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Exploration of the relationship between partial pressure of brain tissue oxygen and intracranial pressure

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ABSTRACT

Introduction: Partial pressure of brain tissue oxygen (PbtO2) has been shown to be a safe an effective monitoring modality to compliment intracranial pressure (ICP) monitoring. It is related to metabolic activity, disease severity and mortality.
Research question: Understanding the complex relationship between PbtO2 and ICP for patients with traumatic brain injury will enable better clinical decision making beyond simple threshold treatment strategies.
Material and methods: Patients with PbtO2 monitoring were identified from the BrainIT database, a multi-centre dataset, containing minute by minute PbtO2 and ICP readings. Missing data was imputed and a multi-level log-normal regression model with a compound symmetry correlation structure was built. This accounted for any increased correlation due to the repeated measurements. The model was adjusted for mean arterial pressure and the partial pressure of carbon dioxide. Non-linearity was assessed using analysis of deviance and trends using expected marginal means.
Results: 11 subjects with over 82,000 readings were included. They had a median age of 38 (IQR: 37–47), 73% were male, a median length of stay of 11.8 (IQR: 6.6–19.7) days and a median extended Glasgow outcome scale of 7.00 (IQR: 5–8).
There is a statistically significant ($p < 0.001$) non-linear effect of ICP on PbtO2. With an overall increase in PbtO2 of 5.2% (95% CI 4%–6.4%, $p < 0.001$) for a 10 mmHg increase in ICP below 22 mmHg and a decrease of 5.5% (95% CI 2.7%–8.3%, $p=<0.001$) in PbtO2 for a 10 mmHg increase in ICP above 22 mmHg. As well as a decrease of 40.9% (95% CI 2.3%–64.3%, $p = 0.040$) in PbtO2 per day in the intensive care unit.
Discussion and conclusion: This model demonstrates that there is a significant non-linear relationship between ICP and PbtO2, however, this is a small heterogeneous cohort and further validation will be required.

1. Introduction

Traumatic brain injury (TBI) is a leading cause of death and long-term disability worldwide, with 346 (interquartile range (IQR) 298, 401) per 100,000 people injured every year (Traumatic brain injury, 2022). In Europe, mortality from TBI is between 9 and 28.1 per 100,000 people with similar incidence recorded in America (Brazinova et al., 2021). Clinical management of this population is focused on minimising any secondary injury, such as ischemia or raised intracranial pressure (ICP) (Carney et al., 2016). To help quantify the current pathophysiology and provide information on changing injury status, a variety of vital signs monitoring modalities are used concurrently in neuro-intensive care unit (ICU)s. Monitoring of ICP is indicated in the current neurotrauma guidelines for patients with TBI (Carney et al., 2016) and management protocols including ICP have also been shown to have better functional outcomes (Chesnut et al., 2023). Metabolic activity, disease severity and mortality is related to the partial pressure of brain tissue oxygen (PbtO2) (Ngwenya et al., 2016). Monitoring PbtO2

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has been shown to be safe, effective, and when used in conjunction with ICP monitoring, adds additional contextual information on the overall patient state (Okonkwo et al., 2017).

The currently proposed treatment protocols using a combined PbtO2 and ICP monitoring strategy are still using singular cut-offs, 20 mmHg for PbtO2 and 22 mmHg for ICP, for these parameters (Bernard et al., 2022; BONANZA-GT, 2020). Worsening outcome driven by ICP has a dynamic threshold that is related to time above this cut-off (Güiza et al., 2015). There is also a known non-linear effect of PbtO2 on cerebral perfusion pressure (CPP) (Megjhani et al., 2023), which is the net pressure differential driving cerebral blood flow across the cerebrovascular bed and directly influenced by ICP. The relationship between these two parameters has been investigated previously (Flynn et al., 2015) and the non-linear nature of the relationship assessed in a paediatric context (Figaji et al., 2009; Rohlwink et al., 2012). Finally, the increased correlation in temporal trends between PbtO2 and ICP has been quantified and shown to improve the overall fit when accounted for (Zeiler et al., 2021).

The main aim of this study was to investigate the non-linear nature of the relationship between PbtO2 and ICP whilst accounting for the temporal correlation over the length of the ICU stay. The study will contribute to a more complete understanding of the complex relationship for patients with TBI and hence enable better clinical decision making beyond the currently proposed simple threshold treatment strategies.

2. Methods

2.1. Study design

The study utilised a retrospective observational cohort of prospectively collected data from the BrainIT Group clinical database (Shaw et al., 2008). This database consists of 261 TBI patients, recruited from 22 neuro-ICU's across 11 countries as part of two EU framework grants (FP5 QLGT-2002-00160 and FP7 IST-2007-217049). It contains 2.9 million measurements of vital signs monitoring data such as minute by minute arterial blood pressure (ABP), ICP and PbtO2.

2.2. Eligibility

Every patient that had a minimum of 60 min of continuous PbtO2 monitoring values contiguous with continuous ICP monitoring values. All information contained in the database for this study cohort was then extracted.

2.3. Outcomes

The primary outcome for the analysis was minute by minute PbtO2 over the course of the neuro-ICU stay.

2.4. Statistical analysis

All statistical analyses were carried out in the statistical software R (Version 4.4.0) (R Core Team, 2024) using the glmmTMB package (Brooks et al., 2024) for regression modelling, the mice package (van Buuren and Groothuis-Oudshoorn, 2023) for imputation, and the emmeans package (Lenth, 2024) for inference. All categorical data is reported as a count and percentages and all numeric data is reported as median and IQR.

Missing values for all demographic and single episode variables were imputed using multiple imputation via chained equations (MICE). This was carried out with a classification and regression trees (CART) methodology to allow both numeric and categorical data in the same multiple imputation analysis. Time series data was interpolated using a spline methodology to minimise any discontinuities that could be generated.

Table 1
Cohort demographic and outcome summary stratified by the extended Glasgow outcome scale (GOSe).

Characteristic	Overall, N = 11	GOSe: 1–4, N = 3	GOSe: 5–8, N = 8
Gender (Male), n (%)	8 (73%)	2 (67%)	6 (75%)
Age (years), Median (IQR)	38 (37, 47)	38 (38, 51)	38 (33, 44)
Type of Trauma, n (%)			
Fall	6 (60%)	1 (33%)	5 (71%)
Sport	1 (10%)	0 (0%)	1 (14%)
Traffic Accident	3 (30%)	2 (67%)	1 (14%)
GOSe, Median (IQR)[a]	7.00 (4.50, 7.50)	3.00 (2.00, 3.50)	7.00 (6.75, 8.00)
pH, Median (IQR)	7.430 (7.420, 7.450)	7.480 (7.460, 7.500)	7.420 (7.420, 7.430)
pCO2 (mmHg), Median (IQR)[a]	36.0 (32.6, 37.8)	34.2 (32.7, 35.6)	36.0 (33.5, 39.3)
paO2 (mmHg), Median (IQR)[a]	141 (108, 311)	152 (119, 185)	141 (120, 478)
Haematocrit (%), Median (IQR)	27.50 (26.25, 29.50)	23.00 (23.00, 23.00)	28.00 (27.00, 30.00)
Glucose (mmol/l), Median (IQR)	6.16 (5.66, 7.60)	5.66 (5.55, 5.91)	7.41 (6.17, 8.10)
GCS Eye, n (%)[a]			
1	8 (80%)	2 (67%)	6 (86%)
2	2 (20%)	1 (33%)	1 (14%)
GCS Motor, n (%)[a]			
1	8 (80%)	2 (67%)	6 (86%)
2	2 (20%)	1 (33%)	1 (14%)
GCS Verbal, n (%)[a]			
1	8 (80%)	2 (67%)	6 (86%)
2	2 (20%)	1 (33%)	1 (14%)
CT lesion type, n (%)[a]			
Extradural	1 (9.1%)	0 (0%)	1 (13%)
Intraparenchymal	9 (82%)	3 (100%)	6 (75%)
Subdural	1 (9.1%)	0 (0%)	1 (13%)
CT Volume, n (%)[a]			
<25 ml	3 (30%)	0 (0%)	3 (43%)
>25 ml	7 (70%)	3 (100%)	4 (57%)
Initial PbtO2 (mmHg), Median (IQR)[a]	15 (8, 33)	9 (7, 9)	29 (13, 34)
Initial ICP (mmHg), Median (IQR)[a]	13.0 (10.5, 17.0)	13.0 (12.5, 15.0)	13.5 (9.5, 17.8)
Initial ABP (mmHg), Median (IQR)[a]	86 (80, 98)	80 (78, 80)	92 (85, 101)
Length of Stay (days), Median (IQR)	11.8 (6.6, 19.7)	11.8 (10.0, 17.8)	9.5 (6.1, 19.7)

[a] GOSe = Extended Glasgow outcome score, pCO2 = Partial pressure of carbon dioxide, paO2 = Arterial oxygen pressure, GCS = Glasgow comma scale, CT = Computed tomography, PbtO2 = Partial pressure of brain tissue oxygen, ICP = Intracranial pressure, ABP = Arterial blood pressure.

Three multi-level log-normal regression models with compound symmetry correlation structures were constructed with increasing non-linear complexities. A multi-level model compound symmetry correlation structure was used to enable the inclusion of the hierarchical structure of repeated measurements per subject whist accounting for the increased correlation between the points that exists. The log-normal distributional assumption was then used to ensure that predicted PbtO2 cannot be negative.

The initial regression model built was a simple linear interaction model between the time difference from each vital sign's measurement and neuro-ICU admission, called the measurement time for simplicity, and the ICP predicting the PbtO2. The inclusion of the temporal index, measurement time, in the modelling process will account for some of the bias caused from missing confounders.

Secondly, an interaction model was created between the measurement time and a non-linear cubic regression spline fit, with 5 degrees of freedom, of the ICP. Lastly, a model of the interaction between non-linear cubic regression spline fits of both measurement time and ICP was built, with 5 and 5 degrees of freedom respectively. Finally, as a sensitivity analysis a model including the non-linear interaction between ICP and measurement time and additionally accounting for mean

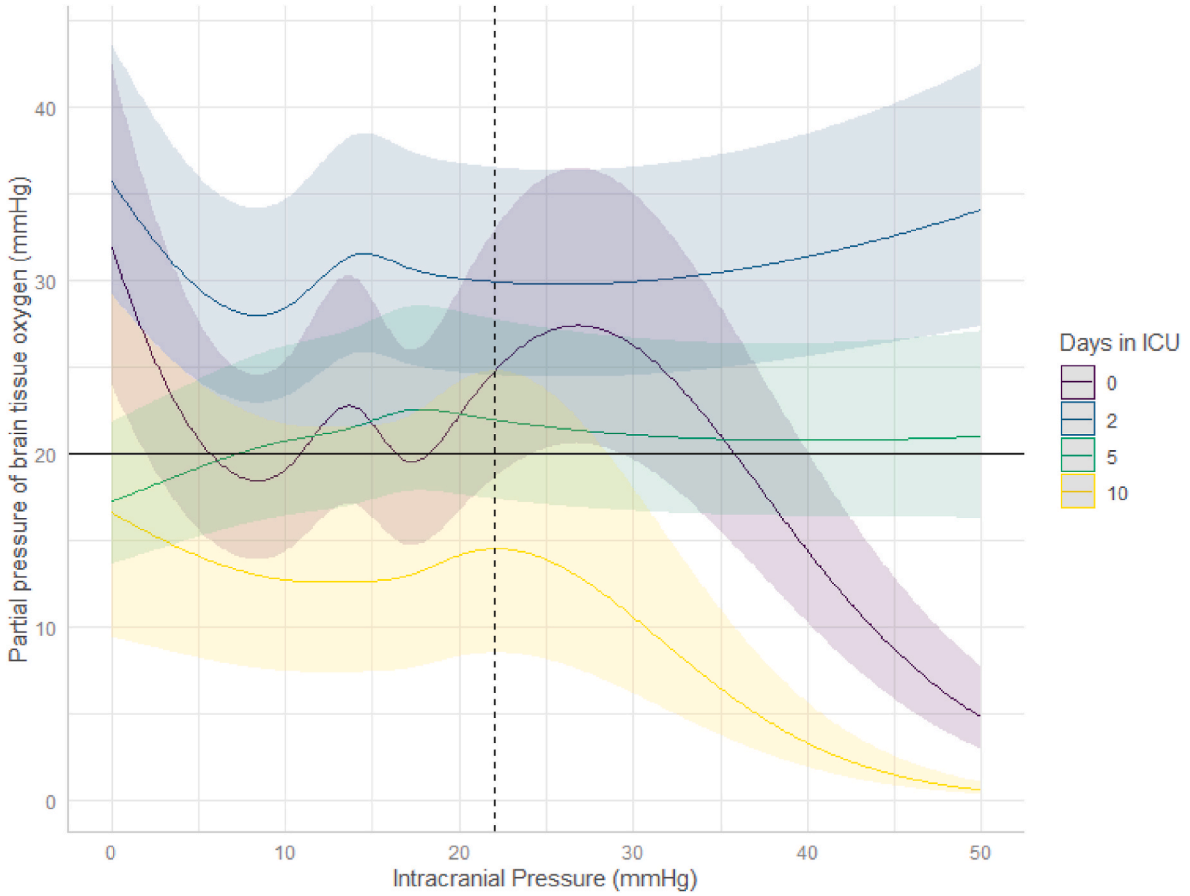

Fig. 1. Partial pressure of brain tissue oxygen over intracranial pressure stratified by days in ICU. Times shown are at admission and days 2, 5 and 10.

arterial blood pressure (MAP) and the partial pressure of carbon dioxide (PaCO2) was built.

The non-linearity assumption was assessed using chi-squared deviance testing between the initial linear interaction model and the second model with a non-linear ICP. Subsequently improvement in overall fit was then assessed, again with chi-squared deviance testing, between the second and third model with non-linearities in both measurement time and ICP.

A marginal effects methodology was then employed to quantify these non-linear changes over localised differences in both measurement time and ICP. Subsequently this approach was also used to generate visualisations of these continuous non-linear changes as both localised strata as well as a final continuous surface.

The zeroing time of the PbtO2 catheter is incorporated into the main analysis using the non-linear trend in PbtO2 over the measurement time. Enabling the minute-by-minute PbtO2 to be estimated over both the "settling in" time, of approximately 2 h, and all subsequent measurements. A sensitivity analysis was carried out to ensure that any "settling in" time for the PbtO2 catheter has not affected the results. The first 2 h of data was removed from each subject's data and the overall trend marginal effects analysis was carried out again. To understand if the inclusion criteria of a minimum of 60 min of continuous data affected the overall outcome estimation, a sensitivity analysis was carried out. The minimum data amount was raised to 24 h and the overall trend analysis was rerun.

3. Results

Eleven subjects with 82060 minute by minute vital signs measurements were included in the final analysis. They had a median age of 38 (IQR: 37–47) of which 73% were male and 60% of the trauma were falls. They had a median length of stay of 11.8 (IQR: 6.6–19.7) days and a median extended Glasgow outcome scale of 7.00 (IQR: 5–8). There were 15807 (19.3%) measurements of ICP above 20 mmHg and 9777 (11.9%) above 22 mmHg on aggregate across the whole cohort. All other demographics are summarised in Table 1.

There is a statistically significant ($p < 0.001$) non-linear effect of ICP on PbtO2 based on the Chi-squared test of deviance. The fit is significantly improved ($p < 0.001$) by assuming non-linearity for measurement time, assessed via a Chi-squared test of deviance, compared to only assuming non-linearity in ICP.

An overall increase in PbtO2 of 5.2% (95% CI 4%–6.4%, $p < 0.001$) was observed for a 10 mmHg increase in ICP. Conversely there was a decrease in PbtO2 of 5.5% (95% CI 2.7%–8.3%, p=<0.001) for a 10 mmHg increase in ICP above 22 mmHg. The non-linearity of this relationship is illustrated in Fig. 1 stratified at four different times in the patients ICU stay; on the day of admission, day two, day five and finally day 10.

There is a significant overall decrease of 40.9% (95% CI 2.3%–64.3%, $p = 0.040$) in PbtO2 for the first seven days in ICU. With an increase of 41.7% (95% CI 63.8%–22.6%, p=<0.001) in PbtO2 over the first two days then a decrease of 23.1% (95% CI 11.2%–33.5%, p=<0.001) over the next two.

From the first sensitivity analysis there were significant relationships found for both MAP and PaCO2 with a PbtO2 increase of 0.23% (95% CI 0.22%–0.25%, p=<0.001) of a unit increase in MAP and a PbtO2 decrease of 0.16% (95% CI 0.13%–0.19%, p=<0.001) from a unit increase in PaCO2.

The sensitivity analyses on the whole showed the same overall trend information as the main analysis. The addition of MAP and PaCO2 had a significant overall decrease of 42.2% (95% CI 11.1%–62.5%, $p = 0.013$) in PbtO2 for the first seven days in ICU. After removing the first 2 h of

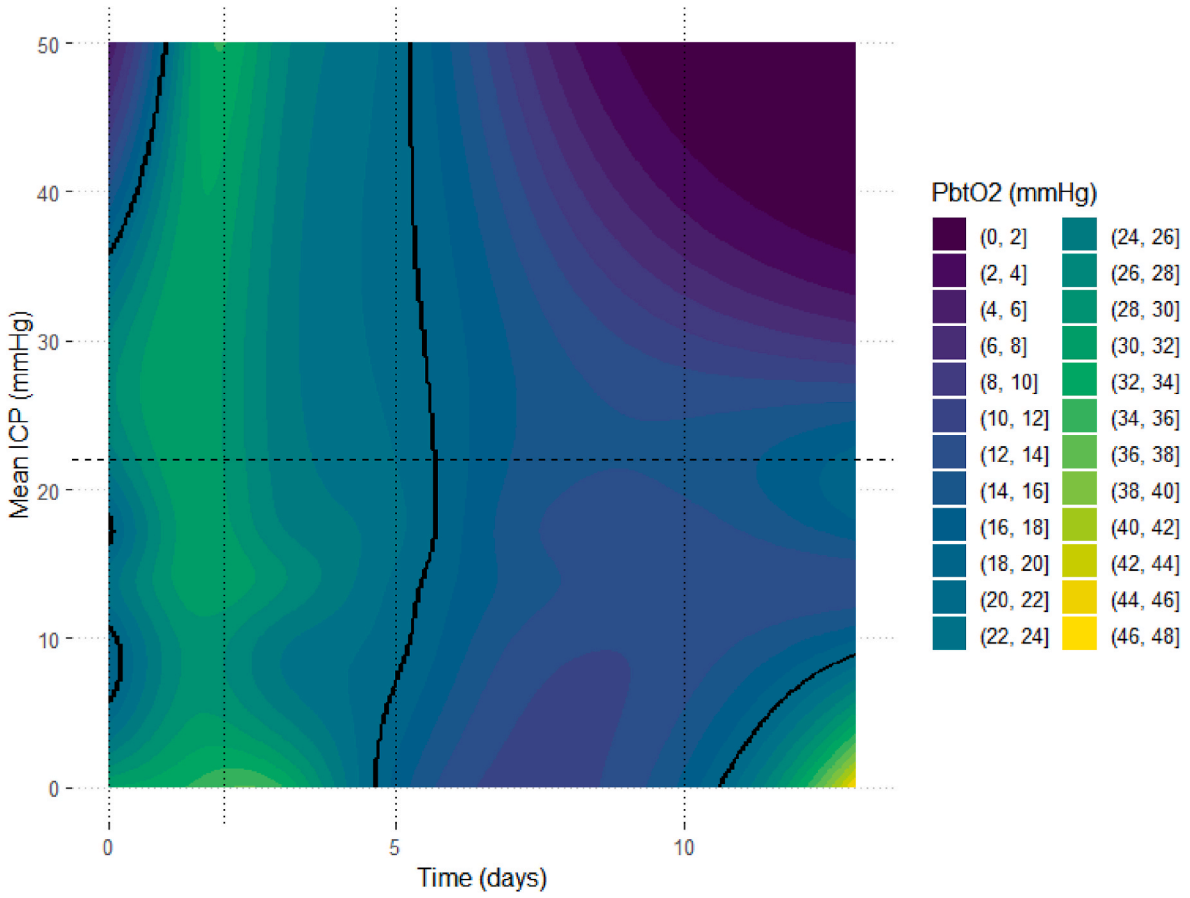

Fig. 2. Regression model of partial pressure of brain tissue oxygen (PbtO2) estimated over a non-linear intracranial pressure (ICP) and non-linear days in ICU. With delineation added for ICP≤22 (dashed line), PbtO2≤20 (solid line) and vertical dotted indicators for Fig. 1 time strata.

data to account for any "settling in" time of the catheter there remained a significant overall decrease of 42.3% (95% CI 11.7%–62.3%, p = 0.011) in PbtO2 for the first seven days in ICU. Finally, increasing the minimum continuous monitoring time inclusion criteria from 60 min to 1 day also gave a similar significant overall decrease of 42.7% (95% CI 10.3%–63.4%, p = 0.015) in PbtO2 for the first seven days in ICU.

Finally, the full non-linear visualisation of PbtO2 against ICP over days in ICU is shown in Fig. 2, highlighting the current common trial protocol thresholds. A second visualisation of the of PbtO2 against ICP over days in ICU adjusting for MAP and PaCO2 is shown in Fig. 3.

4. Discussion

A key hypothesis driving two clinical trials (BOOST3 (Bernard et al., 2022) and BONANZA-GT (BONANZA-GT, 2020)) of combined ICP and PbtO2 protocols currently under way is that an ICP driven treatment plan alone, such as maintenance of intracranial pressure under 22 mmHg in adults, is not enough to guarantee good cerebral blood flow (CBF) and oxygen delivery in traumatic brain injury patients.

The current study cohort were managed using a best practice ICP strategy. It can be seen from both Figs. 1 and 2 as well as the marginal effect analysis that there is a significant decrease, 23.1% (95% CI 11.2%–33.5%, p=<0.001), in PbtO2 over time from day two of their ICU stay. With the PbtO2 dropping below the proposed threshold of 20 mmHg around day 5 with some variation in this estimate based on the current ICP measurement.

Fig. 2 visualises the overall non-linear nature of the relationship of both ICP and measurement time on the estimated PbtO2. With every combination of ICP and measurement time shown on the plot as a colour representing the estimated value of PbtO2. In an attempt to simplify the understanding of this complex interplay Fig. 1 shows a set of PbtO2 projections at a known set of measurement times, admission, day two, day five and day ten. These projections are then the direct effect of ICP on PbtO2 at a given static time, these times are then highlighted on Fig. 2 as four vertical dotted lines. A solid black line is drawn on the contour of the visualisation to delineate above and below 20 mmHg of PbtO2. Finally, a horizontal dashed line indicates ICPs above and below 20 mmHg.

This model demonstrates that in patients admitted with TBI there is a significant non-linear relationship between ICP, days in ICU and the PbtO2 ($p < 0.001$). Therefore, a clinical management strategy for these patients may be more effective if it accounts explicitly for PbtO2, over a solely ICP focused strategy, as the length of stay in ICU increases. However, for shorter lengths of stay the ICP focused strategy may maintain adequate oxygen delivery. Fig. 2 reinforces the overall decreasing trend in PbtO2 across the subjects' stay in ICU, however, it also highlights that there is adequate oxygen delivered over periods less than five days.

The explicit inclusion of both MAP and PaCO2 in the non-liner interaction model moderately attenuated the effect of ICP and measurement time on PbtO2, however, the main decreasing trend and overall significance remained the same. The removal of the initial 2 h of each subject's data to reduce any "settling in" time of the PbtO2 catheter also showed there was no effective difference over the main analysis, indicating the non-linear effect of measurement time on PbtO2 had effectively accounted for the issue.

The primary limitation of this study is the number of participants included in the main analysis cohort. Even though over 82060 minute by minute measurements were included in the final analysis, enabling a comprehensive analysis of the non-linear aspects of this cohort

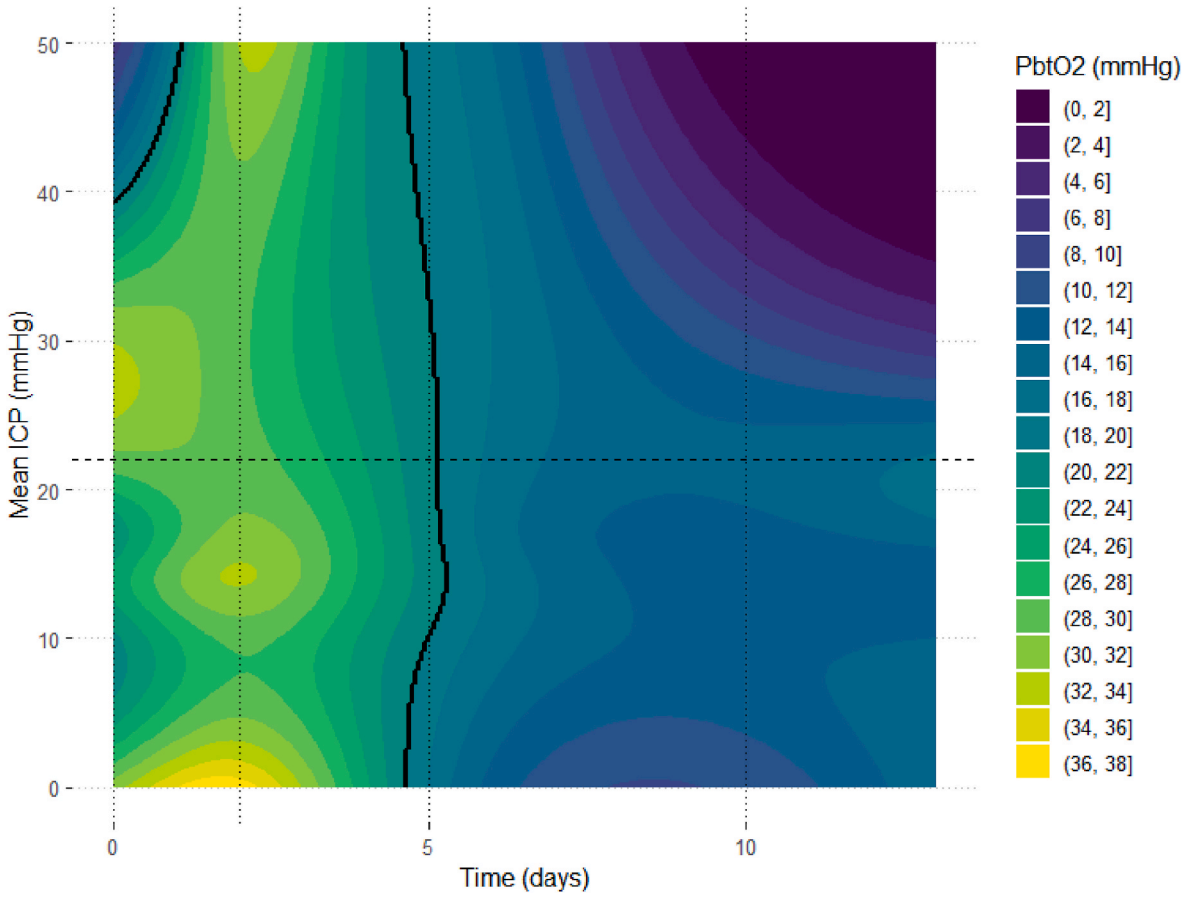

Fig. 3. Regression model of partial pressure of brain tissue oxygen (PbtO2) estimated over a non-linear intracranial pressure (ICP) and non-linear days in ICU adjusted for mean arterial blood pressure (MAP) and partial pressure of arterial carbon dioxide (PaCO2). With delineation added for ICP≤22 (dashed line), PbtO2≤20 (solid line) and vertical dotted indicators for the time strata at admission, two days, five days and 10 days.

accounting for both inter and intra subject variability.

A second limitation with the cohort is the heterogeneity of aetiology; this is likely a driving factor in the similarities of the initial ICP measurements but the significant difference in initial PbtO2, which are seen in Table 1. Accounting for this would improve the generalisability of the overall results, however, due to the current limited sample size this would need to be addressed in future work.

Thirdly, neither the target region nor any confirmation of catheter tip placement was available to be reported from the dataset which would have aided interpretation of these results.

The final limitation is that the cerebral autoregulation status of each subject is unaccounted for directly by the regression modelling as such the impact of autoregulation on PbtO2 cannot be directly assessed. The non-linear effect of measurement time on PbtO2 will account for some of this information but it will combine this with all other unadjusted latent covariates limiting its usefulness for inference about autoregulation specifically.

5. Conclusion

This study has shown that there is a significant non-linear relationship between ICP and PbtO2 over the length of stay in the neuro-intensive care unit. It highlights that adequate delivery of oxygen can be achieved over the short term with an ICP focused management strategy, however, a more comprehensive joint PbtO2 and ICP strategy may be required as the length of stay increases.

Ethics approval

Not applicable.

Consent for publication

Not applicable.

Availability of materials

The datasets used and/or analysed during the current study are available from the BrainIT Group.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Author contributions

MS and IP: conceptualisation of the study.
MS conducted the analysis (formal analysis)
MS, IP, CH, LM and MK contributed to the interpretation of the findings (validation).
All authors critically revised the paper for intellectual content and approved the final version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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