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Full title: Signal Information Prediction of Mortality Identifies Unique Patient Subsets after Severe Traumatic Brain Injury: A Decision-Tree Analysis Approach

Running title: Decision Tree Prediction of Mortality after TBI

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Abstract

Nonlinear physiological signal features that reveal information content and causal flow have recently been shown to be predictors of mortality after severe traumatic brain injury (TBI). The extent to which these features interact together, and with traditional measures

to describe patients in a clinically meaningful way remains unclear. In this study, we incorporated basic demographics (age and initial Glasgow coma scale, GCS) with linear and nonlinear signal information based features - approximate entropy (ApEn), and multivariate conditional Granger causality (GC) to evaluate their relative contributions to mortality using cardio-cerebral monitoring data from 171 severe TBI patients admitted to a single neurocritical care center over a ten-year period. Beyond linear modelling, we employed a decision tree analysis approach to define a predictive hierarchy of features. We found ApEn (p = 0.009) and GC (p = 0.004) based features to be independent predictors of mortality at a time when mean intracranial pressure (ICP) was not. Our combined model with both signal information-based features performed the strongest (area under curve = 0.86 vs 0.77 for linear features only). Although low "intracranial" complexity (ApEn-ICP) out-ranked both age and GCS as crucial drivers of mortality (five-fold increase in mortality where ApEn-ICP < 1.56, 36.2% vs. 7.8%), decision tree analysis revealed clear subsets of patient populations using all three predictors. Patients with lower ApEn-ICP and aged > 60 died, whereas those with higher ApEn-ICP and GCS $\geq$ 5 all survived. Yet, even with low initial intracranial complexity, as long as patients maintained robust GC and "extracranial" complexity (ApEn of mean arterial pressure), they all survived. Incorporating traditional linear and novel, nonlinear signal information features, particularly in a framework such as decision trees, may provide better insight into the 'health' status. However, caution is required when interpreting these results in a clinical setting prior to external validation.

Keywords: traumatic brain injury, signal information, decision tree analysis, complexity

Introduction

As a leading cause of death and disability and with an aging demographic, there is significant motivation to improve the outcomes of patients with traumatic brain injuries

(TBI).[1] This is a highly heterogeneous group of patients and there is great interest in tailoring treatments and physiological targets to individuals in the hope that this might improve outcomes.[2] In order to achieve this, we need to fully characterize the patient phenotype. As our ability to amass complex data increases in the neurocritical care setting, the move towards automation to guide the expert clinician still requires the development and selection of the most relevant clinical information.[3]

Traditionally, the reliance has been on known predictors of outcome such as age and Glasgow coma score (GCS) at presentation (taken to be a surrogate for neurological injury severity). However a clinically useful phenotypic description may also include physiological measures such as intracranial pressure (ICP) or cerebral perfusion pressure (CPP) which are also predictors of outcome. More recently, the incorporation of autoregulation assessment have been proposed as further features that might be helpful to individualise therapy since measurements such as the pressure reactivity index (PRx) have been shown to also be independently associated with outcome.[4–6] Taken together, we refer to these as "linear" signal features owing to their established derivations.

Conversely, nonlinear signal features related to complexity/information content such as approximate entropy (ApEn) are now seen as a potential summary of homeostatic integrity.[7–9] Signal complexity has been shown to be an independent predictor of TBI outcome.[10–13] In prior work, we further demonstrated that information flow between physiological signals (such as Granger causality) may also be linked to mortality.[14] In this

study, we refer to such parameters as ‘signal information’ based features.

The success in discovering these novel prognostic features has led to uncertainty in how the large number of possible measurable or calculatable features, both linear and signal information based, describe the patient in a way that is clinically meaningful and best related to outcome. While it is likely that such features are not completely independent, it remains unclear what subset provides the best ‘description’ of the patient state or whether some of these features are in fact redundant. Previous work has related predictors to outcome with relatively simple linear models but it is not clear that there is a monotonic relationship between predictors and outcome.[15–18]

In the present work, we sought to incorporate basic demographics (age and GCS, both known to be strong drivers of outcome) with linear and signal information-based features to evaluate their relative contributions to mortality. In addition to linear modelling, we employed decision tree analysis, a nonlinear yet highly interpretable classification technique, to define a predictive ‘hierarchy’ of features; this also allowed us to test whether non-linear relationships between features were relevant to mortality by comparing the performance of such a flexible model with a linear predictor.

Materials and methods

Patient selection and data acquisition

Retrospective analysis of data recordings from patients admitted to the Neurosciences and Trauma Critical Care Unit (NCCU) at Cambridge University Hospitals, Cambridge UK

after severe head injury between 2002 and 2012 was performed. ICP was recorded using an intraparenchymal probe placed as per departmental clinical protocol (Codman & Shurtleff Inc., MA, USA). Invasive systolic and diastolic blood pressure was recorded from an indwelling radial artery catheter. HR was derived from routine cardiac monitoring. All signals were continuously sampled using ICM+ software (Cambridge, UK, http://icmplus.neurosurg.cam.ac.uk) at a frequency between 30 to 200 Hz. Data was re-sampled by averaging over ten second epochs in order to suppress pulse and respiratory waves to focus entirely on the slow fluctuations of ICP.

There were 319 patient recordings available; total data recording length varied between patients from <1 hour to 14 days. However, we were interested in those that had time for the disease process to evolve and selected 203 with at least 72 hours recording of ICP, BP and HR. Those without a Glasgow Outcome Score (GOS) (*n* = 5), known to have more than 2-hour gaps (n = 10) and over 24 hours from ictus at the time of admission (*n* = 17) were excluded. 171 patients entered our analysis. Since recordings in the first 24 hours tended to be either incomplete due to surgical intervention or confounded by artefacts due to sedation holds in apparently less severely injured patients, we selected the second 24 hour period for our analysis. All were sedated, mechanically ventilated and managed according to a cerebral perfusion pressure (CPP) orientated protocol during their stay in critical care.[19] Data collection and analysis was approved by institutional review. The pressure reactivity index (PRx), a moving Pearson correlation between ICP and MAP, was additionally calculated as a measure of cerebral autoregulation.

Nonlinear signal information-based features

1) Complexity - approximate entropy (ApEn) was used as the marker for the complexity of heart rate (ApEn-HR), mean arterial pressure (ApEn-MAP), and intracranial pressure (ApEn-ICP) derived using open source MATLAB (R2017a, MathWorks Inc. Natick, Massachusetts, United States) scripts. Following on from our prior findings, we also used a combined "ApEn-Product" (interaction term or product of the three individual ApEns), which was found to be most predictive of outcome.[10]

2) Information flow - conditional multivariate Granger causality (GC) values were derived using code published by Seth *et al* using MATLAB.[20,21] Data was aligned for each subject such that the same 24-hour recording period as for ApEn was used. We used the multivariate extension, often referred to as 'conditional' Granger causality analysis, as a marker for the causal information flow between our three time-series variables.[22] For example, GC could infer a causal relationship from MAP to ICP only if past information in the MAP helped predict future ICP, after taking into account the influence of HR. Mathematical theory behind GC as well as data preparation workflow is described extensively elsewhere.[23–25] Based on our prior study,[14] the Granger causality from ICP to MAP (ICP-to-MAP) and from HR to ICP (HR-to-ICP) were identified as significant predictors of mortality. We tested these, and their interaction term "Granger-Product" (product between ICP-to-MAP and HR-to-ICP) in our models.

Statistical analysis

Linear (PRx, mean values for ICP, CPP, BP, and HR) and signal information-based features (ApEn and GC) for 171 patients over the same 24 hour monitoring period was used for analysis. Mortality was assessed at 6 months after head injury. Between group comparisons were made using with one-way ANOVA, or Kruskal-Wallis non-parametric testing as appropriate. Categorical data were compared using chi-squared testing. Multivariable logistic regression models (using linear only features, linear with ApEn, linear with GC, and a "combined" - linear with both ApEn and GC) were constructed to identify independent predictors of mortality and reported using odds ratios and their 95% confidence intervals. We also calculated the pseudo R-squared given that it also takes into account prevalence.

We employed Chi-square Automatic Interaction Detection, or CHAID, for binary recursive partitioning to construct a decision tree model for the prediction of mortality; the patient population is repeatedly split into increasingly homogenous groups based on the optimum predictors of mortality (using both linear and signal information features) at each split. First introduced by Kass in 1980,[26] recursive partitioning with CHAID is particularly powerful when there are many potential complex interactions between the predictors of interest,[27] We set n = 30 (17.5%) as the minimum patient count at which further partitioning occurred and splits were also pruned if they did not significantly improve the overall model in order to minimise overfitting. Finally, we used cross-validation for constrained optimization using multiple training sets (10 'folds') within the

cohort. The stopping rule terminates splitting when improvement in the cross-validation R^2 is minimal (more specifically, a model is selected when none of the next ten show an improvement of cross-validation R^2 greater than 0.005). This optimised misclassification error, prevented overfitting and limited tree size (number of splits).

Model performance for all possible thresholds for dichotomizing the predicted probabilities of fatality was then assessed using receiver operated characteristics (ROC), and their corresponding area under the curve (AUC) and 95% CI (confidence intervals), as well as differences between model AUCs and corresponding 95% CIs. To assess the accuracy of the prediction models, calibration plots were produced by binning predicted mortality probabilities into deciles, and then plotting the mean observed mortality against the mean predicted mortality within each bin.[28] Statistical analysis was performed using JMP Pro 14 (SAS Institute Inc, Cary, NC, USA). Data are presented as mean (± standard deviation), unless otherwise indicated. GC variables were log transformed due to non-normal distribution prior to inclusion in the models. *P*-values are reported as is without thresholds for statistical significance in accordance with the latest statistical guidance from the American Statistical Association.[29,30] All tests were two-tailed and without correction for multiple comparisons.

Results

Baseline characteristics

In Table 1. 171 patients entered our analysis where 129 (75.4%) were male with an average age of 38.1 (±15) who stayed monitored average 7.3 (3.4) days. The initial post-resuscitation GCS was 6.4 (3.4), which is not surprising given the necessity for neurocritical care admission; overall 107 (62.6%) sustained severe TBI resulting in GCS ≤ 8. Six months post injury, 40 died (23.4%, GOS = 1) and 131 survived (76.6%, GOS = 2-5).

Examining patients excluded from analysis, we did not find statistical difference in any of their baseline characteristics.

Linear and signal information feature differences in survival and death

For linear features, we confirmed significant differences in age (F = 13.8, p = 0.0003), initial GCS (F = 5.0, p = 0.026) and PRx (F = 5.8, p = 0.017) between those that survived versus those that died, using one-way ANOVA (Table 1). While CPP was borderline, no difference was seen with ICP either in keeping with prior studies.[10,14] There was also no difference in the eventual total number of days of monitoring (F = 0.01, p = 0.92). We found ApEn-Product (F = 18.1, p = 0.00004) and Granger-Product (F = 13.0, p = 0.0004) to perform best versus their individual variables (ICP, MAP, and HR derived) for differences between survival and death, shown in Table 1, as our nonlinear signal information features.

Complexity and information flow are independent predictors of mortality

In multivariable logistic regression, we defined our linear only model to include age, GCS, ICP, CPP, and PRx. Subsequently, ApEn-Product (OR 0.60, 95% CI: 0.46-0.77, p = 0.00008) and Granger-Product (OR = 0.48, 95% CI: 0.34-0.69, p = 0.00005) were introduced separately ('with ApEn' and 'with Granger' models, respectively), and together in the 'combined' model in Table 2. We found that our nonlinear signal information features separately somewhat improved the linear only model, but more significantly, both survived in the final combined model as independent predictors - ApEn-Product (OR =

0.70, 95% CI: 0.53-0.93, p = 0.009) and Granger-Product (OR = 0.59, 95% CI: 0.41-0.87, p = 0.004). The combined model explained the largest proportion of the variance for mortality (pseudo R^2= 0.31) and had the highest AUC (0.86, 95% CI: 0.79-0.91).[31]

Decision tree model

We permitted the entry of all linear (age, sex, initial GCS, ICP, CPP and PRX), and signal information features (ApEn and Granger products, as well as their individual components). The final decision tree is shown in Figure 1. Based on our stopping criteria, there were eight splits. In order, the following features and cut-off values for mortality were found; ApEn-ICP < 1.56, age ≥ 60, GCS < 5, Granger < -0.49, CPP < 72.3, ApEn-MAP < 1.63, ICP ≥ 22.4 and PRx ≥ -0.04. The tenfold cross-validation R^2 was 0.38 with an AUC of 0.92 (95% CI 0.87-0.95) and was favorable compared to our combined nonlinear and linear models (see ROC in Figure 2). Formal model comparison revealed that all model AUCs containing signal information features outperformed the linear features only model (see Table 3; p < 0.01 for all). The AUC for the decision tree improved upon that for "with GC" (+0.08, p = 0.029) and marginally for "with ApEn" (+0.08, p = 0.056). While it did improve upon the AUC for the Combined model, at the current sample size, the magnitude of this improvement will need replication (+0.06, p = 0.09).

Those with poor intracranial complexity (ApEn-ICP less than 1.56) were nearly 5 times more likely to die (36.2% vs 7.8%). The clearest paths were the 26.9% of patients identified by robust intracranial complexity (ApEn-ICP greater than 1.56) and good initial

neurological assessment (GCS 5 or above), who all survived. Likewise, all those with poor intracranial complexity (ApEn less than 1.56) aged over 60 died. Poor intracranial complexity (ApEn-ICP less than 1.56) and cardio-cerebral information flow (GC-Product below -0.49), even in those aged below 60, saw nearly half of subjects (n = 85) have a mortality of 45.0%, rising to 77.8% if CPP was also less than 72.3.

However, the decision tree also revealed that even those with poor intracranial complexity, as long as one is relatively young (aged less than 60), had robust cardio-cerebral information flow (GC-Product below -0.49) and good extracranial complexity (ApEn-MAP greater than 1.63), this resulted in 100% survival. Note that PRx ≥ -0.04 and ICP ≥ 22.4 appear in the 7^{th} and 8^{th} splits after CPP < 72.3 and GCS < 5, respectively, however these final splits saw diminishing sample size and must be interpreted with caution. Calibration plots showed acceptable, linear goodness-of-fit for a wide range of observed probabilities of mortality compared to our combined model (Figure 3A) and decision tree (Figure 3B) predicted probabilities.

Discussion

To the best of our knowledge, this is the first study to examine the predictive potential of both the complexity of, and information flow between, the cardio-cerebral vascular systems for mortality after severe traumatic brain injury. We applied approximate entropy and multivariate conditional Granger causality analysis for the assessment of complexity and information flow, using the most commonly measured parameters in the neuro-intensive care setting (ICP, MAP, and HR). We show that ApEn and GC provide independent information related to mortality, which is complimentary to each other, and to traditional linear markers, at an early stage after TBI. Using a relatively simple decision

tree model, predictive performance is enhanced further through maximising both linear and signal information-based features. This revealed clear subsets of patients related to mortality that could provide a framework for potential clinical and research applications.

Nonlinear signal information outperforms linear features

The identification of patients that will have a poor neurological recovery during the early phases of resuscitation is known to be problematic.[15] Our study of 171 moderate to severe TBI patients is unique in the use of a uniform and early 24h time period, and the selection of patients with at least 72 hours of monitoring, to examine a combination of newly derived nonlinear markers of mortality.[10,11,14] This allows potential for earlier clinical interventions, adds temporal information, where secondary injuries are most likely to manifest and be reflected in our analysis. The removal of those with very short data recordings (due to death/futility, withdrawal of care, recovery, de-escalation of care or withdrawal of consent) mitigates against extreme values that can skew group trends.[14] The observed mortality (23.4%) is in keeping with other studies of comparable cohorts from a similar time period.[16] Similarly, age and initial GCS were significant contributors that have long been established as predictors of outcome.[15,16,32] Unfortunately, we did not have access to CT-findings, lab results or extra-cranial injuries for this particular cohort, which is a significant limitation. However, for the purposes of a comparator, the AUC for our basic logistic regression model incorporating only age, GCS and linear signal properties (0.77) was still comparable in terms of performance to established MRC-CRASH, IMPACT, and APACHE II models, which have ranged from AUC 0.76 to 0.82.[16–18]

We observed that incorporating nonlinear signal information derived from all three vital signs (ICP, MAP and HR) in the combined model (ApEn and GC Product plus linear features), were independent predictors of mortality, that outperformed the linear only model, and improved upon models with only one of ApEn or GC Product. Even though including both nonlinear predictors did reduce their effect size and 95% CI of their odds ratio, the combined model had a significantly higher AUC compared to the linear model during model comparisons. The improvement on the single nonlinear only predictor models was consistent but more modest going from 0.84 to 0.86 for AUC and 0.27 to 0.31 for R^2. These did not reach any acceptable threshold for significance during model comparison (see Table 3); we believe this may partly be due to sample size and despite their independent prediction values, a degree of overlap exists. However, to place these results into context, Raj et al. combined IMPACT (including CT and lab results) and APCHE II scores to achieve a similar AUC of 0.85 (95% CI: 0.81-0.89), albeit with higher precision due to larger sample sizes.[33] These results highlight the potential value of early measurements of complexity not only of ICP, but also of extracranial complexity via MAP and HR monitoring that reveal crucial prognostic information beyond the original absolute mean values. Moreover, inclusion of information flow, as measured through multivariate conditional GC between the cardio-cerebral systems appears to offer additional prognostic information.

Beyond simply strong discrimination, we also show that the combined model had good predictive calibration across a range of observed mortality probabilities (Fig. 3A). A robust assessment of model calibration is a crucial element of model validation as highlighted by Steyerberg et al;[34] whilst a poorly calibrated model which systematically over or under-predicts for particular ranges of observed outcome is poorly representative of the underlying biology even though it may still perform discrimination well at a population level. When combining models, as in this work, it is particularly important to assess whether an apparently improved model performance is at the same time offset by changes in calibration. A cross-validation process allows calibration to be assessed against observed mortality without assuming a ground-truth model. However, it is important to bear in mind that over 80% of the data is contributed by those with mortality < 50% due to the nature of the patient population. While it is reassuring that good discrimination is seen at the highest mortality range (> 50%), larger samples are needed to confirm this finding.

Decision tree model as an exploratory clinical and research tool

Given the intriguing finding of independent prediction by ApEn-Product and GC-Product, we were interested in whether the synergy may be better utilized through individual ApEn and GC parameters alongside linear features, especially for subsets of patients. Our decision tree showed the best performance amongst our models. Even though there was improvement on the Combined model's AUC, this will require , this was not the main motivation of the study. The true value in the decision tree lies in its ability to utilise a

multitude of predictors at different branching points; the potential ability to individualize prediction profiles makes a decision tree model more versatile, as was noted by Pang et al. in their cohort of 513 when comparing several prognostication models.[35] It effectively utilised established risk factors that are known to increase mortality (older age, low GCS, low CPP, high ICP and positive PRx) alongside and our novel nonlinear signal information-based features in unique pathways related to mortality.

The importance of low complexity, and in particular for ICP, is highlighted by an almost fivefold increase in mortality, in keeping with prior studies.[10,11] ApEn-MAP also appeared further down the tree, and perhaps is a reflection on the results of early resuscitation. While ApEn-Product was not used, GC-Product outperformed its constituent parts. Despite collinearity, the ability to harness predictors for different subgroup levels reflects a relative strength of decision tree models over linear logistic regression. Again, the predictive calibration plot was good overall, with some slight over-optimism (predicted < observed mortality) in the highest mortality range (Figure 3B). However, due to the binary nature of decision tree paths, only those with mortality < 30% and >70% are well represented in this particular calibration plot.

Whilst technical in nature, the synergy between information flow and complexity analysis shown in this study may be of central importance in understanding a multisystem disease like TBI, where advancements have been notoriously difficult. Bashan et al argued that the human organism is an integrated network where complex physiological systems, each

with its own regulatory mechanisms, continuously interact, and that failure of one system can trigger a breakdown of the entire network.[36] In our everyday airport systems, there are both regional and hub 'nodes', where there exists a level of complexity and information flow that ensures efficient flight paths (i.e. information transfer). For example, poor weather at a regional node may inconvenience local travellers, but a disruption at a major hub often leads to widespread, and crippling effects on the entire network.[37] In the context of TBI, the ICP, MAP, and HR signals themselves are likely 'major hubs' that encompass thousands of individual processes within a complex network.

Limitations

The motivation for this study was to explore a potentially useful tool to better classify heterogeneous patients (traditionally notoriously difficult in TBI). However, the decision tree must be interpreted with caution, particularly in clinical settings, prior to external validation. Due to the nature of TBI and the available sample size, some terminal nodes contain less than 10 subjects, so there is likely some degree of overfitting and overoptimistic predictions.

This is a retrospective, observational study where it was not feasible to control for the effects of clinical interventions (e.g. medication administration and/or ventilator weaning, surgical interventions, or disconnection from monitoring etc). A large part of the earlier data collection period was prior to an electronic record so many patients were limited to

initial presenting GCS as a marker of severity. However, others have shown that inclusion of extracranial injuries did not necessarily add any significant predictive ability.[38] Timing of ictus is only beginning to be captured accurately in more recent data collections and remains a major limitation. Whilst limiting analysis on only those with 72 hours monitoring reduced power, we believe it reduced heterogeneity of the sample and optimized inaccuracies over timing after ictus.

Although all patients were monitored on a single neuro-critical care unit where therapeutic interventions were standardized, variation inevitably occurs. For example, internal validation was rigorously performed, but due to the challenges working with new, data intensive algorithms, we are working on future validation using data from outside our institutions and care settings (e.g. from other developed and developing countries). Concurrently, newer, more robust and flexible nonlinear measures are emerging,[39,40] and some have been applied in a range of healthcare settings;[41–47] the challenge will be to efficiently test and incorporate these tools in the myriad of data collected in the intensive care setting.

Finally, complexity and information flow can only characterise data that is provided and is unable to account for unmeasured variables such as metabolic changes (CO_2 or serum osmolality for example) or therapeutic interventions such as anaesthesia or sedation which was unfortunately not available; these are unlikely to account for the strong link to

mortality, but future studies should look to incorporating treatment, imaging, metabolic and lab variables to enhance these findings.

Conclusions

We propose that incorporating multiple nonlinear signals, particularly in a framework such as decision trees, may provide better insight into the 'health' status of patients with severe TBI. While the results presented here should only be considered as experimental prior to external validation, we believe this does present potentially tangible prediction pathways for clinicians and researchers versus odds ratios, which can be harder to interpret; this framework may in future help triage those who require more intensive neurological management at an earlier stage.

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Disclosures

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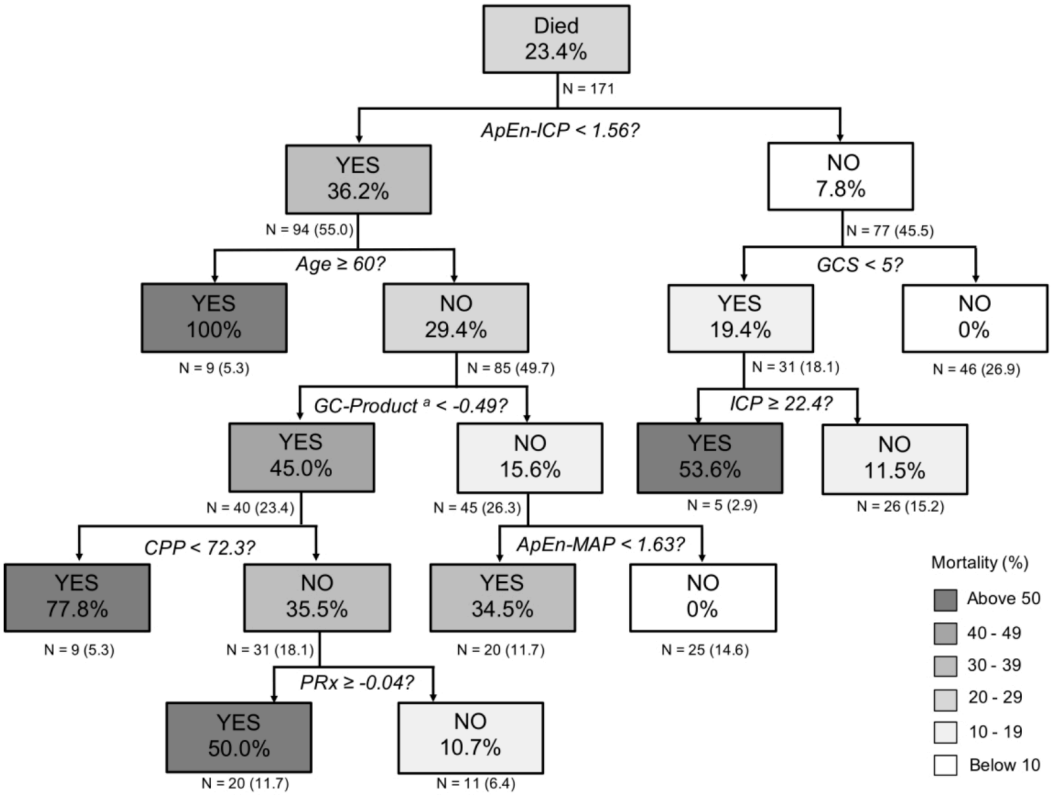


Decision tree model

Figure 1. Decision tree for predicting mortality at 6-months from ictus (GOS=1) in our TBI cohort. Splitting determined by best performing variable for increasing homogeneity regarding those with fatal outcome. Percentages within boxes represent proportion with fatal outcome. *N* (percentage) number of subjects at eath branch, *ApEn-ICP* approximate entropy of intracranial pressure, *GCS* initial presenting Glasgow Coma Score, *GC-Product* granger causality product (ICP-to-MAP x HR-to-ICP), *CPP* cerebral perfusion pressure, *ApEn-MAP* approximate entropy of mean arterial pressure. Shaded color bar reflects increasing proportion of fatalities from less than 10% to over 50%. [a]log transformed.

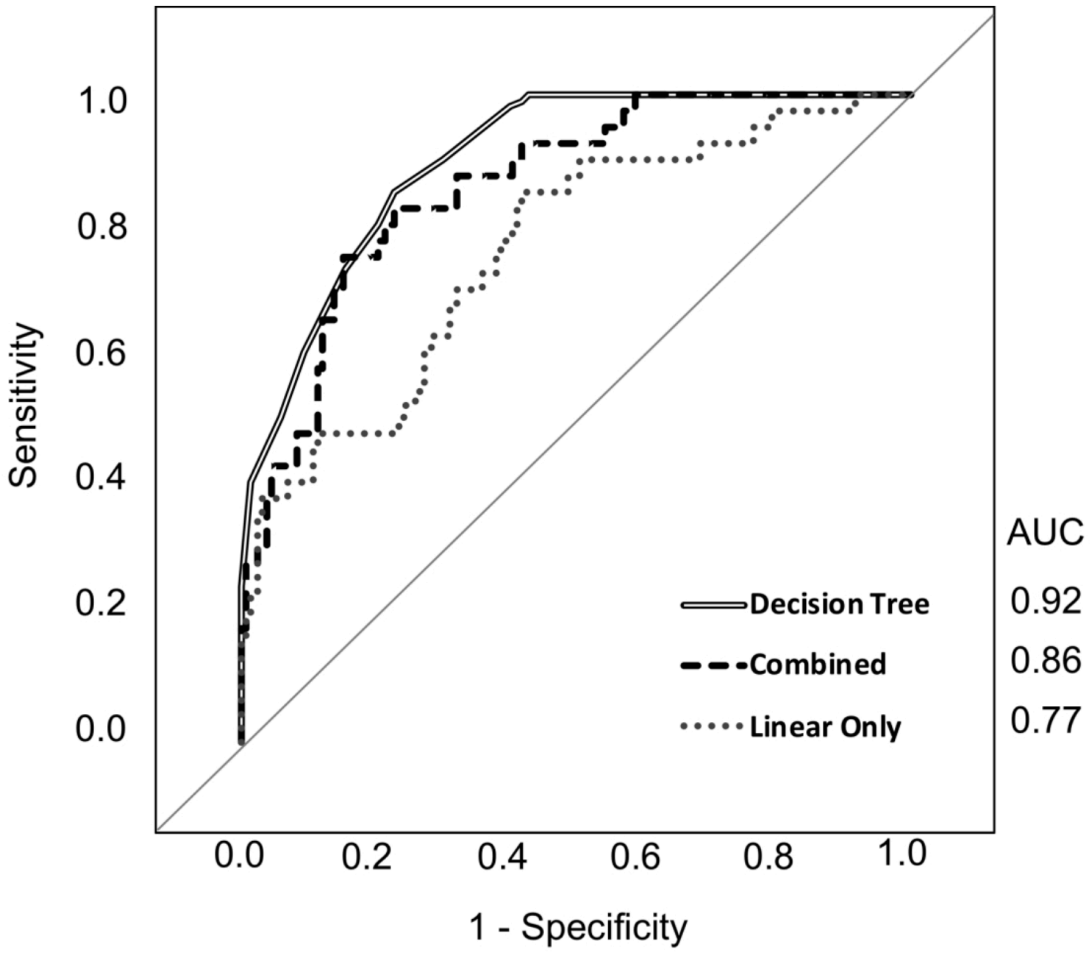
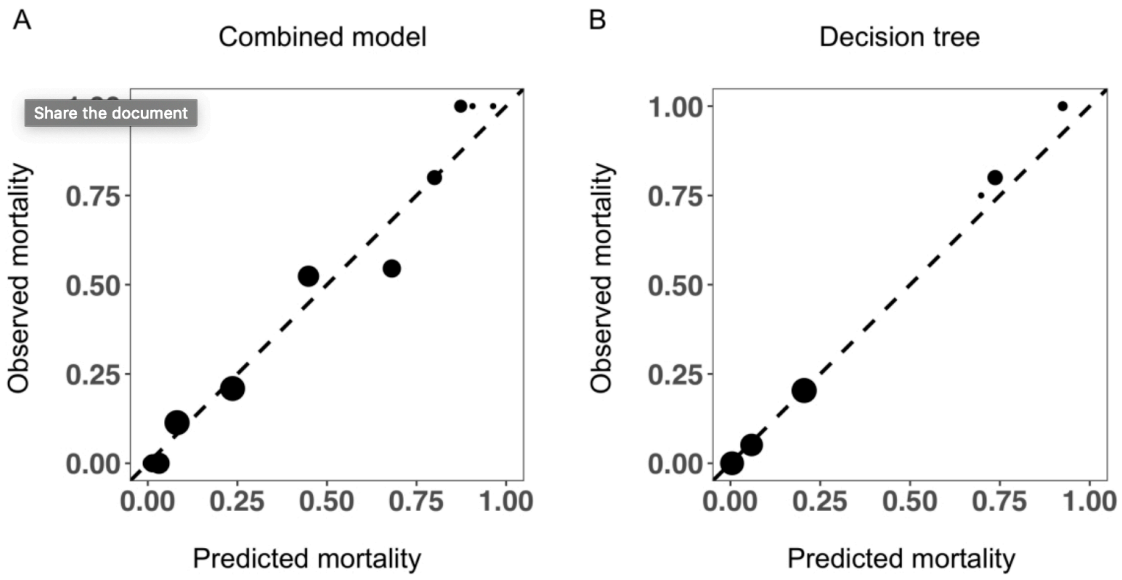


Figure 2. Linear only model (Age, GCS, PRx, ICP, CPP); Combined model (linear only model plus ApEn and Granger products); Decision Tree model (based on Figure 1, best predictor combination selected from linear and nonlinear parameters). GCS Glasgow Coma Scale, PRx pressure reactivity index, ICP intracranial pressure, CPP cerebral perfusion pressure, ApEn approximate entropy, Granger multivariate conditional Granger causality.



Calibration plots for Combined model and Decision tree models

Figure 3. Calibration plots for Combined model and Decision tree. Circles proportionally represent number of patients binned by predicted mortality and plot against actual mortality observed