

Prediction of Large Vessel Occlusions in Acute Stroke: National Institute of Health Stroke Scale Is Hard to Beat

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Objectives: Endovascular treatment for acute ischemic stroke with a large vessel occlusion was recently shown to be effective. We aimed to develop a score capable of predicting large vessel occlusion eligible for endovascular treatment in the early hospital management.

Design: Retrospective, cohort study.

Setting: Two tertiary, Swiss stroke centers.

Patients: Consecutive acute ischemic stroke patients (1,645 patients; Acute STroke Registry and Analysis of Lausanne registry), who had CT angiography within 6 and 12 hours of symptom onset, were categorized according to the occlusion site. Demographic and clinical information was used in logistic regression analysis to derive predictors of large vessel occlusion (defined as intracranial carotid, basilar, and M1 segment of middle cerebral artery occlusions). Based on logistic regression coefficients, an integer score was created and validated internally and externally (848 patients; Bernese Stroke Registry).

Interventions: None.

Measurements and Main Results: Large vessel occlusions were present in 316 patients (21%) in the derivation and 566 (28%) in the external validation cohort. Five predictors added significantly to the score: National Institute of Health Stroke Scale at admission, hemineglect, female sex, atrial fibrillation, and no history of stroke and prestroke handicap (modified Rankin Scale score, < 2). Diagnostic accuracy in internal and external validation cohorts was excellent (area under the receiver operating characteristic curve, 0.84 both). The score performed slightly better than National Institute of Health Stroke Scale alone regarding prediction error (Wilcoxon signed rank test, $p < 0.001$) and regarding discriminatory power in derivation and pooled cohorts (area under the receiver operating characteristic curve, 0.81 vs 0.80; DeLong test, $p = 0.02$).

Conclusions: Our score accurately predicts the presence of emergent large vessel occlusions, which are eligible for endovascular treatment. However, incorporation of additional demographic and historical information available on hospital arrival provides minimal incremental predictive value compared with the National Institute of Health Stroke Scale alone. (*Crit Care Med* 2016; XX:00–00)

Key Words: cerebral revascularization; endovascular procedure; intracranial arterial disease; stroke

Recently, the clinical benefit of endovascular revascularization therapy has been established by randomized, controlled trials for patients with an acute ischemic stroke (AIS) and a large vessel occlusion (LVO) (1–3). These emergent LVOs are well-known predictors of poor outcome (4–7), and rapid revascularization remains a primordial factor to improve clinical outcome (8, 9). In the continuum of prehospital triage, choice of treatment center and revascularization method, and early intensive stroke unit care, the appropriate decisions should be based on rational choices (10). These will be best realized by a multidisciplinary stroke team composed of an well-organized emergency medical system and physicians, diagnostic and interventional neuroradiologic expertise, and neurovascular intensive care teams (11).

So far, only time from onset to angiography, stroke severity (measured by National Institute of Health Stroke Scale [NIHSS]), and stroke classification by the Oxford Community Stroke Project clinical classification were found to predict LVO (12–16). A large arterial occlusion on angiography was found in approximately 80% of patients with baseline NIHSS score of more than 8–10, especially in anterior circulation strokes and within the first hours of symptom onset (8, 12). Given that sensitivities of the NIHSS score cutoffs are rather low (17) and their validity decreases with increasing time from symptom onset to clinical evaluation, we sought to identify other predictors (18). Additional demographic and clinical predictors for the presence of LVO eligible for endovascular treatment (EVT) are, therefore, needed to develop a preclinical triage tool.

PATIENTS AND METHODS

Study Design and Patient Selection

The scoring tool was derived from a cohort of consecutive AIS patients of the Acute STroke Registry and Analysis of Lausanne (ASTRAL) (19). For the current analysis, we selected all ASTRAL patients from January 2003 to July 2012 with acute CT angiography (CTA) performed within 12 hours after last seen well. CTA is performed in all patients without iodized contrast contraindications, such as known allergy or known renal failure. In the original ASTRAL article, 78% of all ischemic strokes had a CTA on arrival (19). The 12-hour time limit was based on a recent publication of the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke-2 investigators where they identified a maximal therapeutic time window of 12 hours for patients with a target mismatch (20).

The derived predictive score was validated externally in an independent cohort from the Bernese Stroke Registry (January 2004 to August 2012) (16).

For the current study, only variables assessable in the pre-hospital phase were selected, that is, demographics, cardiovascular risk factors, comorbidities, prestroke medication, type of clinical deficit, NIHSS and all its individual items, onset-to-admission delay, and physiologic values (blood pressure, heart rate, temperature, and glucose). The initial, total NIHSS score was performed by NIHSS-certified stroke physicians or was supervised by such. In addition, the NIHSS subitems were dichotomized into the presence or absence of the neurologic deficit. The clinical sign “hemineglect” was used according to the NIHSS definition. Stroke mechanism was categorized following the Evolution Study 2, “Trial of Org 10172 in Acute Stroke Treatment” classification, and dissection was added as a stroke mechanism.

The collection, analysis, and publication of data in ASTRAL and the Bernese Stroke Registry were approved by the respective ethical commissions. According to Swiss regulations, individualized informed consent is not required for routinely collected clinical and radiologic data as used in these registries.

Neuroimaging Protocol

From 2003 to November 2005, the acquisition of cerebral and cervical angio-CT in the derivation cohort was performed on a 16-detector scan with a slice thickness of 1.25 mm. Thereafter, this scanner has been replaced by a 64-detector scan with some improved characteristics (e.g., slice thickness of 0.63 mm). Initial stroke MRI protocol in Bernese Stroke Registry included diffusion weighted imaging, T2-weighted imaging, time-of-flight (TOF) magnetic resonance angiogram (MRA), first-pass gadolinium-enhanced MRA of the cervical and intracranial arteries, and perfusion imaging on 1.5-T MRI. Since January 2010, fluid-attenuated inversion recovery and susceptibility-weighted imaging (SWI) imaging have been performed on 3-T MRI system (Magnetom Avanto and Magnetom Verio; Siemens, Erlangen, Germany).

Analysis of the arterial imaging was done by a neuroradiologist and a vascular neurologist who were aware of the neurologic deficit. Occlusion was defined as absent filling of examined arterial segment during the initial acquisition of contrast medium images, and the presence and the site of LVOs and intra- and extracranial stenoses greater than or equal to 50% were recorded as described previously (19). Intracranial occlusions in the ischemic territory were categorized according to their site in “large” versus “intermediate” occlusions. Large intracranial, endovascular treatable occlusions were defined as an occlusion of the basilar artery (with or without intracranial vertebral artery occlusion), the intracranial carotid siphon including the carotid T, and the M1 segment of the middle cerebral artery (MCA) before its bifurcation, with and without ipsilateral carotid occlusion. Intermediate intracranial occlusions were defined as occlusions in anterior cerebral artery (A1 or A2 segments), peripheral MCA (M2), posterior cerebral artery (P1 or P2 segments), intracranial part of the vertebral

artery (V4), and siphon of the internal carotid artery without distal T occlusion; the latter two were considered “intermediate” because thrombus load and clinical symptoms are usually minor in the absence of extension into the basilar artery and the carotid T, respectively. M2 occlusions were considered “intermediate” because of the different outcome and treatment strategy in comparison with M1 MCA occlusions (6, 7). In contrast to the exclusive use of CTA in the derivation cohort, either acute CTA or acute MRA were performed in the Bernese Stroke Registry cohort. Vascular imaging was performed during or immediately after starting IV thrombolysis (IVT) in the imaging facility. It was assumed that this short delay would not influence arterial pathology significantly.

Statistical Analysis

Univariate comparisons between AIS patients with and without LVO were performed for all the variables collected. Then, major predictors of LVO were identified by multiple logistic regression analysis of all candidate variables. We aimed to build a score with a high discriminatory power, as measured by the area under the receiver operating characteristic curve (ROC) (AUC). Accordingly, variable selection was done via AUC maximization, using multifold cross validation (MCV) in order to enhance reproducibility of the results. MCV was implemented by doing a 10-fold random partition of the derivation cohort. A model was built by leaving one part out of the fitting process and using it to calculate AUC, then repeating the operation leaving the next part out, and so on. Variables were included stepwise into the model, until no new variable reduced the summed AUCs (summing over the 10 left-out parts). The random partition process was repeated 500 times, giving rise to 500 different models. Then, the best-of-500 model was identified via MCV as the model with the highest sum of AUCs over 10 new 10-fold random partitions of the derivation cohort. There was no collinearity problem in the final model (maximal variance inflation factor of covariates, 1.16).

Statistical analysis was performed with R statistical software (version 2.15.1, R Core Team [2012], R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics

During the observation period (2003–2012), 2,765 patients were entered in the ASTRAL registry. Of them, 1,120 (40%) were excluded from the analysis because vascular imaging was performed more than 12 hours after symptom onset ($n = 672$, 24%) and/or because of a lack of a good quality CTA ($n = 494$; 18%). The external validation cohort from the Bernese Stroke Registry contained 2,023 AIS patients between January 2004 and August 2012. In this cohort, patients underwent MRA ($n = 1,544$, 73%), CTA ($n = 519$, 25%), or both ($n = 47$, 2%) within 24 hours. Of this patient sample, 1,175 patients (58%) were excluded because one or more of the covariates of the score were absent ($n = 1,037$, 51%), data on the vessel status were unavailable ($n = 87$, 4%), or vascular imaging was performed later than 12 hours after symptom onset ($n = 51$, 3%).

Comparison of data from patients excluded from the study shows similar patient profiles between the included and the radiologic and/or treatment-related excluded strokes.

The demographic and baseline characteristics of the derivation and validation cohorts are described in **Table 1**. The derivation cohort (316, 21%) had a lower percentage of LVO than the internal validation cohort (566, 28%). As expected, the median NIHSS score was higher in the group of LVO than in the group without (17 vs six derivation cohort and 16 vs five validation cohort; $p < 0.01$). The percentages of LVO patients having a NIHSS score of 0–4, 5–9, 10–14, and greater than or equal to 15 was 2.7%, 8.3%, 32.3%, and 47.5%, respectively, in the derivation cohort and 4.4%, 13.8%, 43.7%, and 61.6%, respectively, in the validation cohort. The median time from symptom onset to hospital arrival in the group of patients with a LVO was similar in both cohorts (145 min in ASTRAL and 124 min in Bernese Stroke Registry). Cardiac emboli were most frequent ($n = 556$, 33%), followed by atherosclerotic disease ($n = 243$, 14%), unknown etiology ($n = 410$, 25%), lacunar pathology ($n = 158$, 10%), dissection ($n = 94$, 6%), multiple ($n = 82$, 5%), and rare causes ($n = 67$, 4%). Cerebral imaging was performed within 6 hours in most patients in ASTRAL ($n = 1,225$, 75%). In the derivation cohort, IVT alone was performed in 526 patients (32%) within 4.5 hours and EVT in 43 (3%) within 6 hours; of those, 21 were pretreated with IVT. In the validation cohort, IVT alone was performed in 154 patients (18%), EVT alone in 218 (26%), and combined treatment in 43 (5%).

Development of the Score and Internal Validation

Our selection method identified five relevant predictors of LVO eligible for EVT: NIHSS at admission (odds ratio [OR]: 1.16, uncategorized), hemineglect (OR, 2.24), the absence of prestroke handicap (OR, 1.62), female sex (OR, 1.50), and atrial fibrillation (OR, 1.38). An uncategorized NIHSS score seemed to be the most adequate. The discriminatory power of each individual variable and its added value for the score has been identified (**Supplemental Table 1**, Supplemental Digital Content 1, <http://links.lww.com/CCM/B683>).

For each covariate in the model, integer score points were defined according to the proportionality with the β coefficients: admission NIHSS (1 point for every 1 NIHSS point: 0 to > 42), the absence of prestroke handicap (modified Rankin Scale score, ≤ 2) (3 points), hemineglect (5 points), atrial fibrillation historically or currently (2 points), and female sex (3 points) (**Table 2**).

Figure 1 displays the predicted probability of an LVO based on the score (top) and the sensitivity and positive predictive value (PPV) as a function of cutoff position (bottom) in the derivation cohort. The predicted probability of detecting an LVO with a score of 10, 20, 30, or 40 was 6.7%, 24.0%, 58.0%, and 85.8%, respectively.

External Validation of the Score

The diagnostic performance of the score in the derivation and validation cohorts is shown in **Table 3** (top). The

TABLE 1. Baseline Characteristics and Radiologic Findings in the Derivation and Validation Cohorts, Dichotomized According to the Presence or the Absence of a Large Vessel Occlusion

Clinicoradiological Parameters	Derivation Cohort		Validation Cohort	
	No LVO (n = 1,299)	LVO (n = 346)	No LVO (n = 575)	LVO (n = 273)
Demographics				
Age	70 (59–79)	70 (59–79)	68 (57–77)	71 (59–79)
Female sex (%)	491 (38)	180 (52)	398 (66)	147 (54)
Medical history (%)				
Atrial fibrillation	275 (21)	110 (32)	109 (19)	109 (40)
Arterial hypertension	761 (59)	178 (51)	374 (65)	172 (63)
Hypercholesterolemia	793 (59)	193 (55)	310 (54)	131 (48)
Previous stroke or transient ischemic attack	364 (28)	67 (19)	98 (17)	25 (9)
Clinical assessment on arrival				
Onset-to-arrival time	211 (124–392)	145 (98–256)	152 (90–264)	124 (77–207)
Baseline National Institute of Health Stroke Scale	6 (3–12)	17 (13–21)	5 (3–10)	16 (12–21)
Decreased level of consciousness (%)	116 (9)	86 (25)	75 (13)	123 (45)
Visual field defects (%)	375 (31)	222 (70)	155 (27)	172 (63)
Vessel occlusion site (%)				
Any vessel occlusion	380 (32)	316 (100)	259 (45)	273 (100)
Intracranial vessel occlusion	333 (28)	316 (100)	236 (41)	273 (100)
Anterior circulation occlusion	286 (24)	291 (92)	201 (35)	221 (81)
Posterior circulation occlusion	83 (7)	25 (8)	46 (8)	52 (19)

LVO = large vessel occlusion.

Values are expressed as medians and interquartile range for continuous variables unless stated otherwise and as absolute counts and percentage for categorical variables.

TABLE 2. Predictive Score for Large Vessel Occlusion: Variables Used to Define the Score, With Corresponding Scoring Points

Variable	OR	95% CI	β Coefficient	Score Point
National Institutes of Health Stroke Scale on admission (per point)	1.16	1.13–1.18	0.15	1
No prestroke handicap (modified Rankin Scale score, ≤ 2)	1.62	0.86–3.04	0.48	3
Atrial fibrillation (history or current)	1.38	1.00–1.90	0.32	2
Hemineglect	2.24	1.65–3.05	0.81	5
Female sex	1.50	1.11–2.04	0.41	3

OR = odds ratio.

discriminatory power of the score was excellent in both cohorts (AUC, 0.84). By maximizing the sum of sensitivities and PPVs in the two cohorts and imposing lower bounds on sensitivities and PPVs (0.8 and 0.4, respectively), a cutoff value of 16 was derived as having the best clinical potential. The rationale behind the criterion for cutoff determination is to miss as few treatable patients as possible (hence the sensitivity

maximization) at the same time as minimizing the probability that a patient identified as treatable is in fact nontreatable (hence the PPV maximization).

The sensitivity curves in Figures 1 and 2 are similar, but the PPV is generally higher in the validation cohort because of a higher rate of LVOs (29% in the validation cohort vs 21% in the derivation cohort).

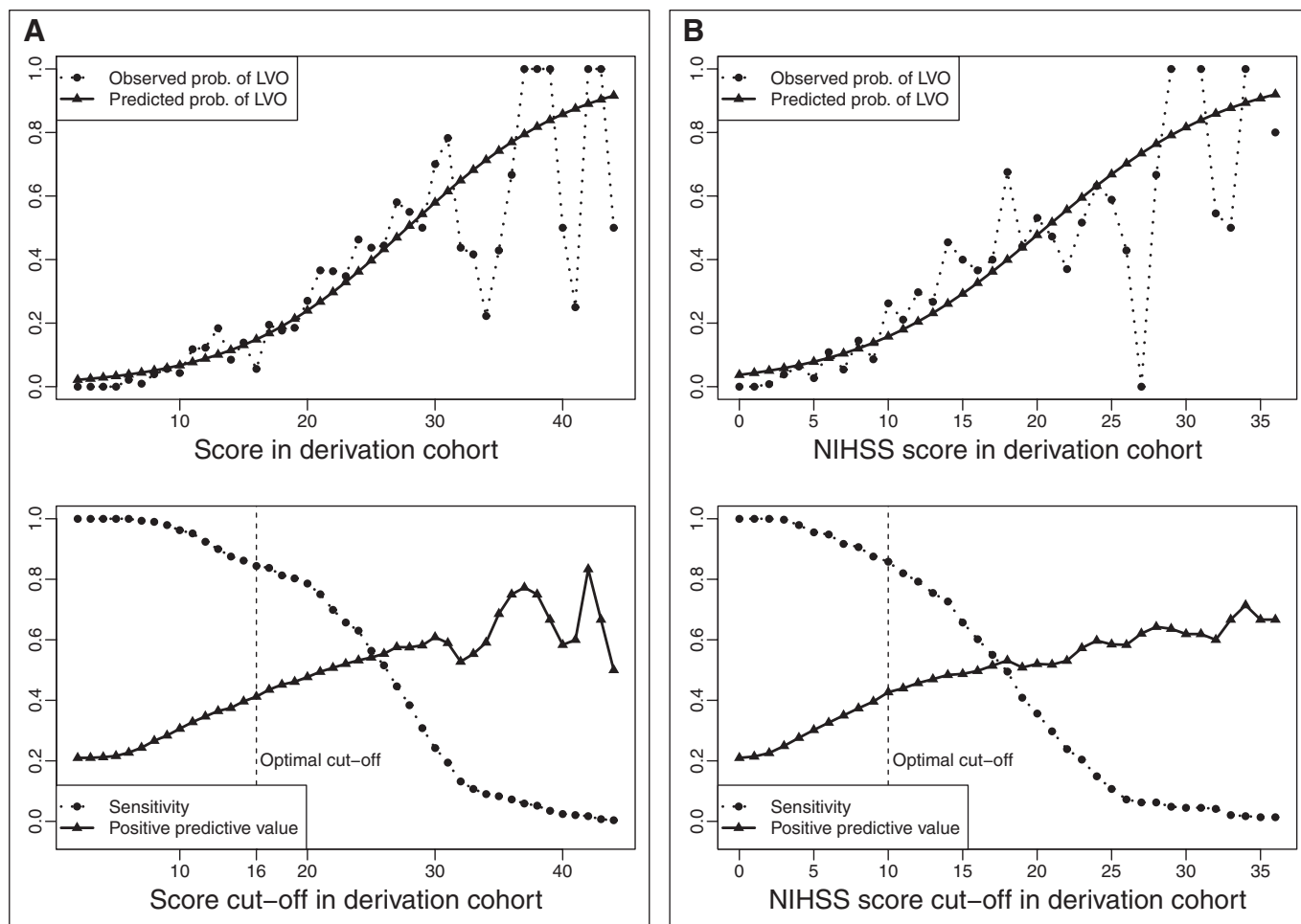


Figure 1. Actual rate and predicted probability (*top*) and sensitivity and positive predictive value with optimal cutoff values (*bottom*) of the score (**A**) and of National Institute of Health Stroke Scale (NIHSS)-based prediction (**B**) of the large vessel occlusion presence in the derivation cohort. MIO = major intracranial occlusion.

Comparison of the Score With NIHSS-Only-Based Prediction

The predicted probabilities of LVO, sensitivities, specificities, PPVs, negative predictive values, and AUCs were calculated for the predictive accuracy of the score and the NIHSS score to predict LVOs eligible for EVT. Overall, the two scores perform

similarly in both the derivation and the validation cohorts as is shown in Table 3 and Figures 1 and 2. The optimal cutoff point for the best performance of the NIHSS, determined with the same criterion as for the score, was 10. In both cohorts, the predicted probabilities were in slightly better concordance with the observed ones based on the score than based on the NIHSS alone

TABLE 3. Comparison Between the Diagnostic Accuracy of the Score (Optimal Cutoff, 16) and Stroke Severity by National Institutes of Health Stroke Scale-Based Prediction (Optimal Cutoff, 10) of the Presence of Large Vessel Occlusion in the Derivation and Validation Cohort

Population	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Area Under the Receiver Operating Characteristic Curve
Score cutoff, 16					
ASTRAL cohort	0.84	0.68	0.41	0.94	0.84
Validation cohort	0.84	0.71	0.54	0.92	0.84
National Institute of Health Stroke Scale cutoff, 10					
ASTRAL cohort	0.86	0.69	0.43	0.95	0.83
Validation cohort	0.85	0.73	0.55	0.92	0.84

ASTRAL = Acute STroke Registry and Analysis of Lausanne.

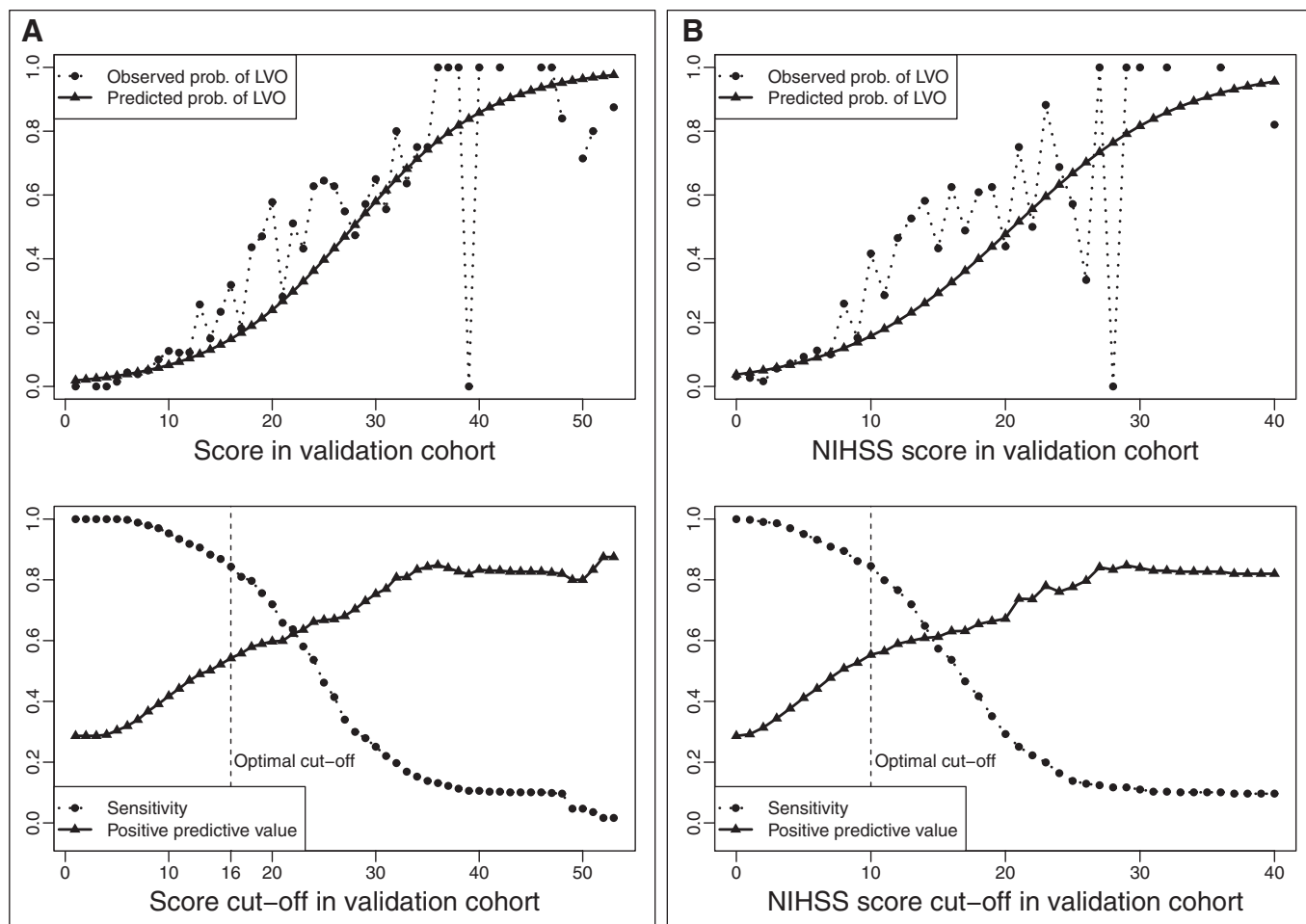


Figure 2. Actual rate and predicted probability (*top*) and sensitivity and positive predictive value with optimal cutoff values (*bottom*) of the score (**A**) and of National Institute of Health Stroke Scale (NIHSS)-based prediction (**B**) of the large vessel occlusion presence in the validation cohort. MIO = major intracranial occlusion.

as shown by the Wilcoxon signed rank test for median of pairwise differences in prediction error ($p < 0.001$). The improvement in AUC was statistically significant in the derivation cohort (DeLong test, $p = 0.047$) but not in the validation cohort. In addition, the AUC calculated in the pooled cohorts was 0.84 for the score and 0.83 for NIHSS alone, and this difference was significant (DeLong test, $p = 0.011$) (**Supplemental Table 2**, Supplemental Digital Content 1, <http://links.lww.com/CCM/B683>). **Figure 3** shows the ROC curves for the score and for the NIHSS alone in the pooled cohorts.

Impact of Selected Time Windows on Score Performance

To evaluate the impact of the selected time window on the score’s performance, we assessed the diagnostic accuracy of the statistical model in the 0- to 6-hour and 6- to 12-hour time delay after symptom onset (**Supplemental Fig. 1**, Supplemental Digital Content 1, <http://links.lww.com/CCM/B683>). Furthermore, we executed two additional analyses among the 0- to 6-hour cohort and 6- to 12-hour cohort separately. In the 0- to 6-hour cohort ($n = 1,225$), an optimized predictive model was created based on the same items as the ASTRAL occlusion score but with the replacement of the history of atrial fibrillation by

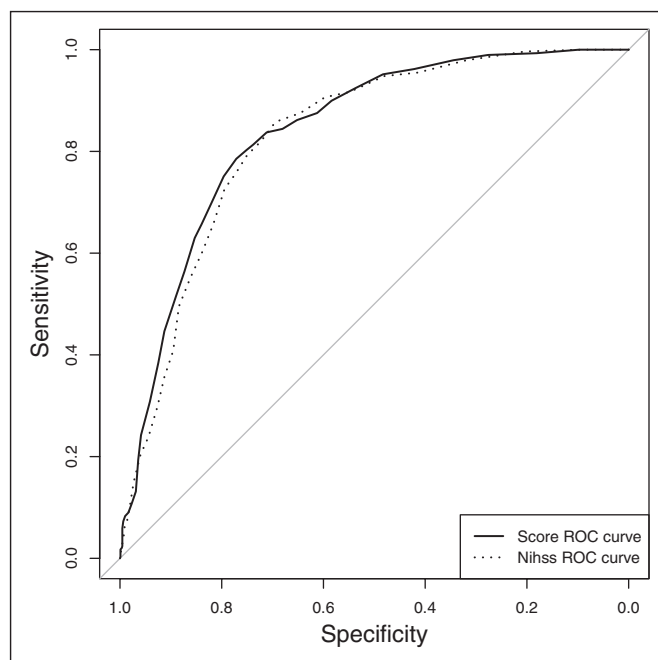


Figure 3. Receiver operating characteristic (ROC) curves for the score and for National Institute of Health Stroke Scale (NIHSS) alone in the pooled cohorts.

the absence of arterial hypertension as a risk factor. Performance in the derivation cohort was good with an AUC of 0.84, which is significantly better than in an NIHSS-alone predictive model (AUC, 0.82; $p = 0.049$). In the 6- to 12-hour population ($n = 420$), the performance of the model was enhanced (AUC, 0.88) by adding decreased vigilance and hypercholesterolemia to three previously used items (admission NIHSS, hemineglect, and the absence of arterial hypertension). Significant difference between this model and NIHSS-alone prediction was not reached in the derivation cohort ($p = 0.27$), partially because of the smaller study population. The optimal NIHSS cutoff for the prediction of LVOs is 10 and 8 in the 0- to 6- and 6- to 12-hour cohorts, respectively.

DISCUSSION

This study presents the development and external validation of a new scoring tool, which estimates the likelihood of an LVO eligible for endovascular revascularization in AIS. Our goal was to define a new score in which we tried to maximize the diagnostic accuracy (calculated by AUC ROC) and manage to improve the NIHSS-alone-based prediction with at least 1%. The discriminatory power to detect LVOs is mainly driven by the baseline NIHSS. This confirms the relationship between the NIHSS score and the location of the occluded vessel as shown earlier by Fischer et al (12) and Heldner et al (16). Our work shows that the NIHSS-based occlusion prediction can statistically be improved by adding four clinical variables with the effect of each single variable (e.g., female sex) in the statistical model being adjusted for the other variables. Sex differences in the rates of large intracranial vessel occlusions have been described in the past (21). Because women are less likely to have a prior stroke with a persistent neurologic deficit, a high NIHSS score in a woman is more likely to reflect the acute stroke severity, not the prior event. The absence of a stroke history and lower prestroke disability correlates with higher rates of LVO, as such patients more often have small vessel disease, silent strokes (34% vs 25%; $p < 0.05$ in univariate analysis), and leukoariosis (29% vs 20%; $p < 0.05$ in univariate analysis). The presence of neglect is often underestimated by the NIHSS score alone as of the 42 possible points on the NIHSS score, 7 points are directly related to measurement of language and only 2 points are related to neglect (22). At last, cardiogenic emboli by atrial fibrillation is well known to be linked with LVOs (23, 24).

Improving selection of patients eligible for EVT may have a major impact on stroke patients' outcome (2, 10). In the prehospital phase, the clinical variables (e.g., NIHSS and hemineglect) are theoretically available and the stroke severity assessment (NIHSS) by Emergency Medical Service personnel have an excellent interrater reliability (25). Still, adding these new variables to the NIHSS does not add clinically meaningful value, and we consider that NIHSS thresholds alone, if possible adapted to the timing and circulation (16), are sufficient to make decisions in most situations where immediate arterial imaging is not available.

The major strength of our study is the large number of patients and variables included in the derivation and validation cohorts, which make our results more robust and generalizable. In

contrast to the recent published prehospital scores, the included variables were broader selected than the NIHSS subitems (26, 27). Second, the score was validated internally and externally and showed good performances in both cohorts. However, our score's performances are slightly weaker than NIHSS-alone prediction in terms of sensitivity and specificity. Third, although noninvasive arterial imaging will remain superior to clinical scores for LVO identification, such imaging may not always be available in the hyperacute phase and at lower level stroke receiving facilities. Furthermore, loss of time with added or repeat imaging may decrease substantial benefit of acute EVT (8, 28).

Several limitations apply: first, intracranial vessel occlusions were classified in consensus among the involved centers into large and intermediate arterial occlusions, mainly based on the anatomical location. LVOs were selected for their poorer outcome independently of the reperfusion treatment and for their accessibility by EVT (4, 6, 7). Second, a substantial percentage (26%) of patients from the validation cohort had to be excluded because of lacking data. However, comparison of data from patients excluded from the study showed similar patient profiles. Third, the observed probability of LVO fluctuates dramatically at an NIHSS score greater than 25 because of the rarity of patients for these NIHSS values. The bad calibration of NIHSS for high values is unlikely to have great influence on AUC as the points above 25 on the calibration curve represent very few observations (< 5%). Fourth, our definition of LVO was not based on a single imaging modality in the validation cohort but on heterogeneous methods (CTA/MRA). However, several comparative studies showed that high-resolution MRI of the intracranial LVOs (incorporated TOF 3D, contrast-enhanced MRA, and SWI) accurately measures the degree of stenosis and occlusion at least as sensitive as CTA in high-risk, symptomatic patients (28, 29). Furthermore, compared with the NIHSS-based prediction, the score may be too complex and time consuming. The magnitude of the improved predictive accuracy may not add a clinical meaningful improvement of the predictive ability to warrant the extra complexity, which may hamper implementation in routine clinical practice. The score must be used in conjunction with the clinical, bedside judgment. Finally, data collection was performed in two tertiary stroke centers during a period of more than 9 years. Any change over time of prehospital triage, imaging techniques (as mentioned in the methods section), or windows for acute revascularization treatments may have influenced results.

CONCLUSIONS

The new five-item score may predict the presence of an LVO eligible for EVT in AIS with a good predictive accuracy. However, the additional complexity involved in its calculation and the marginal gain over the NIHSS make the isolated use of NIHSS alone more attractive.

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