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ORIGINAL COMMUNICATION

Clinical prediction of large vessel occlusion in anterior circulation stroke: mission impossible?

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Abstract Simple clinical scores to predict large vessel occlusion (LVO) in acute ischemic stroke would be helpful to triage patients in the prehospital phase. We assessed the ability of various combinations of National Institutes of Health Stroke Scale (NIHSS) subitems and published stroke scales (i.e., RACE scale, 3I-SS, sNIHSS-8, sNIHSS-5, sNIHSS-1, mNIHSS, a-NIHSS items profiles A–E, CPSS1, CPSS2, and CPSSS) to predict LVO on CT or MR arteriography in 1085 consecutive patients (39.4 % women, mean age 67.7 years) with anterior circulation strokes within 6 h of symptom onset. 657 patients (61 %) had an occlusion of the internal carotid artery or the M1/M2 segment of the middle cerebral artery. Best cut-off value of the total NIHSS score to predict LVO was 7 (PPV 84.2 %, sensitivity 81.0 %, specificity 76.6 %, NPV 72.4 %, ACC 79.3 %). Receiver operating characteristic curves of various combinations of NIHSS subitems and published scores were equally or less predictive to show LVO than the total NIHSS score. At intersection of sensitivity and specificity curves in all scores, at least 1/5 of patients with LVO were missed. Best odds ratios for LVO among NIHSS subitems were best gaze (9.6, 95 %-CI 6.765–13.632), visual fields (7.0, 95 %-CI 3.981–12.370), motor arms (7.6, 95 %-CI 5.589–10.204), and aphasia/neglect (7.1, 95 %-CI 5.352–9.492). There is a significant correlation between clinical scores based on the NIHSS score and LVO on arteriography. However, if clinically relevant thresholds are applied to the scores, a sizable number of LVOs are missed. Therefore, clinical scores cannot replace vessel imaging.

Keywords Acute ischemic stroke · Stroke management · Triage · CT · MRI · Clinical neurological examination

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Introduction

Recent randomized controlled trials have consistently shown that mechanical thrombectomy with stent retrievers in addition to intravenous thrombolysis is superior than intravenous thrombolysis alone in anterior circulation stroke patients with large vessel occlusion (LVO) [1–5]. Therefore, rapid clinical identification of these patients is crucial for patient selection and immediate referral to centers with facilities for endovascular treatment.

The National Institutes of Health Stroke Scale (NIHSS) score is widely used to assess stroke severity and high NIHSS scores predict LVO [6–11]. However, best cut-off values of the total NIHSS score are still controversial, assessment of the scale in the prehospital setting is time-consuming and hardly ever performed, and most paramedics are not trained to perform the NIHSS score. Therefore, several simple scales have been designed and validated for rapid identification of acute stroke in the prehospital phase [12–20]. Some of these simple scales are even supposed to predict LVO [14, 15, 20]. However, it remains unknown, how many patients with LVO in the anterior circulation would be missed when these simple scores are applied.

The aim of the present study was to perform a comparison of these simple scores and various new combinations of NIHSS subitems and the total NIHSS score to predict LVO on CT arteriography (CTA) or MR arteriography (MRA).

Methods

Patients

This study was based on the Bernese stroke center database. We analyzed all patients with persisting clinical symptoms on admission due to acute ischemic stroke or TIA in the anterior circulation. They all presented within 6 h, had a defined time of symptom onset and adequate CTA or MRA for analysis. Patients with posterior circulation stroke, comatose patients and those with previous strokes were excluded. Between January 2004 and August 2012, 1085 patients met our inclusion criteria. Clinical assessment was performed by a stroke neurologist immediately after admission using the NIHSS score [6]. Immediately thereafter, all patients underwent CTA ($n = 245$/22.6 %) or MRA ($n = 840$/77.4 %) that confirmed acute ischemic lesions and the site of vessel occlusion. All images were reviewed for this analysis both by a neuroradiologist and neurologist blinded to clinical signs and NIHSS scores. CTAs were acquired with an 8 or 16 slice multidetector-row CT scanner. Contrast-enhanced MRA of the neck and intracranial vessels and time-of-flight MRA of the intracranial arteries were acquired on 1.5 or 3 T MR scanners. Patients were assigned to subgroups according to the location of their vessel occlusion. LVOs were defined as occlusions of the internal carotid artery (ICA), of the main stem and branch of the middle cerebral artery (MCA; M1/M2); peripheral occlusions as anterior cerebral (ACA) or peripheral branches of the MCA (M3/M4) vessel occlusions.

Scores and statistical analysis

Statistical analysis was performed using SPSS 20 (SPSS Inc., Chicago, Illinois, USA). To predict LVO, we calculated the positive and negative predictive values (PPV and NPV), sensitivities (sens) and specificities (spec), accuracy (ACC) and receiver operating characteristic curves (ROC) with areas under the curve (AUC) for the total NIHSS score and for various published combinations of NIHSS subitems (i.e., RACE scale, 3I-SS, sNIHSS-8, sNIHSS-5, sNIHSS-1, mNIHSS, a-NIHSS items profiles A-E, CPSS1, CPSS2, and CPSSS) [12–16, 18–20]. Detailed information on these scores is provided in the online resource material in Table S1. Since information in our database on agnosia was missing, we replaced it by neglect for calculating the RACE scale [14]. Items of the a-NIHSS profiles (A-E) were weighted according to the items of the total NIHSS score to have a continuous scale [16]. Furthermore, we identified the most predictive subitems of the total NIHSS score to predict LVO by performing odds ratios in univariate and forward stepwise logistic regression analysis. Most predictive subitems were combined to test different new Bernese scores (Table S2 in the online resource material). Finally, we calculated the cumulative percentage of patients with LVO missed at different score values. Categorical variables were compared with Chi-square test and continuous variables with Mann-Whitney test.

Results

1085 consecutive patients fulfilled our inclusion criteria and a detailed flow chart for reasons of exclusion is provided in the online resource material in Fig. S1. 899 (82.9 %) presented with an acute ischemic stroke and 186 with TIA (17.1 %, of which 97.3 % showed lesions on diffusion weighted imaging and would be classified as stroke according to the tissue based definition of TIA and stroke). Baseline characteristics, vascular risk factors, stroke etiology, and radiological findings are shown in Table 1.

Median time to neurological assessment was 116 (range 350) min. 754 patients (69.5 %) showed an occlusion on CTA or MRA, 657 vessel occlusions (VO) were large, and 331 had no VO on arteriography. Median NIHSS score of all patients was 10 (range 0–31), 14 (range 0–31) in patients with LVO, and 4 (range 0–25) in patients with peripheral or no occlusion. Overall, high initial NIHSS scores were associated with both VO and with LVO (both $p < 0.0001$).

Prediction of large vessel occlusion

At the intersection of the sensitivity and specificity curves, the best total NIHSS score cut-off to find LVO in all patients was 7 (PPV 84.2 %, sens 81.0 %, spec 76.6 %, NPV 72.4 %, and ACC 79.3 %) (Fig. S2 in the online material).

Receiver operating characteristic curves (ROC) analyzing the validity of different combinations of NIHSS subitems in predicting LVO compared to the total NIHSS score are shown in Fig. 1. Percentages of patients missed with LVO at different levels of all tested scores are shown in Fig. 2. Overall, the total NIHSS score showed the lowest percentage of patients with LVO missed at the intersection of the sensitivity and specificity curve (19.0 %) (Fig. 2). 9 % of patients with a NIHSS score of 4 or less had a LVO

Table 1 Baseline characteristics, vascular risk factors, stroke etiology, and radiological findings, *n* (%)

Age, mean years (SD)	67.7 (14.4)	
Women	427 (39.4)	
Symptom onset to neurological assessment		
0–1.5 h	383 (35.3)	
>1.5–3 h	394 (36.3)	
>3–6 h	308 (28.4)	
Median time delay in minutes (range)	116 (0–350)	
Symptom onset to imaging		
Median time delay in minutes (range)	162 (10–385)	
Vascular risk factors		
Diabetes mellitus	167/1082 (15.4)	
Arterial hypertension	680/1083 (62.8)	
Current smoking	210/1068 (19.7)	
Hypercholesterolemia	557/1080 (51.6)	
Coronary artery disease	183/1082 (16.9)	
Atrial fibrillation	319/916 (34.8)	
TOAST criteria		
Large artery disease	136 (12.5)	
Cardioembolic	388 (35.8)	
Small artery disease	31 (2.9)	
Others	75 (6.9)	
Unknown, diagnostic work-up complete	166 (15.3)	
Unknown, diagnostic work-up incomplete	212 (19.5)	
More than one cause possible	77 (7.1)	
Baseline NIHSS score, median (range)	10 (31)	
Imaging parameters		
Location of vessel occlusion		
ICA occlusion	220 (20.3)	
M1 occlusion	277 (25.5)	
M2 occlusion	160 (14.7)	
M3/4 occlusion	86 (8.0)	
ACA occlusion	11 (1.0)	
No occlusion	331 (30.5)	
A-/typical lacunar syndromes	*TIA*	*LVO*
Pure motor hemiparesis	5/23 (21.7)	2 ICA, 1 M2 occlusions
Pure sensory syndrome	4/16 (25.0)	1 ICA occlusion
Sensorimotor syndrome	1/13 (7.7)	1 M1 occlusion
Ataxic hemiparesis	2/10 (20.0)	2 ICA occlusions
Pure dysarthria	1/7 (14.3)	1 M1, 1 M2 occlusions
Isolated dysarthria-facial paresis syndrome	2/14 (14.3)	2 M2 occlusions
Partial form of pure motor hemiparesis	4/24 (16.7)	3 ICA, 2 M1, 2 M2 occlusions
Thrombolysis		
Intravenous rt-PA	235 (21.7)	
Endovascular	353 (32.5)	
Bridging	83 (7.6)	

TOAST Trial of Org 10172 in Acute Stroke Treatment, *NIHSS* National Institutes of Health Stroke Scale, *ICA* internal carotid artery, *M1/M2/M3/M4* segments of the middle cerebral artery, *ACA* anterior cerebral artery, *LVO* large vessel occlusion

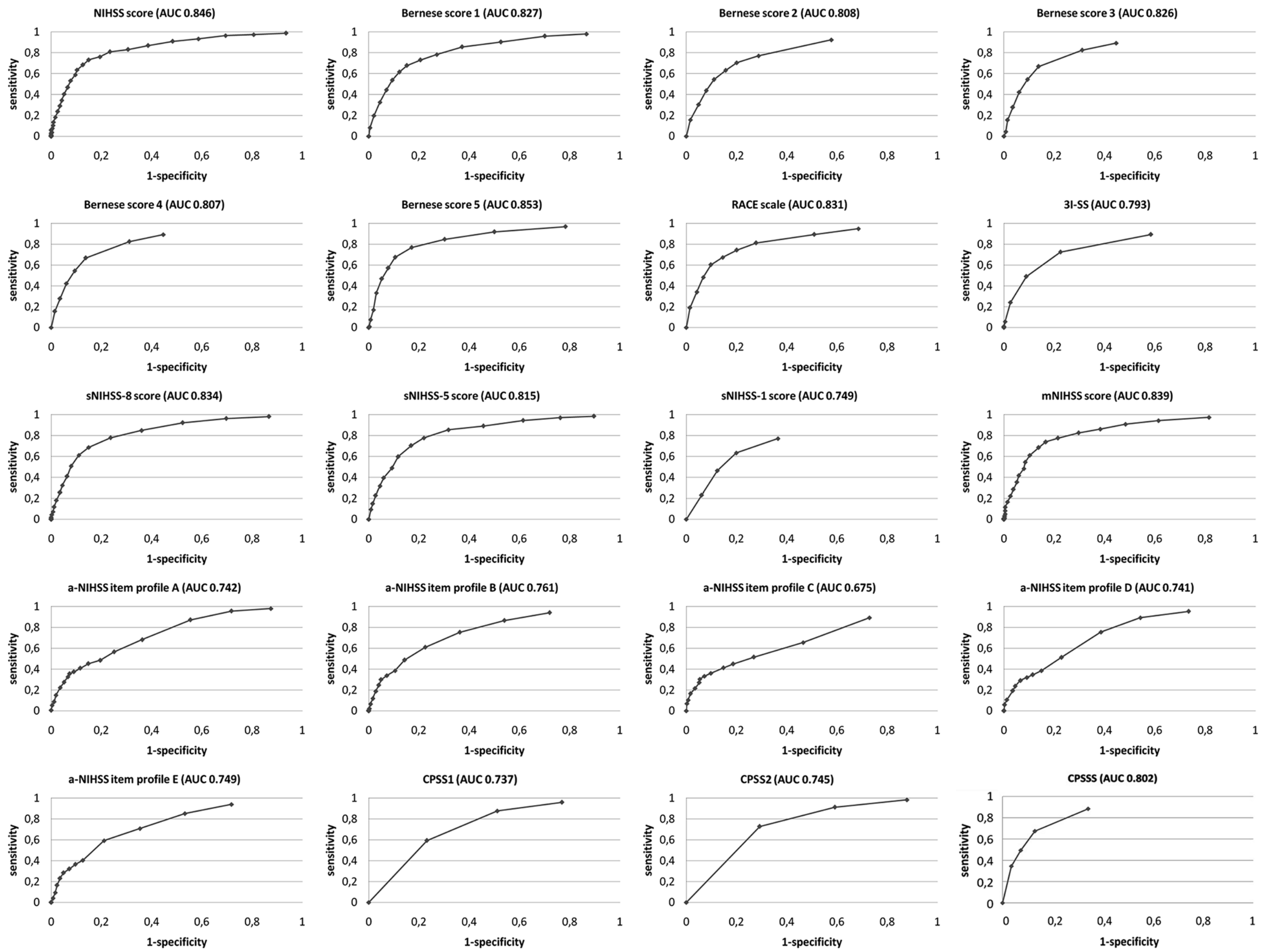

Fig. 1 ROC curves analyzing the validity of various NIHSS subitems combinations in predicting large vessel occlusion (i.e., internal carotid, M1 or M2 segment of the middle cerebral artery occlusion)

(Fig. 2). In all simple clinical scores, no clinically relevant cut-off value could be found to reliably exclude LVO (Fig. 2). Various combinations of NIHSS subitems and all published scores were equally or less predictive to show LVO (Table 2).

Best odds ratios among different NIHSS subitems to predict LVO were best gaze (9.6, 95 %-CI 6.765–13.632), visual fields (7.0, 95 %-CI 3.981–12.370), motor arms (7.6, 95 %-CI 5.589–10.204), and aphasia/neglect (7.1, 95 %-CI 5.352–9.492) (Table 3).

Discussion

Whether clinical prediction of LVO in patients with acute ischemic stroke is possible is one of the major unresolved issues in acute stroke management. In this study, we correlated the total NIHSS score and various simple clinical scores with the presence of LVO in 1085 anterior circulation stroke patients: even though higher scores were associated with LVOs, no clinically relevant cut-off values were found to reliably exclude patients with LVO.

Rapid clinical identification of patients with LVO is of major clinical importance: anterior circulation stroke patients with LVO have better outcomes if treated with thrombectomy, and therefore these patients should be transferred to centers with facilities for endovascular treatment. The gold standard for non-invasive detection of LVO is CTA or MRA, and there is also a correlation between high NIHSS scores and the likelihood of LVOs [7–11]. However, LVOs are not only observed in patients with major strokes, but also in a relevant number of patients with low NIHSS scores at presentation or with rapidly improving symptoms (i.e., false negative) [7]. The previous non-randomized studies have shown that thrombolysis may be safely performed in these patients, which otherwise may deteriorate in a high percentage [21–23]. In our selected cohort of anterior circulation stroke patients

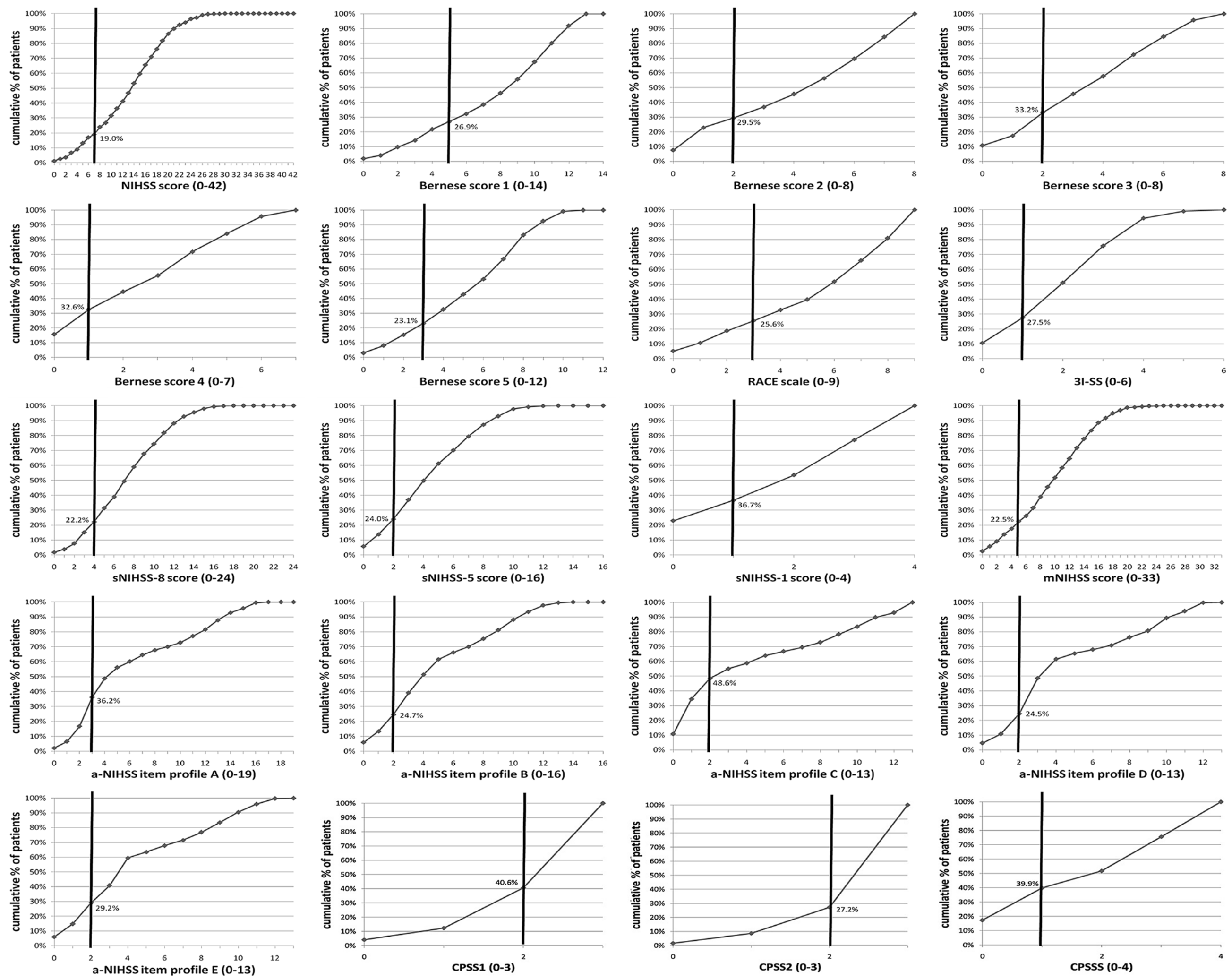

Fig. 2 Cumulative % of patients with large vessel occlusion (i.e., internal carotid, M1 or M2 segment of the middle cerebral artery occlusion) missed—overall and at best cut-off [defined as crossing of sensitivity and specificity (*vertical bar*)]

presenting within 6 h after symptom onset, 9 % of patients with NIHSS score of 4 or less showed a LVO on CTA or MRA and were, therefore, false negative. If we would have included patients presenting after 6 h and those with posterior circulation stroke even more patients would have been missed at a NIHSS score cut-off of 4.

According to Maas et al. roughly every forth patient with a NIHSS score of 4 or less had a LVO after an average time interval of 7.5 h (defined as occlusion of the internal carotid artery, the M1 or M2 segment of the middle cerebral artery, the A1 or A2 segment of the anterior cerebral artery, the posterior cerebral artery, and the basilar or the vertebral artery on CTA) [7].

Recently, several simple clinical scores were designed to identify patients with acute ischemic stroke and some of these simple scales are supposed to predict LVO (Table 4) [14, 15, 20].

The RACE scale has been designed and validated as a prehospital stroke scale to predict LVO (Table 4). A RACE scale score of ≥6 showed a sensitivity of 72 % and a specificity of 77 % to predict LVO, a RACE scale score of ≥5, a sensitivity of 85 %, and a specificity of 68 % [14]. However, when RACE scale was applied to our cohort more than half of patients with LVO as defined in our study would have been missed at a cut-off value of 6, which was the best intersection of the sensitivity and specificity curves. The 3I-SS score is another score designed to identify patients with LVO (Table 4). A 3I-SS score of ≥3 showed a sensitivity of 76 % and specificity of 85 % to predict LVO [15]. However, when 3I-SS was applied to our cohort roughly three of four patients with LVO as defined in our study would have been missed at a cut-off value of 3. The CPSSS is a further score to predict LVO (Table 4). A score of 2 showed a sensitivity of 83 % and a specificity of 40 % to predict LVO [20].

Table 2 Validity of various NIHSS subitems combinations predicting large vessel occlusion (Internal carotid, M1 or M2 segment of the middle cerebral artery occlusions) in acute anterior circulation stroke

	Cut-off	PPV	Sensitivity	Specificity	NPV	ACC
NIHSS score	7	84.2	81.0	76.6	72.4	79.3
Bernese score 1	5	84.5	73.1	79.4	65.8	75.6
Bernese score 2	2	84.3	70.5	79.9	63.8	74.2
Bernese score 3	2	88.2	66.8	86.2	62.9	74.5
Bernese score 4	1	86.0	67.4	83.2	62.5	73.6
Bernese score 5	3	87.4	76.9	82.9	70.0	79.3
RACE scale	3	85.0	74.4	79.9	67.1	76.6
3I-SS	1	83.2	72.5	77.6	64.7	74.5
sNIHSS-8 score	4	83.5	77.8	76.4	69.1	77.2
sNIHSS-5 score	2	83.5	76.1	76.9	67.7	76.4
sNIHSS-1 score	1	83.0	63.3	80.1	58.7	70.0
mNIHSS score	5	84.7	77.5	78.5	69.4	77.9
a-NIHSS item profile A[a]	3	75.9	63.8	68.9	55.3	65.8
a-NIHSS item profile B[a]	2	76.1	75.3	63.8	62.8	70.8
a-NIHSS item profile C[a]	2	74.6	51.4	73.1	49.5	60.0
a-NIHSS item profile D[a]	2	75.0	75.5	61.4	62.0	70.0
a-NIHSS item profile E[a]	2	75.5	70.8	64.7	59.1	68.4
CPSS1	2	79.8	59.4	76.9	55.2	66.3
CPSS2	2	79.3	72.8	70.8	62.9	72.0
CPSSS	1	87.8	60.1	87.1	58.7	70.8

[a] Score consisting of the items profiles (scoring as in NIHSS score)

Table 3 Odds ratios of different NIHSS subitems predicting large vessel occlusion in acute anterior circulation stroke

	Odds ratio	Univariate 95 % CI	*p*
Best Gaze	9.60	6.765–13.632	<0.0001
Motor arms	7.60	5.589–10.204	<0.0001
Aphasia/neglect	7.13	5.352–9.492	<0.0001
Visual fields	7.00	3.981–12.370	<0.0001
Motor legs	5.78	4.436–7.560	<0.0001
LOC[a] altertness	5.64	3.732–8.522	<0.0001
Facial palsy	5.50	4.044–7.468	<0.0001
LOC[a] commands	4.50	3.287–6.157	<0.0001
LOC[a] questions	4.23	3.248–5.503	<0.0001
Dysarthria	3.20	2.480–4.119	<0.0001
Sensation	2.40	1.865–3.088	<0.0001
Limb ataxia	0.87	0.362–2.074	0.747

[a] Level of consciousness

However, when CPSSS was applied to our cohort more than 50 % of patients with LVO as defined in our study would have been missed at the cut-off value of 2.

We tried to find combinations of NIHSS subitems to predict LVO in our cohort: best gaze, visual fields, motor arm, and aphasia/neglect were the items with the strongest correlation. However, various combinations were at the best equally or mostly less accurate than the total NIHSS score to predict LVO. We then also tried to find clinically relevant thresholds in all published and our own scores, but we were unable to find a reasonable cut-off value with a high specificity for LVO without missing a sizable number of patients with important occlusions. Therefore, vessel imaging should also be performed in patients with low scores, since endovascular therapy might also be effective in patients with mild deficits and LVO [23].

Our analysis has several limitations. First, our study was conducted among stroke and TIA patients referred to a stroke center. Therefore, severe strokes and LVOs are overrepresented. Second, comatose patients were excluded from this analysis, because we could not appropriately assess their clinical findings required for most scores. Third, we excluded patients with posterior circulation stroke and those presenting later than 6 h after symptom onset. Finally, since we did not collect data on distal hand paresis in our cohort, and since distal hand paresis is not reflected by the NIHSS score used for this study, we were unable to report the frequency of patients with a "dysarthria-clumsy hand" syndrome [24].

In conclusion the NIHSS score and various simple clinical scores, combining NIHSS subitems provide a gross estimate of the presence or absence of a LVO. However, they are inadequate to exclude LVO in anterior circulation stroke patients presenting within 6 h after symptom onset with certainty. Therefore, vessel imaging should be

Table 4 Simple clinical scales predicting large vessel occlusion

	Number of patients	Definition of LVO	Imaging method to detect LVO	Time intervals from symptom onset to clinical examination
RACE[a]	357[a]	Terminal intracranial ICA, M1, extracranial carotid artery plus MCA or basilar artery occlusion	Transcranial duplex, CTA or MRA	Exact time of symptom onset: unknown in 29 % of patients, mean time from symptom onset to neurological evaluation: 95 (63–180) min in the others
3I-SS score[b]	180[b]	Distal ICA or M1 occlusion	Mainly MRA	Presenting within 6 h
CPSSS[c]	303[c]	Extra- or intracranial ICA, M1, cervical ICA plus M2 or basilar artery occlusion	CTA	Treated by intravenous thrombolysis within 3 h
Our cohort	1085	ICA, M1 or M2 occlusion	CTA or MRA	Median time to neurological assessment: 116 (range 350) min

LVO large vessel occlusion, *ICA* internal carotid artery, *M1/M2* segments of the middle cerebral artery, *MCA* middle cerebral artery

[a] Pérez de la Ossa et al. [14]

[b] Singer et al. [15]

[c] Katz et al. [20]

performed as soon as possible in all acute strokes to triage patients in stroke networks for or against transfer from regional stroke units to the comprehensive stroke center.

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Compliance with ethical standards

Ethical standard The study protocol was approved by our institutional ethics committee in Bern, and the study has, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all patients.

Conflicts of interest Dr. Heldner reports a grant from the Swiss Heart Foundation. Dr. Hsieh reports no disclosures. Dr. Broeg-Morvay reports no disclosures. PD Dr. Mordasini reports no disclosures. Dr. Bühlmann reports no disclosures. PD Dr. Jung reports no disclosures. Prof. Dr. Arnold received honoraria for lectures and advisory boards from Bayer, Boehringer Ingelheim, Bristol Meyer Squibbs, Pfizer and Covidien. Prof. Dr. Mattle reports a grant from the Swiss Heart Foundation. Prof. Dr. Gralla reports a consultant agreement with Medtronic. Prof. Dr. Fischer reports a grant from the Swiss Heart Foundation and received a speaker's honorarium from Covidien.

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