Rescue therapy for vasospasm following aneurysmal subarachnoid hemorrhage

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Rescue therapy for vasospasm following aneurysmal subarachnoid hemorrhage: a propensity score–matched analysis with machine learning

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OBJECTIVE Rescue therapies have been recommended for patients with angiographic vasospasm (aVSP) and delayed cerebral ischemia (DCI) following subarachnoid hemorrhage (SAH). However, there is little evidence from randomized clinical trials that these therapies are safe and effective. The primary aim of this study was to apply game theory–based methods in explainable machine learning (ML) and propensity score matching to determine if rescue therapy was associated with better 3-month outcomes following post-SAH aVSP and DCI. The authors also sought to use these explainable ML methods to identify patient populations that were more likely to receive rescue therapy and factors associated with better outcomes after rescue therapy.

ABBREVIATIONS ALISAH = Albumin in Subarachnoid Hemorrhage; aVSP = angiographic vasospasm; BP = blood pressure; CONSCIOUS-1 = Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After Subarachnoid Hemorrhage; DCI = delayed cerebral ischemia; DSAT = Database of Subarachnoid Treatment; GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; HHU = Heinrich Heine University; ICA = internal carotid artery; ML = machine learning; NEWTON-1 = Nimodipine Microparticles to Enhance Recovery While Reducing Toxicity After Subarachnoid Hemorrhage; RCT = randomized controlled trial; ROC = receiver operating characteristic; SAH = subarachnoid hemorrhage; SAHIT = Subarachnoid Hemorrhage International Trialists; SHAP = Shapley Additive Explanation; TCD = transcranial Doppler; WFNS = World Federation of Neurosurgical Societies.

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METHODS Data for patients with aVSP or DCI after SAH were obtained from 8 clinical trials and 1 observational study in the Subarachnoid Hemorrhage International Trialists repository. Gradient boosting ML models were constructed for each patient to predict the probability of receiving rescue therapy and the 3-month Glasgow Outcome Scale (GOS) score. Favorable outcome was defined as a 3-month GOS score of 4 or 5. Shapley Additive Explanation (SHAP) values were calculated for each patient-derived model to quantify feature importance and interaction effects. Variables with high SHAP importance in predicting rescue therapy administration were used in a propensity score–matched analysis of rescue therapy and 3-month GOS scores.

RESULTS The authors identified 1532 patients with aVSP or DCI. Predictive, explainable ML models revealed that aneurysm characteristics and neurological complications, but not admission neurological scores, carried the highest relative importance rankings in predicting whether rescue therapy was administered. Younger age and absence of cerebral ischemia/infarction were invariably linked to better rescue outcomes, whereas the other important predictors of outcome varied by rescue type (interventional or noninterventional). In a propensity score–matched analysis guided by SHAP-based variable selection, rescue therapy was associated with higher odds of 3-month GOS scores of 4–5 (OR 1.63, 95% CI 1.22–2.17).

CONCLUSIONS Rescue therapy may increase the odds of good outcome in patients with aVSP or DCI after SAH. Given the strong association between cerebral ischemia/infarction and poor outcome, trials focusing on preventative or therapeutic interventions in these patients may be most able to demonstrate improvements in clinical outcomes. Insights developed from these models may be helpful for improving patient selection and trial design.

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KEYWORDS subarachnoid hemorrhage; vasospasm; delayed cerebral ischemia; rescue therapy; machine learning; feature importance; propensity score matching; vascular disorders

Delayed cerebral ischemia (DCI) is a common complication of aneurysmal subarachnoid hemorrhage (SAH) and is strongly associated with angiographic vasospasm (aVSP) and vasospasm on transcranial Doppler (TCD). Rescue therapies, including balloon angioplasty, intraarterial infusion of vasodilatory drugs, and induced hypertension, have been recommended for patients experiencing aVSP or DCI.[1,2] Even though these treatments have been used for more than 40 years, there is little evidence they are safe and effective. Most evidence for their use is drawn from retrospective case series of small numbers of patients from single institutions.[3–10] Furthermore, the few randomized controlled trials (RCTs) that have studied rescue therapy have found no effect on clinical outcome.[11–13] Potential causes for the lack of observed benefit may include true-negative findings, insensitivity of outcome measures, and suboptimal patient selection and trial design. Furthermore, the incomplete understanding of the combinations of patient and disease characteristics that may impact outcomes following different forms of rescue therapy leads to inclusion of patients who are not at risk of poor outcome from aVSP and DCI and who therefore cannot benefit from rescue therapy. For example, an RCT studying induced hypertension found that this treatment doubled the risk of serious adverse events and had no effect on clinical outcome.[13] One possible reason is that patients diagnosed with DCI but who did not have cerebral ischemia were included even though theoretically they could not benefit from rescue therapy. Thus, a major challenge in SAH management is understanding which characteristics and treatment decisions are associated with good or poor outcomes in the setting of post-SAH vasospasm.

To quantitatively investigate the impact of diverse patient risk factors on functional outcomes and to provide insight into which patients might benefit from rescue, we analyzed prospectively collected individual patient data from multiple centers in the Subarachnoid Hemorrhage International Trialists (SAHIT) data repository.[14] The primary aim of this study was to apply novel game theory–based methods in explainable machine learning (ML) (Supplemental Methods) and propensity score matching to determine if rescue therapy was associated with better 3-month outcomes following post-SAH vasospasm. We also sought to identify patient populations that were more likely to receive rescue therapy and factors associated with better outcomes after rescue therapy. These explainable ML techniques carry the advantage of enabling the identification of important variables, as well as potentially obscure variable interactions and data patterns, that contribute to patient outcomes but that may not be easily discovered by researchers using traditional statistical approaches.

Methods

Data Source

Data were obtained from 9 studies in the SAHIT repository: Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After Subarachnoid Hemorrhage (CONSCIOUS-1), a phase 2 RCT that assigned patients to either placebo or one of three doses of clazosentan following SAH;[15] Albumin in Subarachnoid Hemorrhage (ALISAH), a multicenter, open-label, dose-escalation trial in which patients received various dosages of human albumin following SAH;[16] Database of Subarachnoid Treatment (DSAT), a single-center retrospective collection of patients with SAH who had poor clinical grades;[17] a Heinrich Heine University (HHU) open-label phase 2 RCT of intraventricular fibrinolysis and low-frequency rotation after severe SAH conducted in Germany;[18] the Nimodipine Microparticles to Enhance Recovery While Reducing Toxicity After Subarachnoid Hemorrhage (NEWTON-1) study, a multicenter, open-label, phase 1/2a RCT to determine the maximum tolerated intraventricular dose of a sustained release form of nimodipine following SAH;[19] and data from 4 prospective phase 3 RCTs investigating tirilazad mesylate in patients with SAH (Tirilazad study).[20–22]

These studies were used because they recorded aVSP and/or DCI using criteria compatible with current recognized definitions of these terms,[23] rescue therapy, and clinical outcome at 3 months. Although both the experimental and control groups for each trial were included in the data set, it is important to note that the RCTs included in this study did not show a treatment effect for their interventions. Furthermore, none of the included RCTs showed a statistically significant serious adverse event related to the treatment given in their respective treatment arms or described any evidence of or concern for selection bias. Patients from these data sets were included in this study if they experienced aVSP (or vasospasm on TCD) or DCI after SAH and if they had a 3-month outcome recorded.

Variables

Baseline admission characteristics were collected, including Glasgow Coma Scale (GCS) score, World Federation of Neurosurgical Societies (WFNS) grade, Fisher grade, and modified Fisher grade.[24,25] Aneurysm data included size (categorized as < 15 mm, 15–24 mm, or ≥ 25 mm) and location—including whether it arose from the anterior cerebral artery, internal carotid artery (ICA), middle cerebral artery, or an artery in the posterior circulation. The method of aneurysm repair and the time after SAH when it was done (time to surgery) were included.

Vasospasm and DCI characteristics and patient complications were documented, including the postoperative day of neurological worsening; whether severe aVSP was evident (defined as > 50% narrowing compared to baseline);[20] if the vasospasm presented symptomatically (DCI), angiographically, on TCD ultrasound, on CT perfusion scan, or with some combination of these; and the presence of cerebral infarct. The CT scan findings of midline shift, hydrocephalus, intraventricular hemorrhage, cerebral edema, and intracerebral hematoma also were included. SAH complication data included CNS infection, urinary tract infection, pneumonia, pulmonary edema, and fever. Patient management characteristics included prophylactic treatments for vasospasm, anticonvulsant administration, and the postoperative day following aneurysm repair on which rescue therapy occurred. Rescue therapy was documented as either interventional (including angioplasty and intraarterial infusions) or noninterventional (including induced hypertension, hypervolemia, or hemodilution [i.e., hemodynamic therapy]). Clinical outcome at 3 months was described with the Glasgow Outcome Scale (GOS) score,[26] with good functional outcome considered at GOS scores of 4–5. The determination of vasospasm from each study was collected from variables representing the investigators' opinions rather than a central review, if it was done in the particular study. This was done to ensure that the diagnosis of vasospasm was driven by the clinical picture of the patient. This distinction was important for one of the goals of this study: understanding the decision of whether or not to provide rescue therapy to a patient, which necessarily relies on the instinct of the investigators. Of note, each study had a well-defined method for detecting vasospasm, including through angiography (CONSCIOUS-1, NEWTON-1, DSAT, HHU, Tirilazad); TCD (ALISAH, CONSCIOUS-1, Tirilazad); CT perfusion scan (HHU); and/or symptomatology (Tirilazad, ALISAH, CONSCIOUS-1, DSAT).

Preprocessing, Supervised ML, and Cross-Validation

Quantitative variables were standardized, scaled to unit variance, and normalized to unit norm by using standard ML practices. Binary representations were created from categorical variables by using a label encoder. Next, for data missing at random in a subset of patients, multivariate feature imputation was used to model these values as functions of other features. Ten imputation sets were selected, estimates and confidence intervals were derived for missing values, and sensitivity analyses were performed to determine if results were satisfactory (Supplemental Table 1).

After data preprocessing, rescue therapy and 3-month GOS were modeled as outcomes for prediction by using various ML classifier algorithms. In conjunction with the results from comparative calibration plots (Supplemental Fig. 1), a gradient boosting algorithm was ultimately implemented due to its ability to learn complex data structures, including high-order interactions and nonlinear relationships, even with high-dimensional data sets, and the algorithm improved handling of data sets with heterogeneous features.[27] A k-fold cross-validation (k = 5) was performed prior to model training, with study population samples randomly split to comprise an internal model validation set (75%) to ensure robust performance, and a model evaluation set (25%) for final model evaluation. On the internal validation set, models were trained using each of the 4 folds as training data, and subsequently validated using the remaining fold of data.

Models were constructed for individual patients in the study population before being aggregated to make population-level inferences. Model predictive capacities were assessed using receiver operating characteristic (ROC) curves and the areas under these curves (i.e., C-statistic). Calibration curves were plotted to ensure that predicted probabilities matched the expected distribution of probabilities for each class. Data preprocessing, supervised ML modeling, and cross-validation were computed using the *scikit-learn 0.23.2* package in Python 3.7.

Feature Importance, Clustering, and Interaction Effects With Shapley Additive Explanation Values

Shapley Additive Explanation (SHAP) values were calculated to interpret predictions from the gradient boosting trees for each patient-level model.[28–30] Hierarchical clustering was performed using the SHAP value feature weightings to compare feature similarities and differences in population subsets across the study population. SHAP interaction values were calculated to quantitatively study interaction effects between features.[31] All SHAP values were computed using the *shap* package in Python 3.7.[29] Additional information regarding the application of SHAP-based methods to explain ML models in this study is provided in the Supplemental Methods.

Propensity Score Matching and Statistical Analysis

Propensity score matching was performed to account for differences in the baseline characteristics between patients who did or did not receive rescue therapy (Supplemental Tables 2 and 3). A logistic regression model was used to estimate a propensity score for individual patients.

TABLE 1. Baseline demographic, comorbidity, neurological grade, aneurysm, SAH, vasospasm, and treatment characteristics on admission for patients in propensity score–matched cohorts

Variable	Rescue Therapy, n = 385	No Rescue Therapy, n = 385	p Value
Demographic & pt characteristics			
Age in yrs (mean ± SEM)	51.0 ± 0.7	52.3 ± 0.7	0.18
Sex (%)			0.26
Female	324 (84)	311 (81)	
Male	61 (16)	74 (19)	
Race (%)			0.24
White	297 (77)	282 (73)	
Other	88 (23)	103 (27)	
Physiological measures & comorbidities			
Systolic BP (mean ± SEM)	139.9 ± 1.4	143.4 ± 1.5	0.05
Diastolic BP (mean ± SEM)	75.3 ± 0.8	76.7 ± 0.7	0.22
Temperature (mean ± SEM)	37.1 ± 0.1	37.2 ± 0.2	0.70
No. of Dxs (mean ± SEM)	3.5 ± 0.2	2.9 ± 0.1	0.001
Smoking (%)			0.01
Yes	254 (66)	216 (56)	
No	131 (34)	169 (44)	
Hypertension (%)			0.50
Yes	139 (36)	129 (34)	
No	246 (64)	256 (67)	
Hyperlipidemia (%)			0.52
Yes	286 (74)	277 (72)	
No	99 (26)	108 (28)	
Vascular disease (%)			0.20
Yes	25 (7)	16 (4)	
No	360 (94)	369 (96)	
COPD (%)			0.45
Yes	240 (62)	251 (65)	
No	145 (38)	134 (35)	
Thyroid disease (%)			0.80
Yes	35 (9)	32 (8)	
No	350 (91)	353 (92)	
Migraines (%)			0.01
Yes	100 (26)	67 (17)	
No	285 (74)	318 (83)	
Diabetes mellitus (%)			0.52
Yes	18 (5)	23 (6)	
No	367 (95)	362 (94)	
Angina (%)			0.70
Yes	15 (4)	12 (3)	
No	370 (96)	373 (97)	
Coronary artery disease (%)			0.36
Yes	26 (7)	19 (5)	
No	359 (93)	366 (95)	
Myocardial infarction (%)			0.32
Yes	16 (4)	10 (3)	
No	369 (96)	375 (97)	

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TABLE 1. Baseline demographic, comorbidity, neurological grade, aneurysm, SAH, vasospasm, and treatment characteristics on admission for patients in propensity score–matched cohorts

Variable	Rescue Therapy, n = 385	No Rescue Therapy, n = 385	p Value
Physiological measures & comorbidities (*continued*)			
Hepatic disease (%)			0.26
Yes	11 (3)	18 (5)	
No	374 (97)	367 (95)	
Previous SAH (%)			0.17
Yes	41 (11)	29 (8)	
No	344 (89)	356 (92)	
Baseline characteristics on admission			
Total GCS score (mean ± SEM)	11.7 ± 0.2	11.1 ± 0.2	0.28
Admission WFNS grade (mean ± SEM)	2.5 ± 0.1	2.7 ± 0.1	0.18
Fisher grade (mean ± SEM)	3.4 ± 0.04	3.4 ± 0.04	0.59
Modified Fisher grade (mean ± SEM)	3.2 ± 0.1	3.2 ± 0.1	0.38
Aneurysm characteristics			
Aneurysm size (%)			0.46
Small (<15 mm)	274 (71)	258 (67)	
Midsize (15–24 mm)	95 (25)	108 (28)	
Large (≥25 mm)	16 (4)	19 (5)	
Aneurysm location (%)			0.26
ACA	127 (33)	157 (41)	
ICA	115 (30)	98 (26)	
MCA	80 (21)	75 (19)	
PCA, VA, or BA	54 (14)	46 (12)	
Other location	9 (2)	9 (2)	
Aneurysm circulation location (%)			0.45
Anterior	331 (86)	339 (88)	
Posterior	54 (14)	46 (12)	
SAH treatment characteristics			
Received surgical clipping or coiling (%)			0.26
Yes	355 (92)	345 (90)	
No	30 (8)	40 (10)	
Time from SAH to surgery (mean ± SEM)	54.0 ± 6.5	63.9 ± 4.9	0.22
Sedation (%)			0.75
Yes	53 (14)	49 (13)	
No	332 (86)	336 (87)	
Vasospasm characteristics & complications			
POD of neuro worsening (mean ± SEM)	4.7 ± 0.3	4.9 ± 0.3	0.57
Severe aVSP (%)			0.28
Yes	89 (23)	103 (27)	
No	296 (77)	282 (73)	
Radiographic vasospasm detection (%)*			0.14
Angiographic	89 (23)	103 (27)	
TCD	337 (88)	286 (74)	
DCI/cerebral infarct (%)			0.72
Yes	180 (47)	186 (48)	
No	205 (53)	199 (52)	

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TABLE 1. Baseline demographic, comorbidity, neurological grade, aneurysm, SAH, vasospasm, and treatment characteristics on admission for patients in propensity score–matched cohorts

Variable	Rescue Therapy, n = 385	No Rescue Therapy, n = 385	p Value
Vasospasm characteristics & complications (*continued*)			
Midline shift (%)			0.09
Yes	237 (62)	213 (55)	
No	148 (38)	172 (45)	
Hydrocephalus (%)			0.35
Yes	210 (54)	196 (51)	
No	175 (46)	189 (49)	
Intraventricular hemorrhage (%)			0.77
Yes	202 (53)	207 (54)	
No	183 (47)	178 (46)	
Cerebral edema (%)			0.01
Yes	96 (25)	128 (33)	
No	289 (75)	257 (67)	
Hematoma (%)			1.00
Yes	102 (27)	103 (27)	
No	283 (73)	282 (73)	
CNS infection (%)			0.001
Yes	62 (16)	102 (27)	
No	323 (84)	283 (73)	
UTI (%)			0.63
Yes	105 (27)	112 (29)	
No	280 (73)	273 (71)	
Pneumonia (%)			0.01
Yes	35 (9)	62 (16)	
No	350 (91)	323 (84)	
Lung edema (%)			0.001
Yes	62 (16)	30 (8)	
No	323 (84)	355 (92)	
Day 8 fever (%)			0.03
Yes	165 (43)	135 (35)	
No	220 (57)	250 (65)	
Pt management characteristics			
Prophylactic treatment received (%)			0.09
Prophylactic hypertension	129 (34)	95 (25)	
Prophylactic hypervolemia	269 (70)	214 (56)	
Prophylactic hemodilution	134 (35)	141 (37)	
Anticonvulsant use (%)			0.42
Yes	282 (73)	271 (70)	
No	103 (27)	114 (30)	
Day of vasospasm management (mean ± SEM)	4.9 ± 0.2	7.2 ± 1.4	0.10

ACA = anterior cerebral artery; BA = basilar artery; COPD = chronic obstructive pulmonary disease; Dx = diagnosis; MCA = middle cerebral artery; neuro = neurological; PCA = posterior cerebral artery; POD = postoperative day; pt = patient; SEM = standard error of the mean; UTI = urinary tract infection; VA = vertebral artery.

* For radiographic vasospasm detection, patients may have been evaluated with multiple imaging modalities.

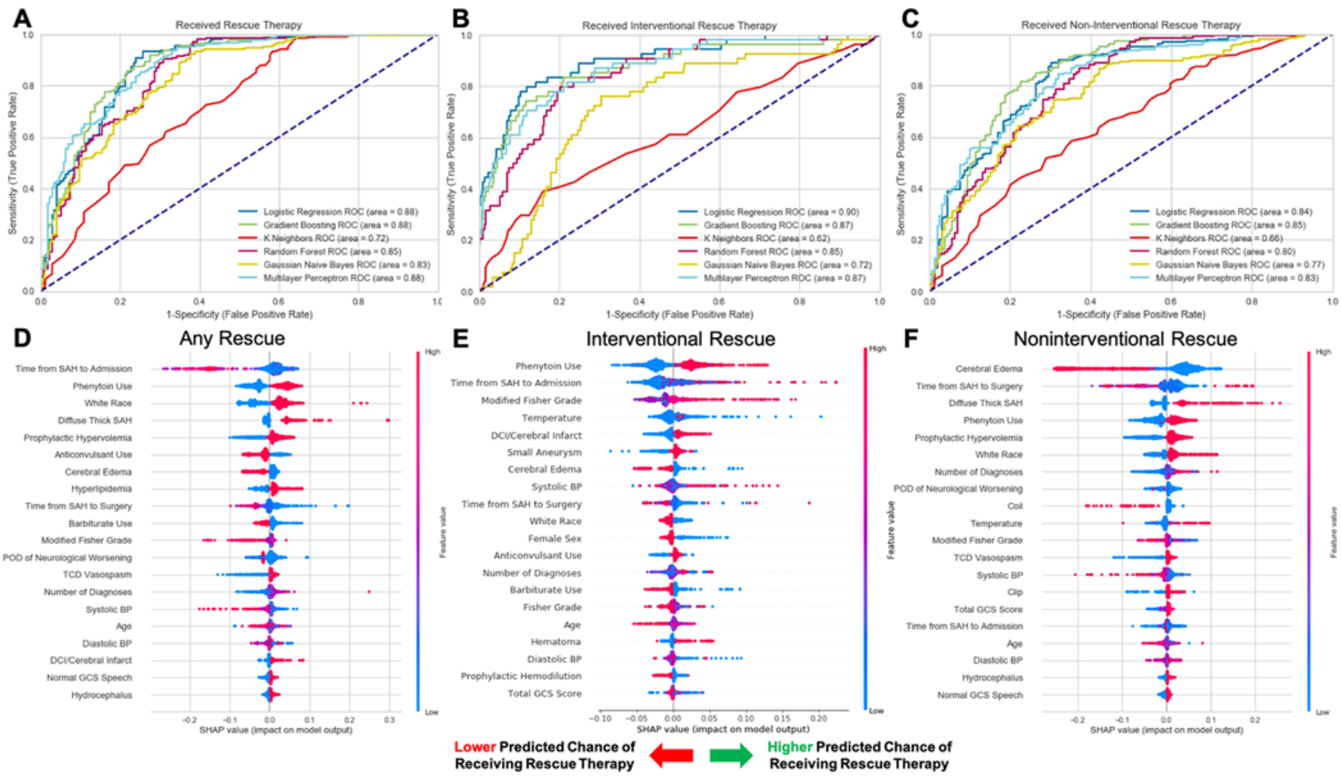

FIG. 1. ROC curves for model ensembles predicting the delivery of any form of rescue therapy (**A**), interventional rescue therapy (**B**), and noninterventional rescue therapy (**C**). Areas under the ROC curves are shown in the lower right side. *Dashed line* denotes random chance with an area under the ROC curve = 0.50. SHAP summary plots showing the most important features for predicting delivery of any form of rescue therapy (**D**), interventional rescue therapy (**E**), and noninterventional rescue therapy (**F**). SHAP values for each feature were computed for each patient-derived model, which is represented by a single dot in which color is based on the feature's value. *Red dots* indicate high feature values for that individual patient, whereas *blue dots* indicate low underlying feature values. For binary categorical features, a "low" feature value indicates its absence and a "high" value indicates its presence. Visualizing patient-specific SHAP values for each feature directly shows how each feature's values (dot color) relate to its impact on predicted model output (left or right shift on x-axis). POD = postoperative day. Figure is available in color online only.

Rescue therapy was regressed on age, sex, race, admission neurological status, admission modified Fisher score, number of medical diagnoses on record, time from SAH to surgery, hypertension, hyperlipidemia, DCI/cerebral infarct, severe aVSP, anticonvulsant use, SAH characteristics, and cerebral edema. Variables were chosen for their known clinical significance or their importance in rescue therapy allocation, demonstrated by increased SHAP importance in models predicting rescue therapy delivery.[32] After confirming sufficient overlap in the propensity score distributions between the patients who did and did not receive rescue therapy, cohorts were matched 1:1 on the logit of the propensity score by using the strict criteria of calipers equal to 0.1 of the SD.

Matched patients with and without rescue therapy were compared in terms of baseline measures and comorbidities, aneurysm and SAH characteristics, vasospasm characteristics, and complications and outcome measures. Categorical variables were compared using the chi-square and Fisher exact tests, whereas continuous variables were compared with the Student t-test or Wilcoxon rank-sum test, depending on distribution normality. Univariate logistic regression associations between rescue therapy and good outcomes were performed. A 2-tailed p value < 0.05 determined statistical significance. All statistical analyses were performed in SAS 9.4 (SAS Institute).

Results

We analyzed 1532 patients who developed aVSP or DCI. Of these patients, 470 (31%) had severe aVSP; 1254 (82%) had vasospasm on TCD ultrasound; 652 (43%) experienced DCI/cerebral infarct; 823 (54%) received rescue therapy; and 890 (58%) had a 3-month GOS score of 4 or 5 (Table 1).

Predicting Delivery of Rescue Therapy

The gradient boosting algorithm consistently yielded the strongest results in using only prerescue data to predict the probability that patients had received any rescue therapy (Fig. 1A), interventional rescue therapy (Fig. 1B), or noninterventional rescue therapy (Fig. 1C) (C-statistic [C] = 0.88, 0.87, and 0.85, respectively). Calibration curves suggested that the gradient boosting models were well calibrated and did not require additional calibration from isotonic or sigmoid regression (Supplemental Fig. 1). After constructing predictive models of the decision to deliver rescue therapy for individual patients, we calculated

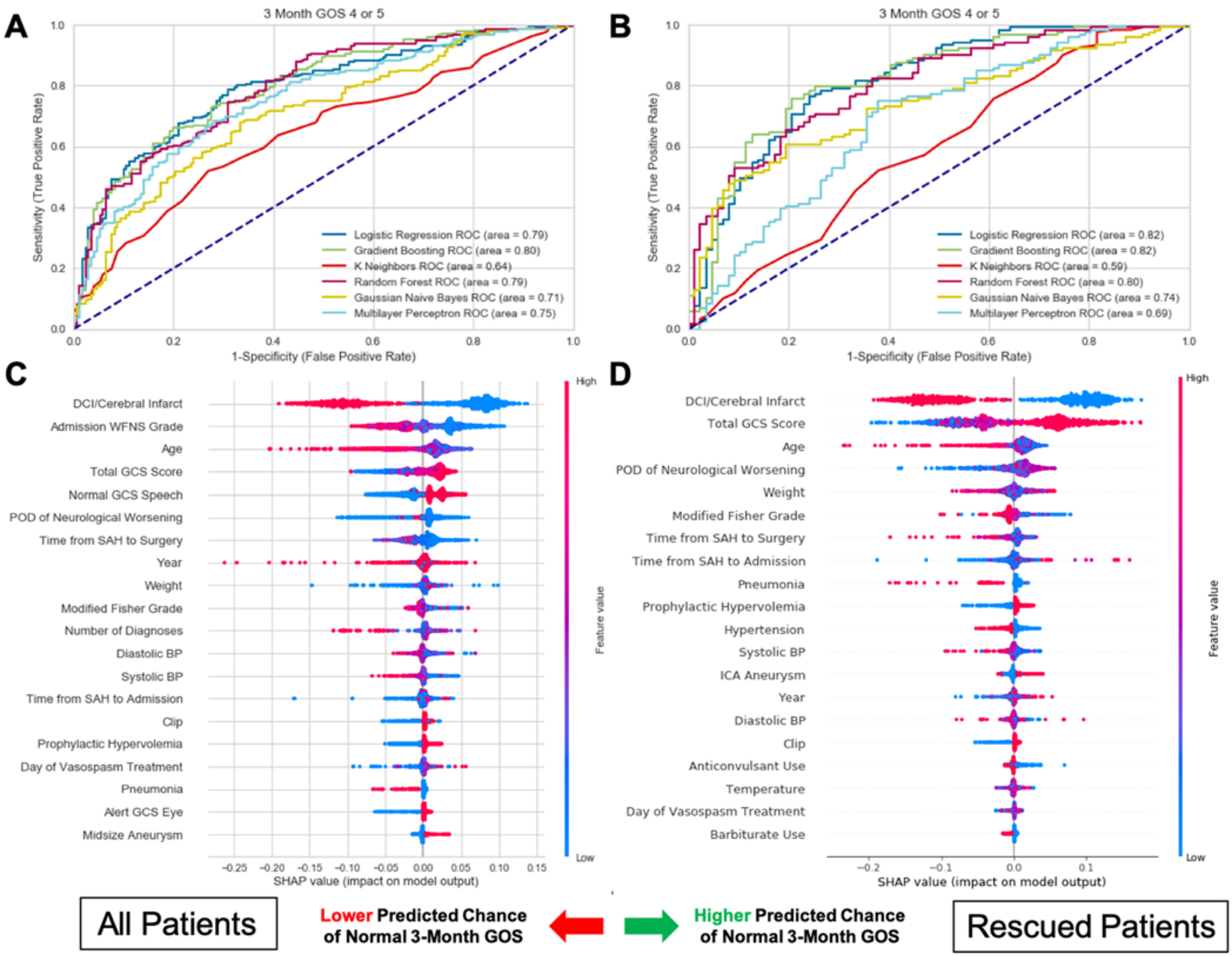

FIG. 2. ROC curves for model ensembles predicting good functional outcomes (3-month GOS score 4 or 5) for all patients with vasospasm (**A**) and in patients with vasospasm who received rescue therapy (**B**). SHAP summary plots showing the most important features for predicting good functional outcomes for all patients with vasospasm (**C**) and in patients who received rescue therapy (**D**). *Red dots* indicate high feature values for that individual patient, whereas *blue dots* indicate low underlying feature values. For binary categorical features, a "low" feature value indicates its absence and a "high" value indicates its presence. Figure is available in color online only.

the SHAP values for each patient-derived model and used them to determine global feature importance rankings across the study population (Fig. 2). We found that the time from SAH to admission was the most important feature for determining which patients received rescue therapy, with a lower predicted chance occurring after a greater lapsed time between SAH and admission. Conversely, patients with white race, diffuse thick SAH, hyperlipidemia, and no cerebral edema had a higher predicted chance of receiving rescue therapy (Fig. 1D). In comparison, the decision to administer interventional versus noninterventional rescue therapy depended on different patient and treatment characteristics. Interventional rescue was more likely to be administered if the patient received prophylactic phenytoin or had a higher modified Fisher grade on admission (Fig. 1E), whereas the decision to deliver noninterventional rescue was more likely in the absence of cerebral edema, the presence of diffuse thick SAH consistency, and a greater number of medical diagnoses on record (Fig. 1F). Of note, the presence of DCI/cerebral infarct only played a mild role in the decision to administer any rescue therapy, shown by a relatively weak effect on model prediction (Fig. 1D).

Predicting 3-Month GOS Score by Rescue Therapy Status

We next sought to use a similar approach to understand the determinants of good outcomes across all patients who experienced post-SAH vasospasm as well as the subset of those who received rescue therapy. ML modeling again showed that the gradient boosting algorithm yielded the best results for predicting good outcome in all patients with vasospasm (C = 0.80; Fig. 2A) and the rescue therapy subset (C = 0.82; Fig. 2B), demonstrating good predictive capacity in this classification task. Calculating and ranking SHAP values for each patient-derived model of

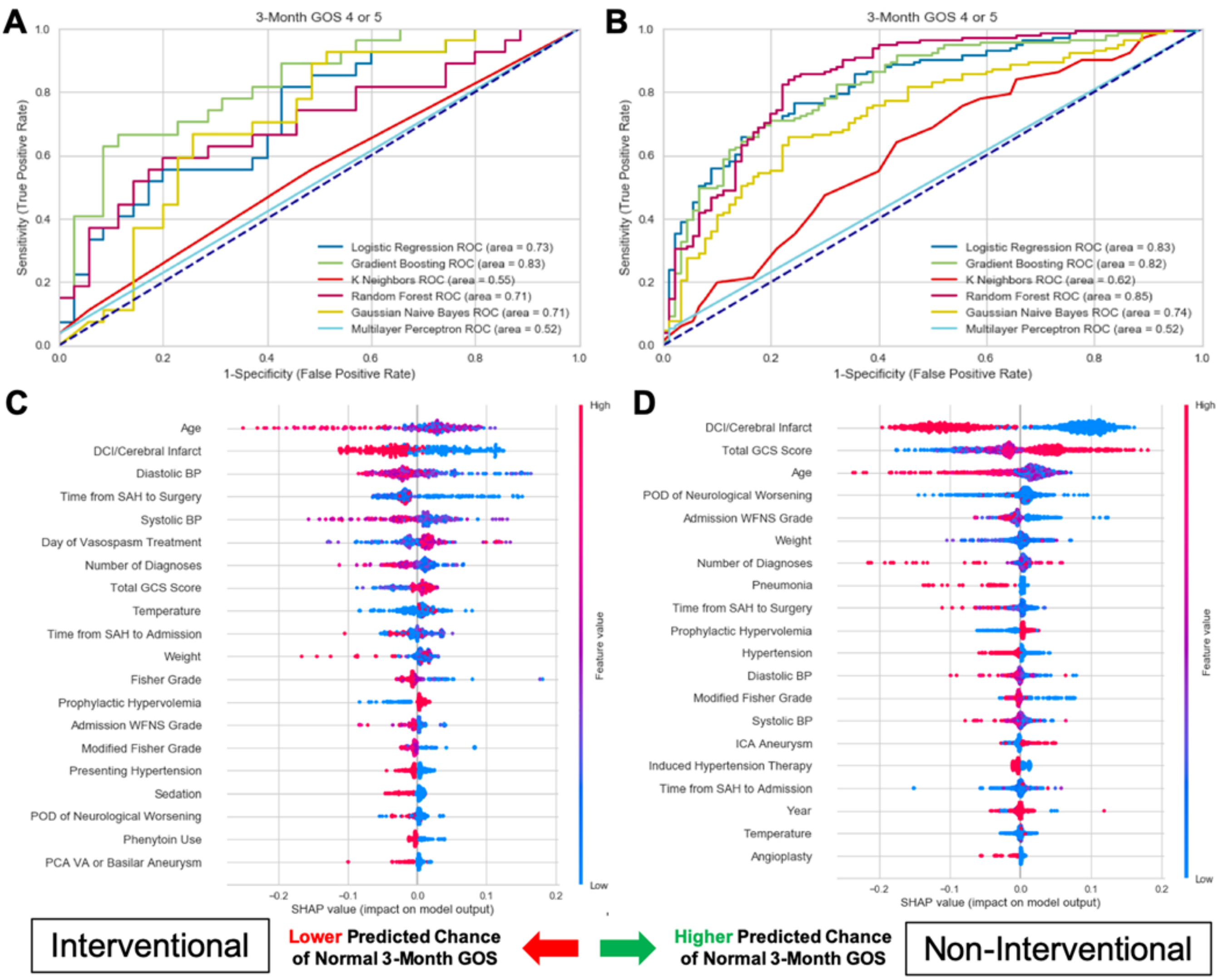

FIG. 3. ROC curves for model ensembles predicting good functional outcomes (3-month GOS score 4 or 5) for patients with vasospasm who received interventional rescue therapy (**A**) and noninterventional rescue therapy (**B**). SHAP summary plots showing the most important features for predicting good functional outcomes for patients who received interventional rescue therapy (**C**) and noninterventional rescue therapy (**D**). *Red dots* indicate high feature values for that individual patient, whereas *blue dots* indicate low underlying feature values. For binary categorical features, a "low" feature value indicates its absence and a "high" value indicates its presence. PCA = posterior cerebral artery; VA = vertebral artery. Figure is available in color online only.

functional outcome revealed that the absence of DCI/cerebral infarct, favorable (low) WFNS grade, younger age, and good (high) total GCS score on admission were the most important features for a greater predicted chance of good functional outcome across all patients with vasospasm (Fig. 2C). The feature importance profile for predicting good functional outcome in the rescue therapy subset differed with respect to several patient characteristics. For example, although no DCI/cerebral infarct, favorable total GCS score, and lower age remained the most important predictors of good functional outcome, factors such as a later postoperative day of neurological worsening, no pneumonia, no history of hypertension, aneurysm located on the ICA, and no anticonvulsant use also became important for predicting good functional outcome in patients in whom rescue therapy was administered (Fig. 2D).

Predicting 3-Month GOS Score by Rescue Therapy Type

We applied ML to study differences in the factors that influenced 3-month GOS scores in patients who received interventional or noninterventional rescue therapy. Gradient boosting classifiers demonstrated good performance in predicting good outcome following both interventional (C = 0.83) and noninterventional (C = 0.82) rescue therapy for vasospasm (Fig. 3A and B). SHAP-based feature importance rankings elucidated several differences in the most important predictors of outcome by rescue type. For example, lower systolic and diastolic blood pressures (BPs) were more important for predicting good 3-month GOS scores following interventional rescue compared to noninterventional rescue (Fig. 3C). Similarly, a greater number of postoperative days until vasospasm treatment was also

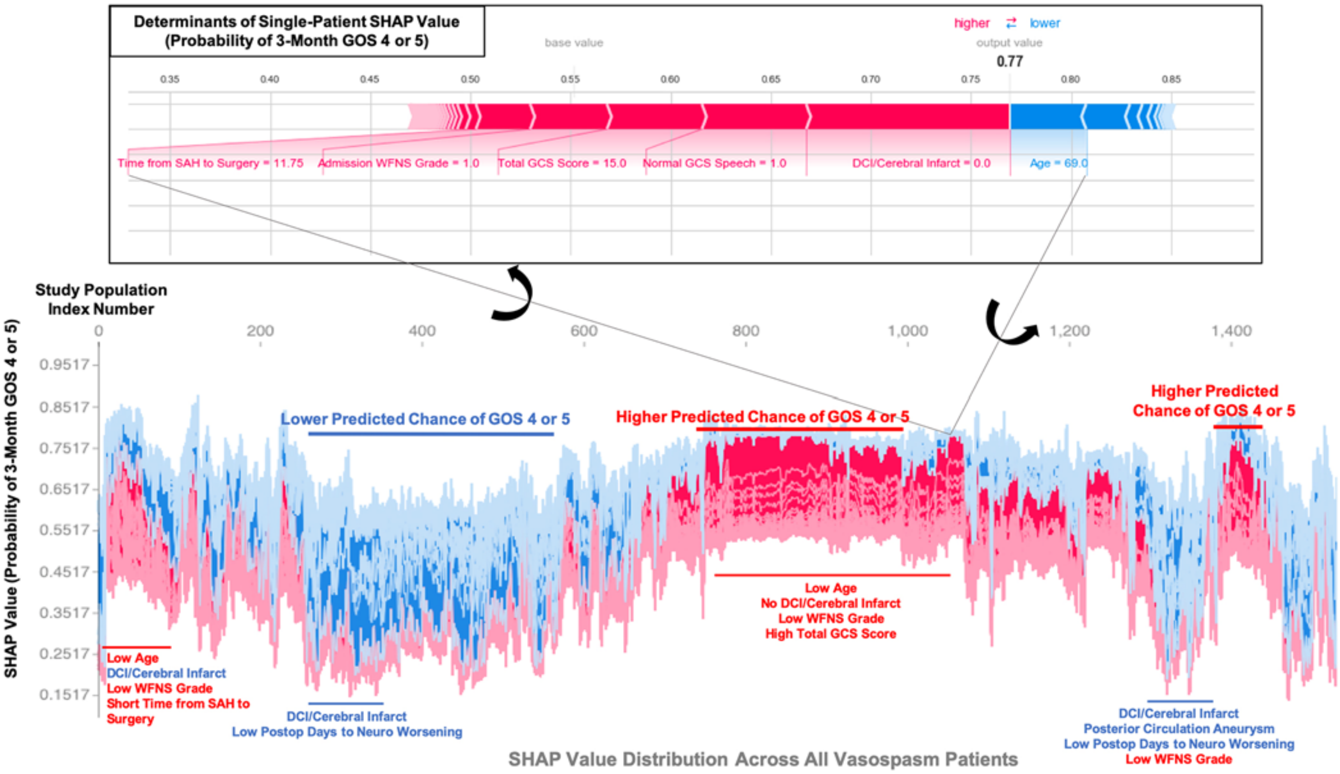

FIG. 4. Hierarchical study population clustering using SHAP value feature weightings to quantify patient similarity. **Upper:** A "force plot" is used to determine each patient's overall SHAP value. Features pushing the overall SHAP value higher (*red*, denotes a better chance of good clinical outcome) and those pushing it lower (*blue*, denotes a worse chance of good clinical outcome) combine to yield the overall net SHAP value of predicted risk of prolonged hospitalization for that patient (e.g., 0.77). **Lower:** Rotating the force plot 90° counterclockwise and repeating this process for all patients in the study population provides a global picture of the probability of a 3-month GOS score of 4 or 5 in all patients with vasospasm in the study, clustered by similar risk factor combinations. Common characteristics of patient subpopulations with high (*red*) or low (*blue*) predicted probabilities are shown below the plot. GCS denotes the change to GCS score throughout. Figure is available in color online only.

important for predicting good 3-month GOS scores after interventional but not noninterventional rescue. Conversely, a favorable WFNS grade on admission and the absence of pneumonia were ranked as important predictors of better 3-month GOS scores for noninterventional rescue but not for interventional rescue (Fig. 3D).

Hierarchical Population Clustering and Interaction Effects

In agreement with the summary plot of ranked importance, hierarchical clustering showed that patient populations with various combinations of no DCI/cerebral infarct, favorable admission WFNS grade, young age, and high admission total GCS score tended to comprise the population subsets with higher predicted chance of good functional outcome (Fig. 4, red labels). Of note, clustering revealed patient subsets with mixed predictive factors that did not always have the expected predicted chance of a good functional outcome. For example, a patient subpopulation was found in which DCI/cerebral infarct was noted, yet the group still had a high predicted chance of GOS scores of 4–5 at 3 months, possibly due to their other attributes, which included younger age, favorable WFNS grade, and short time from SAH to surgery (Fig. 4, lower panel). Conversely, a subpopulation of patients with favorable WFNS grades but a lower predicted chance of good functional outcomes was observed, possibly due to the presence of concurrent DCI/cerebral infarct, posterior circulation aneurysms, and a low number of postoperative days until neurological worsening occurred.

When examining the SHAP interaction values, the strongest and most consistent interactions were noted with age. In particular, age was found to clearly interact with GCS verbal scores, prophylactic hypervolemia, and midline shift (Fig. 5). These analyses revealed that age and normal GCS verbal scores interacted, such that having a normal GCS verbal score at an older age was far more important for predicting a good clinical outcome than having a normal GCS verbal score at a younger age (Fig. 5A). Similarly, age and prophylactic hypervolemia interacted, such that not receiving prophylactic hypervolemia at an older age was more detrimental to good clinical outcome than if it was not provided to patients at younger ages (Fig. 5B). Finally, age and midline shift interacted, such that having midline shift and being elderly resulted in a much worse predicted outcome than if it was present in a younger patient (Fig. 5C). Taken together, the observed interaction effects demonstrate that age is an important variable to consider given its modulatory effects on the importance of other clinical factors.

Propensity Score Matching

Using the important variables identified from ML modeling along with clinically recognized important variables, we generated two propensity score–matched cohorts with 385 patients each to determine the effect of rescue therapy on outcomes. In contrast to the many baseline differences in the full study population (Supplemental Tables 2 and 3), the matched cohorts were highly similar in baseline demographics and comorbidities, as well as aneurysm, SAH, and vasospasm characteristics (Table 1). There were 150 patients (39%) in the rescue therapy cohort and 128 (33%) in the nonrescue cohort who reached a 3-month GOS score of 5 (OR 1.28, 95% CI 0.95–1.72; p = 0.10), suggesting no statistically significant association with good recovery. Using the 3-month GOS score of 4 or 5 as an indicator for good outcomes, however, we found that 238 patients (62%) in the rescue therapy cohort and 192 (50%) in the nonrescue cohort reached this outcome (OR 1.63, 95% CI 1.22–2.17; p = 0.001), suggesting that rescue therapy was associated with an increase in moderate disability or good recovery (Table 2).

Discussion

One of the foremost challenges in SAH management is understanding which patient characteristics and treatment decisions are associated with good outcomes (Table 3). We endeavored to address this by using a big data approach applying predictive ML models to a large patient data set before opening up the models and explaining their predictions with game theory–based solution concepts. We found that the presence of DCI/infarction was the most important feature influencing 3-month GOS scores in the full data set of patients with vasospasm and in those who received rescue therapy (Fig. 1). Previous studies have also shown that the combination of DCI and cerebral infarction correlates more strongly with poor outcome than aVSP,[33,34] which confirms that this ML-based approach seems to produce valid results. Although several other features, such as admission GCS score and age, were also very important in both groups, we observed several variables that influenced good 3-month GOS scores in patients whose vasospasm was treated with rescue therapy, but not in the "all vasospasm" patient group. For example, the absence of certain patient comorbidities and complications, such as hypertension and pneumonia, became a much more important predictor of good clinical outcome specifically in patients treated with rescue therapy (Fig. 2D). Together, these findings suggest that DCI/cerebral infarction is the most important event to target and prevent in SAH management because it is invariably linked to poor outcome. Clinical trials focusing specifically on preventative or therapeutic interventions in patients with DCI/infarction should therefore be most able to demonstrate improvements in clinical outcomes. However, our analyses also suggest that additional monitoring of patients with hypertensive histories, and prevention or timely treatment of new-onset pneumonia may further improve clinical outcomes in patients receiving rescue therapy. Similarly, the negative interaction effects observed between older age, low GCS verbal scores, and midline shift leading to worse outcomes (Fig. 5) also suggest room for

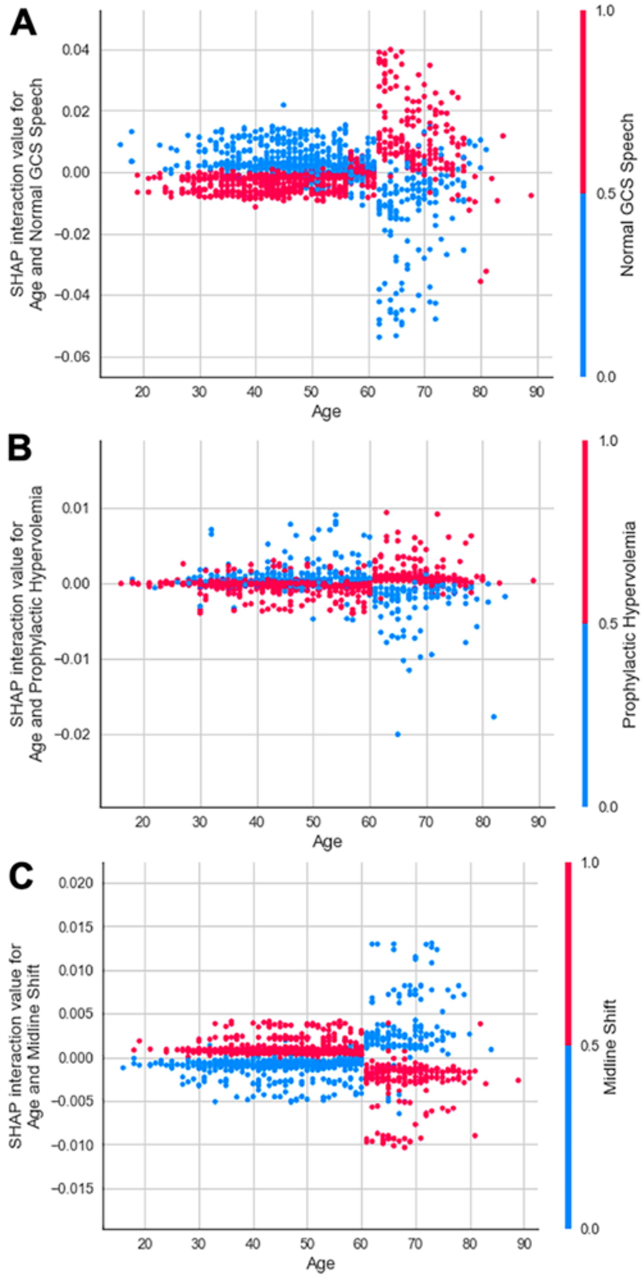

FIG. 5. Interaction effects between key variables influence the predicted chance of a 3-month GOS score of 4 or 5. SHAP interaction values quantified variable interaction effects and revealed strong interactions between age and normal GCS verbal scores (**A**), delivery of prophylactic hypervolemia (**B**), and the presence of midline shift (**C**). *Red dots* indicate the presence of the variable interacting with age (including normal GCS verbal score, prophylactic hypervolemia, and midline shift), whereas *blue dots* indicate the absence of these variables. Visualizing the SHAP interaction values (y-axis) as a function of the patient's age (x-axis) and the value of the interacting variable (dot color) shows distinct trends that highlight patient characteristics that lead to greater interaction effects. Greater interaction effects are indicated by increased vertical dispersion of dots. Figure is available in color online only.

TABLE 2. Three-month GOS scores and ORs for patients in propensity score–matched cohorts

Outcome Metrics	Rescue Therapy, n = 385	No Rescue Therapy, n = 385	p Value
3-mo GOS score 5 (%)			0.12
Yes	150 (39)	128 (33)	
No	235 (61)	257 (67)	
OR (95% CI)		1.28 (0.95–1.72)	0.10
3-mo GOS score 4 or 5 (%)			0.001
Yes	238 (62)	192 (50)	
No	147 (38)	193 (50)	
OR (95% CI)		1.63 (1.22–2.17)	0.001

ORs were computed using univariate regression modeling.

clinical benefit in patients with these combinations of characteristics in rescue therapy RCTs.

Another focus of this study was to determine the factors influencing the likelihood of an individual to receive rescue therapy for vasospasm. Although vasospasm could be detected through either angiography, TCD, CT perfusion, or symptomatology, the determination of vasospasm was ultimately the result of investigators' opinions, and the decision to give rescue therapy was undoubtedly influenced by the investigators' interpretations of the patients'

TABLE 3. Summary of the top feature effects on the chance of receiving rescue therapy and of achieving a 3-month GOS score of 4 or 5 in various patient cohorts

Pt Characteristic	Effect on Chance of Receiving Rescue Therapy	Observed in Pts w/ Interventional Rescue	Observed in Pts w/ Noninterventional Rescue
Increased time from SAH to admission	Negative	Yes	No
Diffuse, thick SAH on admission	Positive	No	Yes
White race	Positive	No	Yes
Cerebral edema	Negative	No	Yes
Phenytoin use	Positive	Yes	Yes
Severe aVSP	Positive	Yes	No
Greater no. of medical Dxs on record	Positive	Yes	Yes
Higher temperature	Positive	Yes	Yes
Pt Characteristic	**Effect on Chance of Good 3-Mo GOS Score**	**Observed in Total Study Population**	**Observed in Pts w/ Rescue**
Cerebral infarct	Negative	Yes	Yes
Lower admission WFNS grade	Positive	Yes	No
Higher total GCS score	Positive	Yes	Yes
Higher age	Negative	Yes	Yes
Earlier POD of neuro worsening	Negative	No	Yes
Pneumonia	Negative	Yes	Yes
Positive history of hypertension	Negative	No	Yes
Higher systolic BP	Negative	Yes	Yes
Pt Characteristic	**Effect on Chance of Good 3-Mo GOS Score**	**Observed in Pts w/ Interventional Rescue**	**Observed in Pts w/ Noninterventional Rescue**
Cerebral infarct	Negative	Yes	Yes
Higher age	Negative	Yes	Yes
Pneumonia	Negative	No	Yes
Higher POD of vasospasm treatment	Positive	Yes	No
Did not receive prophylactic hypervolemia	Negative	Yes	Yes
Aneurysm located on ICA	Positive	No	Yes
Aneurysm in posterior circulation	Negative	Yes	No

Results are based on the features with the highest SHAP values and clearest trends in various patient cohorts, as depicted in the SHAP summary plots.

clinical pictures. The well-defined definitions and data in the data sets that support the diagnosis create an optimal opportunity to understand some of the fundamental factors associated with clinicians' decisions whether or not to give rescue therapy. Our explainable ML models revealed that, whereas SAH volume on CT scans and neurological sequelae such as the presence of cerebral edema were important factors likely to influence the decision to give rescue therapy, admission WFNS grade and total GCS scores were less important considerations in predicting which patients ultimately received rescue therapy (Fig. 1). Given that admission neurological condition has been described as an indicator of early brain injury and an important prognostic variable for outcome,[32] its lack of consideration in the decision to administer rescue therapy suggests that DCI may not depend on early brain injury. Of note, the most important features for predicting delivery of rescue therapy also varied depending on the type of rescue therapy. The decision to administer interventional rescue appeared to be more likely in the setting of prophylactic phenytoin use and a higher modified Fisher grade on admission, whereas noninterventional rescue decisions were more likely in the presence of cerebral edema and a shorter time from SAH to surgery.

Finally, the ML-based propensity score–matched analysis revealed that rescue therapy was associated with increased odds of good outcome, when this was categorized as moderate disability and good recovery (GOS score of 4 or 5). Whereas existing evidence thus far generally suggests that endovascular and pharmacological rescue therapies that dilate arteries or induce hypertension to increase perfusion can reduce aVSP, they have yet to improve clinical outcomes in the setting of RCTs.[13,34,35] As such, there is currently no level 1 evidence to support using rescue therapy, and the use of induced hypertension and endovascular treatment varies greatly between centers. This study, which applies a novel propensity score–matched analysis guided by ML-based variable selection to data derived from several previous RCTs studying SAH, supports the use of rescue therapy and provides another piece of data to the literature on this topic. However, formal RCTs with well-defined patient populations and clinical indications will be needed to confidently shift the current paradigm for rescue therapy. Nevertheless, this study improves our understanding of the determinants of 90-day outcome after rescue therapy and may facilitate the development of prognostic prediction tools that could help clinicians better predict the optimal indications and outcomes for rescue therapy.

There are limitations of this study that deserve to be mentioned. Although drawing from multiple sources of high-quality clinical data may increase the power of our analyses, most studies had defined inclusion criteria, which could limit the external validity of our findings. Furthermore, limiting the analysis to only data available within the clinical data sets could prevent detection of other factors that influence rescue therapy decisions and outcomes. In addition, the included trials were conducted across many years, which could mean that temporal artifacts reflecting changes in SAH management and clinical practice over time may be inherent in the data. Given the retrospective nature of this analysis, it is important to note that the reported findings are associational, not causational. Finally, even propensity score matching cannot exclude all treatment biases and hence residual confounding.

Conclusions

These results suggest that rescue therapy may increase the odds of a good clinical outcome, and that although the absence of DCI/cerebral infarct is the most important indicator of good clinical outcomes overall, certain patient comorbidities and complications, specifically absence of hypertension and pneumonia, may also be important predictors of better clinical outcome in patients who undergo rescue therapy. Clinical trials focusing specifically on therapeutic interventions in patients with DCI/cerebral infarction or those with protocols for preventing hypertension and pneumonia may be most able to demonstrate improvements in clinical outcomes. Similarly, the negative interaction effects observed between older age and the presence of low GCS verbal scores and midline shift leading to worse outcomes also suggest room for clinical benefit in patients with these combinations of characteristics in rescue RCTs.

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Disclosures

Dr. Macdonald is a consultant for Grace Biotechnology and Idorsia Pharmaceuticals. Dr. Oermann owns equity in MedAugur and Whiteboard Coordinator; receives consulting fees from Google; and is employed at Merck. Dr. Mocco is a consultant for Cerebrotech, Rebound Therapeutics, TSP Inc., Lazarus Effect, Medina, Pulsar Vascular, Imperative Care, Viseon, Endostream, Vastrax, RIST, Synchron, Viz.ai, Perflow, and CVAid; is an investor in Blockade, Medina, Lazarus Effect, TSP Inc., Cerebrotech, Imperative Care, Endostream, Viseon, BlinkTBI, Serenity, Cardinal Consulting, NTI, RIST, Viz.ai, and Synchron; and receives research support from Penumbra, Stryker, and Microvention.

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