Predictive and discriminative power of pressure reactivity indices in traumatic brain injury

Lennart Riemann[1,2], Erta Beqiri MD[2,3], Alexander Younsi MD[1], Marek Czosnyka PhD*[2], Peter Smielewski PhD*[2]

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

[2]Brain Physics Laboratory, Division of Neurosurgery, Department of Clinical Neurosciences, Addenbrooke's hospital, University of Cambridge, United Kingdom

[3]Department of Physiopathology and Transplantation, Milan University, Italy

** PS and MC share senior authorship of this study*

LR does not hold an academic degree yet as he is currently in the final year of his MD and doctoral degree program

FUNDING

LR received a CENTER-TBI scholarship to visit the Brain Physics Laboratory in Cambridge. MC and PS receive part of the licensing fee for the ICM+ software. The

remaining authors have nothing to disclose and no additional financial support was used for this study.

Corresponding author: Lennart Riemann

Department of Neurosurgery

Heidelberg University Hospital

Im Neuenheimer Feld 400

D-69120 Heidelberg

Germany

Phone: +49 1577 3348494

Mail: l.riemann@stud.uni-heidelberg.de

ABSTRACT

Background: Dysfunctional cerebral blood flow autoregulation (CA) plays a crucial role in the secondary damage after traumatic brain injury (TBI). The pressure reactivity index (PRx) can be used monitor dynamic CA indirectly.

Objective: In this study, we tested different versions of the long pressure reactivity index (LPRx), which is based on minute-by-minute data and calculated over extended time windows. We studied their predictive ability and examined whether combining 'long' and 'short' pressure reactivity indices could improve predictive power.

Methods: PRx and three versions of the LPRx calculated over 20-, 60-, and 240 min time windows were assessed in relation to outcome at six months in 855 patients with TBI. Predictive power and discriminative ability of indices were evaluated using area under the operator curves and determination of critical thresholds. PRx and LPR-indices were combined to evaluate whether LPR-indices could improve outcome prediction by adding information about static components of autoregulation.

Results: Correlation of each LPRx with the PRx decreased with increased time windows. LPR-indices performed successively worse in their predictive and discriminative ability from 20min to 240min time frames. PRx had a significantly higher predictive ability compared to each LPRx. Combining LPRx and PRx did not lead to an improvement of predictive power compared to the PRx alone.

Conclusion: The critical threshold and predictive value of the PRx for unfavourable outcome and mortality has been confirmed in one of the largest so far published patient cohorts. LPRx performed significantly worse, and its discriminative and predictive abilities decreased with an increasing calculation window.

KEYWORDS

Cerebral Autoregulation

Cerebrovascular reactivity

Pressure reactivity index

Outcome

Traumatic brain injury

RUNNING TITLE

Pressure reactivity indices in traumatic brain injury

ABBREVIATIONS

ABP	arterial blood pressure
AUC	area under the curve
CA	cerebrovascular autoregulation
CBF	cerebral blood flow
CPP	cerebral perfusion pressure
ICP	intracranial pressure
IQR	interquartile range
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
LPRx	long pressure reactivity index

MAP	mean arterial pressure
NCCU	Neurocritical Care Unit
PRx	pressure reactivity index
TBI	traumatic brain injury

INTRODUCTION

Cerebral autoregulation (CA) is a protective mechanism maintaining constant blood flow (CBF) in the brain over a wide range of blood pressures [1,2]. Although both, short and longer term physiologic mechanisms contribute to autoregulation, it can be conceptualized into a static and dynamic component, based on the measurement approach used[3]. Static autoregulation is commonly described as a CBF stabilizing mechanism that acts over several minutes to hours after sustained changes in mean arterial blood pressure (MAP) [3–5]. Dynamic autoregulation on the other hand reflects the rapid response of CA within the range of seconds to minutes after transient fluctuations in MAP [4,6]. Dysfunction of both static and dynamic cerebral autoregulation has been linked to secondary damage after traumatic brain injury (TBI) and is associated with poor outcome [4,7–11]. While autoregulation is a complex concept involving many regulatory processes, a key mechanism is cerebrovascular pressure reactivity, defined as the ability of vascular smooth muscle to respond to changes in transmural pressure [2,12]. With functional pressure reactivity, an increase in MAP will induce dynamic vasoconstriction within 5-30 s, leading to a decreased cerebral blood volume and intracranial pressure (ICP) [12]. If pressure reactivity is dysfunctional, a transient rise in MAP will not be counter-balanced and the cerebral blood volume and thus ICP will rise [12,13]. The pressure reactivity index (PRx) can be used to quantify the dynamic component of cerebrovascular pressure reactivity and thus evaluate the state of CBF regulation [10,14]. It is calculated as the correlation of spontaneous waves in ICP and MAP in the frequency range of 0.003-0.05 Hz, with signals averaged over 10s in a moving time window of 5 min. It does not require any additional interventions as it is derived from patient parameters (ICP and ABP) that are routinely monitored in neurocritical care units. By measuring the degree of defective vascular reactivity, PRx

has been shown to be associated with patient outcome in TBI in many previous studies and has been subsequently proposed to guide clinical management of cerebral perfusion pressure (albeit on the basis of retrospective studies) [10,12,15–17]. Correlation coefficient values that are negative or close to zero are thought to represent vessels with normal reactivity, while increased correlation coefficients occur when vessels do not counter-react to increases in ABP. A variant of the PRx metric, termed long pressure reactivity index (LPRx) has later been introduced in an attempt to make autoregulation monitoring more accessible to critical care units equipped with standard electronic medical records systems with no means of acquiring full resolution waveforms. The LPRx considers slower ABP and ICP changes and was calculated in previous studies using averaged minute-by-minute signals over a time window of 20 min, which translates to the frequency range of 0.0008-0.008 Hz [18,19]. After initial promising results in two smaller studies, the LPRx was however concluded to be inferior to the PRx in its outcome prediction in a later study with 307 patients [18–20].

In this single-center study, we tested the PRx and three different versions of the LPRx with 20-,60-, and 240-min moving time windows for their discriminative and predictive ability in regard to fatal and unfavorable outcome (death, persistent vegetative state, and severe disability) in 855 patients with TBI. We assumed that the PRx reflects the dynamic component of autoregulation because it considers spontaneous ABP and ICP variability in the range of seconds. On the other hand, the LPR-indices could be seen as surrogate measures for the static component of autoregulation, given that they consider slower signal changes in the range of minutes to hours. Impairment of both static and dynamic autoregulation has been linked to patient outcome in TBI. Under those assumptions we tested the hypothesis that combining ‘long’ and ‘short’ pressure reactivity indices as measures of both static and dynamic autoregulation could lead to improved predictive power in patients with TBI.

MATERIALS AND METHODS

Patients

All TBI patients admitted to the neurocritical care unit (NCCU) at our institution, between 1996 to 2018 and requiring ICP monitoring, were screened and included in this retrospective study if both intensive care monitoring data (ICP, ABP, PRx, LPRx) and outcome evaluation at six months (Glasgow Outcome Scale, GOS) were available. Additional demographic data (age, sex, Glasgow Coma Scale (GCS) at admission) for each patient was retrieved from medical records. Patients were dichotomized into both fatal (GOS 1) vs. non-fatal outcome (GOS 2-5) and unfavourable (GOS 1-3) vs. favourable (GOS 4-5) outcome. Monitoring of ICP and ABP is part of standard clinical care at this NCCU. Different treatment protocols were followed over the observed time:[21] Briefly, a protocol to keep CPP > 70 mmHg and ICP < 20 mmHg was introduced in 1994. This CPP target was modified to CPP > 60 mmHg in 2003. Since 2012, individual CPP targets based on the PRx have been available as an additional parameter. ABP was changed from the level of the right atrium to the Foramen of Monroe in 2015. For research purposes, recorded monitoring data (ABP, ICP) and routine clinical data (age, sex, GCS, GOS) is entered into a fully anonymized database which can then be used for research without local ethical committee approval at this institution. Likewise, formal patient consent was not required for this type of study.

Data recording and PRx/LPRx calculation

ICP and ABP were continuously recorded in all patients using the ICM for DOS software (374 patients from 1996-2002) or the ICM+ software (481 patients from 2002-2018; Cambridge Enterprise Ltd., Cambridge, UK, http://icmplus.neurosurg.cam.ac.uk). All signal analyses were performed using ICM+. PRx was calculated as a moving Pearson correlation coefficient between 10 s averaged values of ICP and MAP in a moving time window of 5 min (i.e. 30 data points per window). In the 1996-2002 cohort, PRx was already calculated at the time of data collection and stored with 1 min resolution. Thus, only 1 min averaged signals were available in this cohort, whereas high-resolution data (sampling frequency: 0.1 Hz) was available for the 2002-2018 cohort. The LPRx was calculated similarly to the PRx, but the ICP and MAP were instead averaged over 1 min. Three different versions of the LPRx (20-LPRx, 60-LPRx, 240-LPRx) were calculated using three different moving time windows: 20 min, 60 min, and 240 min. A guide on how PRx can be calculated with the ICM+ software is provided elsewhere.[22] LPRx can be calculated accordingly by using minutely averaged data (extractable from most standard electronic medical records systems) and longer time frames (e.g. 20min). An example of PRx and LPRx monitoring over a time course of 8 hours in an individual patient can be seen in **FIGURE 1**.

Additionally, two different digital filters were respectively applied to the ABP and ICP signals in the high-resolution dataset (2002-2018). A low-pass filter was applied to filter out wave frequencies higher than 0.002 Hz. The filtered ABP and ICP signals were then used to calculate filtered LPR-indices that were only based on lower signal frequencies. Correspondingly, a high-pass filter was applied to ICP and ABP signals to filter out wave frequencies lower than 0.003 Hz in order to calculate a filtered PRx that was only based on higher signal frequencies. We applied those filters in an effort

to separate the influence of higher wave frequencies for the PRx-based estimation of dynamic autoregulation from lower wave frequencies for the LPRx-based estimation of static autoregulation. For all calculated indices, moving time windows were updated every minute. Finally, all monitoring parameters were averaged over the entire recording time for each patient. In the statistical analysis, each patient is thus represented by one averaged PRx/LPRx value obtained from all minutely updated PRx/LPRx data points.

Statistical analysis

Demographics and physiologic variables were summarized using descriptive statistics and compared between dichotomized groups using the Mann-Whitney *U* test for non-parametric variables. Correlations were calculated via Spearman's method. Sequential chi square tests were conducted for PRx and LPR-indices to find critical thresholds discriminating most accurately between fatal vs. non-fatal and unfavourable vs. favourable outcome, as previously described [15]. Univariate logistic regression was performed to assess outcome prediction of PRx and LPR-indices in regard to fatal and unfavourable outcome. The predictive value of univariate regression models was evaluated using area under the receiver operating curves (AUC) and compared via DeLong's test. Multivariate regression analysis was subsequently conducted with GCS, age, ICP and CPP as baseline model plus each index with respect to fatal and unfavourable outcome. Additionally, each LPRx was combined with PRx and AUCs of each combined model were evaluated. In all performed statistical tests, p-values < 0.05 were considered significant. No p-value adjustment for multiple testing was applied due to the exploratory and retrospective design of this study. All statistical analyses were conducted with the statistical software R [23].

RESULTS

Patient cohort

855 patients were included in this study. The median age of patients was 38 years (IQR: 24-54) and 78% of patients were males. 201 patients were dead at 6-months follow-up, yielding a mortality rate of 23.5%. 249 patients underwent decompressive craniectomy. Patient demographics as well as neuromonitoring data arranged by outcome group are given in **SUPPLEMENT DIGITAL CONTENT 1 (TABLE)**.

LPRx correlations

There was a reasonable correlation between PRx and 20-LPRx ($r = 0.65$, $p < 0.001$). 60-LPRx and 240-LPRx displayed a considerably lower correlation with PRx ($r = 0.52$, $p < 0.001$ and $r = 0.31$, $p < .001$, respectively). Bland-Altman plots for agreement analysis between PRx and each LPR-index showed in comparison with PRx a mean bias for the 20-LPRx, 60-LPRx, and 240-LPRx of 0.077 (95% limits of agreement -0.223 to 0.377), 0.006 (95% limits of agreement -0.330 to 0.342), and -0.067 (95% limits of agreement -0.464 to 0.330), respectively (**SUPPLEMENT DIGITAL CONTENT 2 (FIGURE**)).

Critical thresholds

The critical threshold for fatal and unfavourable outcome was examined for each index using the method of sequential chi squares. The highest chi square score for each index was assumed to reflect the index threshold that discriminates patients best with regard to fatal and unfavourable outcome. It is based on the averaged index values and describes their discriminative ability and does not represent a potential treatment target in patients. For PRx, the critical threshold for mortality was found to be +0.25 (**FIGURE 2 A**). Maximum chi square values of LPR-indices were distinctively lower compared to the PRx and decreased with longer time windows, indicating that the discriminative ability decreases when using longer time frames (**FIGURE 2 B-D).** Sequential chi-squared tests in regard to unfavourable outcome yielded much lower chi-square values and a clear maximum could only be detected for PRx (also at +0.25) (**SUPPLEMENT DIGITAL CONTENT 3 (FIGURE)).**

Association with outcome

PRx, 20-LPRx, and 60-LPRx but not 240-LPRx were significantly higher in the group with fatal outcome when respectively compared to the non-fatal outcome group (**SUPPLEMENT DIGITAL CONTENT 4 (TABLE))**. When dichotomizing patients into favourable and unfavourable outcome, only mean PRx and 20-LPRx but not 60-, and 240-LPRx were significantly higher in the group with unfavourable outcome. In the univariate regression analysis, only PRx, 20-LPRx, and 60-LPrx but not 240-LPRx were found to be significant predictors of fatal outcome (**SUPPLEMENT DIGITAL CONTENT 5 (TABLE**). For prediction of unfavourable outcome, only PRx and 20-LPRx reached statistical significance in univariate regression analysis (**SUPPLEMENT DIGITAL CONTENT 6 (TABLE)**. AUCs were determined to evaluate the predictive power of indices, and PRx displayed the highest AUC of all indices for both outcomes

of interest (**TABLE 1 and FIGURE 3 A**). PRx displayed a significantly higher AUC compared to each LPRx (DeLong's test), indicating superiority in prediction of both mortality and unfavourable outcome (**TABLE 1**). In multivariate regression analysis with each index added to a baseline model that included the variables GCS, age, ICP, and CPP, only PRx, 20-LPRx and 60-LPRx were significant predictors of mortality in their respective model (**TABLE 2**; for extended version see **SUPPLEMENT DIGITAL CONTENT 7 (TABLE**), with PRx showing far superior odd ratio (41.0) as opposed to LPRx indices (8.4, 2.9 and 0.86 for 20, 60, and 240 min versions respectively). The baseline variables GCS, age, ICP, CPP also demonstrated significance in each model except for the PRx-based model where CPP just missed statistical significance. When assessing prediction of unfavourable outcome, only PRx reached statistical significance in multivariate regression analysis and of the baseline variables, only age, GCS, and ICP but not CPP displayed statistical significance in each model (**TABLE 3**, for extended version see **SUPPLEMENT DIGITAL CONTENT 8 (TABLE)**. AUCs for each multivariate model are presented in **TABLE 4**. The PRx-based multivariate models demonstrated superior AUCs for both prediction of mortality and unfavourable outcome when compared to LPRx-based models. In an additional step, each LPRx was combined with the PRx to evaluate predictive power of combined models via AUCs. However, when compared to the PRx-based model alone, the AUCs for those models showed almost no increase at all when predicting mortality and only minimally increased when predicting unfavourable outcome (**TABLE 2 and FIGURE 3 B-D**).

Filtered PRx and LPR-indices

In the patient cohort with available high-resolution data, the mean filtered PRx was significantly higher in patients with fatal and unfavourable outcome

(**SUPPLEMENT DIGITAL CONTENT 9 (TABLE)** compared to patients with non-fatal and favourable outcome. The filtered 20-LPRx displayed a significant difference between fatal and non-fatal outcome but not between unfavourable and favourable outcome. There were no significant differences between outcome groups for the filtered versions of the 60-and 240-LPRx. Corresponding to the results from the analysis with unfiltered indices, only PRx, 20-LPRx and 60-LPRx were significant predictors for mortality in univariate analysis (**SUPPLEMENT DIGITAL CONTENT 10 (TABLE)**. With regards to unfavourable outcome, only the filtered PRx reached statistical significance as predictor (**SUPPLEMENT DIGITAL CONTENT 11 (TABLE)**. AUCs were lower for all filtered indices compared to their unfiltered counterparts (**SUPPLEMENT DIGITAL CONTENT 12 (TABLE)** of which the filtered PRx displayed the highest AUC for prediction of both fatal und unfavourable outcome. In multivariate analysis analogous to the one performed on unfiltered indices, only the filtered PRx was identified as a significant predictor for both outcomes of interest (**SUPPLEMENT DIGITAL CONTENT 13+14 (TABLES)**. AUCs for models consisting of baseline variables plus each filtered index were very similar to those with unfiltered signals. Accordingly, filtered PRx in combination with filtered LPR-indices did not increase the predictive power of the filtered PRx alone. (**SUPPLEMENT DIGITAL CONTENT 15 (TABLE).**

DISCUSSION

In this study, we investigated the predictive value of PRx, different versions of the LPRx, and combinations of PRx and LPRx in a single-center cohort of 855 patients with TBI. Discriminative and predictive ability decreased when extending the time windows in LPR-indices. Even though more data points were added to the index

calculation when increasing time windows, this did not seem to contribute to a better prediction of outcome. On the contrary, the longer-term variability captured by the extended calculation windows seems to have overshadowed the clinically important information from the higher frequency components.

To follow on from our assumption that LPR-indices might reflect the state of static autoregulation as opposed to the PRx reflecting dynamic autoregulation, we respectively applied low-pass and high-pass filters to ABP and ICP signals in an attempt to separate lower and higher frequencies for LPRx- and PRx calculation. Thus, the filtered PRx was solely based on higher frequencies (> 0.003 Hz) as a measure of dynamic autoregulation whereas the filtered LPR-indices were based on isolated lower frequencies (< 0.002 Hz) as measures of static autoregulation. The outcome association analysis of these showed very similar results to those obtained from the unfiltered indices, with the filtered PRx displaying higher predictive power than filtered LPR-indices. Of particular importance is that filtered LPRx-indices performed worse in outcome prediction than their unfiltered counterparts. This might strengthen the notion that the clinical relevance of LPRx is predominantly due to the higher frequency content.

Even though all LPR-indices were found to be inferior in outcome prediction compared to the PRx in univariate und multivariate regression analyses, we investigated whether combining PRx and LPRx, as possible indictors of dynamic and static autoregulation, could significantly improve outcome prediction compared to PRx alone. However, all combined models showed almost no improvement in outcome prediction as evaluated by AUCs when compared to the mere PRx-model. Static autoregulation has been shown before to be associated with outcome in patients with severe TBI [4,11]. However, in those studies static autoregulation was measured using intervention techniques. LPRx might not be a suitable alternative to those tests in the

assessment of static autoregulation. PRx and LPRx are based on monitoring of spontaneous fluctuations in ABP and ICP whereas intervention methods induce ABP changes of high magnitude to observe the resulting responses in other monitored parameters in a patient. Those robust, sustained changes over longer periods of time might be needed to evaluate static autoregulation and usually do not occur spontaneously in patients or if they do, they may be accompanied by other, independent effects resetting the static levels of intracranial pressure. LPR-indices correlate ICP and ABP, however it is the CPP that ultimately induces vasoreactivity in the brain. While ABP variability likely dominates spontaneous CPP changes when considering shorter time periods, ICP might have a stronger influence on CPP when observing longer time periods (e.g. due to brain swelling), an effect that LPR-indices would not account for. This might also partly explain why LPR-indices performed worse with longer time windows. The state of static autoregulation might still be very important in patients with TBI, but it is likely only accurately assessed with interventional methods, which might not always be safe to perform in acute TBI.

The difference in the strength of outcome prediction between PRx and LPRx is not an unexpected finding when considering the different frequency ranges they are based upon. In an experimental work in a swine model, Fraser and colleagues found an optimal frequency for autoregulation monitoring at 0.017 Hz that falls well into the frequency range of the PRx [24]. They also reported a decreased ability to discriminate between intact and impaired autoregulation when monitoring signals in frequencies lower than 0.017 Hz. Our study might indicate that the findings of their experimental work is also true in the clinical setting which is in agreement with a study by Howells and colleagues who found an optimal frequency range for PRx assessment between 0.018-0.067 Hz.[25] Minute-by-minute averaging and increasing the time-window for calculation of the LPRx successively decreased its predictive ability in patients with

TBI. If the PRx concept (e.g. through optimal CPP-targeted therapy) can be successfully translated to clinical practice, it has subsequently to be evaluated if the 20-LPRx still contains enough clinically-relevant information for improvement of outcome in centers that do not have high-resolution signal recording. Future research is also warranted to find and test additional monitoring parameters that can complement the PRx and increase its predictive power.

LIMITATIONS

There are several limitations of this study: Due to the retrospective design of the study, there is likely a substantial heterogeneity in injury characteristics (e.g. type of TBI), co-morbidities and critical care treatment of patients (e.g. ICP management protocols) over a large period of time, which might all influence the results. In particular, both patients with and without decompressive craniectomy were included. Furthermore, both PRx and LPRx can only be seen as surrogate markers for cerebrovascular autoregulation. Static autoregulation could still play a major role in injury pathogenesis and outcome of patients with traumatic brain injury and LPR-indices might be inadequate to measure its degree of functionality. Finally, it remains unknown if and how pressure reactivity indices can be used to improve outcome in TBI patients. Although promising approaches such as the optimal CPP-targeted therapy exist, their clinical benefit have yet to be shown in prospective studies.

CONCLUSION

In TBI patients, LPR-indices calculated over 20-and 60 min time windows are associated with outcome but significantly weaker than the PRx. The predictive power of LPR-indices successively decreases with longer time windows. Combining PRx and LPRx does not lead to increased outcome prediction. The critical threshold discriminating most accurately between outcome scenarios in patients and predictive value of the PRx has been confirmed in the largest so far published single- center patient cohort.

REFERENCES

1. LASSEN NA. Cerebral blood flow and oxygen consumption in man. Physiol Rev [Internet] 1959 [cited 2019 May 18];39(2):183–238. Available from: http://www.ncbi.nlm.nih.gov/pubmed/13645234
2. Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. Cerebrovasc Brain Metab Rev [Internet] 1990 [cited 2019 May 1];2(2):161–92. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2201348
3. Numan T, Bain AR, Hoiland RL, Smirl JD, Lewis NC, Ainslie PN. Static autoregulation in humans: a review and reanalysis. Med Eng Phys [Internet] 2014 [cited 2019 May 17];36(11):1487–95. Available from: https://www.sciencedirect.com/science/article/pii/S1350453314002033?via%3Dihub#bib0010
4. Schramm P, Klein KU, Pape M, et al. Serial measurement of static and dynamic cerebrovascular autoregulation after brain injury. J Neurosurg Anesthesiol [Internet] 2011 [cited 2019 May 17];23(1):41–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21252706
5. Panerai RB. Assessment of cerebral pressure autoregulation in humans - a review of measurement methods. Physiol Meas [Internet] 1998 [cited 2019 May 18];19(3):305–38. Available from: http://stacks.iop.org/0967-3334/19/i=3/a=001?key=crossref.256353ae1fd14e163b30aedb56b93d4c

6. Aaslid R, Lindegaard KF, Sorteberg W, Nornes H. Cerebral autoregulation dynamics in humans. Stroke [Internet] 1989 [cited 2019 May 18];20(1):45–52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2492126
7. Rangel-Castilla L, Gasco J, Nauta HJW, Okonkwo DO, Robertson CS. Cerebral pressure autoregulation in traumatic brain injury. Neurosurg Focus [Internet] 2008 [cited 2019 May 1];25(4):E7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18828705
8. Toth P, Szarka N, Farkas E, et al. Traumatic brain injury-induced autoregulatory dysfunction and spreading depression-related neurovascular uncoupling: Pathomechanisms, perspectives, and therapeutic implications. Am J Physiol Circ Physiol [Internet] 2016 [cited 2019 May 3];311(5):H1118–31. Available from: http://www.physiology.org/doi/10.1152/ajpheart.00267.2016
9. Panerai RB, Kerins V, Fan L, Yeoman PM, Hope T, Evans DH. Association between dynamic cerebral autoregulation and mortality in severe head injury. Br J Neurosurg [Internet] 2004 [cited 2019 May 3];18(5):471–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15799148
10. Czosnyka M, Smielewski P, Kirkpatrick P, Laing RJ, Menon D, Pickard JD. Continuous assessment of the cerebral vasomotor reactivity in head injury. Neurosurgery [Internet] 1997 [cited 2019 May 1];41(1):11–7; discussion 17-9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9218290
11. Puppo C, López L, Caragna E, Biestro A. One-Minute Dynamic Cerebral Autoregulation in Severe Head Injury Patients and its Comparison with Static Autoregulation. A Transcranial Doppler Study. Neurocrit Care [Internet] 2008 [cited 2019 May 17];8(3):344–52. Available from: http://link.springer.com/10.1007/s12028-008-9069-8
12. Steiner LA, Czosnyka M, Piechnik SK, et al. Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. Crit Care Med [Internet] 2002;30(4). Available from: https://journals.lww.com/ccmjournal/Fulltext/2002/04000/Continuous_monitoring_of_cerebrovascular_pressure.2.aspx
13. Rosner MJ, Becker DP. Origin and evolution of plateau waves. J Neurosurg [Internet] 1984 [cited 2019 May 1];60(2):312–24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6693959

14. Zweifel C, Lavinio A, Steiner LA, et al. Continuous monitoring of cerebrovascular pressure reactivity in patients with head injury. Neurosurg Focus [Internet] 2008 [cited 2019 May 3];25(4):E2. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18828700
15. Sorrentino E, Diedler J, Kasprowicz M, et al. Critical Thresholds for Cerebrovascular Reactivity After Traumatic Brain Injury. Neurocrit Care [Internet] 2012 [cited 2019 Apr 30];16(2):258–66. Available from: http://link.springer.com/10.1007/s12028-011-9630-8
16. Johnson U, Lewén A, Ronne-Engström E, Howells T, Enblad P. Should the Neurointensive Care Management of Traumatic Brain Injury Patients be Individualized According to Autoregulation Status and Injury Subtype? Neurocrit Care [Internet] 2014 [cited 2019 May 1];21(2):259–65. Available from: http://link.springer.com/10.1007/s12028-014-9954-2
17. Czosnyka M, Czosnyka Z, Smielewski P. Pressure reactivity index: journey through the past 20 years. Acta Neurochir (Wien) [Internet] 2017 [cited 2019 Jun 14];159(11):2063–5. Available from: http://link.springer.com/10.1007/s00701-017-3310-1
18. Santos E, Diedler J, Sykora M, et al. Low-frequency sampling for PRx calculation does not reduce prognostication and produces similar CPPopt in intracerebral haemorrhage patients. Acta Neurochir (Wien) [Internet] 2011 [cited 2018 Aug 26];153(11):2189–95. Available from: http://link.springer.com/10.1007/s00701-011-1148-5
19. Lang EW, Kasprowicz M, Smielewski P, Santos E, Pickard J, Czosnyka M. Short pressure reactivity index versus long pressure reactivity index in the management of traumatic brain injury. J Neurosurg [Internet] 2015 [cited 2018 Sep 9];122(3):588–94. Available from: http://thejns.org/doi/10.3171/2014.10.JNS14602
20. Sánchez-Porras R, Santos E, Czosnyka M, Zheng Z, Unterberg AW, Sakowitz OW. 'Long' pressure reactivity index (L-PRx) as a measure of autoregulation correlates with outcome in traumatic brain injury patients. Acta Neurochir (Wien) [Internet] 2012 [cited 2018 Aug 26];154(9):1575–81. Available from: http://link.springer.com/10.1007/s00701-012-1423-0
21. Donnelly J, Czosnyka M, Adams H, et al. Twenty-Five Years of Intracranial Pressure Monitoring After Severe Traumatic Brain Injury: A Retrospective,

Single-Center Analysis. Neurosurgery [Internet] 2019 [cited 2019 Oct 2];85(1):E75–82. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30476233

22. Pressure reactivity index (PRx) [Internet]. [cited 2019 Nov 23];Available from: http://cppopt.org/prx/
23. R Core Team. R: A Language and Environment for Statistical Computing [Internet]. 2018;Available from: https://www.r-project.org/
24. Fraser CD, Brady KM, Rhee CJ, et al. The frequency response of cerebral autoregulation. J Appl Physiol [Internet] 2013 [cited 2019 May 2];115(1):52–6. Available from: http://www.physiology.org/doi/10.1152/japplphysiol.00068.2013
25. Howells T, Johnson U, McKelvey T, Enblad P. An optimal frequency range for assessing the pressure reactivity index in patients with traumatic brain injury. J Clin Monit Comput [Internet] 2015 [cited 2019 Oct 1];29(1):97–105. Available from: http://link.springer.com/10.1007/s10877-014-9573-7

FIGURES

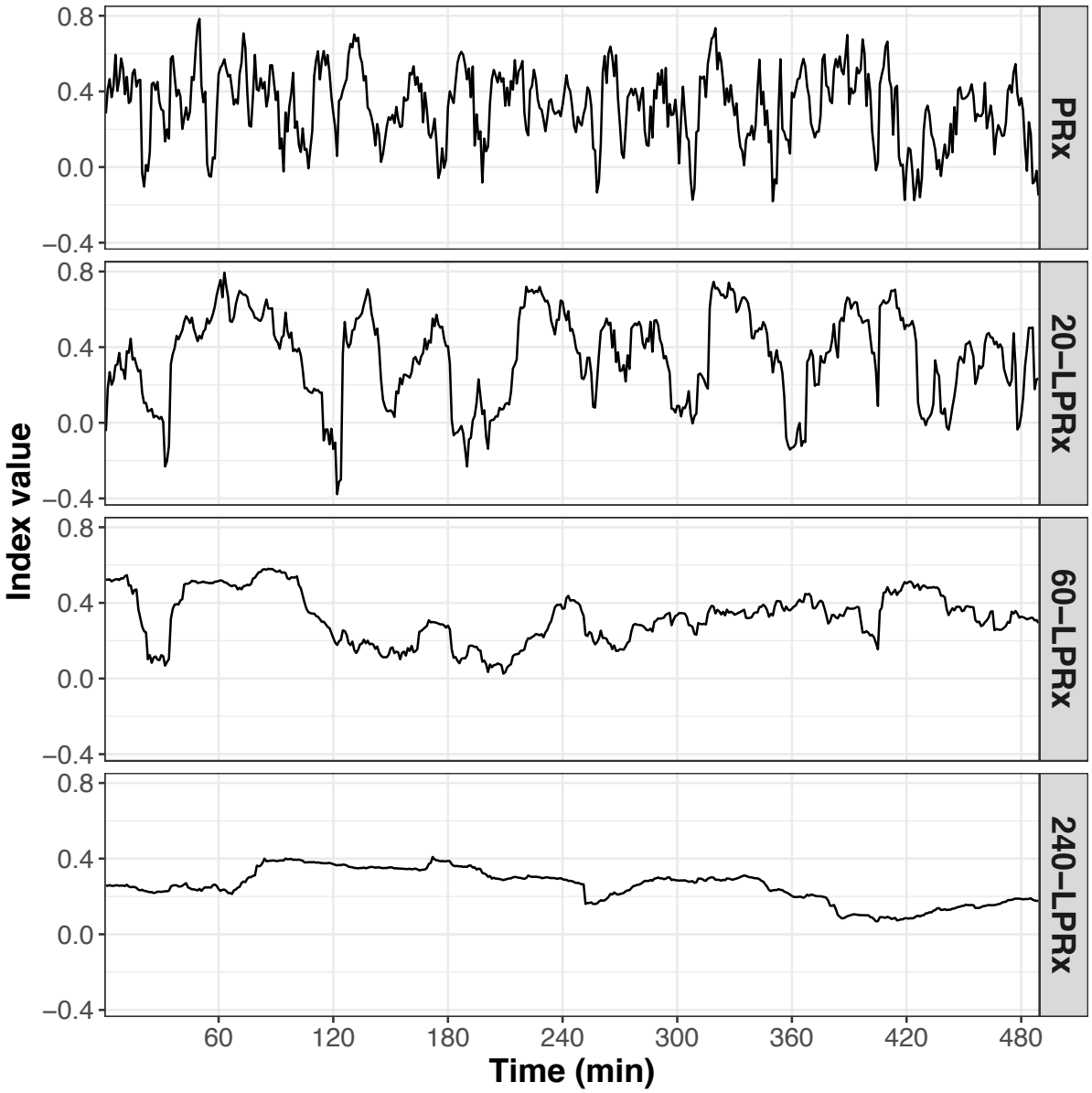


FIGURE 1: Monitoring of PRx, 20-LPRx, 60-LPRx, and 240-LPRx in a patient with traumatic brain injury over a time course of 8 hours.

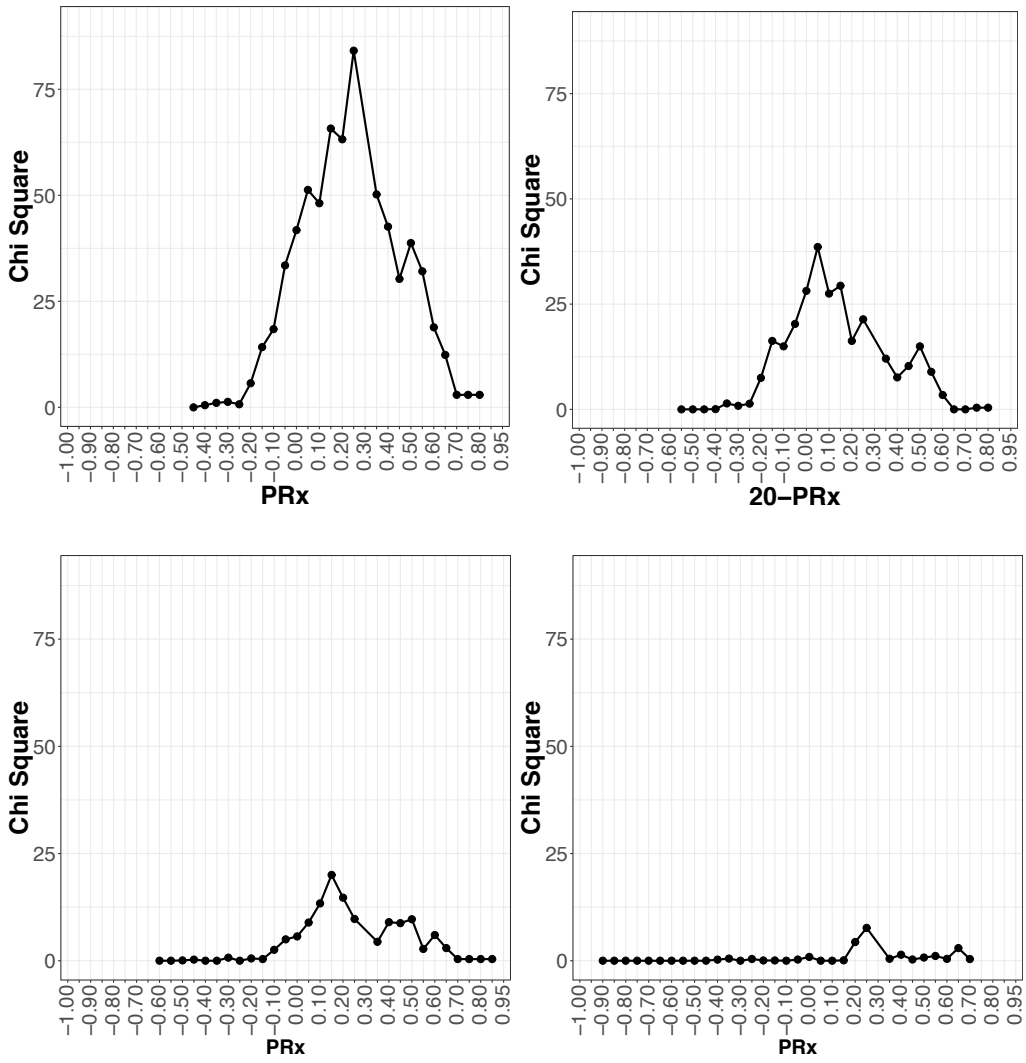


FIGURE 2: **A** Threshold plot for PRx: The sequential chi square method yields a distinct maximum chi square score for mortality at +0.25, indicating the maximal discriminative ability for mortality at this threshold. **B-D** Threshold plots for LPR-indices: Chi square values are successively decreasing with longer time windows, indicating decreased discriminative ability for mortality of LPR-indices.

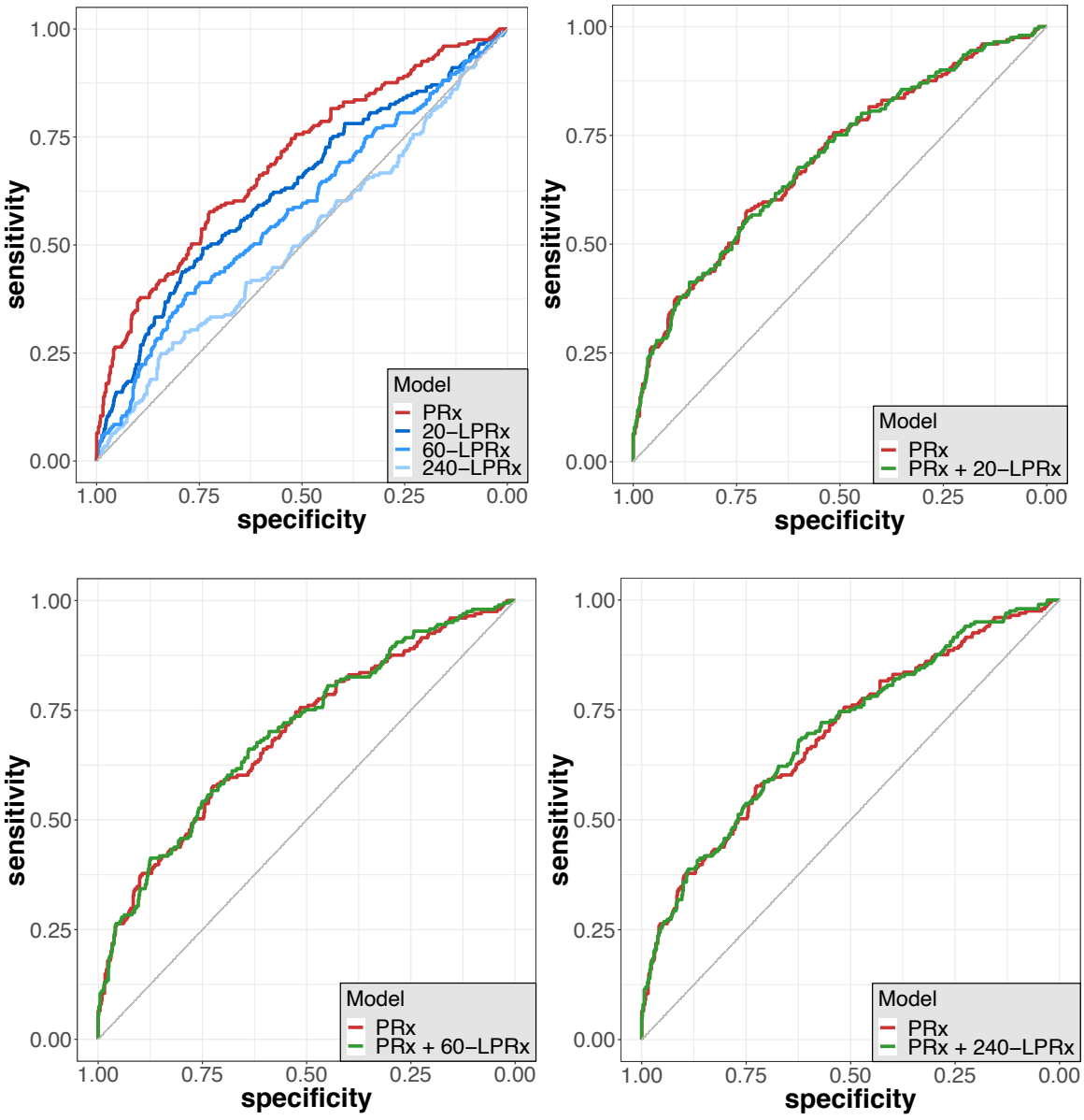


FIGURE 3: A AUCs for pressure reactivity indices decrease with increasing time windows. The AUC was significantly higher for the PRx when compared to each LPRx via DeLong's test. **B-D** Adding different LPR-indices to the PRx-model did not increase AUCs and seems therefore not to improve predictive power.

TABLE 1: Area under the receiver operator curves for prediction of fatal und unfavourable outcome for different indices

Index	Fatal outcome		Unfavourable outcome	
	AUC (95% CI)	**p-value (DeLong's test)***	**AUC (95% CI)**	**p-value (DeLong's test)***
PRx	0.69 (0.65-0.74)	-	0.63 (0.59-9.66)	-
20-LPRx	0.63 (0.58-0.68)	**<0.001**	0.54 (0.50-0.58)	**<0.001**
60-LPRx	0.58 (0.53-0.63)	**<0.001**	0.50 (0.46-0.54)	**<0.001**
240-LPRx	0.51 (0.47-0.56)	**<0.001**	0.54 (0.50-0.58)	**<0.001**

* compared to the AUC of the PRx

AUC, area under the receiver operating curve; CI, confidence interval;LPRx, long pressure reactivity index; PRx, pressure reactivity index

TABLE 2: Multivariate logistic regression analysis to fatal outcome for each pressure reactivity index in addition to a baseline model with the variables age, GCS, CPP, and ICP

Variable	**Index: PRx**		**Index: 20-LPRx**	
	Coefficient	p-value	Coefficient	p-value
Age	0.043	<0.001	0.046	<0.001
GCS	-0.155	<0.001	-0.161	<0.001
CPP	-0.026	0.066	-0.029	0.035
ICP	0.118	<0.001	0.129	<0.001
Index	3.713	<0.001	2.131	<0.001
Variable	**Index: 60-LPRx**		**Index: 240-LPRx**	
	Coefficient	p-value	Coefficient	p-value
Age	0.047	<0.001	0.048	<0.001
GCS	-0.159	<0.001	-0.016	<0.001
CPP	-0.033	0.160	-0.038	0.005
ICP	0.124	<0.001	0.122	<0.001
Index	1.062	0.035	-0152	0.776

CPP, cerebral perfusion pressure; GCS, Glasgow Coma Scale; ICP, intracranial pressure; LPRx, long pressure reactivity index; PRx, pressure reactivity index

TABLE 3: Multivariate logistic regression analysis to unfavourable outcome for each pressure reactivity index in addition to a baseline model with the variables age, GCS, CPP, and ICP

Variable	**Index: PRx**		**Index: 20-LPRx**	
	Coefficient	p-value	Coefficient	p-value
Age	0.031	<0.001	0.035	<0.001
GCS	-0.200	<0.001	-0.202	<0.001
CPP	-0.002	0.829	-0.004	0.735
ICP	0.050	<0.001	0.055	<0.001
Index	2.493	<0.001	0.623	0.133
Variable	**Index: 60-LPRx**		**Index: 240-LPRx**	
	Coefficient	p-value	Coefficient	p-value
Age	0.036	<0.001	0.037	<0.001
GCS	-0.200	<0.001	-0.198	<0.001
CPP	-0.006	0.578	-0.007	0.488
ICP	0.053	<0.001	0.053	<0.001
Index	-0.106	0.802	-0.832	0.069

CPP, cerebral perfusion pressure; GCS, Glasgow Coma Scale; ICP, intracranial pressure; LPRx, long pressure reactivity index; PRx, pressure reactivity index

TABLE 4: Area under the receiver operator curves for prediction of fatal und unfavourable outcome for different combined index models

Model	Fatal outcome		Unfavourable outcome	
	AUC	**95% CI**	**AUC**	**95% CI**
Baseline* + PRx	0.81	0.78-0.85	0.75	0.72-0.78
Baseline* + 20-LPRx	0.79	0.75-0.83	0.73	0.70-0.77
Baseline* + 60-LPRx	0.78	0.74-0.82	0.73	0.70-0.77
Baseline* + 240-LPRx	0.78	0.74-0.82	0.73	0.70-0.77
PRx + 20-LPRx	0.69	0.65-0.74	0.64	0.61-0.68
PRx + 60-LPRx	0.70	0.66-0.74	0.66	0.62-0.70
PRx + 240-LPRx	0.70	0.66-0.74	0.65	0.62-0.69

* Baseline model consisting of the variables age, GCS, CPP, and ICP

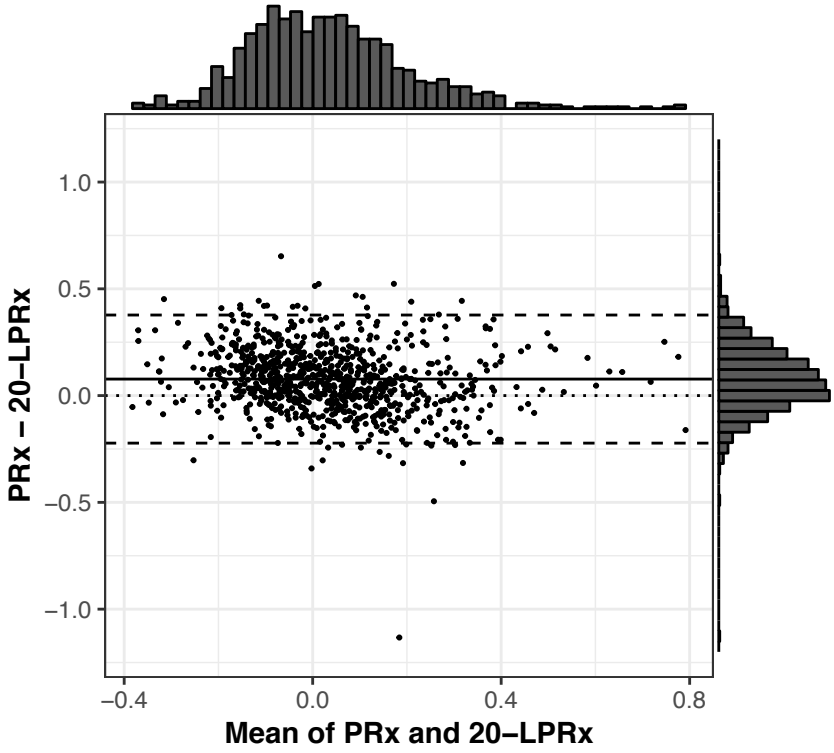
AUC, area under the receiver operating curve; CI, confidence interval;LPRx, long pressure reactivity index; PRx, pressure reactivity index

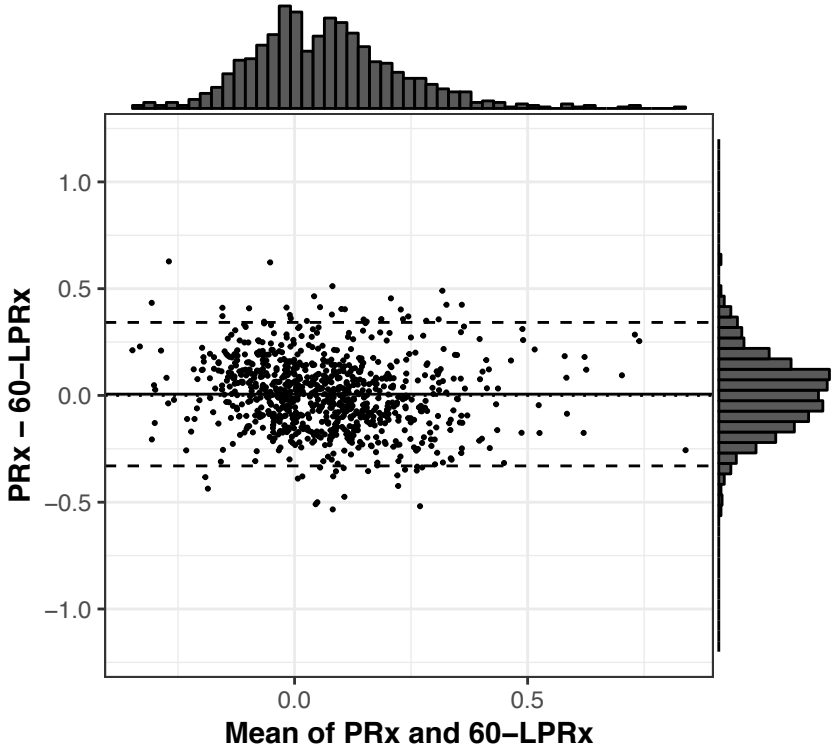
SUPPLEMENT DIGITAL CONTENT

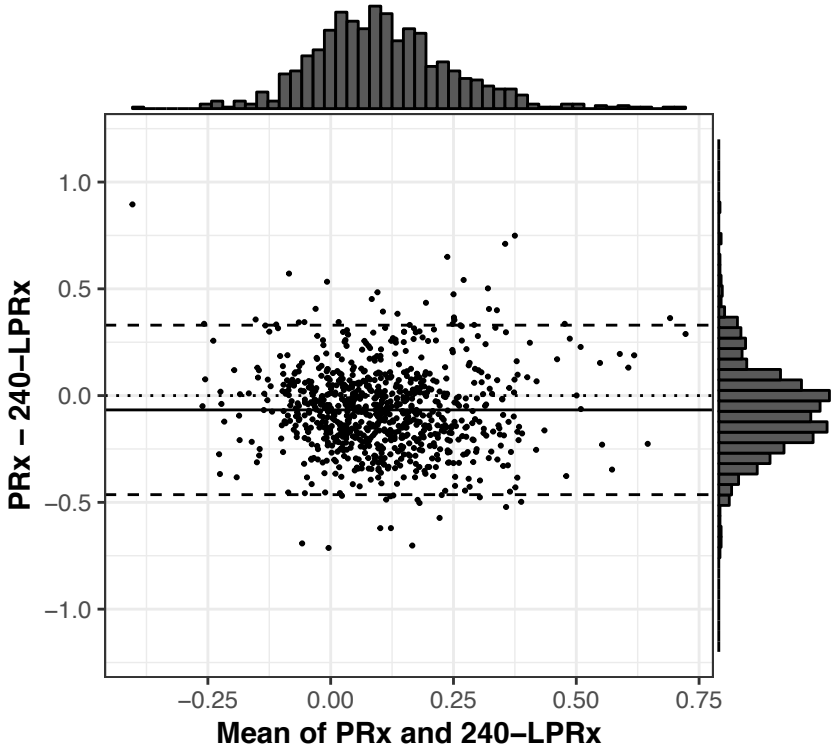
SUPPLEMENT DIGITAL CONTENT 1 (TABLE):

Patient demographics and neuromonitoring data by outcome group

GOS	No.	Age (years)	No. of males (%)	GCS	ABP (mmHg)	ICP (mmHg)	CPP (mmHg)	PRx	20-LPRx	60-LPRx	240-LPRx
1	201	49 (29-63)	160 (80%)	5 (3-8)	92.8 (86.9-99.5)	16.4 (11.9-22.5)	75.7 (70.5-80.0)	0.139 (0.035-0.301)	0.068 (-0.078-0.205)	0.097 (-0.025-0.245)	0.138 (0.013-0.287)
2	15	38 (22-50)	10 (67%)	4 (3-6)	87.3 (83.9-97.2)	13.8 (10.5-17.7)	75.8 (72.5-79.6)	0.027 (-0.025-0.159)	-0.106 (-0.195-0.094)	-0.091 (-0.148-0.156)	0.065 (-0.008-0.168)
3	274	40 (26-53)	205 (75%)	6 (4-8)	94.1 (88.2-98.8)	14.0 (9.8-17.4)	79.2 (74.3-83.5)	0.048 (-0.041-0.146)	-0.040 (-0.167-0.085)	0.033 (-0.098-0.153)	0.108 (0.006-0.224)
4	212	33 (23-49)	175 (83%)	8 (5-10)	92.5 (85.9-97.1)	14.0 (10.5-17.5)	77.6 (74.2-81.3)	0.029 (-0.053-0.143)	-0.044 (-0.138-0.071)	0.058 (-0.053-0.154)	0.149 (0.031-0.249)
5	153	28 (19-43)	119 (78%)	8 (6-10)	92.5 (89.3-96.5)	13.2 (11.0-16.9)	77.5 (74.7-82.0)	0.009 (-0.089-0.097)	-0.024 (-0.137-0.091)	0.058 (-0.033-0.194)	0.149 (0.052-0.255)
Total	855	38 (24-54)	669 (78%)	7 (4-9)	92.9 (87.5-97.5)	14.3 (10.7-18.2)	77.6 (73.7-82.1)	0.054 (-0.044-0.161)	-0.021 (-0.144-0.118)	0.057 (-0.064-0.187)	0.136 (0.020-0.248)

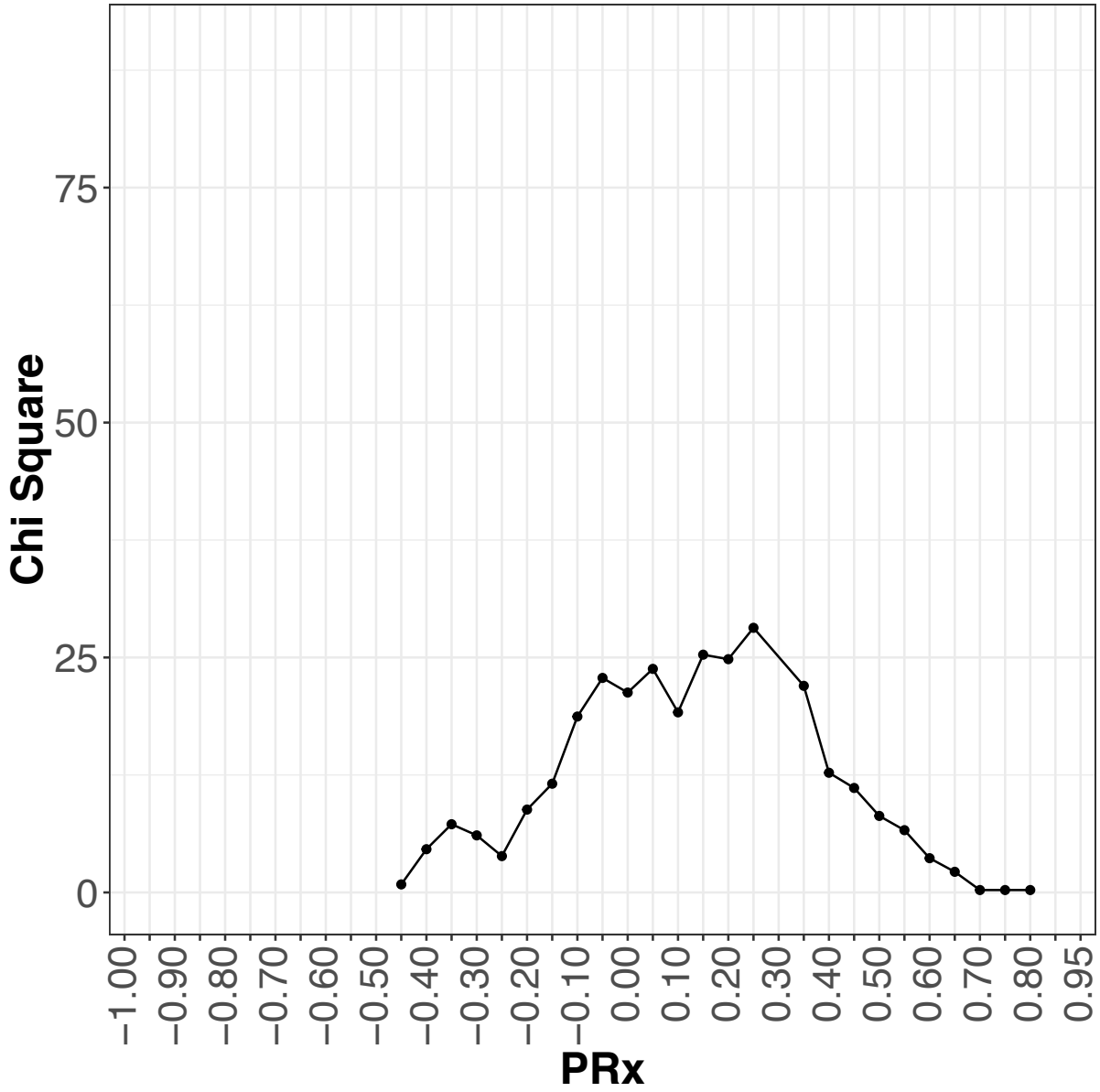

1.0
0.5
0.0
−0.5
−1.0
PRx − 20−LPRx
−0.4
0.0
0.4
0.8
Mean of PRx and 20−LPRx


1.0
0.5
0.0
−0.5
−1.0
PRx − 60−LPRx
0.0
0.5
Mean of PRx and 60−LPRx

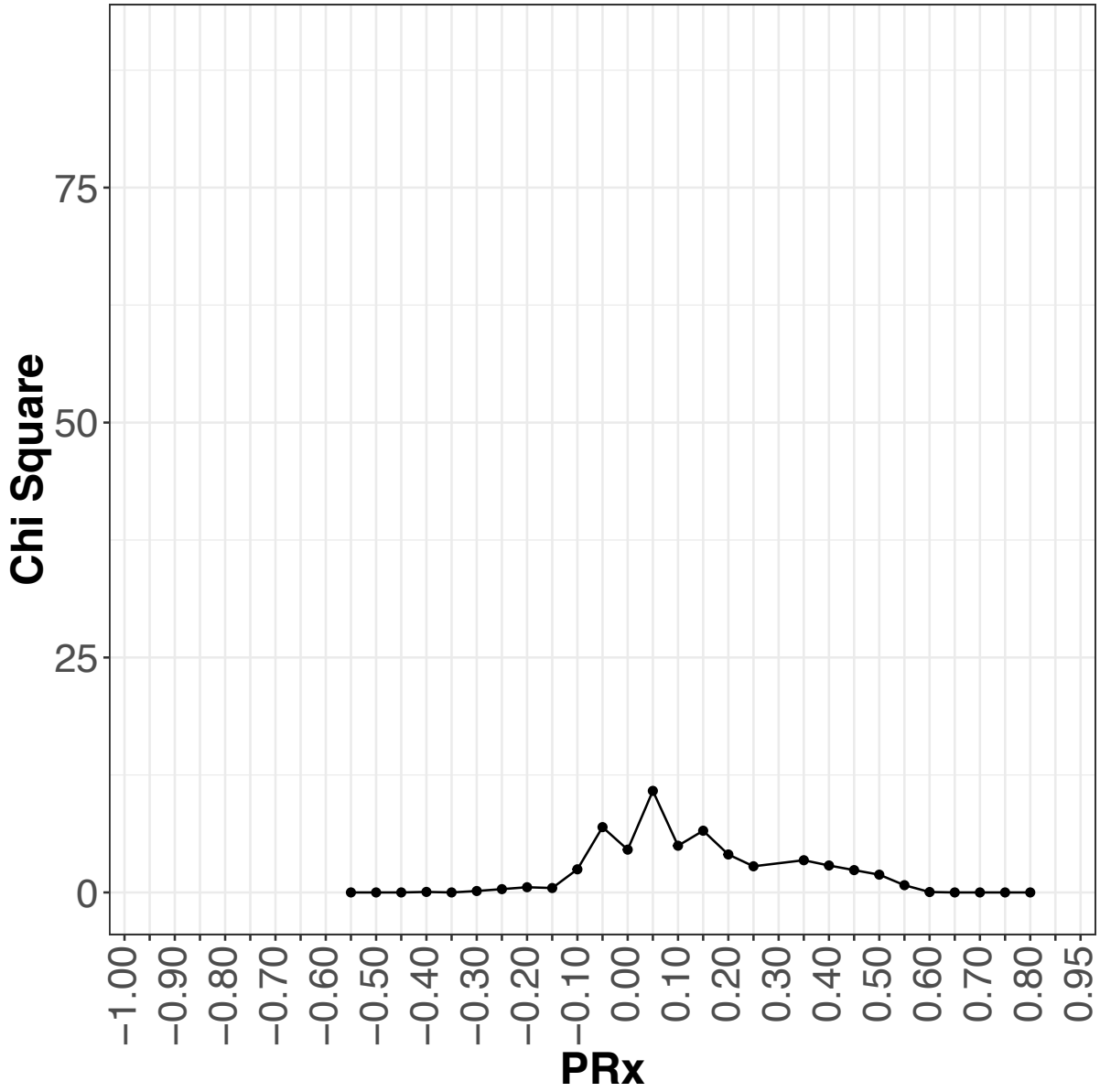


Bland-Altman-plots showing mean bias (solid line), no difference (thin stacked line), and 95% lines of agreement (thick dashed lines) between PRx and each LPRx.

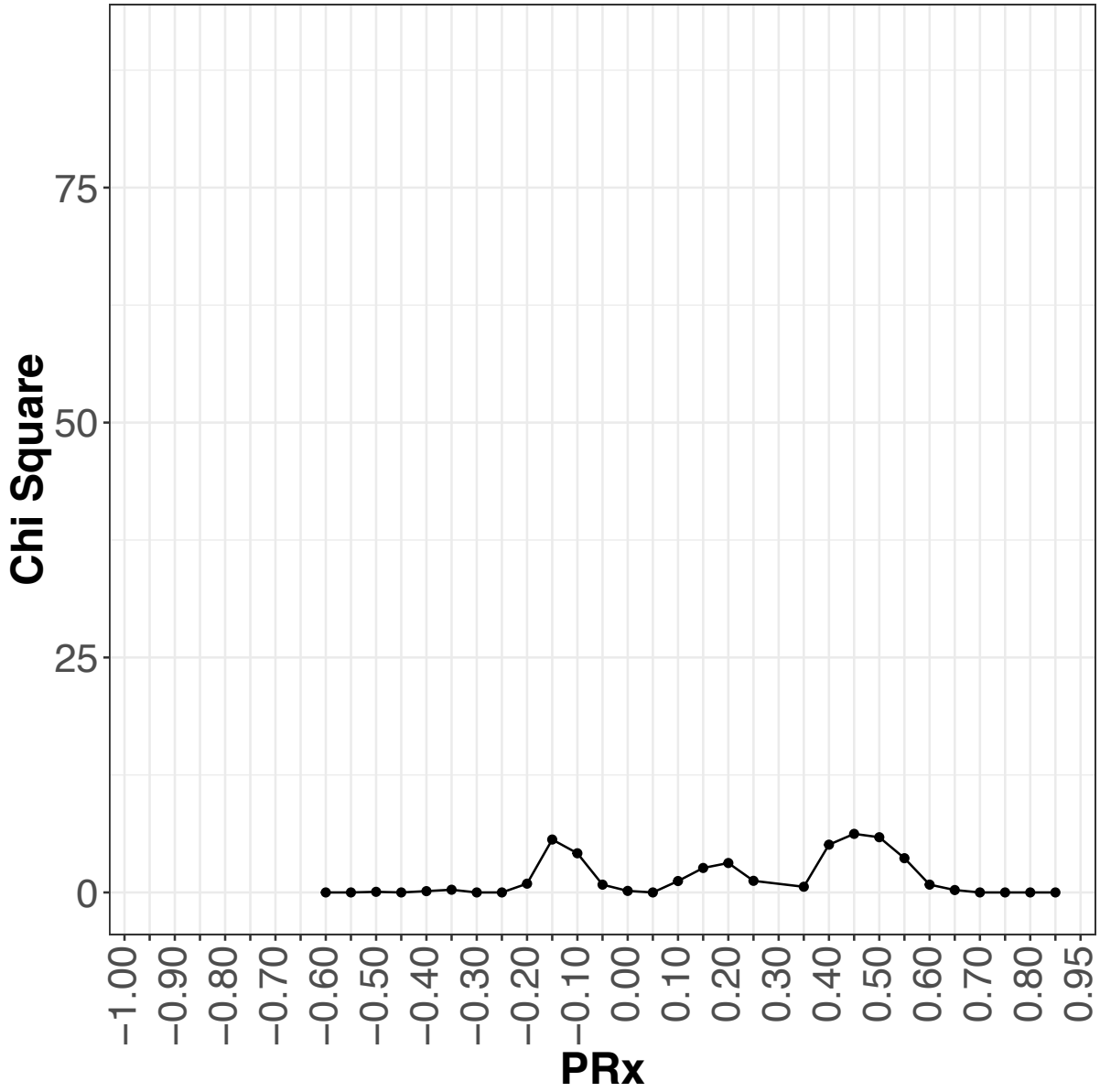
SUPPLEMENT DIGITAL CONTENT 2 (FIGURE): Bland-Altman-plots showing mean bias (solid line), no difference (thin stacked line), and 95% lines of agreement (thick dashed lines) between PRx and each LPRx.


Chi Square
75
50
25
0
−1.00
−0.90
−0.80
−0.70
−0.60
−0.50
−0.40
−0.30
−0.20
−0.10
0.00
0.10
0.20
0.30
0.40
0.50
0.60
0.70
0.80
0.95
PRx

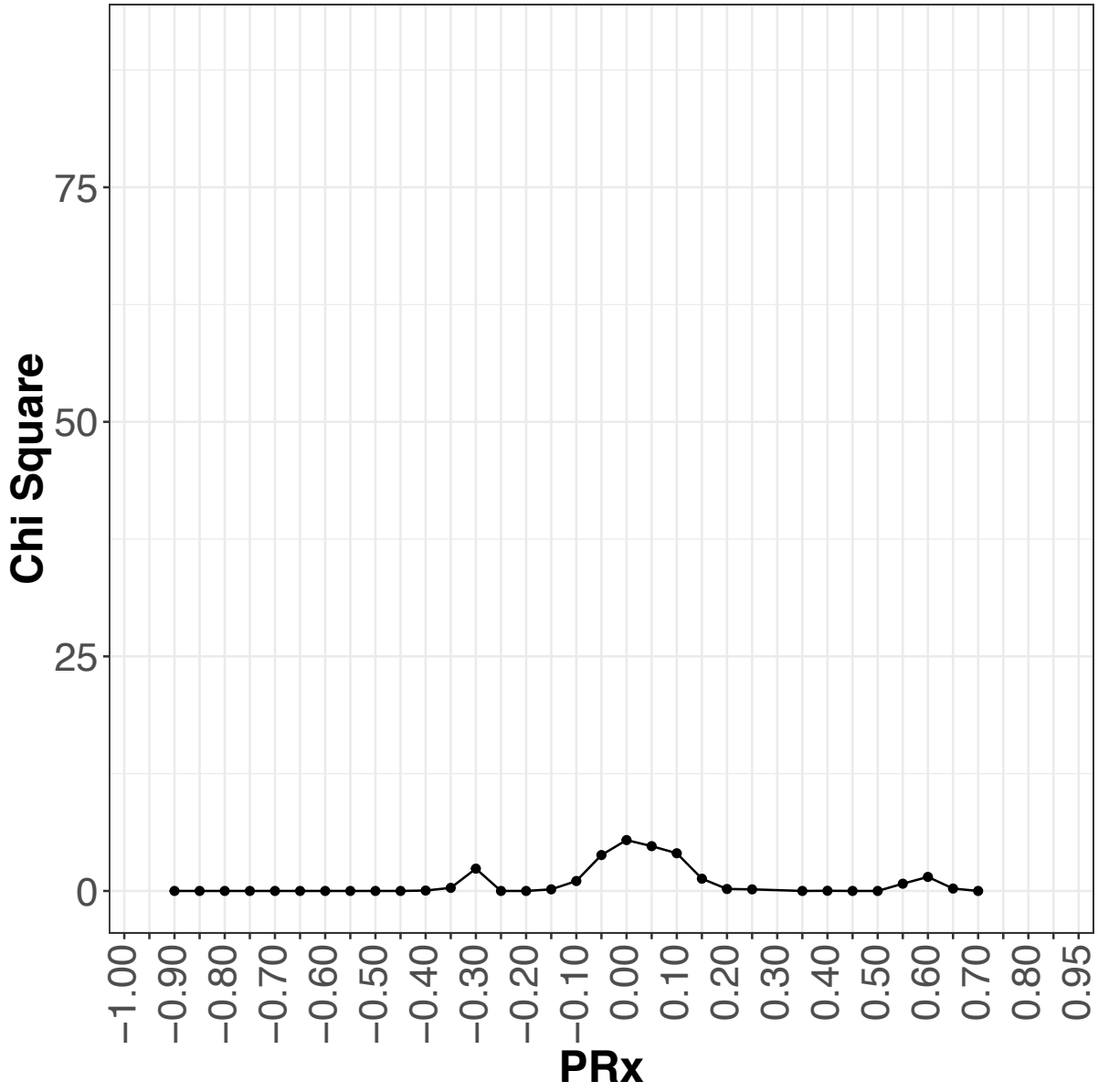
A


Chi Square
75
50
25
0
−1.00
−0.90
−0.80
−0.70
−0.60
−0.50
−0.40
−0.30
−0.20
−0.10
0.00
0.10
0.20
0.30
0.40
0.50
0.60
0.70
0.80
0.95
PRx

B


Chi Square
75
50
25
0
−1.00
−0.90
−0.80
−0.70
−0.60
−0.50
−0.40
−0.30
−0.20
−0.10
0.00
0.10
0.20
0.30
0.40
0.50
0.60
0.70
0.80
0.95
PRx

c



D

SUPPLEMENT DIGITAL CONTENT 3 (FIGURE): Sequential chi-squared tests in regard to unfavourable outcome yielded much lower chi-square values and a clear maximum could only be detected for PRx (also at +0.25).

SUPPLEMENT DIGITAL CONTENT 4 (TABLE): Group comparisons between the fatal vs. non-fatal and favourable vs. unfavourable outcome group

	Alive (GOS 2-5)	**Dead (GOS 1)**	**p-value**
Number of patients	654 (76%)	201 (24%)	-
Median Age (years)	49 (29-63)	35 (22-50)	**<0.001**
Sex: Female (%) Male (%)	 145 (22%) 509 (78%)	 41 (20%) 160 (80%)	0.663
GCS	7 (4-9)	5 (3-8)	**<0.001**
ABP (mmHg)	92.9 (87.7-97.3)	92.8 (86.9-99.5)	0.975
ICP (mmHg)	13.9 (10.5-17.4)	16.4 (11.9-22.5)	**<0.001**
CPP (mmHg)	78.1 (74.3-82.6)	75.7 (70.5-80.0)	**<0.001**
PRx	0.030 (-0.053-0.127)	0.139 (0.035-0.301)	**<0.001**
20-LPRx	-0.041 (-0.155-0.085)	0.068 (-0.078-0.205)	**<0.001**
60-LPRx	0.043 (-0.070-0.158)	0.097 (-0.025-0.245)	**<0.001**
240-LPRx	0.135 (0.026-0.239)	0.138 (0.013-0.286)	0.552

	Favourable (GOS 4-5)	**Unfavourable (GOS 1-3)**	**p-value**
Number of patients	365 (43%)	490 (57%)	-
Median Age (years)	31 (21-47)	43 (27-58)	**<0.001**
Sex: Female (%) Male (%)	 71 (19%) 294 (81%)	 115 (23%) 375 (77%)	0.185
GCS	8 (5-10)	5 (3-8)	**<0.001**
ABP (mmHg)	92.5 (87.7-96.9)	93.5 (87.4-98.8)	0.186
ICP (mmHg)	13.9 (10.7-17.4)	14.8 (10.8-19.3)	**0.013**
CPP (mmHg)	77.5 (74.3-81.6)	77.7 (72.6-82.7)	0.437
PRx	0.019 (-0.069-0.110)	0.074 (-0.017-0.196)	**<0.001**
20-LPRx	-0.040 (-0.137-0.083)	-0.002 (-0.149-0.138)	**0.043**
60-LPRx	0.058 (-0.035-0.165)	0.052 (-0.082-0.202)	0.896
240-LPRx	0.149 (0.044-0.253)	0.120 (0.006-0.244)	0.065

SUPPLEMENT DIGITAL CONTENT 5 (TABLE): Univariate logistic regression analysis to fatal outcome for each pressure reactivity index

	Model 1: PRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	-1.645	0.106	<0.001	0.193 (0.156-0.237)
PRx	4.605	0.525	<0.001	100.017 (36.636-287.592)
Chi-Squared	91.577 (df=1, p < 0.001)			
Nagelkerke R^2	0.153			
Cox-Snell R^2	0.102			
Hosmer-Lemeshow R^2	0.098			

	Model 2: 20-LPRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	-1.225	0.084	<0.001	0.294 (0.248-0.345)
20-LPRx	2.412	0.412	<0.001	11.216 (5.047-25.412)
Chi-Squared	35.977 (df=1, p < 0.001)			
Nagelkerke R^2	0.062			
Cox-Snell R^2	0.041			
Hosmer-Lemeshow R^2	0.039			

	Model 3: 60-LPRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	-1.312	0.091	<0.001	0.269 (0.224-0.321)
60-LPRx	1.625	0.422	<0.001	5.077 (2.230-11.682)
Chi-Squared	15.029 (df=1, p < 0.001)			
Nagelkerke R^2	0.026			
Cox-Snell R^2	0.017			
Hosmer-Lemeshow R^2	0.016			

	Model 4: 240-LPRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	-1.255	0.106	<0.001	0.285 (0.231-0.349)
240-LPRx	0.520	0.459	0.257	1.683 (0.685-4.153)
Chi-Squared	1.286 (df=1, p=0.257)			
Nagelkerke R^2	0.002			
Cox-Snell R^2	0.002			
Hosmer-Lemeshow R^2	0.001			

SUPPLEMENT DIGITAL CONTENT 6 (TABLE): Univariate logistic regression analysis to unfavourable outcome for each pressure reactivity index

	Model 1: PRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	0.093	0.076	0.219	1.097 (0.946-1.273)
PRx	3.175	0.472	<0.001	23.918 (9.685-61.610)
Chi-Squared	52.340 (df=1, p < 0.001)			
Nagelkerke R^2	0.080			
Cox-Snell R^2	0.060			
Hosmer-Lemeshow R^2	0.045			

	Model 2: 20-LPRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	0.300	0.069	<0.001	1.351 (1.180-1.550)
20-LPRx	0.826	0.353	0.019	2.285 (1.150-4.592)
Chi-Squared	5.573 (df=1, p = 0.018)			
Nagelkerke R^2	0.009			
Cox-Snell R^2	0.006			
Hosmer-Lemeshow R^2	0.005			

	Model 3: 60-LPRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	0.285	0.073	<0.001	1.330 (1.153-1.536)
60-LPRx	0.141	0.361	0.696	1.152 (0.568-2.344)
Chi-Squared	0.153 (df=1, p = 0.695)			
Nagelkerke R^2	<0.001			
Cox-Snell R^2	<0.001			
Hosmer-Lemeshow R^2	<0.001			

	Model 4: 240-LPRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	0.377	0.089	<0.001	1.457 (1.225-1.738)
240-LPRx	-0.584	0.395	<0.001	0.558(0.256-1.208)
Chi-Squared	2.192 (df=1, p = 0.139)			
Nagelkerke R^2	0.003			
Cox-Snell R^2	0.003			
Hosmer-Lemeshow R^2	0.002			

SUPPLEMENT DIGITAL CONTENT 7 (TABLE): Multivariate logistic regression analysis to fatal outcome for each pressure reactivity index in addition to a baseline model with the variables age, GCS, CPP, and ICP

	Model 1: Baseline + PRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	-2.234	1.236	0.071	0.107 (0.009-1.201)
Age	0.043	0.006	<0.001	1.044 (1.031-1.057)
GCS	-0.155	0.033	<0.001	0.856 (0.802-0.911)
CPP	-0.026	0.014	0.066	0.975 (0.948-1.001)
ICP	0.118	0.019	<0.001	1.125 (1.086-1.167)
PRx	3.713	0.621	<0.001	40.968 (12.353-141.498)
Chi-Squared	196.739 (df=5, p < 0.001)			
Nagelkerke R^2	0.419			

Cox-Snell R^2	0.286
Hosmer-Lemeshow R^2	0.230

	Model 2: Baseline + 20-LPRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	-1.925	1.212	<0.001	0.146 (0.013-1.555)
Age	0.046	0.006	<0.001	1.047 (1.034-1.059)
GCS	-0.161	0.032	<0.001	0.851 (0.798-0.905)
CPP	-0.029	0.014	0.035	0.972 (0.945-0.998)
ICP	0.129	0.018	<0.001	1.138 (1.099-1.181)
20-LPRx	2.131	0.498	<0.001	8.421 (3.202-22.616)
Chi-Squared	177.248 (df=5, p < 0.001)			
Nagelkerke R^2	0.393			
Cox-Snell R^2	0.269			
Hosmer-Lemeshow R^2	0.207			

	Model 1: Baseline + 60-LPRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	-1.665	1.196	0.164	0.189 (0.018-1.956)
Age	0.047	0.006	<0.001	1.048 (1.036-1.060)
GCS	-0.159	0.032	<0.001	0.853 (0.800-0.906)
CPP	-0.033	0.014	0.0160	0.968 (0.942-0.994)
ICP	0.124	0.018	<0.001	1.132 (1.094-1.174)
60-LPRx	1.062	0.505	0.035	2.893 (1.082-7.853)
Chi-Squared	162.777 (df=5, p < 0.001)			
Nagelkerke R^2	0.374			
Cox-Snell R^2	0.255			
Hosmer-Lemeshow R^2	0.190			

	Model 1: Baseline + 240-LPRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	-1.256	1.170	0.283	0.285 (0.028-2.808)
Age	0.048	0.006	<0.001	1.050 (1.037-1.062)
GCS	-0.016	0.032	<0.001	0.855 (0.802-0.908)
CPP	-0.038	0.013	0.005	0.963 (0.938-0.988)
ICP	0.122	0.018	<0.001	1.130 (1.092-1.171)
240-LPRx	-0.152	0.535	0.776	0.859 (0.302-2.469)
Chi-Squared	158.372 (df=5, p < 0.001)			
Nagelkerke R^2	0.368			
Cox-Snell R^2	0.251			
Hosmer-Lemeshow R^2	0.185			

SUPPLEMENT DIGITAL CONTENT 8 (TABLE): Multivariate logistic regression analysis to unfavourable outcome for each pressure reactivity index in addition to a baseline model with the variables age, GCS, CPP, and ICP

	Model 1: Baseline + PRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	-0.265	0.975	0.786	0.767 (0.113-5.186)
Age	0.031	0.005	<0.001	1.032 (1.022-1.042)
GCS	-0.200	0.025	<0.001	0.819 (0.780-0.859)
CPP	-0.002	0.011	0.829	0.998 (0.976-1.020)
ICP	0.050	0.015	<0.001	1.051 (1.022-1.082)
PRx	2.493	0.535	<0.001	12.094 (4.311-35.261)
Chi-Squared	157.337 (df=5, p < 0.001)			
Nagelkerke R^2	0.303			
Cox-Snell R^2	0.231			
Hosmer-Lemeshow R^2	0.142			

	Model 1: Baseline + 20-LPRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	-0.226	0.957	0.813	0.798 (0.121-5.193)
Age	0.035	0.005	<0.001	1.036 (1.026-1.046)
GCS	-0.202	0.025	<0.001	0.817 (0.778-0.857)
CPP	-0.004	0.011	0.735	0.996 (0.975-1.018)
ICP	0.055	0.014	<0.001	1.056 (1.028-1.087)
20-LPRx	0.623	0.415	0.133	1.864 (0.829-4.225)
Chi-Squared	136.244 (df=5, p < 0.001)			
Nagelkerke R^2	0.276			
Cox-Snell R^2	0.211			
Hosmer-Lemeshow R^2	0.123			

	Model 1: Baseline + 60-LPRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	-0.062	0.956	0.948	0.940 (0.143-6.097)
Age	0.036	0.005	<0.001	1.037 (1.027-1.047)
GCS	-0.200	0.025	<0.001	0.818 (0.779-0.858)
CPP	-0.006	0.011	0.578	0.994 (0.973-1.015)
ICP	0.053	0.014	<0.001	1.054 (1.026-1.085)
60-LPRx	-0.106	0.424	0.802	0.899 (0.391-2.069)
Chi-Squared	134.038 (df=5, p<0.001)			
Nagelkerke R^2	0.274			
Cox-Snell R^2	0.209			
Hosmer-Lemeshow R^2	0.121			

	Model 1: Baseline + 240-LPRx

Variable	Coefficient	Standard Error	p-value	Odds ratio (95% CI)
Constant	0.104	0.951	0.913	1.110 (0.171-7.141)
Age	0.037	0.005	<0.001	1.038 (1.028-1.048)
GCS	-0.198	0.025	<0.001	0.820 (0.781-0.860)
CPP	-0.007	0.011	0.488	0.993 (0.972-1.014)
ICP	0.053	0.014	<0.001	1.055 (1.026-1.085)
240-LPRx	-0.832	0.457	0.069	0.435 (0.176-1.061)
Chi-Squared	137.320 (df=5, p < 0.001)			
Nagelkerke R^2	0.278			
Cox-Snell R^2	0.212			
Hosmer-Lemeshow R^2	0.124			

SUPPLEMENT DIGITAL CONTENT 9 (TABLE): Group comparisons between the fatal vs. non-fatal and favourable vs. unfavourable outcome group using filtered indices

	Alive (GOS 2-5)	Dead (GOS 1)	p-value	Favourable (GOS 4-5)	Unfavourable (GOS 1-3)	p-value
Filtered PRx	0.116 (0.054-0.205)	0.203 (0.104-0.381)	**<0.001**	0.111 (0.054-0.191)	0.160 (0.071-0.257)	**<0.001**
Filtered 20-LPRx	-0.025 (-0.141-0.094)	0.003 (-0.127-0.193)	**0.037**	-0.023 (-0.126-0.092)	-0.021 (-0.160-0.139)	0.568
Filtered 60-LPRx	0.049 (-0.069-0.159)	0.044 (-0.058-0.237)	0.280	0.052 (-0.037-0.151)	0.043 (-0.089-0.190)	0.871
Filtered 240-LPRx	0.143 (0.023-0.255)	0.123 (0.003-0.258)	0.554	0.149 (0.050-0.262)	0.129 (0.009-0.254)	0.170

SUPPLEMENT DIGITAL CONTENT 10 (TABLE): Univariate logistic regression analysis to fatal outcome for each pressure reactivity index based on filtered signals

	Model 1: filtered PRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	-2.130	0.199	<0.001	0.119 (0.079-0.173)
Filtered PRx	5.093	0.818	<0.001	162.934 (34.358-853.835)
Chi-Squared	44.654 (df=1, p < 0.001)			
Nagelkerke R^2	0.160			
Cox-Snell R^2	0.107			
Hosmer-Lemeshow R^2	0.087			

	Model 2: filtered 20-LPRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	-1.234	0.112	<0.001	0.291 (0.233-0.361)
Filtered 20-LPRx	2.091	0.549	<0.001	8.089 (2.789-24.111)
Chi-Squared	14.888 (df=1, p < 0.001)			
Nagelkerke R^2	0.055			
Cox-Snell R^2	0.036			
Hosmer-Lemeshow R^2	0.029			

	Model 3: filtered 60-LPRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	-1.291	0.120	<0.001	
Filtered 60-LPRx	1.288	0.568	0.024	
Chi-Squared	5.143 (df=1, p = 0.023)			
Nagelkerke R^2	0.025			
Cox-Snell R^2	0.017			
Hosmer-Lemeshow R^2	0.010			

	Model 4: filtered 240-LPRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	-1.223	0.143	<0.001	0.294 (0.221-0.387)
Filtered 240-LPRx	0.231	0.631	0.715	1.260 (0.364-4.349)
Chi-Squared	0.133 (df=1, p = 0.715)			
Nagelkerke R^2	0.009			
Cox-Snell R^2	0.006			
Hosmer-Lemeshow R^2	<0.001			

SUPPLEMENT DIGITAL CONTENT 11 (TABLE): Univariate logistic regression analysis to unfavourable outcome for each pressure reactivity index based on filtered signals

	Model 1: filtered PRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	-0.213	0.152	0.161	0.808 (0.598-1.086)
Filtered PRx	3.360	0.789	<0.001	28.786 (6.443-142.732)
Chi-Squared	20.873 (df=1, p < 0.001)			
Nagelkerke R^2	0.088			
Cox-Snell R^2	0.066			

Hosmer-Lemeshow R^2	0.033

	Model 2: filtered 20-LPRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	0.313	0.093	<0.001	1.367 (1.141-1.642)
Filtered 20-LPRx	0.892	0.480	0.063	2.439 (0.961-6.334)
Chi-Squared	3.516 (df=1, p = 0.061)			
Nagelkerke R^2	0.013			
Cox-Snell R^2	0.010			
Hosmer-Lemeshow R^2	0.005			

	Model 3: filtered 60-LPRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	0.289	0.098	0.003	1.334 (1.102-1.618)
Filtered 60-LPRx	0.341	0.492	0.488	1.406 (0.538-3.710)
Chi-Squared	0.483 (df=1, p = 0.488)			
Nagelkerke R^2	0004			
Cox-Snell R^2	0.003			
Hosmer-Lemeshow R^2	<0.001			

	Model 4: filtered 240-LPRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	0.360	0.122	0.003	1.434 (1.131-1.824)
Filtered 240-LPRx	-0.341	0.542	0.529	0.711 (0.245-2.054)
Chi-Squared	0.397 (df=1, p = 0.528)			
Nagelkerke R^2	0.004			
Cox-Snell R^2	0.003			
Hosmer-Lemeshow R^2	<0.001			

SUPPLEMENT DIGITAL CONTENT 12 (TABLE): Filtered pressure reactivity indices as predictors of fatal and unfavourable outcome

Index	**Fatal outcome**		**Unfavourable outcome**	
	AUC (95% CI)	**p-value (DeLong's test)***	**AUC (95% CI)**	**p-value (DeLong's test)***
Filtered PRx	0.67 (0.61-0.73)	-	0.60 (0.55-0.65)	-
Filtered 20-LPRx	0.57 (0.50-0.63)	**0.004**	0.51 (0.46-0.57)	**0.015**

Filtered 60-LPRx	0.47 (0.40-0.53)	**<0.001**	0.50 (0.45-0.56)	**0.020**
Filtered 240-LPRx	0.51 (0.45-0.58)	**0.001**	0.53 (0.48-0.59)	0.101

SUPPLEMENT DIGITAL CONTENT 13 (TABLE): Multivariate logistic regression analysis to fatal outcome for each pressure reactivity index based on filtered signals in addition to a baseline model with the variables age, GCS, CPP, and ICP

	Model 1: Baseline + filtered PRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	-2.691	1.790	0.132	0.068 (0.002-2.222)
Age	0.035	0.008	<0.001	1.036 (1.020-1.053)
GCS	-0.129	0.041	0.002	0.879 (0.808-0.951)
CPP	-0.014	0.019	0.472	0.986 (0.949-1.024)
ICP	0.071	0.024	0.003	1.073 (1.025-1.127)
Filtered PRx	3.820	0.974	<0.001	45.602 (6.897-318.232)
Chi-Squared	81.572 (df=5, p < 0.001)			
Nagelkerke R^2	0.421			
Cox-Snell R^2	0.294			
Hosmer-Lemeshow R^2	0.180			

	Model 1: Baseline + filtered 20-LPRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	-1.946	1.754	0.267	0.143 (0.004-4.414)
Age	0.036	0.008	<0.001	1.037 (1.021-1.054)
GCS	-0.131	0.040	0.001	0.877 (0.809-0.946)
CPP	-0.018	0.019	0.352	0.982 (0.945-1.020)
ICP	0.084	0.024	<0.001	1.088 (1.040-1.143)
Filtered 20-LPRx	0.844	0.664	0.204	2.326 (0.634-8.641)
Chi-Squared	67.919 (df=5, p < 0.001)			
Nagelkerke R^2	0.373			
Cox-Snell R^2	0.258			
Hosmer-Lemeshow R^2	0.148			

	Model 1: Baseline + filtered 60-LPRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	-1.451	1.751	0.408	0.234 (0.007-7.201)
Age	0.038	0.008	<0.001	1.038 (1.023-1.055)
GCS	-0.131	0.040	0.001	0.878 (0.809-0.945)
CPP	-0.024	0.019	0.207	0.976 (0.939-1.013)
ICP	0.081	0.024	<0.001	1.084 (1.036-1.138)

Filtered 60-LPRx	0.169	0.693	0.807	1.184 (0.304-4.630)
Chi-Squared	66.356 (df=5, p < 0.001)			
Nagelkerke R^2	0.369			
Cox-Snell R^2	0.255			
Hosmer-Lemeshow R^2	0.144			

	Model 1: Baseline + filtered 240-LPRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	-0.956	1.714	0.577	0.384 (0.013-11.007)
Age	0.039	0.008	<0.001	1.040 (1.024-1.057)
GCS	-0.128	0.040	0.001	0.880 (0.811-0.950)
CPP	-0.030	0.019	0.112	0.971 (0.935-1.007)
ICP	0.079	0.023	<0.001	1.082 (1.036-1.135)
Filtered 240-LPRx	-0.845	0.743	0.255	0.429 (0.010-1.852)
Chi-Squared	67.586 (df=5, p < 0.001)			
Nagelkerke R^2	0.372			
Cox-Snell R^2	0.257			
Hosmer-Lemeshow R^2	0.147			

SUPPLEMENT DIGITAL CONTENT 14 (TABLE): Multivariate logistic regression analysis to unfavourable outcome for each pressure reactivity index based on filtered signals in addition to a baseline model with the variables age, GCS, CPP, and ICP

	Model 1: Baseline + filtered PRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	0.410	1.422	0.773	1.507 (0.093-24.923)
Age	0.033	0.007	<0.001	1.034 (1.020-1.048)
GCS	-0.194	0.033	<0.001	0.823 (0.771-0.877)
CPP	-0.016	0.016	0.334	0.985 (0.954-1.016)

ICP	0.053	0.020	0.008	1.054 (1.014-1.097)
Filtered PRx	2.389	0.918	0.009	10.900 (1.866-68.926)
Chi-Squared	85.517 (df=5, p < 0.001)			
Nagelkerke R^2	0.352			
Cox-Snell R^2	0.273			
Hosmer-Lemeshow R^2	0.142			

	Model 1: Baseline + filtered 20-LPRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	0.354	1.399	0.800	1.425 (0.091-22.329)
Age	0.0350	0.007	<0.001	1.036 (1.022-1.050)
GCS	-0.196	0.032	<0.001	0.822 (0.771-0.874)
CPP	-0.012	0.016	0.436	0.988 (0.957-1.019)
ICP	0.061	0.020	0.002	1.063 (1.024-1.106)
Filtered 20-LPRx	0.250	0.586	0.670	1.284 (0.408-4.081)
Chi-Squared	81.313 (df=5, p < 0.001)			
Nagelkerke R^2	0.319			
Cox-Snell R^2	0.246			
Hosmer-Lemeshow R^2	0.133			

	Model 1: Baseline + filtered 60-LPRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	0.508	1.403	0.717	1.663 (0.106-26.335)
Age	0.035	0.007	<0.001	1.036 (1.023-1.050)
GCS	-0.195	0.032	<0.001	0.823 (0.772-0.875)
CPP	-0.014	0.016	0.364	0.986 (0.955-1.020)
ICP	0.060	0.020	0.002	1.062 (1.023-1.105)
Filtered 60-LPRx	-0.057	0.597	0.924	0.945 (0.293-3.055)
Chi-Squared	81.140 (df=5, p < 0.001)			
Nagelkerke R^2	0.319			
Cox-Snell R^2	0.245			
Hosmer-Lemeshow R^2	0.133			

	Model 1: Baseline + filtered 240-LPRx			
Variable	**Coefficient**	**Standard Error**	**p-value**	**Odds ratio (95% CI)**
Constant	0.796	1.395	0.568	2.217 (0.145-34.735)
Age	0.036	0.007	<0.001	1.037 (1.023-1.051)
GCS	-0.191	0.032	<0.001	0.826 (0.774-0.879)
CPP	-0.017	0.016	0.267	0.983 (0.953-1.013)
ICP	0.059	0.020	0.002	1.061 (1.022-1.103)

Filtered 240-LPRx	-0.723	0.641	0.260	0.485 (0.136-1.693)
Chi-Squared	82.413 (df=5, p < 0.001)			
Nagelkerke R^2	0.321			
Cox-Snell R^2	0.247			
Hosmer-Lemeshow R^2	0.135			

SUPPLEMENT DIGITAL CONTENT 15 (TABLE): AUCs for prediction of fatal und unfavourable outcome for different combined index models based on filtered signals

	Fatal outcome		**Unfavourable outcome**	
	AUC	**95% CI**	**AUC**	**95% CI**
Baseline + filtered PRx	0.81	0.75-0.86	0.74	0.70-0.79
Baseline + filtered 20-LPRx	0.78	0.73-0.84	0.73	0.69-0.78
Baseline + filtered 60-LPRx	0.78	0.73-0.84	0.73	0.69-0.78
Baseline + filtered 240-LPRx	0.79	0.74-0.84	0.74	0.69-0.78
Filtered PRx + filtered 20-LPRx	0.67	0.61-0.73	0.60	0.55-0.65
Filtered PRx + filtered 60-LPRx	0.67	0.61-0.73	0.60	0.55-0.66
Filtered PRx + filtered 240-LPRx	0.67	0.61-0.73	0.61	0.56-0.66

Baseline model consisting of the variables age, GCS, CPP, and ICP.