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Systemic Markers of Injury and Injury Response are not Associated with Impaired Cerebrovascular Reactivity in Adult TBI: A CENTER-TBI Study

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Abstract:

The role of extra-cranial injury burden and systemic injury response on cerebrovascular response in traumatic brain injury (TBI) is poorly documented. This study preliminarily assesses the association between admission features of extra-cranial injury burden on cerebrovascular reactivity. Using the CENTER-TBI HR ICU sub-study cohort, we evaluated those patients with both archived high-frequency digital intra-parenchymal ICP monitoring data of a minimum of 6 hours in duration, and the presence of a digital copy of their admission CT scan. Digital physiologic signals were processed for pressure reactivity index (PRx) and both the % time above defined PRx thresholds and mean hourly dose above threshold. This was conducted for both the first 72 hours and entire duration of recording. Admission extra-cranial injury characteristics and CT injury scores were obtained from the database, with quantitative contusion, edema, intraventricular hemorrhage (IVH) and extra-axial lesion volumes were obtained via semi-automated segmentation. Comparison between admission extra-cranial markers of injury and PRx metrics was conducted using Mann-U testing, and logistic regression techniques, adjusting for known CT injury metrics associated with impaired PRx. A total of 165 patients were included. Evaluating the entire ICU recording period, there was limited association between metrics of extra-cranial injury burden and impaired cerebrovascular reactivity. Using the first 72 hours of recording, admission temperature (p=0.042) and white blood cell % (WBC %) (p=0.013) were statistically associated with impaired cerebrovascular reactivity on Mann-U and univariate logistic regression. After adjusting for admission age, pupillary status, GCS motor score, pre-hospital hypoxia/hypotension and intra-cranial CT characteristics associated with impaired reactivity, temperature (p=0.021) and WBC % (p=0.013) remained significantly associated with mean PRx values above +0.25 and +0.35, respectively. Markers of extra-cranial injury burden and systemic injury response do not appear to be strongly associated with impaired cerebrovascular reactivity in TBI, during both the initial and entire ICU stay.
Keywords: autoregulation, cerebrovascular reactivity, extra-cranial injury, injury burden, TBI

Introduction:

Intracranial pressure (ICP) based metrics of cerebrovascular reactivity are increasingly becoming utilized for bedside continuous monitoring in critical care.[1,2] In particular, pressure reactivity index (PRx – the correlation between slow-wave vasogenic fluctuations in ICP and mean arterial pressure (MAP)) has been employed in adult TBI, with a growing literature base supporting its association with global outcome,[3–7] and the ability to derive individualized physiologic targets in moderate and severe TBI.[8–12]

Despite this growing interest in PRx, and other continuous measures of cerebrovascular reactivity, our understanding of what drives impaired reactivity after TBI is limited. Some studies have demonstrated an association between advanced age,[5,13] elevated ICP,[14,15] and impaired cerebrovascular reactivity. Though we know impaired autoregulation occurs in both young TBI patients, and those with low mean ICP values.[16] We have some literature to support the association between diffuse intra-cranial injury patterns and impaired cerebrovascular reactivity,[17] with recent multi-center evidence supporting these findings.[18] Further, some preliminary literature supports the association between impaired reactivity and the presence of cortical spreading depression.[19,20] This small number of studies is the extent of our current knowledge of what drives impaired reactivity in TBI.

The extra-cranial injury burden and host response to extra-cranial injury on admission may be related to intra-cranial vascular responses after TBI.[17] There is the potential that the host systemic injury response may drive impaired cerebrovascular reactivity. To date, only one study has provide very preliminary data documenting an association between the total Acute Physiology and Chronic Health Evaluation II (APACHE II) score and impaired PRx.[17] This study was limited by its retrospective nature and paucity of extra-cranial injury marker data, aside from total APACHE II and Injury Severity Scores (ISS). It remains unclear if the previously identified association between APACHE II and impaired cerebrovascular reactivity[17] was driven by component elements known to be strongly associated with cerebrovascular dysfunction in TBI, such as age and Glasgow Coma Scale (GCS) scores, versus a true association with acute physiology response to injury. GCS scores may simply have been a reflection of intracranial injury severity, driving the association this

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association with APACHE II. This is potentially confounded further by genetic and other variations in host response to injury, or co-morbidities as quantified by the Chronic Health Evaluation component of the APACHE II summative score.[21]

As such, the goal of this study is to evaluate the association between various admission extra-cranial markers of injury and host injury response, with cerebrovascular reactivity, using the prospective observational Collaborative European Neurotrauma Effectiveness Research in TBI (CENTER-TBI)[22] high-resolution intensive care unit (ICU) sub-study cohort. Specifically, we aimed to explore a few facets of the relationship between extra-cranial injury burden and host response with impaired cerebrovascular reactivity. First, we explore the relationship between abbreviated injury score (AIS)/ISS, as robust measure of extra-cranial injury, and impaired reactivity. Second, we examine if individual markers of extra-cranial injury burden and host response to injury were associated with impaired cerebrovascular reactivity. This was done both in isolation, and while adjusting for admission patient characteristics and imaging patterns of intra-cranial injury known to be associated with impaired reactivity. Finally, we explored whether the acute physiology elements of the APACHE II score, in a multi-variate model, were associated with impaired cerebrovascular reactivity.

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. We required the admission CT scans so that we could adjust for the known admission intra-cranial CT characteristics associated with impaired cerebrovascular reactivity, as defined by our recently published work from this cohort.[18] 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

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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.[23]

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, as CENTER-TBI was a prospective observational study. 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

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available CT of each patient were extracted.[24] They included: age, admission best GCS motor score and pupillary reactivity (bilaterally reactive, unilateral reactive, bilateral unreactive), Helsinki CT score,[25] basal cistern compression, pre-hospital hypotension and pre-hospital hypoxia. Further semi-automated segmentation of the admission CT scans was conducted as described in Appendix A of the Supplementary materials, as part of a separate CENTER-TBI study on the association between admission CT characteristics and cerebrovascular reactivity.[18,26] Only the CT variables found to be statistically associated with impaired cerebrovascular reactivity from this previous study were extracted for this project, allowing us to adjust for known associated intra-cranial injury characteristics. These CT characteristics include: Helsinki CT grade, deep contusion edema volume (consisting of basal ganglia, brainstem and cerebellar locations), extra-axial lesion volume and presence of basal cistern compression.[18] CENTER-TBI data version 2.0 was accessed for the purpose of this study, via Opal database software.[27]

Finally, we collected admission extra-cranial markers of injury burden and potential host systemic injury response. Such admission variables can be seen in Table 1.

*Table 1 here

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/). 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.

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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.[4,5] 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.
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.

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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.

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 extra-cranial injury metrics and host response measures, 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 continuous admission extra-cranial injury burden/host injury response measure using Pearson linear correlation coefficients. For all testing described, the alpha was set at 0.05 for significance, given this is a preliminary and exploratory study.

Univariate logistic regression (ULR) was conducted, comparing each extra-cranial injury/host response 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 for those reaching significance. All AUC's and 95% CI's for ULR were determined using bootstrapping techniques with 2000 iterations. Multi-variable logistic regression (MLR) was conducted for those variables reaching significance during ULR. These multi-variable models adjusted for admission: age, pupillary response, GCS motor score, hypoxia, hypotension, and the CT variables known to be associated with impaired cerebrovascular reactivity (Helsinki CT grade, deep contusion edema volume, extra-axial hematoma volume, and presence of cisternal compression). Finally, we created multi-variable models composed of the physiologic response components of the acute physiology score the APACHE II score,[21] assessing the association with impaired cerebrovascular reactivity. In past studies we have shown that the APACHE II scores were associated with autoregulation dysfunction.[17] However, we were concerned that summed

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APACHE II scores may have been heavily influenced by GCS, and when analysed as such provided no information as to which components of the APACHE II score had maximum impact in this context. Consequently, we examined the relationship of autoregulatory dysfunction to individual components of the APACHE II acute physiology score model: temperature, MAP, heart rate, respiratory rate, PaO_2, pH, serum sodium, serum potassium, creatinine, Hct, Hb and WBC.

Results:

Patient Demographics

A total of 165 patients were included in this study. Table 2 provides a break-down of the main admission demographics, while Appendix B outlines the extra-cranial injury burden/host injury response variables. More detailed information on this population's admission CT characteristics can be found in our previous manuscript evaluating the association between admission intra-cranial injury burden and impaired cerebrovascular reactivity.[18,26]

*Table 2 here

Extra-Cranial Injury Characteristics and PRx Thresholds

Comparing the various extra-cranial injury burden/host injury response variables between patients with mean PRx values above/below thresholds, in general, yielded limited statistically significant associations with impaired cerebrovascular reactivity. Table 3 provides an overview of the statistically significant results for both the entire recording and first 72 hours of recording.

*Table 3 here

% Time and Hourly Dose Above PRx Threshold and Extra-Cranial Features

Both % time and mean hourly dose above PRx thresholds of 0, +0.25, +0.35 were compared with the various extracranial features. There were no statistically significant correlations identified between % time and hourly dose with the selected admission extra-cranial injury/host response variables. This held true for both the entire recording, and the

first 72 hours of recording. Of importance was the lack of correlation between these PRx measures and the admission laboratory values. As well, there was no association found between PRx and ISS. Figure 1 provides a box plot of mean hourly dose of PRx above threshold and ISS (minus brain AIS sub-score – to focus on main extra-cranial ISS), highlighting no statistically significant correlation.

*Figure 1 here

Logistic Regression Analysis

We employed ULR and MLR to assess the association between the extra-cranial injury burden/host injury response variables and impaired cerebrovascular reactivity, with mean PRx values above threshold. The entire recording period analysis only displayed a statistically significant association between arrival lactate levels and having a mean PRx above +0.25 (AUC 0.583, 95% CI: 0.409-0.739; p=0.024). All other variables failed to be associated with PRx above 0, +0.25, or +0.35. Of note, correcting for baseline admission characteristics and intra-cranial CT findings known to be associated with impaired reactivity, admission lactate fell out of significance on MLR.

Evaluating the first 72 hours of recording: arrival respiratory rate was associated with PRx above 0 (AUC 0.623, 95% CI: 0.512-0.736; p=0.023), arrival temperature was associate with PRx above +0.25 (AUC 0.762, 95% CI: 0.634-0.872; p=0.042), and arrival WBC % (AUC 0.674, 95% CI; 0.452-0.862; p=0.013). All other admission extra-cranial variables tested were non-significant. Adjusting for admission baseline characteristics and intra-cranial CT injury patterns known to be associated with impaired cerebrovascular reactivity on MLR, temperature (p=0.022) and WBC % (p=0.013) remained significantly associated with mean PRx above +0.25 and +0.35, respectively.

Finally, evaluating multi-variate models consisting of the elements of the APACHE II acute physiology score, neither the overall model or its component variables achieved significance in association with mean PRx above 0, +0.25 or +0.35 during MLR. This was true for both the entire recording period and first 72 hours of recording data sheets.

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Discussion:

This investigation into the association between extra-cranial injury burden/host injury response markers and impaired cerebrovascular reactivity in TBI has produced grossly negative, but interesting findings. The results demonstrate that in our sample there is no association between extra-cranial injury burden markers and impaired cerebrovascular reactivity. ISS, AIS, need for emergent surgery, blood transfusion and correction of coagulopathy, all failed to demonstrate a statistically significant associations with mean PRx or % time/dose above threshold. This was confirmed in both monitoring periods tested, across all statistical tests performed. This is in keeping with the retrospective single center paper on the topic,[17] where total ISS failed to be associated with impaired reactivity.

Further, extra-cranial host response to injury measures, such as admission vitals and various laboratory values, also failed to demonstrate robust relationships with impaired cerebrovascular reactivity. The only exception was the association between admission core body temperature[28] and mean PRx above +0.25 ($p=0.021$ on MLR), and WBC % and mean PRx above +0.35 ($p=0.013$ on MLR), during the first 72 hours of monitoring. These two admission variables were the only two which maintained significance when adjusting for baseline admission demographics[29] and CT variables[18] associated with impaired cerebrovascular reactivity. Such findings suggest that in general there is limited association between host response to injury in trauma, and the development of impaired reactivity. However, there may be a role, based on the two significant results, for systemic host inflammatory response and impaired cerebrovascular reactivity. This finding is supported from preliminary evidence in the aneurysmal subarachnoid hemorrhage literature between elevated pro-inflammatory cytokine profiles and the development of cerebral vasospasm.[30] It must be noted that the finding of this current study would not remain significant if we had corrected for multiple comparisons. Thus, the strength of this potential association cannot be commented on at this time, and much further investigation into the systemic inflammatory response and deranged cerebrovascular reactivity is required.

We were unable to replicate the relationship of dysautoregulation with APACHE II scores, which we had reported in a previous publication.[17] The reason for this is uncertain – but may be because our sample size was smaller and/or the cohort was older (mean age ~50 vs 40 years). The acute physiological derangement seen in the cohorts may have been similar, but we were unable to undertake a direct comparison as our previous publication only had access to summary APACHE II data from a historical database. Regardless of the discordance between the two studies, it is likely that age and GCS may have driven the association that was previously demonstrated.

Thus, overall, the results point towards either a central nervous system host response to intra-cranial injury, or individual genetic differences, as the primary driver(s) of impaired cerebrovascular reactivity in adult moderate/severe TBI. The reality is that impaired cerebrovascular physiology in TBI is likely driven by a complex interaction between both the host response to intra-cranial injury, and its modulation through genetic variation. This is an important preliminary finding, as it carries implications for future investigations into molecular pathways involved in impaired autoregulation, and the development of therapeutic targets for prevention and treatment. Such findings imply the need for studies examining biomarkers that are sampled in close relation to the brain (ie. jugular blood, cerebrospinal fluid, or microdialysate). Furthermore, if the main drivers are within the central nervous system, blood-brain barrier integrity will need to be considered heavily in the development of therapeutics in order to facilitate timely and accurate delivery.

Limitations

Despite the interesting results, there are some important limitations to this study which need to be highlighted. First, the overall sample size was low at 165 patients. Considering the previous retrospective study looking at extra-cranial injury status and cerebrovascular reactivity only had 358 patients,[17] the results pertaining to extra-cranial injury burden and host response factors need to be interpreted with a degree of caution. There exists much need for larger high-resolution data sets to definitively evaluate these relationships.

Second, given this was a preliminary investigation we elected not to correct for multiple comparisons. As such, the small number of significant results found, would not remain

significant if we were to perform such statistical corrections. Consequently, the suggestion of a potential relationship between systemic host inflammatory response and cerebrovascular reactivity should be interpreted as only a theory at this point, requiring extensive future investigation. Such would involve serial serum cytokine profiles in conjunction with continuous high-frequency physiologic monitoring.

Third, in this investigation we were only interested in evaluating the admission extra-cranial features in association with impaired cerebrovascular reactivity. It is possible that such daily laboratory values may display some association with daily vascular reactivity metrics. Such associations would be difficult to assess given the granularity of daily lab sampling, and the myriad of other systemic issues ongoing during complex polytrauma care. Furthermore, many of these systemic laboratory markers may be influenced by intra-cranial trauma and ongoing secondary injury. Thus, even though we assumed that the lab values measured in the serum were primarily related to extra-cranial/systemic injury, they very well could have been influenced by intra-cranial pathology. This highlights the need for simultaneous intra-cranial and extra-cranial lab samples, which would potentially facilitate the quantification of the pure intra-cranial contribution. Such future work would require multi-center data sets with high-resolution physiology, linked with both peripheral and central (ie. jugular) serum sampling, and potentially cerebrospinal fluid/cerebral microdialysis sampling. As such, interpretation of the link between these measures and cerebrovascular reactivity in this study, should be interpreted as very preliminary/exploratory and evaluated with caution at this time.

Finally, all patients were undergoing active treatment for ICP and CPP during their ICU stay. As such, the recorded physiology does not represent the 'natural history' of untreated cerebral physiology in TBI, but reflects various treatment responses. These ongoing therapies may have impacted the associations/lack of associations found in this largely negative study. This also highlights that CENTER-TBI was a prospective observational study, with the HR ICU sub-study consisting of a small niche population from the larger study group. As such, there were small patient numbers and the patients underwent active treatment in keeping with TBI guidelines. There were no specific study interventions given, as this was purely a prospective observational data gathering study.

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Therefore, cerebrovascular reactivity was not targeted in any specific way throughout the study, but merely derived from the prospectively collected physiology data.

Conclusions:

Admission markers of extra-cranial injury burden and systemic host response to injury do not appear to be strongly associated with impaired cerebrovascular reactivity in adult moderate/severe TBI, during both the initial and entire ICU stay. There was a weak association between admission core body temperature and WBC, with mean PRx above +0.25 and +0.35, respectively. This may point to some potential role for host systemic inflammatory response as a driver of impaired cerebrovascular reactivity. Further research in this area is required.

Disclosures:

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Figure Legends:

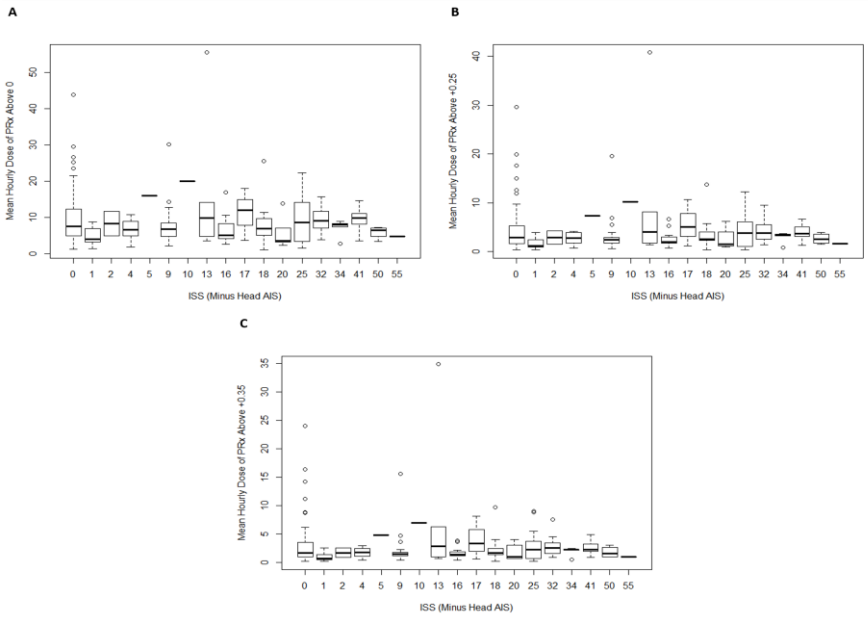

Figure 1: Mean Hourly Dose Above PRx Threshold and ISS – First 72 Hours of Recording

ICP = intra-cranial pressure, ISS = injury severity score, MAP = mean arterial pressure, PRx = pressure reactivity index (correlation between slow-waves of ICP and MAP). Panel A – Mean Hourly Dose of PRx above 0 and ISS, Panel B – Mean Hourly Dose Above PRx of =0.25 and ISS, Panel C – Mean Hourly Dose Above PRx of +0.35 and ISS. *Note: data from first 72 hours of ICU stay. Also, ISS is the ISS score minus the brain contribution, focusing only on the main extra-cranial contributions.

Table 1: Admission Extra-Cranial Injury Burden and Host Response Variables

Admission ISS and AIS Scores		
Total ISS	AIS – Head and Neck	AIS – Face
AIS – Brain	AIS – Cervical Spine	AIS – Chest
AIS – Thoracic Spine	AIS – Abdomen	AIS – Lumbar Spine
AIS – Pelvis	AIS – Upper Extremities	AIS – Lower Extremities
AIS – External		
Admission ED Vital Signs		
ED Heart Rate	ED SBP	ED DBP
ED RR	ED Temperature	
Admission Non-Cranial Emergency Interventions		
Need for Emergent Non-Cranial Surgery	Need for Emergent Blood Transfusion	Need for Emergent Correction of Coagulopathy
Admission ABG Results		
Arterial Lactate	Arterial pH	Arterial pO_2
Admission Laboratory Results		
Serum Sodium	Serum Potassium	Serum Creatinine
WBC %	Neut %	Lymph %
Eosin %	Hematocrit	Hemoglobin
INR	aPTT	CRP

ABG = arterial blood gas, AIS = abbreviated injury score, aPTT = activated partial thromboplastin time, CRP = C reactive protein, DBP = diastolic blood pressure, ED = emergency department, Eosin % = eosinophil percentage, INR = international normalized

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ratio, ISS = injury severity score, Lymph % = lymphocyte percentage, Neut % = neutrophil percentage, WBC % = white blood cell percentage.

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Table 2: Admission Patient Demographics – Median, IQR and Raw Numbers

		Median (IQR) or Raw Number
Core Demographics		
Number of Patients		165
Age (years)		49 (29-64)
Sex	***Male***	129
	Female	36
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
Admission CT Characteristics Associated with Impaired Cerebrovascular Reactivity		
Helsinki CT Score		4 (2 – 7)
Number with Cisternal Compression		66
Total EA Hematoma Volume (cm^3)		0 (0 - 0.05)
Total Deep Contusion Edema Volume (cm^3)		0.03 (0 – 1.3)

*cm^3 = cubic centimetres, CT = computed tomography, EA = extra-axial, GCS = Glasgow Coma Score, GOSE = Glasgow Outcome Score, IQR = inter-quartile range, IQR = intra-quartile range.. *Note: Deep – refers to basal ganglia, brainstem, and cerebellum.*

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Table 3: Statistically Significant Mann-U Testing Results

PRx Threshold and Extra-Cranial Variable		**Above PRx Threshold**	**Below PRx Threshold**	**p-value**
First 72 Hours of Recording				
PRx 0	*ED RR*	17.1 +/- 4.3	15.3 +/- 3.3	0.032
PRx +0.25	*ED Temperature*	34.8 +/- 1.3	35.9 +/- 1.7	0.0006
PRx +0.35	*ED Temperature*	34.7 +/- 1.5	35.9 +/- 1.7	0.026
	INR	1.4 +/- 0.6	1.2 +/- 0.5	0.027
	aPTT	33.3 +/- 6.9	28.0 +/- 5.5	0.007
	Lactate	8.4 +/- 12.8	4.6 +/- 8.2	0.038
Entire Recording Period				
PRx +0.25	*Neut %*	81.0 +/- 15.5	77.4 +/- 12.7	0.028

aPTT = activated partial thromboplastin time, ED = emergency department, ICP = intra-cranial pressure, INR = international normalized ratio, MAP = mean arterial pressure, Neut % = neutrophil percentage, PRx = pressure reactivity index (correlation between slow-wave of ICP and MAP), RR = respiratory rate

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Appendix A – Semi-Automated CT Segmentation Methods for Admission CT Scans

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.[1]

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..[2] 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. 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).[3] 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.

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Appendix B: Admission Extra-Cranial Injury Burden and Host Response Variables – Number, Median/IQR

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Extra-Cranial Injury Burden/Host Response Variables	
Admission ISS and AIS Scores	
Total ISS	34 (25 – 48)
AIS – Head and Neck	5 (3 – 5)
AIS – Face	3 (2 – 4)
AIS – Brain	5 (5 – 5)
AIS – Cervical Spine	0 (0 – 3)
AIS – Chest	4 (3 – 4)
AIS – Thoracic Spine	0 (0 – 3)
AIS – Abdomen	1 (0 – 3)
AIS – Lumbar Spine	0 (0 – 3)
AIS – Pelvis	0 (0 – 3)
AIS – Upper Extremities	1 (0 – 3)
AIS – Lower Extremities	1 (0 – 3)
AIS – External	1 (0 – 2)
Admission ED Vital Signs	
ED Heart Rate	85 (70 – 100)
ED SBP	140.0 (117.5 – 158.5)
ED DBP	80.0 (65.5 – 93.0)
ED RR	16 (14 – 18)13.1
ED Temperature	36.0 (35.1 – 36.7)
Admission Non-Cranial Emergency Interventions	
Number Needing Emergent Non-Cranial Surgery	17
Number Needing Emergent Blood Transfusion	20

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Number Needing Emergent Correction of Coagulopathy	41
Admission ABG Results	
Lactate (mmol/L)	2.3 (1.5 – 4.1)
pH	7.35 (7.31 – 7.40)
pO_2 (mmHg)	168.5 (125.8 – 295.1)
Admission Laboratory Results	
Sodium (mmol/L)	140.0 (138.0 – 142.0)
Potassium (mmol/L)	3.8 (3.5 – 4.2)
Creatinine (mmol/L)	73.0 (59.0 – 84.2)
WBC %	13.1 (9.6 – 16.8)
Neut %	82.1 (74.4 – 87.2)
Lymph %	9.4 (5.9 – 15.3)
Eosin %	0.18 (0.02 – 0.70)
Hematocrit	38.1 (34.0 – 41.5)
Hemoglobin (g/dL)	13.1 (11.6 – 14.3)
INR	1.1 (1.0 – 1.2)
aPTT (sec)	27.6 (24.9 – 30.6)
CRP (mg/L)	4.0 (1.0 – 10.5)

ABG = arterial blood gas, AIS = abbreviated injury score, aPTT = activated partial thromboplastin time, CRP = C reactive protein, DBP = diastolic blood pressure, ED = emergency department, Eosin % = eosinophil percentage, g/dL = grams per deciliter, INR = international normalized ratio, ISS = injury severity score, Lymph % = lymphocyte percentage, mg/L = milligram per liter, mmHg = millimeters of Mercury, mmol/L – milimole per liter, Neut % = neutrophil percentage, WBC % = white blood cell percentage.