"Final publication is available from Mary Ann Liebert, Inc., publishers https://doi.org/10.1089/neu.2019.6808 "

Association between Cerebrovascular Reactivity Monitoring and Mortality is preserved when adjusting for baseline admission characteristics in Adult TBI: A CENTER-TBI Study

Frederick A. Zeiler,[1-4] Ari Ercole,[1] Erta Beqiri,[5] Manuel Cabeleira,[5] Eric P. Thelin,[6] Nino Stocchetti,[7,8] Ewout W Steyerberg,[9] Andrew IR Maas,[10] David K. Menon,[1] Marek Czosnyka,[5,11] Peter Smielewski[5]; and the CENTER-TBI High Resolution ICU (HR ICU) Sub-Study Participants and Investigators[#]

1. Division of Anaesthesia, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK
2. Department of Surgery, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada
3. Department of Human Anatomy and Cell Science, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada
4. Biomedical Engineering, Faculty of Engineering, University of Manitoba, Winnipeg, Canada
5. Brain Physics Laboratory, Division of Neurosurgery, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK
6. Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
7. Neuro ICU Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy
8. Department of Physiopathology and Transplantation, Milan University, Italy
9. Department of Public Health, Erasmus MC - University Medical Center Rotterdam, Rotterdam, the Netherlands and Department of Medical Statistics and Bioinformatics, Leiden University Medical Center, Leiden, the Netherlands
10. Department of Neurosurgery, University Hospital Antwerp, Wilrijkstraat 10, Edegem, Belgium
11. Institute of Electronic Systems, Warsaw University of Technology, Warsaw, Poland

***P Smielewksi and M Czosnyka are joint senior authors.**

 # The CENTER-TBI High Resolution Sub-study Participants and Investigators are listed at the end of the manuscript

Corresponding Author:

Frederick A. Zeiler BSc MD PhD CIP FRCSC (Neurosurgery)

Assistant Professor
Department of Surgery
Rady Faculty of Health Sciences
University of Manitoba
Winnipeg, MB, Canada
R3A 1R9

Email: umzeiler@myumanitoba.ca

Contributing Authors:

Ari Ercole MD PhD FRCA FFICM
Consultant in Intensive Care Medicine
Division of Anaesthesia
University of Cambridge
Email: ae105@cam.ac.uk

Manuel Cabeleira BSc
Brain Physics Laboratory
Division of Neurosurgery
Dept of Clinical Neurosciences
University of Cambridge
Email: mc916@cam.ac.uk

Erta Beqiri MD
Brain Physics Laboratory
Division of Neurosurgery
Dept of Clinical Neurosciences
University of Cambridge
Email: erta.beqiri@gmail.com

Eric P. Thelin MD PhD
Karolinska Universitetssjukhuset
Tema Neuro, BioClinicum J5:20
Eugeniavägen 3
171 76, Stockholm
Sweden
email: eric.thelin@ki.se

Nino Stocchetti MD PhD
Department of physiopathology and transplantation, Milan University

Neuro ICU Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico Milan
ORCID unique identifier: 0000-0003-3250-6834
Email: nino.stocchetti@policlinico.mi.it

Ewout W Steyerberg, PhD
Professor of Medical Decision Making, Department of Public Health
Erasmus University Medical Center
P.O. Box 2040 3000 CA Rotterdam, the Netherlands
Telephone: +31 10 704 34 48
Email: e.steyerberg@erasmusmc.nl

Andrew Maas MD PhD
Professor and Chairman Neurosurgery
Antwerp University Hospital and University of Antwerp
Wilrijkstraat 10, 2650 Edegem, Belgium
Telephone: +32 3 821 46 32
Email: andrew.maas@uza.be

David K. Menon MD PhD FRCP FRCA FFICM FMedSci
Head, Division of Anaesthesia, University of Cambridge
Honorary Consultant, Neurosciences Critical Care Unit, Addenbrooke's Hospital
Professorial Fellow, Queens' College, Cambridge
Senior Investigator, National Institute for Health Research, UK
Email: dkm13@cam.ac.uk

Marek Czosnyka PhD
Professor of Brain Physics
Brain Physics Laboratory, Division of Neurosurgery
University of Cambridge
Cambride, UK
CB2 0QQ
Email: mc141@medschl.cam.ac.uk

Peter Smielewski PhD
Senior Research Associate
Laboratory of Brain Physics
Division of Neurosurgery
University of Cambridge
Email: ps10011@cam.ac.uk

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 intra-cranial 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 (MAP) 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 analysed to assess the association between global outcome (measured as either mortality or dichotomised Glasgow Outcome Score – Extended; GOSE)), and a range of covariates (IMPACT Core and CT variables, ICP, and PRx). The performance of these models in outcome association was compared using area under the receiver operating curve (AUC) and Nagelkerke's Pseudo-R^2. Moderate and severe TBI, with high frequency physiologic monitoring during their ICU stay, and long-term outcome assessments. Association between PRx and dichotomized GOSE at 6 months post injury, when controlling for admission baseline variables and ICP. 193 patients had complete data set for analysis. The addition of % time above threshold for PRx improved AUC and displayed statistically significant increases in Nagelkerke's pseudo-R^2 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 suggests cerebrovascular reactivity monitoring may provide complementary information regarding outcomes in TBI. Keywords: Autoregulation, Cerebrovascular reactivity, IMPACT, outcome analysis

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], 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 the Nagelkerke’s pseudo-R^2 , 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 nonspecific 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 centre data, without formal blinding of outcome assessment. A rigorous assessment of the outcome association of PRx would require testing on a prospective multicentre 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 + 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-centre dataset from critically ill adult patients with moderate/severe TBI (the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) study).[14]

Methods:

Patient Population:

All patients from the multi-center CENTER-TBI high resolution ICU monitoring cohort with parenchymal ICP monitoring were included in this analysis. Patients with EVD 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 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 to 12, and severe = GCS of 8 or less). A minority of patients (n=31) were categorised 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 accordance 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 accordance 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 Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) ("ICH GCP") and the World Medical Association Declaration of Helsinki entitled "Ethical Principles for Medical Research Involving Human Subjects". Informed Consent 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 hours 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 computed tomography (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 haemorrhage (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 (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, via 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 intra-parenchymal strain gauge probe (Codman ICP MicroSensor; Codman & Shurtleff Inc., Raynham, MA), parenchymal fibre optic pressure sensor (Camino ICP Monitor, Integra Life Sciences, Plainsboro, NJ, United States; https://www.integralife.com/). All signals were recorded using digital data transfer or digitized via an A/D converter (DT9803; Data Translation, Marlboro, MA), where appropriate; sampled at frequency of 100 Hertz (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, USA, https://www.moberg.com) or a combination of both. Signal artefacts were removed using both manual and automated methods prior to further processing or analysis.

Signal Processing:

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

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

a. 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]

b. PRx: For each patient the % of time spent above the following clinically defined thresholds were calculated across the entire recording period: 0, +0.25, +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: A. entire recording, and B. the first 72 hours of recording. These two sheets were produced to assess if there was any difference in outcome association when focusing on more acute physiology, such as that seen during the first 72 hours post-injury.

Statistics:

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). The following analysis was conducted for both the entire recording period and the first 72 hours 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 hours of recording.

Normality of continuous variables was assessed via Shapiro-Wilks test, where all variable displayed non-parametric characteristics, and are hence displayed as median (range) or median (IQR). For all testing described, the alpha was set at 0.05 for significance. GOSE was then dichotomized into the following categories: A. Alive (GOSE 2 to 8) vs. Dead (GOSE 1); and B. Favourable (GOSE 5 to 8) vs. Unfavourable (GOSE 4 or less). IMPACT Core and CT variables, along with physiologic variables, were compared between each dichotomized group, using Mann-U, 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. Area under the receiver operating curve (AUC), 95% confidence intervals (CI's) and p-values for the univariate models are reported.

Next, IMPACT Core/Core + CT multi-variable models were created. Using multivariable logistic regression (MLR) analysis, these models and their association with dichotomized GOSE were assessed. AUC, 95% CI's 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. Added account 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 AUC's and 95% CI's 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 physiologic 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. The patient demographics for the entire cohort (n=193) can be found summarized in Table 1. Patient demographics for both the alive/dead and favourable/unfavourable outcome groups can be found in Appendix A of the supplementary materials.

*Table 1 here

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 Appendix B of the supplementary materials, 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 hours of physiologic data.

MLR analysis of the IMPACT Core models for alive/dead and favourable/unfavourable 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 favourable/unfavourable 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 AUC's can be found in Table 2, while IMPACT Core + CT "+" model AUC's and p-values can be seen in 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 addition of % time above PRx thresholds of +0.25 (ex. AUC 0.819, 95% CI 0.735-0.888, AIC 155.6 versus AUC 0.780, 95% CI 0.697-0.855, AIC 164.9; in mean ICP models) and +0.35 (ex. AUC 0.825, 95% CI 0.747-0.893, AIC 154.3 versus AUC 0.780, 95% CI 0.697-0.855, AIC 164.9; in mean ICP models) led to improved AUC's and smaller AIC values. Figure 1 displays the receiver operating curves (ROC) for the alive/dead dichotomized outcome for IMPACT Core and additional representative models.

However, for favourable/unfavourable dichotomized 6 month outcome, there was little to no change 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 ICP is a stronger predictor of mortality, compared to functional outcome. [2,4,18,19]

*Figure 1 here

*Table 2 here

Additional Explanation of Outcome Variance

All MLR models were then compared using Nagelkerke's pseudo-R^2, 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 hours 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 the 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-R^2 (up to 19.2% for alive/dead outcome; p<0.0001).

Similarly, IMPACT Core + ICP + PRx models were compared to IMPACT Core + ICP models (ie. 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-R^2 values in comparing various models for the alive/dead dichotomized outcome for the IMPACT Core only models. Appendix D outlines the pseudo-R^2 values comparing various IMPACT Core + CT models.

However, despite the association with mortality, evaluating favourable/unfavourable dichotomized outcome displayed no significant differences between models when assessed using Nagelkerke's pseudo-R^2, in keeping with the similar AUC and AIC values identified during MLR analysis, for both the Core and Core + CT models.

*Table 3 here

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 hours 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 AUC's, 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 seen in previous large retrospective studies, where adjusting for baseline admission characteristics was not possible.[1,11,17]

We recognised 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 if 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 AUC's seen 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 hours 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 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 AUC's 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 favourable/unfavourable 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 if other cerebrovascular reactivity indices would perform better for favourable/unfavourable outcome association when adjusting for IMPACT and ICP variables. Given the lack of strong association between impaired cerebrovascular reactivity and functional outcome identified in this study, we must acknowledge the results are disappointing. This carries potential implications for ongoing works in PRx/CPPopt directed physiologic 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 multimodal 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 dataset, 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 (ie. presence of complete IMPACT Core/Core + CT variables, high frequency digital physiologic signals from parenchymal ICP monitoring, and a recorded outcome at 6 to 12 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, as this data was collected as a multi-center prospective observational study, there exists the potential impact of patients, injury and treatment heterogeneity on both the recording physiologic 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 favourable/unfavourable. 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 if other ICP derived cerebrovascular reactivity indices, such as PAx[5] or RAC[6], which evaluate other facets of autoregulation and/or intracranial compliance, can provide explanation of variation in favourable/unfavourable outcome, when added to existing IMPACT variables. The main limitation of these indices is the need for high frequency digital physiologic waveforms for analysis of ICP pulse. This will be explored in future studies using the CENTER-TBI high resolution ICU cohort.[14]

Fourth, as 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. As the goal was not to build prognostic models for use, but merely to explore if 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 datasets, 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 hours may suggest that PRx is relatively stable over time. This is far from the case, as we known PRx fluctuates widely in the setting of moderate/severe TBI. Similarly evaluating PRx over such periods, one could argue that the impaired PRx values seen 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 utilizing % time above thresholds, in attempt to capture some of this variability over time. However, we must acknowledge that future work is required evaluating temporal response patterns of PRx over time. It remains unknown if impaired cerebrovascular reactivity is a 'targetable' physiologic 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 physiologic 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 AUC's 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 physiologic 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 suggests cerebrovascular reactivity monitoring may provide complementary information regarding mortality association in TBI.

Disclosures:

Data used in preparation of this manuscript were obtained in the context of CENTER-TBI, a large collaborative project with the support of the European Union 7th Framework program (EC grant 602150). Additional funding was obtained from the Hannelore Kohl Stiftung (Germany), from OneMind (USA) and from Integra LifeSciences Corporation (USA).

PS and MC receive part of licensing fees for the software ICM+ (Cambridge Enterprise Ltd, UK) used for data collection and analysis in this study.

DKM has consultancy agreements and/or research collaborations with GlaxoSmithKline Ltd; Ornim Medical; Shire Medical Ltd; Calico Inc.; Pfizer Ltd; Pressura Ltd; Glide Pharma Ltd; and NeuroTraumaSciences LLC.

MC is supported by NIHR Cambridge Centre.

Acknowledgments:

Data used in preparation of this manuscript were obtained in the context of CENTER-TBI, a large collaborative project with the support of the European Union 7th Framework program (EC grant 602150). Additional funding was obtained from the Hannelore Kohl Stiftung (Germany), from OneMind (USA) and from Integra LifeSciences Corporation (USA).

DKM was also supported by funding from the National Institute for Health Research (NIHR, UK) through a Senior Investigator award and the Cambridge Biomedical Research Centre at the Cambridge University

Hospitals NHS Foundation Trust. The study also received additional support from the NIHR Clinical Research network. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care, UK.

FAZ receives research support from the United States National Institute of Health (NIH) through the National Institute of Neurological Disease and Stroke (NINDS) and the National Institute of Biomedical Imaging and Bioengineering (NIBIB), University of Manitoba Thorlakson Chair in Surgical Research Establishment Fund, the University of Manitoba VPRI Research Investment Fund (RIF), the University of Manitoba Rudy Falk Clinician-Scientist Professorship, and the Health Sciences Centre Foundation Winnipeg.

EPT has received salary support from the Swedish Society of Medicine and Swedish Society for Medical Research.

CENTER-TBI High Resolution Sub-Study Participants and Investigators:

Audny Anke[1], Ronny Beer [2], Bo-Michael Bellander[3], Andras Buki[4], Giorgio Chevallard[5], Arturo Chieregato [5], Giuseppe Citerio [6, 7], Endre Czeiter [8], Bart Depreitere [9], George Eapen †, Shirin Frisvold [10], Raimund Helbok [2], Stefan Jankowski [11], Daniel Kondziella [12], Lars-Owe Koskinen [13], Geert Meyfroidt [14], Kirsten Moeller [15], David Nelson [3], Anna Piippo-

Karjalainen [16], Andreea Radoi [17], Arminas Ragauskas [18], Rahul Raj [16], Jonathan Rhodes [19], Saulius Rocka [18], Rolf Rossaint [20], Juan Sahuquillo [17], Oliver Sakowitz [21, 22], Ana Stevanovic [20], Nina Sundström [23], Riikka Takala [24], Tomas Tamosuitis [25], Olli Tenovuo [26], Peter Vajkoczy [27], Alessia Vargiolu [6], Rimantas Vilcinis [28], Stefan Wolf [29], Alexander Younsi [22]

[1] Department of Physical Medicine and Rehabilitation, University hospital Northern Norway

[2] Department of Neurology, Neurological Intensive Care Unit, Medical University of Innsbruck, Innsbruck, Austria

[3] Department of Neurosurgery & Anesthesia & intensive care medicine, Karolinska University Hospital, Stockholm, Sweden

[4] Department of Neurosurgery, University of Pecs and MTA-PTE Clinical Neuroscience MR Research Group and Janos Szentagothai Research Centre, University of Pecs, Hungarian Brain Research Program, Pecs, Hungary

[5] NeuroIntensive Care, Niguarda Hospital, Milan, Italy

[6] NeuroIntensive Care Unit, Department of Anesthesia & Intensive Care, ASST di Monza, Monza, Italy

[7] School of Medicine and Surgery, Università Milano Bicocca, Milano, Italy

[8] Department of Neurosurgery, University of Pecs and MTA-PTE Clinical Neuroscience MR Research Group and Janos Szentagothai Research Centre, University of Pecs, Hungarian Brain Research Program (Grant No. KTIA 13 NAP-A-II/8), Pecs, Hungary

[9] Department of Neurosurgery, University Hospitals Leuven, Leuven, Belgium

[10] Department of Anesthesiology and Intensive care, University Hospital Northern Norway, Tromso, Norway

[11] Neurointensive Care, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

[12] Departments of Neurology, Clinical Neurophysiology and Neuroanesthesiology, Region Hovedstaden Rigshospitalet, Copenhagen, Denmark

[13] Department of Clinical Neuroscience, Neurosurgery, Umea University Hospital, Umea, Sweden

[14] Intensive Care Medicine, University Hospitals Leuven, Leuven, Belgium

[15] Department Neuroanesthesiology, Region Hovedstaden Rigshospitalet, Copenhagen, Denmark

[16] Helsinki University Central Hospital, Helsinki, Finland

[17] Department of Neurosurgery, Vall d'Hebron University Hospital, Barcelona, Spain

[18] Department of Neurosurgery, Kaunas University of technology and Vilnius University, Vilnius, Lithuania

[19] Department of Anaesthesia, Critical Care & Pain Medicine NHS Lothian & University of Edinburg, Edinburgh, UK

[20] Department of Anaesthesiology, University Hospital of Aachen, Aachen, Germany

[21] Klinik für Neurochirurgie, Klinikum Ludwigsburg, Ludwigsburg, Germany

[22] Department of Neurosurgery, University Hospital Heidelberg, Heidelberg, Germany

[23] Department of Radiation Sciences, Biomedical Engineering, Umea University Hospital, Umea, Sweden

[24] Perioperative Services, Intensive Care Medicine, and Pain Management , Turku University Central Hospital and University of Turku, Turku, Finland

[25] Neuro-intensive Care Unit, Kaunas University of Health Sciences, Kaunas, Lithuania

[26] Rehabilitation and Brain Trauma, Turku University Central Hospital and University of Turku, Turku, Finland

[27] Neurologie, Neurochirurgie und Psychiatrie, Charité – Universitätsmedizin Berlin, Berlin, Germany

[28] Department of Neurosurgery, Kaunas University of Health Sciences, Kaunas, Lithuania

[29] Interdisciplinary Neuro Intensive Care Unit , Charité – Universitätsmedizin Berlin, Berlin, Germany

References:

1. Czosnyka, M., Smielewski, P., Kirkpatrick, P., Laing, R.J., Menon, D., and Pickard, J.D. (1997). Continuous assessment of the cerebral vasomotor reactivity in head injury. Neurosurgery 41, 11–17; discussion 17-19.

2. Le Roux, P., Menon, D.K., Citerio, G., Vespa, P., Bader, M.K., Brophy, G., Diringer, M.N., Stocchetti, N., Videtta, W., Armonda, R., Badjatia, N., Bösel, J., Chesnut, R., Chou, S., Claassen, J., Czosnyka, M., De Georgia, M., Figaji, A., Fugate, J., Helbok, R., Horowitz, D., Hutchinson, P., Kumar, M., McNett, M., Miller, C., Naidech, A., Oddo, M., Olson, D., O'Phelan, K., Provencio, J.J., Puppo, C., Riker, R., Roberson, C., Schmidt, M., and Taccone, F. (2014). The International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care: a list of recommendations and additional conclusions: a statement for healthcare professionals from the Neurocritical Care Society and the European Society of Intensive Care Medicine. Neurocrit Care 21 Suppl 2, S282-296.

3. Czosnyka, M., Miller, C., and Participants in the International Multidisciplinary Consensus Conference on Multimodality Monitoring. (2014). Monitoring of cerebral autoregulation. Neurocrit Care 21 Suppl 2, S95-102.

4. Carney, N., Totten, A.M., O’Reilly, C., Ullman, J.S., Hawryluk, G.W.J., Bell, M.J., Bratton, S.L., Chesnut, R., Harris, O.A., Kissoon, N., Rubiano, A.M., Shutter, L., Tasker, R.C., Vavilala, M.S., Wilberger, J., Wright, D.W., and Ghajar, J. (2017). Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. Neurosurgery 80, 6–15.

5. Aries, M.J.H., Czosnyka, M., Budohoski, K.P., Kolias, A.G., Radolovich, D.K., Lavinio, A., Pickard, J.D., and Smielewski, P. (2012). Continuous monitoring of cerebrovascular reactivity using pulse waveform of intracranial pressure. Neurocrit Care 17, 67–76.

6. Zeiler, F.A., Donnelly, J., Menon, D., Smieleweski, P., Hutchinson, P.J., and Czosnyka, M. (2017). A Description of a New Continuous Physiologic Index in TBI using the Correlation Between Pulse Amplitude of ICP and Cerebral Perfusion Pressure. J. Neurotrauma .

7. Zeiler, F.A., Donnelly, J., Calviello, L., Smielewski, P., Menon, D.K., and Czosnyka, M. (2017). Pressure Autoregulation Measurement Techniques in Adult Traumatic Brain Injury, Part II: A Scoping Review of Continuous Methods. J. Neurotrauma 34, 3224–3237.

8. Needham, E., McFadyen, C., Newcombe, V., Synnot, A.J., Czosnyka, M., and Menon, D. (2017). Cerebral Perfusion Pressure Targets Individualized to Pressure-Reactivity Index in Moderate to Severe Traumatic Brain Injury: A Systematic Review. J. Neurotrauma 34, 963–970.

9. Zeiler, F.A., Donnelly, J., Calviello, L., Menon, D.K., Smielewski, P., and Czosnyka, M. (2017). Pressure Autoregulation Measurement Techniques in Adult Traumatic Brain Injury, Part I: A Scoping Review of Intermittent/Semi-Intermittent Methods. J. Neurotrauma 34, 3207–3223.

10. Sorrentino, E., Budohoski, K.P., Kasprowicz, M., Smielewski, P., Matta, B., Pickard, J.D., and Czosnyka, M. (2011). Critical thresholds for transcranial Doppler indices of cerebral autoregulation in traumatic brain injury. Neurocrit Care 14, 188–193.

11. Sorrentino, E., Diedler, J., Kasprowicz, M., Budohoski, K.P., Haubrich, C., Smielewski, P., Outtrim, J.G., Manktelow, A., Hutchinson, P.J., Pickard, J.D., Menon, D.K., and Czosnyka, M. (2012). Critical thresholds for cerebrovascular reactivity after traumatic brain injury. Neurocrit Care 16, 258–266.

12. Steyerberg, E.W., Mushkudiani, N., Perel, P., Butcher, I., Lu, J., McHugh, G.S., Murray, G.D., Marmarou, A., Roberts, I., Habbema, J.D.F., and Maas, A.I.R. (2008). Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. PLoS Med. 5, e165; discussion e165.

13. Lingsma, H., Andriessen, T.M.J.C., Haitsema, I., Horn, J., van der Naalt, J., Franschman, G., Maas, A.I.R., Vos, P.E., and Steyerberg, E.W. (2013). Prognosis in moderate and severe traumatic brain injury: external validation of the IMPACT models and the role of extracranial injuries. J Trauma Acute Care Surg 74, 639–646.

14. Maas, A.I.R., Menon, D.K., Steyerberg, E.W., Citerio, G., Lecky, F., Manley, G.T., Hill, S., Legrand, V., Sorgner, A., and CENTER-TBI Participants and Investigators. (2015). Collaborative European

NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. Neurosurgery 76, 67–80.

15. Marshall, L.F., Marshall, S.B., Klauber, M.R., Van Berkum Clark, M., Eisenberg, H., Jane, J.A., Luerssen, T.G., Marmarou, A., and Foulkes, M.A. (1992). The diagnosis of head injury requires a classification based on computed axial tomography. J. Neurotrauma 9 Suppl 1, S287-292.

16. Doiron, D., Marcon, Y., Fortier, I., Burton, P., and Ferretti, V. (2017). Software Application Profile: Opal and Mica: open-source software solutions for epidemiological data management, harmonization and dissemination. Int J Epidemiol 46, 1372–1378.

17. Zeiler, F.A., Donnelly, J., Smieleweski, P., Menon, D., Hutchinson, P.J., and Czosnyka, M. (2018). Critical Thresholds of ICP Derived Continuous Cerebrovascular Reactivity Indices for outcome prediction in Non-Craniectomized TBI Patients: PRx, PAx and RAC. J. Neurotrauma 35, 1107–1115.

18. Helbok, R., Olson, D.M., Le Roux, P.D., Vespa, P., and Participants in the International Multidisciplinary Consensus Conference on Multimodality Monitoring. (2014). Intracranial pressure and cerebral perfusion pressure monitoring in non-TBI patients: special considerations. Neurocrit Care 21 Suppl 2, S85-94.

19. Nourallah, B., Zeiler, F.A., Calviello, L., Smielewski, P., Czosnyka, M., and Menon, D.K. (2018). Critical thresholds for intracranial pressure vary over time in non-craniectomised traumatic brain injury patients. Acta Neurochir (Wien) 160, 1315–1324.

20. Beqiri, E., Smielewski, P., Robba, C., Czosnyka, M., Cabeleira, M.T., Tas, J., Donnelly, J., Outtrim, J.G., Hutchinson, P., Menon, D., Meyfroidt, G., Depreitere, B., Aries, M.J., and Ercole, A. (2019). Feasibility of individualised severe traumatic brain injury management using an automated assessment of optimal cerebral perfusion pressure: the COGiTATE phase II study protocol. BMJ Open 9, e030727.

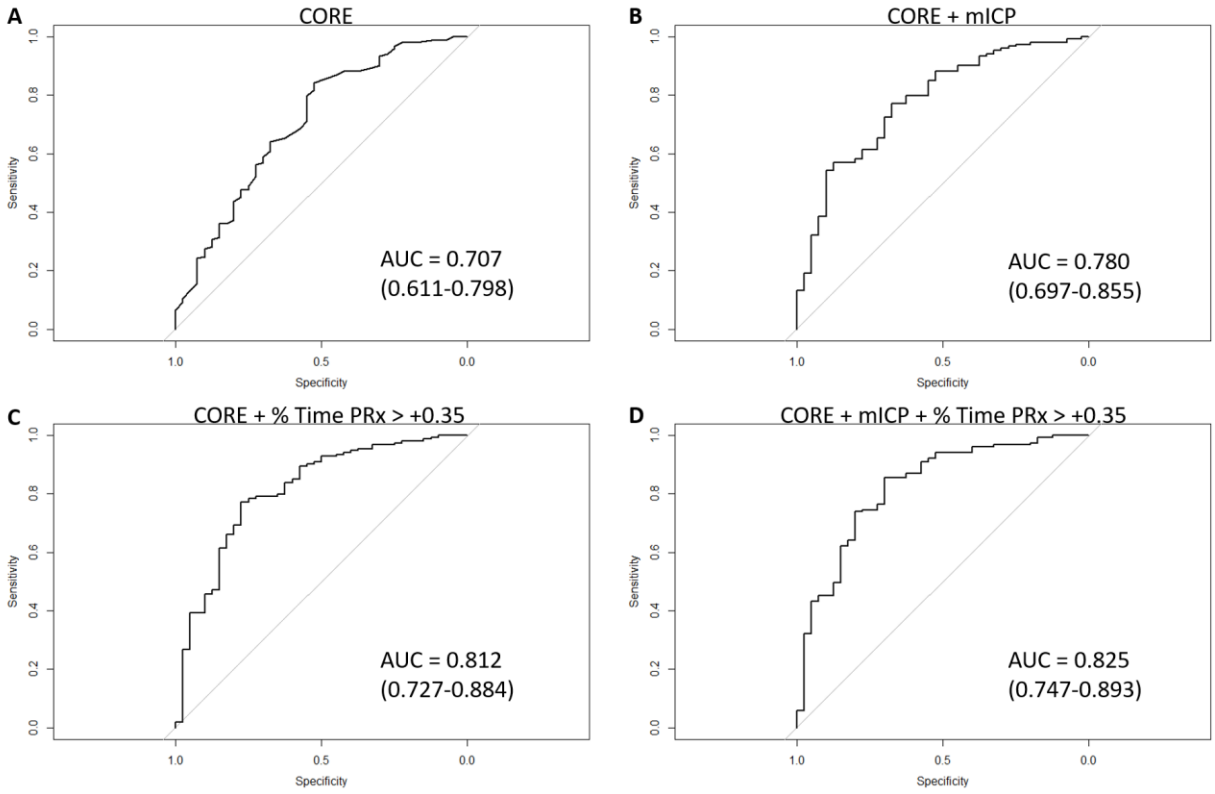
21. Donnelly, J., Czosnyka, M., Adams, H., Cardim, D., Kolias, A.G., Zeiler, F.A., Lavinio, A., Aries, M., Robba, C., Smielewski, P., Hutchinson, P.J.A., Menon, D.K., Pickard, J.D., and Budohoski, K.P. (2019). Twenty-Five Years of Intracranial Pressure Monitoring After Severe Traumatic Brain Injury: A Retrospective, Single-Center Analysis. Neurosurgery 85, E75–E82.

22. Zeiler, F.A., Ercole, A., Beqiri, E., Cabeleira, M., Aries, M., Zoerle, T., Carbonara, M., Stocchetti, N., Smieleweski, P., Czosnyka, M., and Menon, D.K. (2019). Cerebrovascular Reactivity is not associated with Therapeutic Intensity in Adult Traumatic Brain Injury: A CENTER-TBI Analysis. Acta Neurochirurgica Epub Ahead of Print.

"Final publication is available from Mary Ann Liebert, Inc., publishers https://doi.org/10.1089/neu.2019.6808 "

Figure Legend

Figure 1: ROC for Alive/Dead Dichotomized Outcome – IMPACT Core, Core + mean ICP, Core + % Time PRx > +0.35, Core + mean ICP + % Time PRx >0.35



ICP = intra-cranial pressure, MAP = mean arterial pressure, mICP = mean ICP, PRx = pressure reactivity index (correlation between ICP and MAP). Panel A: IMPACT Core Variables alone, Panel B: IMPACT Core + mean ICP, Panel C: IMPACT Core + % Time with PRx > +0.35, Panel D: IMPACT Core + mean ICP + % Time with PRx > +0.35.

Table 1: Patient Demographics – Median and IQR

		Median (IQR)
Number of Patients		193
Age (years)		51.0 (30.0 – 64.0)
Sex	***Male***	149
	Female	44
Admission GCS (Total)		6 (3 to 10)
Admission GCS Motor		4 (1 to 5)
Admission Pupil Response	***Bilaterally Reactive***	142
	Unilateral Unreactive	15
	Bilaterally Unreactive	36
Marshall CT Grade		3 (2 to 6)
Number with Traumatic SAH		145
Number with Extra-axial Hematoma		37
Number with Hypoxia Episode		32
Number with Hypotension Episode		24
Duration of High Frequency Physiologic Recording (hours)		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 to 5)
Number Alive – 6 Months		153
Number Dead – 6 Months		40
Number Favourable Outcome – 6 Months (GOSE 5 to 8)		83
Number Unfavourable Outcome – 6 Months (GOSE 1 to 4)		110

CPP = cerebral perfusion pressure, CT = computed tomography, GCS = Glasgow Coma Score, GOSE = Glasgow Outcome Score, ICP = intra-cranial pressure, IQR = inter-quartile range, MAP = mean arterial pressure, mm Hg = millimetres of mercury, PRx = pressure reactivity index (correlation between ICP and MAP), SAH = subarachnoid haemorrhage.

Table 2: Multi-Variable Logistic Regression Analysis - IMPACT Core Model Plus Cerebrovascular Reactivity

Model	AUC A/D (95% CI)	AIC	p-value	AUC F/U (95% CI)	AIC	p-value
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 mmHg + % Time Above PRx Thresholds						
CORE + % Time ICP >20 mmHg + % 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 mmHg + % 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 mmHg + % 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 mmHg + % Time Above PRx Thresholds						
CORE + % Time ICP >22 mmHg + % 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 mmHg + % 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 mmHg + % Time PRx > +0.35	0.817 (0.736-0.889)	153.3	**<0.0001**	0.647 (0.570-0.720)	236.6	**0.0001**

A/D = alive/dead, AUC = area under the receiver operating curve, CPP = cerebral perfusion pressure, CI = confidence interval, F/U = Favourable/Unfavourable outcome (ie. Favourable = Glasgow Outcome Scale of 5 to 8; Unfavourable = Glasgow Outcome Scale of 1 to 4), ICP = intra-cranial pressure, IMPACT = International Mission for Prognosis and Analysis of Clinical Trials, MAP = mean arterial pressure, PRx = pressure reactivity index (correlation between ICP and MAP), CORE model consisted of age, admission Glasgow Coma Scale motor score and pupil response (normal bilaterally, unilateral unreactive, or bilaterally unreactive).

Table 3 - Added Variance in A/D Outcome Association at 6 Months with Cerebrovascular Reactivity Monitoring Over IMPACT Core Models

CORE (n=193)		**Δ Nagelkerke's Pseudo-R^2**
		CORE
+ % Time PRx >0		**0.128**
+ % Time PRx > +0.25		**0.176**
+ % Time PRx > +0.35		**0.193**
CORE (n=193)		**Δ Nagelkerke's Pseudo-R^2**
		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 ICP >20 mmHg	***+ % Time PRx > 0***	NS
	+ % Time PRx > +0.25	**0.077**
	+ % Time PRx > +0.35	**0.086**
		CORE + % Time ICP >22 mm Hg
+ % Time ICP >22 mm Hg	***+ % Time PRx > 0***	NS
	+ % Time PRx > +0.25	**0.076**
	+ % Time PRx > +0.35	**0.086**

A/D = alive/dead dichotomized outcome, CPP = cerebral perfusion pressure, CT = computed tomography, ICP = intra-cranial 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). 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 haemorrhage and presence of extradural hematoma. All numbers reported for Nagelkerke's Pseudo-R^2 are statistically significant (ie. $p<0.05$) increases in accounted variance in outcome association over the CORE or CORE + ICP models.