

ORIGINAL WORK



Toward Causal Relationships of Intracranial Pressure, Cerebrovascular Reactivity, Interventions, and Outcome in Severe Traumatic Brain Injury: A CENTER-TBI High-Resolution Substudy

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Abstract

Background: Most available evidence for treatment and outcome prediction in traumatic brain injuries (TBI) is derived from observational studies. Such association studies provide limited evidence for the causality of relationships. While randomized controlled trials are appropriately regarded as the gold standard for causal inference, there are many domains where such experimental approaches are not feasible. During the last decades however, mathematical methods have been developed to infer causal relationships from observational data. This study aims to investigate causal relations of systemic and cerebral physiological parameters, intracranial pressure (ICP)-lowering interventions, and outcome in patients with severe TBI.

Methods: Patients with severe TBI enrolled in the prospective observational Collaborative European Neurotrauma Effectiveness Research in TBI (CENTER-TBI) High-Resolution Substudy group were included ($n = 201$). We applied a causal inference algorithm to determine causal relations between the first week post-injury mean of values of ICP, cerebrovascular reactivity (PRx), cerebral perfusion pressure (CPP), heart rate, oxygen saturation, arterial partial pressure of carbon dioxide, ICP-lowering therapies [represented by the therapy intensity level (TIL) score], and 6-month outcome represented by Glasgow Outcome Scale-Extended (GOSE).

Results: The median age was 51.5 years [interquartile range (IQR) 31 to 64], 158 were men (77.5%), and median GOSE at 6 months was 3 (IQR 3 to 5). PRx and TIL score were the only features identified as directly related to outcome in this analysis ($r = -0.19, p = 0.003$; $r = -0.20, p = 0.002$, respectively). Significant correlations between ICP and CPP ($r = -0.62, p < 0.0001$); ICP and PRx ($r = 0.31, p < 0.001$); PRx and heart rate ($r = 0.17, p = 0.007$); and PaCO_2 and TIL score ($r = -0.19, p = 0.004$) were identified after conditioning on triples of the other features.

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Conclusions: The results suggest that cerebrovascular autoregulation status (PRx) and ICP-lowering therapies may be more directly associated with outcomes than ICP itself and that these factors should be considered in ICP monitoring and management strategies.

Keywords: Brain injuries, Traumatic, Critical care, Intracranial pressure

Introduction

Traumatic brain injury (TBI) is a global health problem in both high- and low-income countries. It is the main cause of death among young adults and is increasing among the elderly. ¹ Despite much research in the field, few specific treatments exist for patients with TBI. Most of the available evidence in treatment and outcome predictions in TBI is derived from observational studies, which can give guidance in associations, but usually not enough evidence to claim cause-and-effect relationships. Moreover, few randomized controlled trials (RCTs) in intensive care have been positive or reproducible, thus providing limited guidance in deciding optimal patient treatments. Furthermore, when studying physiological interactions and epiphenomena, it may not be possible to manipulate a specific parameter in isolation experimentally. Thus, new methods to identify causal relationships are sorely needed.

Intracranial pressure (ICP) is central to neurointensive care. The brain's location in a rigid shell, its high metabolic rate, and limited energy reserves, combined with a tendency to swell as a response to trauma, prove unique challenges of monitoring and treatment. This involves multiple modes of monitoring of the injured brain, including intracranial pressure, cerebral perfusion pressure, imaging, among others. How to interpret and weigh these complicated, often-conflicting information streams is unclear. Although the positive correlation between high ICP and worse outcome has been well described ^{2–4}, it has not been concluded whether it is the ICP elevations, per se, causing an unfavorable effect or whether ICP is merely a surrogate measure of other composite physiological processes affecting outcome. To understand the causal relationship between ICP and outcome is important, as ICP-directed therapies are a cornerstone in neurocritical care. Such therapies can be summarized in the therapy intensity level (TIL) score, where therapies associated with higher risks for adverse outcomes, such as hyperventilation and decompressive craniectomy, generate higher scores ⁵.

During the last decades, analytical methods to study causal inference from observational data have been developed and more widely accepted, not least in social sciences and economics, where RCTs may be impossible to conduct. In 2021, David Card, Joshua Angrist, and Guido Imbens were awarded the Prize in economic

sciences in memory of Alfred Nobel for their applications of causal inference methods to study observational data from the labor market ⁶. As these methods have proven successful, increasing interest has been seen in the field of medicine, where it has been proven a powerful tool to draw causal inferences from observational data ⁷. Although few RCTs have proven positive in the field of traumatic brain injuries, there is some evidence that both deranged physiology and treatments to normalize it all affect long-term outcome ^{8–12}. This raises the question of whether causal relationships between these factors and outcome can be revealed. In this study, we therefore aim to investigate causal relationships between systemic and cerebral physiological parameters, ICP-lowering treatments, and outcome after TBI.

Methods

Patients enrolled in the prospective observational multicenter study Collaborative European Neurotrauma Effectiveness Research in TBI (CENTER-TBI), between 2014 and 2017, with high-resolution data collection of intraparenchymal ICP and arterial blood pressure (ABP), were included ($n=273$). All patients met the general inclusion criteria for CENTER-TBI: a clinical diagnosis of TBI, a clinical need for a computed tomography (CT) scan, and presentation at hospital within 24 h of injury. Ethical approval was obtained for each recruiting site.

Data Collection and Processing

Data for the CENTER-TBI study were collected through the Quesgen e-CRF (Quesgen Systems Inc, USA), hosted on the INCF platform. We extracted data on daily treatments, TIL scores, demographics, injury mechanisms, computed tomography (CT) scans, laboratory values, and clinical monitoring from the CENTER-TBI core dataset version 3.0 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. Heart rate, oxygen saturation (SpO₂), and arterial pressure of carbon dioxide (PaCO₂) were collected up to 12 times daily, and TIL scores were collected daily. The high-resolution physiological signals of ICP and ABP were collected with frequencies of up to 500 Hz. Pressure reactivity index (PRx)—a measure of cerebrovascular

autoregulation status—was calculated using ICM+ 13 as the moving Pearson correlation coefficient between 30 consecutive 10-s averages of ICP and mean arterial pressure (MAP), with a missing data limit of 50%, updated every minute 14, 15. Minute summaries of ICP, cerebral perfusion pressure (CPP), and PRx were calculated with ICM+. No missing data were imputed. All metrics were extracted from the first week post-injury and averaged for further analysis, except for total TIL score, which was represented by the maximum daily TIL score.

Outcome was represented by 6-month Glasgow Outcome Scale-Extended (GOSE) score. This is an eight-level scale representing functional outcome after TBI, where 1 represents death and 8 full recovery. If GOSE score was missing at 6 months but assessment was made at other time points post-injury, a score was imputed using present data, a derivation made centrally in CENTER-TBI, which has been described previously. 16

Causal Inference

The PC algorithm (named after Peter Spirtes and Clark Glymour) was used to investigate causal relationships in neurointensive care unit (ICU) data from patients with TBI. This algorithm investigates conditional dependencies between multiple features to draw causal inferences and has been described in detail elsewhere 17, 18. Briefly, it consists of three steps: (1) Calculate pairwise correlations between all pairs of features; (2) construct a “skeleton” of direct relations between features, by systematically conditioning on subsets of features, and remove those correlations that become nonsignificant in this process; and (3) try to establish the causal direction of the remaining direct relations. Lacking any external clues on causal direction, the third point can be made by identifying so-called V-structures. Not all causal relations can be found by this method, but some correlations will remain with undetermined direction. However, if there are other clues, such as a clear temporal ordering, this can also be used for deriving causal direction.

We set the threshold for significance of correlations to <0.01 . Correlations between all pairs of features were calculated. The remaining significant correlations were then tested for conditional independence on one feature at a time. Pairs of features still correlated after this conditional testing were tested for conditional independence on pairs of features. The remaining correlated features were then tested for conditional independence on triplets of features. Still correlated features were represented in a graph to visualize dependencies. These correlations were then tested for causal directions by determining so called V-structures in the dataset: If three features $A-B-C$ are correlated, but no correlation is found between A and C directly, it can be concluded that there is a causal effect

on B from both A and C ($A \rightarrow B \leftarrow C$) if B is not in the separation set of (A, C) (that is— A and C were not independent conditioned on B).

Causal relationships were investigated between the following features: ICP, PRx, CPP, heart rate, SpO_2 , (PaCO_2), maximum total TIL score, and GOSE 6 months post-injury. These features were selected because of known importance on intracranial pressure or its derived indices or outcome. The TIL score is a weighted sum of the following ICP-lowering therapies: head elevation for ICP control or lying flat for CPP control, sedation, neuromuscular blockade, cerebrospinal fluid (CSF) drainage therapy, given fluid bolus, vasopressor, hyperventilation, mannitol bolus, hypertonic saline bolus, temperature control, intracranial surgery for ICP control, and decompressive craniectomy. 5

The unconditional and conditional dependencies were calculated using Python version 3.8.15. Graphical representation and other statistical analyses were performed using statistical software R (version 4.3.2).

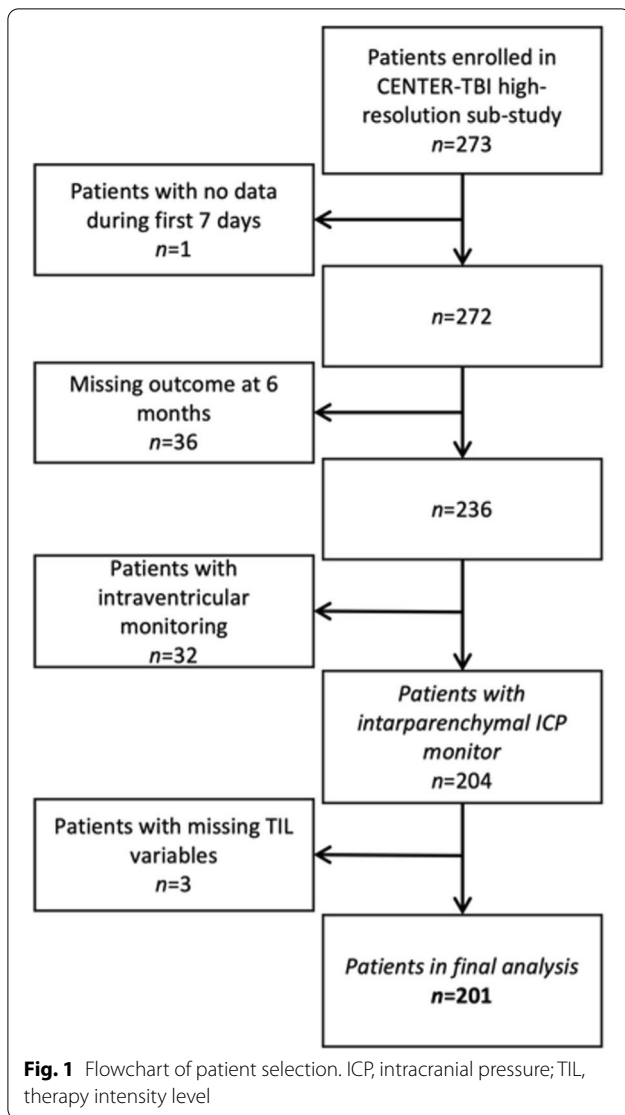
Multivariable Logistic Regression

To investigate direct associations with outcome, the causal inference analysis was complemented by an ordinal multivariable logistic regression. The model included all features, and GOSE at 6 months was used as outcome measure.

Results

Patients with no monitoring data within the first 7 days post-injury ($n=1$), individuals with missing outcome at 6 months ($n=36$), patients with no intraparenchymal ICP monitoring ($n=32$), and those with missing data on ICP-lowering treatments ($n=3$) were excluded, leaving $n=201$ patients for the final analysis (Fig. 1). Overall, 77.5% ($n=158$) were men, with a median age of 51.5 years [interquartile range (IQR) 31 - 64] (Table 1). The median maximum TIL score was 9 (IQR 6–14) and median GOSE at 6 months was 3 (IQR 3–5). The frequency of the used interventions are presented in Table 2. There were no missing data in the weekly averages of parameters used in the analysis.

To investigate direct associations with outcome, distributions of all features stratified by outcome were assessed (Supplementary Material (SM) Supplementary Fig. S1). The PC algorithm was implemented in a stepwise manner, as described in the Methods (Fig. 2). In the first step (Fig. 2a and SM Supplementary Table S1), nonsignificant correlations ($p>0.01$) were removed. Then, nonsignificant correlations conditioned on any other single feature were removed (Fig. 2b and SM Supplementary Table S1). In the third step, Fig. 2c (SM Supplementary Table S1), correlations between all remaining pairs of features were



conditioned on all pairwise combinations of the other remaining features. In the final step, the remaining pairs of features were conditioned on all triples of features (SM Supplementary Table S1), and remaining significant correlations are shown in Fig. 2d. Of the last remaining significant correlations, the algorithm could not identify any unambiguous V-structures (SM Supplementary Table S2). However, as GOSE is determined 6 months later than the measurements of the physiological parameters, a causal relationship can still be considered valid of PRx toward GOSE at 6 months ($r = -0.19$, $p = 0.003$) (SM Supplementary Fig. S2), and TIL score toward GOSE ($r = -0.20$, $p = 0.002$) (SM Supplementary Fig. S3). Neither ICP, CPP, heart rate (HR), nor PaCO_2 were directly related to outcome, but significant correlations were identified between ICP and CPP ($r = -0.62$, $p < 0.001$); ICP and PRx ($r = 0.31$, $p < 0.001$); PRx and HR ($r = 0.17$,

$p = 0.007$); and total TIL score and PaCO_2 ($r = -0.19$, $p = 0.004$) (Table 3).

An ordinal multivariate regression was performed of the investigated features and GOSE, generating a Nagelkerke's pseudo- R^2 of 0.26. PRx [odds ratio (OR) 0.51; 95% confidence interval (CI) 0.36–0.71], CPP [OR 1.61 (95% CI 1.10–2.36)], and heart rate [OR 0.76 (95% CI 0.58–0.99)] were the only significant predictors of GOSE 6 months post-injury (SM Supplementary Table S3).

Because the distributions of PRx and TIL were markedly higher among patients who died (SM Supplementary Fig. S2), two post hoc analyses with dichotomized outcomes were performed. The first compared survivors and nonsurvivors, and the second examined outcomes within the survivor group, categorized as unfavorable (GOSE 2–4) vs. favorable (GOSE 5–8) outcome. In the analysis of survivors/nonsurvivors, the relationship of PRx and GOSE remained significant after conditioning on triples of the other variables ($p < 0.001$). In contrast, within the survivor group, no significant associations between GOSE and any of the other variables were observed after conditioning on triples (SM Supplementary Fig. S4).

Discussion

We have aimed to describe causal inferences between a set of clinical features in a cohort with severe TBI. Our analysis suggests that the cerebrovascular reactivity status and the use of ICP-lowering therapies is more directly related to long-term outcome than the achieved intracranial pressures and cerebral perfusion pressures in this cohort of highly managed neurointensive care patients. These findings require further investigation but imply a utility of individualized PRx-guided CPP in neurointensive care, in addition to targeting general ICP and CPP levels. The findings also support that the interpretation of ICP thresholds 19 might also need to be related to concurrent ICP-lowering therapies.

In the final step of the causal inference analysis, we could not identify any V-structures; however, we believe the results from this study still imply a directional relationship of PRx score toward GOSE as well as TIL score toward GOSE, as the correlation was still highly significant when conditioning on all possible triple combinations of the other features, and a correlation with an outcome 6 months later in time indicates a directional relationship given the temporal pattern.

Our primary causal model identified a direct relationship between PRx, TIL, and GOSE, which was further supported by an ordinal multivariate logistic regression analysis. Post hoc analyses (SM Supplementary Fig. S4) indicate that the PRx–GOSE relationship is driven by mortality, with no significant associations within the survivor group. The TIL–GOSE relationship could not be

Table 1 Patient characteristics

Age, years		51.5 (31–64)
Sex, male		158 (77.5)
Injury severity	Total ISS	34 (25–43)
	Extracranial ISS, highest	9 (0–16)
	Head ISS	25 (25–25)
Pupil response, best	Both reacting	115 (56.4)
	One reacting	15 (7.4)
	None reacting	74 (36.3)
GCS total score at arrival		6 (3–10)
<i>Second insults</i>		
Seizures		31 (15.2)
Hypotension		78 (38.2)
Hypoxia		72 (35.3)
Hypocapnia		13 (6.4)
Heart rate, max		111 (99–125)
MAP, lowest (mmHg)		64 (58–70)
ICP (mmHg)	Max daily mean	22.8 (18.5–29.15)
	Mean first week	11.9 (9–14.9)
PRx	Max daily mean	0.20 (0.07–0.34)
	Mean first week	0.03 (–0.08 to 0.16)
CPP, lowest (mmHg)		37 (29–44)
Intubation		203 (99.5)
Total ICP monitoring time (days)		5.1 (3.6–7.0)
CSF Drainage volume (mL)	Total first week	158 (90.5–520)
Fluid balance (L)	First day	0.9 (0.03–1.7)
	Total first week	2.3 (–0.1 to 5.5)
Monitoring time (days)		5.1 (3.4–7.1)
<i>Laboratory results</i>		
Glucose, daily mean (mmol/L)	Lowest	6.21 (5.33–6.9925)
	Highest	9.5 (8.05–11.42)
Hb, daily mean lowest (g/dL)		96 (86–106.25)
Lactate, first day highest (mmol/L)		2.3 (1.375–3.7)
Base excess, first day highest		–2.6 (–5.75 to –0.65)
SpO ₂ , daily mean lowest (%)		93 (88–95)
pH, daily mean lowest		7.34 (7.28–7.37)
PaCO ₂ , daily mean (kPa)	Lowest	4.1 (3.7–4.4)
	Highest	6.1 (5.7–6.825)
PaO ₂ , daily mean lowest (kPa)		9.5 (8.6–10.9)
Albumin, lowest		28.5 (24–34)
Sodium, highest		146.5 (143–150.5)
<i>CT characteristics</i>		
Midline shift	Yes	60 (29.4)
	Max (mm)	0 (0–5)
Fisher classification		2 (2–4)
Rotterdam CT score		4 (3–5)
aSDH		111 (54.4)
Contusion		129 (63.2)
TAI		57 (27.9)
tSAH		155 (76)
EDH		40 (19.6)
GOSE 6 months post-injury	Median	3 (3–5)

Table 1 (continued)

1	48 (23.5)
2 or 3	55 (27)
4	19 (9.3)
5	38 (18.6)
6	21 (10.3)
7	11 (5.4)
8	12 (5.9)

Data are presented as median (interquartile range) or *n* (%) as appropriate

aSDH Acute subdural hematoma, *CPP* Cerebral perfusion pressure, *CSF* Cerebrospinal fluid, *EDH* Epidural hematoma, *GCS* Glasgow coma scale, *GOSE* Glasgow outcome scale-extended, *Hb* Hemoglobin, *ICP* Intracranial pressure, *ISS* Injury severity score, *MAP* Mean arterial pressure, *Max* maximum, *PaCO₂*, Arterial partial pressure of carbon dioxide, *PaO₂* Arterial partial pressure of oxygen, *SpO₂* Oxygen saturation, *tSAH* Traumatic subarachnoid hemorrhage, *TAI* Traumatic axonal injury

Table 2 Intracranial pressure-lowering treatments

Total TIL score	Mean	5.7 (3.8–9.5)
	Max	9 (6–14)
CSF drainage therapy	No	167 (81.9)
	< 120 mL/day	15 (7.4)
	≥ 120 mL/day	19 (9.3)
Decompressive craniectomy		32 (15.7)
Surgery for ICP control		39 (19.1)
Fluid bolus		130 (63.7)
Hyperventilation therapy	PaCO ₂ 4.6–5.3 kPa	92 (45.1)
	PaCO ₂ 4.0–4.5 kPa	43 (21.1)
	PaCO ₂ < 4.0 kPa	10 (4.9)
	No	56 (27.5)
Mannitol bolus	< 2 g/kg/24 h	43 (21.1)
	> 2 g/kg/24 h	1 (0.5)
	No	157 (77)
Neuromuscular block		59 (28.9)
Head elevation for ICP control		164 (80.4)
Nursed flat for ICP control		45 (22.1)

Data is presented as *n* (%) or median (interquartile range) as appropriate. *CSF* Cerebrospinal fluid, *ICP* Intracranial pressure, *TIL* Therapy intensity level

confirmed in the post hoc analyses of survivors vs. non-survivors (SM Supplementary Fig. S4A), or among survivors only (SM Supplementary Fig. S4B), indicating an effect across functional outcomes.

The association between cerebrovascular autoregulation status and long-term outcome in TBI has been described, and it has been shown to improve current outcome prediction models 15, 19–21. Current guidelines and consensus-based treatment algorithms for patients with severe TBI also recommend assessing autoregulation 22, 23. In a previous study using this dataset, we found that the ICP insult dose (magnitude and duration of elevated pressure) and intracranial hypertension are more poorly tolerated in the presence of impaired autoregulation 24. The same patterns were seen in a previous study investigating tolerability

of CPP insults during intact or impaired autoregulation 25. These results suggest a direct association of cerebrovascular reactivity and outcome, distinct from purely absolute ICP level and CPP levels, suggesting that the autoregulatory state is a main driver of outcome. This study also finds support that the general (mean) autoregulatory state during the first week may be more clearly causally related to outcome than ICP and CPP. However, it must be noted that this applies to grand mean values, and relations at higher temporal resolutions are not investigated here.

We were not able to identify a direct linear relationship of CPP and PRx, as averaged over the first week post-injury, although the relationship could be described as mediated by ICP (Fig. 2 and SM Supplementary Table S1). It is likely that this is also influenced by the fact that the PRx–CPP relationship is on average nonlinear. In addition, in this study, we have investigated relationships between patient averages, which again does not exclude direct relationships between features at higher temporal resolutions. The relationship between CPP–ICP–PRx–GOSE is in line with the emerging focus on PRx-derived CPP targets, and in particular CPPopt 26 and the lower limit of reactivity 27—where treatment is targeted at the CPP where cerebrovascular autoregulation is deemed most highly functioning. In a recent RCT, patients where CPP was targeted at CPPopt were found to have a mortality of 23% compared with 44% in the group with nonindividualized CPP targets 28. However, the study was designed to prove feasibility and safety of CPP-targeted management of severe TBI and thus was underpowered to detect a statistical significance in outcome differences. In the assumed absence of influential unmeasured confounders, our results indicate a direct relationship of PRx and outcome, while the correlation of CPP and ICP and outcome is mediated by PRx. An increase in PRx may indicate loss of neuroprotection due to, e.g., vasoplegia, with a nonlinear relationship with reductions

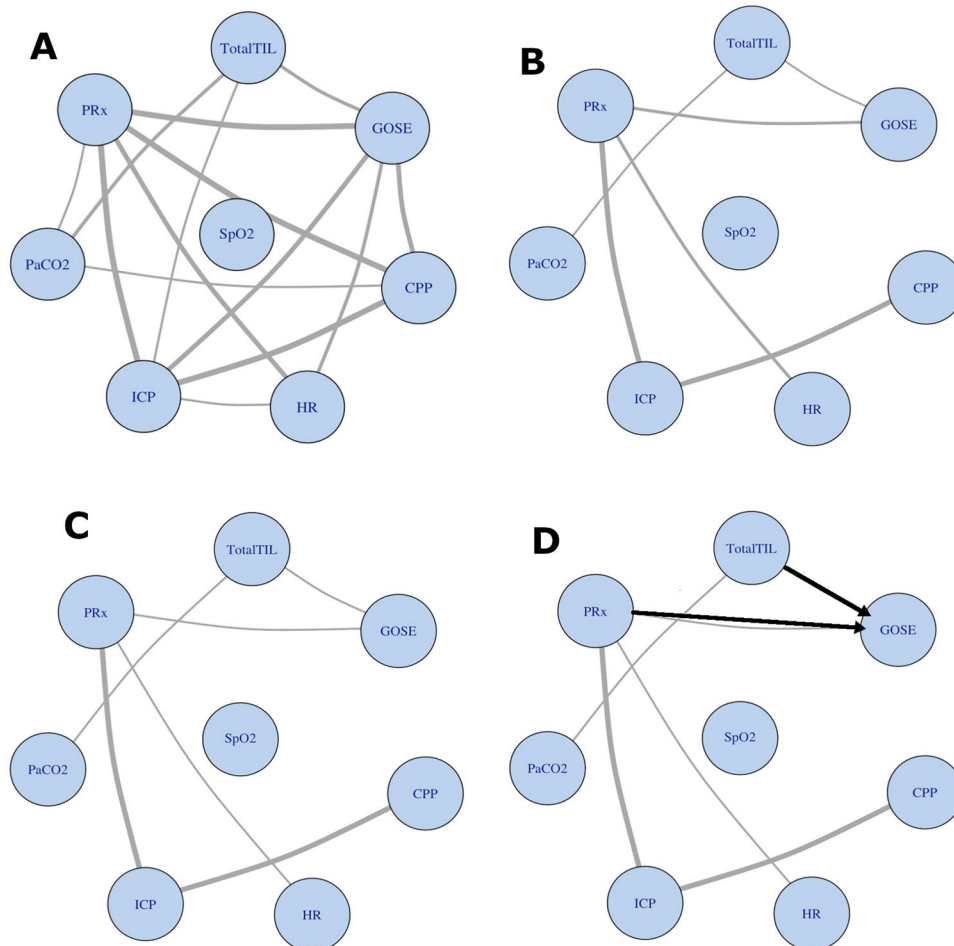


Fig. 2 Relationships between features included in the model in each step of the analysis. All significant correlations are modeled ($p < 0.01$). The line thickness represents level of significance. **A** Significant unconditional relationships. **B** Relations significant after conditioning on one feature. **C** Relations significant after conditioning on all possible pairs of the other features. **D** Significant relations after conditioning on all possible triples of the other features. Arrows indicate a causal relationship. CPP, cerebral perfusion pressure; GOSE, Glasgow Outcome Scale-Extended at 6 months post-injury; HR, heart rate; ICP, intracranial pressure; PaCO₂, arterial partial pressure of carbon dioxide; PRx, pressure reactivity index; SpO₂, oxygen saturation; TIL, therapy intensity level score

in CPP or increases in ICP, an effect that may contribute to these indirect relations of ICP and CPP and outcome. In summary, this supports the rationale of targeting CPP to optimize PRx and thus improve long-term outcomes.

We identified a direct relation between TIL score and outcome. However, caution must be held as this could in part be explained by recommendations in current guidelines and general clinical practice aiming at treating ICP above 20–22 mm Hg [23](#), [29](#). In severe cases of TBI, ICP levels may be lowered toward these levels through an increase in treatment intensity, affecting a potential direct relationship between ICP itself and outcome, a potential confounder that cannot be mitigated. However, the SYNAPSE-ICU observational, multicenter study

of patients with acute brain injury showed an adjusted association of higher TIL score and lower mortality [30](#). In contrast, treatments generating higher TIL scores such as excessive hyperventilation, prophylactic hypothermia, and decompressive craniectomy have independently been associated with worse outcomes [8–12](#). In summary, the relationship between ICP-lowering therapies and long-term functional outcome is not fully elucidated and should be interpreted with caution, and interventional studies may be needed to further explore them.

The association between heart rate and PRx, still significant when conditioned on triples of the other features ($r = 0.17$, $p = 0.007$), has, to our knowledge, not previously been described, although a relation of heart-rate-derived metrics describing autonomic

Table 3 Correlations that remained significant after conditioning on triples of other features

Feature 1	Feature 2	<i>r</i>	<i>p</i> -value
PRx	GOSE	−0.19	0.003
TIL score	GOSE	−0.20	0.002
ICP	PRx	0.31	<0.001
ICP	CPP	0.62	<0.001
PRx	HR	0.17	0.007
PaCO ₂	TIL score	−0.19	0.004

Correlations within six pairs of features were still significant after conditioning on all possible combinations of the remaining features. The causal inference analysis algorithm identified a directional relationship between PRx and GOSE. However, as outcome (GOSE) was determined at a later timepoint than the measurements of the physiological parameters, the relationship of total TIL score toward GOSE can also be considered as unidirectional. A positive correlation coefficient indicates that an increase in one of the features is correlated to an increase in the other feature, and vice versa, and does not indicate any causal direction in the relationship between the features

CPP Cerebral perfusion pressure, GOSE Glasgow outcome scale-extended, HR Heart rate, ICP Intracranial pressure, PRx Pressure reactivity index, PaCO₂ Arterial partial pressure of carbon dioxide, TIL Therapy intensity level

dysfunction such as heart rate variability has been shown to correlate to cerebrovascular autoregulation [31](#). Previous results concerning the relationship between heart rate and ICP are inconsistent: Gao et al. analyzed relationships between time series of ICP, MAP, and heart rate using conditional Granger causality and could not find a significant relationship between heart rate and ICP [31](#), [32](#). In contrast, in a previous study of patients with aneurysmal subarachnoid hemorrhage and causal relationships between systemic and cerebral physiological parameters, a directional relationship of heart rate on ICP was identified using time-series data [33](#). They did not include any measures on cerebrovascular reactivity, and thus, it is possible that cerebrovascular autoregulation is a mediator in this relationship. PRx as a mediator of heart rate and ICP is also physiologically plausible: An increase in heart rate leads to an increase in cardiac output, which—in case of impaired cerebrovascular autoregulation—leads to changes in vascular tonus influencing ICP. Another proposed underlying mechanism for the correlation between ICP and heart rate is dysautonomia, commonly seen in acute brain injury, with an activation of sympathetic or parasympathetic activity. [33](#), [34](#)

In summary, this study has identified a direct relationship between cerebrovascular reactivity and outcome as well as ICP-lowering therapies and outcome, rather than a direct relationship of ICP on outcome itself. This implies that ICP should be interpreted in the context of treatment strategies for intracranial hypertension, and that studies should continue to

focus on PRx-guided therapies of patients with severe traumatic brain injury.

Limitations

Despite the novel and interesting results of this study, there are limitations to address. First, the patient cohort in this study presented with median Glasgow Coma Scale score of 6, indicating severe TBI, and patients were treated in an intensive care unit in a European hospital. The maximum daily mean of ICP and PRx was 22.8 (IQR 18.5–29.2) and 0.2 (IQR 0.07–0.34), respectively, with a mean ICP and PRx of 11.9 (IQR 9–14.9) and 0.03 (IQR −0.08 to 0.16), respectively (Table 1). This may limit the generalizability of the results to less severely injured patients in low-resource settings, and also to patients with sustained impairment in intracranial physiology. Second, there are several possible explanations as to why no more than two directional relationships could be found. In our model, longitudinal data have been represented by 1-week averages, which might have missed physiological disturbances at higher resolutions having causal impact on outcome. The multiple statistical tests performed of relationships conditional on all combinations of up to three of the other variables may further add to the stringency in the results, although the robustness of the results may be affected by the limited size of the patient cohort. Third, artifacts in measurements and unmeasured confounders, such as preinjury factors and nonlinear effects, may all shade known physiological correlations. However, we believe that the insights that our analyses have generated into associations between dimensionality-reduced high-resolution features are valuable and should be seen as a complementing causal analysis of high-resolution time-series data. A natural further step is to further investigate causal relationships with time-dependencies between systemic and intracranial physiologic parameters.

Conclusions

This study of physiological data from patients with TBI treated in neurointensive care has shown a direct relationship of cerebrovascular reactivity and ICP-lowering therapies on outcome, but no direct effect of ICP on outcome. Our results support further investigation of large interventional studies of PRx-targeted therapies as a step to reduce mortality and morbidity in traumatic brain injuries.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1007/s12028-026-02552-w>.

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Author Contributions

CÄ, DN, AH, and AE designed the study. DN, AH, and AE were responsible for the primary supervision of the project. DN, AE, PS, and EB took part in data collection. CÄ, DN, AE, EB, and PS took part in data curation. CÄ performed all the analyses and prepared the manuscript draft. AH developed the core code used for the analyses. All authors contributed to interpretation of results and critical review and revision of the manuscript.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical Approval

The CENTER-TBI study (EC grant 602150) has been conducted in accordance with all relevant laws of the European Union (EU) if directly applicable or of direct effect and all relevant laws of the country where the recruiting sites were located, including but not limited to, the relevant privacy and data protection laws and regulations (the "Privacy Law"), the relevant laws and regulations on the use of human materials, and all relevant guidance relating to clinical studies from time to time in force including, but not limited to, the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) ("ICH GCP") and the World Medical Association Declaration of Helsinki entitled "Ethical Principles for Medical Research Involving Human Subjects." Informed consent was obtained from the patients and/or the legal representative/next of kin, accordingly to the local legislations, for all patients recruited in the core dataset of CENTER-TBI and documented in the e-CRF. Ethical approval was obtained for each recruiting site. The list of sites, ethical committees, approval numbers, and approval dates can be found on the following website: <https://www.center-tbi.eu/project/ethical-approval>.

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