# Diffuse Intra-Cranial Injury Patterns are Associated with Impaired Cerebrovascular Reactivity in Adult Traumatic Brain Injury: A CENTER-TBI Validation Study

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**Abstract:**

Recent single center retrospective analysis displayed the association between admission computed tomography (CT) markers of diffuse intra-cranial (IC) injury and worse cerebrovascular reactivity. The goal of this study is to further explore these associations using the prospective multi-center Collaborative European Neurotrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) high resolution data set (HR ICU). Using the CENTER-TBI HR ICU sub-study cohort, we evaluated those patients with both archived high-frequency digital physiology (100 Hz or higher), and the presence of a digital admission CT scan. Physiologic signals were processed for pressure reactivity index (PRx) and both the % time above defined PRx thresholds and mean hourly dose above threshold. Admission CT injury scores were obtained from the database. Quantitative contusion, edema, intraventricular hemorrhage (IVH) and extra-axial lesion volumes were obtained via semi-automated segmentation. Comparison between admission CT characteristics and PRx metrics was conducted using Mann-U, Jonckheere Terpstra testing, with a combination of univariate linear and logistic regression techniques. A total of 165 patients were included. Cisternal compression and high admission Rotterdam and Helsinki CT scores, and Marshall CT diffuse injury sub-scores were associated with increased % time and hourly dose above PRx threshold of 0, +0.25 and +0.35 ($p<0.02$ for all).Logistic regression analysis displayed an association between deep peri-contusional edema and mean PRx above threshold of +0.25. These results suggest that diffuse injury patterns, consistent with acceleration/deceleration forces, are associated with impaired cerebrovascular reactivity. Diffuse admission IC injury patterns appear to be consistently associated with impaired cerebrovascular reactivity, as measured through PRx. This is in keeping with the previous single center retrospective literature on the topic. This study provides multi-center validation for those results, and provide preliminary data to support potential risk stratification for impaired cerebrovascular reactivity based on injury pattern. Keywords**:** autoregulation, computed tomography, CT, image segmentation, injury patterns, PRx.

**Introduction:**

Impaired cerebrovascular reactivity after traumatic brain injury (TBI) carries important implications for the long-term outcome of patients. Continuous bedside metrics of measuring cerebrovascular reactivity

in adult TBI have received support from international consensus groups on multi-modal monitoring in brain injury.[1,2] Various studies, both retrospective[3–6] and prospective,[7,8] have been published documenting the association between impaired cerebrovascular reactivity and worse 6 month functional outcome. Furthermore, these continuous measures have been applied in the derivation of individualized cerebral perfusion pressure targets,[8–11] triggering ongoing multi-center prospective randomized studies.

Despite the promising nature of this type of monitoring, and the potential for its application in the advancement of personalized medicine approaches in neurocritical care, we currently lack an understanding of the drivers of impaired cerebrovascular reactivity.[12,13] These drivers likely take multiple forms, including admission injury patterns/burden,[13,14] local and systemic host response to injury,[15–19] and baseline genetic variation.[12,20] Understanding such mediators may shed light on potential therapeutic targets directed at prevention and treatment of impaired cerebrovascular reactivity in adult TBI.

Admission intra-cranial injury burden in relation to continuously measured cerebrovascular reactivity has only previous been assessed in two single center retrospective studies.[13,14] One failed to document any significant relationship between admission computed tomography (CT), as measured using the Marshall CT grade, and impaired cerebrovascular reactivity using the PRx threshold of 0.[14] A second larger study, confirmed no significant relationship between such grading systems, but did document an association between admission CT features of diffuse acceleration/deceleration injury and worse vascular reactivity. This was confirmed in this cohort using multiple different intra-cranial pressure (ICP) derived metrics of cerebrovascular reactivity, across various periods of high-frequency physiologic recording post injury.[13]

Both of these studies originated from the same center and suffered from being single center and retrospective. In addition, both studies lacked quantifiable highly reproducible volumetric assessment of intra-parenchymal and extra-axial lesions. The goal of this study was to provide a multi-center validation of previous results using the prospective Collaborative European Neurotrauma Effectiveness Research in TBI (CENTER-TBI)[21] high-resolution intensive care unit (ICU) sub-study cohort, and applying semi-automated lesion segmentation to admission CT scans.

## Methods:

### *Patient Population:*

All patients from the multi-center CENTER-TBI high resolution ICU monitoring cohort with parenchymal ICP monitoring, and with archived digital admission CT scans of the brain, 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 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.[22]

*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, basic admission demographics and centrally reported computed tomography (CT) variables for the first available CT of each patient were extracted.[23] They included: age, admission best GCS motor score and pupillary reactivity (bilaterally reactive, unilateral reactive, bilateral unreactive), Marshall CT Classification,[24] Rotterdam CT score,[25] Helsinki CT score,[26] presence or absence of traumatic subarachnoid haemorrhage (tSAH), extradural hematoma (EDH), subdural hematoma (SDH), intraventricular haemorrhage (IVH), basal cistern compression, skull fracture, pre-hospital hypotension and pre-hospital hypoxia. Further semi-automated segmentation of the admission CT scans was conducted as described below, allowing for volumetric assessment of: contusion core, contusion edema, IVH, and extra-axial haemorrhage (see Image Processing sub-section). A continuous measure of midline shift (MLS) was manually obtained in millimetres, calculated as the perpendicular distance from the septum pellucidum from a line coplanar with the anterior and posterior attachment of the falx on the inner table of the skull. CENTER-TBI data version 2.0 was accessed for the purpose of this study, via Opal database software.[27]

*Signal Acquisition:*

Arterial blood pressure (ABP) was obtained through 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/). ICP monitors, by convention, were placed in the frontal lobe, avoiding areas with traumatic lesions. 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 time-averaged and 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. Mean values over the recording period were calculated, with each patient assessed to see if they were above or below the binary threshold of 0, +0.25 or +0.35.
b. % Time Spend with PRx Above Threshold: 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.[4,6] 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. These three thresholds exist based on the analysis between dichotomized Glasgow Outcome Scale (GOS) values at 6-months post-TBI in two separate TBI populations. In one study, the threshold of 0 is associated with favourable/unfavourable outcome (ie. GOS 3 or less = unfavourable, GOS of 4 or 5 = favourable), and the threshold of +0.25 was associated with mortality.[4] Similarly, in another smaller, more selected TBI patient population consisting of those not having a decompressive procedure, the threshold of +0.35 existed for both favourable/unfavourable outcome and mortality. [6]Hence, both sets of thresholds were utilized. This is in keeping with the previously published retrospective study on the relationship between intracranial injury burden and impaired cerebrovascular reactivity in TBI.[13]
c. Mean Hourly Dose Above PRx Threshold: using the above mentioned defined PRx thresholds, the mean hourly dose above each was determined.

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 CT lesion association when focusing on more acute physiology, such as that seen during the first 72 hours post-injury. The results of the follow analysis displayed similar trends in association for both the entire recording and first 72 hours data sheet. As such, the remainder of this manuscript mainly refers to the entire recording data, making reference to the first 72 hours data results only when required.

*Image Processing:*

Each CT session was automatically processed using a modified version of DeepMedic, a three-dimensional CNN with three parallel pathways that process the images at different resolution scales resulting in a field-of-view of 81 mm. The CNN was trained using 64 previously manually annotated scans and validated on another 34 scans..[28] This step yielded automated lesion predictions corresponding to volumes (in mL) for the lesion subtypes described above (contusion core, pericontusional edema, extra-axial haemorrhage and intraventricular haemorrhage). In order to maximize the accuracy of those predictions, each scan was visually inspected and manually corrected by an expert clinician. The clinician was blinded to the recorded physiology and cerebrovascular reactivity data during CT segmentation. False positive predictions were removed, missed lesions were manually filled in and lesion margin accuracy was optimized using ITK-snap (version 3.8.0-beta).[29] The resulting corrected segmentation maps were then projected to a CT atlas (constructed from 20 normal CTs) aligned to MNI Space using affine registration methods in order to obtain their neuroanatomical correlates. For the purpose of this analysis we collapsed lesion localization into either lobar/cortical, basal ganglia (basal ganglia), brainstem or deep (consisting of both brainstem, cerebellar and basal ganglia locations). In total, 25 CT lesion variables were utilized for comparison with the high-frequency physiology. Appendix A provides a list of the CT variables.

*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 variables displayed non-parametric characteristics, and are hence displayed as median (range) or median (IQR). Admission demographics and CT variables, were compared between patients dichotomized for mean PRx above/below the defined thresholds, using Mann-U, or chi-square testing where appropriate. Similarly, mean % time and mean hourly dose above PRx threshold metrics were compared for each admission CT ordinal characteristic, using Mann-U testing, and for admission CT grading systems using Kruskal-Wallis or Jonckheere-Terpstra testing, where appropriate. For all testing described, the alpha was set at 0.002 for significance, after correction using Bonferroni methodology. We corrected for 25 separate imaging characteristics that were tested against each PRx threshold (ie. Each dependent variable). The p-values reported throughout are the raw p-values for the statistical tests performed, which were compared against the Bonferroni corrected alpha of 0.002 for significance.

Univariate logistic regression (ULR) was conducted, comparing each CT variable to the dichotomized mean PRx values for above/below the defined thresholds of 0, +0.25 and +0.35. Area under the receiver operating curve (AUC), Akaike Information Criterion (AIC), 95% confidence intervals (CI's) and p-values for the univariate models are reported. All AUC's and 95% CI's for ULR were determined using bootstrapping techniques with 2000 iterations. Similarly, comparison between continuous CT metrics and PRx metrics was conducted using Pearson correlation and linear regression modelling.

**Results:**

*Patient Demographics:*

A total of 165 patients from the CENTER-TBI high-resolution ICU sub-study were included in this analysis. These patients had archived high-frequency digital physiologic recording of 6 hours or greater duration and digital archived files for their admission CT scan of the brain. The median age was 49 years (IQR: 29 to 64), with 129 males. The median duration of physiologic recording was 126.9 hours (IQR: 82.5 to 169.9). Median admission GCS motor score was 4 (IQR: 1 to 5). Table 1 provides a summary of the admission patient demographics and CT characteristics.

*Table 1 here

*CT Characteristics and PRx Thresholds:*

Evaluating the association between the categorical, ordinal and continuous admission CT metrics and whether a patient displayed mean PRx values above thresholds of 0, +0.25 and +0.35, our results of Mann-U and chi-square testing are in keeping with the previously published retrospective analysis.[13] After correction for multiple comparisons, for the PRx threshold of 0, only advanced age (mean 51.4 vs.

41.4 years; p=0.0007), higher Rotterdam CT score (p=0.0007), larger total extra-axial hematoma volume (31.0 vs. 13.3 $cm^3$; p=0.0003), and higher total cortical contusion edema volume (8.3 vs. 4.4 $cm^3$; p=0.002) were noted to remain significant. For the PRx threshold of +0.25 and +0.35, none of the evaluated CT characteristics were found to be different amongst those patients with mean PRx values above/below these thresholds. The above results were the same for the entire recording period and first 72 hours of recording. Table 2 provides a summary of the Mann-U and chi-square results.

*Table 2 here

*% Time and Hourly Dose Above PRx Threshold and CT Variables:*

Evaluating the difference in mean % time spent above PRx threshold, and mean hourly dose of PRx spent above threshold, compared to categorical/ordinal CT characteristics, the results were identical for the entire recording period and 1st 72 hours analyses. For all PRx thresholds tested (0, +0.25, +0.35), only the presence of cisternal compression was noted to have a statistically significant higher % time and mean hourly dose above threshold ($p<=0.002$ for all; except mean hourly dose above PRx +0.35 – $p=0.003$). Presence of EDH, aSDH, SAH, IVH or skull fracture had no impact on % time or hourly dose of PRx above threshold. Table 3 provides a summary of the Mann-U testing for the categorical CT characteristics.

Similarly, we assessed if there was a difference across the categories in standard admission CT scoring systems: Marshall CT grade, Rotterdam CT score, and Helsinki CT score. The results were identical for the entire recording and 1st 72 hour analyses. Percent time and hourly dose above threshold for PRx was found not to be statistically different between Marshall CT categories ($p>0.05$ on Kruskal-Wallis testing for all threshold variables). When comparing the Marshall CT diffuse sub-categories only (I through IV), Jonckheere-Terpstra testing demonstrates a trend towards statistically significant increase in % time and mean hourly dose spent above PRx of 0, +0.25 and +0.35, with increasing CT score ($p\leq0.01$ for all). Increasing severity of Rotterdam and Helsinki CT scores were associated with a trends to statistically significant increase % time and hourly dose above threshold for PRx 0, +0.25 and +0.35 using Jonckheere-Terpstra testing ($p<0.02$ for all). Figure 1 displays the box-plots for % time and hourly dose above threshold of +0.25, with the p-values reflecting the Kruskal-Wallis and Jonckheere-Terpstra testing, where appropriate.

*Linear Relationships Between Continuous CT and PRx Metrics:*

Linear correlation analysis between continuous CT volumetric measures and continuous PRx metrics, such as % time and hourly dose above threshold, demonstrated poor linear correlation ($r<0.300$ for all testing). Linear regression analysis failed to demonstrate any linear relationship between PRx and CT measures. This was confirmed in both the entire recording and first 72 hours analyses. Subsequently, no further results will be reported.

**Table 3 here*

**Figure 1 here*

*Univariate Logistic Regression Analysis:*

Logistic regression analysis of the various admission CT variables in association with mean PRx values above/below binary PRx thresholds (0, +0.25, +0.35) found identical trends for both the entire recording and 1st 72 hours analyses. Table 4 highlights the AUC, AIC, 95% CI's and p-values for the univariate logistic regression analysis performed. After correction for multiple comparisons, the PRx threshold of 0 displayed statistically significant association with: higher Rotterdam CT score (p=0.0008), worse midline shift (p=0.0002), and larger total extra-axial hematoma volume (0.001). The PRx threshold of +0.25 and +0.35 were associated with total basal ganglia contusion edema (p=0.002 for both) and total deep contusion edema volume (basal ganglia + insula + brainstem + cerebellar) (p=0.001 for PRx threshold +0.25; p=0.018 for PRx +0.35 – non-significant).

**Table 4 here*

**Discussion:**

Using the CENTER-TBI HR ICU sub-study cohort we have been able to provide prospective multi-center data validating the recent retrospective literature findings.[13,14] Some important aspects deserve highlighting. First, the Marshall CT grade system has little association with impaired cerebrovascular reactivity, through logistic regression against binary PRx thresholds, or in comparison to continuous PRx metrics such as % time or hourly dose above threshold. Though, we tested the Marshall CT diffuse injury sub-scores only (ie. I through IV) using Jonckheere-Terpstra testing, which found a trend to statistically significant increases in % time with PRx above all thresholds with increasing sub-score. This finding was supported by increasing Rotterdam and Helsinki CT scores appearing to be associated with worsening % time and hourly dose above PRx threshold, with Jonckheere-Terpstra testing. This is in keeping with some of the previous retrospective studies which found diffuse injury patterns and impaired cerebrovascular reactivity. The newer CT grading systems demonstrated stronger associations with PRx, given they constitute a more comprehensive account of injury pattern and diffusivity of insult. Subsequently, the results of this study, and the prior, indicate that high CT scores consistent with diffuse TBI patterns are associated with impaired cerebrovascular reactivity. These findings may aid in impaired reactivity risk stratification of patients admitted with moderate/severe TBI.

Second, evaluating categorical admission CT metrics, the majority lack association with impaired cerebrovascular reactivity. However, the presence of cisternal compression on admission CT was associated with higher % time and hourly dose above PRx thresholds. This is consistent with the findings

suggesting more diffuse injury patterns, not focal lesions, consistent with acceleration/deceleration forces, are associated with impaired autoregulation.

Third, quantitative volumetric analysis of CT lesions demonstrated interesting patterns of association with cerebrovascular reactivity metrics. In general, after correction for multiple comparisons, parenchymal contusion core volumes were not associated with impaired cerebrovascular reactivity. However, peri-lesional edema volumes, particular deeply located edema volume, was strongly associated with mean PRx values above thresholds of 0 and +0.25, with trend to significance for +0.35. Extra-axial hematoma volume was also found to be associated with having PRx above 0. This is also in keeping with previous retrospective results suggesting that contusion core volume is not related, but markers of diffusivity of insult are associated with impaired vascular reactivity. Furthermore, that deep markers, in keeping with acceleration/deceleration forces and diffuse injury appear associated with impaired autoregulation.

Finally, advanced age, poorly controlled ICP were also demonstrated to be associated with mean PRx values above threshold. This is in keeping with previously documented relationships in other retrospective and prospective studies on the topic.[7,30,31]

Practically speaking, the relationship between admission CT injury characteristics and impaired cerebrovascular reactivity carries implications for predicting a patient's physiologic course during the ICU stay. At the moment, our treatment protocols for TBI care fail to impact cerebrovascular reactivity measures, with many patients spending significant periods of time with impaired reactivity.[5,32] Understanding which injury patterns are more closely associated with, and may drive, impaired cerebrovascular reactivity in TBI allows the treating team to anticipate the risk of ongoing secondary injury. In the future this may allow for us to stratify patients, improve prognostication/communication with families, and allow for the consideration of individualized physiology treatment thresholds based on cerebrovascular reactivity data.[9,10,33] Furthermore, with emerging data supporting the link between impaired cerebrovascular reactivity and CT based lesion progression during ICU stay, being able to predict who may develop impaired reactivity may also allow the treating team to anticipate which patients may develop clinically significant lesion progression.[34,34] Finally, as we advance our knowledge in the area of what drives impaired cerebrovascular reactivity after TBI, we hope to uncover directed therapeutics for prevention and treatment. In such a future, being able to anticipate who is at higher risk for developing impaired reactivity may allow for earlier pre-emptive therapeutic intervention. Obviously much further work is required to better understand the drivers and mechanisms involved in impaired cerebrovascular reactivity after TBI. Such work will involve the integration of proteomics and genomic information which cerebrovascular physiology, in order to uncover the molecular pathways and therapeutic targets to prevent and treat impaired cerebrovascular reactivity.[35,36]

*Limitations:*

Despite the interesting results described above, there are some limitations which deserve attention. First, despite this being a prospective multi-center data collection scheme, our sample size was small. This was secondary to requiring intra-parenchymal ICP monitoring, high-frequency digital physiologic recording longer than 6 hours, and the presence of a digital copy of the admission CT scan for manual image segmentation. As such, the results here cannot be interpreted as definitive.

Second, all patients underwent active ICP and CPP directed therapy during their ICU stay, while the physiology was being recorded. This could have impacted the recorded data and the derived cerebrovascular reactivity metrics. Further to this, given the data was collected from multiple centers, there exists the potential for heterogeneity in treatment patterns. In addition, we did not have the available data to assess the impact of arterial $pCO_2$ or core body temperature on cerebrovascular reactivity. Both of these aspects can impact the measured cerebrovascular reactivity metrics. There is a potential that changes in $pCO_2$ and body temperature may have impacted the recorded physiology, and thus the relationships seen between cerebrovascular reactivity measures and admission CT characteristics. However, despite this limitation, it also must be acknowledged that the findings within this manuscript are in keeping with previously described retrospective analysis on the topic.[13]

Third, CT segmentation employed in this study was semi-automated, requiring a large number of man hours from a highly trained specialist. As such, this methodology isn't easily translatable to other studies, or non-academic centers. This highlights the need to develop fully automated machine learning based methodologies for neuroimaging segmentation. Such work is part on ongoing endeavors as part of specific work packages within CENTER-TBI.

Fourth, we corrected for multiple comparisons, which may have led to loss of significance for some of the admission CT variables in relation to impaired cerebrovascular reactivity. Thus, some of the features that displayed an alpha of less than 0.05 on testing, but failed to reach significant after correction, may still have some important association with impaired cerebrovascular reactivity. This highlights the need for larger studies with high-resolution ICU data.

Fifth, we excluded patients with EVD's as the method of ICP measurement given concerns with signal acquisition. However, we did not exclude those patients undergoing decompressive craniectomy (DC). There exists some uncertainty regarding the impact of DC on cerebrovascular reactivity measures, such as PRx. A previous single center preliminary retrospective work suggested that DC may lead to changes in mean PRx values.[37] However, recent prospective multi-center work on the impact of DC on PRx and the time-series slow-wave relationship between ICP and MAP, from the CENTER-TBI HR-ICU sub-study, has demonstrated that DC has no impact on these aspects of cerebrovascular physiology in TBI. This was confirmed using multiple methods of assessment of both PRx and the slow-wave relationship between ICP and MAP, across varying time periods pre- and post-DC.[38] As such, given these recent findings from the CENTER-TBI HR-ICU cohort, we decided to no exclude craniectomy patients from the analysis. Though we must acknowledge, the current literature body on the effects of DC on cerebrovascular physiology is uncertain, requiring much further investigation *in vivo*, as well as in large experimental animal models.

Sixth, ICP monitoring based on fibre optic or strain-gauge parenchymal technology has limitations. Typically these monitoring devices are placed into the frontal lobe, in areas of brain not containing significant trauma. As such, any monitor closely situated to, or placed inside, traumatic lesions may generate spurious readings in terms of the absolute raw ICP value. This however doesn't impact derived cerebrovascular reactivity measures, as they are mathematically derived from the correlation between slow-wave values of ICP and MAP, producing a surrogate measure of slow-wave phase shift, and remain independent of the magnitude or constant scaling errors of the raw recorded physiology. Further concern can be raised regarding the focal nature of ICP monitoring. We assume the value generated from the ICP monitor represents global intracranial pressure, and thus the metrics of cerebrovascular

reactivity generated from ICP represent global measures as well. However, preliminary retrospective work has pointed to the regional disparity in cerebrovascular reactivity, using near infrared spectroscopy or transcranial Doppler, with hemispheric or regional variations in measurements seen after TBI.[39–43] There exists the potential that local/regional traumatic pathology drives local/regional differences in cerebrovascular reactivity. Unfortunately, currently there have been no such studies evaluating this relationship. This remains an area where much further work is required.

Seventh, we only explored the association between PRx based measures and the admission intracranial injury characteristics. There has been some emerging literature on alternative ICP-derived cerebrovascular reactivity metrics, such as pulse amplitude index (PAx)[44] and RAC (correlation (R) between pulse amplitude of ICP (A) and CPP (C)).[45] Preliminary data suggests that each of these alternative measures may prove useful in prognostication,[6,44] thought their exact role in bedside monitoring remains unclear. The previous retrospective work on admission injury characteristics and cerebrovascular reactivity did evaluate PAx and RAC.[13] We decided, for the purpose of this study, to focus only on PRx. This was based on the fact the PRx has the most literature to date in TBI monitoring, is the most widely utilized continuous cerebrovascular reactivity index,[46] has the largest literature body providing some validation as a measure of cerebral autoregulation,[47–49] and forms the basis for ongoing prospective work into individualized physiology targets in TBI care,[9,10,33] including an ongoing phase II study.[50] As such, the most logical focus for this current work was PRx. This is not to say that PAx and RAC are not important. They are just more difficult to interpret given limited existing literature, and that RAC in particular carries information regarding both cerebrovascular reactivity and compensatory reserve. There is the need for much future investigation into PAx and RAC.

Finally, the extent of IC injury is likely not adequately represented by admission CT scans of the brain. This type of analysis between imaging characteristics and high-frequency cerebral physiology requires evaluation with higher spatial resolution techniques, such are magnetic resonance imaging (MRI). Such analysis is planned with the MRI data acquired in CENTER-TBI.

## Conclusions:

Diffuse admission IC injury patterns appear to be consistently associated with impaired cerebrovascular reactivity, as measured through PRx. This is in keeping with the previous single center retrospective literature on the topic. This study provides multi-center validation for those results, and provide preliminary data to support potential risk stratification for impaired cerebrovascular reactivity based on injury pattern.

## Disclosures:

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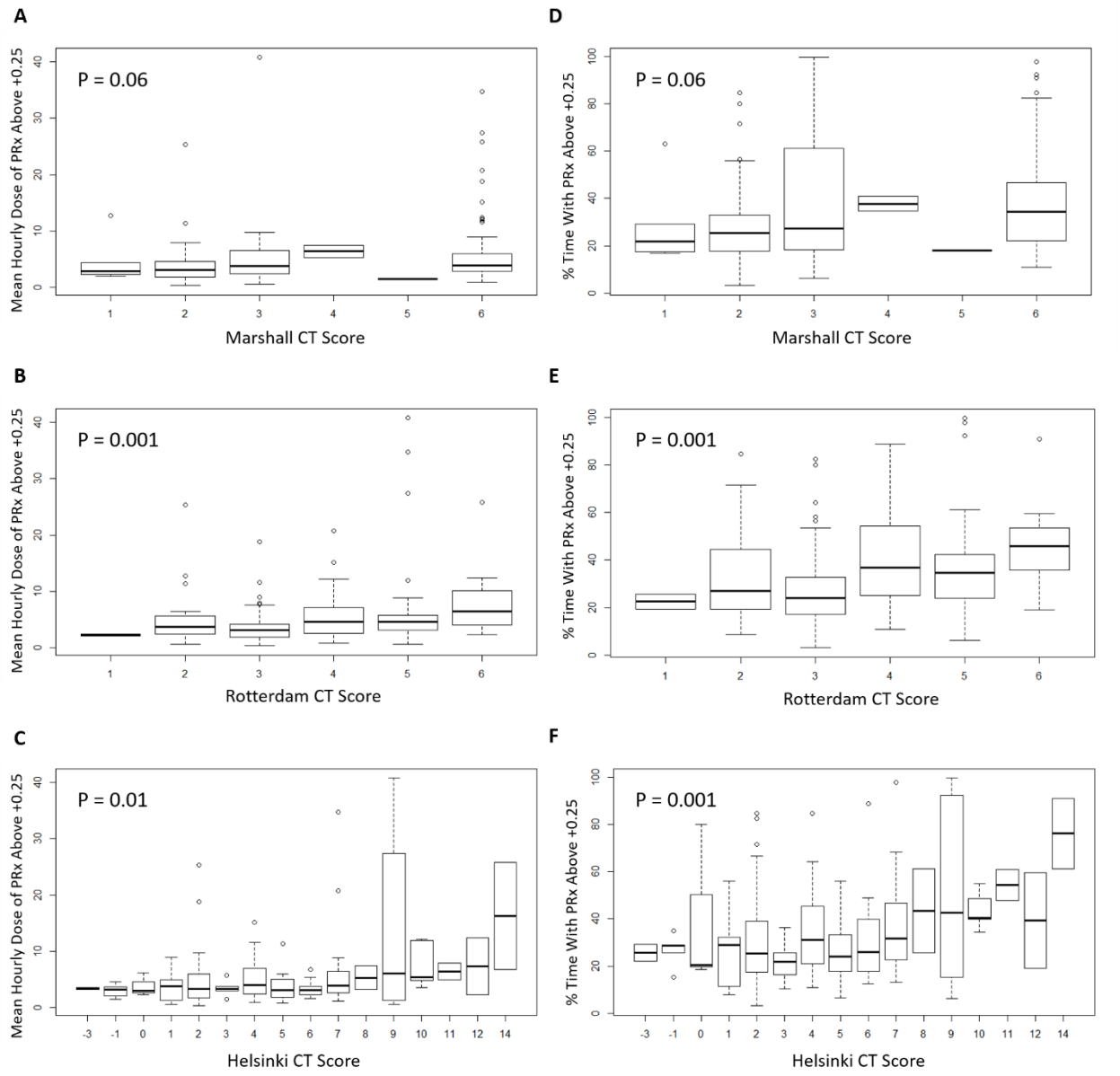
*Figure 1: Box Plots of % Time and Hourly Dose Above PRx +0.25 in Relation to CT Scoring Systems*




*CT = computed tomography, p = p-value, PRx = pressure reactivity index (correlation between slow-waves in intra-cranial pressure and mean arterial pressure), % percent. Panel A – box plot of mean hourly dose above PRx +0.25 and Marshall CT grade, Panel B - box plot of mean hourly dose above PRx +0.25 and Rotterdam CT score, Panel C - box plot of mean hourly dose above PRx +0.25 and Helsinki CT score, Panel D – box plot of % time above PRx +0.25 and Marshall CT grade, Panel B - box plot of % time above PRx +0.25 and Rotterdam CT score, Panel C - box plot of % time above PRx +0.25 and Helsinki CT score. NOTE: p-value for Marshall CT grade reflect Kruskal-Wallis testing, while those for Rotterdam and Helsinki CT scores represent Jonckheere-Terpstra testing.*

*Table 1: Admission Patient Demographics and CT Characteristics – Median, IQR and Raw Numbers*

| | | **Median (IQR) or Raw Number** |
|---|---|---|
| ***Number of Patients*** | | 165 |
| ***Age (years)*** | | 49 (29-64) |
| ***Sex*** | ***Male*** | 129 (78%) |
| | ***Female*** | 36 (22%) |
| ***Duration of High Frequency Physiologic Recording (hours)*** | | 126.9 (82.5 – 169.9) |
| ***Admission GCS (Total)*** | | 7 (3 – 10) |
| ***Admission GCS Motor*** | | 4 (1 – 5) |
| ***Number with Hypoxia Episode*** | | 23 |
| ***Number with Hypotension Episode*** | | 22 |
| ***Admission Pupil Response*** | ***Bilaterally Reactive*** | 125 |
| | ***Unilateral Unreactive*** | 15 |
| | ***Bilaterally Unreactive*** | 25 |
| ***Marshall CT Grade*** | | 3 (2 – 6) |
| ***Rotterdam CT Grade*** | | 3 (3 – 4) |
| ***Helsinki CT Score*** | | 4 (2 – 7) |
| ***Number with Traumatic SAH*** | | 137 |
| ***Number with Epidural Hematoma*** | | 41 |
| ***Number with Subdural Hematoma*** | | 101 |
| ***Number with Cisternal Compression*** | | 66 |
| ***Number with Skull Fracture*** | | 106 |
| ***Number with IVH*** | | 54 |
| ***MLS (mm)*** | | 1.0 (0 – 5.0) |
| ***Total Contusion Core Volume ($cm^3$)*** | | 0.83 (0.09 – 4.2) |
| ***Total Contusion Edema Volume ($cm^3$)*** | | 1.6 (0.07 – 9.7) |
| ***Total EA Hematoma Volume ($cm^3$)*** | | 0 (0 - 0.05) |
| ***Total IVH Volume ($cm^3$)*** | | 10.2 (0.85 – 30.6) |
| ***Total Cortical Contusion Core Volume ($cm^3$)*** | | 0.76 (0.05 – 3.79) |
| ***Total Cortical Contusion Edema Volume ($cm^3$)*** | | 1.29 (0.05 – 7.50) |
| ***Total BG Contusion Core Volume ($cm^3$)*** | | 0 (0 – 0.06) |
| ***Total BG Contusion Edema Volume ($cm^3$)*** | | 0 (0 – 0.67) |
| ***Total BS Contusion Core Volume ($cm^3$)*** | | 0 (0 – 0.004) |
| ***Total BS Contusion Edema Volume ($cm^3$)*** | | 0 (0 – 0.04) |
| ***Total Deep Contusion Core Volume ($cm^3$)*** | | 0.001 (0 – 0.31) |
| ***Total Deep Contusion Edema Volume ($cm^3$)*** | | 0.03 (0 – 1.3) |

*BG = basal ganglia (includes basal ganglia and insula), BS = brainstem (includes cerebellar lesions), $cm^3$ = cubic centimetres, CT = computed tomography, GCS = Glasgow Coma Score, GOSE = Glasgow Outcome Score, IQR = inter-quartile range, IQR = intra-quartile range, IVH = intra-ventricular hemorrhage, mm = millimetres, mmHg = millimetres of mercury, SAH = subarachnoid hemorrhage.*

*Table 2: Admission Demographics, ICP and CT Characteristics in Relation to PRx Thresholds – Mann-U and Chi-Square Testing*

| ***Demographic/CT Variable*** | **Mean Values (sd) or Raw Number** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **PRx Threshold of 0** | | | **PRx Threshold of +0.25** | | | **PRx Threshold of +0.35** | | |
| | **Above (n=96)** | **Below (n=69)** | **p-value** | **Above (n=24)** | **Below (n=141)** | **p-value** | **Above (n=13)** | **Below (n=152)** | **p-value** |
| ***Age*** | 51.4 (20.1) | 41.4 (16.1) | **0.0007** | 50.0 (23.3) | 46.8 (18.4) | 0.381 | 50.4 (22.0) | 46.9 (18.9) | 0.529 |
| ***GCS-M*** | 3 (IQR: 1 – 5) | 4 (IQR: 1 – 5) | 0.999 | 2 (IQR: 1 – 4) | 4 (IQR: 1 – 5) | 0.199 | 2 (IQR: 1 – 4) | 4 (IQR: 1 – 5) | 0.294 |
| ***Pupillary Response*** | NA | NA | 0.273 | NA | NA | 0.299 | NA | NA | 0.200 |
| ***Hypoxic Episode*** | 9 | 14 | 0.077 | 5 | 18 | 0.461 | 5 | 18 | 0.025 |
| ***Hypotensive Episode*** | 10 | 12 | 0.286 | 2 | 20 | 0.649 | 1 | 21 | 0.843 |
| ***AMP (mmHg)*** | 2.7 (2.1) | 2.1 (1.3) | 0.120 | 4.1 (3.2) | 2.1 (1.3) | 0.0005 | 5.7 (3.5) | 2.1 (1.3) | **<0.0001** |
| ***ICP (mmHg)*** | 15.2 (11.7) | 12.1 (4.4) | 0.265 | 22.8 (19.5) | 12.4 (5.2) | 0.021 | 34.2 (20.1) | 12.2 (5.2) | **<0.0001** |
| ***% Time with ICP over 20 mmHg*** | 18.3 (28.3) | 10.0 (17.2) | 0.110 | 38.2 (41.2) | 10.9 (17.9) | 0.004 | 65.0 (38.8) | 10.5 (17.4) | **<0.0001** |
| ***% Time with ICP over 22 mmHg*** | 14.6 (26.5) | 6.0 (12.4) | 0.039 | 34.3 (40.6) | 7.0 (13.8) | **0.002** | 60.1 (39.7) | 6.8 (13.4) | **<0.0001** |
| ***Marshall CT Score*** | 6 (IQR: 2 - 6) | 2 (IQR: 2 – 6) | 0.003 | 6 (IQR: 3 – 6) | 3 (IQR: 2 – 6) | 0.1656 | 6 (IQR: 2 – 6) | 3 (IQR: 2 – 6) | 0.510 |
| ***Rotterdam CT Score*** | 4 (IQR 3 – 5) | 3 (IQR: 3 – 3) | **0.0007** | 4 (IQR: 3 – 5) | 3 (IQR: 3 – 4) | 0.118 | 4 (IQR: 3 – 5) | 3 (IQR: 3 – 4) | 0.684 |
| ***Helsinki CT Score*** | 5 (IQR: 2 – 7) | 4 (IQR: 2 – 5) | 0.053 | 6 (IQR: 3 – 9) | 4 (IQR: 2 – 6) | 0.045 | 5 (IQR: 2 – 8) | 4 (IQR: 2 – 6) | 0.465 |
| ***MLS (mm)*** | 4.2 (5.4 ) | 1.8 (3.6) | 0.003 | 3.5 (4.5) | 3.2 (4.9) | 0.251 | 2.7 (3.0) | 3.3 (5.0) | 0.670 |
| ***Presence of Cisternal Compression*** | 47 | 19 | 0.009 | 14 | 52 | 0.079 | 7 | 59 | 0.443 |
| ***Presence of EDH*** | 24 | 17 | 0.999 | 6 | 35 | 0.999 | 3 | 38 | 0.999 |
| ***Presence of aSDH*** | 63 | 38 | 0.234 | 14 | 87 | 0.865 | 6 | 95 | 0.344 |
| ***Presence of SAH*** | 79 | 58 | 0.881 | 19 | 118 | 0.685 | 9 | 128 | 0.260 |
| ***Presence of IVH*** | 32 | 22 | 0.978 | 12 | 42 | 0.086 | 6 | 48 | 0.563 |
| ***Presence of Skull Fracture*** | 66 | 40 | 0.215 | 15 | 91 | 0.960 | 7 | 99 | 0.443 |
| ***Total Contusion Core Volume ($cm^3$)*** | 7.4 (15.3) | 2.5 (4.9) | 0.020 | 11.4 (19.3) | 4.4 (10.4) | 0.029 | 14.0 (25.2) | 4.6 (10.3) | 0.400 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ***Total Contusion Edema Volume ($cm^3$)*** | 10.0 (15.5) | 5.3 (11.7) | 0.004 | 14.9 (20.2) | 6.8 (12.6) | 0.012 | 15.5 (26.1) | 7.4 (12.6) | 0.825 |
| ***Total EA Hematoma Volume ($cm^3$)*** | 31.0 (39.4) | 13.3 (22.1) | **0.0003** | 27.1 (34.3) | 23.0 (34.4) | 0.489 | 20.0 (21.9) | 23.9 (35.2) | 0.975 |
| ***Total IVH Volume ($cm^3$)*** | 0.37 (2.3) | 0.09 (0.24) | 0.705 | 1.1 (4.5) | 0.1 (0.3) | 0.051 | 0.08 (0.2) | 0.3 (1.8) | 0.540 |
| ***Total Cortical Contusion Core Volume ($cm^3$)*** | 6.0 (11.7) | 2.2 (4.1) | 0.032 | 9.1 (14.8) | 3.6 (8.0) | 0.030 | 11.4 (18.9) | 3.8 (8.0) | 0.301 |
| ***Total Cortical Contusion Edema Volume ($cm^3$)*** | 8.3 (12.8) | 4.4 (9.9) | **0.002** | 11.8 (16.1) | 5.8 (10.7) | 0.021 | 12.2 (20.6 ) | 6.2 (10.7) | 0.844 |
| ***Total BG Contusion Core Volume ($cm^3$)*** | 0.94 (3.6) | 0.22 (0.82) | 0.592 | 1.8 (5.1) | 0.4 (2.1) | 0.199 | 2.1 (6.1) | 0.5 (2.3) | 0.480 |
| ***Total BG Contusion Edema Volume ($cm^3$)*** | 1.2 (2.5) | 0.62 (1.9) | 0.312 | 2.2 (3.7) | 0.7 (1.8) | 0.105 | 2.7 (4.8) | 0.8 (1.8) | 0.300 |
| ***Total BS Contusion Core Volume ($cm^3$)*** | 0.30 (2.1) | 0.15 (0.69) | 0.316 | 0.3 (1.0) | 0.1 (0.2) | 0.435 | 0.03 (0.1) | 0.3 (1.8) | 0.703 |
| ***Total BS Contusion Edema Volume ($cm^3$)*** | 0.32 (1.0) | 0.27 (1.1) | 0.065 | 0.5 (1.1) | 0.3 (1.0) | 0.023 | 0.1 (0.4) | 0.3 (1.1) | 0.973 |
| ***Total Deep Contusion Core Volume ($cm^3$)*** | 1.2 (4.1) | 0.37 (1.0) | 0.248 | 1.9 (5.1) | 0.7 (2.7) | 0.174 | 2.1 (6.1) | 0.8 (2.8) | 0.750 |
| ***Total Deep Contusion Edema Volume ($cm^3$)*** | 1.5 (2.7) | 0.88 (2.1) | 0.076 | 2.8 (3.9) | 1.0 (2.1) | 0.004 | 2.8 (5.1) | 1.1 (2.2) | 0.417 |

*AMP = pulse amplitude of ICP, aSDH = acute subdural hematoma, BG = basal ganglia (includes basal ganglia and insula), BS = brainstem (includes cerebellar lesions), $cm^3$ = cubic centimetres, CT = computed tomography, EDH = epidural hematoma, GCS = Glasgow Coma Score, GOSE = Glasgow Outcome Score, ICP = intra-cranial pressure, IQR = inter-quartile range, IVH = intra-ventricular hemorrhage, mm = millimetres, mmHg = millimetres of mercury, PRx = pressure reactivity index (correlation between slow waves of ICP and mean arterial pressure), SAH = subarachnoid hemorrhage, sd = standard deviation. *NOTE: bolded p-values are those reaching statistical significance after Bonferroni correction for multiple comparisons (alpha 0.002).*

*Table 3: Categorical Admission CT Characteristics and Continuous PRx Metrics - % Time and Mean Hourly Dose Above Threshold – Mann-U Testing*

| ***Demographic/CT Variable*** | **Mean Values (sd)** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Mean % Time with PRx Above Threshold of 0** | | | **Mean % Time with PRx Above Threshold of +0.25** | | | **Mean % Time with PRx Above Threshold of +0.35** | | |
| | **Present** | **Absent** | **p-value** | **Present** | **Absent** | **p-value** | **Present** | **Absent** | **p-value** |
| ***Presence of Cisternal Compression*** | 60.1 (20.1) | 49.5 (18.0) | **0.0008*** | 39.1 (22.6) | 28.7 (16.7) | **0.001*** | 31.6 (22.5) | 21.9 (15.4) | **0.001*** |
| ***Presence of EDH*** | 52.2 (19.5) | 54.3 (19.6) | 0.488 | 30.3 (19.1) | 33.7 (20.1) | 0.263 | 23.2 (17.8) | 26.6 (19.5) | 0.859 |
| ***Presence of aSDH*** | 55.0 (18.8) | 51.7 (20.6) | 0.298 | 33.5 (19.8) | 31.7 (20.1) | 0.390 | 26.3 (19.2) | 24.9 (19.0) | 0.487 |
| ***Presence of SAH*** | 53.4 (20.0) | 55.5 (17.4) | 0.695 | 32.5 (20.2) | 34.4 (18.8) | 0.448 | 25.5 (19.4) | 27.0 (18.1) | 0.440 |
| ***Presence of IVH*** | 55.7 (21.0) | 52.8 (18.8) | 0.392 | 36.3 (22.1) | 31.1 (18.5) | 0.207 | 29.5 (21.4) | 23.9 (17.7) | 0.122 |
| ***Presence of Skull Fracture*** | 55.3 (18.9) | 51.0 (20.4) | 0.112 | 33.8 (19.4) | 31.1 (20.7) | 0.178 | 26.5 (18.7) | 24.5 (20.0) | 0.189 |
| | **Mean Values** | | | | | | | | |
| | **Mean Hourly Dose of PRx Above 0** | | | **Mean Hourly Dose of PRx Above +0.25** | | | **Mean Hourly Dose of PRx Above +0.35** | | |
| | **Present** | **Absent** | **p-value** | **Present** | **Absent** | **p-value** | **Present** | **Absent** | **p-value** |
| ***Presence of Cisternal Compression*** | 13.2 (10.2) | 9.1 (5.9) | **0.0009*** | 6.6 (7.4) | 4.1 (3.7) | **0.002*** | 4.8 (6.3) | 2.8 (3.0) | **0.003** |
| ***Presence of EDH*** | 9.5 (5.6) | 11.2 (8.7) | 0.408 | 4.1 (3.3) | 5.4 (6.2) | 0.343 | 2.8 (2.5) | 3.9 (5.2) | 0.374 |
| ***Presence of aSDH*** | 11.2 (8.6) | 10.1 (7.3) | 0.235 | 5.3 (6.1) | 4.8 (4.8) | 0.316 | 3.8 (5.2) | 3.2 (3.8) | 0.362 |
| ***Presence of SAH*** | 10.6 (8.3) | 11.3 (6.9) | 0.288 | 5.1 (5.8) | 5.4 (4.9) | 0.327 | 3.6 (4.8) | 3.8 (4.1) | 0.381 |
| ***Presence of IVH*** | 12.1 (8.7) | 10.1 (7.7) | 0.192 | 6.0 (5.9) | 4.7 (5.5) | 0.111 | 4.3 (4.8) | 3.3 (4.6) | 0.104 |
| ***Presence of Skull Fracture*** | 11.0 (7.8) | 10.2 (8.7) | 0.106 | 5.2 (5.4) | 4.9 (6.1) | 0.131 | 3.6 (4.5) | 3.5 (5.0) | 0.130 |

*aSDH = acute subdural hematoma, BG = basal ganglia (includes basal ganglia and insula), BS = brainstem (includes cerebellar lesions), $cm^3$ = cubic centimetres, CT = computed tomography, EDH = epidural hematoma, GCS = Glasgow Coma Score, GOSE = Glasgow Outcome Score, IVH = intra-ventricular hemorrhage, mm = millimetres, mmHg = millimetres of mercury, PRx = pressure reactivity index (correlation between slow waves of ICP and mean arterial pressure), SAH = subarachnoid hemorrhage, sd = standard deviation. *NOTE: bolded p-values are those reaching statistical significance (alpha 0.05), the "*" denotes those remaining significant after Bonferroni correction for multiple comparisons (alpha 0.002).*

*Table 4: Univariate Logistic Regression Analysis – AUC, 95% CI - Admission Demographics, ICP and Admission CT Characteristics in Relation to PRx Thresholds*

| | **PRx Threshold of 0** | **PRx Threshold of +0.25** | **PRx Threshold of +0.35** |
|---|---|---|---|

| | AUC | 95% CI | AIC | p-value | AUC | 95% CI | AIC | p-value | AUC | 95% CI | AIC | p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Age*** | 0.655 | 0.571-0.737 | 229.6 | **0.0008*** | 0.556 | 0.407-0.697 | 129.6 | 0.450 | 0.447 | 0.296-0.626 | 41.0 | 0.527 |
| ***GCS-M*** | 0.500 | 0.413-0.590 | 228.2 | 0.724 | 0.580 | 0.458-0.691 | 138.7 | 0.149 | 0.585 | 0.410-0.743 | 93.9 | 0.286 |
| ***Pupillary Response*** | 0.481 | 0.408-0.551 | 225.9 | 0.418 | 0.566 | 0.465-0.671 | 129.2 | 0.240 | 0.615 | 0.478-0.754 | 44.3 | 0.078 |
| ***Hypoxic Episode*** | 0.445 | 0.386-0.499 | 237.0 | **0.046** | 0.540 | 0.460-0.634 | 129.1 | 0.294 | 0.633 | 0.505-0.768 | 34.2 | **0.008** |
| ***Hypotensive Episode*** | 0.465 | 0.411-0.521 | 239.3 | 0.196 | 0.470 | 0.415-0.540 | 129.6 | 0.439 | 0.469 | 0.422-0.560 | 41.1 | 0.535 |
| ***AMP (mmHg)*** | 0.571 | 0.480-0.656 | 236.9 | **0.043** | 0.722 | 0.608-0.835 | 103.0 | **<0.00001*** | 0.868 | 0.763-0.952 | -14.0 | **<0.00001*** |
| ***ICP (mmHg)*** | 0.551 | 0.464-0.641 | 236.7 | **0.038** | 0.648 | 0.512-0.783 | 103.4 | **<0.00001*** | 0.875 | 0.648-0.971 | -40.8 | **<0.00001*** |
| ***% Time with ICP over 20 mmHg*** | 0.573 | 0.488-0.662 | 236.4 | **0.033** | 0.684 | 0.544-0.817 | 102.5 | **<0.00001*** | 0.881 | 0.737-0.977 | -33.8 | **<0.00001*** |
| ***% Time with ICP over 22 mmHg*** | 0.594 | 0.510-0.679 | 234.8 | **0.013** | 0.691 | 0.542-0.822 | 95.2 | **<0.00001*** | 0.878 | 0.724-0.978 | -50.0 | **<0.00001*** |
| ***Marshall CT Score*** | 0.627 | 0.544-0.704 | 225.9 | **0.003** | 0.582 | 0.466-0.685 | 129.2 | 0.248 | 0.551 | 0.399-0.695 | 44.5 | 0.535 |
| ***Rotterdam CT Score*** | 0.649 | 0.567-0.729 | 223.18 | **0.0008*** | 0.595 | 0.460-0.720 | 128.0 | 0.113 | 0.523 | 0.354-0.705 | 44.6 | 0.616 |
| ***Helsinki CT Score*** | 0.592 | 0.505-0.678 | 217.6 | **0.034** | 0.631 | 0.491-0.762 | 116.9 | 0.004 | 0.563 | 0.373-0.746 | 37.7 | 0.272 |
| ***MLS (mm)*** | 0.635 | 0.559-0.714 | 231.1 | **0.0002*** | 0.569 | 0.454-0.677 | 130.2 | 0.810 | 0.534 | 0.398-0.674 | 41.3 | 0.664 |
| ***Presence of Cisternal Compression*** | 0.607 | 0.534-0.678 | 233.2 | **0.005** | 0.607 | 0.496-0.718 | 126.3 | 0.048 | 0.575 | 0.441-0.710 | 40.3 | 0.291 |
| ***Presence of EDH*** | 0.501 | 0.435-0.566 | 238.1 | 0.970 | 0.499 | 0.412-0.590 | 130.4 | 0.985 | 0.489 | 0.382-0.617 | 42.8 | 0.858 |
| ***Presence of aSDH*** | 0.552 | 0.474-0.629 | 236.2 | 0.178 | 0.479 | 0.377-0.584 | 130.2 | 0.693 | 0.586 | 0.444-0.726 | 41.3 | 0.223 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Presence of SAH*** | 0.489 | 0.434-0.547 | 237.9 | 0.710 | 0.471 | 0.374-0.552 | 129.9 | 0.482 | 0.420 | 0.289-0.538 | 40.5 | 0.130 |
| ***Presence of IVH*** | 0.507 | 0.434-0.581 | 241.0 | 0.846 | 0.601 | 0.493-0.708 | 126.4 | 0.051 | 0.573 | 0.438-0.718 | 40.3 | 0.285 |
| ***Presence of Skull Fracture*** | 0.553 | 0.478-0.627 | 236.1 | 0.162 | 0.485 | 0.374-0.587 | 130.3 | 0.779 | 0.439 | 0.299-0.575 | 42.1 | 0.381 |
| ***Total Contusion Core Volume ($cm^3$)*** | 0.606 | 0.515-0.690 | 234.6 | **0.011** | 0.640 | 0.506-0.756 | 123.3 | **0.009** | 0.580 | 0.405-0.753 | 34.3 | **0.008** |
| ***Total Contusion Edema Volume ($cm^3$)*** | 0.632 | 0.546-0.729 | 236.7 | **0.034** | 0.661 | 0.542-0.778 | 123.4 | **0.009** | 0.481 | 0.302-0.660 | 37.5 | **0.048** |
| ***Total EA Hematoma Volume ($cm^3$)*** | 0.667 | 0.581-0.751 | 229.9 | **0.001*** | 0.544 | 0.416-0.671 | 129.9 | 0.589 | 0.503 | 0.335-0.670 | 41.3 | 0.697 |
| ***Total IVH Volume ($cm^3$)*** | 0.515 | 0.440-0.588 | 240.0 | 0.304 | 0.604 | 0.500-0.719 | 123.2 | **0.009** | 0.543 | 0.418-0.674 | 41.3 | 0.709 |
| ***Total Cortical Contusion Core Volume ($cm^3$)*** | 0.598 | 0.509-0.680 | 234.2 | **0.009** | 0.638 | 0.514-0.759 | 123.1 | **0.008** | 0.587 | 0.405-0.765 | 33.6 | **0.005** |
| ***Total Cortical Contusion Edema Volume ($cm^3$)*** | 0.637 | 0.551-0.718 | 236.5 | **0.035** | 0.648 | 0.523-0.763 | 124.8 | 0.021 | 0.483 | 0.300-0.664 | 38.3 | 0.079 |
| ***Total BG Contusion Core Volume ($cm^3$)*** | 0.522 | 0.447-0.602 | 238.3 | 0.103 | 0.572 | 0.451-0.692 | 0.021 | 124.8 | 0.552 | 0.401-0.702 | 37.5 | **0.049** |
| ***Total BG Contusion Edema Volume ($cm^3$)*** | 0.543 | 0.459-0.624 | 238.6 | 0.123 | 0.596 | 0.464-0.731 | 120.8 | **0.002*** | 0.581 | 0.404-0.744 | 32.4 | **0.002*** |
| ***Total BS Contusion Core Volume ($cm^3$)*** | 0.536 | 0.466-0.607 | 240.7 | 0.581 | 0.539 | 0.441-0.647 | 130.0 | 0.654 | 0.475 | 0.365-0.602 | 41.2 | 0.645 |
| ***Total BS Contusion*** | 0.575 | 0.496-0.649 | 240.9 | 0.757 | 0.630 | 0.513-0.745 | 128.7 | 0.226 | 0.497 | 0.367-0.626 | 41.0 | 0.508 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Edema Volume ($cm^3$)*** | | | | | | | | | | | | |
| ***Total Deep Contusion Core Volume ($cm^3$)*** | 0.550 | 0.466-0.631 | 238.1 | 0.089 | 0.582 | 0.451-0.705 | 127.1 | 0.078 | 0.525 | 0.364-0.691 | 39.2 | 0.141 |
| ***Total Deep Contusion Edema Volume ($cm^3$)*** | 0.579 | 0.493-0.658 | 238.7 | 0.132 | 0.679 | 0.553-0.795 | 119.6 | **0.001*** | 0.566 | 0.387-0.730 | 35.7 | **0.018** |

*AIC = Akaike Information Criterion, AMP = pulse amplitude of ICP, aSDH = acute subdural hematoma, AUC = area under receive operating curve, BG = basal ganglia (includes basal ganglia and insula), BS = brainstem (includes cerebellar lesions), $cm^3$ = cubic centimetres, CT = computed tomography, EDH = epidural hematoma, GCS = Glasgow Coma Score, GOSE = Glasgow Outcome Score, ICP = intra-cranial pressure, IQR = inter-quartile range, IVH = intra-ventricular hemorrhage, mm = millimetres, mmHg = millimetres of mercury, PRx = pressure reactivity index (correlation between slow waves of ICP and mean arterial pressure), SAH = subarachnoid haemorrhage, 95% CI = 95% confidence intervals *NOTE: bolded p-values are those reaching statistical significance (alpha of 0.05), the "*" denotes those remaining significant after Bonferroni correction for multiple comparisons (alpha 0.002); all AUC and 95% CI's were determined using bootstrap methodology with 2000 iterations.*