Comparing the Prognostic Impact of Age and Baseline National Institutes of Health Stroke Scale in Acute Stroke due to Large Vessel Occlusion

Stroke

CLINICAL AND POPULATION SCIENCES

Comparing the Prognostic Impact of Age and Baseline National Institutes of Health Stroke Scale in Acute Stroke due to Large Vessel Occlusion

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BACKGROUND AND PURPOSE: Little is known about the combined effect of age and National Institutes of Health Stroke Scale (NIHSS) in endovascular treatment (EVT) for acute ischemic stroke due to large vessel occlusion, and it is not clear how the effects of baseline age and NIHSS on outcome compare to each other. The previously described Stroke Prognostication Using Age and NIHSS (SPAN) index adds up NIHSS and age to a 1:1 combined prognostic index. We added a weighting factor to the NIHSS/age SPAN index to compare the relative prognostic impact of NIHSS and age and assessed EVT effect based on weighted age and NIHSS.

METHODS: We performed adjusted logistic regression with good outcome (90-day modified Rankin Scale score 0–2) as primary outcome. From this model, the coefficients for NIHSS and age were obtained. The ratio between the NIHSS and age coefficients was calculated to determine a weighted SPAN index. We obtained adjusted effect size estimates for EVT in patient subgroups defined by weighted SPAN increments of 3, to evaluate potential changes in treatment effect.

RESULTS: We included 1750/1766 patients from the HERMES collaboration (Highly Effective Reperfusion Using Multiple Endovascular Devices) with available age and NIHSS data. Median NIHSS was 17 (interquartile range, 13–21), and median age was 68 (interquartile range, 57–76). Good outcome was achieved by 682/1743 (39%) patients. The NIHSS/age effect coefficient ratio was ([−0.0032]/[−0.111])=3.4, which was rounded to 3, resulting in a weighted SPAN index defined as ([3×NIHSS]+age). Cumulative EVT effect size estimates across weighted SPAN subgroups consistently favored EVT, with a number needed to treat ranging from 5.3 to 8.7.

CONCLUSIONS: The impact on chance of good outcome of a 1-point increase in NIHSS roughly corresponded to a 3-year increase in patient age. EVT was beneficial across all weighted age/NIHSS subgroups.

GRAPHIC ABSTRACT: An online graphic abstract is available for this article.

Key Words: ischemic stroke ■ National Institutes of Health ■ patients ■ thrombectomy

Patient age and the National Institutes of Health Stroke Scale (NIHSS) are the 2 clinical factors with the most robust evidence regarding their impact on outcome in patients with acute ischemic stroke.[1–6] While it is clear that patients with high baseline NIHSS and older patients generally suffer worse

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Nonstandard Abbreviations and Acronyms

(w)SPAN	(weighted) Stroke Prognostication Using Age and NIHSS index
AIC	Akaike Information Criterion
EVT	endovascular treatment
IQR	interquartile range
NIHSS	National Institutes of Health Stroke Scale

outcomes, little is known about the combined effect of age and NIHSS, which is neither explicitly addressed in current endovascular treatment (EVT) guidelines nor in past and ongoing randomized trials. Furthermore, it is not entirely clear how the effects of baseline age and NIHSS on outcome compare to each other, that is, how much increase in patient age leads to an equal worsening in prognosis compared with a one-point NIHSS increase and vice versa.

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Weighing the prognostic impact of patient age and NIHSS against each other would be of great interest for physicians who are treating acute ischemic stroke patients, as it could support their treatment decision-making and could guide communication with family members on likely poststroke outcomes and the expected degree of disability.

Saposnik et al[7] have described the Stroke Prognostication Using Age and NIHSS (SPAN) index to estimate clinical response and complication risks for acute ischemic stroke patients treated with intravenous alteplase. The SPAN index is calculated by simply adding patient age and baseline NIHSS, that is, one point in the NIHSS score has equal weight compared with 1 year of patient age. The authors were able to show that a SPAN index >100 was associated with increased risk of hemorrhagic complications and decreased clinical benefit in AIS patients treated with intravenous alteplase.[7] In another study, Almekhlafi et al have shown that AIS patients undergoing EVT were less likely to achieve a favorable outcome if their SPAN index exceeded 100.

However, the SPAN index does not address the relative importance of NIHSS compared with patient age, and no studies have investigated whether there are certain age/NIHSS combinations in which EVT is of no benefit or even harmful. We aimed to modify the SPAN index according to the relative prognostic impact of patient age and NIHSS (weighted SPAN index [wSPAN]), compared the predictive utility of wSPAN and SPAN, and assessed EVT treatment effect in patient subsets with different wSPAN.

METHODS

The data underlying the analyses reported in this article will be made available by the corresponding author upon reasonable request after approval by the HERMES executive committee. This study was conducted according to the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis statement (see checklist in the Data Supplement).[8]

Patient Sample

The HERMES collaboration pooled patient data of 7 randomized controlled trials that investigated safety and efficacy of EVT in patients with acute ischemic stroke (n=1766).[4,9–15] Inclusion criteria of the individual trials have been previously published.[9–15] Patients who were randomized to the control arm received usual care, including intravenous alteplase if indicated. Those randomized to the intervention arm were treated with additional EVT. Baseline NIHSS was assessed upon patient arrival by the local stroke neurologist in charge. Ethics approval was obtained from the local institutional ethics committees of the principal investigators' sites. Patient consent was obtained unless the local boards allowed for deferral of consent. The current study includes all HERMES patients with available age and baseline NIHSS data.

Outcomes of Interest

The primary outcome of interest was good outcome, defined as modified Rankin Scale (mRS score: ranging from 0 [no symptoms] to 6 [death]) of 0–2, measured at 90 days post-stroke. Secondary outcome measures were excellent outcome defined as mRS score 0–1, and moderate outcome defined as mRS score 0–3.

Statistical Analysis

To compare the impact of a 1-year increase in age to a 1-point increase in NIHSS on primary and secondary outcomes, adjusted logistic regression was performed in the entire patient sample, and the effect coefficients for age and NIHSS were obtained. Regression analyses (unadjusted and adjusted) were repeated with a multiplicative interaction term (age×NIHSS) to assess for interaction between the 2 variables. Significant interaction would indicate a nonlinear optimal model and hence, a nonconstant NIHSS-age coefficient ratio. Similarly, adjusted interaction analysis between wSPAN and EVT versus control arm treatment was performed to assess whether the association between wSPAN and outcome differed between treatment arms. Next, the ratio of the NIHSS and age coefficients (NIHSS coefficient ÷ age coefficient) was calculated and used to determine the weighting for the wSPAN index. For example, an NIHSS/age coefficient ratio of 5 would indicate a 5-fold weighting of NIHSS compared with age, while an NIHSS/age coefficient of 0.5 would indicate a 2-fold weighting of age compared with NIHSS.

Adjusted models including the wSPAN (model 1) and SPAN (model 2) indices were then compared with respect to their predictive utility for primary and secondary outcomes by calculating and comparing their area under the curve, Bayesian information criterion, and Akaike Information Criterion in the entire patient sample, in the EVT and the control arm, respectively.

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Last, cumulative proportions for good, moderate, and excellent outcome were calculated for patient subgroups defined by the smallest number of wSPAN increments with a meaningful clinical correlate (eg, with an increase of at least one whole point of both age and NIHSS). Effect size estimates for EVT for these subgroups were obtained and compared to evaluate potential changes in treatment effect. Cumulative percentages of good outcome in the EVT and control arms were calculated for each patient subgroup. For example, the percentage of good outcome in patients with wSPAN ≥ x was calculated, and in the next step, the percentage of good outcome in patients with wSPAN ≥ (x+i) was calculated whereby i indicates the fixed increment, and so forth. Proportions of good outcome were then individually plotted to visualize treatment effect over the full wSPAN spectrum.

All analyses were adjusted for patient sex, intravenous alteplase treatment, time from stroke onset to randomization, comorbidities (atrial fibrillation, diabetes, and hypertension), and occlusion site (internal carotid artery versus M1 versus M2). Imputation was not used as the amount of missing data for age, ASPECTS, and mRS at 90 days was minimal. All statistical tests were 2-sided, and conventional levels of significance (α=0.05) were used for interpretation. SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria) were used for data analysis.

RESULTS

Of the 1766 patients from the HERMES collaboration, 1750 were included in the analysis (Figure I in the Data Supplement). Patient baseline characteristics, treatment, and clinical outcomes have been described previously.[16] Median NIHSS was 17 (interquartile range [IQR], 13–21) and median age was 68 (IQR, 57–76). In the control arm, median NIHSS was 17 (IQR, 13–21) and median age was 68 (IQR, 58–76), while in the EVT arm, median NIHSS was 17 (IQR, 14–20) and median age was 67 (IQR, 57–76). A good outcome (mRS score 0–2) at 90 days was achieved by 682/1743 (39%) patients; by 268/877 (31%) in the control arm and 414/866 (48%) in the EVT arm. There was no evidence of interaction between age and NIHSS with regard to the primary or any of the secondary outcomes (Table I in the Data Supplement).

Generating the wSPAN Index

Effect coefficients for 1-point NIHSS increase were consistently higher than the coefficients for a 1-year increase in patient age, resulting in NIHSS/age effect coefficient ratios of 3.4 (for good outcome), 2.1 (for moderate outcome), and 7.7 (for excellent outcome, see Table 1). Based on the results shown in Table 1, we used the effect coefficient ratio for the primary outcome that ranked between the 2 coefficient ratios of the secondary outcomes, as a basis for the wSPAN index, which translated into a weighting of 3 in favor of NIHSS (ie, wSPAN=age +[3×NIHSS]). The ratio was rounded to an integer number for the sake of practicability.

Table 1. Effect Coefficient Ratios of Age and NIHSS for Primary and Secondary Outcomes in the Entire Patient Sample*

Outcome	Effect coefficient for a 1-year increase in patient age	Effect coefficient for a 1-point increase in baseline NIHSS	NIHSS/age effect coefficient ratio†
mRS score 0–2 at 90 d	−0.032	−0.111	3.4
mRS score 0–1 at 90 d	−0.012	−0.095	7.7
mRS score 0–3 at 90 d	−0.045	−0.096	2.1

The results indicate that a 1-point of NIHSS corresponds to roughly 3 y of age as a predictor of good outcome. mRS indicates modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

*Effect coefficients were obtained from binary logistic regression models with adjustment for patient sex, baseline NIHSS, intravenous alteplase treatment (yes/no), endovascular treatment (yes/no), time from stroke onset to randomization, comorbidities (atrial fibrillation, diabetes, and hypertension), and occlusion site (internal carotid artery vs M1 vs M2).

†Rounded to once decimal point.

Comparing wSPAN and SPAN

Adjusted comparison of the wSPAN and SPAN indices showed better discrimination and decreased information loss with the wSPAN index for the primary and both secondary outcomes in the overall patient sample (Figure 1, Table 2) and when patients were stratified by treatment arm (Table 2).

Treatment Effect of EVT for Different Age/NIHSS Subgroups

To assess whether and to which extent EVT treatment effect varies in patient subsets with different wSPAN and to evaluate if there is a wSPAN cutoff above which no treatment benefit with EVT is seen, cumulative proportions of good outcome in the EVT and control arm were calculated across the wSPAN spectrum. We found no evidence that the effect of wSPAN on chances of good outcome differed by treatment arm (interaction *P*=0.858). While cumulative proportions of good outcome decreased with higher wSPAN, the difference between both arms was largely maintained (Figure 2). Figure II in the Data Supplement shows the cumulative outcome proportions for the original SPAN index. Cumulative effect size estimates that were calculated based on 3-point increments in wSPAN consistently favored EVT, with a number needed to treat ranging from 5.3 to 8.7 (Table II in the Data Supplement).

DISCUSSION

In this randomized sample of acute ischemic stroke patients with large vessel occlusion, the impact on chance of good outcome of a 1-point increase in NIHSS

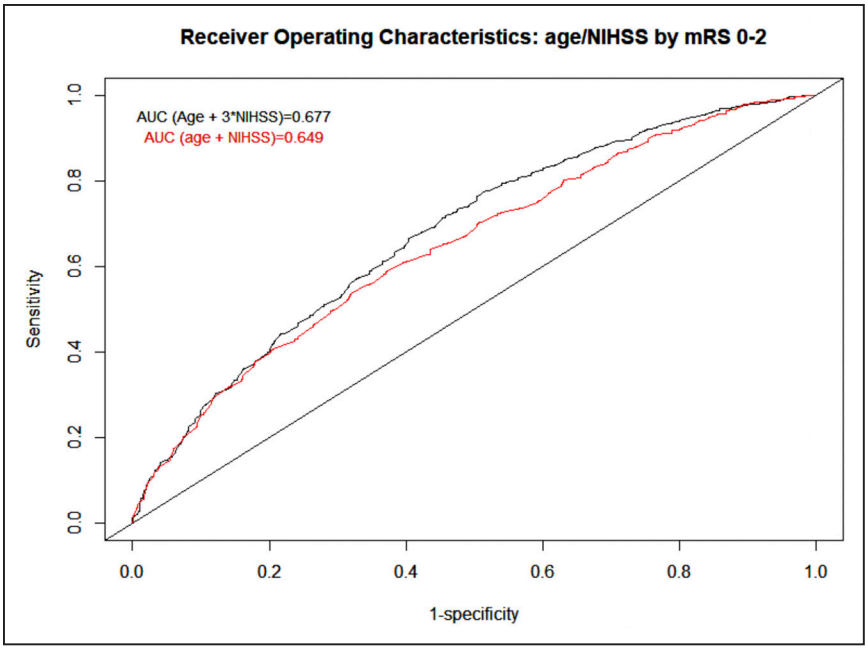

Figure 1. Area under the curve (AUC) of adjusted weighted Stroke Prognostication Using Age and National Institutes of Health Stroke Scale (NIHSS) index (wSPAN; black line) and SPAN (red line) models in the overall patient sample for modified Rankin Scale (mRS) score 0–2 (primary outcome).
The AUC for SPAN and wSPAN was 0.649 (95% CI, 0.623–0.675) and 0.677 (95% CI, 0.651–0.703), respectively; *P*<0.001.

roughly corresponded to a 3-year increase in patient age. The absence of a significant age×NIHSS interaction term suggests that this relative weighting of age and NIHSS remains valid across the entire age/NIHSS spectrum. Taking this relationship into account in the form of a weighted wSPAN index improved outcome prediction slightly compared with the previously described SPAN index, which adds up age and NIHSS without a weighting factor. There was no wSPAN cutoff above which effect size estimates did not favor EVT.

Numerous factors have been shown to influence patient outcome in the acute ischemic stroke setting. However, some of these associations are rather weak and might not necessarily be relevant for treatment decision-making and estimating patient prognosis in the clinical setting. Besides time to treatment, 2 factors that have consistently been

Table 2. AUC, AIC, and BIC of Adjusted wSPAN and SPAN Models for Primary and Secondary Outcomes in the Entire Patient Sample and After Stratification by Endovascular Treatment

Outcome	Index used*	Treatment	Area under the curve (95% CI)	$_{adj}$AIC	$_{adj}$BIC
mRS score 0–2	SPAN	All patients	0.649 (0.623–0.675)	2049.2	2048.9
		EVT	0.649 (0.612–0.685)	1080.7	1080.3
		No EVT	0.658 (0.618–0.697)	983.5	983.1
mRS score 0–2	wSPAN	All patients	0.677 (0.651–0.703)	2008.8	2008.2
		EVT	0.672 (0.636–0.708) *P*=0.010	1065.2	1064.8
		No EVT	0.695 (0.656–0.733) *P*<0.001	956.6	956.2
mRS score 0–1	SPAN	All patients	0.588 (0.557–0.619)	1697.7	1697.2
		EVT	0.568 (0.527–0.609)	977.6	977.2
		No EVT	0.619 (0.569–0.668)	737.2	736.8
mRS score 0–1	wSPAN	All patients	0.625 (0.594–0.656)	1671.5	1671.0
		EVT	0.606 (0.565–0.647) *P*<0.001	964.2	963.8
		No EVT	0.659 (0.610–0.708) *P*=0.001	723.1	722.7
mRS score 0–3	SPAN	All patients	0.676 (0.651–0.701)	2096.7	2096.4
		EVT	0.658 (0.621–0.696)	1039.4	1038.9
		No EVT	0.701 (0.667–0.735)	1059.1	1058.6
mRS score 0–3	wSPAN	All patients	0.691 (0.666–0.715)	2084.4	2083.9
		EVT	0.671 (0.634–0.708)	1035.2	1034.7
		No EVT	0.718 (0.684–0.752) *P*=0.055	1048.0	1047.6

$_{adj}$AIC indicates adjusted Akaike Information Criterion; $_{adj}$BIC, adjusted Bayesian information criterion; EVT, endovascular treatment; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.
*P values are shown in case of a significant difference between the wSPAN and SPAN models.

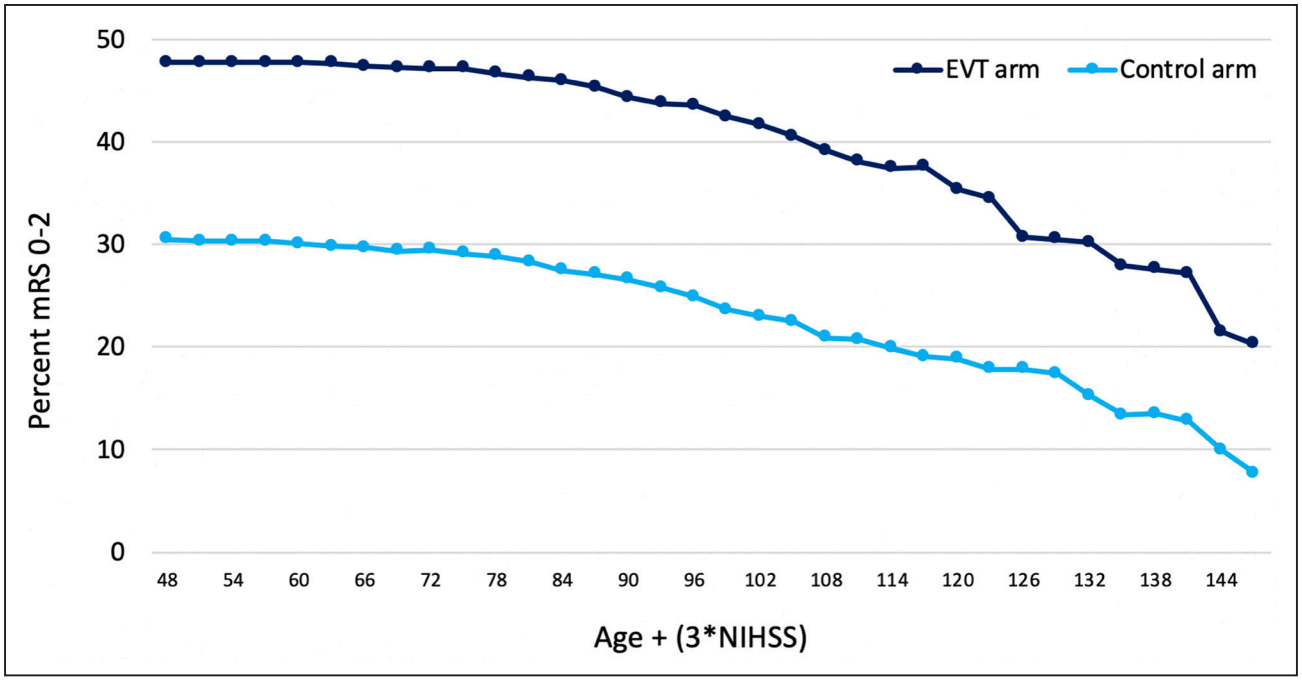

Figure 2. Cumulative proportions of good outcome (modified Rankin Scale [mRS] score 0–2 at 90 d) in the endovascular treatment (EVT) arm (dark blue line) and control arm (light blue line), as shown on the *y* axis for different weighted Stroke Prognostication Using Age and National Institutes of Health Stroke Scale (NIHSS) index (wSPAN) scores, as shown on the *x* axis. With increasing wSPAN, the cumulative proportion of good outcomes decreases in the EVT and the control arm but the difference between the 2 arms is largely maintained.

shown to have a large influence on patient outcome are age and symptom severity, as measured by the NIHSS scale.[1–6] The SPAN index, which adds patient age and baseline NIHSS, was created to provide a simple and straightforward prognostic tool for clinicians. While the SPAN is indeed much easier to calculate than other prognostic scores, which often require physicians to enter numerous values into a web interface,[17,18] it does not address the relative importance of age and NIHSS: since NIHSS and age get simply added up, 1 year of increase in patient age is considered as impactful as a 1-point increase in NIHSS, which results in a rather arbitrary 1:1 weighting of the 2 variables. Our results show that the prognostic impact of a 1-point increase in NIHSS roughly corresponds to a 3-year increase in patient age. A comparison of the wSPAN and SPAN indices revealed a slightly though significantly improved predictive performance of wSPAN, in the overall patient sample as well as in the EVT and control arms, respectively, suggesting that the 3:1 ratio remains valid irrespective of treatment. Effect coefficient ratios that were obtained for the secondary outcomes were somewhat different, but nevertheless, outcome prediction using wSPAN was slightly better compared with SPAN for all secondary outcomes, raising the question whether physicians should use a weighted index rather than merely adding age and NIHSS. However, we do acknowledge that the relatively minor improvement in outcome prediction might not necessarily justify modifying the SPAN index.

Probably more importantly than the index itself is the fact that this study gives us some insight into the association of age and NIHSS and their relative impact on patient outcomes; as it shows that the prognostic impact of 1-point NIHSS increase roughly corresponds to a 3-year increase in age.

A recent study from the STAR registry (Stroke Thrombectomy and Aneurysm Registry) has shown that a (unweighted) SPAN index >100 is associated with significantly lower odds of achieving good outcome following EVT,[2] but so far, no studies have investigated how the combination of age and NIHSS affects EVT treatment effect. In keeping with previously published literature,[2] overall cumulative proportions of good outcome in this study decreased with increasing age and NIHSS and, therefore, with increasing wSPAN, but the difference in proportions of good outcome between the EVT and control arms was largely maintained. This was supported by the observation that cumulative effect size estimates across a range of wSPAN cutoffs consistently favored EVT. If anything, the effect of EVT seemed to be more pronounced in patients with higher wSPAN (Table II in the Data Supplement), suggesting that there is no evidence to withhold EVT based on a combination of patient age and baseline NIHSS.

Limitations

This study has several limitations. First, the NIHSS/age weighting that was chosen for the wSPAN index was rounded and therefore did not correspond to the exact effect coefficient ratio; and it would have been different had we chosen another primary outcome. However,

outcome prediction with respect to primary and secondary outcomes was improved when wSPAN was used, supporting the choice of the weighting factor. Second, predicting outcomes using only 2 baseline variables may be considered overly simplistic, since other clinical baseline variables, such as time from symptom onset[19] and atrial fibrillation[20,21] are also known to impact post-stroke outcomes; but these variables are not infrequently unknown at the time of admission. Third, the HERMES collaboration pooled data from 7 randomized controlled EVT trials, each of which had their own subset of inclusion and exclusion criteria. In particular, the ESCAPE trial (Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke) enrolled patients up to 12 hours,[12] while the other 4 trials restricted enrollment to patients presenting within 6 hours from last seen well, and 3 of the 7 trials in HERMES applied upper age limits for enrollment. Considering the rather stringent inclusion criteria of most trials and given the expanding EVT indications in the late time window,[22] it is likely that most acute ischemic stroke patients treated with EVT nowadays differ in their baseline characteristics from our patient sample, and our results might therefore not be fully generalizable to current clinical routine. Fourth, this analysis assumed a linear relationship of age and NIHSS with outcome, which is an assumption that probably does not hold true in clinical reality. However, our goal was not necessarily to accurately model these relationships, we aimed to determine a better ratio for the combination of age and NIHSS than the commonly used 1:1 ratio, and the improved predictive power of the identified 3:1 ratio confirms that this was possible. Fifth, knowing with certainty whether the wSPAN index consistently outperforms SPAN or not will require validation in further data sets. Sixth, the overall discrimination of the models described was modest, with area under the curve values mostly below 0.7. Last, future studies that attempt to classify patients into risk categories based on their wSPAN index will need to undergo both internal and external validation.

Conclusions

In this randomized sample of acute ischemic stroke patients with large vessel occlusion, the impact of a 1-point increase in NIHSS on clinical outcomes roughly corresponded to a 3-year increase in patient age. No weighted age/NIHSS cutoff was identified above which EVT was not beneficial, and there was no significant multiplicative interaction of age and NIHSS on outcomes, suggesting that EVT should not be withheld based on a combination of age and NIHSS.

ARTICLE INFORMATION

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Supplemental Materials

Online Tables I–II
Online Figures I–II
TRIPOD checklist

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