Supplementary Data

SUPPLEMENTARY APPENDIX 1

Predictors Used in the Prognostic Algorithm

Several non-dynamic (baseline or static) and dynamic (longitudinal) predictors were considered during model building and are described below.

Non-dynamic predictors

Baseline predictors we considered were the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) core model prognostic score of unfavorable outcome (a score that contains information on patient's admission motor Glasgow Coma Scale (GCS), pupillary reactivity, and age); Marshall Computed Tomography (CT) scan classification (I, II, III, IV, diffuse injury; V, evacuated mass lesion; VI, non-evacuated mass lesion), presence of subarachnoid hemorrhage (SAH), presence of epidural hematoma (EDH), presence of hypotension, the Injury Severity Score (ISS), and the first intracranial pressure (ICP) value recorded. Other variables collected on admission such as presence of hypoxia, glucose, and hemoglobin, were excluded from the analyses because they were not available for many patients.

Dynamic predictors

We considered the following physiological variables recorded during the first 24 h after intensive care unit (ICU) admission: ICP,

SUPPLEMENTARY TABLE S1. UNIVARIATE ICP/MAP/CPP DYNAMIC PREDICTORS OF UNFAVORABLE 6-MONTH GOS

Total number of predictors	*Physiological/injury severity/ treatment variable*	*Predictor*	*Time interval*
9	ICP, MAP, CPP[a]	Mean/median/standard deviation	1–24 h
258	ICP, MAP, CPP	Median	22–24 h
		Standard deviation	every 5 min, 23–24 h every 10 min, 22–24 h every 30 min, 18–24 h every hour, 12–24 h every 2 h, 12–24 h
3	ICP, MAP, CPP	Coefficient of variation	1–24 h
2	ICP	Number of hours that ICP >20/25 mm Hg	1–24 h
2	CPP	Number of hours that CPP <50/60 mm Hg	1–24 h
1	ICP	Number of times ICP >20 mm Hg for at least 15 consecutive min	1–24 h
1	ICP	Number of times ICP >30 mm Hg for at least 10 consecutive min	1–24 h
270	ICP, MAP, CPP	Membership to 1 of 10 clusters, using Euclidean distance/correlation distance/cosine distance[b]	1–24 h 18–24 h 12–24 h
2	ICP	Area enclosed by a threshold of 20/25 mm Hg and ICP signal that is above the threshold[c]	1–24 h
2	CPP	Area enclosed by a threshold of 50/60 mm Hg and CPP signal that is below the threshold	1–24 h
9	ICP, MAP, CPP	FPCA scores[d]	1–24 h
90	ICP, MAP, CPP	Membership to 1 of 10 clusters, using Euclidean distance/correlation distance/cosine distance, with FPCA scores as subject curves	1–24 h
30	ICP, MAP, CPP	Ten largest coefficients of the Fourier transform of the signal	1–24 h
30	ICP, MAP, CPP	First 10 coefficients of the cepstrum of the signal	1–24 h
1	Motor Glasgow Coma Scale (GCS)	Best motor GCS	1–24 h
1	surgery	Indicator of whether surgery for increased ICP was performed	1–24 h
1	drug	Indicator of whether mannitol or barbiturates were given to decrease ICP	1–24 h

[a]ICP = intracranial pressure; MAP = mean arterial pressure; CPP = cerebral perfusion pressure.
[b]Clusters are generated via k-means, using three types of distance-measures: Euclidean distance, correlation distance, and cosine distance. Membership is a binary variable that indicates membership or non-membership to a specific cluster.
[c]The area is calculated using the trapezoid rule.
[d]Functional Principal Component Analysis (FPCA) scores after applying FPCA to each physiological variable.
GOS, Glasgow Outcome Score.

SUPPLEMENTARY TABLE S2. MULTIVARIATE DYNAMIC PREDICTORS OF UNFAVORABLE 6-MONTH GOS

Total number of predictors	*Physiological/treatment variables*	*Predictor*	*Time interval*
2	ICP, CPP[a]	Area enclosed by a threshold of 2/3 mm Hg and the ratio between mean CPP and ICP in 5-min intervals that is below the threshold	1–24 h
8	MAP, ICP	Mean, standard deviation, minimum, and maximum of simultaneous Spearman correlations[b]	1–24 h
8	MAP, ICP	Mean, standard deviation, minimum, and maximum of lagged Spearman correlations[c]	1–24 h
190	ICP, CPP	Renyi entropy using 15-min sliding windows ($\alpha = 0.1$ to 2 in 0.01 increments)[d]	1–24 h
2	ICP, SaO_2, $ETCO_2$, MAP, temperature, surgery, drug[e]	ICP adjusted transition rate (≤ 20 mm Hg to >20 mm Hg) ICP adjusted transition rate (> 20 mm Hg to ≤20 mm Hg)[f]	1–24 h
2	ICP, SaO_2, $ETCO_2$, MAP, temperature, surgery, drug	ICP adjusted transition rate (≤ 25 mm Hg to >25 mm Hg) ICP adjusted transition rate (> 25 mm Hg to ≤25 mm Hg)	1–24 h
5	ICP, CPP	Multivariate FPCA (MFPCA) scores	1–24 h
30	ICP, CPP	Membership to 1 of 10 clusters, Euclidean distance/correlation distance/cosine distance, with MFPCA scores as subject curves.	1–24 h

[a]ICP = intracranial pressure; MAP = mean arterial pressure; CPP = cerebral perfusion pressure.

[b]Correlations between ICP and MAP in the same time interval are computed every 10/25 min, where the range of MAP is at least 10 mm Hg.

[c]Correlations between ICP and MAP for an ICP time interval that starts 36 sec later than a MAP time interval are computed every 10/25 min, where the range of MAP is at least 10 mm Hg.

[d]Renyi entropy defined as: $R_L^{\alpha} = \frac{1}{1-\alpha}\log\left(\sum_{\pi_k \in S_L} P(\pi_k)^{\alpha}\right)$, where $P(\pi_k)$ is the probability of the ICP/CPP sequence π_k, L indicates the length of the sliding window and α is the selector of probabilities. A ICP/CPP sequence is determined by concatenating ordered 5-min averaged ICP and CPP values in a sliding window.

[e]SaO_2 = oxygen saturation of arterial blood; $ETCO_2$ = end-tidal CO_2.

[f]ICP transition rates of a two-state continuous-time Markov chain, of moving from a low or normal to a high ICP state and vice versa, adjusted by number of hours that SaO_2, $ETCO_2$, MAP, and temperature were abnormal; for ICP transition rate from high to low ICP, also adjusted by whether patient had surgery for increased ICP and whether they received mannitol or barbiturates to decrease ICP.

MAP, mean arterial pressure; FPCA, ; MFPCA, .

MAP, cerebral perfusion pressure (CPP), SaO_2, temperature, end-tidal CO_2 ($ETCO_2$), partial pressure of oxygen in arterial blood (PaO_2), and partial pressure oxygen of carbon dioxide in the arterial blood ($PaCO_2$). For ICP, MAP, and CPP, we calculated several summary measures per subject in different time intervals, including means, standard deviations, correlations, areas under the curve, duration of increased ICP episodes, and membership to clusters of signals.[1–4] For SaO_2, temperature, and $ETCO_2$, we calculated the number of hours that the variable was outside a specific threshold, and included these summarized physiological data as covariates in adjusted ICP transition rates from a two-state continuous-time Markov chain (CTMC) model. In addition, we considered the best motor GCS achieved in the first 24 h post-ICU admission, an indicator of whether a patient had surgery done for increased ICP, and an indicator of whether a patient received either barbiturates or mannitol to decrease ICP.

Supplementary Table S1 displays predictors of 6-month GOS for a single physiological, injury severity, or treatment variable, computed on the full first 24 h-period after ICU admission or on certain periods of time during those first 24 h. Supplementary Table S2 shows predictors that involve 2 or more physiological or treatment variables. In general, predictors displayed in Supplementary Tables S1 and S2 have been previously proposed.[2–7] For the ICP transition rates of Supplementary Table S2, we fitted regular two-state adjusted CTMC models, that is, we only used the Markov chain portion of the joint model proposed by Rubin and colleagues.[7]

Supplementary References

1. Kahraman, S., Dutton, R. P., Hu, P., Aarabi, B., Stein, D. M., and Scalea, T. M. (2010). Automated measurement of ''pressure times time dose'' of intracranial hypertension best predicts outcome after severe traumatic brain injury. J. Trauma 69,110–118.
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Pre-Processing and Imputation of Physiological Variables

We removed artifacts and imputed missing data before computing subject features of the 36-sec automated physiological data.

To reduce signal-to-noise ratio and avoid distorted results, we applied repeated median (RM) regression, a fast method that is robust to outliers, capable of tracing trends, trend changes and level shifts, and it is stable with respect to moderate variations in the data.[1] For the RM algorithm, we used a window of width 1 h (100 measurements every 36 sec) and we required a minimum of five non-missing observations in that time window to get a smoothed signal. Before applying the smoothing technique, we set to missing artifacts that fell outside of usual ranges of physiological variables, where a sequence of unusual values was not observed.

For the missing data problem, we first imputed intracranial pressure (ICP), mean arterial pressure (MAP), or cerebral perfusion pressure (CPP) based on the relationship between these variables (CPP = MAP-ICP). Secondly, we applied an imputation procedure on the ICP and MAP smoothed data that is similar to the procedure applied by Yamal and colleagues.[2] Briefly, for each patient we used interpolation to impute intermittent missing data, and for two or more consecutive missing values, we pooled 2 h of self-data before or after missingness and imputed from a normal distribution with mean and standard deviation equal to the mean and standard deviation of the pooled data, respectively. When hourly physiological data were available in periods of missing twice per minute data, the mean of the normal distribution was computed from the hourly data. This last approach was adopted only in subsets of the data where the non-missing 36-sec smoothed data correlated well with the non-missing hourly data. Once ICP and MAP were complete, remaining missing CPP values were calculated from these two.

For temperature, $ETCO_2$, and SaO_2, we first categorized the twice per minute smoothed data in normal and abnormal categories, based on pre-specified thresholds. Then, if data were missing between two normal categories, we imputed a normal category; if data were missing between abnormal categories, we imputed an abnormal category; and, when missingness occurred between a normal and an abnormal category (in that order), a normal category was imputed. After applying this procedure, if there were still missing values, we imputed values from the hourly physiological data, only for subsets of the data where the non-missing 36-sec smoothed data correlated well with the non-missing hourly data. We also used hourly $PaCO_2$ and PaO_2 as surrogate measures to impute $ETCO_2$ and SaO_2, respectively.

Supplementary References

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2. Yamal, J., Rubin, M. L., Benoit, J. S., Tilley, B. C., Gopinath, S., Hannay, H. J., Doshi, P., Aisiku, I. P., and Robertson, C. S. (2015). Effect of hemoglobin transfusion threshold on cerebral hemodynamics and oxygenation. J. Neurotrauma 32, 1239–1245.

Supervised Learning Algorithms used in the Study

Supplementary Table S3 shows a brief description of the supervised learning algorithms applied to the training set of our study to make predictions on the test set.

In particular, the LASSO algorithm is a linear regularization method commonly used to perform model selection for models with many explanatory variables. For a logistic regression model with a binary response y, a vector of covariates $\mathbf{x} = (1, x_1, x_2, \ldots x_p)$ with associated parameter vector $\boldsymbol{\beta} = (\beta_0, \beta_1, \ldots \beta_p)$, and N subjects, the LASSO regularization method solves the following problem:

$$\max_{(\beta_0,\beta)\in\mathbb{R}^{p+1}} \left[\sum_{i=1}^{N} y_i(\beta_0 + \mathbf{x}_i^T\beta) - \log\left(1 + e^{\beta_0 + \mathbf{x}_i^T\beta}\right) - \lambda\sum_{j=1}^{p}|\beta_j|\right]$$

where $\sum_{j=1}^{p}|\beta_j|$ is an L_1 penalty term and λ is a tuning parameter that controls the importance of the regularization term. For a sufficient large value of λ, the use of the L_1 penalty term causes that some of the regression coefficients shrink to zero.

More details about the algorithms presented on Supplementary Table S3 can be found in Friedman and colleagues.[1]

Supplementary Reference

1. Friedman, J., Hastie, T., and Tibshirani, R. (2001). *The Elements of Statistical Learning*. Springer: New York, NY.

SUPPLEMENTARY TABLE S3. SUPERVISED LEARNING ALGORITHMS APPLIED TO THE TBI DATA

Algorithm	*Description*
Decision trees (DT)	Recursively partitions the data space by doing binary splits on variables
Random forests (RF)	Combines a number of decision trees on bootstrapped training samples based on a random sample of predictors.
Support vector machines (SVM)	Finds an optimal hyperplane between two classes using nonlinear boundaries. The feature space is mapped to a higher dimension using a kernel function, the hyperplane is fit in that higher dimension, then mapped back to the original feature space.
Linear discriminant analysis (LDA)/ Quadratic discriminant analysis (QDA)	Uses a linear/quadratic decision functions to classify an observation into a class. It is based on the multivariate normal distribution and Bayes theorem.
Least absolute shrink and selector operator (LASSO)	Linear regularization method that penalizes the absolute magnitude of the coefficients in a model, effectively doing variable selection.
Logistic regression (LR)	Based on the logistic function, a set of predictors are combined linearly using weights or coefficient values to predict a binary response.

Comparison of Baseline Characteristics

SUPPLEMENTARY TABLE S4. BASELINE CHARACTERISTICS OF PATIENTS IN THE TRAINING AND TEST SETS

Patient characteristics	*Test* n = *158*	*Training* n = *472*	p *value*[a]
Motor GCS, *n* (%)			
none/extension	48 (31.58)	163 (34.98)	0.369
abnormal flexion	13 (8.55)	34 (7.3)	
normal flexion/withdrawal	17 (11.18)	72 (15.45)	
localizes/obeys	74 (48.68)	197 (42.27)	
Injury severity score, median (IQR)			
n = 630	29 (10)	25 (9)	< 0.001
Pupil reactivity, *n* (%)			
neither reactive	49 (31.01)	136 (28.94)	0.843
one reactive	18 (11.39)	51 (10.85)	
both reactive	91 (57.59)	283 (60.21)	
Hypotension, *n* (%)			
Yes	23 (14.56)	56 (11.86)	0.456
No	135 (85.44)	416 (88.14)	
Age, median (IQR)			
n = 629	29.5 (23)	30 (21)	0.825
Initial ICP, median (IQR)			
n = 630	14 (13.75)	13 (13.07)	0.261
Subarachnoid hemorrhage, No. (%)			
Yes	109 (68.99)	290 (61.44)	0.179[b]
No	49 (31.01)	173 (36.65)	
unknown	0 (0)	9 (1.91)	
Epidural hematoma, No. (%)			
Yes	22 (13.92)	63 (13.35)	>0.99[b]
No	136 (86.08)	400 (84.75)	
unknown	0 (0)	9 (1.91)	
Marshall CT classification, No. (%)			
I	0 (0)	8 (1.69)	< 0.001
II	69 (43.67)	124 (26.27)	
III/IV	32 (20.25)	104 (22.03)	
V/VI	57 (36.08)	236 (50)	

[a]Two-sided chi-square or Fisher's exact test *p* value for categorical variables, and Wilcoxon rank sum test *p* value for continuous variables.
[b]The *p* values were computed excluding the 'unknown' category.
GCS, Glasgow Coma Scale; IQR, interquartile range; ICP, intracranial pressure; CT, computed tomography.

Supplementary Table S5. Baseline Characteristics of Patients with Missing GOS and Physiological Data Recorded versus Patients with Recorded GOS and Physiological Data

Patient characteristics	*Recorded GOS and physiological data* n = *630*	*Missing GOS and recorded physiological data*[a] n = *193*	p *value*[b]
Motor GCS, *n* (%)			
none/extension	211 (34.14)	53 (27.75)	0.151
abnormal flexion	47 (7.61)	10 (5.24)	
normal flexion/withdrawal	89 (14.4)	28 (14.66)	
localizes/obeys	271 (43.85)	100 (52.36)	
Injury severity score, median (IQR)			
n = 823	25 (9)	25 (9)	0.249
Pupil reactivity, *n* (%)			
neither reactive	185 (29.37)	41 (21.24)	0.181[c]
one reactive	69 (10.95)	19 (9.84)	
both reactive	374 (59.37)	120 (62.18)	
unknown	2 (0.32)	13 (6.74)	
Hypotension, *n* (%)			
Yes	79 (12.54)	24 (12.5)	>0.99
No	551 (87.46)	168 (87.5)	
Age, median (IQR)			
n = 822	30 (21)	31 (18)	0.992
Initial ICP, median (IQR)			
n = 797	14 (13)	11 (10)	0.001
Subarachnoid hemorrhage, *n* (%)			
Yes	399 (63.33)	124 (64.25)	0.799[c]
No	222 (35.24)	65 (33.68)	
unknown	9 (1.43)	4 (2.07)	
Epidural hematoma, *n* (%)			
Yes	85 (13.49)	37 (19.17)	0.062[c]
No	536 (85.08)	152 (78.76)	
unknown	9 (1.43)	4 (2.07)	
Marshall CT classification, *n* (%)			
I	8 (1.27)	4 (2.07)	0.094
II	193 (30.63)	76 (39.38)	
III/IV	136 (21.59)	36 (18.65)	
V/VI	293 (46.51)	77 (39.9)	
Best motor GCS in 24 h post-injury, *n* (%)			
none/extension	100 (15.95)	10 (5.21)	<0.001
abnormal flexion	19 (3.03)	2 (1.04)	
normal flexion/withdrawal	96 (15.31)	25 (13.02)	
localizes/obeys	412 (65.71)	155 (80.73)	

[a]Twice per minute or hourly physiological data recorded.
[b]Two-sided chi-squared or Fisher's exact test *p* value for categorical variables, and Wilcoxon rank sum test p-value for continuous variables.
[c]The *p* values were computed excluding the "unknown" category.

Supplementary Table S6. Summary of Models Developed on Patients with TBI to Predict 6-Month Glasgow Outcome Scale

Studies (reference)	*Clinical severity of TBI*	*Time window of model development*	*Type of predictors considered*	*Model development (N*)*	*External validation (N*)*	*Model performance***	
						Development	*Validation*
Steyerberg and colleagues (2008)	Moderate and severe TBI (GCS ≤12) patients	Hospital admission	Baseline characteristics	8509	6681	AUC = 0.66–0.84	AUC = 0.78–0.796
MCT Collaborators and colleagues (2008)	GCS ≤14	Hospital admission	Baseline characteristics	10,008	8,509	C = 0.81–0.84	C = 0.77
Guiza and colleagues (2013)	Severe TBI patients	First 24 h post-injury	Baseline characteristics+physiological data	160	—	AUC = 0.87	—
Current study	Motor GCS <6	First 24 h post-injury	Baseline characteristics+ injury severity data+ physiological data	472	158	AUC = 0.90	AUC = 0.85–0.86

*Maximum sample size considered.
**Model performance or range of model performance for studies with several models or populations.
TBI, traumatic brain injury; AUC, area under the receiving operating characteristic curve; C, C-index.