Triage of stroke patients in the chain of acute stroke care

Nguyen, T.T.M.

Part II

PREHOSPITAL TRIAGE

Chapter 3

Clinical prediction of thrombectomy eligibility: A systematic review and 4-item decision tree

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Gaia T Koster, T Truc My Nguyen, Erik W van Zwet, Bjarty L Garcia, Hannah R Rowling, J Bosch, Wouter J Schonewille, Birgitta K Velthuis, Ido R van den Wijngaard, Heleen M den Hertog, Yvo BWEM Roos, Marianne AA van Walderveen, Marieke JH Wermer and Nyika D Kruyt

ABSTRACT

Background and purpose

A clinical large anterior vessel occlusion (LAVO)-prediction scale could reduce treatment delays by allocating endovascular treatment (EVT)-eligible patients directly to a comprehensive stroke center. The study aim was to subtract, validate and compare existing LAVO-prediction scales, and develop a straightforward decision support tool to assess EVT-eligibility.

Methods

We performed a systematic literature search to identify LAVO-prediction scales. Performance was compared in a prospective, multicenter validation cohort of the Dutch acute Stroke study (DUST) by calculating area under the receiver operating curves (AUROC). With group lasso regression analysis, we constructed a prediction model, incorporating patient characteristics next to National Institutes of Health Stroke Scale (NIHSS) items. Finally, we developed a decision tree algorithm based on dichotomized NIHSS items.

Results

We identified seven LAVO-prediction scales. From DUST, 1316 patients (35.8% LAVO-rate) from 14 centers were available for validation. FAST-ED and RACE had the highest AUROC (both >0.81, $p<0.01$ for comparison with other scales). Group lasso analysis revealed a LAVO-prediction model containing seven NIHSS items (AUROC 0.84). With the GACE (Gaze, facial Asymmetry, level of Consciousness, Extinction/inattention) decision tree, LAVO is predicted (AUROC 0.76) for 61% of patients with assessment of only two dichotomized NIHSS items, and for all patients with four items.

Conclusion

External validation of seven LAVO-prediction scales showed AUROCs between 0.75 and 0.83. Most scales, however, appear too complex for Emergency Medical Services use with prehospital validation generally lacking. GACE is the first LAVO-prediction scale using a simple decision tree as such increasing feasibility, while maintaining high accuracy. Prehospital prospective validation is planned.

INTRODUCTION

Time is the most crucial factor limiting clinical effectiveness of endovascular treatment (EVT) in stroke due to large anterior vessel occlusion (LAVO).[1,2] With every minute of delay, 4.2 days of disability-free life are lost, and chances of undergoing EVT are reduced by 2.5%.[3,4] A clinical scale to identify LAVO in the prehospital Emergency Medical Services (EMS) setting could reduce treatment delays by allocating EVT-eligible patients directly to a comprehensive stroke center (CSC).[5,6] Ideally, such a scale should be straightforward, widely applicable, have high interrater reliability and high accuracy in terms of LAVO-prediction.[7] Various scales have been designed, but it is unclear which performs best in clinical practice.[8-14] The National Institutes of Health Stroke Score (NIHSS) retains the highest overall accuracy predicting LAVO,[15,16] but is too extensive for EMS personnel. The Face-arm-speech-time (FAST) score is widely used by EMS personnel but was primarily developed to distinguish stroke from non-stroke rather than stroke subtype.[17,18]

LAVO-prediction scales were compared before, but never systematically, and in different datasets with radiological endpoints not reflecting current clinical practice.[14,19,20]

Patient characteristics may improve a LAVO prediction model but were not included in previous scales.[21,22]

We aimed to (i) systematically identify published LAVO-prediction scales designed for prehospital use, (ii) assess these scales in terms of feasibility, (iii) assess predictive value in a large, multicenter, prospective dataset with EVT-eligible LAVO as a well-defined radiological outcome measure, (iv) compare these scales to NIHSS and FAST, and finally, (v) develop a prediction model assessing both NIHSS items and patient characteristics associated with LAVO.

METHODS

A computerized literature search was performed in the following databases: MEDLINE, EMBASE, EMCARE and Web of Science from October 1991 to June 2017 using the following search terms: "stroke," "cerebrovascular accident," "scales," "scores," "large vessel occlusion," "large artery occlusion," "Emergency Medical Services," "prehospital" and "triage." Two reviewers (GTK and TTMN) independently screened titles and abstracts for eligibility. Full-text versions were obtained from all studies that were considered to be potentially relevant by one or both reviewers. After a first selection, bibliographies of all relevant studies were searched manually for additional studies and this method of crosschecking was continued until no further publications were found. Authors of relevant articles were contacted for supplementary information.

Cohort studies were reviewed with the STROBE (Strengthening the Reporting of OBservational studies in Epidemiology) statement and had to comply with the following inclusion criteria: (1) original data report on an inception cohort or a clinical trial; (2) a clinical score had to be assessed within 6 hours from stroke onset; (3) it had to be clear from the paper at what moment and by whom (e.g. EMS personnel, neurologist) a clinical score was assessed; (4) assessment of LAVO had to be done with either CT angiography (CTA), magnetic resonance angiography, or digital subtraction angiography; (5) data available on the performance of clinical score(s) used had to be expressed as: area under the receiver operating characteristics curve (AUROC), sensitivity/specificity or likelihood ratio, and (6) the clinical score had to be retrievable from NIHSS. Because studies had to fulfill these strict inclusion criteria, no further formal quality assessment was undertaken.

We estimated and/or retrieved the following characteristics from identified studies: feasibility for EMS use, interrater reliability and external validity (i.e., applicability to the unselected population of suspected acute stroke patients).

Validation cohort

To assess validity, we used the Dutch acute Stroke study (DUST) cohort.[23] DUST is a multicenter, prospective, observational cohort study conducted in six university and eight non-university hospitals in the Netherlands. From May 2009 to August 2013, consecutive patients >18 years presented at the emergency department with a suspicion of acute (<9 h) ischemic stroke (based on clinical assessment and non-contrast CT (NCCT) imaging) and NIHSS >1 and/or considered eligible for intravenous thrombolysis (IVT) were included. All patients received CTA within 9 hours after symptom onset as part of the CT stroke workup including NCCT, CT perfusion and CTA. The DUST imaging protocol has been described before.[24]

ANALYSIS

Patients with CTA yielding insufficient diagnostic quality to assess LAVO were excluded. We defined LAVO according to current EVT-eligible criteria: proximal middle cerebral artery (MCA: M1- and/or M2-segment), proximal anterior cerebral artery (ACA: A1- and/or A2-segment), intracranial carotid artery (ICA) or tandem (ICA plus MCA) occlusion.[25] Patients with incomplete admission NIHSS were excluded from analyses related to validation of existing scales, since NIHSS was required to reconstruct these.

Descriptive statistics were used to determine baseline characteristics of the validation cohort. Categorical variables were compared with the X^2 test and presented as number (percentage). Continuous variables are compared using the t test or Mann–Whitney U test and are presented as mean ± standard deviation or median (interquartile range, IQR) if appropriate. To assess predictive value, we computed AUROC and respective 95% confidence intervals (CIs) per identified LAVO-prediction scale, and for the NIHSS and FAST score.

Having data from 14 sites participating in DUST, we performed external validation by excluding one site at a time (cross-validation) for every scale. This is an important advantage, because external validation gives a better indication of the generalization error. We performed all pairwise comparisons of the cross-validated AUROCs of the various scales using the DeLong's test.[26]

For the development of a new prediction model, we did not exclude patients with NIHSS items that could not be assessed since this reflects clinical practice. In addition, we introduced (combinations of) patient characteristics into the model that we considered to be predictive of LAVO provided that these also differed on baseline between LAVO and non-LAVO patients. These include: history of atrial fibrillation (AF), AF without the use of anticoagulation, and AF without diabetes mellitus and/or hyperlipidemia.

Group lasso regression analysis was used to reveal (a combination of) NIHSS items and patient characteristics yielding the highest predictive value for LAVO.[27] The lasso is a popular method for penalized regression and classification that also performs variable selection.[28] The group lasso is a variant where the user can specify groups of variables (e.g. all variables within one NIHSS item) that are either all in or all out of the model.[29] We used the R package "grpreg" with default settings to fit the group lasso.[30]

In addition, a decision tree algorithm and diagram based on dichotomized NIHSS items ((1) 'yes/present/abnormal', or (0) 'no/absent/normal') was developed. A decision tree works by consecutively assessing

the item with the highest predictive value in the (remaining) cohort, as such leading to a minimum number of items to be assessed to reach an outcome (i.e., LAVO or non-LAVO), with the highest possible predictive value. Cross-validation (as described before) will determine the number of knots in the decision tree. The decision tree was fitted using the R-package "rpart" using default settings. In particular, this means that the default priors are proportional to the data counts, the losses default to 1, and the split defaults to the Gini index.

Statistical analysis was performed using SPSS software (version 23, IBM, New York, USA), and R software (version 3.4.1).

RESULTS

Systematic literature search

The MEDLINE search yielded 185 citations, the EMBASE search 263 citations, the EMCARE search 58 citations, and the Web of Science search 163 citations. After removal of duplicates, 522 records remained; 446 records were excluded based on title and abstract; 28 additional relevant studies were found by searching the bibliographies. Screening reference lists and a search of the Science Citation Index yielded 12 additional studies. One-hundred-and-sixteen citations remained for full text assessment. A total of seven clinical scales meeting pre-defined criteria were identified (see Figure 1). Clinical scale characteristics and methods of validation are shown in Supplementary Material I. Except for the RACE scale, all validations were performed retrospectively and/or in-hospital and validation cohorts ranged between 62 and 3505 patients. Generally, patients with intracerebral hemorrhage (ICH) were excluded. Definition of LAVO varied substantially between studies (ranging from 'MCA occlusion' to 'anterior or posterior circulation occlusion'), and LAVO-rate ranged between 21 and 73%. .

Validation cohort

A total of 1393 patients were included in DUST. Of these, 59 (4%) were excluded because of incomplete NIHSS and 18 (1%) because CTA was of insufficient diagnostic quality to assess LAVO. This left 1316 patients for analysis.

LAVO was present in 471 patients (35.8%). Demographic details of the validation cohort, stratified by presence of LAVO, are presented in Table 1. LAVO-patients were similar in age and sex compared to non-LAVO patients. AF was more prevalent in LAVO-patients, whereas other cardiovascular risk factors (previous stroke, hyperlipidemia) and antiplatelet therapy were more prevalent in non-LAVO patients. LAVO-patients had higher baseline NIHSS compared to non-LAVO patients; NIHSS 12 [IQR 7–17] versus NIHSS 4 [2–7] were more frequently treated with IVT, and onset-to-needle time was shorter; 97 [72–140] min in LAVO-patients versus 115 [85–170] in non-LAVO patients. Median systolic blood pressure was lower in LAVO-patients: 150 mmHg [133–167] versus 157 mmHg [140–180] in non-LAVO patients.

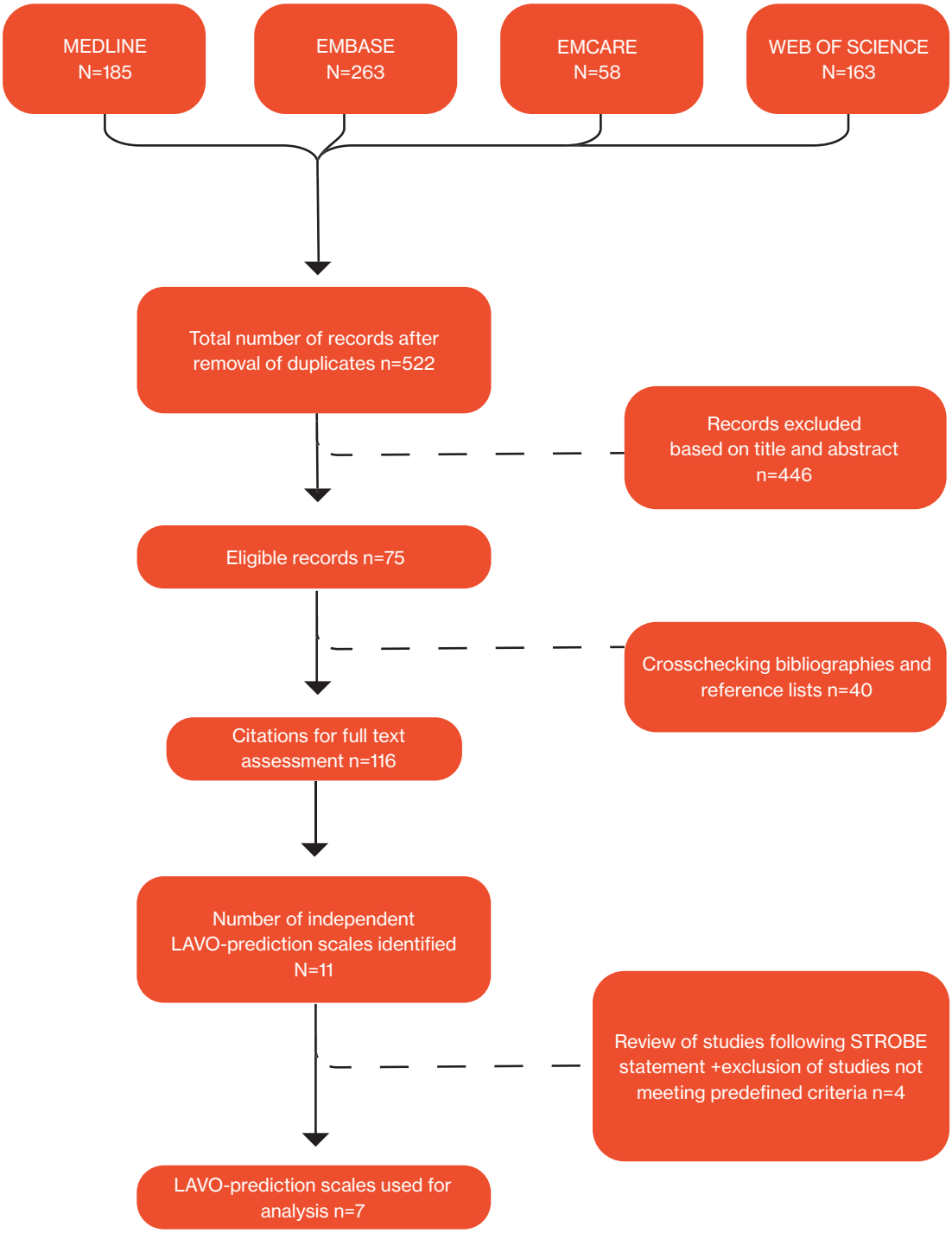

Figure 1.
Flowchart systematic literature search

LAVO: large anterior vessel occlusion; STROBE: strengthening the reporting of observational studies in epidemiology.

Table 1.
Baseline characteristics of DUST validation cohort

	Total patients n=1316	LAVO n=471 (36%)	non-LAVO n=845 (64%)	p-value
Demographics				
Age (years)	69 [57-78]	68 [55-77]	69 [58-78]	0.14
Male sex	752 (57)	264 (56)	488 (58)	0.55
Medical history				
Atrial fibrillation, 18 missings,	168 (13)	72 (15)	96 (11)	0.04
Atrial fibrillation without anticoagulation, 27 missings	88 (7)	44 (9)	44 (5)	<0.01
Diabetes mellitus, 11 missings	198 (15)	59 (13)	139 (16)	0.05
Previous stroke, 12 missings	316 (24)	82 (17)	234 (28)	<0.01
Hypertension, 16 missings	680 (52)	238 (51)	442 (52)	0.43
Hyperlipidemia, 41 missings	433 (33)	135 (29)	298 (35)	0.01
Coronary artery disease, 42 missings	242 (18)	79 (17)	163 (19)	0.48
Medication on admission				
Anticoagulation, 9 missings	154 (12)	49 (10)	105 (12)	0.54
Antiplatelet therapy, 10 missings	443 (34)	141 (30)	302 (36)	0.07
Clinical parameters on admission				
Systolic blood pressure (mmHg), 11 missings	154 [138-177]	150 [133-167]	157 [140-180]	<0.01
Diastolic blood pressure (mmHg), 11 missings	85 [75-95]	82 [72-96]	85 [75-95]	0.02
Glucose (mmol/L), 20 missings	6.6 [5.8-8.1]	6.6 [5.9-7.8]	6.6 [5.7-8.1]	0.43
NIHSS at admission	6 [3-12]	12 [7-17]	4 [2-7]	<0.01
Reperfusion therapy				
Intravenous thrombolysis	815 (62)	331 (70)	484 (57)	<0.01

Values are expressed as median [interquartile range] for continuous variables unless stated otherwise and as absolute counts (percentage) for categorical variables. LAVO: large anterior vessel occlusion; NIHSS: National Institutes of Health Stroke Scale.

Comparison of clinical scales

The FAST-ED (AUROC 0.83, 95% CI 0.80–0.85), RACE scale (AUROC 0.82, 95% CI 0.79–0.84) and NIHSS (AUROC 0.81, 95% CI 0.79–0.84) showed the highest AUROC for detecting LAVO in comparison with other scales (p<0.01). FAST-ED showed a comparable AUROC to RACE but a significantly higher AUROC than NIHSS (p<0.01). The FAST score showed the lowest specificity, and the 3I-SS scale showed the lowest sensitivity (see Figure 2 and Table 2).

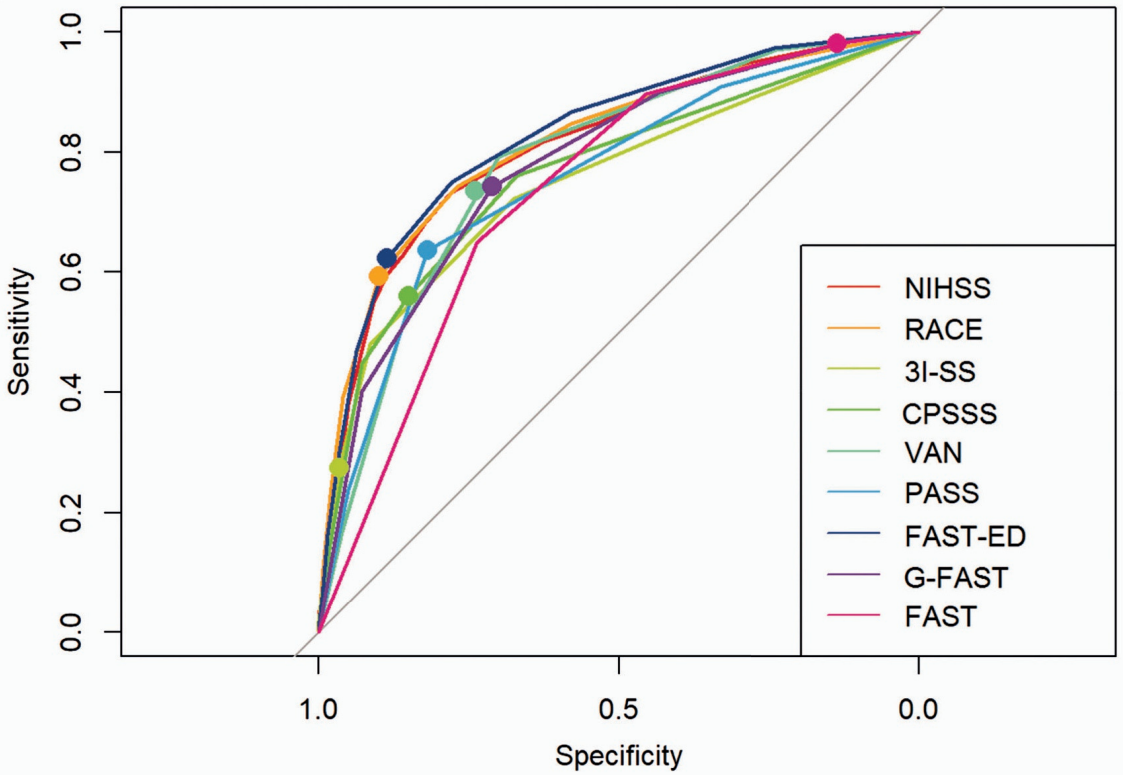

Figure 2.
Receiver operating characteristics (ROC) curves of identified LAVO-prediction scales, and the NIHSS and FAST score.

For every LAVO-prediction scale, the marked point in the ROC indicates the combination of sensitivity and specificity at the original authors' recommended cut-off point. 3I-SS: 3-item stroke scale; CPSSS: Cincinnati prehospital stroke severity scale; FAST: Face-arm-speech-time; FAST-ED: Face-arm-speech-time-eye deviation-denial/neglect; G-FAST: Gaze-face-arm-speech-time; NIHSS: National institutes of health stroke scale; PASS: Prehospital acute stroke severity; RACE: Rapid arterial occlusion evaluation; VAN: Vision aphasia neglect.

Table 2. AUROCs and respective 95%-CIs with corresponding p-values comparing identified LAVO-prediction scales, NIHSS and FAST

Clinical Scale	AUC (95% CI)	FAST	3I-SS	PASS	CPSSS	G-FAST	VAN	NIHSS	RACE	FAST-ED
FAST	0.74 (0.71-0.76)	X								
31-SS	0.75 (0.72-0.78)	0.25	X							
PASS	0.76 (0.73-0.78)	0.10	0.55	X						
CPSSS	0.76 (0.74-0.79)	0.04	0.08	0.31	X					
G-FAST	0.78 (0.76-0.81)	<0.01	<0.01	<0.01	0.12	X				
VAN	0.78 (0.76-0.81)	<0.01	<0.01	<0.01	0.09	0.79	X			
NIHSS	0.81 (0.79-0.84)	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	X		
RACE	0.82 (0.79-0.84)	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.34	X	
FAST-ED	0.83 (0.80-0.85)	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.17	X

3I-SS: 3-item stroke scale; CPSSS: Cincinnati prehospital stroke severity scale; FAST: Face-arm-speech-time; FAST-ED: Face-arm-speech-time-eye deviation-denial/neglect; G-FAST: Gaze-face-arm-speech-time; NIHSS: National institutes of health stroke scale; PASS: Prehospital acute stroke severity; RACE: Rapid arterial occlusion evaluation; VAN: Vision aphasia neglect.

Group lasso LAVO-prediction model

Group lasso analysis showed a prediction model containing a combination of the following NIHSS items (AUROC 0.84, 95% CI 0.81–0.87): (1) level of consciousness (LOC) questions, (2) gaze, (3) visual fields, (4) facial asymmetry, (5) arm motor function, (6) aphasia, and (7) extinction/ inattention. Whereas AF was more prevalent in LAVO-patients, it did not contribute to the prediction model as a separate variable or in combination with other patient characteristics as outlined before.

Decision tree

Figure 3 displays the GACE (Gaze, facial Asymmetry, level of Consciousness, Extinction/inattention) decision tree. The GACE decision tree enables prediction of LAVO by assessment of a maximum of only four predefined dichotomized NIHSS items with an AUROC of 0.76 (95% CI 0.68–0.83). 'Gaze', the item with the highest predictive value for LAVO in our cohort, is the first item to be assessed. For both the group of patients with an abnormal gaze (27%, left side of the diagram) as for the group of patients with a normal gaze (73%, right side of diagram), the following item with the highest predictive value for LAVO is determined. For both subgroups, this item is 'facial asymmetry'. Assessment of this second item leads directly to an outcome (i.e., LAVO or non-LAVO) in 61% of all patients (scoring (a) gaze 'yes' plus facial asymmetry 'yes', (b) gaze 'yes' plus facial asymmetry 'no', or (c) gaze 'no' plus facial asymmetry 'no'). Only for the remaining 39% of patients, the full 4-item decision tree (adding 'LOC questions', followed by 'LOC commands' or 'extinction/ inattention' has to be completed (see Figure 3 and Table 3)

Table 3. Number of patients (%) reaching a LAVO/ non-LAVO outcome per number of completed items within GACE

Number of completed Items	Total patients (n=1370)
2 items *ie (i)gaze, (ii) Facial asymmetry*	830 (60.6%)
4 items *ie (i)gaze, (ii) Facial asymmetry (iii) LOC questions,* *(iv) LOC commands or extinction/inattention*[a]	540 (39.4%)

Abbreviations: LOC = level of consciousness
[a] *dependent on result of assessment of item*

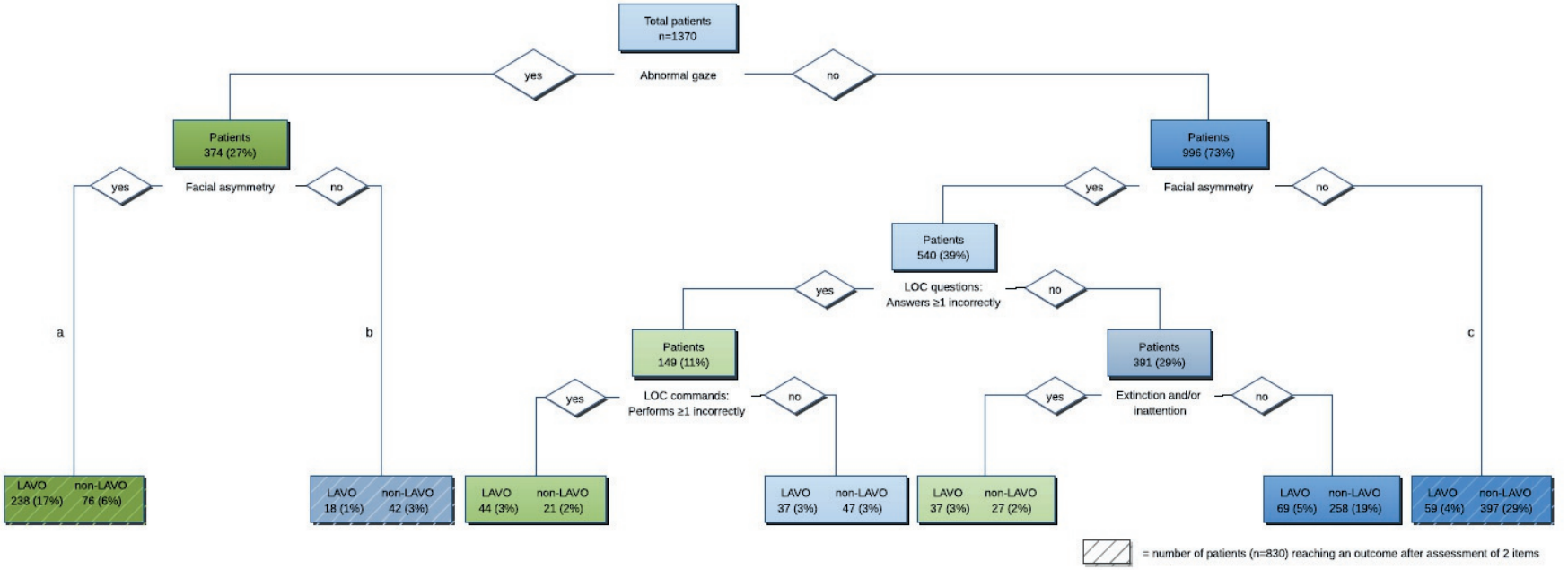

Figure 3.
GACE decision tree diagram based on dichotomized NIHSS items (assessed in DUST)

Numbers on the left side of each bottom box indicate the number of patients (percentage) with a LAVO outcome, whereas numbers on the right side of each bottom box indicate the number of patients (percentage) with a non-LAVO outcome. The color of each box indicates the ratio of LAVO (green) and non-LAVO patients (blue): the higher intensity of the color, the higher the ratio. 830 patients (61%, group a, b and c) reach an outcome (i.e. LAVO or non-LAVO) after assessment of only 2 items. LAVO: large anterior vessel occlusion; LOC: level of consciousness.

DISCUSSION

Our systematic search revealed seven LAVO-prediction scales designed for use in the prehospital phase. However, the majority was retrospectively validated in (small) monocenter cohorts in an in-hospital setting, making it difficult to determine which scale outperforms the other in prehospital clinical practice.

In our large multicenter validation cohort, we found that FAST-ED and RACE had the highest AUROC for prediction of LAVO. A seemingly important advantage of RACE over FAST-ED is that it was validated in the prehospital setting. Nevertheless, RACE appears too complex for prehospital EMS use, comprising a 5-item, 9-point assessment in which the decision to use or omit certain scale items (i.e. agnosia, aphasia) depends on the assumed involved hemisphere.[9] Indeed, during the validation phase, the scale was not performed in 40% of suspected stroke patients.[9] Although FAST-ED is based on the widely used FAST score and outperforms the NIHSS for prediction of LAVO in our database, it has potential drawbacks as it (a) imposes scoring a 'partial', 'mild' or 'moderate' deficit in most items, hampering interrater reliability; and (b) uses complex items (e.g. extinction/inattention) which are difficult for EMS personnel to assess.[13,31]

G-FAST seems more feasible for EMS use. However, in the original G-FAST study (i) vessel imaging modality to detect LAVO is unclear, and more importantly, (ii) definition of LAVO does not meet current clinical EVT-criteria (excluding ACA and M2 occlusion).[14]

In our cohort, as expected, AF was more common in LAVO-patients. Although neither this nor other patient characteristics improved the group lasso model, the model including seven NIHSS-items had a higher AUROC (0.84) than the scales derived from the literature.

Despite significant differences in performance of the scales, it should be pointed out that many of these differences are associated with small absolute differences in AUROC (i.e., 0.02). We accepted a small reduction in AUROC for the GACE decision tree (compared with the group lasso model), as we estimate that the prehospital feasibility is high since EMS personnel only need to take two steps to rule out transportation to a CSC for a substantial proportion of patients (61%, see Table 3), and only four for the remainder.

From a clinical perspective, it seems remarkable that facial asymmetry is such an important scoring item for GACE since it appears to have little localizing value.[32] It is important, however, to bear in mind that it is not this separate item, but the combination with gaze assessment that leads to a high predictive value for LAVO in our cohort.

In addition to LAVO prediction, allocation decision also depends on

(1) the impact of delay on clinical efficacy of both IVT and EVT, (2) patient characteristics (e.g. medical history, time from symptom onset, course of the disease) and (3) logistic factors (e.g. urban/rural area, number of comprehensive and primary stroke centers (PSC) and distance to scene of stroke, interhospital distance, in-hospital door-to-needle and door-to-groin times).[33] Therefore, we chose to display ROCs, enabling determination of a clinically relevant cut-off point considering local circumstances.

Moreover, allocation decision highly depends on what kind of error one is willing to allow: (a) having more patients come to a CSC accepting that some of these may not have LAVO and incorrectly bypass a PSC delaying IVT (false-positives); or (b) being focused on only allocating LAVO-patients to a CSC accepting that some LAVO-patients will primarily be transported to a PSC without EVT-facilities (false-negatives).

For example, a 75-year-old patient presenting with a partial gaze palsy, facial asymmetry, dysarthria and moderate left hemiparesis is assessed by EMS personnel 2.5 hours after symptom onset. Scores for this patient on the best performing LAVO-prediction scales in our validation cohort are: RACE 4/9, FAST-ED 2/13 and G-FAST 4/4. When applying the original authors' cut-off point, the patient has a moderate to high chance of LAVO, advising direct transport to a CSC with G-FAST, and a transport to the nearest PSC with RACE and FAST-ED. These scales, however, do not take local circumstances into account.

Consider that a PSC is located 10 min and a CSC 20 min from scene of stroke (with equal door-to-needle times). Bypassing the PSC is associated with a 10 min delay to IVT but a more substantial time delay to EVT is avoided by preventing inter-hospital transfer. Keeping in mind that IVT has limited efficacy in LAVO-patients,[25,34-39] a scale with a high sensitivity (such as G-FAST) seems the more desirable for this specific situation.

However, when transport time to a PSC is only 10 min and to a CSC is 50 min, a scale with a high sensitivity is less desirable. Most patients (including false-positives) will then be transported to the CSC with a more substantial time delay to IVT (40 min) for non-LAVO patients and, in addition, overloading the CSC with a large volume of patients. Therefore, in this situation, a scale with a high specificity (such as RACE or FASTED) would probably be the more desired choice.

Overall, time is brain, but since LAVO-patients appear to clinically benefit more substantially from earlier EVT than overall stroke patients benefit from earlier IVT,[3,40] a moderate to high likelihood of LAVO seems to allow a fair time delay to IVT. How much delay exactly, however, remains complex, as logistics (which are dynamic as resources shift over time) determine the amount of accepted time delay at expense of the number of false-positively referred patients. To what extent implementation of a clinical LAVO-prediction scale affects local logistics and health care-related costs must be estimated,

since no formal cost-effectiveness analysis was performed.

Our study has several limitations. First, our study was performed retrospectively which could have led to selection bias. Data, however, were collected prospectively minimizing such an effect. Second, our cohort does not represent an unselected prehospital cohort. For example, ICHs were not included, leading to an artificially high prevalence of LAVO and IVT-treated patients, which could result in an overestimation of the prediction scales. To what extent this influences a decision to use a scale depends very much on local circumstances since ICHs are often concentrated in CSCs.

Of note, the retrospective nature and lack of an unselected cohort account for all LAVO-prediction scales included in our analysis and therefore do not diminish validity of between scale comparisons.

Finally, clinical scale assessment was performed in the in-hospital setting, rendering translation to the prehospital setting limited. Indeed, prospective validation in this setting is much warranted and our results should primarily be considered an important step towards a large prehospital prospective validation study which we planned to embed in the ongoing 'A Reduction in Time with Electronic Monitoring in Stroke' (ARTEMIS) trial conducted within three EMS regions, which allows patients to be electronically tracked from the first moment the dispatch office is alarmed up until start of reperfusion therapy (clinicaltrials.gov identifier: NCT02808806).[41]

Nevertheless, clinical LAVO-detection could also be very helpful in order to optimize in-hospital logistics of potential EVT-eligible patients (e.g. pre-notification of neuro-interventional team and preparation of the angio suite can reduce door-to-groin times).[42]

CONCLUSION

We identified seven LAVO-prediction scales of which FAST-ED and RACE performed best and comparable to the NIHSS. An important limitation remains; however, that prospective validation in the prehospital EMS setting is lacking.

We developed a practical and easy-to-use decision tree that utilizes only two dichotomized NIHSS items for LAVO prediction for 61% of patients, and four items for the remaining patients in our cohort. Prospective validation of GACE in the prehospital setting is planned.

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SUPPLEMENTAL

Supplemental 1.
LAVO-prediction scales characteristics

	RACE[43]	3I-SS[8]	CPSSS[1]	VAN[44]	PASS[12]	FAST-ED[45]	G-FAST[14]
Clinical scale							
Scale items	facial asymmetry, arm motor function, leg motor function, gaze, aphasia or agnosia	LOC, gaze, 'hemiparesis'	gaze, LOC questions, LOC commands, arm motor function	arm motor function, 'visual disturbance', aphasia, gaze, extinction/ inattention	LOC questions, gaze, arm motor function	facial asymmetry, arm motor function, aphasia, gaze, extinction/ inattention	gaze, facial asymmetry, arm motor function, aphasia
Scouring range (points)	0-9	0-6	0-4	N/A	0-3	0-13	0-4
Cut-off point	RACE ≥ 5	31-SS ≥ 4	CPSSS ≥2	VAN-positive	PASS ≥2	FAST-ED≥4	G-FAST≥3
Validation cohort							
n	357	83	303	62	1057	727	3505
Multicenter	No	No	Yes	No	Yes	Yes	Yes
Suspected stroke patients potentially eligible for reperfusion therapy	Yes	Yes	Yes	Yes	Yes	Yes	Yes
NIHSS at admission, median [IQR]	8 [3-16]	N/S	>8[N/S]	N/S	N/S	5 [2-12]	9 [6-16]
Reperfusion therapy, % (IVT/EVT)	N/S	N/S	100(IVT)	N/S	100 (IVT)	N/S	100(N/s)

	RACE[43]	3I-SS[8]	CPSSS[1]	VAN[44]	PASS[12]	FAST-ED[45]	G-FAST[14]
Final diagnosis							
Ischemic stroke, n (%)	240 (67.2)	N/S	303 (100)	N/S	N/S	N/S	N/S
TIA, n (%)	20 (5.6)	N/S	Excluded	N/S	N/S	N/S	N/S
ICH, n (%)	52 (14.6)	Excluded	Excluded	N/S	N/S	Excluded	Excluded
Stroke mimic, n (%)	45 (12.6)	N/S	Excluded	N/S	N/S	N/S	N/S
Setting							
Study Design	Prospective	Prospective	retro-spective	Prospective	retro-spective	retro-spective	retro-spective
Setting	Prehospital	in-hospital	in-hospital	in-hospital	in-hospital	in-hospital	in-hospital
Raters	EMS - Personel	Neurolo-gists	physicians	ER nurses	N/S	research personnel	N/S
	N/S	0.95	N/A	1.00	N/A	N/A	N/A
Outcome							
LAVO definition (site of occlusion)	ICA, M1, tandem, basilar artery	MCA	ICA, M1, tandem, basilar artery	ICA, M1, M2	anterior or posterior circulation	ICA, M1, M2 basilar artery	ICA, M1
Imaging modality	trans-cranial duplex, CTA, MRA	MRA	CTA	CTA	CTA, MRA	CTA	i.a. CTA, MRA
Vessel imaging done be-fore IVT	N/S	N/S	Yes	No	Yes	N/S	Yes

	RACE[43]	3I-SS[8]	CPSSS[1]	VAN[44]	PASS[12]	FAST-ED[45]	G-FAST[14]
LAVO rate n (%)	76 (21.3)	27 (32.5)	222(73.3)	14 (22.6)	N/S	240 (33)	827 (23.6)
Performance							
Sensitivity	0.85	0.67	0.83	1.00	0.61	0.60	0.89
Specificity	0.68	0.92	0.40	0.90	0.83	0.89	0.39
accuracy	0.72	0.86	N/S	0.92	N/S	0.79	0.51
AUC (95% CI)	0.82 (0.77-0.87)	N/S	0.67 (N/S)	N/s	0.72	0.81 (N/S)	0.72 (0.71-0.74)

Characteristics of identified LAVO-prediction scales. Abbreviations: 3I-SS = 3-Item Stroke Scale; CPSSS = Cincinnati Prehospital Stroke Severity Scale; CTA = CT angiography; EMS = Emergency Medical Services; ER = Emergency Room; FAST-ED = Face-Arm-Speech-Time-Eye deviation-Denial/neglect; G-FAST = Gaze-Face-Arm-Speech-Time; ICA = intracranial carotid artery; ICH = intracerebral haemorrhage; IVT = intravenous thrombolysis; EVT = endovascular treatment; LAVO = large anterior vessel occlusion; LOC = level of consciousness; MCA = middle cerebral artery; MRA = magnetic resonance angiography; NIHSS = National Institutes of Health Stroke Scale; PASS = Prehospital Acute Stroke Severity; RACE = Rapid Arterial Occlusion Evaluation; VAN = Vision Aphasia Neglect a as defined by original authors b based on cut-off point, as defined by original authors

Supplemental 2.
DUST investigators

The DUST investigators are: Academic Medical Center, Amsterdam, The Netherlands (Majoie CB, Roos YB); Catharina Hospital, Eindhoven, The Netherlands (Duijm LE, Keizer K); Erasmus Medical Center, Rotterdam, The Netherlands (van der Lugt A, Dippel DW); Gelre Hospitals, Apeldoorn, The Netherlands (Droogh - de Greve KE, Bienfait HP); Leiden University Medical Center, Leiden, The Netherlands (van Walderveen MA, Wermer MJ); Medical Center Haaglanden, The Hague, The Netherlands (Lycklama à Nijeholt GJ, Boiten J); Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands (Duyndam D, Kwa VI); Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands (Meijer FJ, van Dijk EJ); Rijnstate Hospital, Arnhem, The Netherlands (Kesselring FO, Hofmeijer J); St. Antonius Hospital, Nieuwegein, The Netherlands (Vos JA, Schonewille WJ); St. Elisabeth Hospital, Tilburg, The Netherlands (van Rooij WJ, de Kort PL); St. Franciscus Hospital, Rotterdam, The Netherlands (Pleiter CC, Bakker SL); VU Medical Center, Amsterdam, The Netherlands (Bot J, Visser MC); University Medical Center Utrecht, Utrecht, The Netherlands (Velthuis BK, van der Schaaf IC, Dankbaar JW, Mali WP, van Seeters T, Horsch AD, Niesten JM, Biessels GJ, Kappelle LJ, Luitse MJ, van der Graaf Y).