Development of a Complication- and Treatment-Aware Prediction Model for Favorable Functional Outcome in Aneurysmal Subarachnoid Hemorrhage Based on Machine Learning

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BACKGROUND: Current prognostic tools in aneurysmal subarachnoid hemorrhage (aSAH) are constrained by being primarily based on patient and disease characteristics on admission.

OBJECTIVE: To develop and validate a complication- and treatment-aware outcome prediction tool in aSAH.

METHODS: This cohort study included data from an ongoing prospective nationwide multicenter registry on all aSAH patients in Switzerland (Swiss SOS [Swiss Study on aSAH]; 2009-2015). We trained supervised machine learning algorithms to predict a binary outcome at discharge (modified Rankin scale [mRS] $\leq$ 3: favorable; mRS 4-6: unfavorable). Clinical and radiological variables on admission ("Early" Model) as well as additional variables regarding secondary complications and disease management ("Late" Model) were used. Performance of both models was assessed by classification performance metrics on an out-of-sample test dataset.

RESULTS: Favorable functional outcome at discharge was observed in 1156 (62.0%) of 1866 patients. Both models scored a high accuracy of 75% to 76% on the test set. The "Late" outcome model outperformed the "Early" model with an area under the receiver operator characteristics curve (AUC) of 0.85 vs 0.79, corresponding to a specificity of 0.81 vs 0.70 and a sensitivity of 0.71 vs 0.79, respectively.

CONCLUSION: Both machine learning models show good discrimination and calibration confirmed on application to an internal test dataset of patients with a wide range of disease severity treated in different institutions within a nationwide registry. Our study indicates that the inclusion of variables reflecting the clinical course of the patient may lead to outcome predictions with superior predictive power compared to a model based on admission data only.

KEY WORDS: Aneurysmal subarachnoid hemorrhage, Machine learning, Complication- and treatment-aware, Outcome prediction

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Aneurysmal subarachnoid hemorrhage (aSAH) is associated with a high mortality and morbidity but a substantial variation in the clinical course.[1,2] Around 50% of aSAH patients do not survive or do not regain functional independence, while the other half recovers without severe disability.[3,4] The broad range in patient outcome is explained by the severity of the initial ictus as well as devastating secondary complications such as

ABBREVIATIONS: aSAH, aneurysmal subarachnoid hemorrhage; **CT,** computed tomography; **DCI,** delayed cerebral ischemia; **EVD,** external ventricular drain; **ICH,** intracerebral hematoma; **mRS,** modified Rankin scale; **ROC,** receiver operating characteristic; **VP,** ventriculoperitoneal; **WFNS,** World Federation of Neurosurgical Societies

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aneurysmal re-bleeding, delayed cerebral ischemia (DCI) or hydrocephalus.[2,5,6]

Several tools for prognostic evaluation in aSAH are available that focus on prognostication at admission to guide decision making at that critical juncture.[7-12] However those models are designed to be uniformly based on patient and disease characteristics at time of first encounter therefore cannot consider the aforementioned frequent complications and following countermeasures. While those sequelae are believed to largely affect outcome, their dynamic nature makes them difficult to integrate in prognostic models. Thus, their additional prognostic benefit to outcome prediction in aSAH is yet unknown.[8,12] Machine learning algorithms promise to improve event and outcome prediction due to their ability to implement complex pattern recognition and detection of nonlinear contributions in large data sets. [13-15]

Our study objective was to use machine learning to develop and validate a complication- and treatment-aware aSAH outcome prediction tool within the framework of a national European multicenter registry (Swiss SOS [Swiss Study on Aneurysmal Subarachnoid Hemmorhage]). We hypothesize that the inclusion of additional variables on secondary complications and disease management, reflecting the clinical course of the patient, will lead to an outcome model with superior predictive power compared to a model based on admission data only.

METHODS

Study Design and Patient Population

This is a retrospective analysis of the prospectively collected Swiss SOS dataset. All registered aSAH patients between January 2009 and December 2015 were included. The Swiss SOS (http://www.swiss-sos.ch) is a nationwide, prospective registry on aSAH patients admitted to an acute neurovascular center in Switzerland.[1]

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Study Variables and Definitions

A set of prespecified uniformly defined variables were collected by the local study teams in real time and parallel to patient care. Anonymized data were prospectively entered into a Secutrial database as described previously (**Supplemental Methods**).[2]

Statistical Analysis and Prediction Modeling

We used a binary outcome to train supervised machine learning algorithms: favorable outcome was defined as modified Rankin scale [mRS] $\leq$ 3, while unfavorable outcome was defined as mRS 4 to 6 at discharge.[16] Two models were built using "IBM SPSS Modeler 18.1.1." (IBM Corp., Armonk, New York) and "R 3.3.3" (R Core Team, 2018, RStudio: Integrated Development for R. RStudio, Inc., Boston, Massachusetts, http://www.rstudio.com/.) to test the hypophysis that an algorithm which considers disease management and complications for outcome prediction would yield superior predictive power: The first "Early" model included all clinical and radiological variables on admission. The second "Late" model included clinical and radiological variables on admission as well as all variables regarding treatment and complications.

To develop and validate the predictive outcome models the Swiss SOS dataset was divided into a training set (75%) and a test set (25%) with random case selection. Performance and predictive accuracy of the "Early" and "Late" model were then assessed using receiver operating characteristics (ROCs) analysis in the training and test dataset. The area under the curve (AUC) and a confusion matrix are provided for each model. Risk flowcharts depicting the decision tree paths for each dependent variable with regard to the presence or absence of the independent variable were created. No correction for missing data (**Supplemental Table**) was performed.

More extensive explanation of methods used to build the machine learning prediction models can be found in the **Supplemental Methods**.

RESULTS

The registry comprised data on 1866 admitted aSAH patients. There were 644 (34.5%) male and 1222 (65.5%) female patients with a mean age of 55.8 $\pm$ 13.4 yr. Detailed patient and radiological baseline characteristics which were used to create the "Early" statistical outcome model are listed in Table 1. Detailed variables on complication and disease management which are listed in Table 2 were added to the baseline characteristics to construct the "Late" outcome model.

Favorable functional outcome at discharge was observed in 1156 (62.0%) of patients. In both the "Early" and "Late" outcome model Chi-square Automatic Interaction Detectors (CHAID) machine learning algorithms performed best in the training set and were used for further analysis. Figure A and B depicts the ROC curves and Table 3A and 3B presents the confusion matrix of the performance of the "Early" and "Late" model on the training and test dataset. The "Late" model outperformed the "Early" model as detailed below.

"Early" Outcome Model

The "Early" model scored an AUC of 0.87 on the training data with a sensitivity and specificity of 0.82 and 0.76. The precision of

TABLE 1. Patient and Radiological Baseline Characteristics of the n = 1866 aSAH Patients From the Swiss SOS Database

Variable	Value
Patient baseline characteristics, count (%)	
Sex	
Female	1222 (65.5)
Male	644 (34.5)
Age in years	55.8 ± 13.4
Weight in kg	70.3 ± 15.5
Height in cm	168.0 ± 9.9
BMI	24.8 ± 4.4
Clinical status on admission, count (%)	
WFNS grade	
1	664 (35.5)
2	348 (18.6)
3	138 (7.4)
4	185 (9.9)
5	516 (27.6)
Unspecified	15 (0.8)
Epileptic seizure	189 (10.1)
Neurological deficits	461 (24.7)
Cranial nerve deficit	348 (18.6)
Sedated on admission	397 (21.3%)
Intubated on admission	417 (22.3)
Ictus to admission in days	1.1 ± 3.3
GCS on admission, median (IQR)	14 (10)
Radiological baseline characteristics, count (%)	
Aneurysm location	
ACA incl Acom	700 (37.5)
ICA incl Pcom	429 (23.0)
MCA	413 (22.1)
Posterior circulation	264 (14.1)
Other/unspecified	60 (3.2)
Fisher grade	
1	54 (2.9)
2	169 (9.1)
3	1037 (55.6)
4	602 (32.3)
Unspecified	4 (0.2)
Aneurysm side	
Left	557 (29.8)
Right	625 (33.5)
Middle	590 (31.6)
Unspecified	94 (5.0)
Aneurysm location according to ISAT	
Anterior	1.542 (82.6)
Posterior	264 (14.1)
Unspecified	60 (3.2)
Thick Clot	1639 (87.8)
IVH	582 (31.2)
SDH	150 (8.0)
ICH	288 (15.4)
ICH diameter in mm	11.04 ± 20.39
MLS	210 (11.2)
MLS in mm	0.68 ± 2.3
Total number of aneurysms, median (IQR)	1.00 (1.00)
Ruptured aneurysm diameter in mm	7.25 ± 4.6

Data are presented as count (%) or average ± standard deviation unless stated otherwise. Table do not include missing data. ACA, anterior cerebral artery; Acom, anterior communicating artery; BMI, body mass index; GCS, Glasgow Coma Scale; IA, intracranial aneurysm; ICA, internal carotid artery; ICH, intracerebral hematoma; IQR, interquartile range; ISAT, International subarachnoid aneurysm trial; IVH, intraventricular hemorrhage; MCA, middle cerebral artery; MLS, midline shift; mRS, modified Rankin Scale; Pcom, posterior communicating artery; Posterior, posterior circulation; SD, standard deviation ; SDH, subdural hematoma; WFNS, World Federation of Neurosurgical Societies.

TABLE 2. Complication and Disease Management of the n = 1866 aSAH Patients From the Swiss SOS Database

Variable	Value
Management, count (%)	
Craniectomy	247 (13.2)
Removal of ICH	127 (6.8)
EVD placement	954 (51.1)
Lumbar drain placement	234 (12.5)
VP-Shunt placement	371 (19.9)
Chemical or mechanical dilatation of vasospasm	346 (18.5)
Aneurysm occlusion	
Surgery	652 (35.0)
Endovascular	921 (49.3)
Combined	48 (2.6)
None	244 (13.1)
Unspecified	1 (0.1)
Complications, count (%)	
Aneurysm re-bleeding	68 (3.6)
Cerebral infarction attributable to DCI	192 (10.3)
New cerebral infarct on postoperative CT	285 (15.3)
New cerebral infarct on last CT	24.8 (4.4)

Data are presented as count (%) or average ± standard deviation unless stated otherwise. Table do not include missing data. CT, computed tomography; DCI, delayed cerebral ischemia; EVD, external ventricular drain; ICH, intracerebral hematoma; VP-Shunt, ventriculoperitoneal Shunt.

the model was 0.84 with an error rate of 20% indicating that the model correctly predicted 80% of cases. On the test set the model scored an AUC of 0.79 with a sensitivity of 0.79 and a specificity of 0.70. Of 320 cases with a favorable outcome the "Early" model correctly predicted 253. With a precision rate of 0.83 the model predicted 51 cases incorrectly as favorable. Overall 76% of cases were correctly predicted corresponding to an error rate of 24%.

The variables with the strongest predictive power (Table 4) were intracerebral hematoma (ICH) diameter, World Federation of Neurosurgical Societies (WFNS) followed by age and presence of ICH.

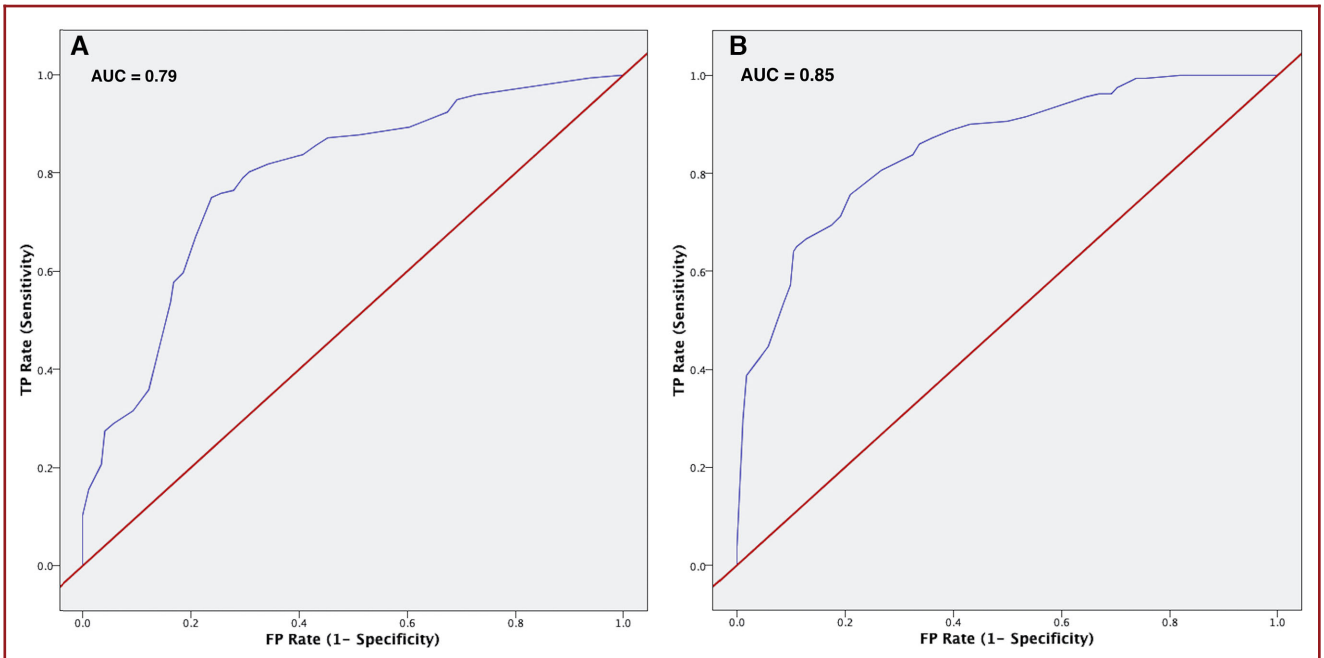

FIGURE 1. **A**, *ROC for the "Early" Model predicting favorable outcome on the test data. The "Early" Model scored an AUC of* ***0.79***. **B**, *ROC for the "Late" Model predicting favorable outcome on the test data. The "Late" Model scored an AUC of* ***0.85***.

TABLE 3A. Confusion Matrix for the "Early" Outcome Model

Training data				Statistical analysis	
Predicted True	0	1	Total	Accuracy	0.80
0	408	130	538	Precision	0.84
1	148	688	836	Sensitvity	0.82
Total	556	818	1374	Specificity	0.76
				AUC	0.87
Test data				**Statistical analysis**	
Predicted True	0	1	Total	Accuracy	0.76
0	121	51	172	Precision	0.83
1	67	253	320	Sensitivity	0.79
Total	188	304	492	Specificity	0.70
				AUC	0.79

TABLE 3B. Confusion Matrix for the "Late" Outcome Model

Training data				Statistical analysis	
Predicted True	0	1	Total	Accuracy	0.79
0	461	77	538	Precision	0.89
1	214	622	836	Sensitivity	0.74
Total	675	699	1374	Specificity	0.86
				AUC	0.90
Test data				**Statistical analysis**	
Predicted True	0	1	Total	Accuracy	0.75
0	139	33	172	Precision	0.87
1	92	228	320	Sensitivity	0.71
Total	231	261	492	Specificity	0.81
				AUC	0.85

A detailed flowchart for the "Early" decision tree model is provided as **Supplemental Figure 1**.

"Late" Outcome Model

The "Late" model scored an AUC of 0.90 on the training data with a sensitivity and specificity of 0.74 and 0.86. The precision of the model was 0.89 and the model correctly predicted 79% of cases corresponding to an error rate of 21%. On the test set, the model scored an AUC of 0.85 with a sensitivity of 0.71 and a specificity of 0.81. Of 320 cases with a favorable outcome the "Late" model correctly predicted 228. With a precision rate of 0.87 the model predicted 33 incorrectly as favorable. Overall 75% of cases were correctly predicted corresponding to an error rate of 25%.

The variable with the strongest predictive power (Table 4) was cerebral infarction on last computed tomography (CT) scan while a series of different variables shared the second rank with equal importance.

A detailed flowchart for the "Late" decision tree model is provided as **Supplemental Figure 2**.

DISCUSSION

We present the development and validation of a high-performing complication and treatment-aware outcome

TABLE 4. Variable Importance Sorted by Their Predictive Power in Descending Order for the "Early" and "Late" Outcome Model

Early model		Late model	
Variable	**Importance**	**Variable**	**Importance**
ICH diameter	0.1606	Cerebral infarct on last CT	0.0527
WFNS	0.1229	BMI	0.0511
Age	0.0734	Epileptic seizure	0.0511
ICH	0.0659	Aneurysm location according to ISAT	0.0511
Aneurysm diameter	0.0622	Fisher	0.0511
Weight	0.0622	Removal of ICH	0.0511
Intubated on admission	0.0622	Type of aneurysm occlusion	0.0511
Fisher	0.0622	Intubated on admission	0.0511
Epilepsy on admission	0.0622	IVH	0.0511
Total numbers Of aneurysms	0.0622	ICH	0.0511

Please note that multiple variables in the "Early" and "Late" Model present with equal importance which results that they share the same rank. BMI, body mass index; ICH, intracerebral hematoma; ISAT, International subarachnoid aneurysm trial; IVH, intraventricular hemorrhage; WFNS, World Federation of Neurosurgical Societies.

prediction models based on machine learning algorithms in aSAH. The models show very good precision and accuracy, confirmed on application to an internal test dataset of patients with a wide range of disease severity treated in different institutions within a national registry. To our knowledge, this study is the first to systematically indicate that the inclusion of variables on secondary complications and disease management in aSAH may lead to an outcome model with superior predictive power compared to a model on admission.

Clinical experience has shown that the occurrence of common secondary complications as well as countermeasures and treatment choices can have a significant impact on patient's prognosis.[2,7,10] Several outcome prediction models for aSAH have been described in the literature but their clinical use is rather scarce. We think this can in parts be explained by the static nature of the published models and scores. Few models consider complication and treatment specific variables in their prediction and almost none incorporate information later than 72 h after ictus.[8]

Pegoli et al[17] showed that excellent long-term functional outcome (follow-up within 1 yr of aSAH) can be reliably predicted with logistic regression analysis using variables collected during the clinical course of the patient in a single center cohort of 373 patients. The recently published SAHIT cohort study combined individual data of 10.936 patients from a collaboration of different data repositories to develop a series of outcome predication models.[8] The "core" model, included patient age, premorbid hypertension and WFNS grade on admission to reach an AUC of 0.80 to detect functional outcome in a separate test dataset of 3355 patients. A "full" model extended the analysis by including neuroimaging variables and treatment modality as only variable that occurred during the patients clinical course, achieving an AUC of 0.81, still well below the predictive performance of our model. [8]

Another limitation of existing outcome prediction lies within the inherent restriction of conventional statistical methods. Published outcome models based on linear correlations can only cope with a small amount of potentially nonlinear and codependent variables.[8] In addition, multivariate logistic regression is particularly susceptible to missing data.[15] In contrast, machine learning algorithms are increasingly being used to predict various clinical or diagnostic outcome measures in medicine as well as in neurosurgery in particular.[13,15,18,19] We choose machine learning over conventional statistics because of its superior capability in dealing with complex patterns in large datasets with a high amount of input variables. Moreover, machine learning is not, as conventional statistics, limited by missing data.[15]

Our 2 outcome models presented several interesting features: Based on AUC curve analysis, high model performance could be achieved in both the "Early" and "Late" model (Figures A and B). While both outcome models scored a high accuracy of around 75% in the test dataset the "Late" model outperformed the "Early" model with a small margin with an AUC of 0.85 compared to 0.79. Interestingly, the chosen "Late" model somewhat underestimated the total amount of patients with "favorable" outcome but showed a considerably lower rate of "false positives". From a clinical perspective and in the context of patient safety and counseling one might argue that it is more desirable to inaccurately predict patients who will have a favorable outcome than to inaccurately predict patients who will not have a favorable outcome. In this it is distinctively different to the prediction of negative events like complications.[15]

AUC values of <1.0 in both models indicate that outcome is dependent on several other factors that were not included in this study. We have to acknowledge that important sources of data, namely physiological ICU data, eg, ICP and blood pressure monitoring, as well as laboratory results, could not be collected within the registry and are therefore missing from the analysis.[20] While the inclusion of this data would certainly be quite challenging from a statistical standpoint, it could arguably

improve the prediction of our outcome model. Valid criticism can be made in regard to the inclusion or exclusion of treatment decision variables. We chose the former to account for disease characteristics along the clinical course of the patient that would otherwise have been ignored (eg, hydrocephalus in case of external ventricular drain (EVD) or ventriculoperitoneal [VP]-Shunt placement). While constructing the outcome models we experienced a certain limit of perfection in prognostic power which might also be explained by the fact that history cannot always accurately predict the future when the system involves people, especially in a complex disease like aSAH.[14] Considering the aforementioned circumstances and that certain data sources could not be included, the models performed very well.

The ideal prediction model would take all events that occurred until a specific time point into account and provide a real-time outcome prediction that could guide a physician's treatment decision. However, since this is a retrospective analysis of an observational study, all patient data was deemed complete at time of model calculation and any associations identified in our analysis cannot be proven to be causal. The Swiss SOS registry does not provide the time of every single complication and/or countermeasure therefore we cannot provide the exact interval in which a patients final "Late" Model can be created. However, we see our complication- and treatment-aware model as a tool to quantify the risk of subsequent sequelae after the initial ictus in aSAH. This analysis should support experienced clinical judgment and provide patients and their next of kin with reliable information on the importance of secondary events on outcome prognosis. The models may also aid in identifying modifiable risk factors as well as patients who might need more or less aggressive monitoring. Investigators can enter new patient data into the models to predict outcome and the 2-stage assessment allows for a quantification of change between initial ictus and a later stage of the disease. At present the model may simulate alternative patient journeys; however, it is not designed to support physicians in the clinical decision making for or against any specific treatment choice, which would require a significantly greater amount of time sensitive patient data in a complex disease like aSAH. However, our study ought to be the first step towards a truly dynamic and learning algorithm that should be able to predict complications and outcome in aSAH. Going forward, adding more prospective patient data and testing our outcome prediction at predefined intervals we envision this method to evolve to be able to estimate the probability of a favorable recovery for an individual patient at any given time point during the hospital stay based on the available data.

Strengths and Weaknesses

A strength of the presented study and the Swiss SOS registry in general is that all neurovascular centers in Switzerland contributed to a prospective, unselected database of aSAH patients. While our analysis lacks an external validation cohort, the multicenter and multicultural framework of the study and the fact that the observed association parallel our clinical observations increase the likelihood that our results can be generalized to other settings and populations. However, our approach has limitations that need to be addressed. First, our study could not capture all treatments and possible complications that occurred during the hospital stay. In a future prospective arm of the study we would like to increase the number of predefined time points of model development. Since patient was enrolled within a 7-yr time frame we cannot exclude the possibility of specific changes in treatment philosophy or technology that might have influenced outcome. Moreover, our study did not aim to determine the exact cause of a certain favorable/unfavorable outcome. Our model cannot replace clinical judgment and outcome prediction that is based on longtime human experience may still outperform the best algorithm. As in other aSAH outcome tools, development is based on group comparison with the intention to cluster outcome assessment. The application for outcome prediction in the individual patient should therefore be treated with caution. Finally, our analysis only considered clinical outcome at discharge and does therefore not consider any potential long-term progress of patients, in particular during their rehabilitation.

CONCLUSION

Both machine learning outcome models show good discrimination and calibration confirmed on application to an out-of-sample test dataset of patients with a wide range of disease severity treated in different institutions within a nationwide registry. Our study indicates that the inclusion of variables reflecting the clinical course of the patient may lead to outcome prediction with superior predictive power compared to a model on admission.

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Disclosures

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Supplemental Methods. The Supplemental Digital Content expands on the Methods provided.

Supplemental Table. Missing Values for Patient and Radiological Baseline Characteristics as well as Complication and Disease Management Variables of the n = 1866 aSAH Patients from the Swiss SOS Database Data are presented as number of patients with missing value (%).

Supplemental Figure 1. Decision tree flowchart for the "Early" Outcome Model with dichotomized outcome. Each split was evaluated using Pearson Chi-Square test with *p* value threshold of .05 after Bonferroni correction. Bar charts presents the percentage of cases on the y-axis with limits of 0% to 100%. BMI, body mass index; CT, computed tomography; DCI, delayed cerebral ischemia; EVD, external ventricular drain; ICH, intracerebral hematoma; ISAT, International subarachnoid aneurysm trial; IVH, intraventricular hemorrhage; mRS, modified Rankin Scale; VP-Shunt, ventriculoperitoneal Shunt; WFNS, World Federation of Neurosurgical Societies.

Supplemental Figure 2. Decision tree flowchart for the "Late" Outcome Model with dichotomized outcome. Each split was evaluated using Pearson Chi-Square test with *p* value threshold of .05 after Bonferroni correction. Bar charts presents the percentage of cases on the y-axis with limits of 0% to 100%. BMI, body mass index; CT, computed tomography; DCI, delayed cerebral ischemia; EVD, external ventricular drain; ICH, intracerebral hematoma; ISAT, international subarachnoid aneurysm trial; IVH, intraventricular hemorrhage; mRS, modified Rankin Scale; VP-Shunt, ventriculoperitoneal Shunt; WFNS, World Federation of Neurosurgical Societies.

COMMENT

These authors demonstrate the performance of a machine learning algorithm to predict outcome from subarachnoid hemorrhage in 1156 patients. The algorithm incorporates complications and treatment effects that occur throughout the hospital course but it does not account for improvement of modifiable complications such as vasospasm or acute hydrocephalus. Their results illustrate that while it is possible to teach a computer to adapt to new information, outcome prediction is very difficult and currently limited to a binary result. Patients are categorized simply as either favorable or unfavorable outcome. The data was collected prospectively in a registry but the study was based on retrospective analysis of data elements that were not initially configured for the purposes of the current study.

It is challenging to imbue a machine with the experience and judgement of a seasoned clinician. It would be an interesting experiment to test the machine algorithm prospectively against the prediction of a variety of clinicians including those with little experience managing

subarachnoid hemorrhage. My sense is that prognosticating between favorable and unfavorable outcome may not be that difficult for a human. In my own experience, I am rarely surprised by an unexpected outcome that is either good or bad.

The authors should be commended for their efforts to improve risk prediction for subarachnoid hemorrhage based on disease specific variable. Hopefully, they will continue this important work and improve the utility of their algorithm.

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