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Posttreatment Variables Improve Outcome Prediction after Intra-Arterial Therapy for Acute Ischemic Stroke

Shyam Prabhakaran[a], **Tudor G. Jovin**[b], **Ashis H. Tayal**[c], **Muhammad S. Hussain**[d], **Thanh N. Nguyen**[e], **Kevin N. Sheth**[f], **John B. Terry**[g], **Raul G. Nogueira**[h], **Anat Horev**[b], **Dheeraj Gandhi**[i], **Dolora Wisco**[d], **Brenda A. Glenn**[h], **Bryan Ludwig**[g], **Paul F. Clemmons**[j], **Carolyn A. Cronin**[i], **Melissa Tian**[c], **David Liebeskind**[k], **Osama O. Zaidat**[l], **Alicia C. Castonguay**[l], **Coleman Martin**[m], **Nils Mueller-Kronast**[n], **Joey D. English**[o], **Italo Linfante**[p], **Timothy W. Malisch**[q], and **Rishi Gupta**[h]

[a]Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, Ill

[b]Department of Neurology, Stroke Institute, University of Pittsburgh Medical Center

[c]Department of Neurology, Allegheny General Hospital, Pittsburgh, Pa

[d]Cerebrovascular Center, The Cleveland Clinic Foundation, Cleveland, Ohio

[e]Departments of Neurology and Radiology, Boston University School of Medicine, Boston, Mass

[f]Department of Neurology, Yale University School of Medicine, New Haven, Conn

[g]Department of Internal Medicine (Neurology), Miami Valley Hospital, Wright State University, Boonshoft School of Medicine, Dayton, Ohio

[h]Department of Neurology, Marcus Stroke and Neuroscience Center, Grady Memorial Hospital, Emory University School of Medicine, Atlanta, Ga

[l]Department of Neurology, University of Maryland School of Medicine, Baltimore, Md

[j]Department of Radiology, Vanderbilt University School of Medicine, Nashville, Tenn

[k]Department of Neurology, University of California Los Angeles, Los Angeles, Calif

[l]Department of Neurology, Neurosurgery and Radiology, Medical College of Wisconsin, Milwaukee, Wis

[m]St. Luke's Kansas City, Kansas City, Mo

[n]Department of Neurology, Delray Medical Center, Delray Beach, Fla

[o]California Pacific Medical Center, San Francisco, Calif

Shyam Prabhakaran, MD, Suite 1417, 710 N. Lake Shore Dr., Chicago, IL 60611 (USA), shyam.prabhakaran@northwestern.edu.

Disclosure Statement

T.G. Jovin: Consultant/Advisory Board, Modest, Concentric Medical, CoAxia, EV3, Neurointerventions; R.G. Nogueira: Consultant/Advisory Board, Modest, EV3, Concentric Medical, CoAxia, Rapid Medical; D.S. Liebeskind: Consultant/Advisory Board, Modest, CoAxia, Concentric Medical; O.O. Zaidat: Consultant/Advisory Board, Modest, EV3, Stryker Neurovascular, Penumbra; R. Gupta: Consultant/Advisory Board, Modest, Concentric Medical, CoAxia, Rapid Medical, Codman Corporation.

None of the other authors have any relevant interests to declare.

[p]Division of Interventional Neuroradiology, Baptist Cardiac and Vascular Institute, Miami, Fla

[q]Alexian Brothers Medical Center, Elk Grove Village, Ill., USA

Abstract

Background—There are multiple clinical and radiographic factors that influence outcomes after endovascular reperfusion therapy (ERT) in acute ischemic stroke (AIS). We sought to derive and validate an outcome prediction score for AIS patients undergoing ERT based on readily available pretreatment and posttreatment factors.

Methods—The derivation cohort included 511 patients with anterior circulation AIS treated with ERT at 10 centers between September 2009 and July 2011. The prospective validation cohort included 223 patients with anterior circulation AIS treated in the North American Solitaire Acute Stroke registry. Multivariable logistic regression identified predictors of good outcome (modified Rankin score ≤2 at 3 months) in the derivation cohort; model β coefficients were used to assign points and calculate a risk score. Discrimination was tested using C statistics with 95% confidence intervals (CIs) in the derivation and validation cohorts. Calibration was assessed using the Hosmer-Lemeshow test and plots of observed to expected outcomes. We assessed the net reclassification improvement for the derived score compared to the Totaled Health Risks in Vascular Events (THRIVE) score. Subgroup analysis in patients with pretreatment Alberta Stroke Program Early CT Score (ASPECTS) and posttreatment final infarct volume measurements was also performed to identify whether these radiographic predictors improved the model compared to simpler models.

Results—Good outcome was noted in 186 (36.4%) and 100 patients (44.8%) in the derivation and validation cohorts, respectively. Combining readily available pretreatment and posttreatment variables, we created a score (acronym: SNARL) based on the following parameters: symptomatic hemorrhage [2 points: none, hemorrhagic infarction (HI)1–2 or parenchymal hematoma (PH) type 1; 0 points: PH2], baseline National Institutes of Health Stroke Scale score (3 points: 0–10; 1 point: 11–20; 0 points: >20), age (2 points: <60 years; 1 point: 60–79 years; 0 points: >79 years), reperfusion (3 points: Thrombolysis In Cerebral Ischemia score 2b or 3) and location of clot (1 point: M2; 0 points: M1 or internal carotid artery). The SNARL score demonstrated good discrimination in the derivation (C statistic 0.79, 95% CI 0.75–0.83) and validation cohorts (C statistic 0.74, 95% CI 0.68–0.81) and was superior to the THRIVE score (derivation cohort: C statistic 0.65, 95% CI 0.60–0.70; validation cohort: C-statistic 0.59, 95% CI 0.52–0.67; $p < 0.01$ in both cohorts) but was inferior to a score that included age, ASPECTS, reperfusion status and final infarct volume (C statistic 0.86, 95% CI 0.82–0.91; $p = 0.04$). Compared with the THRIVE score, the SNARL score resulted in a net reclassification improvement of 34.8%.

Conclusions—Among AIS patients treated with ERT, pretreatment scores such as the THRIVE score provide only fair prognostic information. Inclusion of posttreatment variables such as reperfusion and symptomatic hemorrhage greatly influences outcome and results in improved outcome prediction.

Keywords

Prediction tools; Revascularization; Reperfusion

Introduction

Ischemic stroke is a leading cause of death and disability in the USA [1]. Early reperfusion remains a mainstay of acute therapy. Though not proven in randomized clinical trials, endovascular reperfusion therapy (ERT) may also benefit select patients with acute ischemic stroke (AIS) [2]. Several scores have been developed to improve patient selection for ERT [3–6] but none have included treatment factors to predict outcome after ERT. It is well established that reperfusion success is an important driver of good outcomes in endovascular treatment studies [7–10]. Despite disappointing recent trials of ERT, these continued to show the strong association between reperfusion success and good functional outcome [11, 12]. Other factors such as age, medical history, laboratory and radiographic findings, treatment success and complications may also influence outcomes. A valid prediction score may have clinical utility if it can both improve patient selection for ERT and predict long-term patient outcome after ERT.

We sought to develop and validate a simple outcome prediction score for anterior circulation AIS patients treated with ERT based on readily available pre- and posttreatment variables. We utilized a large multicenter cohort for score derivation and the North American Solitaire Acute Stroke (NASA) registry for score validation.

Methods

Data Sources

We analyzed a retrospective registry of consecutive patients treated with endovascular therapy at 10 tertiary stroke centers from September 2009 to July 2011. Participating hospitals submit information on consecutive ischemic stroke patients treated with ERT. Details of the registry have been described previously [13]. Only de-identified information was used for the purposes of this analysis after internal review board approval from each participating center.

Inclusion criteria for this study included patients with AIS who presented within 8 h of symptom onset with anterior circulation large vessel occlusions. Data were analyzed regarding demographics (age and sex), previous medical history (hypertension, atrial fibrillation, diabetes mellitus and dyslipidemia), radiographic interpretation of hemorrhages, location of arterial occlusion on angiography, reperfusion status and clinical outcomes. Successful re-perfusion was defined as a Thrombolysis In Cerebral Ischemia (TICI) score of 2b or higher on the final angiographic image and was rated by the treating interventionalist. Symptomatic hemorrhage was defined as a parenchymal hematoma (PH) type 2 using the European Cooperative Acute Stroke Study definition [14]. The Alberta Stroke Program Early CT Score (ASPECTS) [15] was based on available pretreatment CT scans, and final infarct volume was measured using the ABC/2 approach [16]. Outcomes were assessed by trained stroke neurologists at each site, and a modified Rankin score of less than or equal to 2 at 90 days was considered a good clinical outcome. Of 556 patients with anterior circulation large artery occlusions treated with ERT in the registry, 511 had complete data for inclusion in the derivation cohort. In a subset of patients, pretreatment ASPECTS (n = 263) and final infarct volume (n = 312) were available. From the NASA prospective cohort

[17], we acquired similarly defined data to serve as the validation dataset for the prediction score. Of the 354 patients in the NASA registry, 223 patients with anterior circulation large artery occlusions treated with ERT within 8 h of onset had complete data and were included in the analysis.

Statistical Analysis

Using univariable tests, we assessed associations between pre- and post treatment variables using χ^2 tests (or Fisher's exact test if appropriate) for categorical variables and t tests (or Mann-Whitney test if appropriate) for continuous variables. A multivariable logistic regression analysis was performed in the derivation cohort to identify independent predictors of good outcome. Candidate variables were selected based on statistically significant univariable relationships ($p<0.20$) with good outcome (modified Rankin score 0–2 at 90 days) after ERT. Continuous variables were then categorized into appropriate clinically relevant strata (cut points). The multivariable final model included important predictors based on statistical significance ($p<0.05$). The calibration of the final model was tested using the Hosmer-Lemeshow test.

A risk score was developed by multiplying each independent predictor's β coefficient in the final model by 1.5 and rounding to the nearest integer. For each patient, the weighted integers were summed to obtain a total risk score with a range from 0 to 11 points. The discriminatory ability of the model was assessed using the C statistic, or the probability that a randomly selected patient who experienced an outcome will have a higher predicted probability of having that outcome occur compared to another randomly selected patient who did not experience that outcome. A C statistic value of 0.5 indicates that the model is no better than chance, while a value of 1.0 indicates that the model has perfect discrimination. Calibration was visually assessed by comparing plots of predicted versus observed good outcome. The risk score was then validated by assessing discrimination and calibration in the validation cohort (NASA). We performed several subgroup analyses in the patients from the derivation cohort for whom imaging data were collected. We compared C statistics for pretreatment models such as the Totaled Health Risks in Vascular Events (THRIVE) score, posttreatment models including final infarct volume and combined pre- and posttreatment models. Lastly, we assessed the net reclassification improvement for our prediction score compared to the THRIVE score [18]. All p values are two-sided, with $p<0.05$ considered statistically significant. Analyses were performed using IBM SPSS software version 21 (Armonk, N.Y., USA).

Results

The derivation cohort consisted of 511 patients [mean age 65.3 ± 15.0 years; 48.1% male; median National Institutes of Health Stroke Scale (NIHSS) score 18]. The sites of arterial occlusion were the middle cerebral artery (M1 60.7%, M2 10.8%) and the internal carotid artery (ICA; 28.6%). In this cohort, 233 patients (45.6%) received intravenous tissue plasminogen activator (t-PA) prior to ERT. TICI 2b/3 reperfusion was achieved in 300 patients (58.7%), and symptomatic hemorrhage (PH2) occurred in 36 (7.0%). Good outcome at 3 months was noted in 186 patients (36.4%) of the derivation cohort. The validation

cohort was comparable with regard to age (68.1 ± 15.0 years) and sites of occlusion (ICA: 26.0%; M1: 61.0%; M2 13.0%), but the symptomatic hemorrhage rate was higher (12.6%) and final TICI grade 3 was more common (35.0%). One hundred patients (44.8%) of the validation cohort achieved a good outcome (table 1).

In the derivation cohort, univariable analysis identified age, baseline NIHSS score, location of occlusion, intravenous t-PA use, reperfusion grade and hemorrhage as associated with outcome (table 2). Patients with good outcome at 90 days were younger (62.6 vs. 66.9 years, $p<0.01$), had lower baseline NIHSS scores (16 vs. 19, $p<0.01$), received intravenous t-PA more commonly (51.4 vs. 41.8%, $p= 0.04$), differed by location of occlusion (M2 vs. M1 vs. ICA: 56.4 vs. 36.5 vs. 26.5%; $p<0.01$), had higher reperfusion grades (TICI 2b/3 vs. TICI 0/1/2a: 82.8 vs. 44.9%; $p<0.01$) and had fewer postprocedure PH2 hemorrhages (2.7 vs. 9.5%, $p<0.01$). There were trends for association between poor outcome and hypertension ($p= 0.08$) and diabetes mellitus ($p= 0.11$). In the subset of patients in whom final infarct volume was measured (n= 312), final infarct volume was a strong predictor of outcome (23.5 vs. 91.0 ml, $p<0.01$). Lastly, in a subset of patients with pretreatment ASPECTS recorded (n= 263), ASPECTS >7 was strongly associated with good outcome (84.5 vs. 61.3%, $p<0.01$).

In the full data derivation cohort, age, baseline NIHSS score, location of occlusion, reperfusion grade and symptomatic hemorrhage remained independent predictors of good outcome while diabetes was marginally significant ($p= 0.06$) in multivariable analyses; intravenous t-PA and hypertension were no longer significant (table 3). A score including age, NIHSS score, reperfusion status, symptomatic hemorrhage and location of occlusion [score= −0.262 + 0.675(TICI 2b or 3 reperfusion status) – 0.012(age) – 0.128(initial NIHSS score) + 0.778(M2 clot) – 0.722(symptomatic hemorrhage)] showed good discrimination (C statistic 0.80, 95% CI 0.76–0.84).

After simplification of continuous variables into relevant strata and weighting by strength in the model, a prediction score (acronym: SNARL) was developed (table 3). The Hosmer-Lemeshow test showed that the model was well calibrated (derivation cohort: $\chi^2 = 5.66$, $p= 0.58$; validation cohort: $\chi^2 = 0.22$, $p= 0.98$). The simplified SNARL score demonstrated good discrimination in the derivation cohort (C statistic 0.79, 95% CI 0.75–0.83) and validation cohort (C statistic 0.74, 95% CI 0.68–0.81); a comparison of these yielded no difference ($p= 0.22$). Furthermore, this simplified categorical variable model was not significantly different from the continuous variable model ($p= 0.37$). The observed probability of good outcome in groups of patients divided according to SNARL scores (0–3, 4–7, 8–11) is shown in figure 1a for the derivation and validation cohorts separately, while a plot of observed to predicted outcomes is shown in figure 1b. The predicted probability of good outcome by SNARL score in each cohort is shown in figure 2. We compared the SNARL score to the THRIVE score in the derivation cohort and validation cohorts and found the SNARL score was superior (C statistic 0.79 vs. 0.65 and 0.59, $p<0.01$ for both comparisons). The reclassification of outcomes based on THRIVE score versus the SNARL score is shown in table 4; the net reclassification improvement was 34.8%.

We performed several explorations in an attempt to further improve discrimination (fig. 3). These showed that generally, posttreatment models were superior to pretreatment prediction models. A scoring system with age, ASPECTS, reperfusion status and final infarct volume (C statistic 0.86, 95% CI 0.82–0.91) was significantly better than the simpler SNARL score (p= 0.04). However, since ASPECTS and infarct volumes were not uniformly captured in the derivation cohort, we did not include them for consideration in the validation cohort.

Discussion

In this study, we developed and validated a prediction tool for outcome following ERT. The 12-point SNARL score combines 5 readily available pre- and posttreatment factors (symptomatic hemorrhage, baseline NIHSS score, age, reperfusion grade and location of occlusion) and demonstrated good discrimination and calibration in 2 independent cohorts. It was superior to the pretreatment THRIVE score but inferior to scores that incorporate final infarct volume. The simplified score performed similarly to a more complex formulaic score using continuous variables. The SNARL score may provide clinicians a tool to discuss expectations of outcomes with patients and their families and make early decisions regarding post-stroke care.

Previous scores have focused on pretreatment clinical, laboratory and radiographic predictors of outcomes with good results (C statistics ranging from 0.69–0.76) [3–6, 19]. These scoring systems serve primarily to select patients who are most likely to benefit from ERT, omit the strong influence of treatment factors on that prediction and may not serve to guide clinicians on functional outcome *following* ERT. Scores including posttreatment variables such as final infarct volume show excellent discrimination for outcome after MCA infarction [20–22]. Our study confirms that posttreatment variables, especially reperfusion status, symptomatic hemorrhage and final infarct volume, have significant influence on outcomes and should be included in prognostication [7, 10]. Furthermore, our study suggests that the THRIVE score may erroneously predict the outcome in one third of patients.

While the SNARL score is simple, it also excludes several variables that could further improve its discrimination. Clinical improvement at 24–36 h could provide a surrogate for long-term outcome but was not available in our datasets. In addition, factors such as sedation and mechanical ventilation may limit examination and also bias the NIHSS score towards those in whom measurement was feasible (i.e. milder strokes). Patients with smaller baseline infarct volumes [23], greater ratios of penumbra to core infarct tissue [24, 25] and collateral flow distal to the occlusion may be more likely to benefit from reperfusion strategies [26, 27]; these radiographic variables were not uniformly available in the derivation cohort. Likewise, medical factors including hyperglycemia, blood pressure and complications such as pneumonia contribute to long-term outcome after ischemic stroke [28, 29]. Lastly, the intensity and timing of rehabilitation would be expected to influence poststroke disability [30, 31]. Outcomes following ERT are also likely dependent on time to and mode of reperfusion [32]. Ascertaining reperfusion time is often challenging in clinical practice due to the nature of the procedure, whereby slow and steady reperfusion or partial followed by complete reperfusion may be impossible to time exactly. As the technology evolves, the recent advances in retrievable stents may further improve the technique,

allowing for earlier and higher rates of reperfusion with less hemorrhage risk [8, 9]. Despite these missing elements, improvement in discrimination, if included, is likely to be small.

Besides the lack of the aforementioned parameters, our study has other limitations. As mentioned above, post-treatment neurologic impairment was not measured and might also be a strong predictor of 3-month outcome. Clinical and radiographic data such as reperfusion status and 3-month outcomes were entered by local sites without central adjudication or blinding, raising the potential for bias. Grading of TICI scores can demonstrate significant interobserver variability, depending on whether the primary arterial occlusion was completely or partially recanalized and the presence of distal emboli. Grading of final reperfusion can also demonstrate site bias in favor of better scores, compared to central adjudication, as demonstrated in the SWIFT trial [9]. However, most sites have participated in large endovascular clinical trials, and consensus definitions were used to define key variables such as TICI grade and symptomatic hemorrhage. Site characteristics such as volume of cases per year and experience may also drive outcomes but were not included in this study [33]. We also do not know how many patients were excluded from treatment, thus preventing us from defining the denominator population considered for ERT. Nevertheless, the proportion with good outcomes in our derivation cohort (36%) is similar to those in embolectomy studies [7, 10] but lower than those in the more recent retrievable stent studies [8, 9]. Finally, missing data and data-dependent predictor selection may have introduced biases, and model assumptions may have been erroneous if they did not behave in an additive or linear manner.

The SNARL score is a simple 12-point scoring system to predict 3-month disability after ERT for anterior circulation AIS. It was derived from a multicenter registry and was validated in a large prospective contemporary registry of the Solitaire stent retriever. Further external validation is warranted.

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Appendix

NASA Site Investigators

Medical College of Wisconsin/Froedtert Hospital, Milwaukee, Wisc.: Osama O. Zaidat, Brian-Fred Fitzsimmons, John R. Lynch, Marc A. Lazzaro, Alicia C. Castonguay, Mohammad Issa; Emory University School of Medicine, Atlanta, Ga.: Rishi Gupta, Raul G. Nogueira, Chung-Huan Johnny Sun; St. Luke's Kansas City, Kansas City, Mo.: Coleman O. Martin, William E. Holloway; Delray Medical Center, Delray Beach, Fla.: Nils Mueller-Kronast; California Pacific Medical Center, San Francisco, Calif.: Joey English, Nobl Barazangi, Christine Wong, Charlene Chen, Oana Spataru, Ann Bedenk, Megan Morrow, David Tong; Baptist Cardiac and Vascular Institute, Miami, Fla.: Italo Linfante, Guilherme Dabus, Eugene Lin, Edgar Samaniego; Alexian Brothers Medical Center, Elk Grove Village, Ill.: Tim W. Malisch, Franklin Marden; Oregon Health and Science University, Portland, Oreg.: Hormozd Bozorgchami; Wayne State University School of Medicine, Detroit, Mich.: Andrew Xavier; West Virginia University Hospital, Morgantown, W.Va.: Ansaar Rai, Jennifer Domico; Vanderbilt University Medical Center, Nashville, Tenn.: Michael T. Froehler; University of Iowa, Iowa City, Iowa: Jeri Sieren, Heena Olalde; Provena Saint Joseph Medical Center, Joliet, Ill.: Aamir Badruddin; Boston Medical Center, Boston, Mass.: Thanh N. Nguyen, Alexander M. Norbash, Hesham Masoud, Judith Clark; Desert Regional Medical Center, Palm Springs, Calif.: Muhammad A. Taqi, Tom Wolfe, Ajeet Sodhi; University of Kansas Medical Center, Kansas City, Kans.: Michael G. Abraham;

Texas Stroke Institute, Plano, Tex.: Vallabh Janardhan; University of Texas Health Science Center, Houston, Tex.: Hashem Shaltoni; UT Southwestern Medical Center, Dallas, Tex.: Roberta Novakovic, G. Lee Pride Jr., Kim L. Rickert, Babu G. Welch, Jonathan A. White; Massachusetts General Hospital, Boston, Mass.: Albert J. Yoo, Thabele M. Leslie-Mazwi, Joshua A. Hirsch; University of Louisville Medical School, Louisville, Ky.: Alex Abou-Chebl; University of Texas, Houston, Tex.: Peng Roc Chen, Aditya Sanzgiri; Methodist Neurological Institute, Houston, Tex.: Gavin Britz; Duke University Medical Center, Durham, N.C.: Abhishek Agrawal; St. Louis University, St. Louis, Mo.: Ritesh Kaushal; University of Missouri, Columbia, Mo.: Ashish Nanda.

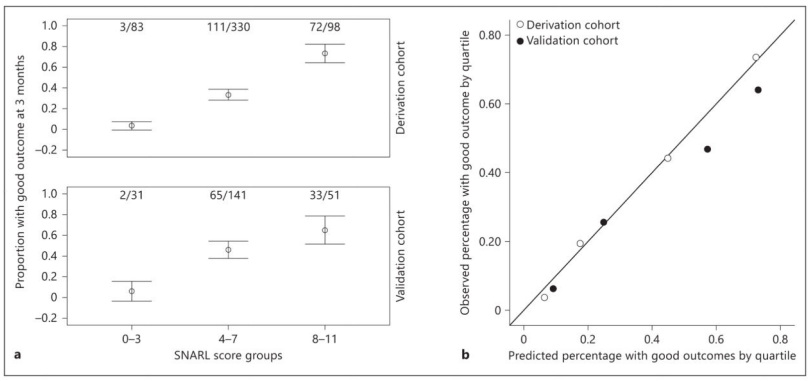

Fig. 1.

a Proportions are shown with 95% CIs for good outcome (modified Rankin score 0–2) in 3 groups divided according to the SNARL score (0–3, 4–7, 8–11) in both derivation and validation cohorts. Numbers shown above each graph are absolute numbers in each bin. **b** Calibration of the prediction tool in the derivation and validation samples according to observed versus predicted rate of good outcome at 3 months in quartiles of predicted probability.

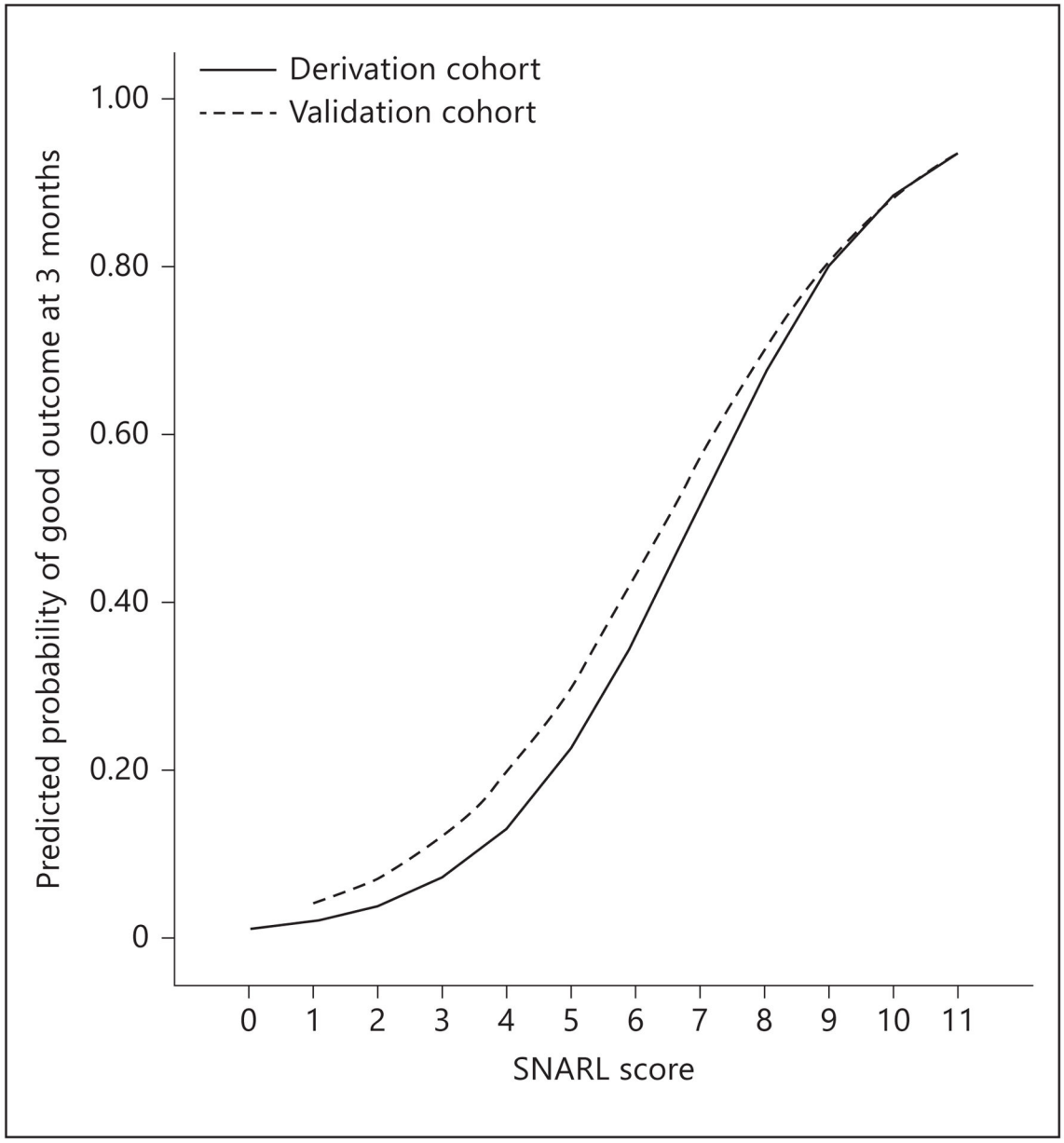

Fig. 2.
Predicted probability of good outcome (modified Rankin score 0–2) across the range of the SNARL score in the derivation and validation datasets.

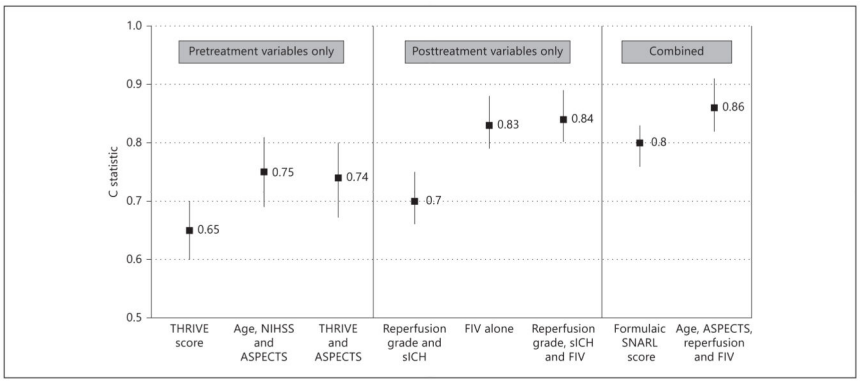

Fig. 3.

Comparison of C statistics for several pretreatment, posttreatment and combined prediction models in the derivation cohort. sICH= Symptomatic hemorrhage; FIV= final infarct volume.

Table 1

Clinical and treatment characteristics of the derivation (n= 511) and validation (n= 223) cohorts

	Derivation cohort	Validation cohort	p value
Mean age (SD), years	65.3 (15.0)	68.1 (15.0)	0.02
Male, n	246 (48.1)	100 (45.0)	0.44
Atrial fibrillation[1], n	161 (31.7)	103 (46.2)	<0.01
Hypertension, n	359 (70.3)	171 (76.7)	0.07
Diabetes mellitus, n	116 (22.7)	57 (25.6)	0.40
Median initial NIHSS score (IQR)	18 (14–22)	18 (14–22)	0.90
Vascular location, n			0.48
ICA	146 (28.6)	58 (26.0)	
Middle cerebral artery (M1)	310 (60.7)	136 (61.0)	
Middle cerebral artery (M2)	55 (10.8)	29 (13.0)	
Intravenous t-PA prior to ERT, n	231 (45.3)	114 (51.4)	0.13
Interhospital transfer, n	284 (55.6)	96 (52.5)	0.47
PH2 sICH, n	36 (7.0)	28 (12.6)	0.02
Final TICI grade, n			<0.01
0	84 (16.4)	18 (8.1)	
1	36 (7.0)	6 (2.7)	
2a	91 (17.8)	36 (16.1)	
2b	227 (44.4)	84 (37.7)	
3	73 (14.3)	78 (35.0)	
Good outcome, n	186 (36.4)	100 (44.8)	0.03

Values in parentheses represent percentages, except where indicated otherwise. IQR= Interquartile range; sICH= symptomatic hemorrhage.

[1]Data missing in 3 patients in the derivation cohort.

Table 2

Comparison of baseline clinical and treatment characteristics in association with good outcome in the full derivation cohort (n= 511)

	Good outcome (n= 186)	Poor outcome (n= 325)	p value
Mean age (SD), years	62.3 (15.0)	67.0 (14.8)	<0.01
Male, n	89 (47.8)	157 (48.3)	0.92
Atrial fibrillation[1], n	56 (30.1)	105 (32.6)	0.56
Hypertension, n	122 (65.6)	237 (72.9)	0.08
Diabetes mellitus, n	35 (18.8)	81 (24.9)	0.11
Median initial NIHSS score (IQR)	16 (12–20)	19 (16–22)	<0.01
Vascular location, n			<0.01
ICA	42 (22.6)	104 (32.0)	
Middle cerebral artery (M1)	113 (60.8)	197 (60.6)	
Middle cerebral artery (M2)	31 (16.7)	24 (7.4)	
Intravenous t-PA prior to ERT, n	95 (51.4)	136 (41.8)	0.04
Interhospital transfer, n	99 (53.2)	185 (56.9)	0.42
PH2 sICH, n	5 (2.7)	31 (9.5)	<0.01
Final TICI grade, n			<0.01
0	9 (4.8)	75 (23.1)	
1	5 (2.7)	31 (9.5)	
2a	18 (9.7)	73 (22.5)	
2b	116 (62.4)	111 (34.2)	
3	38 (20.4)	35 (10.8)	

Values in parentheses represent percentages, except where indicated otherwise. IQR= Interquartile range; sICH= symptomatic hemorrhage.

[1] Data missing in 3 patients.

Table 3

Final multivariable logistic regression model of good outcome at 3 months (modified Rankin score 0–2) according to the SNARL score in the full derivation cohort (n= 511)

Category	β coefficient	Points (0–11)	Adjusted OR (95% CI)	p value
Symptomatic hemorrhage (PH2)				
Yes	reference	0	–	<0.01
No	1.44	2	4.21 (0.08–0.71)	
Baseline NIHSS score				
>20	reference	0	–	<0.01
10–20	0.83	1	2.29 (1.42–3.68)	
<10	2.14	3	8.46 (3.54–20.21)	
Age				
>80 years	reference	0	–	<0.01
60–79 years	0.78	1	2.18 (1.18–4.03)	
<60 years	1.05	2	2.85 (1.51–5.39)	
Reperfusion (TICI 2b or 3)				
No	reference	0	–	<0.01
Yes	2.03	3	7.57 (4.66–12.31)	
Location of occlusion (M2 or distal)				
No	reference	0	–	<0.01
Yes	0.92	1	2.52 (1.29–4.93)	

The Hosmer-Lemeshow test showed good fitness (8 groups and 6 degrees of freedom; p= 0.58).

Table 4

Reclassification of outcome comparing THRIVE and SNARL scores among 731 patients in both the derivation and validation cohorts with all elements available (shaded cells show reclassification)

THRIVE score classification	SNARL score classification good outcome			
	<30% probability	**30–50% probability**	**>50% probability**	**total**
<30% probability	23	10	11	44
30–50% probability	43	30	82	155
>50% probability	4	22	61	87
Total	70	62	154	286

	poor outcome			
	<30% probability	**30–50% probability**	**>50% probability**	**total**
<30% probability	97	20	13	130
30–50% probability	152	33	55	240
>50% probability	31	7	37	75
Total	280	60	105	445