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Article

Integrated Cerebral Autoregulation Score for Early Risk Stratification in Severe TBI

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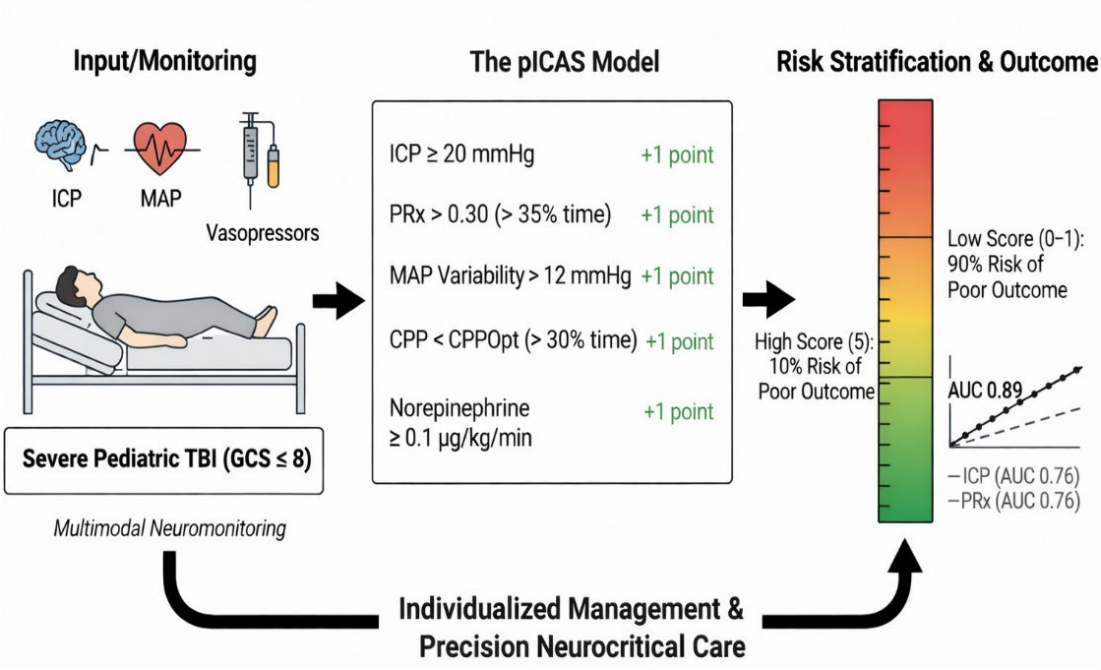
ABSTRACT

In a scenario where precise tools are crucial, a 10-year-old boy arrives at the emergency room with a Glasgow Coma Scale of 5 following a car accident, requiring immediate vasopressor support. This situation highlights the urgent need for effective tools in pediatric neurocritical care. Impaired cerebral autoregulation is associated with poor outcomes in severe pediatric traumatic brain injury (TBI), yet integrated bedside assessment tools are lacking. We conducted a retrospective multicenter cohort study including 100 children (ages 0–18) with severe TBI (Glasgow Coma Scale ≤8) who required vasopressor support within 72 hours of admission. Our objective was to identify early predictors of autoregulatory failure and develop the Pediatric Integrated Cerebral Autoregulation Score (pICAS). Multimodal neuromonitoring included intracranial pressure (ICP), cerebral perfusion pressure (CPP), pressure reactivity index (PRx), and mean arterial pressure (MAP) variability. The primary outcome was poor clinical result (mortality or PGOS ≤3), observed in 46% of patients. The pICAS was created to predict clinical deterioration by integrating PRx and other physiological variables. Multivariate logistic regression identified five early predictors for the pICAS (score range 0–5): ICP ≥20 mmHg, PRx >0.30 for >35% of monitoring time, MAP variability >12 mmHg, CPP below optimal for >30% of the time, and norepinephrine-equivalent dose ≥0.1 µg/kg/min. The pICAS demonstrated higher accuracy (AUC 0.89, 95% CI 0.83–0.95) than ICP alone (AUC 0.72) or PRx alone (AUC 0.76) ($p < 0.01$), and showed excellent calibration (Hosmer-Lemeshow p=0.62) with internal validation (optimism-corrected AUC 0.87). Risk of impaired autoregulation increased from 10% (score 0–1) to 90% (score 5). At a cutoff of ≥3, sensitivity was 85%, specificity was 82%, PPV was 77%, and NPV was 88%. The pICAS offers a practical framework for early risk stratification and individualized management.

Keywords: pediatric traumatic brain injury; cerebral autoregulation; pressure reactivity index; pediatric integrated cerebral autoregulation score (pICAS); risk stratification; prediction model; pediatric neurocritical care.



Graphical Abstract. Schematic representation of the Pediatric Integrated Cerebral Autoregulation Score (pICAS) for early risk stratification in severe pediatric traumatic brain injury. Multimodal neuromonitoring variables—including intracranial pressure, pressure reactivity index, mean arterial pressure variability, cerebral perfusion pressure relative to optimal targets, and vasopressor requirement—are integrated into a five-point score. Increasing scores indicate a higher probability of impaired cerebral autoregulation and poor clinical outcome, supporting individualized management and precision neurocritical care

INTRODUCTION

Severe traumatic brain injury (TBI) is a leading cause of death and long-term neurological disability in children worldwide. It accounts for a large share of pediatric neurocritical care admissions and health resource use [1,2,3]. While the primary mechanical injury is mostly irreversible, secondary brain injury—due to intracranial hypertension, cerebral hypoperfusion, metabolic disturbances, and disordered cerebrovascular control—is a critical, potentially modifiable determinant of outcome [4,5,6].

Cerebral autoregulation is a key mechanism that maintains stable cerebral blood flow across a wide range of blood pressures. In pediatric severe TBI, autoregulation is often impaired. As a result, cerebral perfusion pressure (CPP) depends heavily on systemic hemodynamics and vasopressor therapy [7,8,9]. Loss of autoregulation leaves the developing brain vulnerable: ischemia can occur during hypotension, and hyperemia and edema can develop during hypertension.

The pressure reactivity index (PRx), derived from the correlation between slow waves in mean arterial pressure (MAP) and intracranial pressure (ICP), has emerged as a validated, continuous, bedside marker of cerebrovascular reactivity and outcome in pediatric TBI [10,11,12]. PRx-based approaches allow estimation of individualized optimal CPP (CPPopt), highlighting the heterogeneity of perfusion requirements across children and over time. Importantly, impaired autoregulation rarely occurs in isolation; it reflects the interaction of systemic hemodynamic instability, vasopressor exposure, intracranial compliance, cerebral oxygenation, and metabolic stress unique to pediatric physiology [13].

Rationale and Knowledge Gap

Despite the growing use of multimodal neuromonitoring, including ICP, CPP, PRx, and brain tissue oxygen tension ($PbtO_2$), current pediatric TBI management relies mainly on population-based MAP and CPP targets. These targets do not consider individual autoregulatory capacity or its interaction with systemic hemodynamics [14,15]. Clinicians today face significant uncertainty in achieving optimal CPP targets, as these are typically derived from generalized data rather than personalized patient metrics. The Pediatric Integrated Cerebral Autoregulation Score (pICAS) offers an opportunity to redefine this standard by enabling individualized assessment and management of cerebral perfusion in children. While vasopressor therapy is essential to maintain CPP, it may worsen cerebral perfusion instability in children with impaired autoregulation by increasing MAP variability and encouraging pressure-passive cerebral blood flow [16].

No integrated bedside tool combines available cerebral and systemic data to help quickly identify children at high risk for autoregulatory failure and poor outcomes. Previous studies focused on single variables or domains, limiting personalized bedside use [17,18,19,20].

We hypothesized that impaired cerebral autoregulation in pediatric severe TBI reflects a multidimensional interplay among intracranial dynamics, individualized CPP targets, and systemic hemodynamic instability. We conducted a retrospective observational study of 100 children with severe TBI requiring vasopressor support and continuous multimodal neuromonitoring to develop and internally validate the Pediatric Integrated Cerebral Autoregulation Score (pICAS), a bedside tool designed to stratify risk of impaired autoregulation, neurological deterioration, and PICU mortality.

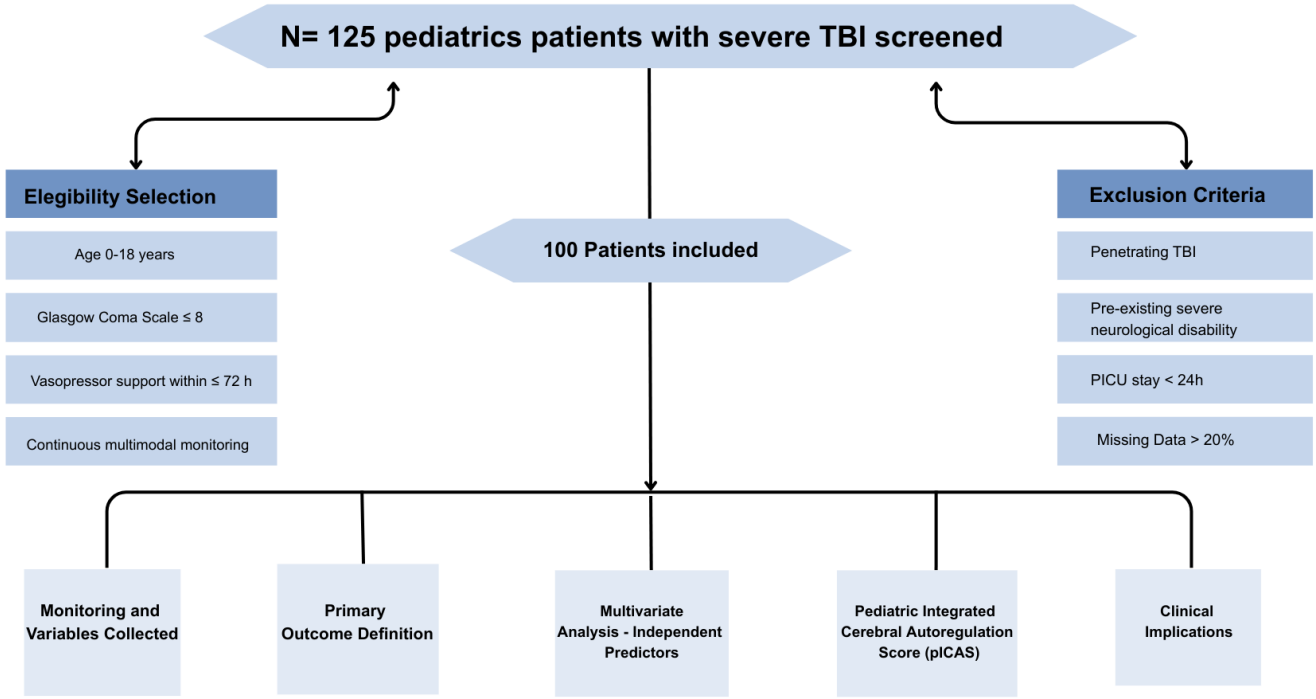
METHODS

Study Design and Setting

This retrospective, multicenter observational cohort study included 100 consecutive children with severe traumatic brain injury (TBI) admitted to tertiary-level Pediatric Neurocritical Care Units between January 2018 and December 2023 (Fig. 1). The centers participating in this study represented a diverse range of geographic regions, including urban centers in Europe and Latin America, which provided access to varied demographic populations. The study sites ranged in resource availability, with some having comprehensive multimodal monitoring capabilities while others operated with more limited resources. The study was conducted and reported in accordance with the TRIPOD guidelines for prediction model development and the STROBE checklist for observational studies. Institutional Review Board approval was obtained at all participating centers, with a waiver of informed consent due to the retrospective design and use of anonymized data, in compliance with the Declaration of Helsinki. By adhering to these guidelines, we aim to reassure reviewers about the rigor and transparency of our methodological approach.

Physiological signals were measured at high speed (100 times per second) and analyzed using ICM+ software (a system for processing brain monitoring data). The pressure reactivity index (PRx) was calculated as a moving Pearson correlation coefficient (a measure of how closely two variables are related) between mean arterial pressure (MAP, average blood pressure) and intracranial pressure (ICP, pressure inside the skull). This was done every minute, based on 30 samples, each averaging 10 seconds, with the data set updated every minute and using a 50% overlapping window for more accuracy. Individual optimal cerebral perfusion pressure (CPPopt) was determined using a multi-window, weighted parabolic fit algorithm (a mathematical

method to find the best CPP for each child) applied over a rolling 4-hour period, provided at least half of the data points were present to ensure accuracy.



Flow diagram illustrating the selection process for the pediatric severe traumatic brain injury (TBI) cohort. Of 125 screened patients, 100 met eligibility criteria and were included in the final analysis, stratified by cerebral autoregulation status.

Abbreviations: *PICU: Pediatric Intensive Care Unit; pICAS: Pediatric Integrated Cerebral Autoregulation Score; TBI: Traumatic Brain Injury.*

Figure 1. Flow diagram of the patient selection process for the pediatric severe traumatic brain injury (TBI) cohort.

Patient Selection

Children aged 0–18 years with severe TBI (Glasgow Coma Scale ≤8 after initial resuscitation) were eligible if they required vasopressor support within the first 72 hours of Pediatric Intensive Care Unit (PICU) admission and underwent continuous ICP and cerebral autoregulation monitoring.

Patients were excluded based on the following criteria:

- Penetrating TBI
- Pre-existing severe neurological disability (baseline Pediatric Glasgow Outcome Scale ≤3)
- PICU length of stay: 24 hours
- Absence of continuous multimodal neuromonitoring
- Missing data >20% for key physiological variables

Multimodal Cerebral Monitoring

ICP was continuously monitored using special devices: either probes placed in the brain tissue or cerebrospinal fluid drainage (external ventricular drainage), both set up according to hospital protocols for children. MAP (mean arterial pressure, or average blood pressure) was measured invasively using an arterial catheter. CPP (cerebral perfusion pressure) was calculated as the difference between MAP and ICP, using age-based normal values [21,22].

Cerebral autoregulation was assessed using the pressure reactivity index (PRx), a measure of the temporal relationship between changes in mean arterial pressure (MAP) and intracranial pressure (ICP). Impaired autoregulation was defined as an average PRx greater than 0.30 during the patient's monitoring period [23].
Individualized optimal CPP (CPPopt) was estimated using established PRx-based algorithms, and CPP deviation from CPPopt was quantified as the proportion of monitored time below the individualized optimal range. Brain tissue oxygen tension ($PbtO_2$) was recorded when available, with cerebral hypoxia defined as $PbtO_2$ < 20 mmHg for >10% of monitoring duration, a threshold commonly extrapolated from adult neurocritical care and previously applied in pediatric TBI studies [24].

Systemic Hemodynamic and Metabolic Variables

Systemic hemodynamics included mean, minimum, and variability (standard deviation) of MAP, heart rate, and central venous pressure when available. Vasopressor therapy was characterized by agent type, maximum and cumulative dose (expressed as norepinephrine-equivalent µg/kg/min), and duration [25,26,27].
Metabolic stress was assessed via serum lactate levels at PICU admission and 24 hours, and lactate clearance over the first 24 hours. Episodes of hypotension and MAP variability were quantified to evaluate hemodynamic instability [28,29,30].

Outcome Measures

The primary outcome was redefined as a poor clinical outcome, a composite endpoint comprising PICU mortality or an unfavorable neurological status at hospital discharge (Pediatric Glasgow Outcome Scale ≤ 3). This change was implemented to evaluate the pICAS as a prognostic tool and to avoid mathematical circularity, as PRx is now treated strictly as a predictor of clinical deterioration rather than the primary endpoint itself.

Development of the Pediatric Integrated Cerebral Autoregulation Score (pICAS)

Candidate variables were selected a priori based on physiological plausibility and prior literature, encompassing cerebral variables such as ICP burden, PRx, CPPopt deviation, and $PbtO_2$ hypoxia burden; hemodynamic variables including MAP variability, vasopressor dose, and duration; and metabolic variables such as lactate levels and clearance. To eliminate mathematical circularity and ensure clinical relevance, the final pICAS was constructed using five independent predictors of poor clinical outcome, defined as PICU mortality or unfavorable neurological status at discharge, identified through multivariate logistic regression. Notably, lactate levels were retained in the final score over $PbtO_2$ due to their stronger association with systemic perfusion deficits and clinical outcomes. These selected predictors are clinically actionable, as they can guide targeted interventions within management protocols. These components include an ICP burden ≥ 20 mmHg, a PRx > 0.30 for > 35% of monitoring time, a CPP deviation from CPPopt > 30% of monitoring time, a MAP variability > 12 mmHg, and a norepinephrine-equivalent dose ≥ 0.1 µg/kg/min. Each predictor was assigned 1 point, yielding a total pICAS score ranging from 0 to 5, with higher scores indicating a greater risk of adverse clinical outcomes.

Statistical Analysis

Continuous variables are presented as median (interquartile range, IQR), and categorical variables as counts (percentages). Univariate comparisons used the Mann–Whitney U test or chi-square test, as appropriate. Variables with $p < 0.10$ in univariate analysis were entered into a multivariate logistic regression with backward stepwise elimination to identify independent predictors of impaired autoregulation. In addition to

excluding patients with more than 20% missing data, smaller gaps in secondary physiological variables were addressed using Multiple Imputation by Chained Equations (MICE). For these imputations, variables such as serum lactate levels, MAP variability, and norepinephrine doses were included. A total of 10 imputations were conducted, and diagnostics verified the accuracy and reliability of the imputed datasets. Overall, 6% of all candidate values were imputed, helping readers assess the potential impact on the analysis. To ensure the robustness of the pICAS, a sensitivity analysis was conducted comparing the complete-case cohort with the imputed dataset, which showed no significant differences in the model's coefficients or AUC (0.89 vs 0.88, p=0.45).

Cutoff values for continuous predictors included in the Pediatric Integrated Cerebral Autoregulation Score (pICAS) were determined a priori based on physiological relevance and further refined using receiver operating characteristic (ROC) analysis, selecting thresholds that maximized the Youden index for predicting impaired cerebral autoregulation. The MAP variability threshold represents a high-risk extreme of hemodynamic instability rather than the population median, consistent with its intended use in identifying clinically relevant autoregulatory failure.

Model performance was assessed using the area under the receiver operating characteristic curve (AUC) for discrimination, the Hosmer–Lemeshow test for calibration, and the Nagelkerke pseudo-R^2 for overall performance. Internal validation employed 1,000 bootstrap resamples to evaluate model stability and optimism-corrected performance. Statistical significance was set at $p = 0.05$ (two-tailed). Notably, while the AUC provides a measure of statistical discrimination, the clinical utility becomes apparent when considering the real-world impact of a pICAS cutoff of 3. Such a threshold can fundamentally alter therapy by prioritizing more intensive hemodynamic monitoring and customized interventions for those patients identified at heightened risk of clinical deterioration [31,32].

RESULTS

Study Population

A total of 100 pediatric patients with severe traumatic brain injury (TBI) requiring vasopressor support were included in the analysis (median age 9 years, IQR 4–14; 63% male). The predominant mechanisms of injury were falls (45%), motor vehicle collisions (38%), and non-accidental trauma/assaults (17%). At PICU admission, the median Pediatric Glasgow Coma Scale (GCS) score was 6 (IQR 5–7).

Overall, 49 patients (49%) developed impaired cerebral autoregulation (mean PRx >0.30), 24 patients (24%) died during PICU stay, and 46 patients (46%) had an unfavorable neurological outcome at hospital discharge (Pediatric Glasgow Outcome Scale ≤3).

Baseline demographic, injury, and hemodynamic characteristics of the cohort are summarized in Table 1. Patients with impaired autoregulation had higher ICP, MAP variability, norepinephrine requirements, and lactate levels, and experienced worse neurological outcomes compared with those with preserved autoregulation.

Variable	Total (N = 100)	Preserved Autoregulation (n = 51)	Impaired Autoregulation (n = 49)	P value
Age, years	9 (4–14)	8 (4–13)	10 (5–15)	0.18
Male sex, n (%)	63 (63%)	32 (63%)	31 (63%)	0.99
Mechanism of injury, n (%)	–	–	–	0.32

• Fall	45 (45%)	23 (45%)	22 (45%)	–
• Motor vehicle collision	38 (38%)	19 (37%)	19 (39%)	–
• Assault / Non-accidental trauma	17 (17%)	9 (18%)	8 (16%)	–
GCS at admission	6 (5–7)	6 (5–7)	5 (4–7)	0.12
ICP, mmHg	18 (14–26)	15 (13–29)	24 (21–28)	<0.0001
Mean MAP, mmHg	82 (75–92)	81 (75–89)	84 (77–95)	0.09
MAP variability (SD), mmHg	6.2 (4.5–8.5)	5.1 (4.8–5.7)	7.5 (7.2–7.7)	<0.0001
Norepinephrine-equivalent dose, µg/kg/min	0.12 (0.08–0.25)	0.10 (0.08–0.11)	0.20 (0.18–0.28)	<0.001
Lactate at 24 h, mmol/L	2.1 (1.4–3.3)	1.8 (1.4–2.0)	2.7 (2.5–2.95)	<0.0001
Lactate clearance at 24 h, %	28 (12–45)	35 (20–50)	20 (8–35)	<0.0001
ICU mortality, n (%)	24 (24%)	5 (10%)	19 (39%)	<0.0001
Unfavorable neurological outcome (GOS ≤3), n (%)	46 (46%)	12 (24%)	34 (69%)	<0.0001

Baseline characteristics by cerebral autoregulation status (N=100). Data are median (IQR) or n (%). Comparisons by Mann–Whitney U or chi-square test; p 0.05 considered significant.

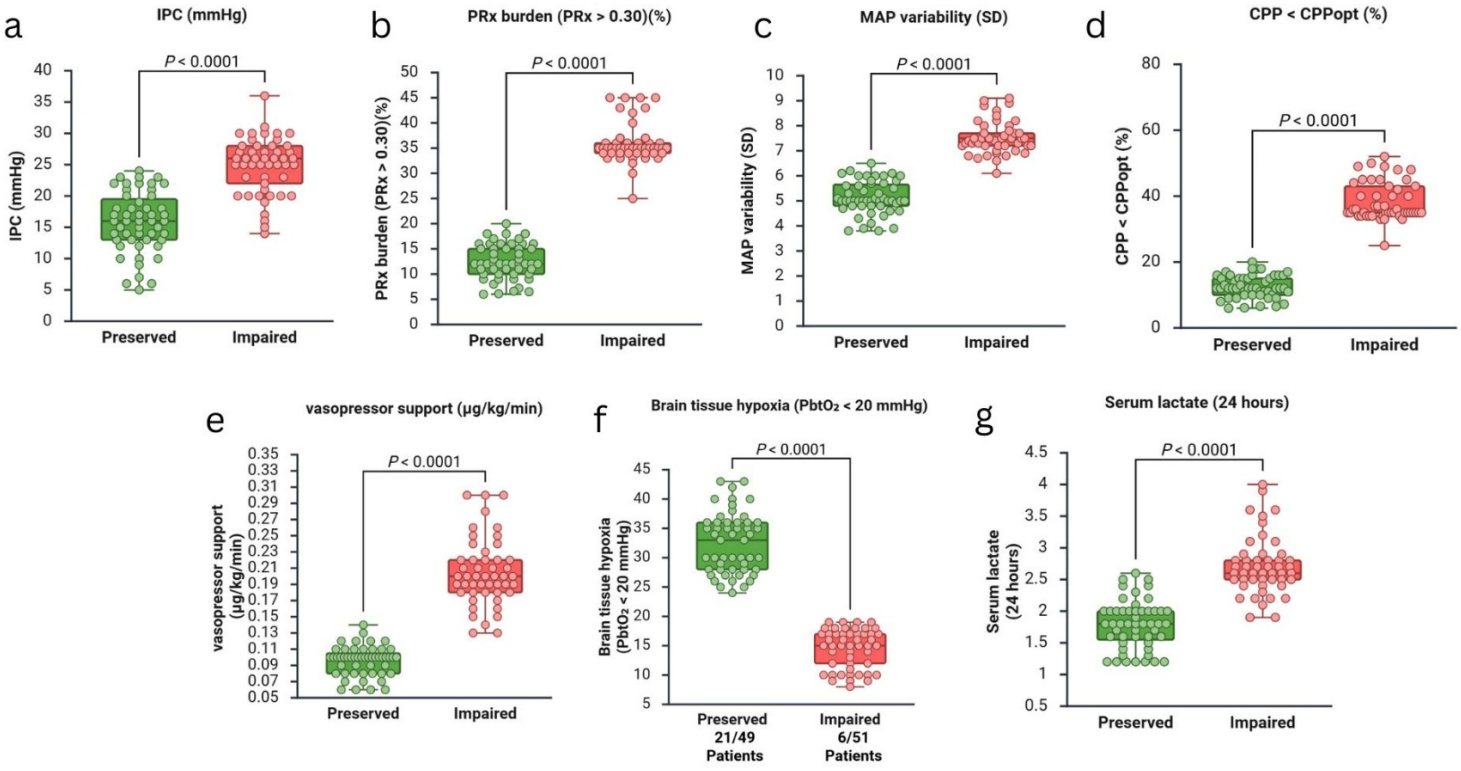
Abbreviations: *GCS, Glasgow Coma Scale; ICP, intracranial pressure; MAP, mean arterial pressure; ICU, intensive care unit; GOS, Glasgow Outcome Scale.*

Table 1. Baseline Demographic, Injury, and Hemodynamic Characteristics According to Cerebral Autoregulation Status

Cerebral and Hemodynamic Characteristics

Children with impaired autoregulation exhibited significant differences in both cerebral and systemic hemodynamic parameters compared with those with preserved autoregulation. Specifically, the median intracranial pressure (ICP) was 24 mmHg (IQR 21–28) versus 15 mmHg (IQR 13–29) ($p < 0.0001$) (Fig. 2a), while the PRx burden (PRx > 0.30) reached a median of 35% of monitoring time (IQR 34–42%) compared to 12% (IQR 10–15%) in the preserved group ($p < 0.0001$) (Fig. 2b). Systemic variability was also more pronounced in the impaired group, with a MAP variability SD of 7.5 mmHg (IQR 7.2–7.7) versus 5.1 mmHg (IQR 4.8–5.7) ($p < 0.0001$) (Fig. 2c). Furthermore, the duration of CPP below CPPopt was significantly higher in affected children, occupying 38% of monitoring time (IQR 35–43%) compared to 12% (IQR 10–15%) ($p < 0.0001$) (Fig. 2d).

Vasopressor requirements were significantly higher in patients with impaired autoregulation (median norepinephrine-equivalent dose 0.20 µg/kg/min, IQR 0.18–0.28) compared with patients with preserved autoregulation (median 0.10 µg/kg/min, IQR 0.08–0.11; $p < 0.0001$) (Fig. 2e). Brain tissue hypoxia ($PbtO_2 <$ 20 mmHg for > 10% of monitoring time) occurred in 21/49 patients (44%) with impaired autoregulation versus 6/51 (12%) in the preserved group ($p < 0.0001$) (Fig. 2f). Serum lactate at 24 hours was also higher in the impaired autoregulation group (median 2.7 mmol/L, IQR 2.5–2.95) compared with the preserved group (median 1.8 mmol/L, IQR 1.4–2.0; $p < 0.0001$) (Fig. 2g).



Patients with impaired cerebral autoregulation demonstrated worse physiological and metabolic parameters compared with those with preserved autoregulation. (a) ICP: Impaired patients showed significantly higher pressure (24 vs 15 mmHg). (b) PRx Burden: Impaired group spent more time in pressure-passive state (35% vs 12% of time). (c) MAP Variability: The impaired group showed greater hemodynamic instability (SD 7.5 vs 5.1 mmHg). (d) CPP < CPPopt: Impaired patients spent more time below optimal perfusion (38% vs 12% of time). Vasopressors: Higher doses needed for impaired autoregulation (0.20 vs 0.10 µg/kg/min). (f) Hypoxia: Higher incidence of brain tissue hypoxia in the impaired group (44% vs 12%). (g) Lactate: Elevated serum lactate in impaired patients (2.7 vs 1.8 mmol/L).

***Abbreviations**: ICP: Intracranial Pressure; MAP: Mean Arterial Pressure; CPP: Cerebral Perfusion Pressure; CPPopt: Optimal Cerebral Perfusion Pressure; SD: Standard Deviation; PRx: Pressure Reactivity Index; $PbtO_2$: Brain tissue oxygen tension; IQR: Interquartile Range.*

Figure 2. Physiological and metabolic differences between patients with preserved and impaired cerebral autoregulation in severe pediatric traumatic brain injury.

Pediatric Integrated Cerebral Autoregulation Score (pICAS) Derivation

Multivariate logistic regression identified five independent predictors of impaired cerebral autoregulation, which were used to construct the Pediatric Integrated Cerebral Autoregulation Score (pICAS) (Table 2). Each predictor was assigned 1 point, yielding a total score of 0-5. The scoring components included ICP ≥ 20 mmHg, PRx > 0.30 for > 35% of monitoring time, MAP variability > 12 mmHg, CPP below CPPopt for> 30% of monitoring time, and a norepinephrine-equivalent dose of 0.1 µg/kg/min.

Variable	Definition / Threshold	Adjusted OR	95% CI	P value	pICAS points
Intracranial hypertension	ICP ≥20 mmHg	5.4	2.1–13.9	<0.0001	1

Impaired pressure reactivity	PRx >0.30 for >35% of monitoring time	6.1	2.5–14.2	<0.0001	1
MAP variability	MAP SD >12 mmHg	4.3	1.9–10.0	<0.0001	1
CPPopt deviation	CPP below CPPopt for >30% of monitoring time	5.0	2.1–12.0	<0.0001	1
Vasopressor exposure	Norepinephrine-equivalent dose ≥0.1 µg/kg/min	3.7	1.5–8.5	0.0004	1

Multivariate logistic regression identified independent predictors of impaired cerebral autoregulation in children with severe TBI (N=100). Each predictor was assigned 1 point for the pICAS (0–5). $P < 0.05$ was considered significant.

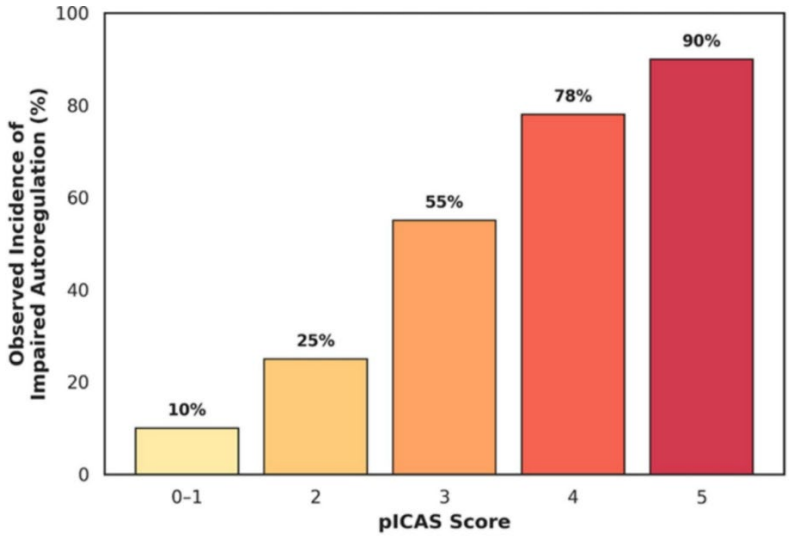
Abbreviations: *OR, odds ratio; CI, confidence interval; ICP, intracranial pressure; PRx, pressure reactivity index; MAP, mean arterial pressure; CPPopt, optimal cerebral perfusion pressure; pICAS, Pediatric Integrated Cerebral Autoregulation Score.*

Table 2. Multivariate Logistic Regression Model for Impaired Cerebral Autoregulation and pICAS Derivation.

Model Performance and Risk Stratification

To demonstrate the incremental value of the pICAS, we compared its discriminative ability with that of isolated monitoring variables. The pICAS showed significantly higher accuracy (AUC 0.89, 95% CI 0.83–0.95) for predicting poor clinical outcome, defined as PICU mortality or unfavorable neurological status at discharge, compared to ICP alone (AUC 0.72) or PRx alone (AUC 0.76) ($p < 0.01$). This confirms that integrating systemic hemodynamics with individualized autoregulation metrics provides superior risk stratification compared with traditional population-based targets. The distribution of the cohort according to the pICAS was: score 0–1 (n=22), score 2 (n=18), score 3 (n=20), score 4 (n=25), and score 5 (n=15). In addition to the Hosmer–Lemeshow test (p=0.62), a calibration plot showed strong alignment between the predicted probability of poor clinical outcome and the observed event rate across all risk deciles, with a slight overestimation in the highest risk category (score 5).

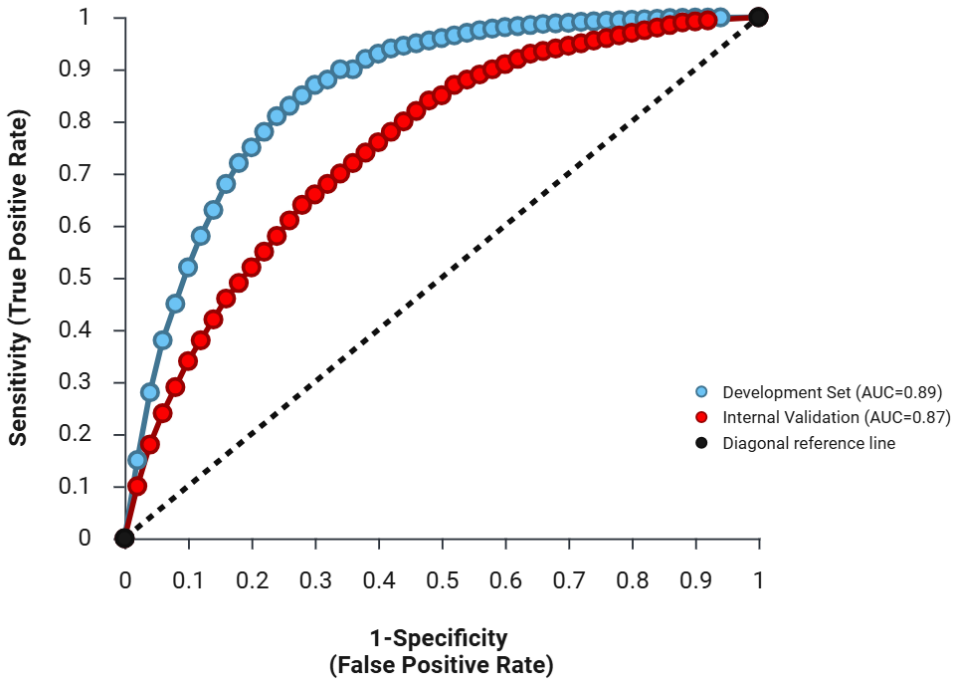
Furthermore, the observed incidence of poor clinical outcome increased in a stepwise manner with increasing pICAS score. Patients with a score of 0-1 showed an incidence of 10%, which increased to 25% for a score of 2, 55% for a score of 3, 78% for a score of 4, and reached 90% for a score of 5 (Fig. 3). At a cutoff of ≥ 3 points, the pICAS demonstrated sensitivity of 85%, specificity of 82%, positive predictive value of 77%, and negative predictive value of 88%. The model showed excellent discrimination and adequate calibration, with a Hosmer–Lemeshow p-value of 0.62 (Fig. 4). Multimodal neuromonitoring parameters and the associated risk of poor clinical outcome across pICAS categories are presented in Table 3.



The bar chart shows a stepwise increase in the observed incidence of impaired autoregulation (mean PRx > 0.30) as the pICAS score increases from 0 to 5.

Abbreviations: *pICAS: Pediatric Integrated Cerebral Autoregulation Score; PRx: Pressure Reactivity Index. Data labels indicate the percentage of patients within each score tier.*

Figure 3. Risk stratification according to the Pediatric Integrated Cerebral Autoregulation Score (pICAS).



The blue curve represents the Development Set (AUC = 0.89), while the red curve shows the Internal Validation (AUC = 0.87). Both curves demonstrate strong predictive accuracy, remaining well above the diagonal reference line representing chance-level performance (AUC = 0.50).

Abbreviations: *AUC: Area Under the Curve; ROC: Receiver Operating Characteristic; Sensitivity: True Positive Rate (TPR); 1-Specificity: False Positive Rate (FPR)*

Figure 4. Receiver Operating Characteristic (ROC) curves evaluate model performance.

Parameter	Preserved autoregulation (n=51)	Impaired autoregulation (n=49)	OR (95% CI)	p-value
PRx, median (IQR)	0.12 (0.06–0.20)	0.42 (0.35–0.53)	7.8 (3.6–16.8)	<0.0001
CPP deviation (% time <CPPopt)	12% (6–20)	38% (25–52)	6.2 (2.9–13.1)	<0.0001
$PbtO_2$ hypoxia burden (% time <20 mmHg)	4% (1–9)	18% (10–28)	5.4 (2.5–11.7)	<0.0001
ICP >20 mmHg burden (% time)	18% (10–30)	45% (32–58)	4.9 (2.2–10.9)	<0.0001
MAP variability (SD)	5.1 (4.8–5.7)	7.5 (7.2–7.7)	3.8 (1.7–8.5)	<0.0001
Norepinephrine-equivalent dose (µg/kg/min)	0.10 (0.08–0.11)	0.20 (0.18–0.28)	4.1 (1.8–9.2)	<0.0001
pICAS score 0–1	23 (45%)	2 (4%)	Reference	–
pICAS score 2	15 (29%)	8 (16%)	4.5 (1.3–15.4)	0.018
pICAS score 3	9 (18%)	12 (24%)	10.2 (3.0–34.8)	<0.001
pICAS score 4	3 (6%)	15 (31%)	21.7 (5.5–85.8)	<0.001
pICAS score 5	1 (2%)	12 (24%)	48.3 (5.5–423)	<0.001

Comparison of neuromonitoring parameters and pICAS categories between patients with preserved and impaired cerebral autoregulation. Odds ratios represent the risk of impaired autoregulation; pICAS 0–1 used as a reference. $P < 0.05$ is considered significant.
Abbreviations: *OR, odds ratio; CI, confidence interval; PRx, pressure reactivity index; CPPopt, optimal cerebral perfusion pressure; $PbtO_2$, brain tissue oxygen tension; ICP, intracranial pressure; MAP, mean arterial pressure; pICAS, Integrated Cerebral Autoregulation Score.*

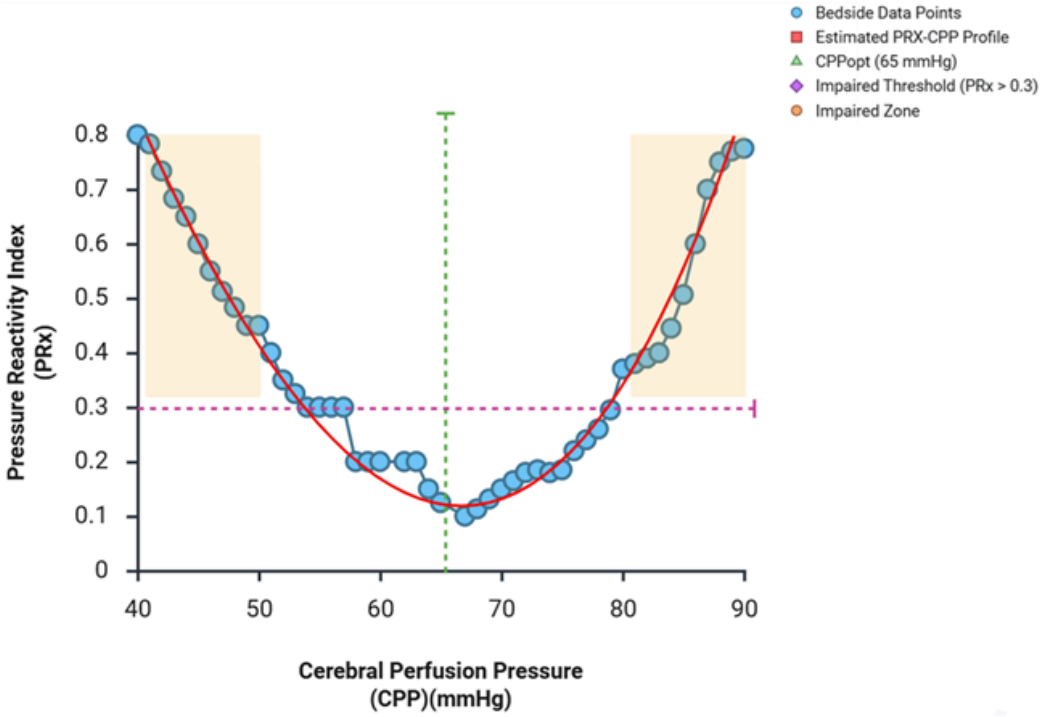
Table 3. Multimodal Physiologic Parameters and Performance of the Integrated Cerebral Autoregulation Score (pICAS).

Internal Validation

Internal validation using 1,000 bootstrap resamples confirmed model stability, yielding an optimism-corrected AUC of 0.87, indicating robust performance and reproducibility. Subgroup analyses demonstrated consistent predictive performance across age groups (infants, children, adolescents), sex, and injury mechanisms, supporting the generalizability of the pICAS within a pediatric severe TBI population requiring vasopressors. Furthermore, to address the application of pICAS in resource-limited PICUs, we propose several adaptation strategies. Firstly, simpler variables, such as easily measurable physiological parameters, could be used in place of complex neuromonitoring data. Secondly, adjusted thresholds that align with the available data in these settings can be established to ensure accurate predictions. These adaptations can enable broader implementation and enhance stakeholder engagement even with varying levels of monitoring capacity. Future research should explore pragmatic modifications to tailor the pICAS to diverse medical environments.

Multimodal Insights into Autoregulatory Dysfunction

Children with impaired autoregulation in our cohort exhibited elevated ICP, prolonged time with CPP below CPPopt, increased MAP variability, and frequent episodes of brain tissue hypoxia ($PbtO_2$ 20 mmHg). These findings highlight the dynamic, pressure-passive nature of cerebral perfusion in pediatric patients with severe TBI. Elevated serum lactate and reduced lactate clearance indicate systemic perfusion deficits contributing to autoregulatory failure, emphasizing the importance of integrating both cerebral and systemic parameters for early risk prediction. Individualized optimal CPP (CPPopt) was derived from the U-shaped relationship between PRx and CPP (Fig. 5).



The blue circles represent real-time bedside data points, while the red line indicates the estimated PRx-CPP parabolic profile. The green dashed line identifies the Optimal Cerebral Perfusion Pressure (CPPOpt) at 65 mmHg, where PRx is at its lowest. The purple dashed line marks the Impaired Threshold (PRx > 0.3), with shaded tan areas indicating the Impaired Zones where cerebrovascular reactivity is compromised.

Abbreviations: *PRx: Pressure Reactivity Index; CPP: Cerebral Perfusion Pressure; CPPopt: Optimal Cerebral Perfusion Pressure; mmHg: Millimeters of Mercury*

Figure 5. Cerebral Autoregulation Profile showing the relationship between Pressure Reactivity Index (PRx) and Cerebral Perfusion Pressure (CPP).

DISCUSSION

Principal Findings

This study demonstrates that impaired cerebral autoregulation in children with severe traumatic brain injury (TBI) requiring vasopressor support results from a multidimensional interplay among intracranial hypertension, systemic hemodynamic instability, deviation from individualized optimal CPP (CPPopt), and vasopressor exposure. The Pediatric Integrated Cerebral Autoregulation Score (pICAS) consolidates these factors into a bedside-applicable tool for early risk stratification of children at highest risk for neurological deterioration and PICU mortality [33,34,35].

Vasopressor Therapy and Cerebrovascular Coupling

While vasopressors are essential to maintain CPP, our data show that higher doses and prolonged exposure were independently associated with impaired autoregulation. By integrating cerebral, hemodynamic, and metabolic factors, the pICAS captures this critical interaction, providing a practical framework to guide individualized vasopressor titration and minimize episodes of pressure-passive cerebral perfusion [36,37].

Clinical Implications

The pICAS enables early identification of pediatric patients at high risk of autoregulatory failure, supporting closer hemodynamic monitoring, individualized CPP optimization based on CPPopt, and judicious vasopressor management to reduce MAP variability. By combining multiple routinely available multimodal parameters, pICAS facilitates pragmatic bedside decision-making, complementing traditional PRx-based approaches and age-based CPP/MAP targets. This tool has the potential to enhance precision neurocritical care in pediatric TBI [38].

Comparison with Existing Literature

Previous studies in pediatric TBI have largely focused on isolated neuromonitoring variables, such as ICP, CPP, and PRx, often without considering the dynamic interplay among cerebral perfusion, systemic hemodynamics, and metabolic stress. Unlike population-based targets, pICAS provides patient-specific risk stratification, supporting individualized, physiology-guided perfusion management. The incremental value of the pICAS lies in its transition from static measures to functional assessment; while ICP measures static volume and pressure, the pICAS captures the underlying physiological reserve by integrating vascular reactivity (PRx) and metabolic stress (lactate). Its performance (AUC 0.89, internal validation AUC 0.87) aligns with prior adult and pediatric studies demonstrating the predictive value of multimodal autoregulation metrics [39,40].

STRENGTHS AND LIMITATIONS

This study presents several key strengths, including the use of high-quality, continuous multimodal monitoring in a large pediatric cohort (N=100) and the integration of cerebral, hemodynamic, and metabolic parameters into a simple, bedside-applicable score. Furthermore, the findings are supported by robust internal validation using bootstrap resampling.

Despite these strengths, certain limitations must be acknowledged, primarily the retrospective design, which may introduce selection bias. Since the study's data were collected from tertiary-level centers with advanced monitoring capabilities, the findings may be skewed toward resource-rich settings, potentially limiting the applicability of the pICAS to less-equipped centers. Additionally, referral patterns might have led to the inclusion of patients with specific profiles, influencing the generalizability of the results. Furthermore, $PbtO_2$ monitoring was incomplete in some patients. To address these limitations, future studies could include broader sampling across hospital settings to minimize selection bias and better reflect the broader population. Efforts to ensure more comprehensive monitoring by implementing standardized protocols across centers could also enhance data completeness. Moreover, external validation across diverse multicenter pediatric cohorts is essential to confirm the generalizability of the pICAS score.

Future Directions

Prospective studies are necessary to evaluate real-time pICAS-guided interventions for CPP optimization and vasopressor titration, and to implement digital dashboards for continuous bedside scoring. Moreover, future research should focus on integrating advanced neuromonitoring modalities, such as microdialysis and transcranial Doppler (TCD), to refine risk stratification and improve neurological outcomes in pediatric TBI.

Will real-time pICAS feedback alter vasopressor dosing patterns and outcomes? Framing the next trial as a question may inspire collaborative exploration.

CONCLUSIONS

The Pediatric Integrated Cerebral Autoregulation Score (pICAS) represents a novel, evidence-based bedside tool for early identification of children with severe traumatic brain injury (TBI) at high risk of impaired cerebral autoregulation and adverse neurological outcomes. By integrating multimodal cerebral parameters, including intracranial pressure (ICP), pressure reactivity index (PRx), deviation from individualized optimal cerebral perfusion pressure (CPPopt), and brain tissue oxygenation ($PbtO_2$), with systemic hemodynamic and metabolic variables such as mean arterial pressure (MAP) variability, vasopressor dose and duration, and lactate dynamics, pICAS provides a comprehensive framework reflecting the multidimensional pathophysiology of autoregulatory failure in pediatric TBI.

Unlike approaches relying solely on isolated metrics or age-based CPP targets, pICAS contextualizes cerebrovascular reactivity within systemic physiology, enabling individualized risk stratification and precision-guided neurocritical care. It supports early identification of children most likely to benefit from targeted interventions, including optimized vasopressor titration, CPP management tailored to each child's autoregulatory capacity, and proactive neuroprotective strategies. Additionally, pICAS can assist in prioritizing monitoring resources, guiding escalation of care, and informing real-time decision-making in high-acuity PICU settings.

Our findings emphasize that impaired autoregulation in pediatric severe TBI is not a static cerebral phenomenon but a dynamic interplay of intracranial, systemic, and metabolic factors. By capturing the cumulative burden across these domains, pICAS moves beyond single-parameter assessment, offering a holistic, physiologically informed approach to pediatric TBI management.

While internal validation demonstrates robust predictive performance and reproducibility, prospective multicenter external validation is warranted to confirm generalizability across diverse pediatric populations. We are currently planning a multicenter validation study spanning several institutions across different geographic regions to thoroughly evaluate the pICAS tool in varied clinical settings. We invite collaboration from research centers interested in contributing to this effort, as their involvement would be invaluable in ensuring the clinical relevance and applicability of the pICAS. The tool effectively identifies children at high risk of secondary injury in severe TBI. Future applications may include real-time digital dashboards, adaptive algorithms to guide individualized CPP targets, and interventional studies assessing the impact of pICAS-guided management on long-term neurological outcomes and mortality.

In summary, the pICAS offers a promising, multidimensional framework for risk stratification in pediatric TBI. While our results demonstrate its potential utility in identifying patients at risk of secondary injury, prospective external validation is strictly required before this tool can be considered a definitive guide for clinical decision-making. Future research should confirm its incremental value as an actionable bedside metric. To further the impact of our research, we invite medical professionals and researchers to validate the pICAS within their own datasets and clinical environments. By sharing findings and adaptations, the broader community can collectively refine and optimize this tool, fostering communal progress in pediatric neurocritical care.

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