the results still need to be regarded as hypothesis-generating. If external validation is successful, restratification according to the proposed subgroups of study cohorts in previous interventional studies could be performed, to investigate treatment effects in the hypothesized groups. Only then, if the endotypes still seem promising, may a clinical implementation of these results be feasible.

In summary, the temporal patterns of both intra- and extracranial features such as glucose variation, brain biomarkers and serum creatinine may add valuable information towards outcome in TBI. However, underlying mechanisms still need to be investigated further.

6.5 Methodological considerations

The results in this thesis are all derived from prospectively collected observational data from 63 centers in 19 European countries. Data was often irregularly sampled and not complete, with different mechanisms for missingness. In addition, physiological features could not be assumed to be linearly dependent, and not only continuous but also categorical features were collected, adding further demands to choice of analytical methods and considerations.

To enhance the quality of the data in CENTER-TBI, much time was spent on data curation through a team effort between clinical experts and persons with technical expertise. With time, the awareness of its importance increased. No matter how careful you are in designing databases and CRFs – when data will be collected by people from 19 centers in different countries with different practices and habits, individual interpretations are to some extent inevitable. The importance of data curation is often overseen. It is indeed a time-consuming task, but not only will it increase the quality of the dataset, but also lead to a better understanding of a study's strengths and limitations.

6.5.1 High-resolution ICP signals

In **study I**, we analyzed data from high-resolution ICP signals. Patients with both EVD and parenchymal ICP sensors were included. In other studies, patients with EVD are often excluded as the dynamics of registered ICP signals are difficult to interpret in relation to open drains. To not limit our already small sample size (n=227) we decided to include these patients (n=23 [10%]) after manual inspection of the ICP signals, where we could not identify longer periods

of open drains. Patients with decompressive craniectomy (DC) were included in the analysis (*n*=53 [23%]) as well. This choice was justified as sub-analyses excluding craniectomized patients showed no large differences in the intensity and duration plots in concert with results from a previous study on the same cohort which could not identify large differences in pressure dynamics between DC and non-DC patients.[154]

6.5.2 Clustering considerations

When deciding which clustering method to use, we searched for a method suitable for handling not only continuous but also categorical data. The method should preferably be insensitive to missingness, as we wanted to avoid imputation, and not require linear dependency of included features. In addition, we wanted to perform unsupervised clustering, as we were searching for patterns beyond those that could immediately be related to outcome but may still benefit from differentiated therapies. This led us to the choice of probabilistic graph models and expectation maximization algorithm in **study II and III**.

Results generated by clustering are left to some degree of interpretation. Results are sensitive to which features were included in generating the model, the number of clusters decided to use, and method selection. These are reasons why results generated by unsupervised clustering should be regarded as hypothesis-generating rather than hypothesis-tested. Trying to objectify our interpretations, we limited our primary feature selection to previously known outcome predictions in TBI and other features of clinical interest, judged by clinical experience in the team. Number of clusters was sought by the optimization of the cluster similarity index in combination with clinical feasibility. For the final interpretation of the clusters, mutual information – commonly used in machine learning for this purpose – was used to limit the features for interpretation. Nevertheless, it is impossible to claim that the final interpretation is completely objective and that the results can be generalized without further validation and testing.

6.5.3 A few remarks on causal inference

In **study IV**, we wanted to investigate causal relationships between signals of different frequencies, such as high-frequency physiologic signals of ICP, MAP, and PRx, low-frequency $PaCO_2$, and ICP-lowering treatments and outcome. The main question was the causal relations to outcome. One may argue that a correlation identified through classic logistic regression analysis would be enough to claim causality to outcome, as there is a clear temporal relationship between the measurements and outcome six months later. However, as we also wanted to understand the inter-relationships and its directions of ICP and related measures, logistic regression would not be enough to answer our question.

We had access to high-resolution signals of ICP, MAP and PRx. Averaging signals over time will lead to loss of information, such as variability and intermittent peaks. To be able to analyze these signals in relation to other less frequently sampled signals, reducing the high-frequency signals was necessary. Despite this, we could identify a directional relationship of PRx on outcome and TIL on outcome. However, it is possible that averaging over shorter time periods

may have revealed additional causal relationships, which should be investigated further in follow-up analyses. The validity of the causal relationship of TIL on outcome may be debated as high tier-treatments are related to injury severity, which we did not adjust for in our analysis. To investigate the relationship of TIL on outcome further, injury severity score (ISS) should be included in future models.

7 Conclusions

In this thesis we have characterized TBI patients by previously unidentified patterns:

- There is a variation in ICP magnitude and duration thresholds associated with outcome, with a stronger association and lower thresholds if cerebrovascular autoregulation is impaired. The pressure time dose of ICP shows an even stronger association with outcome when autoregulation is impaired. Causal inference analysis suggests impaired cerebrovascular autoregulation to be more directly causally related to outcome than ICP itself. The results highlight the importance of ICP dose, individualized ICP thresholds and a continued focus on cerebrovascular autoregulation.

- TBI patients may be characterized not only by brain-specific pathophysiology, but through extracranial manifestations, such as metabolic derangement. Whether these are markers of disease severity or concurrent extracranial disease or rather aggravators of second insult, remains to be investigated.

- Glycemic variation and serial brain biomarker sampling were identified as the most important descriptors of trajectories in TBI patients in the ICU. These trajectories were found to relate with outcome. This points to a need for studies on the effects of glycemic variation in TBI patients and supports the use of serial biomarkers as a monitoring modality.

- Unsupervised clustering methods and novel causal inference methods may complement traditional statistical methods and RCTs, but generated results need to be validated before potential clinical implementation.

8 Future directions

Given the observational nature of the study, the results presented in this thesis should be regarded as hypothesis-generating rather than scientific proof. Before the findings can be clinically implemented, results need to be externally validated to prove generalizability, and underlying mechanisms needs to be better understood.

The ICP dose has been extensively studied from different perspectives and studies are currently underway aiming to bring the concept into clinical practice. However, the lack of a consensus on how to define the dose – by number of events above thresholds of ICP and duration or by pressure time dose (PTD), and if so, above which threshold – may slow down its clinical implementation. A review of the available literature in the field may be an important next step followed by a consensus statement to unify the TBI research community.

The admission clusters and longitudinal trajectories found in these studies need to be validated in external datasets. If validation is successful, a next step towards implementation is to classify patients in previous interventional studies according to the endotypes to investigate differences in treatment responses. If the endotypes still are promising, stratification of patients in prospective RCTs may increase the probability of identifying effective treatments.

The proposed endotypes support an important role of extracranial manifestations of TBI and its potential to aggravate brain injury. Though recognized, exact mechanisms remain largely unclear. Future studies are needed to better understand the interplay of TBI and systemic manifestations such as inflammation and sympathetic hyperactivation. Additionally, investigating if genetic patterns might be related to clusters could help identify mechanisms.

Causal inference in TBI is still largely an understudied area of research. These tools are gaining momentum in several fields but have been used to a limited extent in medicine. If proven advantageous in TBI research, they may act as a complement to RCTs, although it is unlikely that analytical methods on observational data will outperform well-conducted RCTs.

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