Investigating cerebrovascular pressure reactivity in a large cohort of children with severe traumatic brain injury

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SMTCLA014

Submitted to the University of Cape Town

In fulfilment of the requirements for the degree

MSc (Med) in Neuroscience

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UNIVERSITY OF CAPE TOWN

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Declaration

I, Claudia Ann Smith, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Date: 15 March 2021

Acknowledgements

First and foremost, I would like to thank my supervisors, Professor Anthony Figaji and Dr Ursula Rohlwink. You have both dedicated so much time, effort, and expertise not only to this project, but to my education over the last couple of years. I have learnt so much from both of you, and you have helped me realise the kind of researcher I want to be. It is a privilege to be your student. Thank you.

To my family, ever supportive and understanding – thank you for celebrating with me on the good days and holding my hand on the bad. My parents, Simon and Lorrayne – I am eternally grateful for your investment in my happiness and dreams. To my brother and best friend, Ross, thank you for your constant encouragement and reassurance – you are my biggest supporter and finest colleague.

A special thanks to Gabby for your endless support and our laughs together. Thanks also to Dr Erta Beqiri for your help with some of the data handling.

TJ and Jo, our friendship got me through a pandemic. Thank you for everything.

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ABSTRACT

Introduction: Traumatic brain injury (TBI) contributes to worldwide death and disability more than any other traumatic event, but it is of particular concern in children in developing resource-scarce countries. Cerebral autoregulation (CA) is a homeostatic mechanism that aims to maintain constant cerebral blood flow within a range of systemic blood pressures, and the loss of this mechanism has been associated with mortality and worse outcomes in adult TBI. Paediatric studies of CA disturbance are few and consist of small cohorts. Given the differences between adult and paediatric TBI pathophysiology, CA needs examination in a larger cohort of paediatric TBI.

This study aimed to describe the profile of PRx, a mathematical indicator of cerebrovascular pressure reactivity, in a large cohort of children with severe TBI. The specific aims were to 1) describe the characteristics of PRx; 2) examine associations between PRx, clinical and physiological variables, and 3) examine associations between PRx and mortality at 6 months, and PRx and dichotomized outcome (as well as survivors only) at $\geq$ 6 months post-injury.

Methods: Patient demographics, clinical and monitoring data were recorded, and the temporal profile of median PRx was plotted by outcome groups. The associations between PRx, Glasgow Coma Score (GCS), intracranial pressure (ICP), and cerebral perfusion pressure (CPP) were examined with both summary measures and correlation analysis using high frequency data. Associations between PRx and mortality/outcome were examined with multiple regression analysis, and the prognostic ability of PRx, ICP and CPP was investigated with receiver operating curve analysis.

Results: We examined 196 children with severe TBI. Mortality rate was 10.7%, and 70.4% of the cohort had unfavourable outcome. PRx was consistently higher in patients with poor outcome when examined by various summary statistics and over time. Hourly analysis showed that PRx had a moderate positive correlation with ICP ($r = 0.35$; $p < 0.001$) and a weak negative correlation with MAP ($r = -0.10$; $p < 0.001$) and CPP ($r = -0.27$; $p < 0.001$). PRx had a strong and independent association with mortality.

Conclusion: This study calculated, described, and analysed PRx in the largest known cohort of children with severe TBI. PRx had a strong association with outcome (particularly mortality) that was independent of ICP, CPP and GCS. However, a combination of several PRx and ICP-related variables will likely be important for overall prognostication in paediatric severe TBI. Whether CA should be incorporated into clinical care, and if so, how, requires separate investigation.

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ABBREVIATIONS

AUC	Area under the curve
CA	Cerebral autoregulation
CBF	Cerebral blood flow
CBV	Cerebral blood volume
CI	Confidence interval
CPP	Cerebral perfusion pressure
CT	Computed tomography
DC	Decompressive craniectomy
GCS	Glasgow Coma Score
GOS	Glasgow Outcome Scale
GOS-E	Glasgow Outcome Scale Extended version
GSW	Gunshot wound to head
ICP	Intracranial pressure
LLA	Lower limit of autoregulation
MAP	Mean arterial pressure
MVA	Motor vehicle accident
NAI	Non-accidental injury
PbtO2	Brain tissue oxygen tension
PRx	Pressure reactivity index
PVA	Pedestrian in a motor vehicle accident
ROC	Receiver operating curve
TBI	Traumatic brain injury
TCD	Transcranial Doppler
ULA	Upper limit of autoregulation

Chapter 1: Introduction

Traumatic brain injury (TBI) remains a large global health problem, as it contributes to worldwide death and disability more than any other traumatic event. Head injury is a particular cause for concern in children as it causes more premature deaths and long-term disability than any other brain condition. TBI is often dubbed the 'silent epidemic'[1], especially in developing countries where resources are limited, the disease burden high, and there is an overshadowing of infectious diseases.

There are several unknowns in TBI treatment and a key aim in treatment protocols is preventing secondary injury. Cerebral ischaemia and hypoxic neuronal death are the result of secondary injuries that are common in TBI. There are many pathophysiological pathways that lead to secondary brain injury; one such pathway may be the loss of cerebral autoregulation (CA).

CA is the brain's physiological mechanism used to maintain cerebral blood flow (CBF) despite variations in systemic blood pressure[2,3]. The loss of CA in severe TBI is associated with worse functional outcomes in both adults and children[4,5,6,7]. Cerebrovascular pressure reactivity (hereafter referred to as pressure reactivity) is a distinct component of CA, and PRx (a pressure reactivity index) is a mathematical calculation that is used as an indication of the status of CA. However, the vast majority of existing literature is based on adult patients; very little is known about PRx in children. Its utility as a functional tool in the management of children with TBI is yet to be definitively established.

This review discusses the treatment challenges in paediatric TBI and why extrapolation of adult research to children is inadequate. It focuses on CA literature relevant to this study and discusses its complexities in TBI and the need for basic exploration of PRx in children.

Chapter 2: Paediatric Traumatic Brain Injury

TBI is a major cause of morbidity and mortality in children[8]. The primary goal of neurocritical care in TBI is to improve outcome by avoiding secondary brain injury. However, despite ‘optimal’ management by current standards, secondary insults are still common[9], and evidence is particularly sparse for paediatric TBI. Therefore, a better understanding of paediatric TBI pathophysiology is needed to improve treatment protocols.

Children are different to adults: challenges in treating paediatric TBI

Standard treatment protocols are developed from clinical experience and scientific evidence. One of the biggest challenges in developing these protocols is identifying mechanisms and cascades involved in the development of secondary injuries post-TBI. Possible treatment protocols are then aimed at avoiding or ameliorating secondary injury, and thereby improving treatment strategies and patient outcome. Managing injured children is particularly difficult, in part because protocols are largely extrapolated from adult TBI research. This practice can be inadequate, and at worst, dangerous.

Relevant to TBI, children and adults have important anatomical, physiological, and pathophysiological differences. What is considered normal physiological values of blood pressure, intracranial pressure (ICP) and CBF differ between children and adults, and certain treatment strategies used in TBI have varying effects in the two populations. For example, decompressive craniectomy (DC) and therapeutic hypothermia may have better outcomes in children compared to adults[10,11]. The plasticity of the child’s nervous system may improve recovery; however increased developmental immaturity in children may make them more vulnerable to *secondary* injuries following severe TBI compared to adults. Additionally, the mechanisms underpinning these secondary injuries may be different in children compared to adults. One such mechanism could be the loss of CA following a head injury.

Many components of cerebral haemodynamics are known to be different in children. CBF rates are a function of age, and so differences exist not only between children and adults but across the age range in children. Exact values of CBF are measurement-specific, but generally CBF starts low in new-borns and increases until the CBF peak at age 7 to 10 years, and then decreases steadily until reaching adult values[12]. The developing brain has a higher metabolic rate, and so children have a higher CBF and proportionally greater cardiac flow to the brain compared to adults. The vascular response to interventions or stimuli is greater in children: when stimulated, children experience a greater absolute CBF increase compared to adults, and this seems to be age dependent[13]. Clinically, this hemodynamic difference may manifest in “brittle” ICP changes – i.e. ICP rapidly increasing and decreasing in response to interventions or stimulation[14]. The differences in cerebral haemodynamics may be important when considering CA testing.

Chapter 3: Cerebral Autoregulation

1. Secondary Injuries: the role of ischaemia

Primary brain injury is irreversible damage to the cerebral brain tissue as a result of the immediate forces of the injury itself, and thus can only be combated with prevention. Therefore, treatments are directed at avoiding or ameliorating secondary injury.

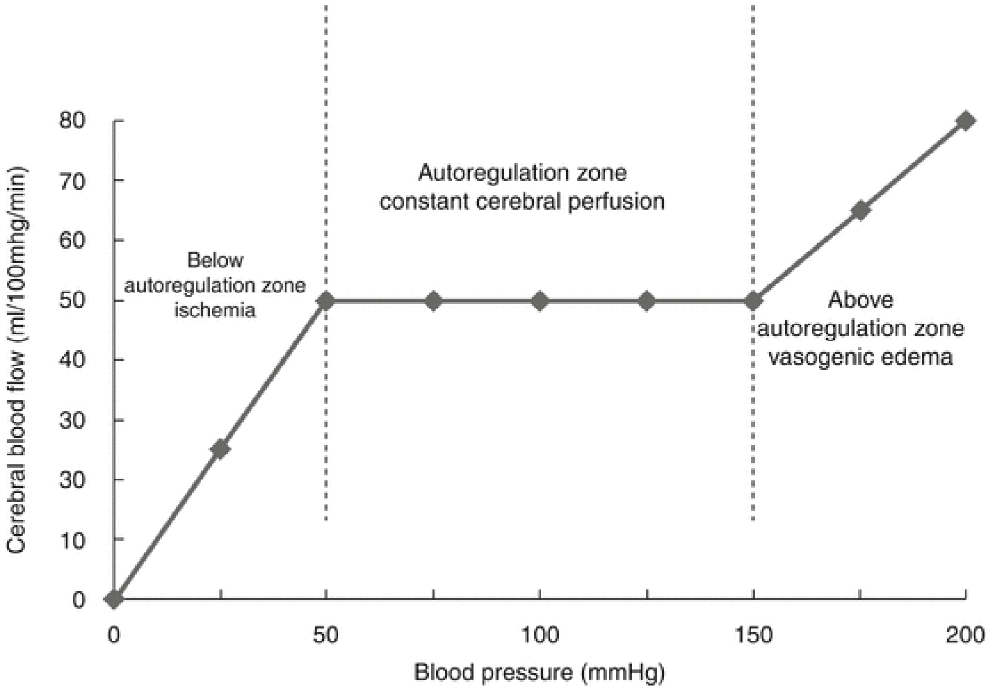
Secondary injury can occur through multiple mechanisms, several of which end in cerebral ischaemia. Cerebral ischaemia is characterised by inadequate blood supply to the brain, which results in oxygen deprivation and interruption of normal cell metabolism. The duration and depth of oxygen deprivation determines the extent of hypoxic tissue injury. Cerebral ischaemia is common and often fatal in TBI, with post-mortem studies showing that 90% of patients who die from TBI have evidence of ischaemic tissue damage[15].

CBF is reduced in the acute stages after head injury in both adults[16] and children[17,18]. In healthy individuals, CBF is tightly coupled with cerebral metabolism, with normal CBF ranging between 45 and 60ml/100g/min (average for grey and white matter). A reduction in CBF below the ischaemic threshold of 18ml/100g/min is associated with corresponding disruptions in cerebral metabolism, including the metabolic shift to anaerobic glycolysis, the inhibition of cellular protein synthesis, the decline in glucose metabolism and the loss of homeostatic cellular ion concentrations[19]. The relationship between CBF and cerebral metabolism following head injury is much more complex. The injured tissue may have decreased metabolic needs, and therefore decreased CBF may be appropriate. On the other hand, CBF may be uncoupled from metabolism, and seemingly normal CBF levels may be inadequate to meet the increased metabolic demand in the TBI patient. This complex relationship, as well as other factors such as mitochondrial dysfunction and adjusted cerebral metabolic needs, complicates the interpretation of CBF in TBI treatment.

2. Definition and importance of cerebral autoregulation:

CA is the brain's homeostatic mechanism of maintaining a relatively constant CBF within a range of blood pressure[2, 20, 21], allowing substrate delivery balanced with the metabolic needs of the brain. As figure 1 shows, CA functions in a range of blood pressures, but if the blood pressure drops below the lower limit of autoregulation (LLA), CBF decreases and the brain will be at risk of cerebral ischaemia. If blood pressure rises above the upper limit of cerebral autoregulation (ULA), CBF rises passively and the brain may be at risk of capillary damage, diffuse haemorrhage, cerebral oedema, and intracranial hypertension[20]. This autoregulatory function is a fundamental protective mechanism of the brain.

Figure 1: Schematic of the autoregulation curve



The dotted lines represent the lower and upper limits of autoregulation. Blood pressures outside of the autoregulation zone cause passive changes in CBF and puts the patient at risk for secondary injury[22].

Pressure reactivity is a distinct component of CA and refers to the ability of smooth vascular cells to react to changes in transmural pressure[23, 24]. A pressure reactivity index has been described which quantifies the relationship between the arterial blood pressure and ICP[2, 25], and is widely used as a measure of pressure reactivity, and as an indication of the CA status in the patient[2,3,26]. It should be noted that pressure reactivity and CA cannot be used interchangeably, as vasodilation only functions within the lower thresholds for constant CBF[27].

3. Impaired CA in TBI and why this is important for treatment protocols:

When pressure reactivity is intact, a rise in mean arterial pressure (MAP) will lead to cerebral vasoconstriction and a reduction of cerebral blood volume (CBV), which may decrease ICP. If CA is impaired, increasing blood pressure increases CBV, and ICP may increase[27]. In severe TBI, CA is often impaired; therefore CBF cannot be regulated. This may lead to hypoperfusion (and therefore hypoxia), or hyperaemia[25] as part of the secondary injury cascade[28, 29]. It has been shown that impaired CA in TBI is associated with unfavourable patient outcome in adults[25, 30]. The extent to which this association reflects the relationship between CA and injury severity, or an adverse effect of impaired CA on outcome, is not clear.

Current protocols focus on therapies for ICP and cerebral perfusion pressure (CPP; the mathematical difference between mean arterial pressure [MAP] and ICP)[25], but seldom take into account how CA may influence treatment. Incorporating the CA status of the patient into treatment protocols may be beneficial to clinicians, as it may provide insights into how specific physiological parameters are interacting in the patient. CA disturbance is associated with mortality and worse patient outcomes in adults, and so understanding when a patient is at risk of ischaemia allows clinicians to intervene and potentially prevent hypoxic tissue damage.

Specifically, CA status is an important factor impacting the management of CPP. As previously discussed, depending on whether pressure reactivity is intact or not, the relationship between MAP and ICP is completely different, and an induced change in blood pressure can have very different effects. Knowing the CA status of the patient may help to direct CPP/ blood pressure protocols, as it is clear that a one-size-fits-all approach to CPP thresholds is inappropriate.

4. Autoregulation testing is difficult:

CA is not commonly assessed in most centres and testing does not form part of current recommendations, presumably in part because of the difficulty in testing. The assessment of CA status requires MAP and a measure of CBV, or a proxy thereof. Currently, there are static and dynamic measurements of CA. Static readings can be calculated using the administration of drugs that alter MAP without changing metabolism and can be used to generate the classic autoregulation curve as seen in Figure 1. However, these require provocative tests such as raising or lowering the blood pressure. These tests are invasive, time consuming, and technique dependent. Dynamic measurements may be more clinically useful as they take time into consideration, and this allows for continuous patient monitoring. One dynamic measurement of pressure reactivity is PRx, the pressure reactivity index. PRx is a form of continuous assessment that correlates well with CA status. It is generally accepted that a negative correlation between MAP and ICP can be interpreted as good vasoreactivity, whereas a positive correlation between these variables represents impaired vasoreactivity[27, 31]. PRx is calculated as a moving linear correlation coefficient and expresses the relationship between spontaneous slow (20secs to 2mins) waves of MAP and ICP. It has a range of values between -1 and 1: PRx ≤ 0 suggests *intact* pressure reactivity, whereas PRx > 0.25 suggests *impaired* pressure reactivity, with PRx between 0 and 0.25 indicating a “grey area” [32]. PRx has been shown to correlate well with pressure reactivity[33] and therefore may guide the treatment of patients and help clinicians target and conserve CA in severe TBI.

PRx requires ICP monitoring and the use of specialist software to calculate it. Not all centres use invasive ICP monitoring for all TBI patients. Clinicians often rely on ICP measurements as a surrogate marker of CBV and CBF, however this relationship is not well established, and CBF changes may occur without ICP alteration[34]. Also, the software required is not widely available.

If an accurate measurement of ICP is not available, one may attempt to investigate cerebrovascular function, however, there is no reliable and accurate standard measurement for CBF at the bedside. Possible ways of determining measures of CBF include proxy indicator methods, as well as Transcranial Doppler (TCD) flow ultrasonography which measures the velocity of blood flow. Jugular bulb oximetry can also be used to provide an indirect measurement of cerebral perfusion. These are helpful but they may be problematic as they can have high levels of error with poor sensitivity and specificity[35].

5. Utility of PRx in TBI:

Previous adult studies have shown a significant correlation between PRx and patient outcome after TBI[25, 27, 33], with some showing a time-dependent element: for example, if PRx was > 0.2 for more than 6 hours, this was usually associated with death[36]. A 2017 study by Adams *et al.* examined temporal profiles of PRx and ICP after severe TBI in adult patients and found that both variables have particularly valuable prognostic value, especially in the first 3 days after injury, and may advise an early treatment window. This group suggests that modelling outcomes based on temporal patterns may help improve the accuracy and usefulness of clinical models, however there is little to no data on how PRx changes over time in children with TBI[37].

Despite developments made in understanding adult TBI dynamic cerebral autoregulation monitoring, mortality and outcome have remained relatively unchanged in the last two decades[38]. This may be because outcomes will not improve by simply monitoring disturbed CA, an intervention must be applied to see an improvement. The Cambridge group has done extensive adult research on optimal CPP values (CPPopt), which is calculated as the CPP when PRx is at its lowest. Phase II clinical trials of COGiTATE (CPPopt Guided Therapy: Assessment of Target Effectiveness) are currently ongoing[39]. This theoretical idea is promising as it allows for an individualised CPP treatment target; however it must be carefully considered when applied to the clinical setting as many factors contribute to outcome, and applying interventions that aim for CPP values higher than currently recommended may result in unnecessary detrimental effects on the patient[40].

PRx is useful because, unlike TCD based measurements, it is a graded and continuous measurement and can therefore show evolving intracranial dynamics over time. The signal is inherently noisy as the PRx calculation may be disproportionately influenced by outliers of ICP and MAP, but this effect can be decreased with time-averaging. A potential factor that must be considered is that PRx uses ICP as a proxy of CBV, and that it assumes a causal relationship between MAP, CBV, and ICP. These assumptions may not always be valid. While PRx may be affected by some confounding variables (such as cerebral metabolism and certain medications/clinical interventions[41]), PRx provides a continuous, long-term, and robust prognostic measurement of pressure reactivity in adult TBI[21]. In the clinical setting, PRx is useful as a prognostic marker in TBI. Possibly, it may also help identify patients at risk of developing ischaemia and help guide CPP management.

While adult TBI studies are advancing into using PRx to guide treatment, paediatric TBI research is lacking in basic PRx studies.

6. PRx has not been adequately examined in paediatrics with TBI:

PRx and pressure reactivity status has not been as extensively studied in children with severe TBI. Existing studies have small cohort sizes. Table 1 summarises the known literature of PRx and its association with outcome in children with severe TBI.

Brady *et al.* showed that the loss of pressure reactivity is associated with death[6]. This association between PRx and mortality was also found in the study by Young *et al.*[42]. Despite both studies having the limitation of a small sample cohort, the groups performed a broad descriptive analysis of the cohort and examined PRx in relation to CPP. Brady *et al.* authors suggested that PRx is CPP-dependent in children, because PRx monitoring at lower levels of CPP showed impaired pressure reactivity and intact pressure reactivity at higher CPP levels[6].

Hockel *et al.* had a small cohort of 15 patients for dichotomized outcome analysis. For three of these patients, discharge Glasgow Outcome Scale (GOS) was used as they were lost for follow up examination. The group found no significant difference between overall ICP, CPP, and PRx between outcome groups. The group reported that time spent with a PRx > 0.2 was significantly higher in patients that had an unfavourable outcome compared to the favourable group (64 hours versus 6 hours; p = 0.001), however the results were not significant when time above 0.2 was normalised for individual monitoring time: the unfavourable group spent 20.5 ± 2.3% with a PRx above 0.2 compared to that of the favourable group (7.7 ± 1.7%; p = 0.06). Therefore, the absolute time p value of 0.001 may not indicate a robust difference between time spent above a PRx of 0.2 between outcome groups. In addition, because the cohort includes children with a large age range, the authors separated the cohort into equal groups, with 5 patients in each group: group 1: < 1 year, group 2: 1 – 4 years old, and group 3: > 4 years. However, outcome was more favourable with increasing age in this cohort, with median GOS scores of 3, 4, and 5 respectively. CPP was age-dependent, with all age groups showing negative PRx values with higher CPPs[43].

Lewis *et al.* also found that PRx associates with dichotomized outcome, with PRx being higher in patients with unfavourable outcome (0.23 versus -0.09; p = 0.009). Non-survivors had a higher PRx than survivors (0.81 vs -0.09) but this was not statistically tested because of the small sample size. The PRx outcome threshold of 0 was found using Chi-square testing between favourable and unfavourable groups, suggesting that a PRx of more than 0 increases the risk of unfavourable outcome in children with TBI. This study also found that patients who spent more time above the suggested thresholds of 0 and 0.25 had worse outcome (PRx threshold of 0, p = 0.008; PRx threshold of 0.25, p = 0.01)[3]. While PRx threshold values are useful to guide clinical practice, specific PRx threshold cut-off values must be used with understanding, as rigid thresholds do not always indicate a CPP below the LLA[21].

All of these studies have a cohort of 40 children or less for analysis and therefore statistical power is limited, and results may be biased by single patient cases and effects of treatment.

Few studies have attempted to find an association between patient admission variables (admission Glasgow Coma Score [GCS], injury severity score, initial blood glucose level, and radiological imaging findings) and outcome in paediatric severe TBI patients. Lewis *et al*. found a significant association between mean GCS and outcome (p = 0.049), as well as between patients that had computed tomography (CT) findings of subarachnoid haemorrhage (p = 0.005), oedema (p = 0.01), and diffuse axonal injury (p = 0.01) with an unfavourable outcome. In addition, patient's mean ICP and CPP levels were significantly associated with outcome (p = 0.023 and 0.013 respectively)[3]. The correlation between GCS, ICP, CPP and outcome is not supported by results from the small studies done by Hockel *et al* [43] and Nagel *et al* [44]. There is little data associating these clinical and radiological variables with PRx in children, as these studies associate the variables (including PRx) with outcome. Therefore, it is not always clear whether PRx, or any other measure of autoregulation, reflects an association with a more injured brain or if it is an independent contributor to adverse outcomes. This is important because the latter would imply the potential to adapt treatment based on PRx to improve outcome.

The studies also attempted to explore patient-specific optimal CPP targets in children. While this has been extensively studied in adults and may be useful in children with TBI, primary descriptions and analysis of PRx needs to be studied in children first. Before CPP-orientated targets can be considered, the association between PRx and outcome in children with severe TBI needs to be explored in a large cohort. This is the first and essential step in addressing impaired autoregulation in children because we cannot simply presume that what has been found in adults is true for children.

Table 1: The known literature of PRx and its association with outcome in children with severe TBI

Study group	**Cohort characteristics**	**Outcome assessment used:**	**Main results:**
Brady *et al.*, 2009[6]	n = 21 (< 18 years old)	Survival	PRx is associated with mortality: p = 0.0009 - Mean PRx for survivors = 0.08 ± 0.19 - Mean PRx for non-survivors = 0.69 ± 0.21
Hockel *et al.*, 2017[43]	n = 15 (1 day – 14 years old)	Dichotomized outcome at discharge	Absolute time PRx > 0.2 associated with outcome: p = 0.001 - Unfavourable patients spent longer with PRx > 0.2 compared to the favourable group (64hrs versus 6hrs)
Lewis *et al.*, 2015[3]	n = 36 (6 months – 16 years old) total; 30 for outcome analysis	Dichotomized outcome at 6 months post-injury	PRx is associated with outcome: p = 0.009 - Median PRx for patients with favourable outcome = -0.09 (range of -0.25 to -0.02) - Median PRx for patients with unfavourable outcome = 0.23 (range of 0.04 to 0.74) Patients that spent more time above PRx thresholds of 0 and 0.25 had worse outcome
Nagel *et al.*, 2016[44]	n = 10 (1 day – 14 years) total; 7 for outcome analysis	Dichotomized outcome at 6 months post-injury	PRx is associated with outcome: p = 0.006 - Median PRx is correlated with outcome (r = -0.79)
Young *et al.*, 2016[42]	n = 12 (3 months – 13 years old)	Mortality at 6 months post-injury	PRx is associated with mortality: p = 0.02 - Median PRx for survivors = 0.02 ± 0.19 - Median PRx for non-survivors = 0.39 ± 0.62

A summary of the main paediatric study results of PRx and outcome. PRx = pressure reactivity indicator; hrs = hours

7. Gaps in the literature:

The prognostic value of PRx in adult TBI has been widely accepted, however, there is a paucity of PRx studies that relate this mathematical indicator to outcome in children with severe TBI. Because of the considerable physiological differences between adults and children, adult data may not be generalizable to children. A large cohort of children undergoing PRx assessment is needed. Investigations into PRx will help to define this indicator measurement in the context of this specific population – do impaired PRx values simply represent a more injured brain, or is it a reflection of an ongoing secondary injury process? If so, is this specific indicator associated with mortality and/or outcome in children with TBI? Is this association independent of other important predictors such as ICP? And importantly, does PRx tell the clinician something new about intracranial dynamics that they don't already know from current ICP, CPP and PbtO2 monitoring?

An analysis of PRx in a large cohort of paediatric TBI patients will begin to address these questions. The goal is that this will provide a reasonable basis for future work that aims to address pressure reactivity disturbance and improve outcome in this vulnerable population.

Chapter 4: Aim and Objectives

This study aimed to describe the profile of PRx in a large cohort of children with severe TBI, and to examine its association with key intracranial variables and outcome.

The objectives were:

1. To describe the characteristics of PRx in children with severe TBI

This analysis provides an overall description of PRx and other relevant monitored variables for this cohort of patients. Patient results are reported as an entire cohort, as well as by mortality and outcome groups. The differences in temporal profiles by mortality/ outcome groups are explored.

2. To examine associations between PRx, clinical and physiological variables

Correlations between GCS, ICP, MAP, CPP and PRx were examined to investigate the relationship between PRx and markers of injury severity, and perturbation in intracranial dynamics.

3. To examine associations between PRx and mortality at 6 months, and PRx and dichotomized outcome (as well as survivors only) at ≥ 6 months post-injury

Regression analysis was used to investigate the relationship between PRx and measures of patient outcome, including relevant covariates. The diagnostic ability of PRx and other physiological variables is further explored with Receiver Operating Curve (ROC) analysis.

Chapter 5: Methods

1. Patient Selection

Red Cross War Memorial Children's Hospital has an ongoing record of paediatric TBI data started in 2006. Children who underwent monitoring for severe TBI (post-resuscitation Glasgow Coma Score [GCS] of ≤ 8) are included in the database. At this hospital, children are generally considered as individuals under the age of 13 years, but the institution has treated specific cases where patients have been 14 years old, and these cases are included in the study where other criteria are met.

Patients were included in this study if continuous recordings of ICP and MAP were available, and if there was at least 24 cumulative hours within the acute period (first 3 days) of monitoring for which PRx could be calculated.

2. Clinical Management

Patients were managed in keeping with management guidelines for children with TBI [45, 46], but adapted into a local protocol. Broadly, initial thresholds for treatment were as follows: ICP ≥ 20mmHg; CPP ≥ 50mmHg (or 40-45mmHg in children aged 2 or younger); and PbtO2 ≤ 20mmHg (10mmHg hard threshold). Thresholds are then titrated based on clinical observation and interaction between variables.

3. Data Recording and Collection

All data were recorded as part of clinical management. ICP was monitored using an intraparenchymal catheter (CODMAN® ICP EXPRESS® Monitor, Integra Life Sciences, USA) inserted as soon as possible after patient admission and continued until the ICP was considered stable for ≥ 24 – 48 hours, or until the patient died. CPP was mathematically calculated as MAP-ICP. All physiological data was collected in real-time at the beside using the computerised recording system ICMPlus® developed by Cambridge University, set at a frequency of 100Hz.

Clinical and demographic data were collected from patient folders. Mortality at 6 months post-injury was used as the primary endpoint. Clinical outcome at ≥ 6 months post-injury was based on the Glasgow Outcome Scale Extended version (GOSE-E) which has been verified in paediatrics[47]. Scoring system is as follows: GOS-E 1 = upper good recovery, 2 = lower good recovery, 3 = upper moderate disability, 4 = lower moderate disability, 5 = upper severe disability, 6 = lower severe disability, 7 = vegetative state, 8 = death. Therefore, dichotomization produces favourable (GOS-E: 1 – 4) and unfavourable (GOS-E: 5 – 8) outcome groups.

4. Data Analysis

The calculation of PRx:

Basic data cleaning and artefact removal was done manually in the raw files of ICMPlus. Artefacts resulting from monitor disconnections or patient handling were removed, as well as mis-calibrations and technical artefacts.

PRx was calculated in ICMPlus as the moving Pearson correlation coefficient between 30 consecutive 10 second averaged data points of ICP and MAP[3, 25]. One-minute averages of all parameters were calculated for the entire cohort. Single descriptive values of each parameter for each individual patient were calculated from this minute-by-minute data. Further, to derive hourly data points for each patient, minute-by-minute data were averaged for every hour or part thereof.

The following variables were calculated for analysis:

- An average data point per hour
- A single median value for each patient's entire monitoring period
- The percentage time spent with a PRx above 0, 0.2, 0.25, and 0.3
- The percentage time spent with an ICP above 20mmHg
- Median PRx per monitoring day
- Median PRx per CPP bin
- Median PRx per patient when hourly ICP ≤ 20mmHg

To describe the characteristics of PRx in children with severe TBI:

Demographic, clinical and monitoring data were reported. The entire cohort's descriptives were reported, as well as by mortality and outcome groups. To investigate the changes in PRx over time, the median hourly PRx for each monitoring day was plotted by outcome groups.

To examine associations between PRx, clinical and physiological variables:

Spearman's Rank Correlation Analysis:

The relationship between PRx, ICP, MAP, and CPP was investigated with correlation analysis. Spearman's rank analysis was done using two sub-datasets. The first correlation analysis used the overall median of each patient's entire monitoring period, i.e. 196 data points were included for each variable. GCS and age were included in the analysis, with post-resuscitation GCS analysis excluding one patient from the cohort (n = 195) because of uncertainty about the post-resuscitation score. To graphically demonstrate the relationship between overall PRx and CPP, CPP was calculated in bins of 10mmHg, against which median PRx was plotted.

In the second correlation analysis, the hourly data were used – one data point per hour for each patient's variables for their entire monitoring period resulted in 24807 data points included in this analysis.

To examine associations between PRx and outcome:

Clinical outcome was analysed in three ways: mortality at 6 months post-injury (primary endpoint), dichotomized clinical outcome, and functional outcome for survivors (where unfavourable outcome excluded patients that died). The latter was done to exclude the weighting of patients who died in the unfavourable group, i.e. to determine if PRx associated with functional outcome groups for survivors.

Statistical differences in median PRx between clinical outcome groups were determined using the Mann Whitney's *U* test given the non-parametric data distribution. Binary logistic regression and ROC analyses were done to investigate the relationship between PRx and clinical outcome.

Binary Logistic Regression Analysis:

First, binary logistic regression was done with PRx as the only predictor of outcome. Then, co-variate predictors of ICP, CPP, and GCS were added to the model. The overall per patient median of PRx, ICP, and CPP were used. PRx values were multiplied by 10 to enable meaningful interpretation of the resulting odds ratios[3].

Receiver Operating Curve Analysis:

The overall median PRx and ICP for each patient were predictors in all ROC analyses of outcome prediction. Investigations for death and unfavourable outcome prediction also included the median percentage time spent above various PRx thresholds and above an ICP of 20mmHg. These variables were calculated using the hourly data – the number of hours PRx/ICP was above a given value divided by the entire period for which PRx/ICP data were available, reported as a percentage of time. The PRx threshold values of 0, 0.25 and 0.3 have previously been described in both adults[32, 33, 36] and children[3] as mortality thresholds. The PRx threshold of 0.2 was identified as the PRx at which sensitivity and specificity were highest in the ROC analysis of median PRx and mortality for this study's cohort (Figure 4.1). This threshold value was then described (Tables 1 and 2) and used in further analysis. Threshold values for dichotomized and functional outcome were not investigated.

We also examined PRx when ICP was in the 'normal' range. To do this, we created a ROC analysis where the hourly ICPs above 20mmHg were excluded. The median PRx per patient when ICP ≤ 20mmHg was then recalculated and tested for its ability to predict mortality and unfavourable outcome (n = 194 patients).

Statistical significance was set as *p* values less than 0.05. All statistical analysis was done using IBM SPSS Statistics 27.0. As this was an exploratory analysis, we did not account for multiple testing.

Ethical clearance was previously obtained as this project forms part of larger TBI research projects (HREC 166/2009).

Chapter 5: Results

From our database of children monitored for severe TBI at Red Cross War Memorial Children's Hospital, 196 patients fit the eligibility criteria. All patients had an admission/post-resuscitation GCS recorded as ≤ 8 or deteriorated to that level requiring intubation and ventilation. One patient was excluded from GCS analysis as there was uncertainty surrounding their post-resuscitation score. Mortality and outcome at 6 months minimum were obtained for all 196 patients.

1. Demographic, clinical and monitoring data

Data are summarised in Table 1, showing descriptives for the entire cohort, separated into survivors (n = 175; 89.3%) and non-survivors (n = 21, 10.7%). The median age was 6.63 years (range of 4 days – 14 years old), with no statistically significant difference between outcome groups. The most common mechanism of injury was as a pedestrian in a motor vehicle accident (PVA, n = 118; 60.2%). Non-survivors presented with a median post-resuscitation GCS of 5, which is significantly lower than that of patients that survived (GCS of 6; $p = 0.002$).

The total monitoring duration was 28 634 hours (1193 days). A median value per patient was calculated, and the overall median of those 196 values are reported in Tables 1 and 2. The pooled median PRx was 0.01, with a median ICP of 12.4mmHg.

All monitoring variables except for MAP were significantly different between survivors and non-survivors. The overall median PRx for survivors was 0.00, compared to a PRx of 0.37 of patients who died ($p < 0.001$). The percentage of time that patients spent above PRx threshold values of 0, 0.2, 0.25 and 0.3 was significantly greater in patients that died versus those that survived ($p < 0.001$ for all analyses). Median ICP differed between outcome groups (ICP of 11.9mmHg for survivors, 19.2mmHg for non-survivors; $p < 0.001$), and the percentage time spent above an ICP of 20 was significantly lower in survivors (4.8% versus 44.2%, $p < 0.001$).

Table 2 shows the same descriptives based on dichotomized outcome (GOS-E 1 – 4 versus 5 – 8). Overall monitoring duration was significantly shorter in patients who had a favourable outcome ($p = 0.006$). Patients who had a favourable outcome had a lower overall median PRx (PRx = -0.03 versus 0.16; $p < 0.001$), spent less time above the various threshold values of PRx ($p < 0.001$ for all analyses), had a lower overall median ICP (11.4mmHg versus 14.4mmHg; $p < 0.001$), and spent less time with an ICP above 20mmHg (3.7% versus 20.5% $p < 0.001$) compared to patients with an unfavourable outcome.

Monitoring variable summaries based on functional outcome groups, i.e. survivors only (GOS-E 1 – 4 versus 5 – 7) are available in Appendix A. The bad functional outcome group had a greater overall median PRx compared to patients that had a good functional outcome (0.02 versus -0.03), and this difference was borderline significant with a p value of 0.051. Time spent above the PRx threshold of

0.3 showed the most significant difference between the groups, with bad outcome spending a median of 18.3% above a PRx of 0.3, compared to the good functional outcome group median of 9.6% (p = 0.008).

Table 1: Demographic, clinical and monitoring data for the entire cohort and by mortality groups

Variable	Entire Cohort	Survivors	Non-survivors	*p*
Total, n (%)	196	175 (89.3)	21 (10.7)	
Demographics				
Age, median, years	6.63 (4.3 – 9.1)	6.58 (4.3 – 9.1)	7.05 (4.73 – 10.1)	0.396
Males, n (%)	131 (66.8)	118 (67.4)	13 (61.9)	
Mechanism, n (%)				
MVA	50 (25.5)	46 (26.3)	4 (19.1)	
PVA	118 (60.2)	107 (61.1)	11 (52.4)	
Fall from height	8 (4.1)	5 (2.9)	3 (14.3)	
GSW to head	7 (3.6)	6 (3.4)	1 (4.8)	
Crush injury	6 (3.1)	6 (3.4)	0 (0.0)	
NAI	6 (3.1)	5 (2.9)	1 (4.8)	
Unknown	1 (0.5)	0 (0.0)	1 (4.8)	
Presentation				
Post-resus GCS, median	6 (5 – 7)	6 (5 – 8)	5 (4 – 6)	**0.002**
Overall Monitoring Period				
Total monitoring time, days	5.1 (3.9 – 8.7)	5.1 (4.0 – 8.5)	4.2 (1.7 – 9.4)	0.264
ICP, median, mmHg	12.4 (9.6 – 15.3)	11.9 (9.1 – 14.3)	19.2 (16.3 – 23.5)	< **0.001**
ICP > 20 (median % time)	6.6 (0.0 – 18.4)	4.8 (0.0 – 13.2)	44.2 (25.6 – 78.5)	< **0.001**
MAP, median, mmHg	80.0 (74.0 – 85.6)	80.3 (74.0 – 85.6)	77.8 (72.6 – 89.7)	0.599
CPP, median, mmHg	67.7 (60.2 – 73.5)	68.2 (60.9 – 73.6)	58.1 (48.2 – 66.0)	< **0.001**
PRx, median	0.01 (-0.12 – 0.20)	0.00 (-0.14 – 1.22)	0.37 (0.26 – 0.61)	< **0.001**
PRx > 0 (median % time)	55.3 (34.6 – 74.0)	49.7 (32.1 – 67.8)	84.1 (77.9 – 99.1)	< **0.001**
PRx > 0.2 (median % time)	25.0 (11.8 – 44.1)	22.3 (11.1 – 38.4)	62.0 (48.3 – 86.9)	< **0.001**
PRx > 0.25 (median % time)	19.5 (9.0 – 37.8)	16.3 (7.2 – 31.7)	59.3 (43.8 – 87.9)	< **0.001**
PRx > 0.3 (median % time)	15.2 (6.0 – 33.3)	13.2 (5.2 – 23.5)	54.0 (36.9 – 86.0)	< **0.001**

Note: medians reported with 25th and 75th percentiles in brackets. Percentage time calculated using hourly data. All numbers rounded to one decimal place except for PRx and *p* values. Bold *p* values indicate statistical significance between mortality groups at the 0.05 level. MVA = motor vehicle accident as a passenger; PVA = pedestrian in motor vehicle accident; GSW = gunshot wound; NAI = any non-accidental injury (including but not limited to shaken baby syndrome); Post-resus GCS = post-resuscitation Glasgow Coma Score; N/A = not applicable; ICP = intracranial pressure; MAP = mean arterial pressure; CPP = cerebral perfusion pressure; PRx = pressure reactivity index.

Table 2: Demographic, clinical and monitoring data for the entire cohort and by dichotomized outcome groups

Variable	**Entire Cohort**	**Favourable**	**Unfavourable**	***p***
Total, n (%)	196	138 (70.4)	58 (29.6)	
Demographics				
Age, median, years	6.63 (4.3 – 9.1)	6.56 (4.1 – 9.0)	6.9 (4.9 – 9.6)	0.407
Males, n (%)	131 (66.8)	93 (67.4)	38 (65.5)	
Mechanism, n (%)				
MVA	50 (25.5)	33 (23.9)	17 (29.3)	
PVA	118 (60.2)	87 (63.0)	31 (53.5)	
Fall from height	8 (4.1)	4 (2.9)	4 (6.9)	
GSW to head	7 (3.6)	5 (3.6)	2 (3.5)	
Crush injury	6 (3.1)	6 (4.4)	0 (0.0)	
NAI	6 (3.1)	3 (2.2)	3 (5.2)	
Unknown	1 (0.5)	0 (0.0)	1 (1.7)	
Presentation				
Post-resus GCS, median	6 (5 – 7)	7 (6 – 8)	6 (5 – 7)	< **0.001**
Overall Monitoring Period				
Total monitoring time, days	5.1 (3.9 – 8.7)	4.9 (3.9 – 7.5)	8.3 (3.3 – 11.0)	**0.006**
ICP, median, mmHg	12.4 (9.6 – 15.3)	11.4 (8.7 – 13.8)	14.4 (12.2 – 17.8)	< **0.001**
ICP > 20 (median % time)	6.6 (0.0 – 18.4)	3.7 (0.0 – 11.0)	20.5 (6.2 – 34.4)	< **0.001**
MAP, median, mmHg	80.0 (74.0 – 85.6)	80.2 (74.1 – 85.6)	79.3 (73.8 – 85.4)	0.624
CPP, median, mmHg	67.7 (60.2 – 73.5)	68.3 (61.2 – 74.0)	63.2 (56.1 – 70.5)	**0.002**
PRx, median	0.01 (-0.12 – 0.20)	-0.03 (-0.15 – 0.11)	0.16 (0.01 – 0.37)	< **0.001**
PRx > 0 (median % time)	55.3 (34.6 – 74.0)	46.5 (30.5 – 67.3)	63.6 (51.1 – 88.9)	< **0.001**
PRx > 0.2 (median % time)	25.0 (11.8 – 44.1)	19.5 (10.6 – 36.2)	42.0 (23.3 – 65.3)	< **0.001**
PRx > 0.25 (median % time)	19.5 (9.0 – 37.8)	14.1 (7.0 – 28.6)	35.7 (20.1 – 59.6)	< **0.001**
PRx > 0.3 (median % time)	15.2 (6.0 – 33.3)	9.6 (4.7 – 21.8)	28.4 (15.0 – 54.0)	< **0.001**

Note: medians reported with 25th and 75th percentiles in brackets. Glasgow Outcome Scale Extended version (GOS-E) for outcome groups as follows: favourable = 1-4, and unfavourable = 5-8. All numbers rounded to one decimal place except for PRx and *p* values. Bold *p* values indicate statistical significance between outcome groups at the 0.05 level. MVA = motor vehicle accident as a passenger; PVA = pedestrian in motor vehicle accident; GSW = gunshot wound; NAI = any non-accidental injury (including but not limited to shaken baby syndrome); Post-resus GCS = post-resuscitation Glasgow Coma Score; ICP = intracranial pressure; MAP = mean arterial pressure; CPP = cerebral perfusion pressure; PRx = pressure reactivity index.

2. Temporal profile of PRx

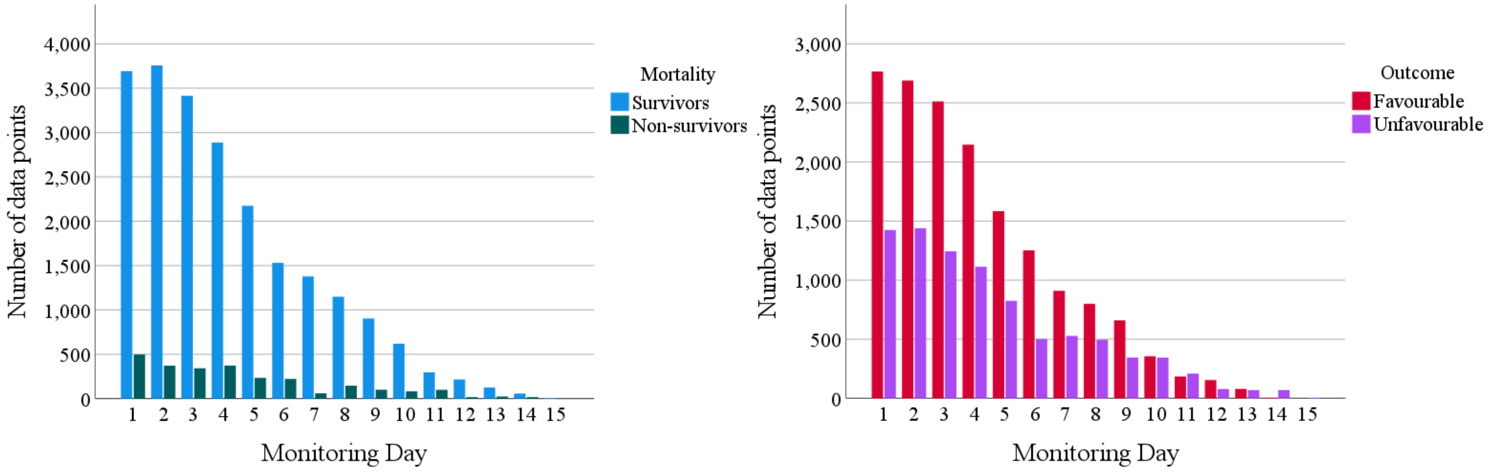
The median PRx per monitoring day plotted for groups based on mortality is shown in Figure 2.1, for dichotomized outcome in Figure 2.2, and for functional outcome of survivors in Figure 2.3. Given the decrease in data points after day 10 (Figure 1), the temporal profile of PRx is shown for the first 10 days only. Plots showing median PRx for the full duration of monitoring (15 days) for mortality and dichotomized outcome is included in Appendix B.

Survivors had a consistently lower median PRx over 10 days of monitoring compared to non-survivors. Similarly, patients who did favourably had a consistently lower median PRx compared to the unfavourable group.

The patients that had a bad functional outcome had a consistently greater PRx over the 10 days compared to patients that had a good functional outcome. The bad outcome group's PRx increases on day 6.

Figure 1

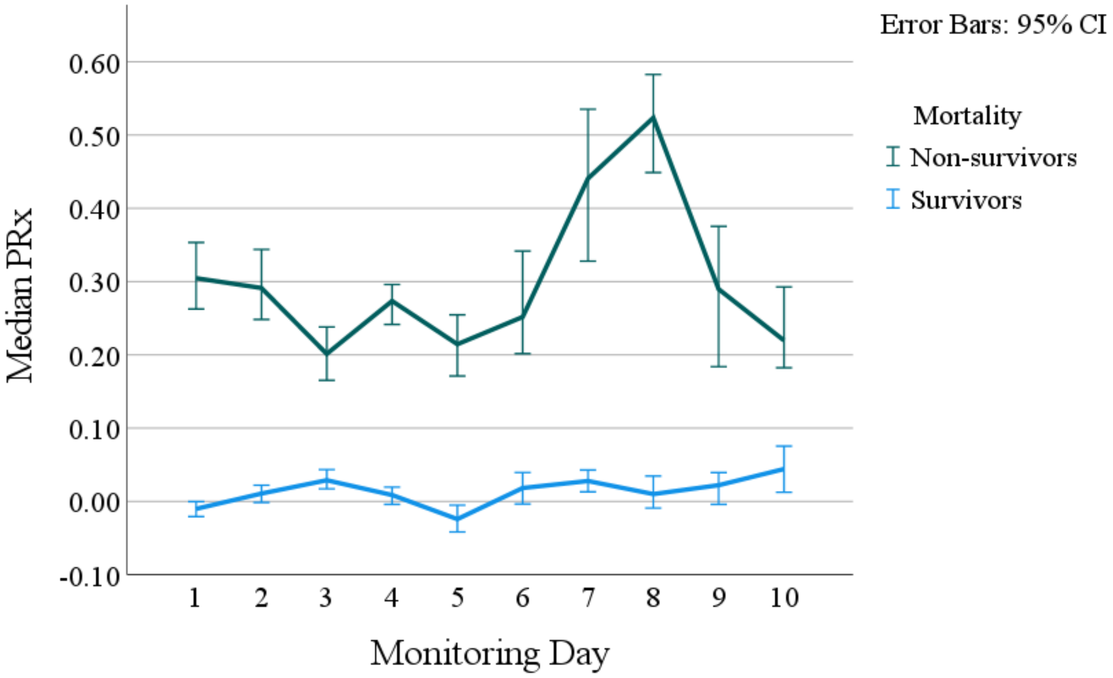
The number of data points per monitoring day for both mortality and dichotomized outcome groups



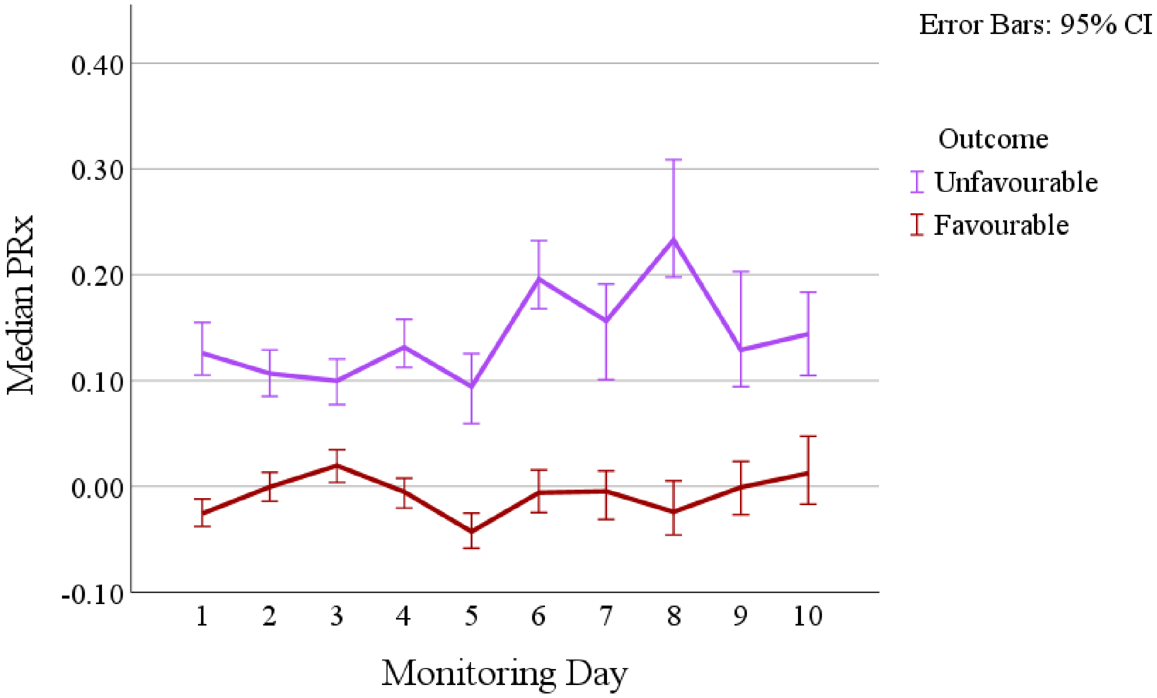
Temporal profiles exclude days 11 – 15 due to inadequate data. Survivors = 175 patients, non-survivors = 21 patients, favourable = 138 patients, unfavourable = 58 patients.

Figure 2: The temporal profiles of PRx by outcome groups

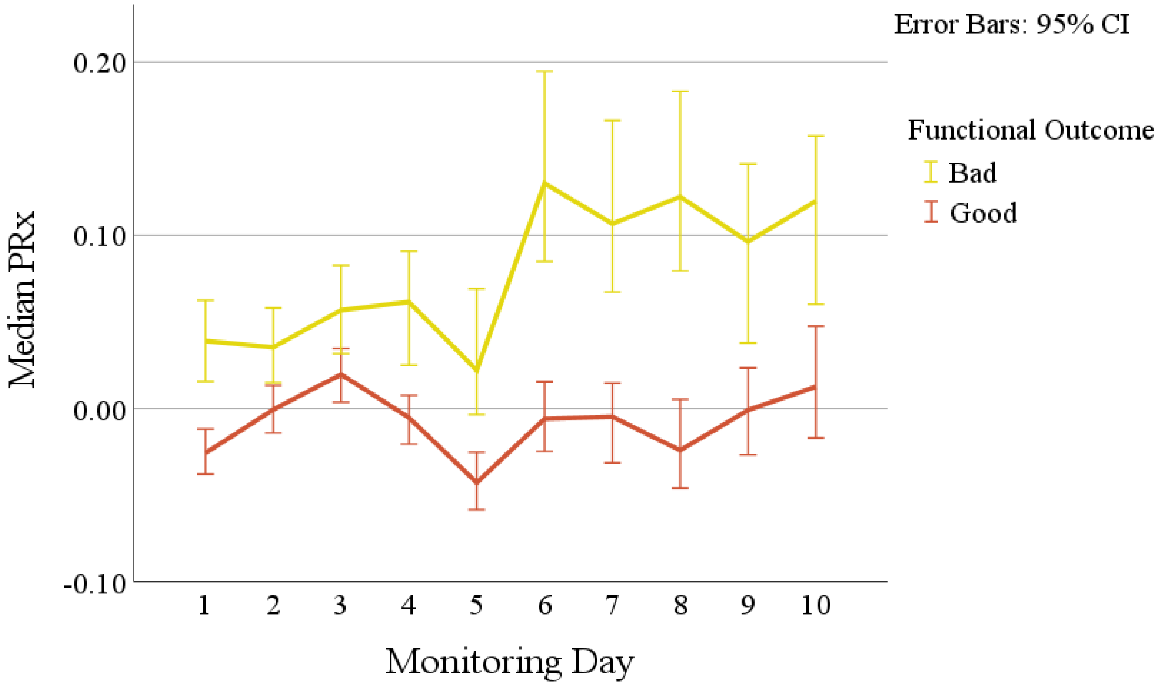
2.1 Median PRx over time for survivors and non-survivors



2.2 Median PRx over time for favourable and unfavourable outcome groups



2.3 Median PRx over time for good and bad functional outcome groups



Median PRx plotted for the first 10 days of monitoring only due to adequate patient numbers per day; full monitoring period plots for mortality and dichotomized outcome available in Appendix B. Glasgow Outcome Score Extended version for the groups as follows: Favourable outcome = 1-4, Unfavourable outcome = 5-8, Good functional outcome = 1-4, Bad functional outcome = 5-7. Error bars represent the 95% confidence interval (CI). PRx = pressure reactivity index.

3. The relationship between PRx, and clinical and physiological variables

To investigate the relationship between PRx, clinical variables (age and post-resuscitation GCS) and physiological variables (ICP, MAP, and CPP), two analyses were done. The results are summarised in Table 3. The first correlation analysis used a median value for each patient's entire monitoring period using various variables. This analysis included age and GCS as it used a single data point per patient.

To account for the dynamic changes over a patient's clinical course, the second correlation analysis uses the hourly data – the minute-by-minute data were averaged to create a single value per hour per patient. As Table 3 demonstrates, this analysis used 24 807 data points compared to the 196 used in the first analysis.

The overall median analysis found no significant correlations between PRx and age or post-resuscitation GCS. However, age was positively correlated with MAP ($r = 0.40$; $p < 0.001$) and CPP ($r = 0.32$; $p < 0.001$).

Both analyses found a significant positive correlation between PRx and ICP, with both correlations producing a p value of less than 0.001. The hourly analysis produced a slightly lower r value compared to the overall median correlation (0.36 versus 0.44). PRx and CPP were negatively correlated for the hourly analysis ($r = -0.27$) and the overall median analysis ($r = -0.43$); $p < 0.001$ for both analyses. A significant negative correlation between PRx and MAP was found in both analyses, however this relationship was weak (hourly dataset $r = -0.10$ versus overall median $r = -0.21$, $p < 0.001$).

Table 3: Results of the correlation analyses

3 A: Correlation analysis using a single median value per patient

		Age	GCS	PRx	ICP	MAP
GCS	*r*	0.06				
	p	0.431				
	n	195				
PRx	*r*	-0.13	-0.09			
	p	0.08	0.19			
	n	196	195			
ICP	*r*	0.07	-0.08	0.44		
	p	0.360	0.271	< **0.001**		
	n	196	195	196		
MAP	*r*	0.40	0.06	-0.21	-0.07	
	p	< **0.001**	0.365	**0.004**	0.356	
	n	196	195	196	196	
CPP	*r*	0.32	0.09	-0.43	-0.51	0.84
	p	< **0.001**	0.192	< **0.001**	< **0.001**	< **0.001**
	n	196	195	196	196	196

3 B: Correlation analysis using hourly data

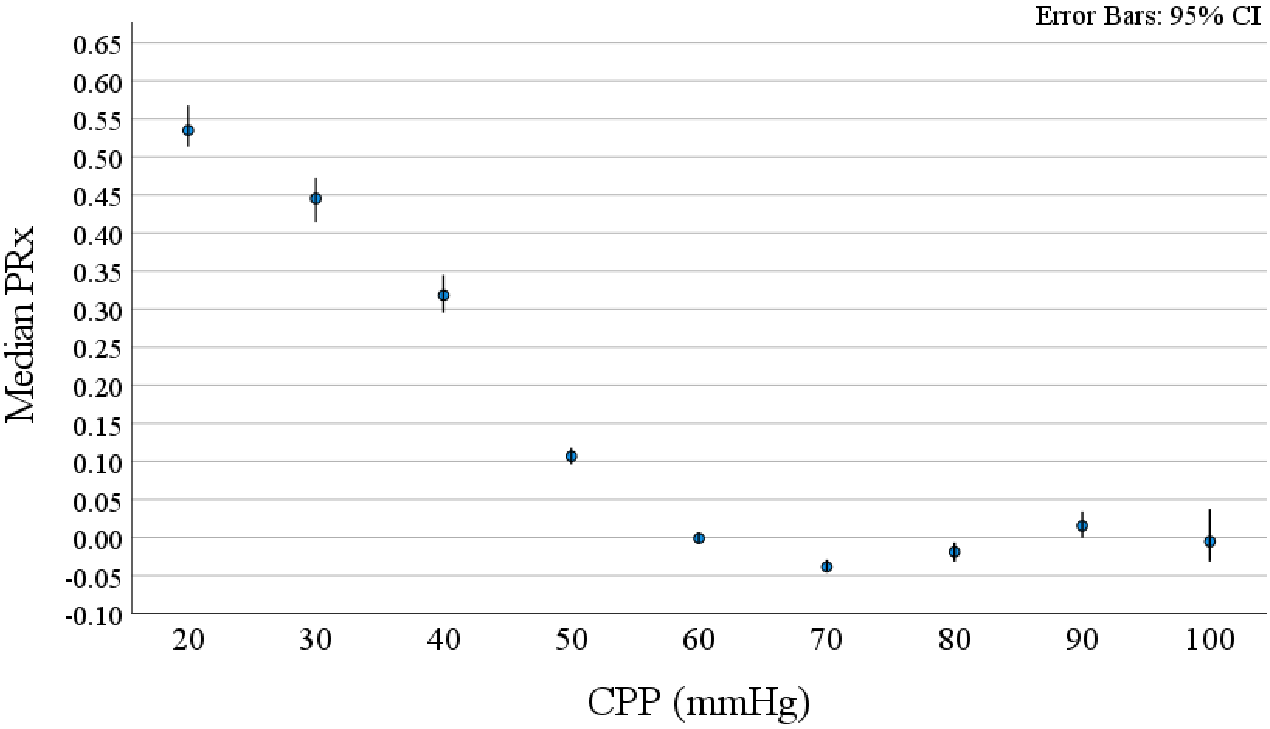
		PRx	ICP	MAP
ICP	*r*	0.36		
	p	< **0.001**		
	n	24807		
MAP	*r*	-0.10	0.02	
	p	< **0.001**	< **0.001**	
	n	24807	24807	
CPP	*r*	-0.27	-0.43	0.86
	p	< **0.001**	< **0.001**	< **0.001**
	n	24807	24807	24807

Note: Numbers rounded to two decimal places, except for *p* values. Bold *p* values indicate significance at the 0.05 level. *r* = Spearman's rank correlation coefficient, n = number of data points, GCS = post-resuscitation Glasgow Coma Score; PRx = pressure reactivity index; ICP = intracranial pressure; MAP = mean arterial pressure; CPP = cerebral perfusion pressure.

Median PRx plotted against CPP bins is shown in Figure 3. PRx starts high at low CPPs and gradually decreases as CPP increases, with PRx at its lowest of -0.04 corresponding to a CPP bin of 70-80mmHg. PRx plateaus around 0 between a CPP of 60 and 100mmHg. A plot using the mean instead of the median PRx is available in Appendix C.

Figure 3

Median PRx versus CPP



Median PRx of 10mmHg CPP bins of the entire 196 patient cohort. The mean PRx per CPP bin can be found in Appendix C. Error bars represent the 95% confidence interval (CI). PRx = pressure reactivity index; CPP = cerebral perfusion pressure.

4. The relationship between PRx and outcome

Associations between monitoring variables and outcome were explored using the Mann Whitney's *U* Test, with results shown in Tables 1 and 2.

Table 4 shows the results of binary logistic regression analysis to investigate the relationship between overall median PRx and mortality, dichotomized outcome, and functional outcome. Table 4.1 shows that when PRx is used as a single predictor variable for mortality the odds ratio is 1.87, with a 95% confidence interval (CI) of 1.48 – 2.40 ($p < 0.001$). When ICP, CPP, and GCS were added as co-variates, this odds ratio decreased to 1.62 (95% CI of 1.23 – 1.63; $p = 0.002$). Similarly, in the regression analysis with dichotomized outcome, the odds ratio for PRx decreases from 1.42 (95% CI of 1.23 – 1.63; $p < 0.001$) to 1.28 (95% CI of 1.07 – 1.52; $p = 0.007$) when ICP, CPP, and GCS are included as co-variates (Table 4.2).

To investigate whether this relationship is affected by the inclusion of the non-survivors in the unfavourable outcome group (and therefore the existing relationship between the variables and mortality), regression analysis was done with the variables and functional outcome of survivors (Table 4.3). When overall median PRx is used as a single predictor variable, the odds ratio is 1.20 with a 95% CI of 1.01 – 1.41. The relationship is significant ($p = 0.034$); however, when the co-variates of median ICP, CPP, and GCS are included, the odds ratio decreases to 1.15 (95% CI of 0.96 – 1.40) and it is no longer significant ($p = 0.140$). In fact, none of the tested variables have a significant association with functional outcome except for post-resuscitation GCS, with an odds ratio of 0.77 (95% CI of 0.62 – 0.96; $p = 0.021$).

Table 4: Binary logistic regression analysis for PRx and the various outcome groups

4.1 Summary of binary logistic regression analysis for PRx and mortality

	Odds Ratio	95% CI	*p*
PRx as single predictor:			
Median PRx	1.87	1.48 – 2.40	< **0.001**
Analysis with co-variates:			
Median PRx	1.62	1.20 - 2.19	**0.002**
Median ICP	1.27	1.05 - 1.53	**0.013**
Median CPP	1.01	0.94 - 1.09	0.745
GCS	0.63	0.44 - 0.90	**0.012**

4.2 Summary of binary logistic regression analysis for PRx and dichotomized outcome

	Odds Ratio	95% CI	*p*
PRx as single predictor:			
Median PRx	1.42	1.23 – 1.63	< **0.001**
Analysis with co-variates:			
Median PRx	1.28	1.07 – 1.52	**0.007**
Median ICP	1.16	1.04 - 1.29	**0.008**
Median CPP	1.01	0.97 - 1.05	0.765
GCS	0.73	0.59 - 0.89	**0.002**

4.3 Summary of binary logistic regression analysis for PRx and functional outcome

	Odds Ratio	95% CI	*p*
PRx as single predictor:			
Median PRx	1.20	1.01 – 1.41	**0.034**
Analysis with co-variates:			
Median PRx	1.15	0.96 – 1.40	0.140
Median ICP	1.12	1.00 – 1.27	0.060
Median CPP	1.00	0.96 – 1.05	1.000
GCS	0.77	0.62 – 0.96	**0.021**

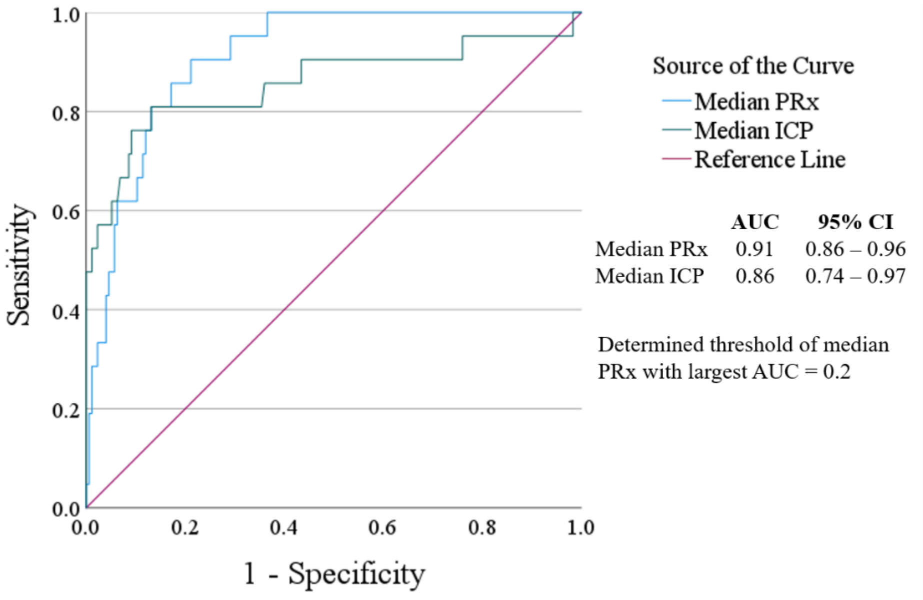
Binary logistic regression analysis done for PRx and mortality, PRx and dichotomized outcome, and PRx and functional outcome. The tables report results of median PRx as a single predictor, and median ICP, CPP and GCS as co-variate predictors of mortality/outcome. All numbers rounded to two decimal places, except *p* values. Bold *p* values indicate significance at the 0.05 level. PRx = pressure reactivity index; ICP = intracranial pressure; CPP = cerebral perfusion pressure; GCS = post-resuscitation Glasgow Coma Score; CI = confidence interval.

ROCs were generated to investigate the predictive strength of the overall median PRx, ICP, and CPP. Figure 4 shows that median PRx had the strongest ability to predict mortality with an area under the curve (AUC) of 0.91 (95% CI of 0.86 – 0.96). Figure 4.1 was used to determine the mortality threshold of PRx = 0.2. This means that a PRx of 0.2 has the greatest sensitivity and specificity of discerning between the survivor and non-survivor groups. This threshold of 0.2 was used in descriptive analysis (Table 1). ICP also had a strong predictive ability, with an AUC of 0.86 (95% CI of 0.74 – 0.97). CPP had the weakest predictive ability for mortality, with an AUC of 0.76 (95% CI of 0.63 – 0.89).

Figure 5 shows that percentage time spent above all PRx thresholds had strong abilities to predict mortality, the highest AUC value of all the thresholds being that of percentage time spent with a PRx > 0.25 at 0.91 (95% CI of 0.86 – 0.96). Median PRx when hourly ICP was less than 20mmHg only, also produced a high AUC of 0.88 (95% CI of 0.83 – 0.93) in mortality prediction. The median percentage time ICP was above 20mmHg was the strongest predictor of mortality, with an AUC of 0.94 (95% CI of 0.89 – 0.99).

Figure 4: Receiver operating curves using median PRx, ICP, and CPP in mortality prediction

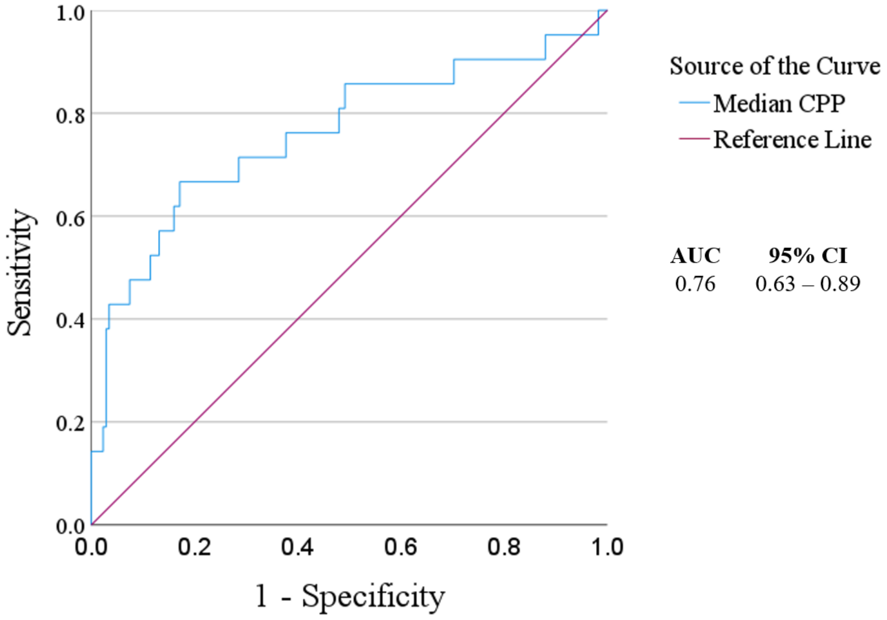
4.1 ROC for median PRx and ICP for mortality



	AUC	95% CI
Median PRx	0.91	0.86 – 0.96
Median ICP	0.86	0.74 – 0.97

Determined threshold of median PRx with largest AUC = 0.2

4.2 ROC for median CPP for mortality

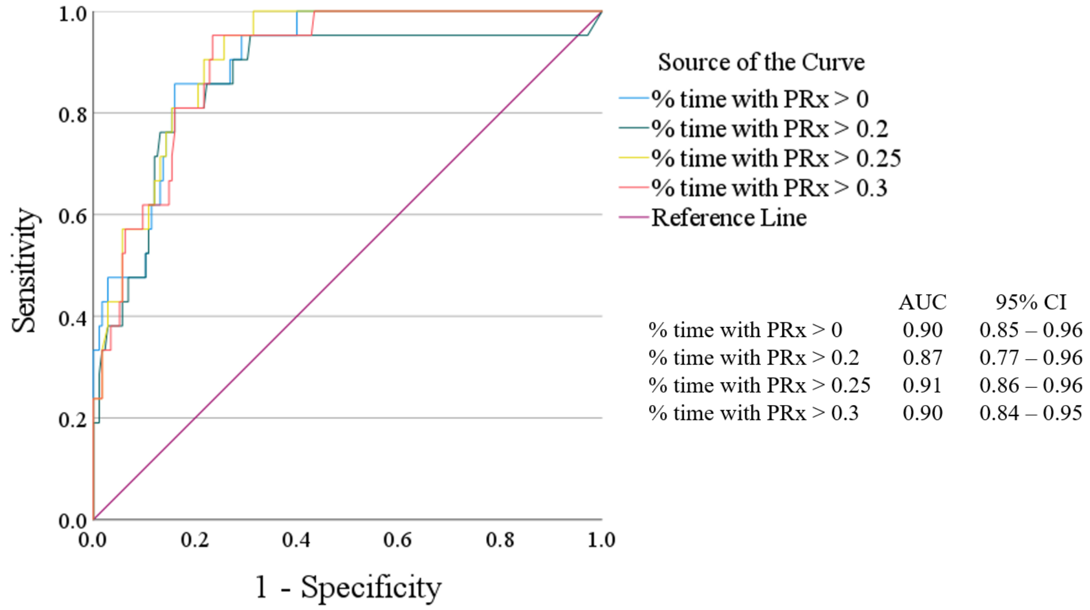


AUC	95% CI
0.76	0.63 – 0.89

Receiver operating curves (ROCs) for mortality show the predictive strength of the plotted variables, with the greatest area under the curve indicating the strongest predictive ability. AUC = area under curve, presented with 95% confidence intervals (CI). All numbers rounded to 2 decimal places. PRx = pressure reactivity; ICP = intracranial pressure; CPP = cerebral perfusion pressure

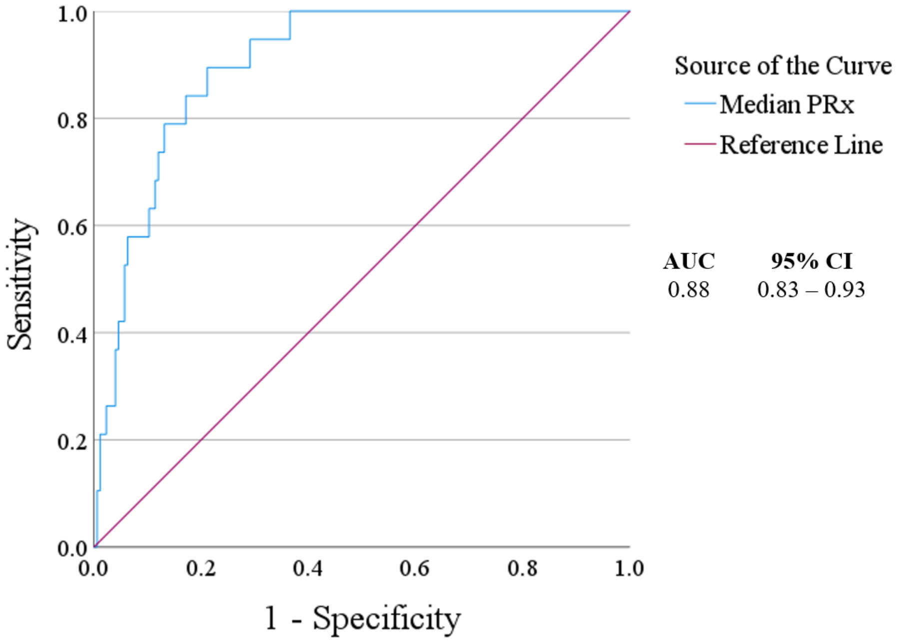
Figure 5: Receiver operating curves using specific inclusion criteria in mortality prediction

5.1 ROC for median % time PRx > thresholds for mortality



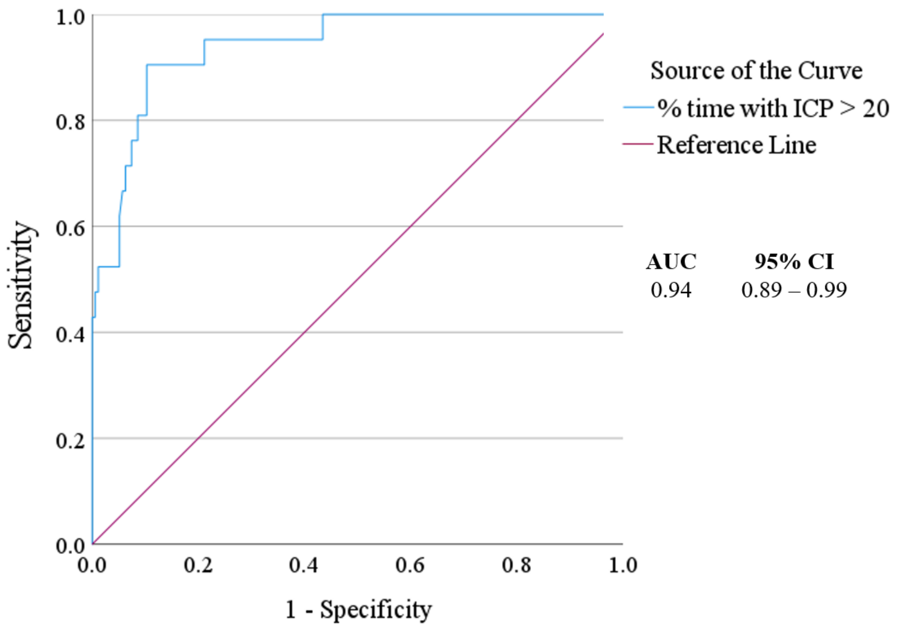
	AUC	95% CI
% time with PRx > 0	0.90	0.85 – 0.96
% time with PRx > 0.2	0.87	0.77 – 0.96
% time with PRx > 0.25	0.91	0.86 – 0.96
% time with PRx > 0.3	0.90	0.84 – 0.95

5.2 ROC for median PRx for mortality (hourly ICP ≤ 20 only)



AUC	**95% CI**
0.88	0.83 – 0.93

5.3 ROC for median % time ICP > 20 for mortality



Receiver operating curves (ROCs) for mortality show the predictive strength of the plotted variables, with the greatest area under the curve indicating the strongest predictive ability. Variables calculated using hourly data. AUC = area under curve, presented with the 95% confidence interval (CI). All numbers rounded to two decimal places. PRx = pressure reactivity; ICP = intracranial pressure.

The AUC analyses were repeated for *unfavourable outcome*, and these curves are available in Appendix D. Summary results of all outcome analyses is shown in Table 5. In general, all AUC values were less for association with unfavourable outcome compared to mortality. Median PRx and ICP had similar AUC values in association with unfavourable outcome (AUCs of 0.72 and 0.73 respectively). Time spent above an ICP of 20mmHg had an AUC of 0.76 in unfavourable outcome prediction. This variable seems to be the strongest predictor of unfavourable outcome out of all the tested variables. However, none of these variables demonstrate a strong ability to predict unfavourable outcome.

Functional outcome was also briefly explored with ROC analysis. Median PRx and ICP had low AUC values (0.60 and 0.65 respectively; Table 5), demonstrating poor abilities to predict *bad functional outcome* in survivors. The ROC curves for this analysis are available in Appendix D.

All analyses were repeated using *survival, favourable* and *good functional outcome* as the positive test variable in the ROC analysis. AUC values were the same for both tests, as seen in Table 5.

Table 5: Comparing AUC values from the ROC tests for the various outcome groups

	AUC values produced when predicting:					
Tested predictor	**Survival**	**Mortality**	**Favourable**	**Unfavourable**	**Good functional**	**Bad functional**
n	175	21	138	58	138	37
Median PRx	0.91	0.91	0.72	0.72	0.60	0.60
Median ICP	0.86	0.86	0.73	0.73	0.65	0.65
Median CPP	0.76	0.76	0.64	0.64	0.57	0.57
Median % time PRx > thresholds of:						
0	0.90	0.90	-	-	-	-
0.2	0.87	0.87	-	-	-	-
0.25	0.91	0.91	-	-	-	-
0.3	0.90	0.90	-	-	-	-
Overall median ICP ≤ 20mmHg:						
Median PRx	0.87	0.87	0.67	0.67	-	-
Median ICP	0.73	0.73	0.67	0.67	-	-
Median PRx when ICP ≤ 20mmHg	0.88	0.90	0.69	0.71	-	-
Median % time ICP > 20mmHg	0.94	0.94	0.76	0.76	-	-

Receiver operating curve (ROC) analysis was done using both survival and mortality, favourable and unfavourable, and good and bad functional groups as the outcome variable. The AUC values are consistent regardless of the outcome variable used. Functional outcome groups refer to survivors only. Percentage time variables calculated using the hourly data. Time spent above PRx thresholds evaluated for mortality groups only; basic analysis done for functional outcome with overall median PRx, ICP, and CPP tested only. All numbers rounded to two decimal places. AUC = area under curve, PRx = pressure reactivity index, ICP = intracranial pressure, CPP = cerebral perfusion pressure.

Chapter 6: Discussion

This retrospective analysis investigated PRx, the mathematical indicator of the pressure reactivity component of CA, in a large cohort of children with severe TBI. While there is evidence for an association between PRx and outcome in adult severe TBI, data on paediatric studies are lacking, with published studies including cohorts of less than 40 individuals. This study described PRx in 196 children with severe TBI, examined its temporal profile, its relationship with key clinical and physiological variables, and its association with outcome. The key findings of this study include: 1) PRx was consistently higher in patients with poor outcome when examined by various summary statistics and over time, 2) PRx had a moderate positive correlation with ICP but a weak negative correlation with MAP and CPP; 3) PRx and ICP were strong predictors of outcome on ROC analysis, and the relationship between PRx and outcome was moderated by ICP and GCS.

1. Describing PRx in this cohort

A PRx below 0 is considered intact and values above 0.25 are thought to represent disturbed pressure reactivity[32]. The pooled median PRx of this 196-patient cohort was 0.01 with a median of 55.3% of values recorded above 0. Overall, patients who had a favourable outcome had PRx values that fell within the intact pressure reactivity range over the duration of monitoring, while the predominance of elevated PRx values was observed in patients who had an unfavourable outcome. Further, non-survivors had a median PRx consistently above 0.2. From the timeline, it would appear that the impaired PRx persists for a protracted time. Interpretation of data beyond day 8-10 is difficult because of the decreased number of data points.

2. The relationship between PRx and clinical, and physiological variables

Correlation analysis showed no significant relationship between the overall median PRx and GCS (r = -0.09; p = 0.191). This finding is supported by results in adult TBI[27, 48] and may suggest that PRx is not merely a reflection of injury severity but may be an indication of hemodynamic changes post-injury, or at least adds to the evaluation of injury severity. However, further analysis incorporating other markers of injury severity and radiological findings is needed.

Analysis using the overall patient summary values showed that median PRx correlated moderately with ICP (r = 0.44; $p < 0.001$) and CPP (r = -0.43; $p < 0.001$), and weakly with MAP (r = -0.21; p = 0.004). These findings are broadly consistent with correlation analysis done in adults, but with some differences. Aries *et al.* analysed data from 327 adults and found significant correlations with ICP and CPP but with smaller effect sizes (ICP r = 0.16; p = 0.004; CPP r = -0.11; p = 0.05; MAP r = -0.02; p = 0.71). They found an association between PRx and age (r = 0.17; p = 0.004) but this likely reflected the inclusion of older adults in their cohort[48]. On the other hand, another adult study found no significant relationship between PRx and ICP, but PRx was significantly correlated with CPP (r = 0.225; p = 0.016)[27], but their correlation with CPP was positive, whereas our data and that of Aries *et al*. showed a negative correlation. To some extent this may reflect the dominance of the CPP values with respect to the lower or upper inflection points of the autoregulation curve – the association between CPP and PRx may be different at low versus high values of CPP.

PRx data in children are sparce, with few investigations into correlation between PRx and GCS, ICP, and CPP. The study done with 36 children by Lewis *et al*. showed no significant correlations between PRx and these variables[3]. Our correlations held when analysis used hourly data, but with lower coefficient values.

Adult TBI studies have shown a U-shaped curve when PRx is plotted against 5 or 10mmHg CPP bins[21, 27, 48]. In individual patients, the lowest point of the U represents the lowest PRx value and therefore this is interpreted as the patient's CPPopt value. While the intention of this analysis in our cohort was not to calculate CPPopt, the PRx-CPP profile was explored briefly across the full cohort (Figure 3). Our cohort demonstrated a gradual decrease in median PRx values with increasing CPPs in the lower range (showing improved pressure reactivity). This is consistent with CPP values below the lower inflection point of the AR curve. It is also consistent with the fact that these patients likely also had high ICP and PRx was correlated with ICP. Interestingly, the curve remained relatively flat at higher CPP values - PRx values remaining low within a large CPP range of 60 to 100mmHg. There was no significant rise of PRx values at higher CPP values. It would seem that in this cohort of children with severe TBI, pressure reactivity remains relatively intact at higher values of CPPs within the range reflected here. This finding is similar to that of Brady *et al.* as their PRx versus 5mmHg CPP bins showed lower values of PRx at the upper bins of CPP – pressure reactivity was intact at CPPs as high as 100mmHg[6]. However, differences in methodology between our study and that of Brady *et al.* must be acknowledged, as we plotted median CPP per bin from the hourly data, whereas that group plotted a mean of individual patient means, with equal weight assigned to each patient. While this may impact CPPopt calculations, the overall trend between PRx and CPP seems to be consistent. Our findings could suggest that children can tolerate higher levels of CPP and have a more robust vascular protection against high CPP values compared to adults. In contrast, Lewis *et al.* show the characteristic U-shape with PRx plotted against CPP, with authors suggesting that the group's CPPopt range is 60-65mmHg, which is lower than reported for adults, but higher than values that we would normally target for perfusion purposes. Upper levels of CPP corresponded to higher PRx values and therefore more impaired pressure reactivity[3], a finding that is not confirmed in our data. Again, the therapeutic strategy at individual institutions may affect the results.

Adult studies have demonstrated this signature U-shaped curve and have found that pressure reactivity deteriorates at a CPP below 60mmHg and above 80mmHg. However, some findings do not see such a robust upper CPP limit despite still producing this characteristic U-shape, with higher absolute values of PRx corresponding with lower levels of CPP compared to higher CPPs[48]. One possible explanation for this is that cerebral vessels may have better compensation for hypertension rather than hypotension. Also, if vasoreactivity is intact, one would expect an active response across a wider plateau.

Some caveats are important: the purpose of this specific analysis was purely to depict the relationship between PRx and CPP, not to calculate CPPopt for the cohort. Therefore, methodological steps of CPPopt calculation were not followed, and all PRx values were included in the CPP bin calculation, even if it included < 2.5% of the total dataset[27]. Note that this analysis is a summary of the entire cohort's dataset, and individual PRx-CPP relationship curves may look different. In addition, clinical management of severe TBI patients at Red Cross War Memorial Children's Hospital does not follow a CPP-driven approach. CPP management considers ICP and brain tissue oxygenation (PbtO2), as well as radiological findings, and while a minimum threshold of 40-50mmHg (with an age-dependent approach) is maintained, CPP values above 50mmHg are not targeted when ICP and PbtO2 are acceptable. This is to avoid overtreatment, and the risk of unnecessary treatment complications that comes with blood pressure manipulation[40]. Therefore, the CPP range may not reflect higher values, and where these higher values occur, they do so spontaneously, and usually in response to an active CPP augmentation approach. These factors may account for some of the differences of findings between analyses.

Further analysis is needed to investigate this PRx-CPP relationship in children. Additionally, the age dependent nature of CPP should be explored. The median age of our cohort was 6.63 years old with a range of 4 days to 14 years old. It is acknowledged that there are physiological differences within the paediatric population, and physiological variables such as CPP and ICP vary with age. Therefore, investigations into the relationship between PRx and monitoring variables at specific age groups is needed.

3. The relationship between PRx and outcome

Summary statistics for PRx and the duration of time spent above thresholds for mortality described in published literature (0, 0.25 and 0.3) as well as the threshold of 0.2 derived from this cohort's data, showed that there is a difference in PRx between outcome groups. These data reflect previous findings in children[3, 43], and suggest that pressure reactivity as measured by PRx, is disturbed in patients with a poor prognosis, and that this disturbance can continue throughout the first 7-10 days of monitoring. An ongoing trend of abnormal PRx values may serve as an indicator of poor prognosis to the treating clinician, but the impact of treatment on this disturbance remains to be shown.

This study found that median PRx is significantly associated with *mortality*, even when ICP, CPP, and GCS are included as co-variates. The odds ratio for PRx in the multiple regression analysis was 1.62 with a 95% CI of 1.20 – 2.19 ($p = 0.002$). Median ICP and GCS also had strong associations with mortality in this model (odds ratio of 1.27; 95% CI of 1.05 – 1.53; $p = 0.013$ and odds ratio 0.63; 95% CI of 0.44 – 0.90; $p = 0.012$ respectively). Median PRx seems to have a weaker yet still significant association with *dichotomized outcome* (odds ratio of 1.28, 95% CI of 1.07 – 1.52; $p = 0.007$). The same is true for ICP (odds ratio of 1.16, 95% CI 1.04 – 1.29; $p = 0.008$). However, GCS showed a slightly stronger relationship with dichotomized outcome (odds ratio 0.73, 95% CI of 0.59 – 0.89; $p = 0.002$) compared to mortality (odds ratio of 0.63, 95% CI of 0.44 – 0.90; $p = 0.012$). Further regression analysis rejected median PRx, ICP, and CPP as independent predictors of *functional outcome*. This result suggests that the original regression analysis done (where median PRx and ICP were found to have significant associations with dichotomized outcome) was influenced by the inclusion of the non-survivors in the unfavourable cohort. Therefore, the main finding from the regression analysis suggests that PRx, ICP and GCS are independently associated with mortality in children with severe TBI.

This finding is similar to that of Lewis *et al.*[3] who found an odds ratio for PRx and mortality of 1.67 (95% CI of 1.26 – 2.23; $p < 0.001$). However that regression analysis did not use ICP or GCS as co-variates, as they adjusted for monitoring day and admission day on which monitoring commenced only. Our analysis showed that the odds ratio decreased when the co-variates were added, suggesting that ICP and GCS should be included in the analysis with outcome to produce a more accurate indication of the strength of the relationship between PRx and mortality. The adult study by Sorrentino *et al.* performed a multiple logistic regression that included age, gender, GCS, CPP, ICP, and PRx as predictor variables. They found that age, GCS, ICP, and PRx have independent associations with mortality, with an odds ratio for PRx of 1.63 ($p = 0.014$)[32].

To further investigate the ability of PRx and ICP in predicting mortality, ROC analysis was done. Using the overall median measures, PRx had a greater predictive ability compared to ICP. CPP had the weakest predictive ability for mortality. Median time spent above the investigated PRx thresholds all showed strong predictive abilities, with all area under the curve (AUC) values being above 0.86, thus suggesting that PRx may have a dose-dependent effect on mortality prediction. Although the percentage of time ICP was above 20mmHg was the strongest predictor of mortality of all the variables tested, PRx remained a powerful predictor of mortality when ICP is considered normal, confirming the independent association with mortality. These data suggest that while raised ICP has an important role in injury severity and outcome, PRx does not just reflect abnormal ICP but offers additional insight into disease mechanisms at play.

Overall, the regression and ROC analyses from this study showed that PRx is a strong and independent predictor of mortality rather than unfavourable outcome, even when ICP is considered normal.

4. Implications of this study

This study suggests that PRx may be a useful prognostic variable in children with severe TBI. This study is the largest study to date in children. This pressure reactivity indicator shows promise in paediatrics as it may provide additional information about intracranial dynamics of the injured developing brain, over and above ICP and CPP measures. The differences between PRx in children and adults requires further exploration, as does the potential impact of PRx monitoring on treatment strategies.

Future research on pressure reactivity in paediatric TBI should explore PRx in a dose-dependent analysis: classification of PRx could include both a temporal element (time spent above threshold value) and a measurement of the distance of PRx was from that threshold, which could then be normalised for monitoring duration. This dose description of PRx would account for a more inclusive and descriptive analysis of PRx because a single measurement (like the median over time) does not accurately explain such a dynamic and complex variable. Note that while PRx (both median and time-dependent variables) had strong prognostic abilities in this cohort, the variable with the strongest predictor of mortality is percentage time spent with abnormal ICP values. It is likely that future prognostication methods will need to take the dynamic nature of multiple variables and their interactions into account.

It is widely accepted that PRx has a prognostic ability in adults, however the clinical use of PRx has been highlighted in the creation of potentially individualised patient CPPopt targets. There are other potential strategies. For example, management of CPP at higher levels may be more liberal in patients with good vasoreactivity, whereas a narrower range may be advisable in a patient with impaired vasoreactivity or a stronger ICP-targeted approach may be preferred. Further investigations into PRx-CPP relationships in paediatric severe TBI are required.

5. Limitations of this study

While this study examines PRx in the largest known cohort of children, there are several limitations that need to be acknowledged and considered. The use of PRx is useful as it is a graded and continuous measurement of intracranial dynamics that can be used to aid clinical management; however we must be reminded that it is an *indicator* of pressure reactivity, and not a direct measurement. No formal autoregulation testing was done for comparison, and so validation of PRx with a more complex static measure of autoregulation is lacking. Additionally, PRx itself is an inherently noisy signal. Some of this work has already been done in adults and may be extrapolatable, but this cannot automatically be assumed.

A notable limitation to this and many other PRx studies that investigate the relationship between GCS and PRx, and PRx and outcome is the problem of taking a single summary measure for the entire patient's monitoring period. A single mean or median over the entire clinical course excludes intermittent periods of derangements and overall variability. The patient's full disease course over time is not well represented, and a single descriptive variable is not sufficient to explain physiological measures as dynamic as PRx, ICP, and CPP. It is also recognized that pressure reactivity may vary over the time course after injury, and summary measures dilute the impact of deranged variables that may be harmful but are limited to a short time period. This study attempted to use hourly data where possible, however outcome analysis still made use of the single overall median. In addition, dichotomized outcome was used instead of the GOS-E scores from 1 – 8. The choice to sacrifice variability of outcome description was made to include as many patients as possible in this analysis. Much larger cohort numbers would be needed for a finer categorical analysis of outcome groups.

Furthermore, the radiological findings on brain imaging were not included in this study due to the complexity of classification, especially in paediatric TBI, for which there is no specific descriptive/ classification system currently available. In addition, the effect of medication and surgical intervention (e.g. decompressive craniectomy surgery) was not included in the analysis.

Age differences within this paediatric cohort have not been taken into consideration. It may be true that the associations of PRx vary across the physiological diversity of ages 0-13 years. However, cohort numbers required to do an age-dependent analysis would be larger. Further, this cohort therefore represents a heterogenous population that would reflect the real-world context and having results that are generalizable to the wider paediatric population is of benefit and can provide a platform for future research. Currently, we do not even have age-specific thresholds for ICP.

Although the high frequency data were collected prospectively, some of the clinical and demographic data were gathered retrospectively and missing data was a challenge. Further, given the large dataset error may have occurred during manual data collection, although measures were taken to minimise this risk.

An additional limitation is that multiple testing was not controlled for in this analysis; however, the purpose of this study was to produce hypothesis-generating data, on which future paediatric studies can be based.

Chapter 7: Conclusion

This study calculated, described, and analysed PRx in the largest known cohort of children with severe TBI. Overall median PRx was found to have a strong prognostic ability for outcome (particularly mortality) that was independent of but influenced by ICP, CPP, and GCS. Time spent with elevated ICP was the strongest predictor of mortality, therefore the combination of several PRx and ICP related variables will be important for overall prognostication.

Further analysis is required to improve our understanding of PRx and pressure reactivity in children with severe TBI. This study provides a platform for future work that aims to address CA loss and its implications in this vulnerable population.

APPENDIX A

Table 1: Descriptive monitoring variables for survivors and by functional outcome groups

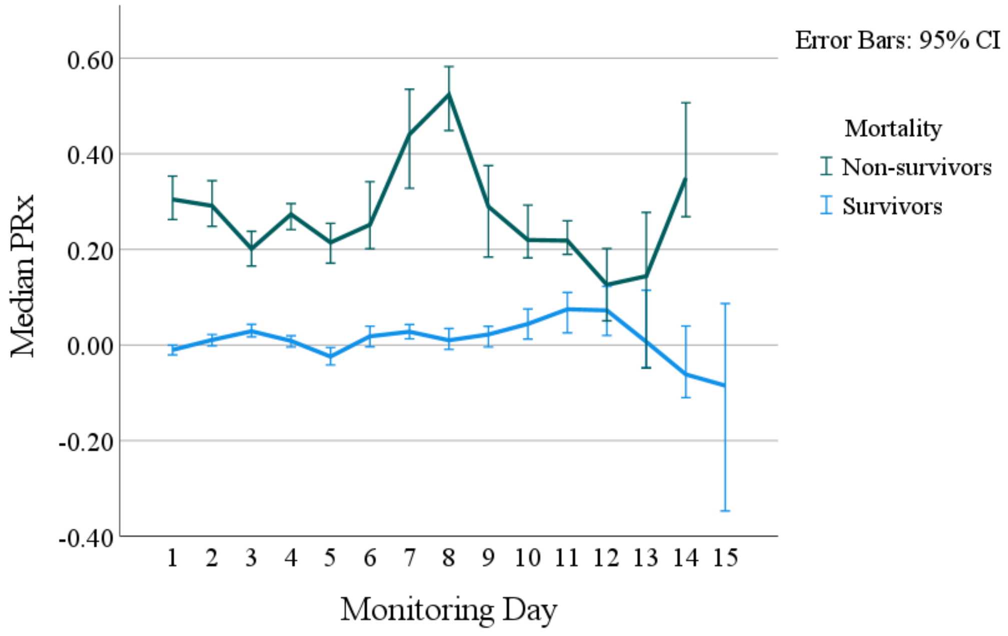
Variable	**Survivors**	**Good functional outcome**	**Bad functional outcome**	***p***
Total, n (%)	175	138 (78.9)	37 (21.1)	
Overall ICP, median, mmHg	12.4 (9.6 – 15.3)	11.4 (8.7 – 13.8)	13.5 (10.8 – 15.8)	**0.006**
ICP > 20 (median % time)	4.8 (0.0 – 13.2)	3.7 (0.0 – 11.0)	13.2 (2.0 – 20.5)	**0.003**
Overall MAP, median, mmHg	80.0 (74.0 – 85.6)	80.2 (74.1 – 85.6)	80.5 (74.0 – 84.9)	0.808
Overall CPP, median, mmHg	67.7 (60.2 – 73.5)	68.3 (61.2 – 74.0)	67.6 (59.7 – 71.9)	0.200
Overall PRx, median	0.01 (-0.12 – 0.20)	-0.03 (-0.15 – 0.11)	0.02 (-0.10 – 0.24)	0.051
PRx > 0 (median % time)	55.3 (34.6 – 74.0)	46.5 (30.5 – 67.3)	55.8 (36.9 – 74.0)	0.114
PRx > 0.2 (median % time)	25.0 (11.8 – 44.1)	19.5 (10.5 – 36.2)	29.4 (17.5 – 17.2)	**0.027**
PRx > 0.25 (median % time)	19.5 (8.9 – 37.8)	14.1 (7.0 – 28.6)	22.4 (14.2 – 45.8)	**0.013**
PRx > 0.3 (median % time)	15.2 (6.0 – 33.3)	9.6 (4.7 – 21.8)	18.3 (11.0 – 42.7)	**0.008**

Note: medians reported with 25th and 75th percentiles in brackets. Glasgow Outcome Scale Extended version for functional outcome groups as follows: good = 1 - 4, and bad = 5 - 7. All numbers rounded to one decimal place except for PRx and *p* values. Bold *p* values indicate statistical significance between functional outcome groups at the 0.05 level. ICP = intracranial pressure; MAP = mean arterial pressure; CPP = cerebral perfusion pressure; PRx = pressure reactivity index.

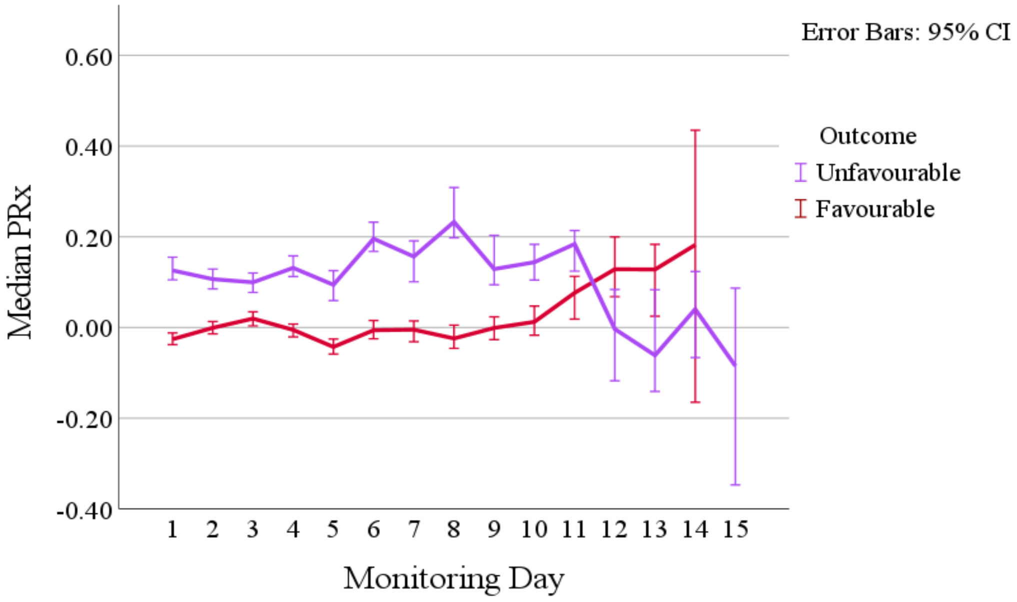
APPENDIX B

Figure 1: The temporal profile of median PRx over the full 15 days of monitoring by mortality and dichotomized outcome groups

1.1 Median PRx over time for survivors and non-survivors



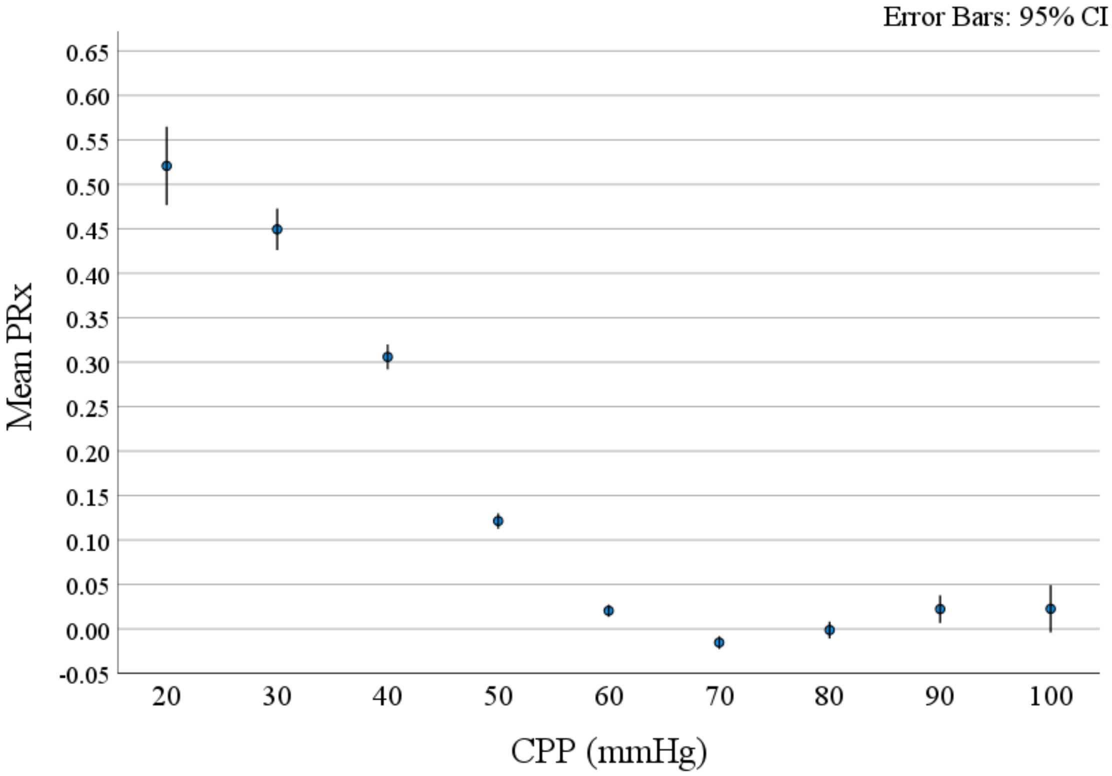
1.2 Median PRx over time for favourable and unfavourable outcome groups



Median PRx plotted for the full 15 days of monitoring, calculated from hourly data. Error bars represent the 95% confidence interval (CI). PRx = pressure reactivity index.

APPENDIX C

Figure 1: Mean PRx versus CPP

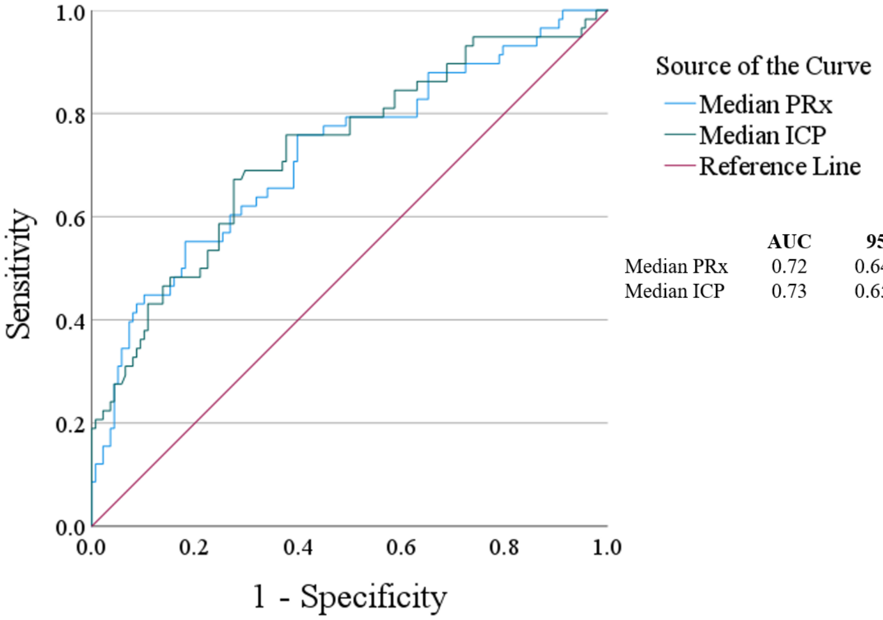


Mean PRx of 10mmHg CPP bins of the entire 196 patient cohort, calculated from hourly data. Error bars represent the 95% confidence interval (CI). PRx = pressure reactivity index; CPP = cerebral perfusion pressure.

APPENDIX D

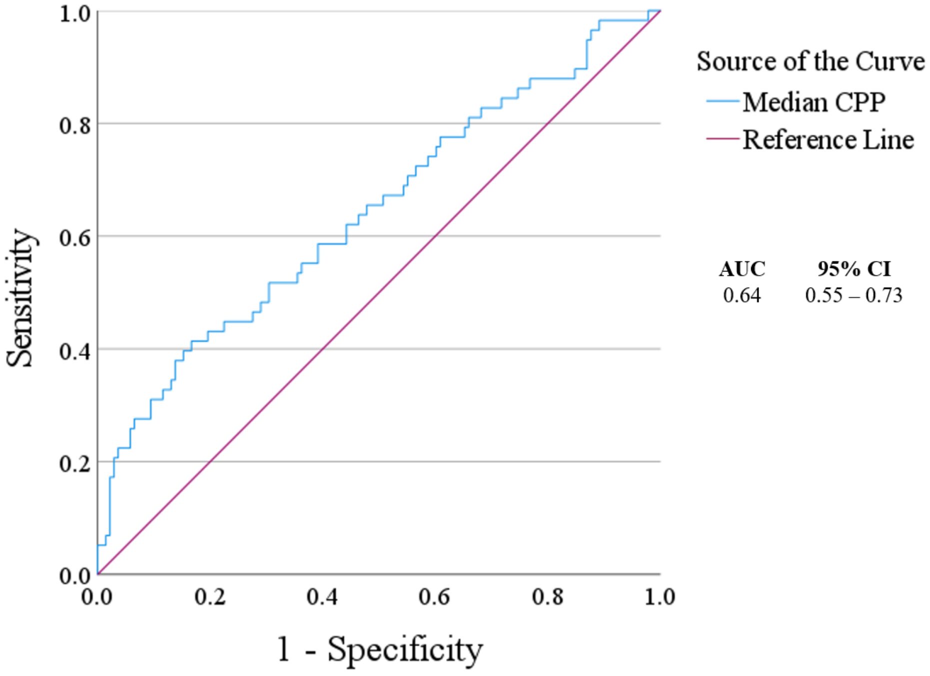
Figure 1: Receiver operating curves using median PRx, ICP and CPP in unfavourable outcome prediction

1.1 ROC for median PRx and ICP for unfavourable outcome



	AUC	95% CI
Median PRx	0.72	0.64 – 0.80
Median ICP	0.73	0.65 – 0.81

1.2 ROC for median CPP for unfavourable outcome

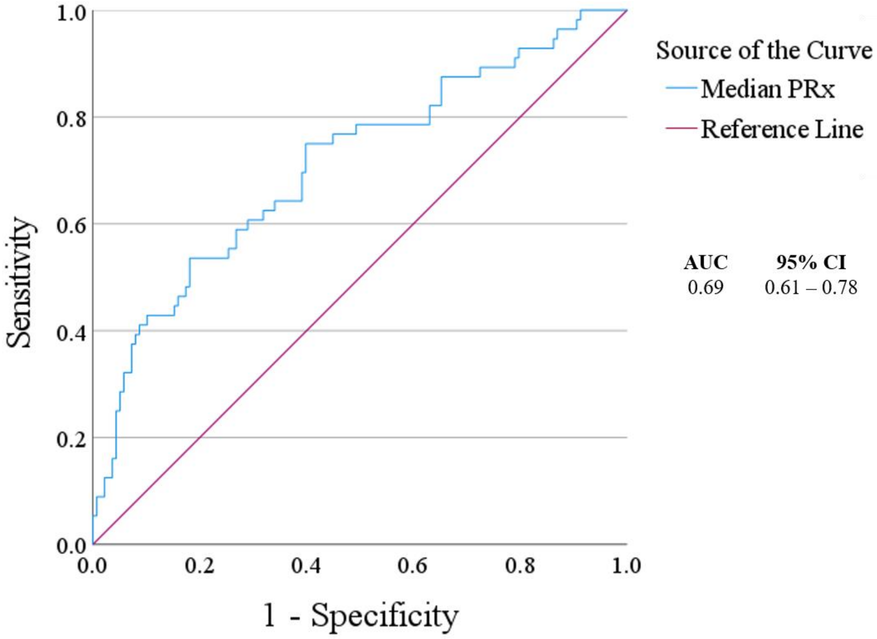


AUC	95% CI
0.64	0.55 – 0.73

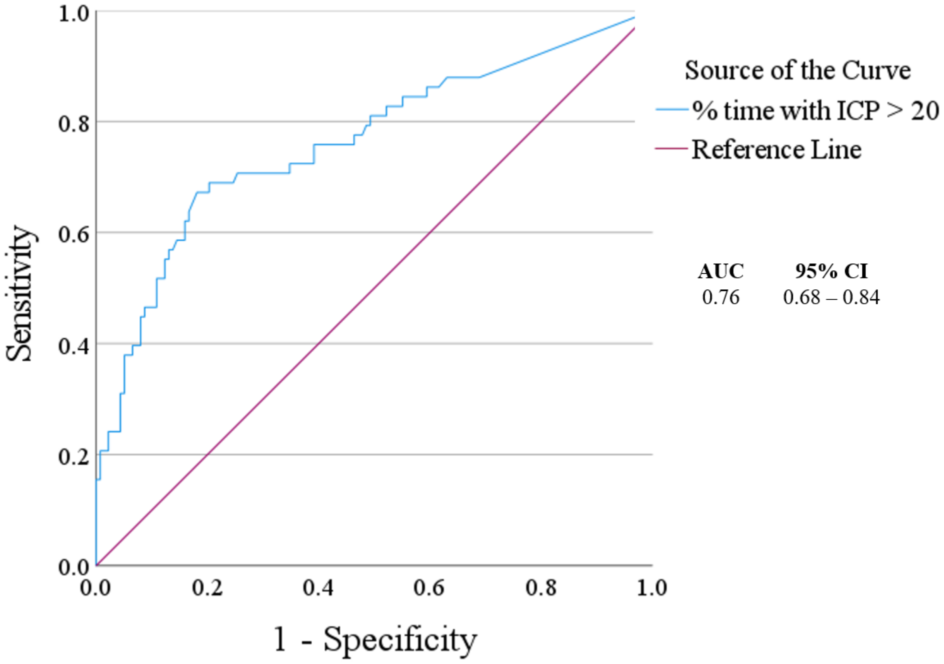
Receiver operating curves (ROCs) for unfavourable outcome show the predictive strength of the plotted variables, with the greatest area under the curve indicating the strongest predictive ability. AUC = area under curve, presented with 95% confidence intervals (CI). All numbers rounded to two decimal places. PRx = pressure reactivity; ICP = intracranial pressure; CPP = cerebral perfusion pressure

Figure 2: Receiver operating curves using specific inclusion criteria in unfavourable outcome prediction

2.1 ROC for median PRx for unfavourable outcome (hourly ICP ≤ 20 only)

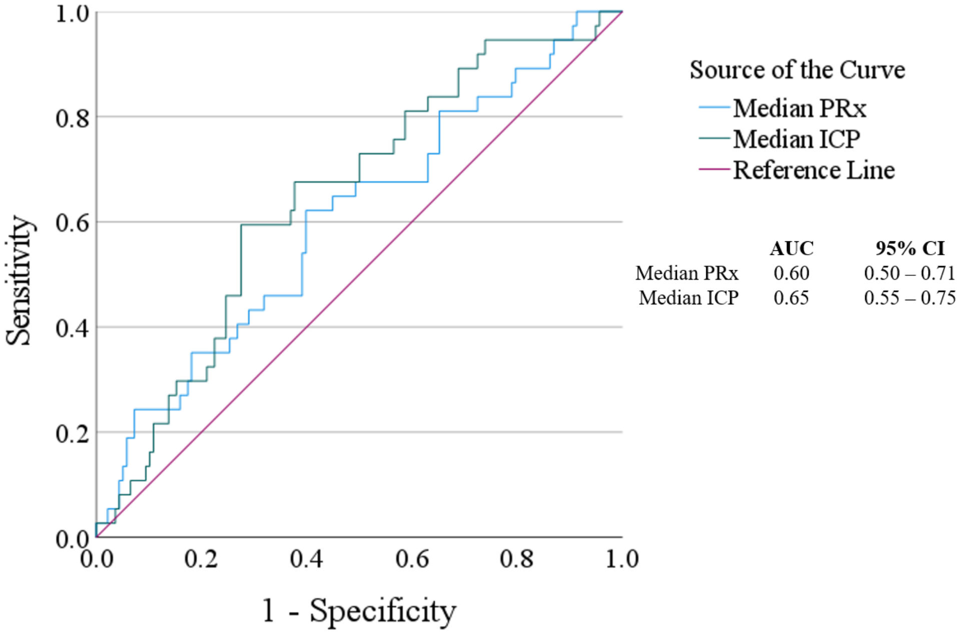


2.2 ROC for median % time ICP > 20 for unfavourable outcome



Receiver operating curves (ROCs) for unfavourable outcome show the predictive strength of the plotted variables, with the greatest area under the curve indicating the strongest predictive ability. Variables calculated using hourly data. AUC = area under curve, presented with the 95% confidence interval (CI). All numbers rounded to two decimal places. PRx = pressure reactivity; ICP = intracranial pressure.

Figure 3: Receiver operating curve for median PRx and ICP for bad functional outcome



	AUC	95% CI
Median PRx	0.60	0.50 – 0.71
Median ICP	0.65	0.55 – 0.75

Receiver operating curve (ROC) for bad functional outcome shows the predictive strength of the plotted variables, with the greatest area under the curve indicating the strongest predictive ability. AUC = area under curve, presented with 95% confidence intervals (CI). All numbers rounded to two decimal places. PRx = pressure reactivity; ICP = intracranial pressure.

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This thesis used the Journal of Neurosurgery referencing style.

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