

Association between Cerebrovascular Reactivity Monitoring and Mortality Is Preserved When Adjusting for Baseline Admission Characteristics in Adult Traumatic Brain Injury: A CENTER-TBI Study

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Abstract

Cerebral autoregulation, as measured using the pressure reactivity index (PRx), has been related to global patient outcome in adult patients with traumatic brain injury (TBI). To date, this has been documented without accounting for standard baseline admission characteristics and intracranial pressure (ICP). We evaluated this association, adjusting for baseline admission characteristics and ICP, in a multi-center, prospective cohort. We derived PRx as the correlation between ICP and mean arterial pressure in prospectively collected multi-center data from the High-Resolution Intensive Care Unit (ICU) cohort of the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) study. Multi-variable logistic regression models were analyzed to assess the association between global outcome (measured as either mortality or dichotomized Glasgow Outcome Score–Extended [GOSE]) and a range of covariates (IMPACT [International Mission for Prognosis and Analysis of Clinical Trials] Core and computed tomography [CT] variables, ICP, and PRx). Performance of these models in outcome association was compared using area under the receiver operating curve (AUC) and Nagelkerke's pseudo-R². One hundred ninety-three patients had a complete data set for analysis. The addition of percent time above threshold for PRx improved AUC and displayed statistically significant increases in Nagelkerke's pseudo-R² over the IMPACT Core and IMPACT Core + CT models for mortality. The addition of PRx monitoring to IMPACT Core ± CT + ICP models accounted for additional variance in mortality, when compared to models with IMPACT Core ± CT + ICP alone. The addition of cerebrovascular reactivity monitoring, through PRx, provides a statistically significant increase in association with mortality at 6 months. Our data suggest that cerebrovascular reactivity monitoring may provide complementary information regarding outcomes in TBI.

Keywords: autoregulation; cerebrovascular reactivity; IMPACT; outcome analysis

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Introduction

THE CONTINUOUS MONITORING OF CEREBROVASCULAR reactivity in critically ill adult patients with moderate and severe traumatic brain injury (TBI) has received support from international multi-modal monitoring consensus statements.^{1–3} Given the common use of intracranial pressure (ICP) monitoring, the use of ICP-derived indices provides the most convenient means of assessing cerebrovascular reactivity in this population and have been cited as an option by the Brain Trauma Foundation (BTF) guidelines.⁴ Of several indices,^{1,5,6} The pressure reactivity index (PRx) has received the most attention and is the most widely described cerebrovascular reactivity index in the literature,^{7,8} with higher values denoting increasing autoregulatory dysfunction.

The biological relevance of PRx and its incorporation into clinical management guidelines are underpinned by its association with outcome in retrospective analysis. These reports demonstrate that during the acute phase, both the magnitude of mean PRx or the duration spent with PRx above a pre-specified threshold are associated with mortality and functional outcome.^{7,9–11} However, this basis for attributing biological relevance and management utility suffers from some shortcomings.

First, it is unclear whether these PRx-related metrics maintain their strong association with outcome when adjusting for admission characteristics incorporated in recognized clinical outcome prediction tools in TBI, the best known of which are the International Mission for Prognosis and Analysis of Clinical Trials (IMPACT) models.¹² The performance of the IMPACT models in predicting outcome, measured using area under the receiver operating curve (AUC), ranges from 0.60 to 0.80 (depending on cohort and the time of the study), and the proportion of outcome association variance they explain, as quantified by Nagelkerke's pseudo-R², ranges up to 0.35.^{12,13} A rigorous assessment of PRx in association with outcome would depend on being able to add to any variance explained by the IMPACT models.

Second, we need to understand whether the association between PRx with outcome is not simply because this metric is a non-specific index of post-admission disease course, rather than a specific effect attributable to deterioration in cerebrovascular reactivity. One rational way to address this issue is to examine whether PRx-derived metrics maintain their strong association with outcome when adjusting for a canonical physiological measure of TBI disease course such as ICP.

Finally, the most substantial publications that relate PRx to outcome come from a retrospective analysis of single-center data, without formal blinding of outcome assessment. A rigorous assessment of the outcome association of PRx would require testing on a prospective multi-center patient cohort, with independent and blinded assessment of outcome.

The goal of this study was to explore PRx cerebrovascular reactivity monitoring and its association with outcome, adjusting for existing admission IMPACT Core and Core + computed tomography (CT) model variables. In addition, the association between PRx and outcome was assessed while adjusting for canonical metrics of TBI disease course (mean ICP and duration of ICP above classical thresholds). This was accomplished through analysis of a prospectively acquired multi-center data set from critically ill adult patients with moderate/severe TBI (the CENTER-TBI [Collaborative European NeuroTrauma Effectiveness Research in TBI] study).¹⁴

Methods

Patient population

All patients from the multi-center CENTER-TBI high-resolution intensive care unit (ICU) monitoring cohort with parenchymal ICP monitoring were included in this analysis. Patients with external ventricular drain-based ICP data were excluded given the interrupted nature of their recordings (i.e., reliable ICP can be recorded only when the drainage is closed). These patients were prospectively recruited between January 2015 and December 2017 from 21 centers in the European Union (EU). All patients were admitted to the ICU for their TBI during the course of the study, with high-frequency digital signals recorded from their ICU monitors during the course of their ICU stay. All patients suffered predominantly from moderate-to-severe TBI (moderate = Glasgow Coma Score [GCS] 9–12; severe = GCS of ≤ 8). A minority of patients ($n = 31$) were categorized at the time of admission as suffering from less-severe TBI, but experienced subsequent early deterioration leading to ICU admission for care and monitoring. All patients in this cohort had invasive ICP monitoring conducted in accord with the BTF guidelines.⁴

Ethics

Data used in these analyses were collected as part of the CENTER-TBI study, which had individual national or local regulatory approval; the UK Ethics approval is provided as an exemplar: (IRAS No: 150943; REC 14/SC/1370). The CENTER-TBI study (EC grant 602150) has been conducted in accord with all relevant laws of the 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 Harmonized 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 by the patients and/or the legal representative/next of kin was obtained, accordingly to the local legislations, for all patients recruited in the Core Dataset of CENTER-TBI and documented in the e-CRF.

Data collection

As part of recruitment to the multi-center high-resolution ICU cohort of CENTER-TBI, all patients had demographics, injury, and imaging data prospectively recorded. Similarly, all patients had high-frequency digital signals from ICU monitoring recorded throughout their ICU stay, with the goal of initiating recording within 24 h of ICU admission. All digital ICU signals were further processed (see Signal Acquisition/Signal Processing). For the purpose of this study, the IMPACT Core and CT variables were extracted from the central study database. They included: age, admission best GCS motor score, and pupillary reactivity (bilaterally reactive, unilateral reactive, bilateral unreactive), Marshall CT classification,¹⁵ presence of traumatic subarachnoid hemorrhage (yes, no), presence of an extradural hematoma (yes, no), presence of pre-hospital hypotension (yes, no), and the presence of pre-hospital hypoxia (yes, no). Patient outcomes were assessed at 6 months using the extended Glasgow Outcome Scale–Extended (GOSE). Outcome assessors in TBI and the researchers involved in analysis of high-resolution data were blinded to each other's work. Finally, we used version 2.0 of the CENTER-TBI data set, where missing GOSE measures at 6 months were imputed. As such, CENTER-TBI data version 2.0 was accessed for the purpose of this study, by Opal database software.¹⁶

Signal acquisition

Arterial blood pressure (ABP) was obtained through either radial or femoral arterial lines connected to pressure transducers. ICP was acquired from an intraparenchymal strain gauge probe (Codman ICP MicroSensor; Codman & Shurtleff Inc., Raynham, MA), parenchymal fibre optic pressure sensor (Camino ICP Monitor; Integra Life Sciences, Plainsboro, NJ; <https://www.integralife.com/>). All signals were recorded using digital data transfer or digitized by an analog-to-digital converter (DT9803; Data Translation, Marlboro, MA), where appropriate; sampled at frequency of 100 Hz or higher, using the ICM+ software (Cambridge Enterprise Ltd, Cambridge, UK; <http://icmplus.neurosurg.cam.ac.uk>) or Moberg CNS Monitor (Moberg Research Inc, Ambler, PA; <https://www.moberg.com>) or a combination of both. Signal artefacts were removed using both manual and automated methods before further processing or analysis.

Signal processing

Post-acquisition processing of the above signals was conducted using ICM+ (Cambridge Enterprise Ltd; <http://icmplus.neurosurg.cam.ac.uk>). Cerebral perfusion pressure (CPP) was determined as mean arterial pressure (MAP) – ICP. Ten-second moving averages (updated every 10 sec to avoid data overlap) were calculated for all recorded signals: ICP, ABP (which produced MAP), pulse amplitude of ICP, and CPP. PRx was calculated as the moving correlation coefficient between 30 consecutive 10-sec mean windows of ICP and MAP, updated every minute.

Data were downsampled to minute-by-minute resolution for the entire duration of recording for each patient. Grand mean values of all physiological variables were calculated per patient. In addition, the following post-processing of this physiological data occurred in R (R Core Team [2018]; R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; <https://www.R-project.org/>):

1. ICP: For each patient, the % of time spent above ICP of 20 mm Hg and 22 mm Hg were calculated for the entire recording period.^{4,11}
2. PRx: For each patient, the % of time spent above the following clinically defined thresholds were calculated across the entire recording period: 0, +0.25, and +0.35.^{11,17} All of these thresholds for PRx have been defined in previous published literature as statistically significant for association with 6-month global outcome in adult TBI patients.

Data were provided in summary sheets for the patient cohort using data from: 1) entire recording and 2) the first 72 h of recording. These two sheets were produced to assess whether there was any difference in outcome association when focusing on more acute physiology, such as that observed during the first 72 h post-injury.

Statistical analysis

All statistical analysis was conducted using R and XLSTAT (Addinsoft, New York, NY; <https://www.xlstat.com/en/>) add-on package to Microsoft Excel (Microsoft Office 15, Version 16.0.7369.1323; Microsoft Corporation, Redmond, WA). The following analysis was conducted for both the entire recording period and the first 72 h of recording, with similar results. As such, only the entire recording period will be reported in detail, with intermittent reference made to the results from the first 72 h of recording.

Normality of continuous variables was assessed by the Shapiro-Wilks test, where all variables displayed non-parametric characteristics and are hence displayed as median (range) or median (interquartile range; IQR). For all testing described, the alpha was set at 0.05 for significance. GOSE was then dichotomized into the

following categories: 1) alive (GOSE 2–8) versus dead (GOSE 1) and 2) favorable (GOSE 5–8) versus unfavorable (GOSE ≤4). IMPACT Core and CT variables, along with physiological variables, were compared between each dichotomized group, using the Mann-Whitney U test or chi-square testing, where appropriate.

Univariate logistic regression (ULR) was first conducted, comparing each IMPACT model variable, and the continuous physiologic variables to the dichotomized outcomes. AUC, 95% confidence intervals (CIs), and *p* values for the univariate models are reported.

Next, IMPACT Core/Core + CT multi-variable models were created. Using multi-variable logistic regression (MLR) analysis, these models and their association with dichotomized GOSE were assessed. AUC, 95% confidence intervals (CIs), and *p* values were reported for each model. Finally, the % time spent above threshold for ICP and PRx were sequentially added to the IMPACT Core/Core + CT models. Similar to the IMPACT Core/Core + CT baseline models, AUC, *p* values, and model Akaike information criteria (AIC) were reported for each dichotomized outcome, with highest AUC, lowest AIC indicating model superiority. Additional accounted variance in association with outcome over the IMPACT Core/Core + CT models was assessed using the relative difference in Nagelkerke's pseudo- R^2 (termed delta pseudo- R^2). All AUCs and 95% CIs for both ULR and MLR were determined using bootstrapping techniques with 2000 iterations.

Results

Patient population

At the time of this analysis, a total of 193 patients from the CENTER-TBI high-resolution ICU cohort had complete data sets, including: 6-month GOSE, high-frequency physiological signals containing at least ICP (from parenchymal monitors) and ABP for PRx derivation, and a complete set of IMPACT Core variables. Looking at those with all of the above, plus IMPACT CT variables, our number of patients with complete data at the time of this extraction was 166. Patient demographics for the entire cohort ($n = 193$) can be found summarized in Table 1. Patient demographics for both the alive/dead and favorable/unfavorable outcome groups can be found in Supplementary Appendix A.

Logistic regression analysis

ULR results, including AUC and *p* values, for each of the IMPACT Core, IMPACT CT, and PRx variables can be found in Supplementary Appendix B, with results for both survival and dichotomized 6-month outcomes. Only the results for the entire recording period are reported here, but similar results were found when limiting analysis to the first 72 h of physiological data.

MLR analysis of the IMPACT Core models for alive/dead and favorable/unfavorable outcomes yielded an AUC of 0.707 (95% CI, 0.11–0.798; $p < 0.0001$) and 0.638 (95% CI, 0.561–0.713; $p < 0.0001$), respectively. The IMPACT Core + CT models for alive/dead and favorable/unfavorable outcomes yielded an AUC of 0.673 (95% CI, 0.567–0.773; $p = 0.015$) and 0.652 (95% CI, 0.570–0.732; $p = 0.001$), respectively.

All the IMPACT Core “+” only model AUCs can be found in Table 2, whereas IMPACT Core + CT “+” model AUCs and *p* values can be seen in Supplementary Appendix C. The results demonstrate that the addition of % time spent with PRx over +0.25 or +0.35, in particular, to both the IMPACT Core and Core + CT, models led to superior AUC values, with lower AIC, for the alive/dead dichotomized outcome over baseline models. This is further exemplified when comparing IMPACT Core + ICP models to IMPACT Core + ICP + PRx variable models (Table 2), where the

TABLE 1. PATIENT DEMOGRAPHICS: MEDIAN AND IQR

Demographics	Median (IQR)
No. of patients	193
Age (years)	51.0 (30.0–64.0)
Sex	
Male	149
Female	44
Admission GCS (total)	6 (3–10)
Admission GCS motor	4 (1–5)
Admission pupil response	
Bilaterally reactive	142
Unilateral unreactive	15
Bilaterally unreactive	36
Marshall CT grade	3 (2–6)
No. with traumatic SAH	145
No. with extra-axial hematoma	37
No. with hypoxia episode	32
No. with hypotension episode	24
Duration of high-frequency physiological recording (h)	119.9 (78.3–157.6)
ICP (mm Hg)	12.6 (9.6–16.6)
CPP (mm Hg)	70.2 (64.3–76.4)
% time with ICP >20 mm Hg	5.3 (1.1–19.9)
% time with ICP >22 mm Hg	2.8 (0.5–14.8)
% time with PRx >0	51.7 (38.9–66.4)
% time with PRx >+0.25	26.9 (18.5–41.7)
% time with PRx >+0.35	19.4 (13.3–31.8)
6-month GOSE	4 (3–5)
No. alive: 6 months	153
No. dead: 6 months	40
No. favorable outcome:	83
6 months (GOSE 5–8)	
No. unfavorable outcome:	110
6 months (GOSE 1–4)	

CPP, cerebral perfusion pressure; CT, computed tomography; GCS, Glasgow Coma Score; GOSE, Glasgow Outcome Scale-Extended; ICP, intracranial pressure; IQR, interquartile range; MAP, mean arterial pressure; mm Hg, millimeters of mercury; PRx, pressure reactivity index (correlation between ICP and MAP); SAH, subarachnoid hemorrhage.

addition of % time above PRx thresholds of +0.25 (e.g., AUC 0.819, 95% CI 0.735–0.888, AIC 155.6 vs. AUC 0.780, 95% CI 0.697–0.855, AIC 164.9; in mean ICP models) and +0.35 (e.g., AUC 0.825, 95% CI 0.747–0.893, AIC 154.3 vs. AUC 0.780, 95% CI 0.697–0.855, AIC 164.9; in mean ICP models) led to improved AUCs and smaller AIC values. Figure 1 displays the receiver operating curves for the alive/dead dichotomized outcome for IMPACT Core and additional representative models.

However, for favorable/unfavorable dichotomized 6-month outcome, there was little to no change in the AUC and AIC for models containing PRx or ICP, above and beyond the IMPACT Core and Core + CT base models. This is in keeping with previous literature suggesting that ICP is a stronger predictor of mortality, compared to functional outcome.^{2,4,18,19}

Additional explanation of outcome variance

All MLR models were then compared using Nagelkerke's pseudo-R², assessing for additional account of variance in outcome association for both dichotomized outcomes. The results were similar for both the entire recording period and first 72 h of recording. The IMPACT Core + PRx models were initially compared to the IMPACT Core baseline model, demonstrating that the addition

of % time above PRx of +0.25 and +0.35 provided statistically significant increases in accounted variance in outcome association over the IMPACT Core model alone (up to 19.3% for alive/dead outcome; $p < 0.0001$). This held true only for alive/dead dichotomized outcome. Similar results occurred for the IMPACT Core + CT models, where the addition of % time with PRx above +0.25 and +0.35 produced statistically significant increases in pseudo-R² (up to 19.2% for alive/dead outcome; $p < 0.0001$).

Similarly, IMPACT Core + ICP + PRx models were compared to IMPACT Core + ICP models (i.e., IMPACT Core + mean ICP; IMPACT Core + % time with ICP >20 mm Hg; and % time with ICP >22 mm Hg), demonstrating statistically significant additional accounted variance in outcome association for the models with % time with PRx >+0.25 and >+0.35 (for alive/dead). Table 3 outlines the pseudo-R² values in comparing various models for the alive/dead dichotomized outcome for the IMPACT Core only models. Supplementary Appendix D outlines the pseudo-R² values comparing various IMPACT Core + CT models.

However, despite the association with mortality, evaluating favorable/unfavorable dichotomized outcome displayed no significant differences between models when assessed using Nagelkerke's pseudo-R², in keeping with the similar AUC and AIC values identified during MLR analysis, for both the Core and Core + CT models.

Discussion

Using the multi-center prospectively collected CENTER-TBI high-resolution ICU cohort, we have been able to demonstrate that metrics derived from cerebrovascular reactivity monitoring (PRx) maintain a strong association with mortality at 6 months, when adjusting for baseline admission characteristics (IMPACT Core and Core + CT variables) and ICP monitoring. These results were replicated using both the entire recording period and first 72 h of recording.

In particular, this is the first study to demonstrate the potential additional benefit to outcome association of cerebrovascular reactivity monitoring in TBI. The percentage of time spent over threshold for PRx of +0.25 and +0.35, when added to the IMPACT Core and Core + CT models, provided improved AUCs, lower AIC values, and statistically significant increases in accounted variance in outcome association for alive/dead dichotomized outcome, with up to 19.3% additional accounted variance in some cases. This provides strong evidence to support this type of monitoring in TBI patients, validating the strong associations with mortality that have been observed in previous large retrospective studies, where adjusting for baseline admission characteristics was not possible.^{1,11,17}

We recognized that the improved mortality association achieved by incorporating PRx metrics may have simply represented the availability of data beyond initial presentation, thus providing information regarding disease evolution, rather than implying a specific biological impact of abnormal cerebrovascular reactivity. In order to test this question, first we asked whether PRx-derived data provided incremental improvements in explaining mortality outcome variance beyond that provided by a more conventional marker of abnormal physiology in this population—ICP. We found that the addition of PRx-derived data provided improved mortality association beyond that provided by incorporating ICP data alone. The AUCs observed for those models with % time PRx over +0.25 or +0.35 trended higher than those models that included both IMPACT Core variables and ICP, with lower AIC values. Second, we evaluated the first 72 h of monitoring, with results from this analysis confirming those from the entire monitoring period. These results confirm that PRx monitoring maintains its association with mortality

TABLE 2. MULTI-VARIABLE LOGISTIC REGRESSION ANALYSIS: IMPACT CORE MODEL PLUS CEREBROVASCULAR REACTIVITY

<i>Model</i>	<i>AUC A/D (95% CI)</i>	<i>AIC</i>	<i>p value</i>	<i>AUC F/U (95% CI)</i>	<i>AIC</i>	<i>p value</i>
CORE	0.707 (0.611–0.798)	176.3	<0.0001	0.638 (0.561–0.713)	236.5	<0.0001
CORE + mean ICP	0.780 (0.697–0.855)	164.9	<0.0001	0.651 (0.574–0.729)	237.2	0.0001
CORE + % time ICP >20 mm Hg	0.811 (0.734–0.881)	158.7	<0.0001	0.647 (0.571–0.724)	235.7	0.0001
CORE + % time ICP >22 mm Hg	0.811 (0.727–0.884)	160.5	<0.0001	0.648 (0.570–0.725)	236.3	0.0001
% time above PRx thresholds						
CORE + % time PRx >0	0.781 (0.694–0.865)	163.3	<0.0001	0.654 (0.575–0.728)	236.3	0.0002
CORE + % time PRx >+0.25	0.803 (0.721–0.877)	157.4	<0.0001	0.661 (0.584–0.758)	235.5	0.0001
CORE + % time PRx >+0.35	0.812 (0.727–0.884)	155.2	<0.0001	0.661 (0.584–0.737)	235.3	0.0001
Mean ICP + % time above PRx thresholds						
CORE + mean ICP + % time PRx >0	0.807 (0.724–0.883)	158.7	<0.0001	0.653 (0.575–0.729)	237.6	0.0001
CORE + mean ICP + % time PRx >+0.25	0.819 (0.735–0.888)	155.6	<0.0001	0.659 (0.582–0.731)	237.1	0.0001
CORE + mean ICP + % time PRx >+0.35	0.825 (0.747–0.893)	154.3	<0.0001	0.661 (0.583–0.733)	237.0	0.0001
% time ICP >20 mm Hg + % time above PRx thresholds						
CORE + % time ICP >20 mm Hg + % time PRx >0	0.812 (0.729–0.883)	154.9	<0.0001	0.647 (0.570–0.730)	236.4	0.0001
CORE + % time ICP >20 mm Hg + % time PRx >+0.25	0.818 (0.744–0.893)	152.6	<0.0001	0.651 (0.566–0.730)	236.1	0.0001
CORE + % time ICP >20 mm Hg + % time PRx >+0.35	0.822 (0.742–0.890)	151.6	<0.0001	0.649 (0.571–0.721)	236.1	0.0001
% time ICP >22 mm Hg + % time above PRx thresholds						
CORE + % time ICP >22 mm Hg + % time PRx >0	0.810 (0.726–0.885)	156.8	<0.0001	0.648 (0.570–0.723)	237.1	0.0001
CORE + % time ICP >22 mm Hg + % time PRx >+0.25	0.814 (0.735–0.886)	154.4	<0.0001	0.647 (0.570–0.720)	236.7	0.0001
CORE + % time ICP >22 mm Hg + % time PRx >+0.35	0.817 (0.736–0.889)	153.3	<0.0001	0.647 (0.570–0.720)	236.6	0.0001

CORE model consisted of age, admission Glasgow Coma Scale motor score, and pupil response (normal bilaterally, unilateral unreactive, or bilaterally unreactive).

A/D, alive/dead; AIC, Akaike information criteria; AUC, area under the receiver operating curve; CPP, cerebral perfusion pressure; CI, confidence interval; F/U, favorable/unfavorable outcome (i.e., favorable=Glasgow Outcome Scale of 5–8; unfavorable=Glasgow Outcome Scale of 1–4); ICP, intracranial pressure; IMPACT, International Mission for Prognosis and Analysis of Clinical Trials; MAP, mean arterial pressure; PRx, pressure reactivity index (correlation between ICP and MAP).

when adjusting for baseline characteristics and ICP, potentially providing added value. However, given only 193 patients for the Core models and 166 patients for the Core + CT models in this study, these results do require further validation.

To confirm the added benefit of PRx monitoring above and beyond ICP monitoring in this cohort, we produced full models containing IMPACT Core/Core + CT and added ICP variables. We then tested the additional benefit of % time above PRx threshold to these models. The addition of PRx monitoring, through the % time above +0.25 and +0.35, produced improved AUCs and statistically significant relative increases in pseudo- R^2 (up to 11.5% in some cases), indicating that the addition of PRx to ICP monitoring provides statistically significant added mortality association. These results are the first of their kind, highlighting the added benefit of PRx monitoring in moderate and severe TBI patients.

Finally, in keeping with the literature supporting that ICP is a stronger predictor of mortality (over functional outcome) in TBI,^{2,4,18,19} IMPACT Core and Core + CT models performed similar to those with ICP and PRx variables included, when evaluating the association with favorable/unfavorable dichotomized outcome. This was highlighted by the similar AUC and AIC values, with no significant difference on Nagelkerke's pseudo- R^2 testing. This emphasizes the role of dysautoregulation (and the use of PRx) in associations with mortality. It is unknown whether other cerebrovascular reactivity indices would perform better for favorable/unfavorable outcome association when adjusting for IMPACT and ICP variables. Given the lack of strong association between impaired cerebrovascular reactivity and functional outcome iden-

tified in this study, we must acknowledge the results are disappointing. This carries potential implications for ongoing works in PRx/optimal cerebral perfusion pressure (CPPopt)-directed physiological targets, though the link between CPPopt and functional outcome has yet to be clearly identified, and is the focus of ongoing phase II studies.²⁰ There is the possibility that the findings here may translate to a lack of association between CPPopt parameters and functional outcome, which one might argue may be more important than mortality as an outcome metric.

Past studies have demonstrated the outcome relevance of abnormal physiology as recorded by multi-modal monitoring, but their explanatory power has not been shown to be additional to that of well-established covariates, such as those included in the IMPACT models. The additional explanation of mortality variance that we demonstrate with PRx has implications for refined prognostication. However, the real aim of continuous monitoring of brain signals is not an outcome prediction, but timely and wisely reactions to a temporary crisis.

Limitations

Despite the interesting and reassuring results of the above analysis, some important limitations deserve attention.

First, despite this being a multi-center prospective data set, the overall patient numbers are relatively low at 193, with only 166 having full Core and CT IMPACT variables. The specific requirements for available data (i.e., presence of complete IMPACT Core/Core + CT variables, high-frequency digital physiologic signals

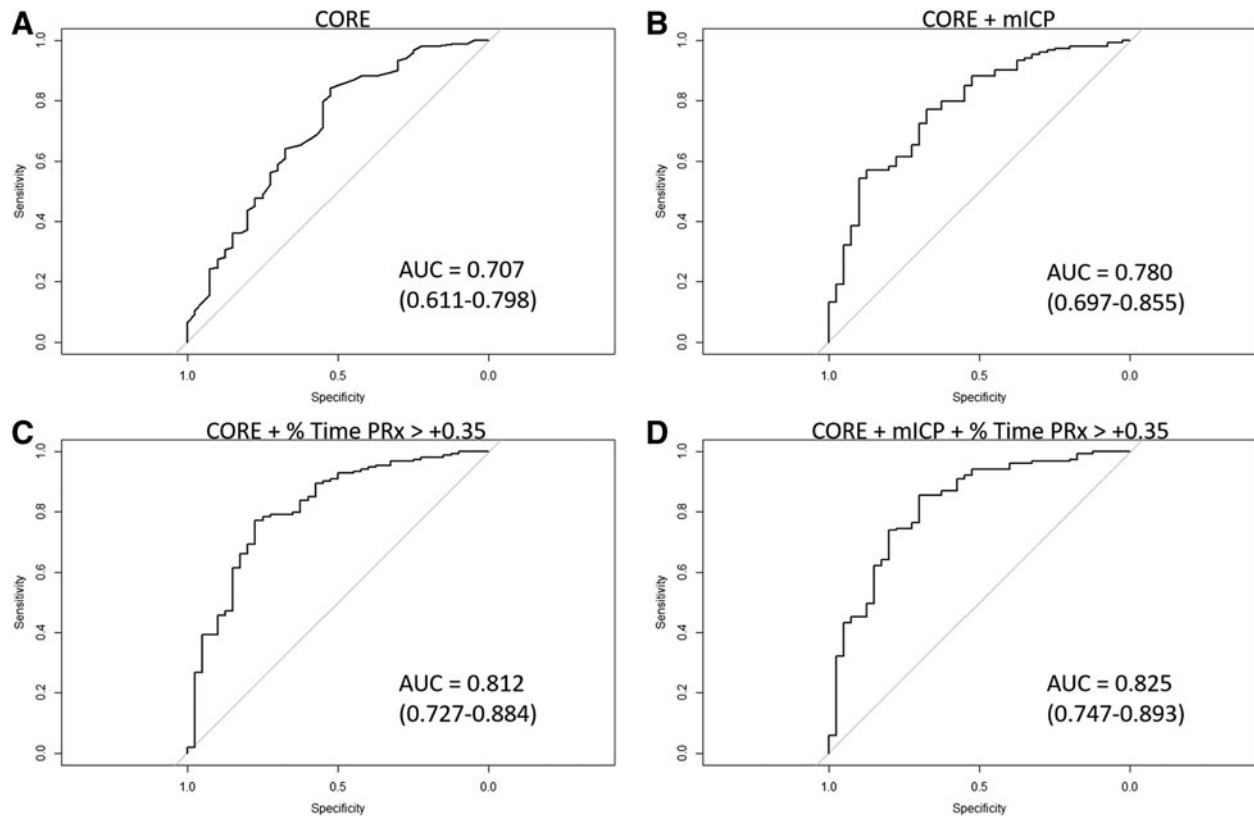


FIG. 1. ROC for alive/dead dichotomized outcome: IMPACT Core, Core + mean ICP, Core + % time PRx >+0.35, and Core + mean ICP + % time PRx >+0.35. (A) IMPACT Core variables alone. (B) IMPACT Core + mean ICP. (C) IMPACT Core + % time with PRx >+0.35. (D) IMPACT Core + mean ICP + % time with PRx >+0.35. ICP, intracranial pressure; MAP, mean arterial pressure; mICP, mean ICP; PRx, pressure reactivity index (correlation between ICP and MAP); AUC, area under the curve; ROC, receiver operating curve.

from parenchymal ICP monitoring, and a recorded outcome at 6 months) limited our patient numbers to 193 and 166 for the Core and Core + CT cohorts, respectively. This was secondary to missing data for the admission CT characteristics. However, it must be acknowledged, despite the limited numbers, our results were statistically significant. As such, the ability to extrapolate the results of this study to other larger TBI populations may be limited; thus, future dedicated studies with this type of high-resolution data sets are needed to provide validation of these results.

Second, given that these data were collected as a multi-center, prospective, observational study, there exists the potential impact of patients, injury, and treatment heterogeneity on both the recorded physiological signals and patient outcomes. However, if anything, we would rather expect this additional heterogeneity to dilute the studied effects.

Third, the association with outcome was much stronger for alive/dead dichotomization, as opposed to favorable/unfavorable. This may be a function of the small patient numbers, or the fact that PRx reflects pressure reactivity more accurately in conditions of low cerebral compliance, associated with high ICP, which in turn is well known for its stronger association with mortality over morbidity.^{2,4,18,19} In further work, we will investigate whether other ICP-derived cerebrovascular reactivity indices, such as pulse amplitude index⁵ or RAC,⁶ which evaluate other facets of auto-regulation and/or intracranial compliance, can provide explanation of variation in favorable/unfavorable outcome, when added to existing IMPACT variables. The main limitation of these indices is the need for high-frequency digital physiological waveforms for

analysis of ICP pulse. This will be explored in future studies using the CENTER-TBI high-resolution ICU cohort.¹⁴

Fourth, given that this was a preliminary multi-center analysis of the association between cerebrovascular reactivity and outcome, adjusting for baseline characteristics, we are limited in our ability to comment on what exact period of monitoring after TBI displays the strongest association with mortality. Given that the goal was not to build prognostic models for use, but merely to explore whether the association between PRx and outcome was preserved when accounting for baseline admission characteristics, this was beyond the scope of this project. It is possible that specific periods of monitoring post-injury are stronger predictors of outcome. Such analysis, while controlling for baseline characteristics, would require extensive daily, or even high-resolution, analysis of outcome association. Given the current limitations with complete data sets, this is something we plan on exploring in the future using amalgamated data from CENTER-TBI and ongoing high-frequency physiology data collection schemes from partner institutions.

Fifth, evaluating PRx over the entire recording period and first 72 h may suggest that PRx is relatively stable over time. This is far from the case, given that we know that PRx fluctuates widely in the setting of moderate/severe TBI. Similarly evaluating PRx over such periods, one could argue that the impaired PRx values observed simply reflect the severity of primary injury and not a fluctuating, targetable parameter. We know that PRx varies over the course of ICU stay and between patients. Instead of using grand average data in the analysis, we utilized % time above thresholds in attempt to capture some of this variability over time. However, we must

TABLE 3. ADDED VARIANCE IN A/D OUTCOME ASSOCIATION AT 6 MONTHS WITH CEREBROVASCULAR REACTIVITY MONITORING OVER IMPACT CORE MODELS

		Δ Nagelkerke's pseudo- R^2
CORE (n = 193)		CORE
+ % time PRx >0		0.128
+ % time PRx >+0.25		0.176
+ % time PRx >+0.35		0.193
		Δ Nagelkerke's pseudo- R^2
CORE (n = 193)		CORE + mean ICP
+ mean ICP	+ % time PRx >0	0.075
	+ % time PRx >+0.25	0.104
	+ % time PRx >+0.35	0.115
CORE + % time ICP >20 mm Hg		
+ % time	+ % time PRx >0	NS
ICP >20 mm Hg	+ % time PRx >+0.25	0.077
	+ % time PRx >+0.35	0.086
CORE + % time ICP >22 mm Hg		
+ % time	+ % time PRx >0	NS
ICP >22 mm Hg	+ % time PRx >+0.25	0.076
	+ % time PRx >+0.35	0.086

CORE model consisted of age, admission Glasgow Coma Scale motor score, and pupil response (normal bilaterally, unilateral unreactive, or bilaterally unreactive). CT variables consisted of admission Marshall CT grade, presence of traumatic subarachnoid hemorrhage, and presence of extradural hematoma. All numbers reported for Nagelkerke's pseudo- R^2 are statistically significant (i.e., $p < 0.05$) increases in accounted variance in outcome association over the CORE or CORE + ICP models.

A/D, alive/dead dichotomized outcome; CPP, cerebral perfusion pressure; CT, computed tomography; ICP, intracranial pressure; IMPACT, International Mission for Prognosis and Analysis of Clinical Trials; MAP, mean arterial pressure; NS, non-significant; PRx, pressure reactivity index (correlation between ICP and MAP).

acknowledge that future work is required evaluating temporal response patterns of PRx over time. It remains unknown whether impaired cerebrovascular reactivity is a "targetable" physiological entity. To date, studies evaluating treatment impact on PRx have demonstrated little-to-no impact of current TBI therapies on cerebrovascular reactivity.^{21,22} With that said, one cannot completely rule out the potential for other, more novel therapeutic strategies for impaired cerebrovascular reactivity in TBI. This aspect is the ongoing work of various TBI research programs globally, integrating proteomic and genomics with high-resolution physiological data, with the goal of uncovering therapeutic targets for prevention and treatment of impaired reactivity.

Finally, on multi-variable analysis, the Core + CT models performed worse than the Core models, with lower absolute AUCs for the Core + CT models. The trend for Core + CT models performing slightly worse may be reflected in the smaller patient cohort ($n = 166$ vs. $n = 193$) for those with complete non-imputed Core + CT data. Future larger multi-center data sets with high-frequency physiological data will be required to definitively answer questions surrounding cerebrovascular reactivity monitoring and its role in TBI care.

Conclusion

PRx maintains its strong association with mortality in adult TBI when adjusting for baseline admission characteristics (IMPACT Core and CT variables) and ICP. The addition of cerebrovascular

reactivity monitoring, through PRx, provides a statistically significant increase in mortality association at 6 months, when added to the IMPACT Core + ICP and Core + CT + ICP models. Our data suggest that cerebrovascular reactivity monitoring may provide complementary information regarding mortality association in TBI.

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