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ORIGINAL RESEARCH

An open source autoregulation-based neuromonitoring algorithm shows PRx and optimal CPP association with pediatric traumatic brain injury

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Abstract

This study aimed to develop an open-source algorithm for the pressure-reactivity index (PRx) to monitor cerebral autoregulation (CA) in pediatric severe traumatic brain injury (sTBI) and compared derived optimal cerebral perfusion pressure (CPPopt) with real-time CPP in relation to long-term outcome. Retrospective study in children (< 18 years) with sTBI admitted to the pediatric intensive care unit (PICU) for intracranial pressure (ICP) monitoring between 2016 and 2023. ICP was analyzed on an insult basis and correlated with outcome. PRx was calculated as Pearson correlation coefficient between ICP and mean arterial pressure. CPPopt was derived as weighted average of CPP-PRx over time. Outcome was determined via Pediatric Cerebral Performance Category (PCPC) scale at one year post-injury. Logistic regression and mixed effect models were developed to associate PRx and CPPopt with outcome. In total 50 children were included, 35 with favorable (PCPC 1–3) and 15 with unfavorable outcome (PCPC 4–6). ICP insults correlated with unfavorable outcome at 20 mmHg for 7 min duration. Mean CPPopt yield was 75.4% of monitoring time. Mean and median PRx and CPPopt yield associated with unfavorable outcome, with odds ratio (OR) 2.49 (1.38–4.50), 1.38 (1.08–1.76) and 0.95 (0.92–0.97) ($p < 0.001$). PRx thresholds 0.0, 0.20, 0.25 and 0.30 resulted in OR 1.01 (1.00–1.02) ($p < 0.006$). CPP in optimal range associated with unfavorable outcome on day one (0.018, $p = 0.029$) and four (-0.026, $p = 0.025$). Our algorithm can obtain optimal targets for pediatric neuromonitoring that showed association with long-term outcome, and is now available open source.

Keywords Autoregulation · Traumatic brain injury · Pressure-reactivity index · Cerebral perfusion pressure · Intracranial pressure

Abbreviations

ABP	Arterial blood pressure
CA	Cerebral autoregulation
CI	Confidence interval
CPP	Cerebral perfusion pressure
CPPopt	Optimal cerebral perfusion pressure
CPR	Cardiopulmonary resuscitation
GCS	Glasgow coma scale
ICP	Intracranial pressure
ISS	Injury severity score
MAP	Mean arterial pressure
PCPC	Pediatric Cerebral Performance Category
PICU	Pediatric intensive care unit
PRx	Pressure reactivity index
SD	Standard deviation

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sTBI Severe traumatic brain injury
TBI Traumatic brain injury

1 Introduction

Clinical management of severe traumatic brain injury (sTBI) in the pediatric intensive care unit (PICU) aims to prevent secondary brain injury and brain herniation through adequate cerebral perfusion [1, 2]. Neuromonitoring is pivotal and may be achieved through invasive measurement of intracranial pressure (ICP) and cerebral perfusion pressure (CPP) [2–4]. Emerging algorithms use high-frequency data and combine various aspects of neuromonitoring to measure cerebral autoregulation (CA) and derive optimal targets for pressure and perfusion at the bedside [5, 6]. Despite growing interest, CA-based neuromonitoring is often not transparent, not standardized and as such not widely adopted in clinical practice due to a paucity of robust evidence and implementational challenges [7, 8].

In normal physiology, cerebral perfusion is relatively constant over a wide range of blood pressures due to intact CA [9]. CA can become impaired after neurotrauma, causing inadequate perfusion and contributing to secondary injury. To prevent this, treatment follows a tiered approach based on ICP, mean arterial blood pressure (MAP) and CPP [10]. Target values for MAP are standardized across age categories, while for ICP a target below 20 mmHg was adopted from adult research due to lacking pediatric target values [10, 11]. These targets disregard pediatric and individual variations in neuro-vascular hemodynamics [12]. Real-time CA monitoring could overcome this problem and research has shown this is feasible through the pressure-reactivity index (PRx), i.e. the correlation between ICP and MAP that can reflect changes in cerebral blood flow [13–15]. The relation between PRx and CPP during intact CA can be used to derive an optimal CPP (CPPopt) target [13–15]. Arguably, a patient-derived CPPopt may better reflect CA than age-standardized CPP. Various CA-based algorithms have been proposed, with considerable association with short-term outcome in adults and to a lesser extent in children [13–16]. However, algorithms are often non-transparent or secured as intellectual property, preventing external validation and widespread clinical implementation [17]. Comparative research between different algorithms also showed variation in simultaneous in-patient CPPopt measurements, stressing the need for transparency and standardization of methodology [18].

Therefore, this study aimed to develop an open-source algorithm to monitor CA via PRx and continuously derive CPPopt. The algorithm was evaluated based on the association of derived indices of PRx, CPPopt and ICP with long-term outcome at one year post-injury in children admitted to the PICU with sTBI.

2 Methods

2.1 Study population

This study was retrospectively conducted at Erasmus MC Sophia Children's Hospital (Rotterdam, The Netherlands) in accordance with the 1975 Helsinki Declaration. Consent was waived by the Medical Ethics Committee (MEC-2020-0265 in 2020; MEC-2021-0937 in 2021). Children (aged 0 to 18 years) with sTBI, defined as Glasgow Coma Scale (GCS) ≤ 8 upon admission, admitted to the PICU for continuous ICP monitoring between January 2016 and September 2023 were eligible for inclusion. Inclusion criteria were availability of outcome data and at least three hours of continuous ICP and MAP data. The latter criterion was based on Güiza et al. who found the lowest identified ICP of 10 mmHg, which is commonly encountered in pediatric sTBI patients in Erasmus MC, could be endured for up to 180 min [19].

2.2 Data acquisition

ICP and MAP were measured at 1 Hz via the patient monitoring system (Dräger, Lübeck, Germany). ICP monitoring was performed with an intraparenchymal catheter (Codman Microsensor ICP Transducer, Integra, Princeton, United States; Pressio Catheter, Sophysa, Orsay, France; Camino Catheter, Nautus Medical Inc., Middleton, United States). MAP was measured by arterial line (Becton and Dickinson, Franklin Lakes, United States). CPP was determined within the monitoring system as the continuous difference between synchronized MAP and ICP. Baseline characteristics of patient, injury and hospital admission including age, gender, GCS on admission, injury severity score (ISS), first pupils, cardiopulmonary resuscitation (CPR), trauma mechanism, interventions and length of stay were retrieved from the electronic health record (HiX, Chipsoft, Amsterdam, The Netherlands). Outcome was determined at one year post-injury during outpatient consultations via the Pediatric Cerebral Performance Category (PCPC). The PCPC scale scores functional outcome ranging from one to six, i.e. age-appropriate functioning, mild disability, moderate disability, severe disability, coma and (brain-)death [20].

2.3 Data preprocessing

Raw data were analyzed using Matlab 2022b (Mathworks, Natick, United States). A simple form of artefact detection

was performed. Artefacts were defined as sudden deflections between consecutive samples (i.e. 1 s) and values outside the pathophysiological range as determined from histogram analysis in consultation with clinicians. For MAP, these are ± 25% deflections and samples outside 30–160 mmHg. For ICP, these are ± 10 mmHg deflections and samples outside 0.01–60 mmHg. Artefacts were removed with a margin of 10 samples before and 60 samples after onset and replaced with the moving mean over a 100 s, as artefacts typically lasted up to one minute. Data were then downsampled (0.1 Hz) to mitigate high frequency noise from pulse rate and respiration [14].

2.4 Algorithm development

2.4.1 Cerebral autoregulation

CA was quantified with PRx, derived as Pearson correlation coefficient between ICP and MAP in a 300 s moving window as described by Czosnyka et al. [14] Mean, median and increased PRx in percentage of time were determined for each patient. Increased PRx may indicate impaired CA through positive correlation between ICP and MAP, but there are no standardized thresholds. As such, thresholds of PRx > 0.0, 0.2, 0.25 and 0.3 were compared [21]. The threshold with the strongest association with PCPC score was adopted for CPPopt calculations.

2.4.2 Optimal cerebral perfusion pressure

The CPPopt and optimal range were determined every minute using our custom algorithm based on literature and consultations with clinicians [5, 22, 23]. In the algorithm as illustrated in Fig. 1, downsampled data were used to calculate mean PRx and CPP per minute. In windows of one, two, four, six and eight hours, mean CPP was binned (divided into 5 mmHg intervals) and the mean (standard deviation (SD)) PRx was determined per CPP bin. A second order polynomial was fitted over CPP bins containing ≥ 1% of data to exclude artefactual data. The local minimum of this curve was identified as CPPopt in that window. In case of increased PRx (based on threshold analysis), CPPopt was replaced with a missing value to prevent targets derived during impaired CA. Calculating CPPopt for all windows resulted in a total of five CPPopt targets per patient. Final CPPopt was determined as the mean between mean CPPopt over all windows and the CPP with the lowest PRx (i.e. best CA). To subsequently determine the optimal CPP range, the mean (SD) PRx per CPP bin of the eight-hour window was used to generate an optimal PRx range. The optimal PRx range was defined as the range between lowest mean PRx (lower limit) and increased PRx, based on threshold analysis and the assumption that ideal PRx is negative or around zero. The optimal CPP range was derived from this PRx range. Measured CPP was considered in range if the mean PRx of the corresponding CPP bin was within optimal PRx range. If the optimal CPP range included increased

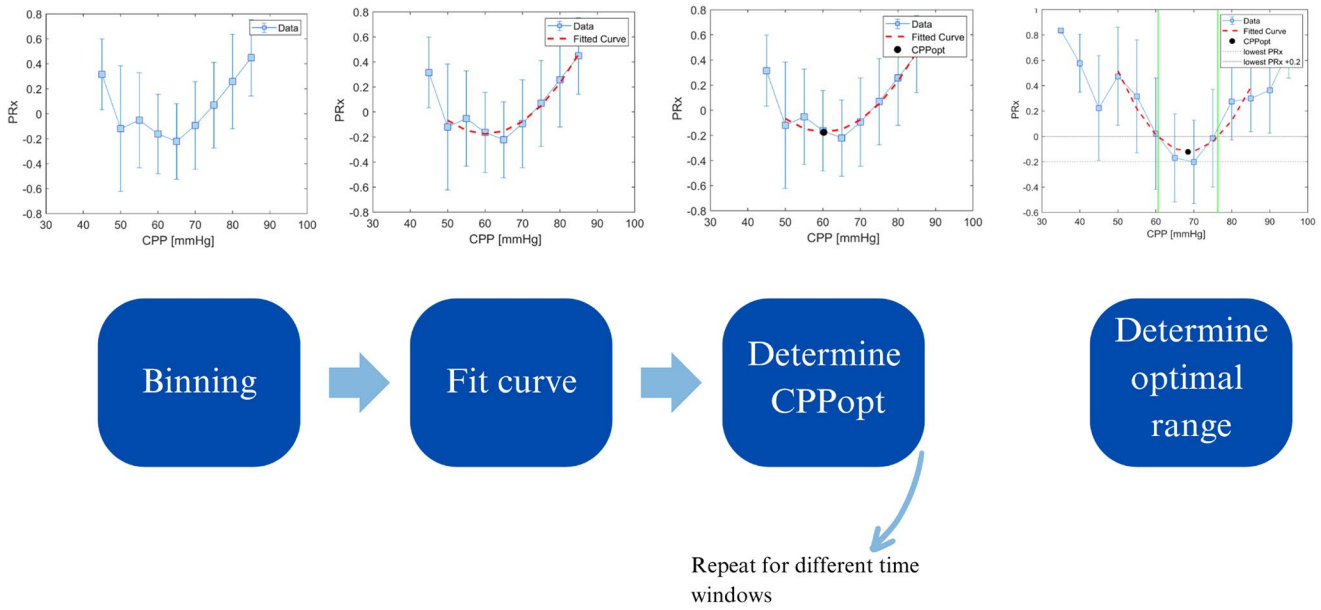

Fig. 1 Schematic overview of the CPPopt algorithm. In windows of one, two, four, six and eight hours, CPPopt was defined as the local minimum of a second order curve fitted along binned CPP and corresponding mean PRx. The optimal CPP range was determined from the corresponding optimal PRx range in the eight hour window between minimum PRx and minimum + 0.2. For illustrative purposes, data of the entire monitoring period was used in this figure. CPP = cerebral perfusion pressure; CPPopt = optimal cerebral perfusion pressure; PRx = pressure reactivity index

PRx (based on threshold analysis) no optimal range could be determined and measured CPP was deemed out of range. Using the algorithm, the CPPopt yield, i.e. the percentage of time that the algorithm returned a CPPopt target, and the percentage of time with CPP within optimal range per admission day were determined for each patient.

2.4.3 Intracranial pressure

ICP was analyzed on an insult basis, according to its intensity (mmHg) and duration (min), as previously described by Guiza et al. [19]. The correlation between the average number of ICP insults and corresponding PCPC score over the entire cohort was visualized using a color scale. Negative correlation indicates the ICP insult occurs more frequently in patients with low PCPC scores, while positive correlation indicates the insult occurs more frequently in patients with high PCPC scores.

2.5 Statistical analysis

For primary analysis, outcome was dichotomized as favorable (survival with favorable neurological outcome, PCPC 1–3) or unfavorable (mortality or survival with unfavorable neurological outcome, PCPC 4–6) [20]. Secondary analyses were conducted for mortality (PCPC 6) versus survival (PCPC 1–5) and favorable neuroloical outcome in survivors (PCPC 1–3) versus unfavorable neurological outcome in survivors (PCPC 4–5) via Mann Whitney-U test [20]. Categorical data were reported as count (percentage) and continuous data were reported as mean (SD) or median (Q1, Q3). Crude and multivariable logistic regression models were developed to assess the association between outcome and PRx indices and CPPopt yield. Models were adjusted for GCS on admission and reported with odds ratios (ORs) and 95% confidence intervals (95% CI). For interpretation of ORs, mean and median PRx were multiplied by 10 to reflect changes in odds as PRx transitions from 0 to 0.1 instead of 0 to 1 [21]. The association between the percentage of time that CPP was within optimal range per consecutive monitoring day and outcome was assessed using mixed effects models, with age and GCS on admission as fixed effects. Subject-specific random intercepts and slopes were used to account for correlation between multilevel data. A two-sided p-value < 0.05 was considered statistically significant.

3 Results

3.1 Patient characteristics

In total 67 sTBI patients were admitted to the PICU during the study period, of which 61 underwent ICP monitoring and 50 patients met inclusion criteria. Reasons for exclusion were irretrievable MAP and/or ICP data or outcome data one-year post injury was not yet available. Of the included patients, 41 (82.0%) survived until one year post-injury. Baseline characteristics of included patients are shown and compared between groups of primary and secondary analysis in Table 1. Survivors with favorable outcome were already represented by the favorable outcome group and were therefore not included as a separate column. Median ICP monitoring time was 5.7 (4.5–7.7) days. On average, 3.5% and 3.7% of raw ICP and MAP was artefactual and removed. Resultantly, missing values increased from 0.2 to 2.2% and 0.1–0.9% for ICP and MAP.

3.2 Algorithm development

Visual assessment of CPP-PRx curves showed unfavorable outcome corresponded with narrow CPP ranges (Supplemental Figure S1). CPPopt analysis was conducted in 49 (98.0%) of included patients. One patient was excluded because of complete absence of CA and subsequent rejection of CPPopt targets by the algorithm. CPPopt yield was 75.4% overall versus 45.6% and 87.3% in patients with unfavorable and favorable outcome, respectively. ICP insult analysis showed a negative correlation between the average number of insults for an intensity between 10 and 20 mmHg with durations 120 and 7 min, and positive correlation for more intense and/or longer insults (Fig. 2).

3.3 Primary analysis

Crude and adjusted associations between mean PRx, median PRx, increased PRx and CPPopt yield and unfavorable outcome are available in Table 2. Associations were significant before and after adjustment for GCS on admission, with increased odds for mean PRx after adjustment. Since all PRx thresholds produced similar OR, the threshold > 0.20 was adopted in the algorithm to define increased PRx and derive an optimal PRx range (lower limit ± 0.20). Optimal CPP range calculations were rejected for PRx > 0.25, allowing a slight error margin in the PRx range. Contrary to a threshold at 0.0, both thresholds allow CPPopt calculations for stable low levels of PRx (e.g. 0.10) and optimal ranges for PRx up to 0.05, which may occur during intact CA. The effects of age, GCS on admission and percentage of time with CPP in optimal range for five consecutive monitoring

Table 1 Baseline characteristics

Variables	Primary analysis		Secondary analysis	
	(Survivors with) Favorable outcome	Unfavorable outcome	Survivors with unfavorable outcome	Mortality
Demographic				
Participants	35 (70.0%)	15 (30.0)	6 (12.0%)	9 (18.0%)
Females	12 (34.3%)	8 (53.3%)	4 (66.7%)	4 (44.4%)
Age	9 (6.5, 14.5)	15 (10.0, 16.0)	14 (11.5, 15.8)	15 (9.0, 16.0)
PCPC				
PCPC 1	12 (34.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PCPC 2	19 (54.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PCPC 3	4 (11.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PCPC 4	0 (0.0%)	6 (40.0%)	6 (40.0%)	0 (0.0%)
PCPC 5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PCPC 6	0 (0.0%)	9 (60.0%)	0 (0.0%)	9 (18.0%)
Injury severity				
ISS	16 (16, 25)	34 (26, 42.5)	33 (25, 42.5)	34 (32.8, 36.3)
GCS on admission	6.0 (4.0, 7.0)	3.0 (3.0, 4.0)	3.0 (3.0, 4.0)	3.0 (3.0, 4.0)
First pupils				
Isocoric	25 (71.4%)	3 (20%)	0 (0.0%)	3 (33.3%)
Anisocoric	10 (28.6%)	5 (30%)	4 (66.7%)	1 (11.1%)
Fixed/dilated	0 (0.0%)	7 (46.7%)	2 (33.3%)	5 (55.6%)
CPR received	1 (2.9%)	1 (6.7%)	0 (0.0%)	1 (11.1%)
Trauma mechanism				
Bicycle accident	11 (31.4%)	6 (40.0%)	3 (50.0%)	3 (33.3%)
Fall	6 (17.1%)	4 (26.7%)	2 (33.3%)	2 (22.2%)
Pedestrian vs. motor vehicle	9 (25.7%)	2 (13.3%)	1 (16.7%)	1 (11.1%)
Passenger	5 (14.3%)	1 (6.7%)	0 (0.0%)	1 (11.1%)
Other	4 (11.4%)	2 (13.3%)	0 (0.0%)	2 (22.2%)
Hospital admission				
PICU length of stay	12.0 (8.0, 19.5)	9.0 (5.0, 26.0)	26.0 (22.3, 42.5)	5.0 (3.0, 8.0)
Hospital length of stay	26.0 (14.0, 34.5)	9.0 (5.0, 42.5)	46.0 (41.3, 57.5)	5.0 (3.0, 8.0)
Interventions				
Craniectomy	9.0 (25.7%)	6 (40.0%)	2.0 (33.3%)	4.0 (44.4%)
External ventricular drainage	0.0 (0.0%)	3 (20.0%)	1.0 (16.7%)	2.0 (22.2%)

Values are expressed as n (%) and median (Q1, Q3) of their respective group. Note that survivors with good outcome were already represented by the favorable outcome group and were therefore not included as a separate column. Favorable outcome = PCPC 1–3; unfavorable outcome = PCPC 4–6; survivors with good outcome = PCPC 1–3; survivors with poor outcome = PCPC 4–5; mortality = PCPC 6; ISS = injury severity score; CPR = cardiopulmonary resuscitation; GCS = Glasgow Coma Scale; PICU = pediatric intensive care unit

days on unfavorable outcome are available in Table 3. Both age and GCS on admission were significantly associated with unfavorable outcome. The association between percentage of time with CPP in optimal range and unfavorable outcome varied over time, with significant associations observed on day one (positive) and on day four (negative).

3.4 Secondary analysis

Subgroup comparison of mean PRx, median PRx, increased PRx, CPPopt yield and percentage of time with CPP in optimal range are available in Table 4. All indices were significantly different between survivors and non-survivors. The largest differences were observed for median PRx (negative in survivors), CPPopt yield and percentage of time with CPP in optimal range. Thresholds of PRx > 0.25 and > 0.30 resulted in similar differences between survivors and non-survivors. Between survivors with favorable and unfavorable neurological outcome, only CPPopt yield was significantly different. Comparing all three subgroups, mean PRx was higher for unfavorable outcome and mortality (Supplemental Figure S2) and mean (SD) percentage of time with CPP in optimal range shows an increasing difference over consecutive days (Supplemental Figure S3).

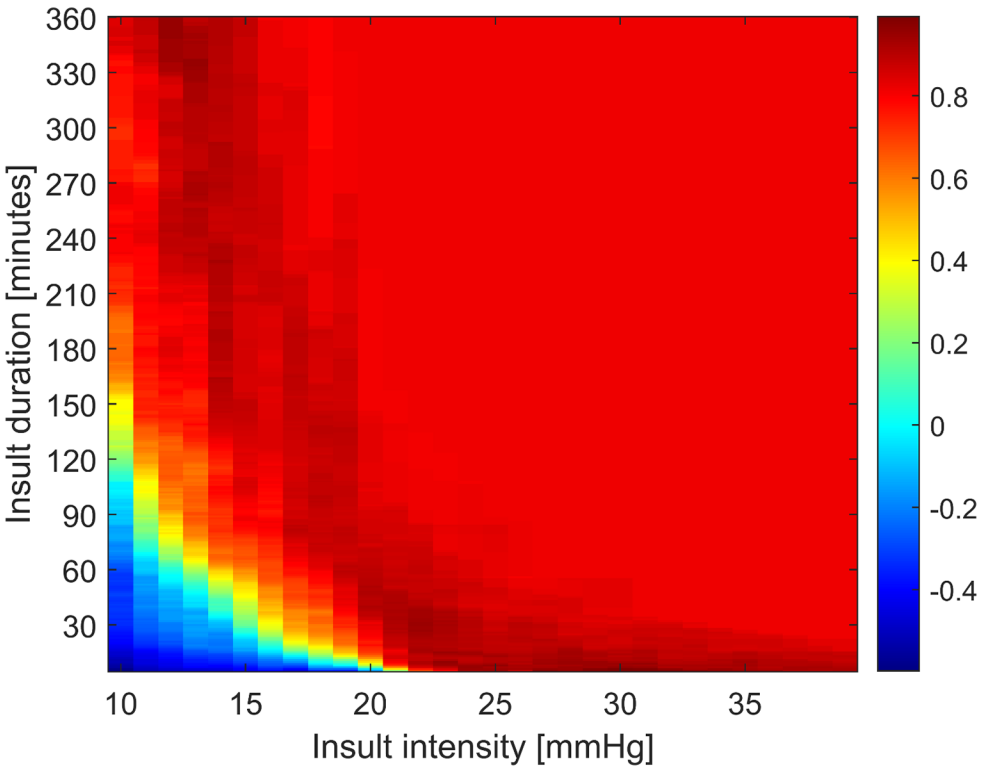

Fig. 2 Color-scaled correlation between average number of ICP insults, expressed according to intensity in mmHg on the x-axis and duration in minutes on the y-axis, and outcome. The color bar on the right represents the correlation, where blue indicates a negative correlation (i.e. the insult occurs more frequently in patients with low PCPC scores) and red indicates a positive correlation (i.e. the insult occurs more frequently in patients with high PCPC scores). The cut-off for correlation with unfavorable outcome occurred at ICP intensity of 20 mmHg for a duration of seven min. ICP = intracranial pressure; PCPC = Pediatric Cerebral Performance Category

Table 2 Univariable and multivariable logistic regression analysis of PRx, CPPopt and outcome

	Crude		Adjusted	
Dependent variable	OR (95% CI)	p-value	OR (95% CI)	p-value
Mean PRx	1.95 (1.32–2.89)	< 0.001	2.49 (1.38–4.50)	0.003
Median PRx	1.43 (1.16–1.76)	< 0.001	1.38 (1.08–1.76)	0.009
PRx > 0.00	1.00 (1.00–1.01)	0.006	1.01 (1.00–1.01)	0.024
PRx > 0.20	1.01 (1.00–1.01)	0.001	1.01 (1.00–1.01)	0.008
PRx > 0.25	1.01 (1.00–1.01)	< 0.001	1.01 (1.00–1.02)	0.007
PRx > 0.30	1.01 (1.00–1.02)	< 0.001	1.01 (1.00–1.02)	0.006
CPPopt yield	0.95 (0.92–0.98)	0.001	0.93 (0.88–0.97)	0.003

All dependent variables were adjusted for GCS on admission. A p-value < 0.05 was considered statistically significant. PRx = pressure-reactivity index; CPPopt = optimal cerebral perfusion pressure; OR = odds ratio; CI = confidence interval

Table 3 Associations of percentage of time with CPP in range over consecutive monitoring days, age and GCS on admission

Fixed effect	Coefficient	95% CI	*p*-value
Age	0.100	0.007–0.193	0.037
GCS on admission	-0.252	-0.455 – -0.060	0.013
CPP in range, time %			
Day 1	0.018	0.002–0.033	0.029
Day 2	-0.016	-0.033–0.001	0.057
Day 3	0.006	-0.011–0.023	0.462
Day 4	-0.026	-0.048 – -0.004	0.025
Day 5	0.002	-0.020–0.023	0.870

Model was adjusted for subject-specific random intercept and slopes. A p-value < 0.05 was considered statistically significant. GCS = Glasgow Coma Scale; CI = confidence interval; CPP = cerebral perfusion pressure

4 Discussion

We present PANDA, a PRx-based Algorithm for Neuromonitoring and Dynamic Autoregulation, the first open-source algorithm enabling personalized CPPopt targets and PRx monitoring in children admitted to the PICU with sTBI with the longest follow-up period to date. Retrospective evaluation of our algorithm demonstrated that increased PRx, reduced CPPopt yield and deviation from optimal CPP range were associated with unfavorable outcome at one-year post-injury. Derived indices of PRx and CPPopt differed between survivors and non-survivors, and between survivors with favorable and unfavorable neurological outcome time with CPP in range differed. Source code and documentation is available at https://github.com/evantwist/panda. PANDA can be adopted for external validation and paves the way towards prospective trials where the algorithm can be used in real-time to assess the effects on individual patient outcomes.

The proposed algorithm is unique. To date, the majority of research on PRx and CPPopt has been conducted in adults

Table 4 Differences in PRx and CPPopt indices between survivors and non-survivors and between outcome in survivors

		Mortality			Outcome in survivors		
Indices	Overall	Survivors	Non-survivors	p-value	Survivors with good outcome	Survivors with poor outcome	p-value
Mean PRx	0.100	0.025	0.441	< 0.001	0.005	0.137	0.128
Median PRx	0.021	-0.062	0.398	0.005	-0.111	0.222	0.067
PRx > 0.00, mean % of time	48.4%	45.6%	61.4%	0.023	43.8%	56.2%	0.285
PRx > 0.20, mean % of time	36.2%	32.0%	55.2%	0.001	30.0%	43.3%	0.149
PRx > 0.25, mean % of time	33.4%	29.1%	53.3%	< 0.001	27.2%	40.1%	0.149
PRx > 0.30, mean % of time	30.8%	26.4%	51.2%	< 0.001	24.5%	37.1%	0.149
CPPopt yield, mean % of time	75.4%	84.7%	27.6%	< 0.001	87.3%	69.5%	0.061
CPP in range, mean % of time	51.0%	56.5%	14.9%	0.046	62.6%	29.9%	0.006

Subgroups were compared via Mann-Whitney U test for all indices. A p-value < 0.05 was considered statistically significant. Favorable outcome = PCPC 1–3; unfavorable outcome = PCPC 4–6; survivors with good outcome = PCPC 1–3; survivors with poor outcome = PCPC 4–5; mortality = PCPC 6; PRx = pressure-reactivity index; CPPopt = optimal cerebral perfusion pressure

using commercialized Intensive Care Monitor+ (ICM+) software (Cambridge Enterprise, University of Cambridge, Cambridge, United Kingdom) [5, 8, 22, 24–26]. Recently, the first prospective trial was conducted using ICM + for CA-based CPP management in adult TBI [27]. During the trial, 32 patients were randomized to CA-based CPP management and 28 to standard management. The trial showed the feasibility and safety of CA-based management, with slightly higher percentages of CPP within target range in the CA-based group and no difference in safety end-points. Individual patient outcomes were not improved. However, this was not the primary objective of the study and therefore not powered accordingly [27]. In ICM+, CPPopt is derived per minute using 36 windows between two and eight hours with 10 min increments [6]. In our algorithm, larger increments were used and we avoided giving undue weight to recent windows in final CPPopt calculation as this could negatively impact cases where CA was suddenly impaired [23]. We also opted to reject increased PR (≥ 0.2) instead of flat curves (span < 0.2) as this could negatively impact patients with stable low PRx (i.e. intact CA). Threshold analysis to define increased PRx was inconclusive. Similarly in pediatric literature, associations with unfavorable outcome were observed for PRx > 0.25 but also for PRx > 0.0 for prolonged duration [21, 28]. This may indicate thresholds need to be personalized within a cohort or individually. In our study, we chose the lowest non-zero threshold (≥ 0.2) for CPPopt calculations, based on the assumption that negative or approximating-zero PRx indicates intact CA, and added a margin for optimal CPP range (0.25). With regard to optimal range, PANDA provides a dynamic range as compared to ICM + where the optimal range equals CPPopt ± 5 mmHg [23]. While the optimal range, derived from lower limit PRx + 0.2, requires further validation we observed all patients with mean PRx < 0.2 were survivors while all patients with mean PRx > 0.2 were non-survivors in our cohort. Altogether, while PANDA required more data input than reported for ICM+ (eight versus five hours), we obtained similar CPPopt yield as in the prospective ICM + trial (mean 75.4% versus 76.6% of time), demonstrating feasibility of PANDA [27].

Both PRx and CPPopt were significantly associated with unfavorable outcome and showed significant differences between survivors and non-survivors, conform previous research [13, 28, 29]. With positive PRx, systemic pressure changes are propagated towards cerebral vasculature [9, 15, 30, 31]. Hence, PRx indices and increased PRx are indicative of CA impairment. Reduced CPPopt yield (as CPPopt targets were rejected for PRx ≥ 0.2) was also mildly associated with unfavorable outcome. This is a unique view on how PANDA may be used in clinical practice. The mean percentage of time with CPP in optimal range was the only index that differed significantly between favorable and unfavorable neurological outcome in survivors. We postulate PRx and CPPopt are inherently markers of secondary injury, while long-term outcome also depends on primary injury. This is supported by previous studies where PRx was independent of neurological score on admission and ICP and CPP were delayed markers of secondary injury [13, 21, 32]. Crude associations between PRx and CPPopt and outcome were also robust when adjusted for GCS on admission. Furthermore, the percentage of time with CPP in optimal range showed the strongest association with outcome on the fourth day of monitoring. On day four, the largest differences in percentage of time with CPP in optimal range were also observed between the three subgroups. Assuming monitoring days coincide with admission days, all outcome groups start with a similar mean percentage CPP in range, but over consecutive days an increasing trend was observed in patients with favorable outcome, while the opposite was observed for mortality.

The present study further showed children benefit from targeting ICP < 20 mmHg, as secondary injury may already manifest after a short duration at this intensity. Our findings are corroborated by previous research, showing that the transition from favorable to unfavorable outcomes occurs at lower intensities and shorter durations of ICP insults in children than in adults [19, 28, 33]. These results emphasize the need for insult or cumulative ICP monitoring and personalized, perhaps more aggressive, targets for sTBI management. This will also benefit CPP, as the overall percentage of time with CPP in optimal range was moderate in this study.

The main strength of the present study is the development of an open source algorithm based on qualitative and high capture data for bedside use. The long follow-up captures the ongoing recovery trajectory of sTBI patients. The transparency of our study allows researchers and clinicians worldwide to adopt PANDA in clinical practice and perform external validation, contributing to clinical impact and which may trigger a shift in neuromonitoring with the establishment of pediatric and personalized therapeutic targets. Finally, through focus on multiple parameters our study paints a comprehensive overview of neurovascular hemodynamics and CA. However, some limitations of the present study need to be addressed. The algorithm requires eight hours of data and intact CA to determine CPPopt, so it inherently cannot generate CPPopt the entire monitoring time. Conversely, the inability to generate CPPopt can indicate impairment of CA. Furthermore, sTBI is a heterogeneous disease in which trauma mechanism, primary injury and complications vary as well as the various therapeutic strategies that influence ICP and CPP [10]. For example decompressive craniectomy, performed in a quarter of favorable and nearly half of unfavorable outcomes, influences cerebral compliance and has been shown to affect PRx [34]. Unfortunately, subgroup analysis was not feasible because of small sample sizes. With regard to outcome, PCPC was used instead of the more widely used Glasgow Outcome Scale (GOS), simply because PCPC is preferred in our center. The PCPC is a functional performance score unable to provide a multidimensional picture on individual outcome. Nonetheless, the score is suitable to categorize patients in functional outcome groups. Finally, we were unable to compare our algorithm to currently available commercial algorithms, such as ICM+®, as these are not available in our center. However, further validation by comparing our algorithm to commercial algorithms is a necessary step in future studies.

With PANDA, the present study presents an open-source algorithm for CA-based neuromonitoring, which obtained significant association with long-term outcome at one year post-injury in retrospective data of children admitted to the PICU with sTBI. This implies that CA-based neuromonitoring is clinically relevant and feasible without commercialized software. Our open-source code can be used to perform external validation on retrospective data and compare findings of CPP in optimal range with age-standardized CPP targets. In the future, we aim to refine PANDA by incorporating personalized PRx thresholds. Such thresholds may be identified through temporal analysis of baseline PRx and changes associated with clinical events, on a patient and age-stratified population level. This final algorithm will be integrated into a neuromonitoring dashboard to enable an overview of various neuromonitoring modalities and their potential interrelation. Ideally, this dashboard will be built using opens source software such as Python. We encourage future research to adopt PANDA and continue collaborative developments in the field of (pediatric) neuromonitoring to advance towards the bedside.

5 Conclusion

We present an open-source algorithm for bedside neuromonitoring in pediatric sTBI admitted to the PICU. The algorithm obtained indices of PRx, CPPopt and ICP that were associated with outcome at one year post-injury. We invite fellow researchers to adopt this algorithm for external validation and comparison to other existing (commercial) algorithms.

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Declarations

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